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Time to second biochemical recurrence as a prognostic indicator in postprostatectomy patients who undergo salvage radiation therapy: An RTOG 9601 based post hoc analysis

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ORIGINAL ARTICLE

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Time to second biochemical recurrence as a prognostic indicator in postprostatectomy patients who undergo salvage radiation therapy: An RTOG 9601 based post hoc analysis

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Abstract

Introduction and Objective: The prognostic significance of a "second" biochemical recurrence (sBCR) after salvage radiation therapy (sRT) with/without hormonal therapy following primary radical prostatectomy in men with prostate cancer has not been examined. We hypothesized that a shorter time to sBCR will be associated with worse cancer control outcomes.

Methods: The RTOG 9601 study included 760 patients with tumor stage pT2/T3, pN0, who had either persistently elevated prostate-specific antigen (PSA) postradical prostatectomy or developed subsequent biochemical recurrence with PSA levels between 0.2 and 4.0 ng/ml. All patients received sRT (with or without 2 years of Bicalutamide) from 1998 to 2015. For our study, we focused on 421 patients who had sBCR after sRT—which was defined as a PSA increase of at least 0.3 ng/ml over the first nadir. Patients were divided into two categories: early sBCR ($n = 210$) and late sBCR ($n = 211$) using median time to sBCR (3.51 years). All patients who experienced sBCR received salvage hormonal therapy. Competing-risk analysis was used to examine the impact of early versus late sBCR on prostate cancer specific mortality (CSM), after accounting for available covariates.

Results: The majority of patients were age 60 years or older (75.8%), had pT3 disease (74.8%), and Gleason score 7 (75.2%). Overall, 13.8% had persistent PSA initially after surgery. At 10 years, starting at the time of sBCR, CSM rate was 31.3% in the early sBCR group versus 20.0% in the late sBCR group. In competing-risk analysis, time to sBCR was an independent predictor of CSM, where patients with early sBCR had 1.7-fold higher CSM risk ($p = 0.026$) than their counterparts with late sBCR.

Conclusions: Time to sBCR after sRT (with or without concomitant Bicalutamide) is a significant predictor of CSM following initial radical prostatectomy. This information can be used to guide subsequent treatments, and to counsel patients.

KEYWORDS
prostate cancer, second biochemical recurrence, salvage radiation therapy

1 | INTRODUCTION

Prostate cancer (PCa) is the leading cause of cancer for the American male, accounting for 26% of cancer diagnoses.[1] While the majority of patients present with low-intermediate risk disease at diagnosis, the main bulk of mortality is derived from those presenting with advanced or metastatic disease.[2] Many patients with advanced disease end-up needing multimodal treatment, which usually consists of radical prostatectomy followed by radiation therapy and/or hormonal therapy upon biochemical recurrence (BCR). The latter is defined by the AUA as a prostate-specific antigen (PSA) level of 0.2 ng/ml or higher on two consecutive measurements.[3] While most patients have a good initial response to such a treatment, around 44%–67.9% of these individuals develop a second BCR after radical prostatectomy and salvage radiation therapy (sRT).[4]

Several reports have addressed the role of the initial or primary BCR after radical prostatectomy as a prognostic variable, and it has been shown to correlate with different cancer control outcomes.[5] On the other hand, there is scarcity of data addressing the meaning or the role of a second BCR after sRT in patients treated initially with radical prostatectomy. This information might play a key role in stratifying patients with advanced disease based on their progression risk, which might improve patient counseling and the individualization of treatment. To address this gap in knowledge, we tested the hypothesis that a second BCR in the setting of patients who fails radical prostatectomy with subsequent sRT is a predictor of PCa specific mortality. Our cohort consisted of patients who were included in the RTOG 9601 study.

2 | MATERIALS AND METHODS

2.1 | Data acquisition

The NCI manages a centralized, controlled-access database (National Clinical Trials Network [NCTN]/NCORP Data Archive) to store and share datasets generated from clinical trials of the NCTN. Using this framework, we requested and obtained clinical trial data to perform secondary analysis on the impact of second BCR on cancer specific mortality (CSM) in patients who underwent radical prostatectomy and subsequent sRT.

