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# Anti-Androgen Therapy Overcomes the Time Delay in Initiation of Salvage Radiation Therapy and Rescues the Oncological Outcomes in Men with Recurrent Prostate Cancer After Radical Prostatectomy: A Post Hoc Analysis of the RTOG-9601 Trial Data

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## ABSTRACT

**Background.** It is unknown whether the addition of anti-androgen therapy (AAT) to late salvage radiation therapy (sRT) can lead to oncological outcomes equivalent to that of early sRT in men with recurrent prostate cancer (CaP) after surgery.

**Methods.** Data on 670 men who participated in the Radiation Therapy Oncology Group (RTOG)-9601 trial and who experienced biochemical recurrence were extracted using the National Clinical Trials Network (NCTN) data archive platform. Patients were stratified into four treatment groups: early sRT (pre-sRT prostate-specific antigen [PSA] $< 0.7$ ng/mL) and late sRT (pre-sRT PSA $\geq 0.7$ ng/mL) with/without concomitant AAT, based on cut-offs reported in the original trial. Time-varying Cox proportional hazards and Fine–Gray competing-risk regression analyses assessed the adjusted hazards of overall mortality, CaP-specific mortality, and metastasis among the four treatment groups.

**Results.** At 15-years (median follow-up of 14.7 years), for patients treated with early sRT, early sRT with AAT, late sRT, and late sRT with AAT, the overall mortality, CaP-specific mortality, and metastasis rates were 22.9, 22.8, 40.1, and 22.9% (log-rank $p = 0.0039$), 12.1, 3.9, 22.7, and 8.0% (Gray's $p = 0.0004$), and 18.8, 14.6, 35.9, and 19.5% (Gray's $p = 0.0004$), respectively. Time-varying multivariable adjusted analysis demonstrated increased hazards of overall mortality in patients receiving delayed sRT versus early sRT (hazards ratio [HR] 1.49, 95% confidence interval [CI] 1.02–2.17); however, no difference remained after the addition of concomitant AAT to late sRT (HR 0.85, 95% CI 0.55–1.32, referent early sRT). Likewise, the hazards of cancer-specific mortality and metastatic progression were worse for late sRT when compared with early sRT, but were no different after the addition of AAT to late sRT.

**Conclusions.** Poorer outcomes associated with late sRT in men with recurrent CaP may be rescued by delivery of concomitant AAT.

Men who experience biochemical failure after radical prostatectomy for localized prostate cancer (CaP) are recommended salvage radiation therapy (sRT) according to the American and European urologic and radiation oncology societal guidelines.[1–3]

With regard to sRT, early initiation, usually defined as sRT at or below the post-prostatectomy prostate-specific antigen (PSA) value of 0.5 ng/mL, is advised. This is based on data from multiple retrospective studies demonstrating



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superior outcomes in patients who are administered early sRT as opposed to those who are not treated or administered late sRT.[4–6] Based on recent level 1 evidence,[7] it is also recommended that these men be offered concomitant anti-androgen therapy (AAT), as certain subgroups may derive benefit from it. Hence, in an ideal scenario, a patient who experiences biochemical recurrence following radical prostatectomy should receive early sRT (PSA $\leq$ 0.5 ng/mL) at the least, with/without concomitant AAT.

However, this is not always the case in the real-world. The variable natural history of CaP progression following biochemical failure,[8] as well as pragmatic issues such as patients' preferences, physicians' beliefs, socioeconomic barriers to timely care, loss to follow-up, etc., often limit timely institution of salvage therapy. A substantial proportion of patients (close to 50%)[4,5] hence end up presenting or agreeing to salvage treatment later in their disease course, when their PSA values are well beyond 0.5 ng/mL. In these patients, there is a concern that the therapeutic window for salvage treatment may have been lost, and therapy with 'delayed' sRT, even with the addition of AAT, may not be able to overcome the time delay in initiation of sRT.

We designed the current study to investigate whether this concern is true or not. Specifically, we sought to answer the question 'Could patients suffering biochemical recurrence and receiving late sRT be rescued with synchronous use of AAT to achieve outcomes at par with the patients who received early sRT?'. We leveraged data from the Radiation Therapy Oncology Group (RTOG)-9601 clinical trial to answer our question. We hypothesized that the answer to our question would be yes, and hoped that our study would provide information to help patients considering delayed sRT with or without concomitant AAT make an informed, shared treatment decision.

## METHODS

### *Data Source, Treatment Protocols, and Follow-Up*

The data were obtained from the National Cancer Institute's (NCI's) National Clinical Trials Network (NCTN) data archive platform and Project Data Sphere (PDS). These data repositories were specifically created and made freely available to the public to promote collaborative analyses of trial data and hasten the discovery of new and more effective anticancer treatments.[9]

A detailed description of the RTOG-9601 trial cohort ($n$ = 760) has been previously published.[7] Briefly, the trial recruited patients at high risk for biochemical failure, i.e. patients with locally advanced CaP or organ-confined disease with positive surgical margin at radical prostatectomy, who ultimately developed biochemical failure post-prostatectomy. All patients were node-negative. Biochemical failure was defined as a PSA value between 0.2 and 4.0 ng/mL postoperatively. All patients had a Karnofsky performance score $\geq$ 80, no previous chemotherapy or radiation therapy for CaP, and no previous hormone therapy other than short-term preoperative hormonal therapy. Patients had a negative bone scan and computed tomography (CT) scan at the time of enrollment. At randomization, these patients with biochemical failure were either assigned to sRT and bicalutamide 150 mg daily for 2 years or sRT and placebo. sRT was started within 12 weeks of randomization with a total dose of 64.8 Gy to the prostatic fossa. Patients were assessed with history, physical examination, biochemical tests, and imaging before and after sRT. Subsequent follow-up evaluation occurred every 3 months for 2 years, then every 6 months for 3 years and yearly afterwards.

