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Clinical Investigation

Duration of Androgen Deprivation in Locally Advanced Prostate Cancer: Long-Term Update of NRG Oncology RTOG 9202

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Summary

Several clinical trials have shown a benefit to adding androgen deprivation therapy (ADT) to definitive radiation therapy (RT) to treat locally advanced adenocarcinoma of

Purpose: Trial RTOG 9202 was a phase 3 randomized trial designed to determine the optimal duration of androgen deprivation therapy (ADT) when combined with definitive radiation therapy (RT) in the treatment of locally advanced nonmetastatic adenocarcinoma of the prostate. Long-term follow-up results of this study now available are relevant to the management of this disease.

Methods and Materials: Men (N = 1554) with adenocarcinoma of the prostate (cT2c-T4, N0-Nx) with a prostate-specific antigen (PSA) <150 ng/mL and no evidence of

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the prostate. The length of time on ADT varied, resulting in a question of the optimal timing. Trial RTOG 9202 addressed this question in a phase 3 randomized trial of RT and 4 months of ADT versus 28 months. Longer ADT was superior to shorter ADT.

distant metastasis were randomized (June 1992 to April 1995) to short-term ADT (STAD: 4 months of flutamide 250 mg 3 times per day and goserelin 3.6 mg per month) and definitive RT versus long-term ADT (LTAD: STAD with definitive RT plus an additional 24 months of monthly goserelin).

Results: Among 1520 protocol-eligible and evaluable patients, the median follow-up time for this analysis was 19.6 years. In analysis adjusted for prognostic covariates, LTAD improved disease-free survival (29% relative reduction in failure rate, $P<.0001$), local progression (46% relative reduction, $P=.02$), distant metastases (36% relative reduction, $P<.0001$), disease-specific survival (30% relative reduction, $P=.003$), and overall survival (12% relative reduction, $P=.03$). Other-cause mortality (non−prostate cancer) did not differ (5% relative reduction, $P=.48$).

Conclusions: LTAD and RT is superior to STAD and RT for the treatment of locally advanced nonmetastatic adenocarcinoma of the prostate and should be considered the standard of care. Published by Elsevier Inc.

Introduction

The benefit of androgen deprivation therapy (ADT) in addition to radiation therapy (RT) for locally advanced adenocarcinoma of the prostate has been well established since the results of several phase 3 randomized trials were reported in the late 1990s and early 2000s (1-3). These trials randomized patients between RT alone versus RT and ADT. The ADT was given for varying lengths of time from 4 months (2) to 3 years (3) to indefinitely (1). Inasmuch as all of these trials showed a benefit to the ADT plus RT arms in terms of prostate cancer control, the next obvious question was what was the optimal duration of ADT. Both the European Organisation for Research and the Treatment of Cancer (EORTC) (4) and the RTOG (5) (Radiation Therapy Oncology Group) addressed this question with a phase 3 randomized trial of short-course versus longer-course ADT in addition to pelvic lymph node and prostate RT for patients with locally advanced disease.

Results from the EORTC trial showed a benefit to the long-term (36 months) arm over the 6-month arm in terms of clinical progression-free survival, the primary endpoint of the study (4). Trial RTOG 9202 investigated the addition of 24 months of adjuvant ADT versus no adjuvant ADT after 4-month duration neoadjuvant and concurrent ADT and standard RT to the prostate and pelvic lymph nodes (6). This report represents the final update of that trial with respect to treatment efficacy outcomes and toxicities.

Patients and Methods

Patient population

Men with histologically confirmed adenocarcinoma of the prostate (clinical T2c-T4, N0-NX, based on the 1992 American Joint Committee on Cancer Staging Manual (7) and meeting the following criteria, were eligible for the trial. Pretreatment prostate-specific antigen (PSA) <150 ng/mL, Karnofsky performance status $\geq 70\%$, no evidence of distant metastasis, and no prior ADT, RT, or chemotherapy. Institutional review board approval was required at each participating center before any patient enrollment or data transfer could occur. Informed consent was obtained for each patient before enrollment, random assignment, and treatment. The details of pretreatment patient evaluations have been summarized in a previous report (5). Follow-up as previously reported occurred after the RT was complete, with PSA determinations occurring every 3 to 6 months during the first 5 years and then annually.