2.2 | Study population

A detailed description of the Radiation Therapy Oncology Group (RTOG) 9601 trial cohort, which was sponsored by the NCI, has been previously published.[4] Briefly, the trial recruited PCa patients with pT2-pT3, N0 disease, who underwent radical prostatectomy and developed primary BCR, defined as postsurgery PSA >0.2 ng/ml. The patients were randomized if they satisfied the following inclusion criteria: Karnofsky Performance Score ≥80, negative bone and CT scans, no previous chemotherapy or radiation therapy for PCa, and no previous hormone therapy other than short-term neoadjuvant hormonal therapy. At randomization, patients were either assigned to sRT with Bicalutamide 150 mg daily, or sRT with placebo. sRT was started within 12 weeks after randomization with a total dose of 64.8 Gy to the prostatic fossa. Patients were assessed by history, physical exam, and biochemical tests before and after sRT. Subsequent follow-up evaluation occurred every 3 months for 2 years, then every 6 months for 3 years, and then yearly. This study was aimed at comparing outcomes of patients with early time to "second" biochemical recurrence (sBCR) and late time to sBCR, thus, patients who did not develop sBCR were excluded from the study.

Following sRT, a second BCR that was defined as a PSA increase of at least 0.3 ng/ml above the nadir after protocol treatment or at the initiation of any subsequent hormone therapy, prompted imaging studies.[4] If metastatic disease was noted or if the PSA level reached above 4.0 ng/ml, then maximum androgen blockade was recommended.

2.3 | Covariates

In the current study, covariates were categorized as reported in the original trial,[4] and consisted of patient age, race, Karnofsky Performance Score, pathological tumor stage, Gleason score, surgical margin status, neo-adjuvant hormone use before radical prostatectomy, time from surgery to first BCR, pre-sRT PSA level (<0.7 ng/ml, 0.7–1.5 ng/ml, 1.5–4.0 ng/ml), and hormonal treatment status with sRT (24 months of Bicalutamide vs. 24 months of placebo). Finally, the time from randomization to second BCR, was used as main predictor variable. The median time to second BCR was used to divide patients into two categories. The "early sBCR" group included patients who were found to have their sBCR earlier than or equal to the median time to second BCR versus the "late sBCR" group included patients who were found to have their sBCR later than the median time to second BCR.

2.4 | Endpoints

The primary outcome of interest was PCa-specific mortality. Disease-specific death included all deaths from PCa or treatment complications as well as death from an unknown process in patients with active PCa, on the basis of centrally reviewed cause of death.[4] This was tracked continuously as long as patients maintained follow up for the duration of the study.

TABLE 1 Descriptive characteristics of the 421 patients found to have a second BCR after radiation therapy with concurrent salvage hormonal therapy with bicalutamide postradical prostatectomy

Patient characteristics	Overall *n* (%)	Early sBCR *n* (%)	Late sBCR *n* (%)	*p* value
	421 (100)	210 (100)	211 (100)	
Age group (years)				
≤59	102 (24.23)	51 (24.29)	51 (24.17)	0.2885
60–69	228 (54.16)	120 (57.14)	108 (51.18)	
≥70	91 (21.62)	39 (18.57)	52 (24.64)	
Gleason score				
<2	1 (0.24)	0 (0)	1 (0.47)	0.0013
2–6	103 (24.47)	39 (18.57)	64 (30.33)	
7	237 (56.29)	119 (56.67)	118 (55.92)	
8–10	80 (19)	52 (24.76)	28 (13.27)	
Pathologic tumor stage				
pT2	106 (25.18)	44 (20.95)	62 (29.38)	0.0463
pT3	315 (74.82)	166 (79.05)	149 (70.62)	
PSA at entry (ng/ml)				
<0.7	200 (47.51)	80 (38.1)	120 (56.87)	0.0005
0.7–1.5	140 (33.25)	80 (38.1)	60 (28.44)	
>1.5	81 (19.24)	50 (23.81)	31 (14.69)	
PSA Nadir (ng/ml)				
<0.5	363 (86.22)	178 (84.76)	185 (87.68)	0.3854
≥0.5	58 (13.78)	32 (15.24)	26 (12.32)	
Race group				
Caucasian	376 (89.31)	191 (90.95)	185 (87.68)	0.5467
African American	35 (8.31)	15 (7.14)	20 (9.48)	
Other	10 (2.38)	4 (1.9)	6 (2.84)	
Karnofsky score				
≤90	103 (24.47)	58 (27.62)	45 (21.33)	0.1332
100	318 (75.53)	152 (72.38)	166 (78.67)	
Surgical margins				
Negative	126 (29.93)	69 (32.86)	57 (27.01)	0.1905
Positive	295 (70.07)	141 (67.14)	154 (72.99)	
Therapy group				
sRT + placebo	252 (59.86)	150 (71.43)	102 (48.34)	<0.0001
sRT + 24 mo Bicalutamide	169 (40.14)	60 (28.57)	109 (51.66)	