### *Study Population and Treatment Groups*

Of the 760 patients who were part of the RTOG-9601 trial, 670 (88.2%) experienced PSA recurrence, while the remaining 90 (11.8%) experienced persistence. The latter were excluded from the current study as we wanted to focus solely on patients who experienced biochemical recurrence (in comparison with a similar study by Dess et al. that included all biochemical failure patients, i.e. patients with biochemical recurrence and persistence[10]). These 670 patients (Fig. 1) were divided into four groups: early sRT alone (post-prostatectomy PSA at sRT $<$ 0.7 ng/mL; $n$ = 190), early sRT with concomitant AAT ($n$ = 204), late sRT alone (post-prostatectomy PSA at sRT $\geq$0.7 ng/mL; $n$ = 142), and late sRT with concomitant AAT ($n$ = 134). It should be noted that AAT was started concomitantly with sRT in those who were randomized to the bicalutamide arm; hence, patients in the early sRT/AAT arm received sRT + bicalutamide at a PSA value of $<$ 0.7, while patients in the late sRT/AAT arm received sRT + bicalutamide at a PSA value of $\geq$ 0.7.

### *Covariates*

In this study, covariates were categorized as reported in the original trial[7] and consisted of age at randomization, race, Karnofsky performance score, pathologic Gleason score, pathological T (pT) stage, surgical margin status, time to biochemical recurrence from surgery, time to salvage treatment from biochemical recurrence, pre-sRT PSA ($<$ 0.7 ng/mL [early] vs. 0.7–4.0 ng/mL [late]), and receipt of bicalutamide versus placebo.

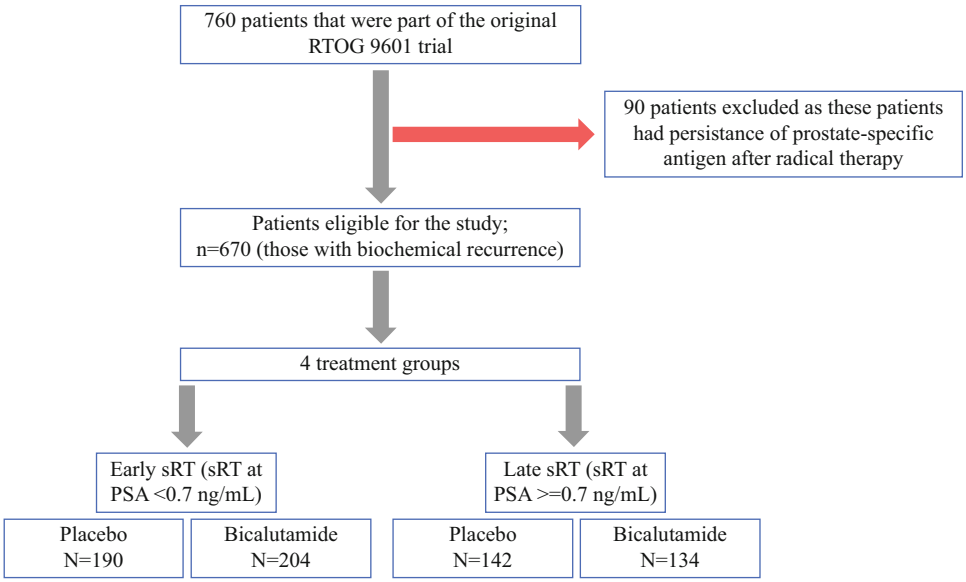


**FIG. 1** Final study population and treatment groups. *sRT* salvage radiation therapy, *PSA* prostate-specific antigen

*Outcome Measures*

The endpoints of interest, as specified in the trial protocol, were (1) overall mortality, defined as death from any cause; (2) CaP-specific death; (3) metastatic disease progression, defined as radiographic evidence of visceral or bony disease; (4) local disease recurrence, defined as development of a palpable mass in the prostatic fossa determined by means of clinical examination; and (5) functional adverse outcomes, including bowel complications (rectal urgency, diarrhea, and/or hematochezia), bladder complications (urinary frequency, dysuria, hematuria, and/or incontinence), and new-onset impotence; adverse reactions occurring within 90 days of the start of sRT were scored using the RTOG Acute Radiation Morbidity Scoring Criteria and reactions beyond 90 days were scored using the RTOG Late Radiation Morbidity Scoring Criteria.

