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Cancer and Leukemia Group B 90203 (Alliance): Radical Prostatectomy With or Without Neoadjuvant Chemohormonal Therapy in Localized, High-Risk Prostate Cancer

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abstract

PURPOSE Radical prostatectomy (RP) alone is often inadequate in curing men with clinically localized, high-risk prostate cancer (PC). We hypothesized that chemohormonal therapy (CHT) with androgen-deprivation therapy plus docetaxel before RP would improve biochemical progression–free survival (BPFS) over RP alone.

PATIENTS AND METHODS Men with clinically localized, high-risk PC were assigned to RP alone or neoadjuvant CHT with androgen deprivation plus docetaxel (75 mg/m^2 body surface area every 3 weeks for 6 cycles) and RP. The primary end point was 3-year BPFS. Biochemical failure was defined as a serum prostate-specific antigen level > 0.2 ng/mL that increased on 2 consecutive occasions that were at least 3 months apart. Secondary end points included 5-year BPFS, overall BPFS, local recurrence, metastasis-free survival (MFS), PC-specific mortality, and overall survival (OS).

RESULTS In total, 788 men were randomly assigned. Median follow-up time was 6.1 years. The overall rates of grade 3 and 4 adverse events during chemotherapy were 26% and 19%, respectively. No difference was seen in 3-year BPFS between neoadjuvant CHT plus RP and RP alone (0.89 *v* 0.84, respectively; 95% CI for the difference, −0.01 to 0.11; $P = .11$). Neoadjuvant CHT was associated with improved overall BPFS (hazard ratio [HR], 0.69; 95% CI, 0.48 to 0.99), improved MFS (HR, 0.70; 95% CI, 0.51 to 0.95), and improved OS (HR, 0.61; 95% CI, 0.40 to 0.94) compared with RP alone.

CONCLUSION The primary study end point, 3-year BPFS, was not met. Although some improvement was seen in secondary end points, any potential benefit must be weighed against toxicity. Our data do not support the routine use of neoadjuvant CHT and RP in patients with clinically localized, high-risk PC at this time.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Prostate cancer (PC) is a heterogeneous disease that can progress slowly with a prolonged natural history or progress rapidly and lead to death despite treatment.[1] Risk assessment based on serum prostate-specific antigen (PSA), clinical stage, prostate biopsy features, and imaging is critical in selecting the right treatment of the right patient at the right time. Local therapy alone is often inadequate in curing men with clinically localized, high-risk PC. The addition of androgen-deprivation therapy (ADT) before, during, and after radiation has been shown to have a beneficial effect on disease-free survival and overall survival (OS).[2] In contrast, multiple published studies evaluating neoadjuvant ADT in men with localized PC undergoing radical prostatectomy (RP) have demonstrated histologic benefits but no apparent improvement in biochemical progression–free survival (BPFS).[3-6] These findings have led investigators to search for systemic therapies to add to RP to improve outcomes, particularly in men with high-risk disease.

Docetaxel prolongs median survival in men with metastatic PC resistant to ADT.[7,8] These results made it logical to test docetaxel earlier in the course of the disease in men at high risk for failure with local therapy alone. Several phase I and II clinical trials have demonstrated that neoadjuvant chemotherapy before RP was well tolerated and resulted in clinical downstaging.[9-11] Consequently, we undertook a phase III multicenter randomized trial to test the hypothesis that the addition of ADT plus docetaxel before RP would improve BPFS and OS in men with clinically localized, high-risk PC.

CONTEXT

Key Objectives

Does the addition of chemohormonal therapy to radical prostatectomy improve outcomes of men with clinically localized, high-risk prostate cancer? This randomized trial examined whether men treated with neoadjuvant docetaxel and androgen-deprivation therapy before radical prostatectomy had improved outcomes compared with men treated with radical prostatectomy alone.

Knowledge Generated

There was no difference in 3- or 5-year biochemical progression–free survival or prostate cancer–specific survival between the treatment groups. There was improvement in overall biochemical progression–free survival, metastasis-free survival, and overall survival in men treated with neoadjuvant chemohormonal therapy and radical prostatectomy.

Relevance

Our findings indicate that the combination of neoadjuvant docetaxel with androgen-deprivation therapy before radical prostatectomy should not be considered as a treatment option for men with clinically localized, high-risk prostate cancer at this time.