Enrollment and treatment

The trial opened for accrual on June 26, 1992, closed April 5, 1995, and enrolled 1554 patients.

After registration and consent, patients were randomized within strata defined by stage (T2c vs T3 vs T4), pretreatment PSA (≤ 30 vs >30 mg/mL), grade (grades 2-5, 6, 7, 8-10), and nodal status (NX-N2) using a permuted block method (8). Patients were randomly assigned to short-term androgen deprivation (STAD) or long-term androgen deprivation (LTAD), as defined below.

External beam radiation therapy was performed on all patients by the use of conventional pelvic fields with a 4-field technique with megavoltage x-rays of ≥ 4 MV. This treatment was delivered at 1.8 to 2.0 Gy once daily to a dose of 44 to 46 Gy and was followed by reduced fields to the prostate for a total of 65 to 70 Gy for T2c tumors and 67.5 to 70 Gy for T3 and T4 tumors. The prescribed dose was recorded as an isocenter dose at the center of the prostate target volume.

All patients began ADT 2 months before the start of RT and received flutamide (250 mg 3 times per day) with goserelin (3.6 mg subcutaneously monthly) until the RT was completed (4 months total duration) and then continued to no further treatment (STAD) or an additional 24 months of monthly goserelin (LTAD), depending on their randomly assigned treatment arm.

Study design and endpoints

The primary trial endpoint was disease-free survival (DFS), defined as time until local progression, distant metastasis, biochemical failure, or death before these events. This study was designed to provide at least 90% power at (1-sided) $\alpha = 0.05$ to detect an absolute 10% improvement in DFS from 40% to 50% at 5 years. Additional endpoints include local progression (LP), distant metastasis (DM), biochemical failure (BF), disease-specific survival (DSS), and overall survival (OS). Local progression was defined as clinical evidence of local recurrence by any method or persistent disease. Distant metastasis was defined as clinical evidence of distant disease by any method. BF was originally defined as the earliest of the following: 3 consecutive rises after a posttreatment PSA nadir (the 1997 American Society for Therapeutic Radiology Oncology [ASTRO] definition), any point where the patients received additional ADT or an absolute PSA >4 ng/mL. In this report we use the more commonly applied Phoenix definition of nadir plus 2.0 ng/mL (9). Disease-specific survival was defined as death resulting from prostate cancer, treatment toxicity, or unknown cause with distant metastasis. All event times were measured from the date of randomization. Acute RT toxicities were defined as those occurring within 90 days from the start of RT. Any toxicity continuing or developing after 90 days was considered a late RT toxicity. These were summarized as frequencies of greatest toxicity grade per type, and for selected adverse events, cumulative probability of occurrence of grade 3 or greater toxicities.

Table 1 Pretreatment characteristics of patients included in analysis

Characteristic	STAD + RT (n=762)		LTAD + RT (n=758)		*P*
	n	%	n	%	
Age, years					.39
Mean	69.4		69.7		
Median (range)	70 (43-87)		70 (43-88)		
Race					.41
White	642	84.3	637	84.0	
Hispanic	17	2.2	10	1.3	
African American	92	12.1	105	13.9	
Native Hawaiian, other Pacific Islanders, American Indian, or Alaska native	6	0.8	4	0.5	
Unknown	5	0.7	2	0.3	
PSA, ng/mL					.88
≤30	510	66.9	510	67.3	
>30	252	33.1	248	32.7	
Karnofsky performance status, %					.04
70	11	1.4	2	0.3	
80	54	7.1	48	6.3	
90	376	49.3	358	47.2	
100	321	42.1	350	46.2	
Intercurrent disease					.89
No	253	33.2	246	32.5	
Yes	503	66.0	508	67.0	
Unknown	6	0.8	4	0.5	
Clinical stage					.07
T2	347	45.5	344	45.4	
T3	394	51.7	376	49.6	
T4	21	2.8	38	5.0	
Pathologic nodal stage					.63
NX	657	86.2	648	85.5	
N0	70	9.2	81	10.7	
N1	24	3.2	18	2.4	
N2	11	1.4	11	1.5	
Institutional Gleason score					.34
2-5	142	18.6	137	18.1	
6	149	19.6	154	20.3	
7	226	29.7	251	33.1	
8-10	187	24.5	174	23.0	
Unknown	58	7.6	42	5.5	

