Time Interval to Biochemical Failure as a Surrogate End Point in Locally Advanced Prostate Cancer: Analysis of Randomized Trial NRG/RTOG 9202

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abstract

BACKGROUND In prostate cancer, end points that reliably portend prognosis and treatment benefit (surrogate end points) can accelerate therapy development. Although surrogate end point candidates have been evaluated in the context of radiotherapy and short-term androgen deprivation (AD), potential surrogates under long-term (24 month) AD, a proven therapy in high-risk localized disease, have not been investigated.

MATERIALS AND METHODS In the NRG/RTOG 9202 randomized trial (N = 1,520) of short-term AD (4 months) versus long-term AD (LTAD; 28 months), the time interval free of biochemical failure (IBF) was evaluated in relation to clinical end points of prostate cancer–specific survival (PCSS) and overall survival (OS). Survival modeling and landmark analysis methods were applied to evaluate LTAD benefit on IBF and clinical end points, association between IBF and clinical end points, and the mediating effect of IBF on LTAD clinical end point benefits.

RESULTS LTAD was superior to short-term AD for both biochemical failure (BF) and the clinical end points. Men remaining free of BF for 3 years had relative risk reductions of 39% for OS and 73% for PCSS. Accounting for 3-year IBF status reduced the LTAD OS benefit from 12% (hazard ratio [HR], 0.88; 95% CI, 0.79 to 0.98) to 6% (HR, 0.94; 95% CI, 0.83 to 1.07). For PCSS, the LTAD benefit was reduced from 30% (HR, 0.70; 95% CI, 0.52 to 0.82) to 6% (HR, 0.94; 95% CI, 0.72 to 1.22). Among men with BF, by 3 years, 50% of subsequent deaths were attributed to prostate cancer, compared with 19% among men free of BF through 3 years.

CONCLUSION The IBF satisfied surrogacy criteria and identified the benefit of LTAD on disease-specific survival and OS. The IBF may serve as a valid end point in clinical trials and may also aid in risk monitoring after initial treatment.

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INTRODUCTION

Localized prostate cancer may have a long natural history, making development of therapies challenging, because disease end points such as distant metastasis and death require a lengthy observation time before definitive evaluation. This has led to the search for end points that could serve as earlier indicators of eventual treatment benefit or what are known as surrogate end points. These early indicators would facilitate more efficient clinical trial design and could also guide clinical care via earlier intervention. Prostate-specific antigen (PSA)-based end points, such as PSA nadir,¹⁻⁴ or PSA doubling time^{2,4-8} have consistently shown an association with more clinically material end points. Similarly, the time interval from treatment to biochemical failure (BF; deemed interval to BF, or IBF) has been evaluated, with a shorter IBF found to be

associated with worse clinical outcome in numerous analyses.^{4,6,9-16} In specific therapy settings, analyses have further demonstrated a mediating effect on randomized treatment, thus meeting classic surrogacy criteria.¹⁷ Our particular interest is in the IBF as a surrogate under evaluation of androgen deprivation therapy (ADT) duration in clinical trials. The IBF has been evaluated in clinical trials of combined radiotherapy (RT) and short courses of ADT (up to 6 months). In the Trans Tasman Radiation Oncology Group (TROG) 96.01 randomized trial comparing RT alone with RT with two short-term androgen deprivation (STAD) therapy regimens (3 and 6 months), it was determined that 30-month IBF status satisfied surrogate end point criteria for the prostate cancer–specific survival (PCSS) benefit realized for the 6-month ADT arm.^{6,18} In a smaller randomized trial

ASSOCIATED CONTENT

Appendix

Data Supplement

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

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comparing RT alone with RT and 6-month ADT, Royce et al⁴ found that an IBF of 30 months met surrogate end point criteria for all-cause mortality among trial participants with minimal or no comorbidities.

Under long-term ADT (LTAD; greater than 6 months), PSA dynamics and related BF end points may differ markedly from that observed under STAD. Several clinical trials have established the benefit of extended ADT compared with short-course therapy.¹⁹⁻²³ The recent update²⁴ of Radiation Therapy Oncology Group (RTOG) 9202, a phase III trial that compared RT and STAD with an additional 24 months of ADT after RT, has further established the benefits of extended-duration ADT on multiple end points, including PCSS and overall survival (OS). It is currently unknown whether a suitably defined IBF would function as a surrogate under longer ADT periods, such as 24 months. Using data from RTOG 9202, this study evaluated a range of IBF definitions that span active LTAD and post-therapy periods. If the IBF proves to be either a full surrogate or a useful intermediate end point in the LTAD setting, it could contribute substantially to the design efficiency and conduct of future clinical trials that compare new agents in the presence of LTAD or further explore ADT duration questions with current or new agents.