PATIENTS AND METHODS

Patient Population

Patients enrolled on the study had histologic documentation of prostatic adenocarcinoma and chose RP as first-line treatment. Patients with small-cell, neuroendocrine, or transitional cell carcinomas of the prostate were not eligible. Pathologic assessment (histology and Gleason grading) was by local review. Eligible patients had clinical T1-3a disease (determined by digital rectal examination), serum PSA levels $\leq$ 100 ng/mL (within 6 weeks before the diagnostic prostate biopsy), negative bone scans, and no radiographic evidence of metastatic disease by either computed tomography or magnetic resonance imaging of the abdomen and pelvis. A negative biopsy was required for any pelvic lymph nodes larger than 1.5 cm.

Definition of High-Risk PC

When the study was originally designed, risk status was determined using the 1998 Kattan preoperative nomogram.[12] We defined high-risk disease as a nomogram-predicted probability of being free from biochemical progression at 5 years after RP of $<$ 60%. At the time of study design, it was estimated that approximately 15% of men undergoing RP would meet the proposed nomogram definition of high risk. After the study opened, we found that only 5% of patients undergoing RP met the nomogram-based eligibility criteria, so the protocol was amended. The eligibility criteria were expanded to also include men with a biopsy Gleason score of 8-10, and by including these patients, we continued to target approximately 15% of patients undergoing RP. The Kattan nomogram probability was calculated for all patients, including those eligible based on Gleason score only. The only prior treatment allowed was up to 3 months of ADT immediately before study enrollment. All patients needed to be candidates for both RP and chemotherapy.

Trial Design

The trial was approved by the institutional review board. Patients were randomly assigned in a 1:1 ratio to either the neoadjuvant arm (neoadjuvant CHT and RP) or the surgery arm (RP only). Random assignment was stratified into risk groups based on the Kattan preoperative nomogram-predicted BPFS at 5 years (group 1, predicted BPFS of 0%-20.9%; group 2, predicted BPFS of 21%-39.9%; group 3, predicted BPFS of 40%-59.9%; group 4, Gleason score 8-10 with nomogram-predicted BPFS $\geq$ 60%).[12]

Patients randomly assigned to the neoadjuvant arm received docetaxel (75 mg/m^2 body surface area every 3 weeks for 6 cycles); oral dexamethasone (8 mg) 12 hours, 3 hours, and 1 hour before docetaxel; and ADT (luteinizing hormone–releasing hormone agonist or antagonist without an antiandrogen) for 18-24 weeks. For details on dose modifications, please see the Appendix (online only). Men who received ADT before enrollment who were randomly assigned to the neoadjuvant arm were treated identically to all other men in the arm and received 6 cycles of chemotherapy and up to 24 weeks of ADT after randomization.

Postsurgery Radiation

Patients with positive surgical margins could receive adjuvant external-beam radiation therapy (with up to 4 months of neoadjuvant/concurrent ADT) to the prostatic fossa and/or whole pelvis. Patients were not considered to have treatment failure and received standard follow-up if radiation therapy was initiated within 6 months of RP and the biochemical recurrence definition was not met. Patients receiving radiation therapy after meeting the definition of biochemical failure or radiation therapy $>$ 6 months after RP were considered as experiencing treatment failure.

Follow-Up and End Points

For details on surgical intervention, see the Appendix. After RP, PSA levels were checked every 3 months for 3 years,

then every 6 months for 3 years, and then annually thereafter up to 15 years. The primary end point was 3-year BPFS. Biochemical failure was defined as a serum PSA level > 0.2 ng/mL that increased on 2 consecutive occasions that were at least 3 months apart. The time of biochemical failure was measured from the date of randomization to the date of the first PSA level > 0.2 ng/mL or death from any cause. Men not undergoing surgery were censored at study entry for the BPFS end point. Secondary end points included 5-year BPFS, overall BPFS, metastasis-free survival (MFS; defined as time from date of randomization to date of evidence of systemic disease on bone scan or cross-sectional imaging), PC-specific mortality (defined as time from date of randomization to date of death as a result of PC), and OS (defined as time from date of randomization to date of death as a result of any cause). Cause of death was assigned by the treating physician. Local recurrence in the prostate bed required pathologic confirmation by biopsy in addition to computed tomography or magnetic resonance imaging scan evidence. Event-free survival (defined as time from date of randomization to date of biochemical progression, subsequent ADT, radiation therapy > 6 months after RP, local or distant progression, or death) was an additional analysis. ADT and/or radiation therapy after 6 months after surgery was given at the discretion of the treating physician. Safety was assessed by monitoring patients for adverse events.

Sample Size Determination and Statistical Analysis

It was determined that 375 patients per treatment arm would provide approximately 90% power for the projected 3-year BPFS rates of 57.7% in the surgery arm and 69.1% in the neoadjuvant arm. For the 3-year BPFS comparison, 7 interim analyses and 1 final analysis were planned using O'Brien-Fleming efficacy and futility boundaries.[13] The nominal significance level for the final O'Brien-Fleming boundary was $P = .018$.