Abbreviations: LTAD = long-term androgen deprivation; RT = radiation therapy; PSA = prostate-specific antigen; STAD = short-term androgen deprivation.

Statistical analysis

The Kaplan-Meier method was used to estimate the OS and DFS distributions (10). The cumulative incidence approach was used to estimate the cumulative probability for LP, DM, BF, and DS deaths in the presence of competing risks (11). In graphical displays, the complement (ie, 1 minus), the probability was plotted against time from randomization to represent the event-free probability over time. The log-rank test was used to test for differences in DFS and OS between treatment arms, and it was also used to compare cause-specific hazards for LP, DM, BF, and DSS (12). For each endpoint, hazard ratios with 95% confidence intervals were computed from the Cox proportional hazards model for hazards (DFS and OS) or cause-specific hazards (LP, DM, BF, DSS) (13). For endpoints where competing risks are present, analyses using the Gray test and the associated competing-risks hazard regression model were also conducted (14, 15), given that both cause-specific hazards and cumulative incidence methods can be relevant to interpretation, particularly in long-term follow-up (16). To explore the potential for larger treatment benefit in patients at particularly high risk, an analysis of treatment outcomes in the subset of patients with a Gleason score of 8 to 10 was performed in earlier analyses, and those findings are updated for this report.

Results

Table 1 shows the pretreatment characteristics of the 1554 patients enrolled (1520 analyzable). There were no statistically significant differences between the 2 treatment arms with regard to the stratification variables and other characteristics. As previously reported, RT as assigned was completed in 96% of the patients in the STAD arm and 95% in the LTAD arm, with 4% and 3% of the reviewed cases judged unacceptable major deviations in the STAD and LTAD arms, respectively. The median follow-up time for all living patients was 19.6 years.