MATERIALS AND METHODS

Data and Patients

The analysis was performed using protocol-eligible patients from RTOG 9202 randomized trials in localized high-risk prostate cancer. Details of the trial design and results have been published previously^{19,20} and were recently updated to 15 years.²⁴ Briefly, RTOG 9202 compared RT and 4 months of ADT (2-month neoadjuvant and 2-month concurrent phases) with the same regimen plus an additional 24 months of ADT after RT completion. The trial was approved by institutional review boards of all participating centers and the central coordinating center, and this study was conducted in accordance with approved use of the trial data.

Statistical Considerations

The goal of this study was to evaluate whether an end point defined by time free from BF can satisfy surrogate end point criteria for the effect of LTAD on clinical failure end points. BF was defined per the consensus Phoenix definition.²⁵ The failure event for OS was death as a result of any cause; for PCSS, it was death attributed to prostate cancer not including unknown causes of death; and for metastasis-free survival, it was time to distant metastasis or death from any cause. For all end points, time to failure was measured from the date of randomization to the date of failure event. However, we describe the IBF in terms of time since the end of RT (4 months after random assignment) and thus refer to the interval length in yearly increments (ie, 1 year, 2 years).

Following established guidelines for evaluation of potential surrogate markers in clinical trials,¹⁷ this analysis sought to establish the effect of LTAD on the ultimate end point(s)—PCSS and OS, establish the effect of LTAD on the potential surrogate end point (IBF), demonstrate an association between the potential surrogate and the ultimate end points, and demonstrate that the effect of LTAD on the ultimate end point is mediated by the effect of LTAD on the potential surrogate. In the analysis, several landmark intervals were investigated for purposes of determining the shortest time interval that would meet all surrogacy criteria and comparing findings to earlier work that examined a range of IBF.^{4,6,15}

The first two surrogacy criteria were addressed by estimating treatment effects separately for the surrogate and ultimate end points, using the Cox proportional hazards model for the cause-specific or overall hazard as appropriate for the end point.^{26,27} The third and fourth criteria were addressed primarily by the method of landmark analysis. In landmark analysis, patients remaining at risk (eg, alive, free of other clinical progression events) to a specific time point are classified according to their status with respect to the surrogate event (BF) as of that time point.²⁸ This binary IBF status (failed, did not fail) was then evaluated for prognostic influence on subsequent (ie, postinterval) clinical end points (third criterion) and mediating effect (fourth criterion) by estimating the treatment benefit in the presence of the surrogate end point. The models include other prognostic covariables to account for any imbalance induced by defining the relevant patient cohorts for the landmark analysis. Unadjusted analyses that corresponded to the graphical presentations were also conducted, and results did not materially differ (Tables A1, A2, A3, and A4, online only). The proportion of treatment effect explained was computed as an evaluation of surrogate marker value.²⁹ Additional methodology and analysis considerations are provided in the Appendix (online only). Survival distributions were estimated using Kaplan-Meier curves,³⁰ and cumulative incidence functions were used to estimate probability of prostate cancer–specific and other-cause death over time.³¹

RESULTS

Trial Characteristics

Patient characteristics and outcome status are listed in Table 1. Median follow-up time was 20 years, and at the known follow-up status from the recent trial update, 20% (n = 311) of patients remained alive. Among 1,209 deaths, 24% (n = 289) were attributed to prostate cancer and 76% (n = 920) to other causes. There were 802 BF events (53% of patients).