Abbreviation: BCR, biochemical recurrence.

2.5 | Statistical analyses

Frequencies and proportions were reported for categorical variables, while median and interquartile range (IQR) were reported for continuous variables. T tests and Chi-square tests were used to evaluate the statistical significance of differences in continuous and categorical variables, respectively. Cumulative Incidence Functions were used to depict cancer specific survival estimates at different time points based on early versus late sBCR status. Moreover, competing-risks regression analysis was used to test the impact of early versus later sBCR on CSM, after adjusting for all available covariates. Death due to causes other than PCa was classified as "other-cause mortality" and accounted for in competing-risk analysis.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina). Two-sided statistical significance was defined as a p value <0.05. Institutional review board approval was obtained before the study was conducted, in accordance with institutional regulations when dealing with deidentified patient data.

3 | RESULTS

3.1 | Descriptive characteristics

From the original RTOG 9601 study, 421 patients were found to have a sBCR after sRT with or without 24 months of Bicalutamide. Complete descriptive characteristics of our patient cohort are provided in Table 1. The majority of patients were age 60 years or older (75.8%), had pathological T3 disease (74.8%), and had a Gleason score ≥7 (75.3%). Additionally, 86.2% of patients had a PSA nadir under 0.5 ng/ml after sRT. Overall, 13.8% had persistent PSA initially after surgery. Overall median follow-up time was 7.3 years (IQR: 4.2–9.9).

The median time to sBCR in our study was 3.51 years (0–14.16 years). Using this cut-off, we identified 210 patients in our cohort who had early sBCR (within ≤3.51 years), while the remaining 211 patients had late BCR (>3.51 years).

When stratified by these categories, patient age was comparable between the two groups, both groups having 76% of patients aged 60 or older. Gleason scores were significantly different with 81.4% of patients in the early sBCR group at or above Gleason 7 PCa while this was only seen in 69.2% of patients in the late sBCR group ($p = 0.001$). Pathologic T3 stage was significantly different with 79.1% of patients in the early sBCR group having pT3 PCa versus 70.6% of patients in the late sBCR group ($p = 0.04$). PSA nadir, patient race, Karnofsky score, and surgical margins were all comparable between the two groups. More patients in the late sBCR group (51.7%) were treated with hormone therapy compared with those in the early sBCR group (28.6%) ($p < 0.001$).

3.2 | Cumulative incidence and competing-risks regression analysis

To compare CSM between the two groups, cumulative incidence functions were used. Overall, in patients who experienced a sBCR, the 5- and 10-year CSM rates were 8% (95% confidence interval [CI]: 5%–11%) and 27% (95% CI: 22%–32%), respectively. When patients were stratified based on median time to second BCR, the 5- and 10-year CSM rate was 11.2% and 31.3% in the early second BCR group versus 4.27% and 20.0% in the late second BCR group (Figure 1, $p = 0.03$).