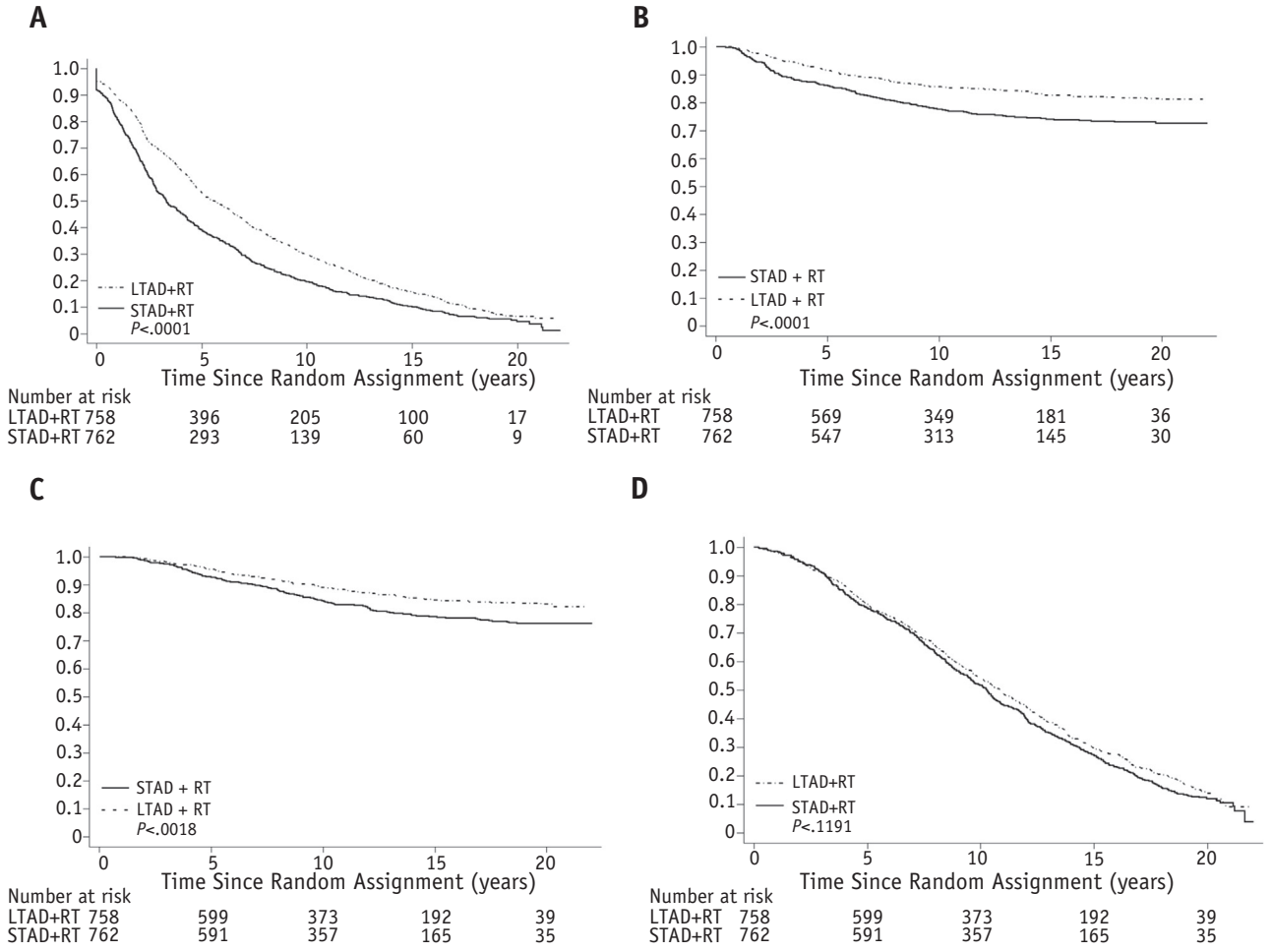

Fig. 1. (A) Disease-free survival, (B) distant metastasis, (C) death of prostate cancer, and (D) overall survival (death of any cause) by treatment group. (A, D) Plots are Kaplan-Meier curves. (B, C) Plots are (1 minus cumulative incidence estimator). *P* values are from unadjusted log-rank tests. See Table 2 for adjusted hazard ratios and *P* values. *Abbreviations:* LTAD = long-term androgen deprivation; RT = radiation therapy; STAD = short-term androgen deprivation.

Table 2 Analysis of LTAD effects on trial endpoints

Outcome	Total events		Unadjusted 15-year estimates, % event-free (95% CI)		Adjusted hazard ratio*		
	STAD	LTAD	STAD	LTAD	LTAD/STAD HR	95% CI	*P*
Disease progression endpoints							
Disease-free survival	700	670	10.0 (6.8-12.4)	15.7 (10.1-18.5)	0.71	0.64-0.79	<.0001
Local progression	176	100	76.8 (73.8-79.8)	87.1 (84.5-89.4)	0.54	0.42-0.69	<.0001
Distant metastasis	198	134	74.0 (70.8-77.1)	82.6 (79.8-85.3)	0.64	0.51-0.80	<.0001
Biochemical failure	461	341	38.8 (35.4-42.4)	54.6 (51.0-58.2)	0.58	0.50-0.66	<.0001
Mortality endpoints							
Disease-specific deaths	168	121	78.4 (75.3-81.4)	84.4 (81.7-87.0)	0.70	0.55-0.89	.003
Noncancer deaths	443	477	48.7 (45.0-52.5)	45.3 (41.7-49.1)	0.95	0.84-1.09	.48
Overall survival	611	598	27.1 (23.8-30.0)	29.8 (26.4-33.2)	0.88	0.79-0.98	.03

Abbreviations: CI = confidence interval; HR = hazard ratio; LTAD = long-term androgen deprivation; STAD = short-term androgen deprivation.
* Adjusted HR from Cox proportional hazard models including the following covariates: prostate-specific antigen (≤30, >30 ng/mL), T stage (T2, T3, T4), N stage (N0/NX, N1/N2), Gleason score (8-10, <8), age, and treatment (STAD + RT, LTAD + RT).