Effect of Treatment on Surrogate and Ultimate End Points

Compared with STAD, LTAD resulted in a clinically material reduction in the risk of prostate cancer–related death and a

TABLE 1. Patient Characteristics and Event Status for the RTOG 9202 Cohort

Characteristic	RT Plus STAD (n = 762)	RT Plus LTAD (n = 758)	All Patients
	No. (%)	No. (%)	No. (%)
Age at trial entry, years			
43-64	150 (19.7)	148 (19.5)	298 (9.6)
65-79	587 (77.0)	575 (75.9)	1,162 (76.4)
≥ 80	25 (3.2)	35 (4.6)	60 (3.9)
Race			
White	642 (84.3)	637 (84.0)	1,279 (84.2)
Black	92 (12.1)	105 (13.9)	197 (13.0)
Hispanic, Asian, other, or unknown	28 (3.7)	16 (2.1)	44 (2.9)
Karnofsky status			
70	11 (1.4)	2 (0.3)	13 (0.9)
80-90	430 (56.4)	406 (53.6)	836 (55.0)
100	321 (42.1)	350 (46.2)	671 (44.2)
Gleason score			
Unknown*	58 (7.6)	42 (5.5)	100 (6.6)
2-5	142 (18.6)	137 (18.1)	279 (18.4)
6-7	375 (49.2)	405 (53.4)	780 (51.3)
8-10	187 (24.5)	174 (23.0)	361 (23.8)
Tumor stage			
II	347 (45.5)	344 (45.4)	691 (45.5)
III/IV	415 (54.5)	414 (54.6)	829 (54.5)
PSA at diagnosis			
< 20	372 (48.8)	386 (50.9)	758 (49.9)
20-80	332 (43.6)	311 (41.0)	643 (42.3)
> 80	58 (7.6)	61 (8.0)	119 (7.8)
Event status			
Biochemical failure			
No event	301 (39.5)	417 (55.0)	718 (49.2)
Event	461 (60.5)	341 (45.0)	802 (52.8)
Distant metastasis			
No event	564 (74.0)	624 (82.3)	1,188 (78.1)
Event	198 (26.0)	134 (17.7)	332 (21.8)
Vital status			
Alive	151 (19.8)	160 (21.1)	311 (20.5)
Prostate cancer death	168 (22.1)	121 (16.0)	289 (19.0)
Other cause of death	443 (58.1)	477 (62.9)	920 (60.5)
Total deaths	611	598	1,209

Abbreviations: LTAD, long-term androgen deprivation; PSA, prostate-specific antigen; RT, radiotherapy; STAD, short-term androgen deprivation.

*Patients with missing Gleason scores were retained in the analysis by creating an unknown category for this covariable. Analyses omitting these patients did not differ materially from the results presented.

modest improvement in OS (Table 2). Distant metastasis-free survival was also improved (mostly because of a reduction in distant failure events). With respect to the candidate surrogate, LTAD resulted in a reduction in BF

overall, but more relevant to this investigation, the reduction was evident at early intervals of follow-up. As listed in Table 2, there was a significant reduction in BF risk for those assigned to LTAD in follow-up intervals from

TABLE 2. Impact of Treatment Arm on Surrogate End Point (biochemical failure) and Clinical End Points (death from prostate cancer and all-cause death)

Treatment Arm	Criterion 1: Treatment Effect on Surrogate: Biochemical Failure (follow-up limited to within the interval shown), HR (95% CI)					Criterion 2: Treatment Effect on Clinical End Point (all follow-up), HR (95% CI)		
	12 Months	24 Months	36 Months	48 Months	Overall Follow-Up	Prostate Cancer-Specific Survival	Distant Metastasis-Free Survival	Overall Survival
LTAD v STAD (reference)	0.35 (0.24 to 0.51)	0.44 (0.35 to 0.57)	0.46 (0.37 to 0.57)	0.51 (0.42 to 0.62)	0.59 (0.51 to 0.68)	0.70 (0.55 to 0.88)	0.84 (0.75 to 0.94)	0.88 (0.79 to 0.98)

NOTE. Times are post-radiation therapy completion. Time from randomization is 4 months longer. Treatment hazard ratios shown with 95% CIs. For all end points, hazard ratios from models including covariables for age, Karnofsky performance status, T stage, prostate-specific antigen, and Gleason score.

Abbreviations: LTAD, long-term androgen deprivation; STAD, short-term androgen deprivation.

12 months post-RT and longer intervals up to 2 years post-LTAD completion. Treatment effects unadjusted for other covariables were similar (Appendix Table A1).