The univariable observations were conferred on multivariable competing-risk analysis, where time to second BCR was an independent predictor of prostate CSM. Specifically, patients in the early sBCR group had a 1.69-fold higher CSM risk (hazard ratio

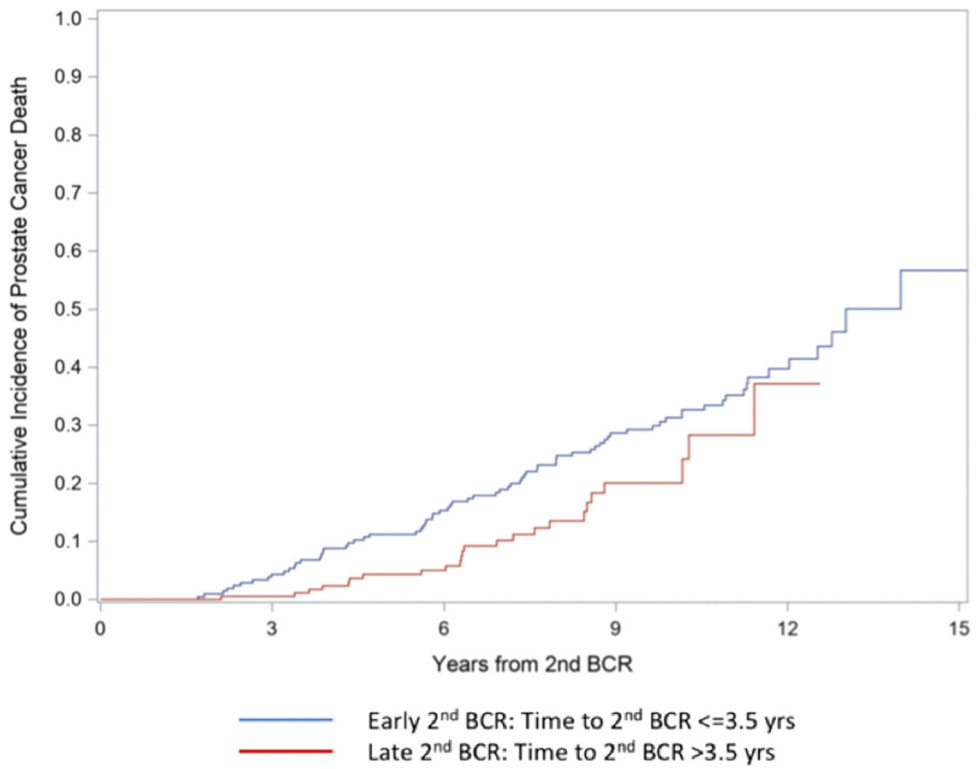

FIGURE 1 Cumulative incidence of prostate cancer-specific mortality in patients with early versus late time to second BCR. BCR, biochemical recurrence [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Multivariable Cox regression evaluating the effects of the selected variables on cancer-specific mortality in postprostatectomy patients who have undergone salvage radiation therapy

	Prostate cancer-specific mortality hazard ratio (95% CI)	*p* value
Early second BCR	1.69 (1.06–2.69)	0.02
Late second BCR	Ref.	
Age ≤59	Ref.	
Age 60–69	1.7 (0.94–3.14)	0.07
Age ≥70	3.53 (1.77–7.06)	0.0004
Caucasian race	Ref.	
African American race	0.67 (0.24–1.86)	0.44
Other race	0.37 (0.04–3.10)	0.36
sRT + Placebo	Ref.	
sRT + Bicalutamide	1.12 (0.72–1.72)	0.62
PSA <0.7 ng/ml	1.08 (0.67–1.75)	0.74
PSA 0.7–1.5 ng/ml	Ref.	
PSA >1.5 ng/ml	1.43 (0.81–2.55)	0.21
Gleason score ≤6	Ref.	
Gleason score 7	1.79 (0.987–3.233)	0.06
Gleason score ≥8	3.08 (1.57–6.04)	0.001
pT stage, T2	Ref.	
pT stage, T3	1.38 (0.80–2.37)	0.23
Negative surgical margins	Ref.	
Positive surgical margins	1.22 (0.76–1.97)	0.40
Karnofsky score, ≤90	Ref.	
Karnofsky score, 100	1.45 (0.85–2.46)	0.17

Abbreviations: BCR, biochemical recurrence; CI, confidence interval.