*Statistical Analyses*

Descriptive statistics were reported using frequencies and proportions for categorical variables, and medians and interquartile range (IQR) for continuous variables. Chi-square and Kruskal–Wallis tests were used to evaluate the statistical significance of differences in categorical and continuous variables, respectively.

Cumulative incidence and Kaplan–Meier methods were used to generate 15-year estimates (start time was set at radical prostatectomy) and assess differences in local disease recurrence, metastatic disease progression, CaP-specific mortality, and overall mortality rates among the four study groups. Cumulative incidence analyses were used for the former three endpoints, as mortality is a competing outcome for these endpoints (i.e. a mortality event from another cause precludes local/metastatic failure and death from CaP). However, for overall mortality, standard Kaplan–Meier survival analysis was conducted as the competing outcome relationship is unidirectional (i.e. local/metastatic disease occurrence or CaP-specific death does not preclude an overall mortality event).

For adjusted analyses, time-varying non-parsimonious Fine–Gray competing-risk and Cox proportional hazards regression modeling was performed to estimate the relative hazards of local disease recurrence, metastatic disease progression, CaP-specific mortality, and overall mortality among the four treatments groups. Similar to the univariable analyses, Fine–Gray competing-risk analyses were utilized for the former three endpoints, while Cox proportional hazards analysis was used for overall survival. Non-parsimonious multivariable logistic regression modeling was performed to estimate the relative odds of early and late functional adverse events among the four treatment groups. Each model (Cox proportional, Fine–Gray, and multivariable logistic) controlled for age, race, Karnofsky performance score, pathologic T stage, pathologic Gleason score, surgical margin status, and time to biochemical recurrence, in addition to the primary independent variable of pre-sRT PSA level + use of AAT (the four treatment groups). It is noteworthy that our primary independent variable was treated as a time-varying factor to account for the immortal time bias that can introduced by time-fixed analysis.[11] Figure 2 provides further details on the time-varying survival analyses.[12]

All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA). A two-sided statistical significance was defined as a $p$-value $< 0.05$. An Institutional Review Board waiver was obtained before the study