Kaplan-Meier estimates[14] were computed for all time-to-event end points except PC-specific survival, where the cumulative incidence function was calculated to account for competing events.[15] For the primary end point, the Wald statistic[14] based on the difference in the 3-year BPFS Kaplan-Meier estimate was computed. For the 5-year BPFS difference, a 95% CI was calculated. The treatment comparisons for all other secondary end points were summarized with hazard ratios (HRs) and 2-sided 95% CIs using stratified Cox proportional hazards models.[16] Tests of the proportional hazards assumption were performed for each model, and no violations were found for the BPFS, MFS, and OS end points; a weighted Cox model was fit for the event-free survival end point, and a competing risks regression model was fit for the prostate-specific survival end point.[17,18] A post hoc analysis for the difference in the restricted mean survival times (up to 10 years) supplemented the OS analysis.[19] All analyses were based on the study database frozen on November 4, 2019.

RESULTS

Between December 2006 and October 2015, 788 men (median age, 62 years; range, 32-83 years) with clinically localized, high-risk PC were randomly assigned in a 1:1 ratio to neoadjuvant CHT and RP (neoadjuvant arm) or RP alone (surgery arm). Fifty patients (26 in the neoadjuvant arm and 24 in the surgery arm) withdrew consent (n = 37), were deemed ineligible after randomization (n = 11), were deemed unresectable (n = 1), or had grossly positive nodes (n = 1) and did not undergo RP; 738 men (391 in the neoadjuvant arm and 397 in the surgery arm) ultimately underwent RP (Fig 1). Age, race, clinical stage, serum PSA levels before

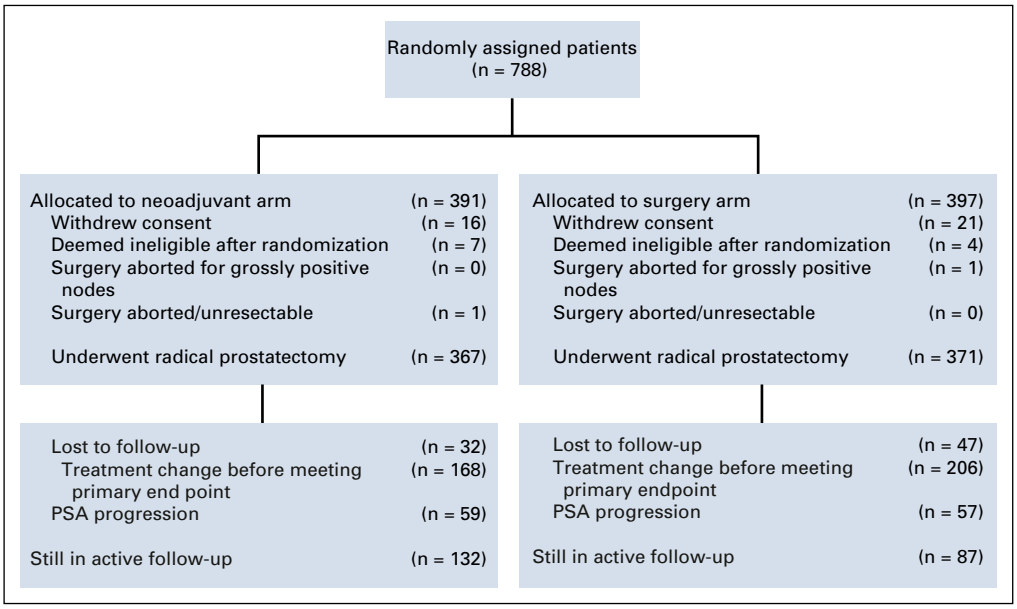

FIG 1. CONSORT diagram of Cancer and Leukemia Group B (Alliance) trial. PSA, prostate-specific antigen.

biopsy, and biopsy Gleason score were comparable between arms (Table 1). Most men (approximately 85%) were White. Approximately 70% had palpable disease (T2-3a). Approximately 54% of men were eligible using nomogram-based criteria (risk groups 1-3), and 46% were eligible based on biopsy Gleason score of 8-10 with a nomogram-predicted BPFS ≥ 60% (risk group 4). Approximately 87% of the total cohort had not received ADT before randomization.

Patients were observed for a median of 6.1 years (range, 0-12.1 years); all patients were included in the primary analysis. Men treated with neoadjuvant CHT had lower pathologic T stage and lower likelihood of having seminal vesicle invasion, positive pelvic lymph nodes, or positive surgical margins (Table 2). There were no pathologic complete responses.