TABLE 3 Multivariable Cox regression evaluating the effects of the selected variables on cancer-specific mortality in postprostatectomy patients who have undergone salvage radiation therapy

	Prostate cancer-specific mortality hazard ratio (95% CI)	*p* value
Time to sBCR	0.81 (0.70–0.94)	0.006
Age ≤59	Ref	
Age 60–69	1.82 (0.98–3.37)	0.057
Age ≥70	3.84 (1.88–7.83)	0.0002
Caucasian race	Ref	
African American race	0.717 (0.26–2.00)	0.52
Other race	0.45 (0.05–3.91)	0.47
sRT + Placebo	Ref	
sRT + Bicalutamide	1.25 (0.81–1.93)	0.32
PSA <0.7 ng/ml	1.15 (0.71–1.88)	0.57
PSA 0.7–1.5 ng/ml	Ref	
PSA >1.5 ng/ml	1.39 (0.80–2.42)	0.25
Gleason score ≤6	Ref	
Gleason score 7	1.76 (0.97–3.18)	0.06
Gleason score ≥8	3.00 (1.55–5.82)	0.001
pT stage, T2	Ref	
pT stage, T3	1.38 (0.81–2.36)	0.24
Negative surgical margins	Ref	
Positive surgical margins	1.26 (0.78–2.02)	0.35
Karnofsky score, ≤90	Ref	
Karnofsky score, 100	1.46 (0.86–2.49)	0.16

Abbreviations: sBCR, "second" biochemical recurrence; CI, confidence interval.

[HR]: 1.69, 95% CI: 1.07–2.69, $p = 0.02$) than their counterparts in the late sBCR group (Table 2). Age ≥70 was found to be an independent predictor of CSM (HR: 3.53, 95% CI: 1.77–7.06, $p = 0.0004$), as was a Gleason score between 8 and 10 (HR: 3.08, 95% CI: 1.57–6.04, $p = 0.001$). A comparison of the model was performed to analyze the time to sBCR as a continuous variable (Table 3)." Time to sBCR was again statistically significant ($p = 0.0079$). Similarly, when coded as a continuous variable, time to sBCR was determined to be a predictor of prostate CSM (Table 3). Age ≥70 was found to be an independent predictor of CSM (HR: 3.84, 95% CI: 1.88–7.83, $p = 0.0002$), as was a Gleason score between 8 and 10 (HR: 3.00, 95% CI: 1.55–5.82, $p = 0.001$). The continuous code of time to sBCR had a hazard ratio of 0.81 (95% CI: 0.70–0.94, $p = 0.006$). Thus, for each additional year to sBCR, the risk of prostate CSM decreases 19%.

A Type 3 Wald Chi-Square analysis was performed to determine if the interaction between time to sBCR and treatment is significant when sBCR is coded as categorical and continuous (Tables S1 and S2). Both analyses do not demonstrate a significant interaction term between time to sBCR and treatment (categorical time to sBCR Wald $\chi^2 = 0.0527$; $p = 0.8184$ & continuous time to sBCR Wald $\chi^2 = 2.3355$; $p = 0.1265$). For sRT+ bicalutamide, the interaction term was found to be nonsignificant (HR: 1.25, 95% CI: 0.81–1.93, $p = 0.32$).

4 | DISCUSSION

The treatment and management of PCa has advanced dramatically in the past few decades. The 5-year disease-free survival rate in patients post-RP is 71.2%,[6] and the 5-year rate of freedom from BCR in patients who received RP and sRT is 87%.[7] At 6.1 years, Tumati et al.[8] found that PCa-specific survival in post-RP patients who received sRT was 83%. However, this still leaves a significant

percentage of patients in whom PSA levels continue to rise despite receiving sRT and thus go on to experience a sBCR. In this aforementioned cohort of patients, the prognostic significance of time to a sBCR has yet to be elucidated. To address this void in the data, we examined the effect of time to second BCR on CSM to better define the characteristics of this disease in patients who are higher risk.