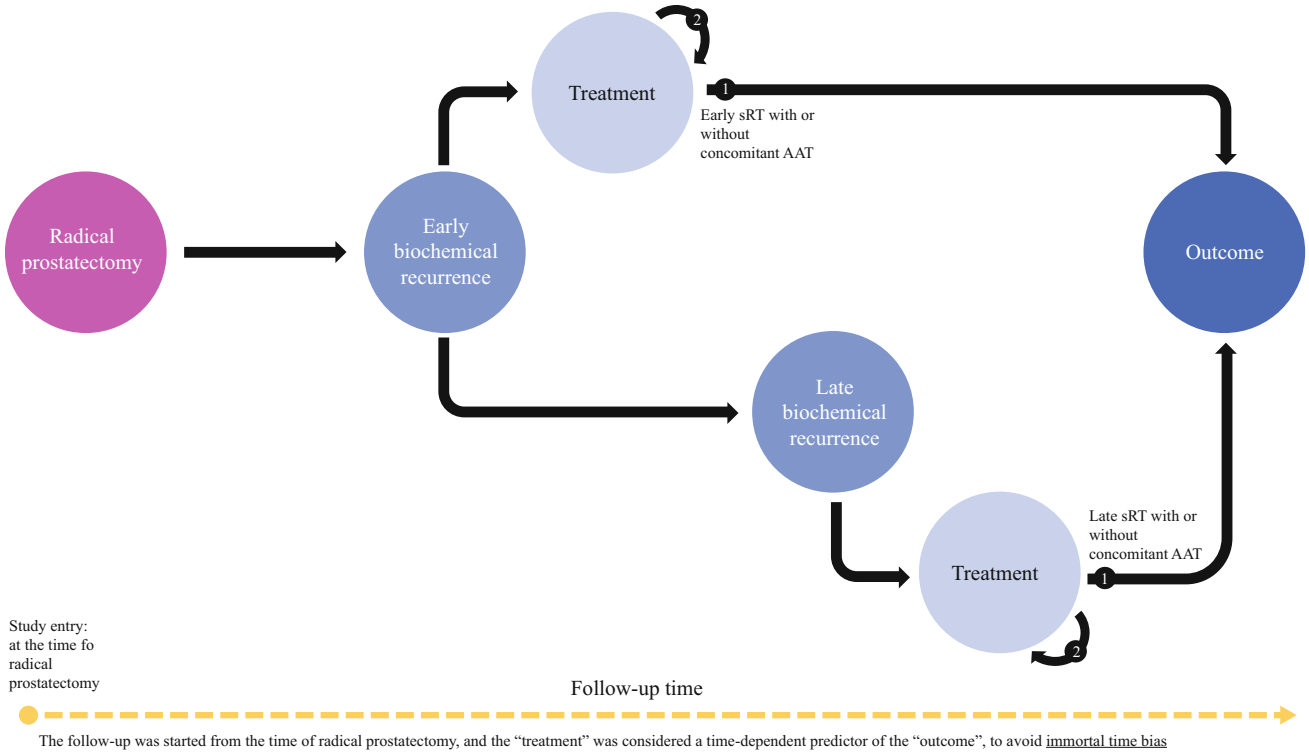


**FIG. 2** A multistate model of treatment strategies that was constructed to account for the immortal time bias. This bubble diagram demonstrates how patients were traced over time within the multistate model according to treatment and survival history. Note: Each bubble represents a possible health state. The included health states were mutually exclusive, meaning that at any given time point a patient could reside in only one health state. Arrows refer to a transition in health states as time evolves, i.e. treatment initiation (early or late sRT with/without AAT) or experiencing an adverse outcome (local recurrence, metastasis, CaP death, or overall death). All patients started in the alive-without-recurrence state of status post-radical prostatectomy and subsequently moved to a post-treatment state at the time sRT was initiated. Patients who experienced an adverse outcome then moved to the 'outcome' state (path #1), an absorbing health state, and patients who survived remained in their post-treatment state until the end of the study or lost to follow-up (right censored, path #2). *sRT* salvage radiation therapy, *AAT* anti-androgen therapy, *CaP* prostate cancer

was conducted, in accordance with institutional regulations on dealing with previously collected de-identified data.

## RESULTS

### *Baseline Characteristics*

Table 1 provides details on the demographic and disease characteristics of the patients in the four treatment groups. The median time to biochemical recurrence was similar in the four groups ($p = 0.375$), ranging between 1.3 and 1.6 years. The median time to treatment from biochemical recurrence was predictably longer for patients in the late sRT groups, i.e. 1–1.1 years, compared with 0.6 years for the early sRT groups ($p = 0.0001$). Patients were otherwise well-matched in all baseline and disease characteristics, including pT stage ($p = 0.107$), pathological Gleason score ($p = 0.930$), surgical margin status ($p = 0.714$), and Karnofsky performance score ($p = 0.589$), except for age ($p = 0.014$).

### *15-Year Overall Mortality, Prostate Cancer-Specific Mortality, and Disease Progression Rates*

The median follow-up was 14.7 years. In Kaplan–Meier analysis, the 15-year overall mortality rates were 22.9, 22.8, 40.1, and 22.9% (log-rank $p = 0.0039$) (Fig. 3a) in the early sRT, early sRT with AAT, late sRT, and late sRT with AAT groups, respectively.

In cumulative incidence analyses, the 15-year CaP-specific mortality rates were 12.1, 3.9, 22.7, and 8.0% (Gray's $p = 0.0004$) (Fig. 3b) in the early sRT, early sRT with AAT, late sRT, and late sRT with AAT groups, respectively. Similarly, the 15-year metastatic and local disease progression rates in the early sRT, early sRT with AAT, late sRT, and late sRT with AAT groups were 18.8, 14.6, 35.9, and 19.5% (Gray's $p = 0.0004$) (Fig. 3c), and 3.8, 1.2, 8.9, and 2.1% (Gray's  = 0.0431) (Fig. 3d), respectively.

**TABLE 1** Baseline characteristics in patients with prostate cancer disease experiencing biochemical recurrence after radical prostatectomy, stratified by early versus late salvage radiation therapy with/without concomitant anti-androgen treatment; RTOG-9601 trial data ($n$ = 670)

| | Overall | Early sRT PSA < 0.7 ng/mL No AAT [$n$ = 190] | Early sRT PSA < 0.7 ng/mL AAT [$n$ = 204] | Late sRT PSA 0.7–4.0 ng/mL No AAT [$n$ = 142] | Late sRT PSA 0.7–4.0 ng/mL AAT [$n$ = 134] | $p$-value |
|---|---|---|---|---|---|---|
| Time, surgery to PSA elevation, years | | | | | | |
| Median (IQR) | 1.4 (0.3–3.1) | 1.4 (0.4–2.8) | 1.4 (0.4–2.9) | 1.6 (0.4–3.9) | 1.3 (0.2–3.7) | 0.3754 |
| Time, PSA elevation to treatment, years | | | | | | |
| Median (IQR) | 0.8 (0.7–1) | 0.6 (0.5–0.9) | 0.6 (0.5–0.7) | 1.1 (0.9–1.1) | 1 (0.9–1.4) | 0.0001 |
| Age, years | | | | | | |
| ≤ 59 | 163 (24.33) | 55 (28.95) | 50 (24.51) | 24 (16.9) | 34 (25.37) | 0.0141 |
| 60–69 | 339 (50.6) | 98 (51.58) | 107 (52.45) | 66 (46.48) | 68 (50.75) | |
| ≥ 70 | 168 (25.07) | 37 (19.47) | 47 (23.04) | 52 (36.62) | 32 (23.88) | |
| Race | | | | | | |
| White | 596 (88.96) | 165 (86.84) | 191 (93.63) | 127 (89.44) | 113 (84.33) | 0.1854 |
| African American | 56 (8.36) | 19 (10) | 10 (4.9) | 12 (8.45) | 15 (11.19) | |
| Other | 18 (2.69) | 6 (3.16) | 3 (1.47) | 3 (2.11) | 6 (4.48) | |
| Karnofsky performance score | | | | | | |
| ≤ 90 | 161 (24.03) | 46 (24.21) | 43 (21.08) | 39 (27.46) | 33 (24.63) | 0.5890 |
| 100 | 509 (75.97) | 144 (75.79) | 161 (78.92) | 103 (72.54) | 101 (75.37) | |
| pT stage | | | | | | |
| T2 | 228 (34.03) | 59 (31.05) | 80 (39.22) | 52 (36.62) | 37 (27.61) | 0.1079 |
| T3 | 442 (65.97) | 131 (68.95) | 124 (60.78) | 90 (63.38) | 97 (72.39) | |
| pGleason score | | | | | | |
| 2–6 | 186 (27.76) | 52 (27.37) | 61 (29.9) | 37 (26.06) | 36 (26.87) | 0.9302 |
| 7 | 375 (55.97) | 110 (57.89) | 112 (54.9) | 79 (55.63) | 74 (55.22) | |
| 8–10 | 108 (16.12) | 28 (14.74) | 30 (14.71) | 26 (18.31) | 24 (17.91) | |
| Surgical margins | | | | | | |
| Positive | 509 (75.97) | 144 (75.79) | 158 (77.45) | 110 (77.46) | 97 (72.39) | 0.7140 |
| PSA level at treatment, ng/mL | | | | | | |
| < 0.7 | 394 (58.81) | 190 (100) | 204 (100) | 0 (0) | 0 (0) | NA |
| 0.7–1.5 | 193 (28.81) | 0 (0) | 0 (0) | 99 (69.72) | 94 (70.15) | |
| > 1.5–4.0 | 83 (12.39) | 0 (0) | 0 (0) | 43 (30.28) | 40 (29.85) | |