Association Between Surrogate and Ultimate End Points

Analyses then proceeded to investigate the relationship between IBF and clinical end points. Intervals within which BF status was defined included 12, 24, 36, and 48 months (post-RT completion), on the basis of previous investigations of BF as a surrogate end point.^{4,6,9} These intervals represent different ADT exposure history depending on treatment arm and thus were examined separately by arm. Results (Appendix Table A1) indicated that for both STAD and LTAD groups, classification by BF status at AD completion or later was strongly associated with the subsequent risk of PCSS. For patients assigned to STAD, results resembled those from other studies, with a four-fold or greater hazard increase for prostate cancer death among

those having had BF. For patients assigned LTAD, BF in any interval from the end of ADT (24 months from RT completion) to 24 months post-ADT (48 months from RT completion) resulted similarly in distinctly greater prostate cancer death risk. Furthermore, this prognostic effect of BF status was apparent for OS for STAD (for IBF of 12 months post-RT or greater) and LTAD (for IBF of 24 months post-RT or greater). These results establish that the surrogate and ultimate end points were associated for both STAD and LTAD, provided the ADT period was complete.

Mediation of Treatment Effect by Surrogate End Point

Finally, to evaluate the mediating influence of the surrogate end point on the treatment effect for the ultimate end point, BF status was incorporated as a covariable in testing of LTAD versus STAD treatment (Table 3). As shown earlier (Table 2), without incorporating BF, LTAD was associated with a substantial improvement in PCSS and modest

TABLE 3. Treatment Effect on Postlandmark Time Clinical Events, After Adjusting for BF Before Indicated Landmark Time

Treatment Effect	Criteria 3 and 4: Concurrent Effect of Surrogate on Ultimate Outcomes and Mediation of Treatment Effect		
	Prostate Cancer-Specific Survival, HR* (95% CI)	Distant Metastasis-Free Survival, HR (95% CI)	Overall Survival, HR* (95% CI)
Treatment effect unadjusted for BF status			
Treatment RT plus LTAD	0.70 (0.55 to 0.88)	0.84 (0.75 to 0.94)	0.88 (0.79 to 0.98)
Adjusted for BF landmark time < 12 months post-RT			
BF event	3.16 (2.38 to 4.20)	1.77 (1.45 to 2.15)	1.61 (1.33 to 1.93)
Treatment RT plus LTAD	0.75 (0.59 to 0.95)	0.86 (0.77 to 0.97)	0.90 (0.80 to 1.01)
Adjusted for BF landmark time < 24 months post-RT			
BF event	3.78 (2.92 to 4.89)	1.46 (1.25 to 1.70)	1.54 (1.33 to 1.78)
Treatment RT plus LTAD	0.92 (0.71 to 1.18)	0.87 (0.77 to 0.97)	0.92 (0.81 to 1.04)
Adjusted for BF landmark time < 36 months post-RT			
BF event	4.32 (3.30 to 5.65)	1.51 (1.31 to 1.75)	1.65 (1.44 to 1.89)
Treatment RT plus LTAD	0.94 (0.72 to 1.22)	0.91 (0.80 to 1.04)	0.94 (0.83 to 1.07)
Adjusted for BF landmark time < 48 months post-RT			
BF event	5.88 (4.46 to 7.74)	1.55 (1.34 to 1.79)	1.66 (1.4 to 1.90)
Treatment RT plus LTAD	1.04 (0.79 to 1.37)	0.92 (0.80 to 1.05)	0.97 (0.85 to 1.10)

Abbreviations: BF, biochemical failure; HR, hazard ratio; LTAD, long-term androgen deprivation; RT, radiotherapy.

*Table entries are HRs (for BF yes v no [reference level]) and RT plus LTAD versus short-term androgen deprivation (reference level) with 95% CIs, adjusted for age, Karnofsky performance status, T stage, prostate-specific antigen, and Gleason score.

FIG 1. (A) Prostate cancer–specific survival, (B) distant metastasis–free survival, and (C) overall survival by androgen deprivation therapy (ADT) treatment arm and 36-month postradiotherapy biochemical failure (BF) status.

improvement in metastasis-free survival and OS. For a short IBF (to 12 months post-RT, still during LTAD therapy), treatment effects were diminished but not eliminated. For the interval that spanned the LTAD period (24 months post-RT), the surrogate met the treatment mediation criterion. For BF status intervals that extended beyond the LTAD period (1 year post-LTAD and 2 years post-LTAD), the mediation effect was larger (treatment hazard ratios closer to null value). For the 36-month IBF, the proportion of treatment effect explained was 85% for PCSS, 47% for metastasis-free survival, and 52% for OS. These proportions were larger, approaching 100%, for an IBF of 48 months. Analyses conducted without adjustment for other covariables yielded similar results (Appendix Table A3).