Adjuvant radiation was given to 49 patients (6%) in the neoadjuvant arm and 87 patients (11%) in the surgery arm. Testosterone recovery data were available for 238 men in the neoadjuvant arm, of whom 216 (91%) experienced testosterone recovery > 150 ng/dL. The median time to

TABLE 1. Baseline Characteristics of Men Treated With Neoadjuvant Chemohormonal Therapy and Radical Prostatectomy (designated neoadjuvant) or Radical Prostatectomy Alone (designated surgery alone)

Characteristic	Neoadjuvant Patients (n = 391)	Surgery Alone Patients (n = 397)
Age, years		
Median	62	63
Range	40–78	33–84
Race[a]		
White	330 (84)	337 (85)
Black	40 (10)	38 (10)
Other	15 (4)	9 (2)
Unknown	6 (2)	13 (3)
Clinical stage by digital rectal examination		
T1	102 (26)	129 (33)
T2	219 (56)	204 (51)
T3a	70 (18)	64 (16)
Biopsy Gleason score		
6 (3 + 3)	2 (1)	2 (1)
7 (3 + 4)	15 (4)	28 (7)
7 (4 + 3)	25 (6)	31 (8)
8	153 (39)	147 (37)
9-10	196 (50)	189 (48)
Prostate-specific antigen level before biopsy, ng/mL		
Median	9.5	10.2
Range	0.3–125.5	0.1–93.0
Risk group[b]		
1	52 (13)	50 (13)
2	67 (17)	68 (17)
3	94 (24)	96 (24)
4	178 (46)	183 (46)
Prior androgen-deprivation therapy		
No	339 (87)	344 (87)
Yes	52 (13)	53 (13)

NOTE. Data presented as No. (%) unless otherwise indicated.

[a]Race was self-reported.

[b]Men were stratified into risk groups based on their nomogram-predicted biochemical progression–free survival at 5 years (group 1, 0%-20.9%; group 2, 21%-39.9%; group 3, 40%-59.9%; and group 4, Gleason score 8-10 with nomogram-predicted biochemical progression–free survival ≥ 60%).

TABLE 2. Pathologic Outcomes in Men Treated With Neoadjuvant Chemohormonal Therapy Plus Radical Prostatectomy (designated neoadjuvant) or Radical Prostatectomy Alone (designated surgery alone)

Outcome	No. of Patients (%)		Adjusted *P*
	Neoadjuvant	Surgery Alone	
Gleason score in surgical specimen	243	350	.10
6 (3 + 3)	5 (2)	4 (1)	
7 (3 + 4)	36 (15)	55 (16)	
7 (4 + 3)	47 (19)	98 (28)	
8	41 (17)	45 (13)	
9-10	114 (47)	148 (42)	
Pathologic T stage	358	366	< .001
T1/2	145 (41)	83 (23)	
T3	211 (59)	274 (75)	
T4	2 (1)	9 (2)	
Seminal vesicle invasion	365	366	.05
Yes	116 (32)	151 (41)	
No	249 (68)	215 (59)	
Pathologic nodal stage	352	356	.05
N0	280 (80)	250 (70)	
N1	68 (19)	97 (27)	
NX	4 (1)	9 (3)	
Surgical margins	303	281	< .001
Positive	56 (18)	126 (45)	
Negative	247 (82)	155 (55)	

NOTE. Summary statistics are calculated for the number of patients with available data for each characteristic.

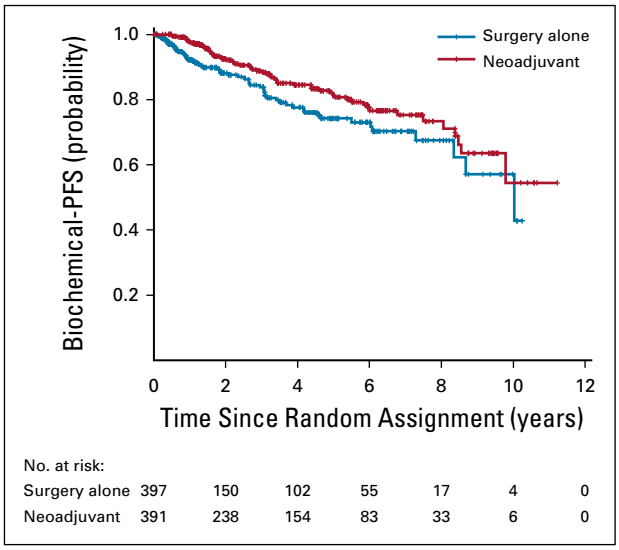

FIG 2. Biochemical progression–free survival (BFS) was compared between men treated with neoadjuvant chemohormonal therapy and radical prostatectomy (designated neoadjuvant) versus radical prostatectomy alone (designated surgery alone). Biochemical failure was defined as a serum prostate-specific antigen (PSA) level > 0.2 ng/mL that increased on 2 consecutive occasions that were at least 3 months apart. The time of biochemical failure is measured from the date of randomization to the date of the first PSA level > 0.2 ng/mL.

testosterone recovery > 150 ng/dL was 196 days (95% CI, 190 to 209 days).