Data are expressed as $n$ (%) unless otherwise specified

*sRT* salvage radiation therapy, *PSA* prostate-specific antigen, *AAT* anti-androgen therapy, *NA* not available, *IQR* interquartile range

### *Rescue of Oncological and Survival Outcomes by Concomitant Anti-Androgen Therapy in Patients Receiving Late Salvage Radiation Therapy*

Time-varying Cox regression analysis demonstrated that the hazards of overall mortality were significantly worse in patients receiving late sRT compared with those receiving early sRT (hazards ratio [HR] 1.49, 95% confidence interval [CI] 1.02–2.17); however, the hazards were no different among patients who received late sRT with AAT versus early sRT (HR 0.85, 95% CI 0.55–1.32) (Table 2, Part A).

Time-varying Fine–Gray competing-risk analysis similarly demonstrated that the increased hazard of CaP-specific mortality in patients undergoing late sRT could be rescued by delivery of concomitant AAT. The HR of CaP-specific mortality in the late sRT-only patients compared with early sRT was 1.64 (95% CI 1.08–2.85), while the HR in the late sRT with concomitant AAT patients was 0.62 (95% CI 0.31–1.22; referent early sRT). Similarly, the HR of metastasis in patients receiving late sRT compared with early sRT was 1.93 (95% CI 1.23–3.03). However, the hazards were no different in patients receiving late sRT with concomitant AAT versus early sRT (HR 0.86, 95% CI 0.51–1.46). On the other hand, the hazards of local disease recurrence did not differ among any of the four treatment groups (Table 2, Part A). Table 2, Part B, serves as a straightforward 'visual aid' to compare the outcomes