To illustrate the influence of BF on outcome and treatment, patients were classified according to BF status and treatment group, and subsequent clinical outcomes were

plotted (Figs 1A to 1C). BF status in the defined interval (shown as 36 months post-RT) was strongly associated with increased failure risk, regardless of treatment, and the LTAD effect was eliminated or diminished. Among those with BF, there remained some residual advantage of LTAD in later follow-up, which may have been due to later occurrences of BF (within a given defined interval) for patients who underwent LTAD. Additional analyses found that surrogacy performance held more strongly for men with a Gleason score of 7 or less than those at higher risk (Gleason score of 8 to 10; Appendix Table A4).

Effect of BF Status on Subsequent Mortality by Cause

Among 1,209 deaths, 289 (24%) were attributed to prostate cancer. The surrogacy analyses strongly indicate that patients who previously experienced BF had greater prostate cancer and all-cause mortality risk. The effect of BF on the proportionate mortality according to cause (Figs

FIG 2. Cumulative incidence of all deaths by cause. (A) Patients who experienced biochemical failure (BF) in the 36-month postradiotherapy landmark interval. (B) Patients who did not experience BF in the landmark interval.

2A and 2B) shows how a history of BF is associated with a substantial increase in the proportion of all deaths that are attributed to prostate cancer. Among men experiencing BF in the first 36 months post-RT, the proportion of deaths as a result of prostate cancer (approximately 50% of the cumulative death rate at 12 years) equals that attributed to other causes (Fig 2A). For those without history of BF in the first 36 months (Fig 2B), the great majority of deaths are attributed to other causes, with less than 20% of deaths attributed to prostate cancer.

DISCUSSION

Although the potential for progression after local treatment is substantial for men with high-risk localized prostate cancer, the realization of substantive clinical end points, such as distant metastasis and mortality, require lengthy follow-up, motivating the search for surrogate end points to shorten therapy development. In this study, we found that the BF status at landmark times relatively early in follow-up (as early as 2 years from completion of neoadjuvant ADT and RT, and more robustly at 3 to 4 years) could satisfactorily discern the ultimate effect of long-duration (24 months) versus short-duration (neoadjuvant and during RT only) ADT on the prostate cancer-specific and overall mortality benefits. These results were observed in a large randomized trial with mature follow-up, with the number of both surrogate and clinical end point events considerably larger than those of other published studies evaluating surrogate end points.

The IBF is a straightforward end point already recorded in prostate cancer management as well as all clinical trials. Previously, investigations in a variety of settings have found short IBF, for example, between 18 and 24 months from the end of RT, was strongly associated with death from prostate cancer.^{9-12,15,16} With regard to studies with full surrogacy

evaluation (with a test for mediation of randomized treatment effect) of the IBF in the setting of ADT, the TROG 96.01 trial demonstrated that an IBF status as of 18, 24, or 30 months post-RT met all surrogacy criteria. With respect to the choice of length of the interval to define the IBF surrogate, in a study by Shilkrut et al,¹⁶ multiple longer interval lengths (through 5 years) performed similarly. This is perhaps not surprising, given that the longest course of ADT was only 6 months. Similarly, in this study, there were minimal differences in the influence of BF status on prognosis and treatment effect when evaluated in intervals ranging between 24 and 48 months after RT (Table 3), and in any case, only those IBFs that span or exceed the LTAD period are practically relevant to the LTAD versus STAD treatment comparison. Furthermore, for establishing an advantage of LTAD over STAD on any end point, the inclusion of post-ADT follow-up time where testosterone recovery occurs may better reflect the genuine benefit on PSA-related outcomes. Indeed, direct incorporation of testosterone recovery status and BF status into a single surrogate end point would likely be a more robust measure. One significant limitation of this study is that reliable serial testosterone data throughout the relevant follow-up periods was unavailable. In absence of this information, an IBF at 1 year post-LTAD completion or greater would seem most appropriate.