No difference was observed in 3-year BPFS between the neoadjuvant and surgery arms (0.89 *v* 0.84, respectively; 95% CI for the difference, −0.01 to 0.11; $P = 0.11$; Fig 2). No difference was observed in 5-year BPFS between the neoadjuvant and surgery arms (0.81 *v* 0.74, respectively; 95% CI for the difference, −0.01 to 0.16; Fig 2). Men in the neoadjuvant arm had improved BPFS over the entire follow-up period (HR, 0.69; 95% CI, 0.48 to 0.99; Fig 2). Our ability to determine BPFS was compromised because 48% of patients (43% in neoadjuvant arm and 52% in the surgery arm) received additional treatment—usually salvage radiation therapy with or without ADT—before meeting the primary end point; these patients were censored at the time of additional therapy for the BPFS comparison as per US Food and Drug Administration guidance (Fig 1).

To attempt to account for the high proportion of men receiving additional treatment, an event-free survival comparison was performed. In contrast to the BPFS analysis, patients receiving subsequent therapies were considered to have treatment failure at the time of subsequent therapy for this analysis. Men in the neoadjuvant arm had improved event-free survival compared with men in the surgery arm (average HR, 0.61; 95% CI, 0.48 to 0.78; Fig 3A). The median event-free survival time was 4.53 years (95% CI, 3.34 to 5.75 years) for the neoadjuvant arm and 1.81 years (95% CI, 1.23 to 2.64 years) for the surgery arm.

Local progression was rare, identified in only 7 and 4 patients in the neoadjuvant and surgery arms, respectively. Patients in the neoadjuvant arm had improved MFS compared with patients in the surgery arm (HR, 0.70; 95% CI, 0.51 to 0.95; Fig 3B). There was no difference in PC-specific mortality (HR, 0.69; 95% CI, 0.32 to 1.07; Fig 3C). Patients in the neoadjuvant arm had improved OS compared with patients in the surgery arm (HR, 0.61; 95% CI, 0.40 to 0.94; Fig 3D). There were 36 deaths (23 from PC) in the neoadjuvant arm and 52 deaths (30 from PC) in the surgery arm. A comparison of restricted mean survival time (up to 10 years) was performed to summarize the results without a model. The difference in the restricted mean survival times between treatments was 4.40 months treatment (95% CI, 0.46 to 8.35 months) in favor of combination; this result was consonant with the model-based HR analysis. At 10 years, the survival probabilities were 0.74 (95% CI, 0.67 to 0.83) in the surgery arm and 0.80 (95% CI, 0.72 to 0.88) in the neoadjuvant arm.

Men in the neoadjuvant arm received a median of 6 cycles of docetaxel (median dose, 900 mg); 323 patients (83%)