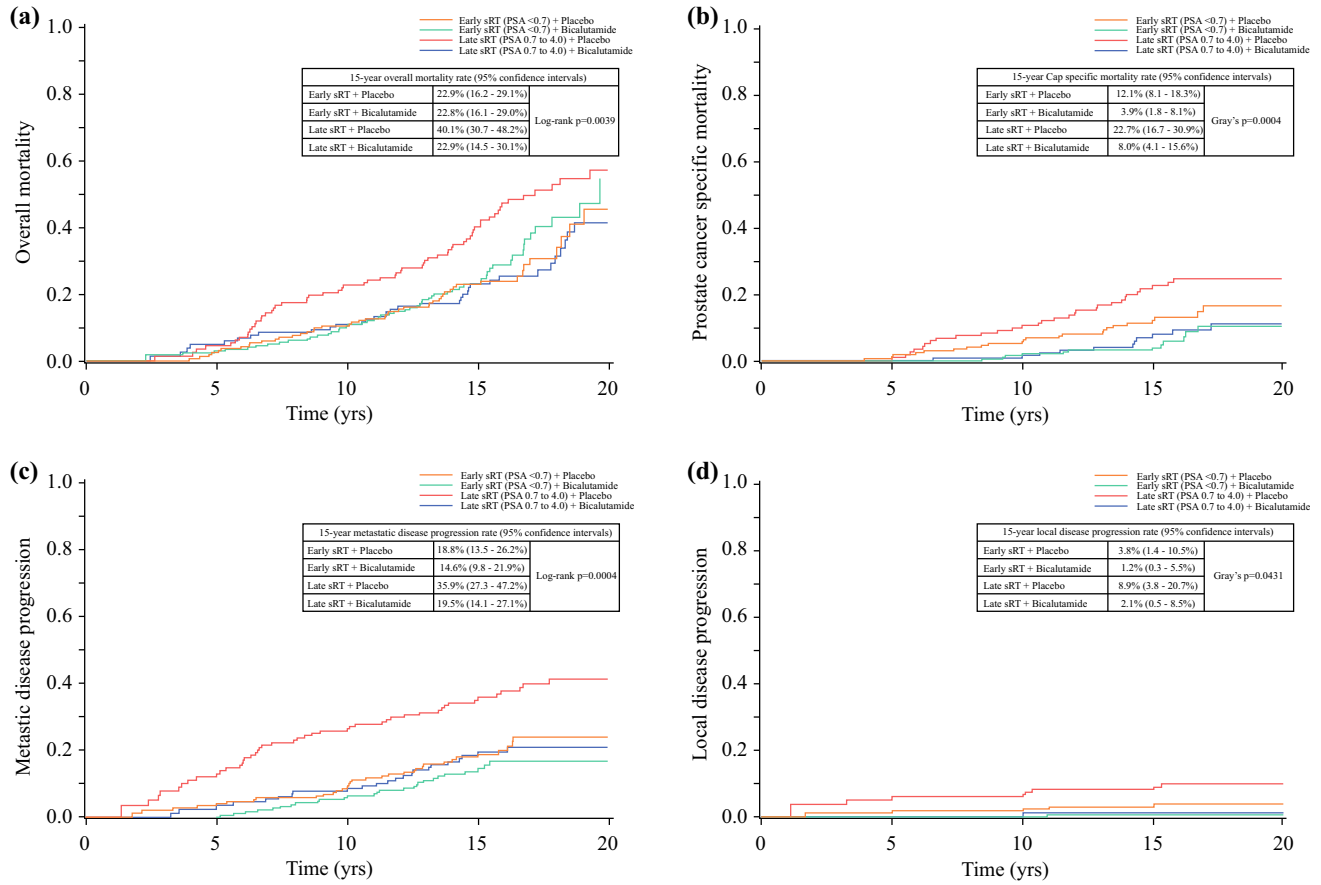


**FIG. 3** Kaplan–Meier analysis of overall mortality with 15-year estimates (**a**), and cumulative incidence analyses of CaP-specific survival (**b**), metastatic disease failure (**c**), and local disease failure (**d**) with 15-year estimates; the four groups correspond to early sRT, early sRT with concomitant AAT, late sRT, and late sRT with concomitant AAT (RTOG-9601 trial data). *CaP* prostate cancer, *sRT* salvage radiation therapy, *AAT* anti-androgen therapy, *PSA* prostate-specific antigen

between the early sRT plus concomitant AAT and late sRT plus concomitant AAT groups, and demonstrates that the rescue of oncological outcomes with AAT use in delayed sRT is actually at par with the outcomes of patients receiving early sRT with concomitant AAT. Table 2, Part C, similarly simplifies the comparison between the late sRT and late sRT with concomitant AAT groups, and demonstrates significant improvement in all oncological outcomes, except local disease recurrence, when concomitant AAT is administered to patients receiving delayed sRT.

### *Functional Adverse Effects*

In time-varying multivariable analyses, delayed sRT with concomitant AAT was not associated with increased odds of new-onset sexual dysfunction when compared with early sRT alone (odds ratio [OR] 1.26, 95% CI 0.68–2.34). Other adverse events including acute and late bowel and bladder toxicities were also equivalent among the four treatment groups (Table 3).

## DISCUSSION

The key finding of our study is the demonstration of the ability of AAT to rescue oncological and survival outcomes in patients who receive delayed sRT after experiencing biochemical recurrence post-prostatectomy. The improvement is substantial and leads to survival rates at par with that of men who received early sRT with or without concomitant AAT. Patients undergoing late sRT had a 48.6, 64.2, and 93.2% increase in hazard of overall death, death from CaP, and metastatic spread, respectively, compared with patients who received early sRT; however, these differences were completely negated once concomitant AAT was delivered alongside late sRT.

Our study also shows that the addition of AAT to late sRT does not increase the risk for new-onset impotence or bowel or bladder dysfunction.

**TABLE 2** Time-varying Cox proportional hazards and Fine–Gray competing-risk pairwise regression analyses evaluating the hazards of mortality and disease progression among patients experiencing biochemical recurrence after radical prostatectomy and undergoing early versus late salvage radiation therapy with/without concomitant anti-androgen treatment; RTOG-9601 trial data [$n = 670$]