Treatment outcomes

The primary endpoint, DFS, was improved with long-term ADT (Fig. 1, Table 2). At 15 years, DFS estimates were 10% in the STAD arm versus 16% in the LTAD arm. Overall, there was a 29% reduction in risk of failure for LTAD relative to STAD ($P<.0001$, Table 2). Disease events constituting DFS were also reduced with LTAD (Table 2), with a 46% relative risk reduction in LP and 15-year failure-free estimates of 77% (STAD) versus 87% (LTAD), a 36% relative risk reduction in DM (74% vs 83% DM-free at 15 years), and a 42% relative risk reduction in BF (Phoenix definition, 39% vs 55% BF-free at 15 years).

Prostate cancer–specific survival at 15 years was 78% for patients receiving STAD and 84% for those receiving LTAD (Fig. 1). Overall, there was a 30% risk reduction in death due to prostate cancer with the use of LTAD ($P=.003$) (Table 2). Death of other causes did not differ significantly by treatment arm: 49% for STAD versus 45% for LTAD at 15 years (Table 2). The relative risk of other-cause mortality was not significantly influenced by treatment arm (hazard ratio = 0.95) (Table 2). Overall survival at 15 years was 27% for STAD versus 30% for LTAD (Table 2, Fig. 1). The risk of death of any cause was reduced approximately 12% by LTAD ($P=.03$) (Table 2).

The influence of patient and disease characteristics on outcomes was largely as expected; characteristics related to more aggressive or advanced disease (higher Gleason score, greater baseline PSA, higher stage) were associated with greater risk of failure for all disease outcomes. Increasing age was associated with greater failure for DFS and OS (Table E1; available online at www.redjournal.org). An additional analysis of endpoints with competing risks (LP, DM, BF, DSS) with an alternative model to the cause-specific hazard did not produce materially different estimates or inference for treatment effects described in Table 2.

Specific patient subsets were identified on the basis of expected prognosis, and the benefit of LTAD was examined within these. As noted in earlier reports from this trial, for patients with high Gleason scores the impact of LTAD was

Table 3 Analysis of LTAD effects on trial endpoints among patients with Gleason score 8-10 and N0/NX

Outcome	Total events		Unadjusted 15-year estimate, % event-free (95% CI)		Adjusted hazard ratio*		
	STAD	LDAT	STAD	LDAT	LDAT/STAD HR	95% CI	*P*
Disease progression endpoints							
Disease-free survival	162	152	5.2 (2.4-9.6)	9.9 (5.8-15.4)	0.64	0.51-0.81	<.0001
Local progression	47	29	72.9 (66.0-79.4)	82.3 (76.1-87.7)	0.57	0.35-0.91	.02
Distant metastasis	72	43	57.0 (49.5-64.7)	74.3 (67.3-80.8)	0.53	0.36-0.77	<.0001
Biochemical failure	117	84	30.9 (24.4-38.6)	48.3 (40.8-56.5)	0.52	0.39-0.69	<.0001
Mortality endpoints							
Disease-specific survival	63	40	62.2 (54.6-69.7)	75.6 (68.5-82.1)	0.54	0.36-0.81	.003
Other cause of death	80	99	54.8 (47.1-62.7)	45.8 (38.2-54.1)	0.87	0.64-1.19	.39
Overall survival	143	139	16.9 (11.4-23.4)	21.4 (15.1-28.3)	0.75	0.59-0.95	.02

Abbreviations: CI = confidence interval; HR = hazard ratio; LTAD = long-term androgen deprivation; STAD = short-term androgen deprivation.
* Adjusted HR from Cox proportional hazard models including the following covariates: prostate-specific antigen (≤30, >30 ng/mL), T stage (T2, T3, T4), N stage (N0/NX, N1/N2), Gleason score (8-10, <8), age, and treatment (STAD + RT, LTAD + RT).