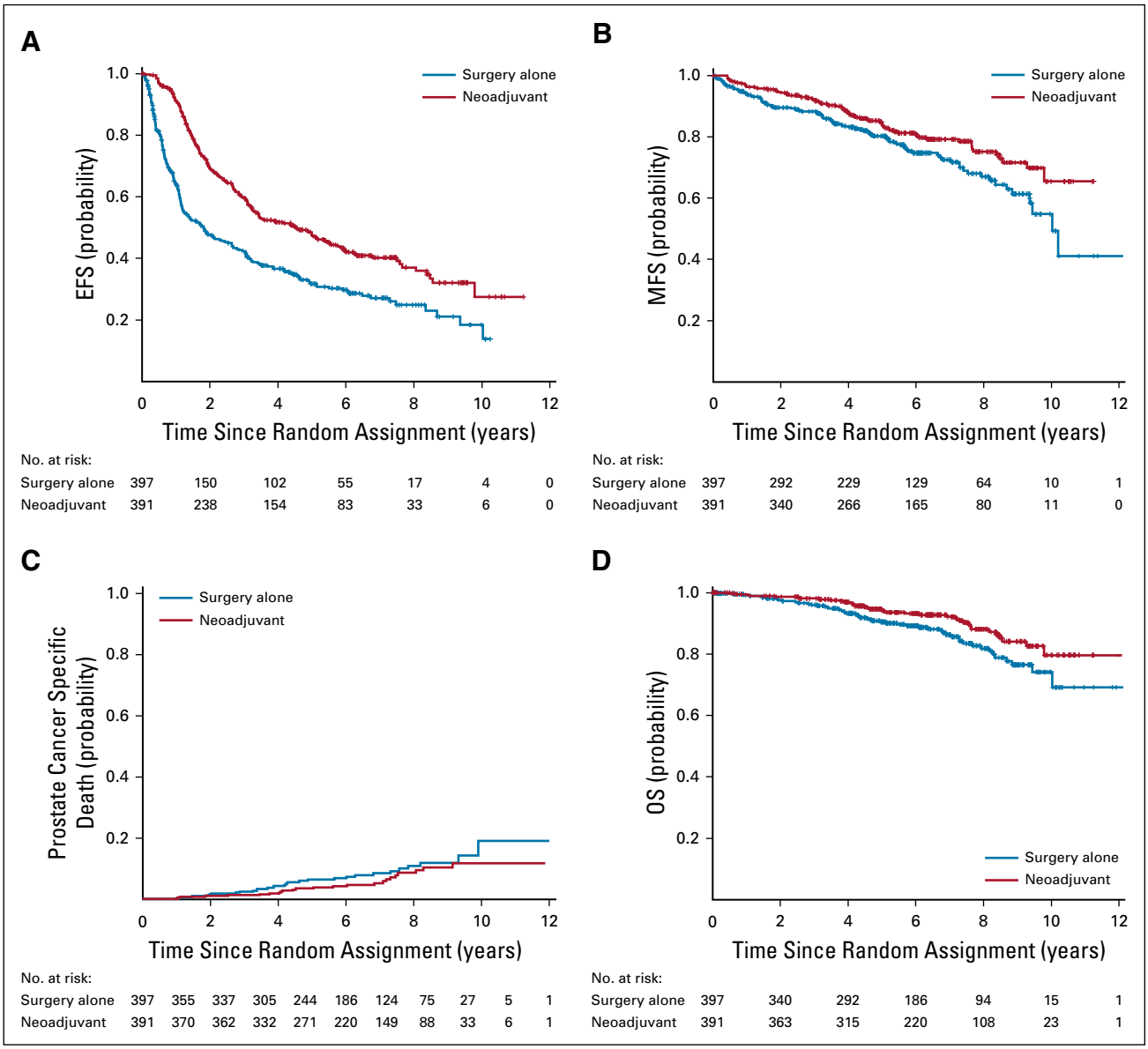

FIG 3. (A) Event-free survival (EFS) or the likelihood of not requiring additional treatment after radical prostatectomy in men treated with neoadjuvant chemohormonal therapy plus radical prostatectomy (designated neoadjuvant) versus radical prostatectomy alone (designated surgery alone). An event is defined as death, prostate-specific antigen progression, local or distant progression, initiation of androgen-deprivation therapy, and/or radiation therapy > 6 months after surgery. (B) Metastasis-free survival (MFS; the time from randomization to metastasis) in men treated with neoadjuvant chemohormonal therapy plus radical prostatectomy versus radical prostatectomy alone. (C) Prostate cancer–specific survival (the time from randomization to death from prostate cancer) in men treated with neoadjuvant chemohormonal therapy plus radical prostatectomy versus radical prostatectomy alone. Cause of death was assigned by the treating physician. (D) Overall survival (OS; the time from randomization to death) in men treated with neoadjuvant chemohormonal therapy plus radical prostatectomy versus radical prostatectomy alone.

received all 6 cycles of treatment, with 57 patients (15%) requiring at least one dose reduction. Adverse events associated with CHT are listed in Table 3. There were no deaths associated with CHT. One patient in the neoadjuvant arm came off study as a result of concerns of disease progression. The rates of grade 3 and 4 adverse events during chemotherapy were 26% and 19%, respectively. Common grade 3 and 4 adverse events included neutropenia (23%), hyperglycemia (6%), fatigue (4%), and febrile neutropenia (4%). Intraoperative complications were rare (3 rectal injuries and 1 ureteral injury) and independent of whether the patient received neoadjuvant CHT. Postoperative complications and morbidity were collected for all patients at days 3 and 30 after RP. There were no deaths within 30 days of RP. In the neoadjuvant arm, compared with the surgery arm, there were more grade 3 levels of low hemoglobin (5 *v* 0 patients, respectively) and postoperative bleeding (9 *v* 3 patients, respectively).