| | Hazards ratio (95% confidence interval) | | | |
|---|---|---|---|---|
| | Early sRT PSA < 0.7 ng/mL No AAT [$n = 190$] | Early sRT PSA < 0.7 ng/mL AAT [$n = 204$] | Late sRT PSA 0.7–4.0 ng/mL No AAT [$n = 142$] | Late sRT PSA 0.7–4.0 ng/mL AAT [$n = 134$] |
| Model[a] (part A)[b] | | | | |
| Overall mortality | Ref. | 1.025 (0.696–1.509), $p = 0.90$ | 1.486 (1.017–2.174), $p = 0.04$ | 0.850 (0.549–1.316), $p = 0.47$ |
| CaP-specific mortality | Ref. | 0.458 (0.235–0.892), $p = 0.01$ | 1.642 (1.080–2.849), $p = 0.04$ | 0.619 (0.314–1.223), $p = 0.25$ |
| Metastatic progression | Ref. | 0.750 (0.462–1.220), $p = 0.24$ | 1.932 (1.230–3.034), $p < 0.01$ | 0.858 (0.505–1.459), $p = 0.57$ |
| Local failure | Ref. | 0.316 (0.064–1.557), $p = 0.21$ | 2.105 (0.742–5.970), $p = 0.10$ | 0.481 (0.096–2.400), $p = 0.36$ |
| Model[a] (Part B)[b] | | | | |
| Overall mortality | 0.976 (0.663–1.437), $p = 0.90$ | Ref. | 1.451 (1.005–2.095), $p = 0.04$ | 0.830 (0.541–1.274), $p = 0.34$ |
| CaP-specific mortality | 2.183 (1.121–4.254), $p = 0.01$ | Ref. | 3.585 (1.893–6.788), $p < 0.01$ | 1.352 (0.627–2.915), $p = 0.24$ |
| Metastatic progression | 1.333 (0.820–2.167), $p = 0.24$ | Ref. | 2.574 (1.596–4.153), $p < 0.01$ | 1.144 (0.653–2.002), $p = 0.83$ |
| Local failure | 3.161 (0.642–15.56), $p = 0.21$ | Ref. | 6.655 (1.418–31.24), $p < 0.01$ | 1.519 (0.211–10.91), $p = 0.62$ |
| Model[a] (Part C)[b] | | | | |
| Overall mortality | 0.673 (0.460–0.984), $p = 0.04$ | 0.689 (0.477–0.995), $p = 0.04$ | Ref. | 0.572 (0.378–0.867), $p = 0.02$ |
| CaP-specific mortality | 0.609 (0.351–0.961), $p = 0.04$ | 0.279 (0.147–0.528), $p < 0.01$ | Ref. | 0.377 (0.193–0.738), $p < 0.01$ |
| Metastatic progression | 0.518 (0.330–0.813), $p < 0.01$ | 0.388 (0.241–0.627), $p < 0.01$ | Ref. | 0.444 (0.263–0.751), $p < 0.01$ |
| Local failure | 0.475 (0.167–1.347), $p = 0.10$ | 0.150 (0.032–0.705), $p < 0.01$ | Ref. | 0.228 (0.049–1.055), $p = 0.07$ |

*sRT* salvage radiation therapy, *PSA* prostate-specific antigen, *AAT* anti-androgen therapy, *CaP* prostate cancer

[a]Each model was adjusted for age, race, Karnofsky performance score, pathologic T stage, pathologic Gleason score, surgical margin status, and time to biochemical recurrence, in addition to the primary independent time-varying variable of pre-sRT PSA + use of AAT, except the model for local failure where univariable time-varying Fine–Gray competing-risk modeling was undertaken as the number of local failure events were <20, hence adjustments for the aforementioned variables would not have been statistically sound

[b]Parts A, B and C of the table represent the same regression models, with the only change being in the referent used, to allow for easy pairwise comparisons

To the best of our knowledge, these data have not been previously published and may aid in the counseling of men who experience biochemical recurrence following radical prostatectomy. Our results offer hope to men who, whether willingly or not, may have missed the window for early sRT. These patients can be told that their chances of dying from their cancer are < 10% at 15 years, and no worse compared with an earlier treatment with sRT, if they now accept combination treatment with sRT and AAT.

Although our findings may be used to allay anxiety in men whose PSA values are beyond 0.5 ng/mL, conversely they may also be used to convince patients to go ahead with early sRT. For example, patients who are experiencing biochemical recurrence with PSA $\leq$ 0.5 ng/mL, and who are doubtful about whether to wait-and-watch or to start early sRT, can be given the two therapeutically equivalent options—early sRT or delayed sRT with AAT. The ultimate decision can be left up to the patients but they may be told that by starting sRT earlier, they may obviate the need for additional hormonal treatment later, and although AAT

**TABLE 3** Multivariable logistic regression analyses evaluating the odds of bowel, bladder, and sexual adverse events among patients experiencing biochemical recurrence after radical prostatectomy and undergoing early versus late salvage radiation therapy with/without concomitant anti-androgen treatment; RTOG-9601 trial data [$n$ = 670]

| Model[a] | Odds ratio (95% confidence interval) | | | |
|---|---|---|---|---|
| | Early sRT<br>PSA < 0.7 ng/mL<br>No AAT [$n$ = 190] | Early sRT<br>PSA < 0.7 ng/mL<br>AAT [$n$ = 204] | Late sRT<br>PSA 0.7–4.0 ng/mL<br>No AAT [$n$ = 142] | Late sRT<br>PSA 0.7–4.0 ng/mL<br>AAT [$n$ = 134] |
| New-onset impotence | Ref. | 1.193 (0.678–2.100), $p$ = 0.54 | 0.634 (0.309–1.300), $p$ = 0.21 | 1.258 (0.676–2.340), $p$ = 0.47 |
| Bladder toxicity | | | | |
| Acute | Ref. | 1.015 (0.678–1.519), $p$ = 0.94 | 0.903 (0.575–1.417), $p$ = 0.66 | 1.288 (0.818–2.029), $p$ = 0.27 |
| Late | Ref. | 1.038 (0.684–1.574), $p$ = 0.86 | 0.795 (0.503–1.255), $p$ = 0.32 | 0.714 (0.451–1.130), $p$ = 0.16 |
| Bowel toxicity | | | | |
| Acute | Ref. | 0.597 (0.393–0.908), $p$ = 0.02 | 0.681 (0.487–1.086), $p$ = 0.11 | 0.805 (0.500–1.296), $p$ = 0.37 |
| Late | Ref. | 1.105 (0.739–1.651), $p$ = 0.63 | 0.733 (0.465–1.153), $p$ = 0.18 | 0.945 (0.601–1.485), $p$ = 0.81 |