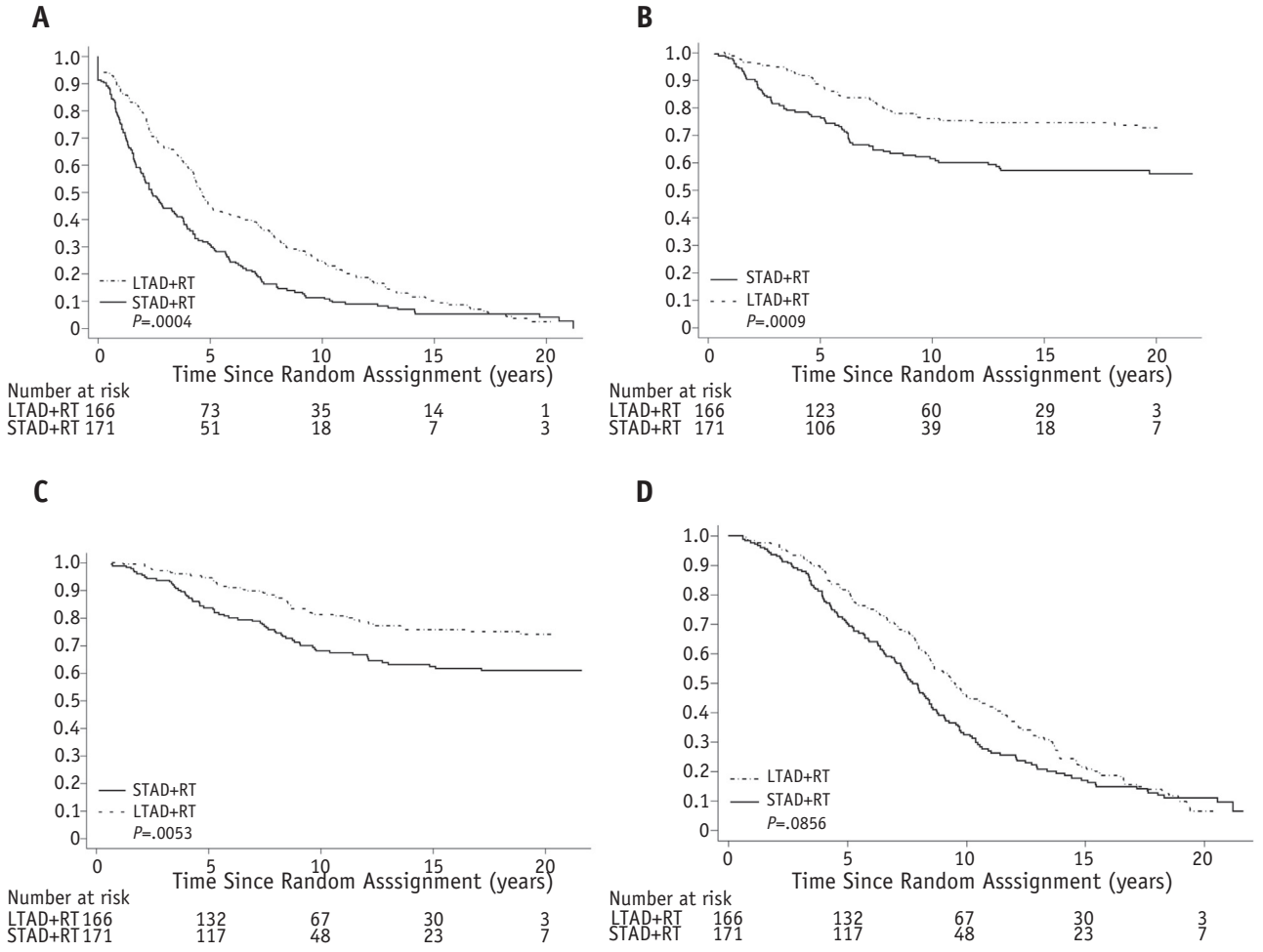

Fig. 2. (A) Disease-free survival, (B) distant metastasis, (C) death of prostate cancer, and (D) overall survival (death of any cause) by treatment group for patients with Gleason score 8 to 10 and N0/NX nodal status. (A, D) Plots are Kaplan-Meier curves. (B, C) Plots are (1 minus cumulative incidence estimator). *P* values are from unadjusted log-rank tests. See Table 3 for adjusted hazard ratios and *P* values. *Abbreviations:* LTAD = long-term androgen deprivation; RT = radiation therapy; STAD = short-term androgen deprivation.

greater (Table 3). For the 337 patients with Gleason scores 8 to 10 and N0/NX node status, there was a relative risk reduction of 33% in DFS, 48% in DM, and 50% in BF in favor of the LTAD arm. Disease-specific death risk was reduced by 45%, and overall mortality was reduced by 25% (Table 3, Fig. 2).

Further explorations into combinations of Gleason score and age at diagnosis were undertaken to investigate how disease-specific risk and other-cause death risk influence the relative benefit of LTAD. These did not reveal clearly differential treatment benefits according to subset examined (data not shown).

Toxicities

Toxicity from treatment was scored according to the previously reported RTOG criteria (17). Acute toxicity has been previously reported (6). There was no statistical difference in acute toxicity by treatment arm, with a maximum acute toxicity of grade ≥3 in 10% of patients on the STAD arm and 8% of those on the LTAD arm. Late toxicity, defined as toxicity developing after 90 days from the start of radiation, is shown in Table E2 (available online at www.redjournal.org). There was no statistical difference in grade ≥3 late genitourinary (GU) toxicity between the 2 arms. However, there was a statistically significant difference in late grade ≥3 gastrointestinal (GI) toxicity, with a frequency of 1.5% (n = 11) in the STAD arm and 3.0% (n = 23) in the LTAD arm ($P = .04$). The frequency of other grade ≥3 toxicity (not GI or GU) was not different between the 2 arms: 0.8% for STAD compared with 1.3% for LTAD. Analysis of the distribution of time to occurrence for late grade ≥3 GU and GI toxicity (Fig. 3) showed that the cumulative probability over time of late GI toxicity was somewhat greater for men in the LTAD arm.

With respect to long-term consequences of LTAD, of particular note is that there was no significant difference in