After adjusting for all available covariables, patients who had a time to sBCR at or below the median of 3.51 years demonstrated a significantly higher rate of death related to PCa (1.67-fold higher, $p = 0.02$) as compared with those who had a time to second BCR greater than the median. These results correlate with prior data surrounding first BCR, and sBCR which revealed that earlier time to BCR is associated with increased mortality.[9,10] Additionally, previous work has shown that PSA kinetics is correlated with disease specific survival and that more rapid rises in PSA indicate a poorer prognosis.[11,12] Together with Gleason score, pathologic T stage, and PSA, the time to second BCR provides useful information and can be factored into the prognostic algorithm to help predict a patient's cancer progression trajectory as well as help stratify these patients into risk groups.

Patients in whom treatment for PCa has failed not once but twice can be considered part of a higher risk cohort. In these patients, limited options remain for continued management of their disease. Hormone therapy remains one of the options still available at this stage in the disease course. Indeed, 40% of patients in our specific study group were given Bicalutamide as part of their regimen. However, the exact impact of hormonal therapy in this setting and how it varies between early versus late time to second BCR warrants further investigation in the future. For example, patients with early time to second BCR may benefit from the early introduction of chemotherapy in their treatment regimen. Studies have shown that adding docetaxel to patients receiving salvage radiation and hormone therapy resulted in improved patient survival,[13] with one study showing a 4-year risk reduction of 30% in overall survival ($p = 0.04$) favoring chemotherapy.[14]

Typically, a sBCR represents a depletion of local therapy options and it may be implied that cancer progression would accelerate from this point resulting in a high probability of death from PCa. However, our results indicate that most patients who experience a sBCR will not die as a result of their disease as the 10-year CSM rate is 20%–31%. This should be considered when counseling and developing treatment strategies for this cohort of patients as a majority of these patients survive despite having more aggressive disease. As noted by Tumati et al.,[8] this rate of CSM following second BCR is comparable to rates of disease-specific mortality following a first BCR. What is interesting to note is that their group used a slightly different definition for second BCR (≥0.2 ng/ml rise in PSA above the nadir following sRT) and found an 83% disease-related survival rate at 6 years. Additionally, their cohort's median time to sBCR was 16 months, much shorter than ours.

Upon investigation of the interaction between time to sBCR and treatment, no significant interaction term was noted. With the small number of patients available, this study is likely not powered to support the idea that there is an interaction term.

By analyzing the RTOG 9601 cohort data, we aim to provide a high level of evidence for this, as of yet, unexamined question. Besides being a randomized clinical trial, this is the largest cohort of patients that has been examined on the subject of sRT following radical prostatectomy and has the longest follow-up time. Moreover, it benefits from regular and systematic follow-up of the patients who are included in this study.

This study represents a secondary analysis of level-one evidence and as such, might be underpowered to examine differences in CSM based on timing of sBCR. However, given that our results found a statistically significant difference between the two examined groups, it can be argued that the available sample size is probably adequate to examine our endpoint. Furthermore, findings must be interpreted within the limitations of a post hoc analysis. Because comparison of time to sBCR was not a planned covariate in the initial study design, any differences between our study groups may be the result of unidentified bias.[15] Furthermore, a limitation in our study is the use of bicalutamide given its side effects, but there also remains the question of whether it is equivalent to standard ADT.

5 | CONCLUSIONS

Based on retrospective analysis of the RTOG 9601 clinical trial cohort, time to sBCR was found to be an independent predictor of CSM. These findings can serve to help characterize the nature of PCa that has failed local treatment and will be able to aid clinicians in charting disease progression and predict patient outcomes. With an understanding of sBCR, its timing, and the relation of that to CSM, physicians can use our findings to counsel patients regarding their prognosis, and guide their treatment. Likewise, patients with sBCR are considered to have an advanced stage disease, and are frequently targeted by new trials to try and improve their outcomes. In this context, our findings can be used to risk-stratify patients in future trials. Continued research on recurrent PCa will build off of this data which will support prospective trials that examine optimal stratification of these higher risk patients.

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CONFLICTS OF INTEREST

Firas Abdollah is an advisor/consultant of Decipher Biosciences.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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