*sRT* salvage radiation therapy, *PSA* prostate-specific antigen, *AAT* anti-androgen therapy, *Ref.* reference

[a]Each model was adjusted for age, race, Karnofsky performance score, pathologic T stage, pathologic Gleason score, surgical margin status, and time to biochemical recurrence, in addition to the primary independent time-varying variable of pre-sRT PSA + use of AAT

does not seem to increase the risk of new-onset impotence, its adverse effect on libido and gynecomastia are well known.[13] These patients may also be told that early sRT will not affect the recovery of their urinary control adversely, as shown by a recent study evaluating the effect of timing of sRT on urinary control.[14]

Data presented at the European Society for Medical Oncology Congress 2019 from the RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery),[15] RAVES (Radiotherapy—Adjuvant versus Early Salvage),[16] and GETUG-AFU17 trials indicate that the adjuvant radiation therapy and early sRT may yield similar outcomes in men at high risk for biochemical recurrence. The final results have verified the initial findings,[17–19] and it is therefore safe to surmise that now more men will be recommended sRT and may find themselves debating early versus late sRT; thus, the findings of this study become even more timely. Furthermore, once the onslaught of the current coronavirus disease 2019 (COVID-19) pandemic is over, it is reasonable to assume that an increasing number of men worldwide will present with higher recurrent PSA values than in the past. These patients may benefit from the knowledge that a combination treatment can offer them an equivalent chance at cure as early sRT.

Our study is not devoid of limitations, within the bounds of which our findings should be interpreted. First, this study represents a post hoc analysis of level 1 evidence, and thus suffers from confounding and selection bias. However, the four treatment groups studied in the present report were quite well-matched at baseline (Table 1), and to account for known confounders and immortal bias, we performed time-varying adjusted analyses, which confirmed the results of our univariable analyses. Furthermore, AAT use consistently demonstrated benefit across all studied outcomes, whether overall mortality or cancer-specific outcomes; taken together, these facts support the reliability and validity of our findings. Another limitation of our study is that the RTOG-9601 trial dataset available through the NCTN data archive provided only limited information regarding pre-sRT PSA; only a single value of PSA was provided, in a categorical fashion (< 0.7 vs. 0.7–1.5 vs. > 1.5–4.0 ng/mL). Because of this, we were not able to classify our patients using a more standard or traditional pre-sRT PSA cut-off, such as that of 0.5 ng/mL. However, on comparing baseline characteristics, including age, pT stage, pathologic Gleason score, and surgical margins, of our patients in the early sRT cohort with those in the other published cohorts, where a pre-sRT PSA cut-off of ≤0.5 ng/mL was used,[4–6] we found no major differences. Furthermore, although our cut-off was not exactly at PSA ≤0.5 ng/mL (it was off by 0.1 ng/mL), the study still provides a proof of principle, and, similarly, although the survival estimates that we note in this study may not wholly translate when using a different pre-sRT PSA cut-off for salvage treatment, the outcome patterns should still hold true. Lastly, the trial included patients undergoing sRT and AATs between the years 1998 and 2003. Substantial changes in radiation therapy techniques and androgen deprivation have come about since then, and thus the results may not be completely generalizable to the contemporary patients undergoing sRT with/without hormonal treatment today. However, as reasoned above for the pre-sRT cut-off, here too, the basic principles of therapy

remain the same and any further variation in technique of sRT or AAT pharmacology should affect the treatment groups equally, thus preserving the overall message of the study.

On the other hand, our study has several other methodological strengths. We corrected for lead time and immortal time biases by utilizing time-varying regression analyses, which none of the prior studies on this subject have done,[10] and can lead to substantial errors.[11] Furthermore, the data were derived from a trial with rigorous patient follow-up, the follow-up duration was substantial (median 14.7 years), and the study focused only on node-negative localized CaP patients (in contrast to prior studies that frequently included patients with nodal disease or persistent PSA after surgery).[10,20,21] Lastly, the outcomes assessed were powerful and clinically meaningful, including overall survival, CaP-specific survival, and clinical metastasis.

## CONCLUSION

Ours is the first study to demonstrate that poorer outcomes associated with late sRT in men with recurrent CaP after radical prostatectomy may be successfully rescued by use of concomitant AAT.

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**DATA AVAILABILITY** From the NCTN Data Archive of the NCI's NCTN.

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