TABLE 3. Adverse Events Among the Patients Who Received Neoadjuvant Chemohormonal Therapy

	No. of Patients (N = 369)			
Adverse Event[a]	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Allergic reaction	19 (5)	27 (7)	8 (2)	1 (0)
Fatigue	199 (54)	111 (30)	15 (4)	1 (0)
Diarrhea	104 (28)	24 (7)	4 (1)	1 (0)
Neuropathy, motor	0 (0)	0 (0)	1 (0)	1 (0)
Neuropathy, sensory	166 (45)	20 (5)	6 (2)	0 (0)
Thromboembolism[b]	0 (0)	0 (0)	6 (2)	1 (0)
Anemia	1 (0)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	11 (3)	0 (0)	1 (0)	0 (0)
Neutropenia/granulocytopenia	9 (2)	8 (2)	23 (6)	61 (17)
Febrile neutropenia	0 (0)	0 (0)	12 (4)	4 (1)
Infection with grade 3/4 absolute neutrophil count	0 (0)	2 (1)	8 (2)	0 (0)
Abdominal pain	1 (0)	0 (0)	1 (0)	0 (0)
Arthralgia	85 (23)	24 (9)	8 (2)	0 (0)
Headache	2 (1)	0 (0)	3 (1)	0 (0)
Myalgia	108 (29)	40 (11)	7 (2)	0 (0)
Rectal pain	0 (0)	0 (0)	1 (0)	0 (0)
Stomach pain	1 (0)	0 (0)	0 (0)	0 (0)
Hyperglycemia	3 (1)	0 (0)	17 (5)	4 (1)
Any event (maximum grade)	103 (28)	95 (26)	97 (26)	69 (19)

NOTE. Data presented as No. (%).

[a]There were no grade 5 events.

[b]Two of the grade 3 events were related to vascular access.

DISCUSSION

We examined whether the addition of neoadjuvant CHT to RP in clinically localized, high-risk PC improved BPFS over RP alone. An improvement in BPFS at 3 years based on a planned 11% benefit with neoadjuvant CHT was not observed. Over the course of the entire trial period, there was evidence of improvement in BPFS, event-free survival, MFS, and OS with CHT and RP versus RP alone.

Several factors potentially affect the interpretability of our primary end point. Patients in the neoadjuvant arm did receive ADT, which is known to affect PSA levels, and adjuvant radiation, with up to 6 months of ADT permitted within 6 months of surgery. However, this should not significantly affect the interpretability of the 3-year BPFS end point, because the median time to testosterone recovery to noncastrate levels was 6 months. The most significant factor affecting the interpretability of the primary end point is that the earlier use of salvage radiation with or without ADT became common during the trial, with 48% of men receiving salvage treatment before reaching the study end point. This reduced the potential number of events for the primary end point and possibly the power of the study. In general, salvage treatment was used when PSA levels became detectable, well before the study-defined serologic progression end point of 0.2 ng/mL. We also chose to evaluate the PSA progression end point at 3 years rather than assessing the progression rate over the entire follow-up period. BPFS was improved for the neoadjuvant arm over the entire follow-up period.

To address the high number of censored patients as a result of treatment changes, we also evaluated event-free survival, MFS, PC-specific mortality, and OS. These analyses revealed improved outcomes with CHT. The comparable result from the overall BPFS and event-free survival analyses provided added confidence that men benefitted from the addition of neoadjuvant CHT to RP. The event-free survival analysis produced a stronger treatment comparison than the BPFS analysis and indicated that men treated with RP alone were more likely to receive additional therapy. Although there was no difference in PC-specific mortality, there were significantly more metastatic events in the surgery arm. Although the study did show an OS benefit favoring neoadjuvant CHT, the overall number of deaths (n = 88) is low, and many deaths (n = 35) were not attributable to PC. In addition, the restricted mean survival benefit of 4.4 months at 10 years is modest at best. Further follow-up (more events) is needed to clarify any OS benefit.

This study confirms the tolerability of neoadjuvant CHT in men undergoing RP for high-risk PC. There were no chemotherapy-associated deaths, and grade 3 and 4 adverse events occurred in 26% and 19% of patients, respectively. A favorable safety profile is not unexpected based on a healthy patient population of untreated men who were surgical candidates.[9-11] These adverse event results are comparable to those in men with clinically localized, high-risk PC treated with ADT and radiation or neoadjuvant docetaxel, ADT, and radiation.[20] Those receiving docetaxel experienced overall rates of grade 3 and 4 adverse events during chemotherapy of approximately 38% and 26%, respectively. There were no intraoperative deaths or deaths within 30 days of RP. There were no discernible differences in 3- and 30-day postoperative complications, although men receiving neoadjuvant CHT were more likely to have low hemoglobin and postoperative bleeding than men receiving RP alone.