The length of the IBF interval has a major bearing on trial duration and thus efficiency of adopting a surrogate measure. In the TROG study, using a 2-year BF status surrogate, findings would have informed the ultimate findings of the trial approximately 4.5 years earlier.⁶ For the RTOG 9202 trial, accrual spanned 3 years and reliable PCSS information was reported after 5 additional years, with more robust PCSS and OS information another 5 years thereafter. Had a 3-year BF status surrogate been used, treatment benefit results may have been reported approximately

3.5 years after accrual closure. A longer interval such as BF status at 4 years provides a more reliable mediating effect (Table 3) at the cost of less savings in trial duration, but is worthy of consideration because it still affords an earlier evaluation relative to the lengthy follow-up required before reliable signals on survival end points emerged in RTOG 9202.

Although this study focused solely on IBF, several other PSA-based surrogate end points have been evaluated. D'Amico et al⁸ proposed a short PSA doubling time as indicative of aggressive disease, and in the TROG 96.01 trial, this end point also satisfied surrogacy criteria. However, PSA doubling time has a number of limitations, most notably that it is dependent on the number and timing of PSA determinations as well as the time since treatment.⁹ Nadir PSA at the end of therapy is another candidate, and in pooled data from the TROG 96.01 and Dana-Farber randomized trials, it was found that a PSA value of less than 0.5 ng/mL (selected from precedent in the literature, rather than an optimized determination) at the end of ADT met surrogacy criteria for PCSS.² Royce et al⁴ recently reported a similar observation using the Dana-Farber cohort alone. Note that these evaluations were all under STAD or RT alone, in contrast to RTOG 9202, where comparisons of PSA nadir or doubling time would be under differential AD exposure. Valicenti et al⁵ found that PSA doubling time was prognostic but did not satisfy treatment effect mediation.

Finally, other time to failure end points might also be considered. Ray et al³² evaluated two potential surrogates in the RTOG 9202 cohort: general clinical failure (which comprises any of distant metastases [DM], PSA greater than 25 ng/mL, or start of ADT) and DM. For the general clinical failure end point, the subjective nature of the introduction of salvage ADT, which can be variable with respect to timing and prior/current treatment, coupled with the relatively unlikely scenario that patients would be

observed without intervention until PSA exceeds 25 ng/mL, renders this end point a less desirable surrogate despite the findings of that study. Ray et al³² also found that DM met criteria for surrogacy. However, DM tends to be a late event both temporally (from trial registration and treatment) and within the clinical course of the disease process; therefore, it may not provide a great efficiency gain in evaluating new therapies relative to PCSS events, particularly because it is nearly always preceded by BF and therapy may already be altered. Nonetheless, the Intermediate Clinical Endpoints in Cancer of the Prostate consortium investigators have validated DM failure as a surrogate end point for survival end points in a cohort of more than 12,000 patients from clinical trials.³³ In the current study, IBF exhibited similar surrogacy properties on DM failure to those seen for survival end points.

Thus, the IBF seems to be a promising surrogate in the setting of ADT evaluation. After having been successfully validated, several phase III trials and a range of ADT duration comparisons (RT alone v RT plus 3, 4, or 6 months of ADT), we now demonstrate that the IBF meets surrogacy criteria for extended versus short-duration ADT comparisons. This is important in that current ADT regimens continue to be evaluated with respect to duration,^{23,34} whereas new agents enter trials alone or in combination with ADT, often for long-duration use. Although surrogacy findings with respect to LTAD versus STAD require validation in other studies, IBF-based end points should be incorporated into clinical trials, at a minimum using IBF as an informative early indicator of potential treatment effect (or lack thereof), useful for futility monitoring or continuation decisions in phase II/III trials. Whether it can be advanced to a primary trial end point remains specific to the context (ie, risk class of patient), but on the basis of the evidence, the IBF would seem to have a clear role in clinical decision making, informing when more intensive surveillance or treatment is warranted.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Time Interval to Biochemical Failure as a Surrogate End Point in Locally Advanced Prostate Cancer: Analysis of Randomized Trial NRG/RTOG 9202**

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APPENDIX

Additional Methodologic and Analysis Considerations

Time-varying covariable analysis: In addition to landmark analysis, modeling of the relationship of the potential surrogate on the ultimate end point was also investigated via a time-varying event indicator covariable (Klein JP and Moeschberger M: New York, NY, Springer, 2003). However, these analyses tended to show highly significant relationships with the ultimate end point, even when failures occurred temporally close to the ultimate end point or late in follow-up, where there was little gain in terms of savings in trial duration time. Hence, for the end point in this study, incorporating the landmark approach was preferred.