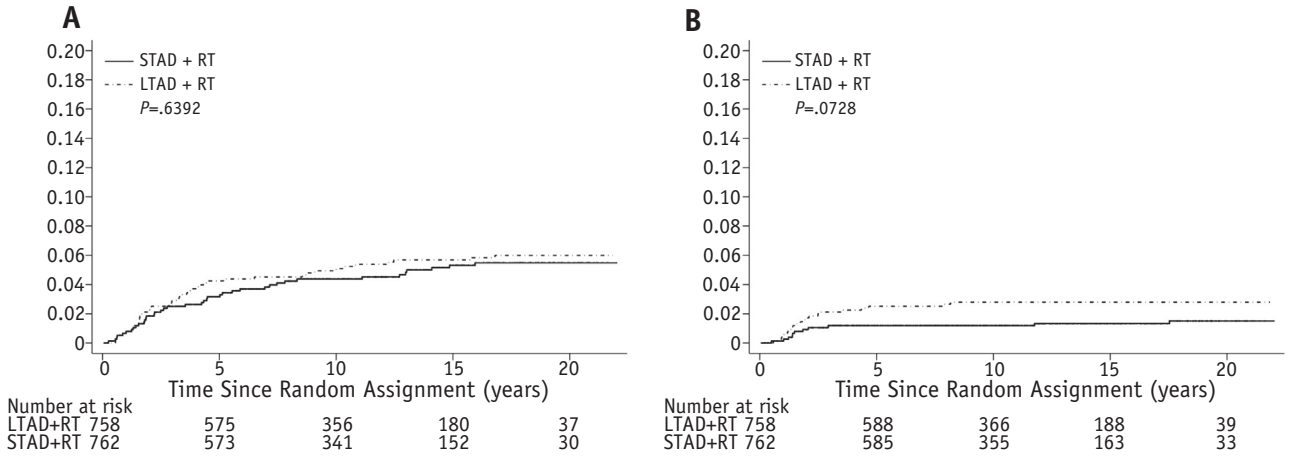

Fig. 3. Cumulative incidence of grade ≥3 late toxicity. (A) Genitourinary. (B) Gastrointestinal. *P* value is from Gray's test. *Abbreviations:* LTAD = long-term androgen deprivation; RT = radiation therapy; STAD = short-term androgen deprivation.

risk of all other-cause death combined between the 2 treatment arms (Table 2).

Discussion

The benefit of the addition of ADT to RT for prostate cancer patients with locally advanced cancer, those at high risk, or both has been well studied (1-3). Each of these randomized trials has shown a clear benefit to the use of ADT in addition to RT for these patients. The challenge among these trials is that although a benefit was seen, the durations of ADT in each of the trials were different, ranging from 4 months to indefinite. Thus, the need for a trial looking at duration of ADT was obvious. Both the EORTC and the RTOG trials addressed this need (4, 5).

This analysis reflects the long-term update of treatment benefits of LTAD in trial RTOG 9202, with a median follow-up time of 20 years. The addition of 2 years of ADT after neoadjuvant and concurrent ADT with RT resulted in significant improvements in DFS, LP, DM, BF, and DSS that have persisted with additional patient follow-up. A modest overall mortality risk reduction of about 8% to 12% and absolute advantage of 2% to 3% for LTAD has been consistently observed since the first report (5) and only nominally reaches conventional statistical significance in this update. The benefits of LTAD were greater for patients with higher Gleason score (scores of 8-10), including a statistically significant OS advantage in the first report and subsequent update (6). In this update, the observed 25% mortality risk reduction and absolute advantage of 4% (Table 3) is slightly smaller than in the earlier report, likely owing in part to most prostate cancer deaths having occurred earlier during follow-up (and more frequently with STAD), whereas at 15 years after diagnosis and beyond, most deaths are due to other causes, resulting in no further separation of the DSS curves and convergence of the OS curves (Fig. 1). This phenomenon causes the hazard ratio to diminish and the corresponding *P* value to increase. However, no causal relationship between treatment group and non-cancer deaths is necessary or implied by such an observation (16). It is reasonable to conclude that LTAD may be associated with a small survival advantage that is difficult to reliably distinguish from chance variation, and for higher risk patients, OS continues to be reliably improved through a reduction in prostate cancer deaths.

It is imperative to put these data into the pool of data regarding this question. Our results mirror similar findings in the EORTC trial of 6 months versus 36 months of ADT in addition to RT for locally advanced prostate cancer patients (4). This data also suggests that longer duration of ADT is clearly better for these patients. Yet, the Canadian Prostate Cancer Study IV (NCT 0023145), which (18) evaluated 18 months of ADT versus 36 months in addition to RT, showed in a preliminary report no difference in OS or DSS. This does point to a question we all should ask: just how long does the longer-course ADT need to be?

Finally, the question of RT dose has to be addressed. The doses used in trial RTOG 9202 of 65 to 70 Gy (isocenter doses) are clearly too low by today's standards. One must ask whether the benefits seen in the LTAD arm could be offset with more appropriate RT doses to the prostate, such as 75 to 80 Gy. The DART 01-05 GICOR trial (19) addressed this question with a phase 3 randomized trial of 4 months versus 28 months of ADT combined with 76 Gy to the prostate. At a median follow-up time of 63 months, the results of this trial showed a benefit to the LTAD arm in terms of OS and biochemical control, especially for high-risk patients. Thus, the answer seems quite clear that for locally advanced/high risk prostate cancer patients, the addition of LTAD improves their chance of cancer control significantly and therefore needs to be viewed as the standard of care for these patients relative to STAD.

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