A more recently investigated neoadjuvant strategy is to use neoadjuvant ADT (leuprolide) with enzalutamide and/or abiraterone before RP.[21] This approach has demonstrated improvements in pathologic features, including a pathologic complete response rate of approximately 10%.[22] Outcome data, including BPFS, suggest that freedom from PSA failure was much better than predicted by nomograms.[23] Whether an intense neoadjuvant androgen-deprivation strategy is equivalent or superior to neoadjuvant CHT requires further investigation (a phase III trial testing intense neoadjuvant ADT is underway). Importantly, neoadjuvant treatment with standard ADT before RP results in pathologic complete responses but does not improve BPFS.[24,25]

Our study highlights several challenges performing randomized trials in the clinically localized, high-risk population. One is defining high-risk disease. The Kattan nomogram and biopsy-based eligibility was considered appropriate when the study was designed, but few men experienced clinical (rather than biochemical) events. Another challenge is determining the appropriate study end point. BPFS is likely not ideal because it has no universally accepted definition and has not been validated as a surrogate for MFS, PC-specific mortality, or OS. In addition, some PSA relapses are salvageable with radiation therapy, resulting in cure. MFS is likely a more clinically meaningful primary end point than BPFS, but our study demonstrates that metastasis and death are rare within 10 years in this population. Designing a trial in this population with MFS as the primary end point would require numerous patients and long follow-up.

Our data do not support the routine use of neoadjuvant CHT and RP in patients with clinically localized, high-risk PC at this time. The primary study end point, 3-year BPFS, was not met. However, this end point was compromised because of the early use of salvage therapy. These patients will be observed long term, and clinical end points such as MFS, PC-specific survival, and OS will mature. Although this longer follow-up will never change the fact that the primary end point is negative, positive clinical findings would require reconsideration of the conclusion not to use neoadjuvant CHT in this setting.

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EQUAL CONTRIBUTION

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PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cancer and Leukemia Group B 90203 (Alliance): Radical Prostatectomy With or Without Neoadjuvant Chemohormonal Therapy in Localized, High-Risk Prostate Cancer

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APPENDIX

Methods

Trial oversight. The study was designed in 2002 by the National Cancer Institute–funded cooperative group Cancer and Leukemia Group B (formerly CALGB; now part of the Alliance for Clinical Trials in Oncology, referred to as Alliance) and was approved by the institutional review board at each participating institution (ClinicalTrials.gov identifier: NCT00430183). All participants gave written informed consent. The study was coordinated by Alliance, and the Alliance Statistical and Data Center collected the data, acted as the data coordinating center, and provided statistical analysis. The first and last author attest that the study was conducted and monitored as specified by the protocol. The first author wrote the first draft of the manuscript, with subsequent contributions by all coauthors. The authors vouch for the accuracy and completeness of the data presented. Sanofi donated the docetaxel but had no role in the design or conduct of the protocol, data collection or analysis, or article preparation. This phase III therapeutic trial was monitored at least twice annually by the Alliance Data and Safety Monitoring Board, a standing committee composed of individuals from within and outside of the Alliance.

Surgical intervention. All patients in both arms underwent standard radical prostatectomy (removal of the prostate and seminal vesicles) with extended bilateral pelvic lymph node dissection including the external iliac, obturator, and hypogastric lymph nodes. A perineal, open retropubic, laparoscopic, or robot-assisted approach was permitted. Surgical quality was monitored by the study chair who reviewed operative reports and surgical quality assessment forms completed by the operating surgeon documenting extent of pelvic lymph node dissection, completeness of surgical resection, and intraoperative staging. For men in the neoadjuvant arm, radical prostatectomy took place within 60 days after completion of therapy. For men in the surgery arm, radical prostatectomy took place within 60 days of randomization.

Dose modifications. No dose modifications for androgen-deprivation therapy (ADT) were allowed. For docetaxel, no more than 2 dose modifications (decreases to 60 mg/m^2 and 50 mg/m^2) were allowed. Dose adjustments were made according to the organ system showing the greatest toxic effects. The study used the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 for toxicity and adverse event reporting.

There was no dose re-escalation once docetaxel dose was reduced. If $>$ 2 dose reductions were required (for any reason) or if docetaxel was postponed for $>$ 3 weeks, no further docetaxel was administered, and the patient completed at least 18 weeks of ADT and subsequently proceeded to radical prostatectomy. The use of growth factors was at the discretion of the treating physician.