Proportion of treatment effect. The proportion of treatment effect explained was computed using the method of Lin et al,²⁹ although this metric is of limited importance here (provided surrogacy criteria are met and the value is reasonably high), because we are not contrasting different surrogate markers other than the interval free of biochemical failure (IBF) and there are other considerations, such as therapy duration on which to base the choice of IBF length. Also, as the interval is made longer, it is expected that the proportion of treatment effect will increase. However, the practical value of a lengthy interval is

diminished, for the same reasons described for a time-varying covariable analysis.

Sensitivity analysis to starting point for IBF. In the study by Denham et al,⁶ a sensitivity analysis was conducted addressing whether IBF should be measured from time of random assignment or from radiotherapy (RT) completion. Results indicated that the surrogate end point was applicable regardless of whether the IBF was measured from the end of RT or from the time of randomization and before the start of neoadjuvant androgen deprivation therapy (ADT).⁶ This is particularly relevant, given the potential differential impact of neoadjuvant ADT and different durations of ADT delivered before RT on post-treatment prostate-specific antigen values and biochemical failure. With the use of long-term androgen deprivation as in RTOG 9202, the differential impact of testosterone recovery between those treated with 4 versus 28 months of ADT might have a substantial impact on the basis of when the clock is started to measure IBF. However, we did not note substantive differences in results when defining IBF as either from randomization or from the end of neoadjuvant/concurrent ADT and RT (4 months from randomization).

TABLE A1. Impact of Treatment Arm on Surrogate End Point (biochemical failure) and Clinical End Points (death from prostate cancer and all-cause death)

Treatment	Criterion 1: Treatment Effect on Surrogate: Biochemical Failure (follow-up limited to within the interval shown), HR (95% CI)					Criterion 2: Treatment Effect on Clinical End Point (all follow-up), HR (95% C)		
	12 Months	24 Months	36 Months	48 Months	Overall Follow-Up	Prostate Cancer-Specific Survival	Distant Metastasis-Free Survival	Overall Survival
LTAD v STAD (reference)	0.35 (0.25 to 0.51)	0.45 (0.35 to 0.57)	0.47 (0.38 to 0.58)	0.51 (0.42 to 0.62)	0.60 (0.52 to 0.69)	0.69 (0.54 to 0.87)	0.87 (0.74 to 0.97)	0.91 (0.82 to 1.02)

NOTE. Times are post-radiotherapy completion. Time from randomization is 4 months longer. Treatment HRs, shown with 95% CIs. For all end points, HRs are unadjusted for other covariables.

Abbreviations: HR, hazard ratio; LTAD, long-term androgen deprivation; STAD, short-term androgen deprivation.

TABLE A2. Effect of BF Status at Designated Landmark Times on Clinical End Points Occurring Postlandmark Time, Separately by Duration of ADT

Landmark Interval (BF status as of time from RT completion; months)	Short-Term ADT Arm			Long-Term ADT Arm		
	Time Since ADT End (months)	PCSS, HR (95% CI)*	OS, HR (95% CI)*	Time Since ADT End (months)	PCSS, HR (95% CI)*	OS, HR (95% CI)*
12	12	4.07 (2.91 to 5.69)	1.81 (1.45 to 2.26)	Receiving ADT	1.57 (0.82 to 3.03)	1.23 (0.86 to 1.75)
24	24	4.55 (3.23 to 6.41)	1.59 (1.32 to 1.92)	0	2.96 (1.94 to 4.53)	1.48 (1.17 to 1.88)
36	36	6.10 (4.17 to 9.20)	1.77 (1.47 to 2.13)	12	2.98 (1.98 to 4.48)	1.55 (1.26 to 1.91)
48	48	7.71 (4.74 to 12.54)	1.66 (1.38 to 2.01)	24	4.61 (3.05 to 6.97)	1.66 (1.36 to 2.04)

Abbreviations: ADT, androgen deprivation therapy; BF, biochemical failure; HR, hazard ratio; OS, overall survival; PCSS, prostate cancer-specific survival; RT, radiotherapy.

*Table entries are HRs for BF versus no BF in the interval, with 95% CIs, adjusted for age, Karnofsky performance status, prostate-specific antigen, T stage, and Gleason score.

TABLE A3. Treatment Effect on Postlandmark Time Clinical Events, After Adjusting for BF Before Indicated Landmark Time**Criteria 3 and 4: Concurrent Effect of Surrogate on Ultimate Outcomes and Mediation of Treatment Effect**

Treatment Effect	Prostate Cancer Death, HR* (95% CI)	Distant Metastasis-Free Survival, HR* (95% CI)	All Deaths, HR* (95% CI)
Treatment effect unadjusted for BF status			
Treatment RT plus LTAD	0.69 (0.54 to 0.87)	0.87 (0.74 to 0.97)	0.91 (0.82 to 1.02)
Adjusted for BF landmark time < 12 months post-RT			
BF event	3.55 (2.68 to 4.70)	1.75 (1.44 to 2.14)	1.65 (1.37 to 1.98)
Treatment RT plus LTAD	0.74 (0.58 to 0.94)	0.89 (0.79 to 0.99)	0.93 (0.83 to 1.04)
Adjusted for BF landmark time < 24 months post-RT			
BF event	4.12 (3.22 to 5.28)	1.42 (1.22 to 1.66)	1.49 (1.30 to 1.72)
Treatment RT plus LTAD	0.89 (0.65 to 1.14)	0.90 (0.81 to 1.03)	0.95 (0.85 to 1.07)
Adjusted for BF landmark time < 36 months post-RT			
BF event	4.72 (3.64 to 6.12)	1.50 (1.30 to 1.73)	1.62 (1.42 to 1.86)
Treatment RT plus LTAD	0.91 (0.70 to 1.17)	0.96 (0.84 to 1.09)	0.99 (0.87 to 1.12)
Adjusted for BF landmark time < 48 months post-RT			
BF event	6.01 (4.46 to 8.09)	1.51 (1.32 to 1.75)	1.60 (1.40 to 1.83)
Treatment RT plus LTAD	1.02 (0.78 to 1.34)	0.95 (0.83 to 1.09)	1.01 (0.89 to 1.15)

Abbreviations: BF, biochemical failure; HR, hazard ratio; LTAD, long-term androgen deprivation; RT, radiotherapy.

*Table entries are HRs (for BF yes v no [reference level]) and RT plus LTAD versus short-term androgen deprivation [reference level]) with 95% CIs, unadjusted for any other covariables.

TABLE A4. Treatment Effect on Postlandmark Time Clinical Events, After Adjusting for BF Before Indicated Landmark Time**Criteria 3 and 4: Concurrent Effect of Surrogate on Ultimate Outcomes and Mediation of Treatment Effect**

Treatment Effect	Prostate Cancer-Specific Survival, HR* (95% CI)	Distant Metastasis-Free Survival, HR (95% CI)	Overall Survival, HR* (95% CI)
Lower-risk patients (Gleason score ≤ 7)			
Treatment effect unadjusted for BF status			
Treatment RT plus LTAD	0.71 (0.52 to 0.98)	0.90 (0.78 to 1.04)	0.92 (0.80 to 1.06)
Adjusted for BF landmark time < 36 months post-RT			
BF event	5.54 (3.97 to 7.74)	1.66 (1.40 to 1.96)	1.75 (1.50 to 2.05)
Treatment RT plus LTAD	1.06 (0.77 to 1.47)	0.95 (0.82 to 1.10)	0.99; 0.86 to 1.14
Higher-risk patients (Gleason score 8-10)			
Treatment effect unadjusted for BF status			
Treatment RT plus LTAD	0.50 (0.32 to 0.79)	0.79 (0.59 to 1.04)	0.73 (0.56 to 0.95)
Adjusted for BF landmark time < 36 months post-RT			
BF event	2.91 (1.84 to 4.60)	1.23 (0.90 to 1.68)	1.46 (1.10 to 1.94)
Treatment RT plus LTAD	0.60 (0.38 to 0.96)	0.79 (0.60 to 1.05)	0.77 (0.59 to 1.00)

NOTE. Analyses were conducted separately according to Gleason score.

Abbreviations: BF, biochemical failure; LTAD, long-term androgen deprivation; RT, radiotherapy.

*Table entries are HRs (for BF yes v no [reference level]) and RT plus LTAD versus short-term androgen deprivation (reference level) with 95% CIs, adjusted for age, Karnofsky performance status, T stage, and prostate-specific antigen.