JAMA Oncology | Original Investigation

Association of Presalvage Radiotherapy PSA Levels After Prostatectomy With Outcomes of Long-term Antiandrogen Therapy in Men With Prostate Cancer

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IMPORTANCE In men with recurrent prostate cancer, addition of long-term antiandrogen therapy to salvage radiotherapy (SRT) was associated with overall survival (OS) in the NRG/RTOG 9601 study. However, hormone therapy has associated morbidity, and there are no validated predictive biomarkers to identify which patients derive most benefit from treatment.

OBJECTIVE To examine the role of pre-SRT prostate-specific antigen (PSA) levels to personalize hormone therapy use with SRT.

INTERVENTIONS Men were randomized to SRT plus high-dose nonsteroidal antiandrogen (bicalutamide, 150 mg/d) or placebo for 2 years.

DESIGN, SETTING, AND PARTICIPANTS In this secondary analysis of the multicenter RTOG 9601 double-blind, placebo-controlled randomized clinical trial conducted from 1998 to 2003 by a multinational cooperative group, men with a positive surgical margin or pathologic T3 disease after radical prostatectomy with pre-SRT PSA of 0.2 to 4.0 ng/mL were included. Analysis was performed between March 4, 2019, and December 20, 2019.

MAIN OUTCOMES AND MEASURES The primary outcome was overall survival (OS). Secondary end points included distant metastasis (DM), other-cause mortality (OCM), and grades 3 to 5 cardiac and neurologic toxic effects. Subgroup analyses were performed using the protocol-specified PSA stratification variable (1.5 ng/mL) and additional PSA cut points, including test for interaction. Competing risk analyses were performed for DM and other-cause mortality (OCM).

RESULTS Overall, 760 men with PSA elevation after radical prostatectomy for prostate cancer were included. The median (range) age of particpants was 65 (40-83) years. Antiandrogen assignment was associated with an OS benefit in the PSA stratum greater than 1.5 ng/mL (n = 118) with a 25% 12-year absolute benefit (hazard ratio [HR], 0.45; 95% CI, 0.25-0.81), but not in the PSA of 1.5 ng/mL or less stratum (n = 642) (1% 12-year absolute difference; HR, 0.87; 95% CI, 0.66-1.16). In a subanalysis of men with PSA of 0.61 to 1.5 (n = 253), there was an OS benefit associated with antiandrogen assignment (HR, 0.61; 95% CI, 0.39-0.94). In those receiving early SRT (PSA ≤0.6 ng/mL, n = 389), there was no improvement in OS (HR, 1.16; 95% CI, 0.79-1.70), an increased OCM hazard (subdistribution HR, 1.94; 95% CI, 1.17-3.20; *P* = .01), and an increased odds of late grades 3 to 5 cardiac and neurologic toxic effects (odds ratio, 3.57; 95% CI, 1.09-15.97; *P* = .05).

CONCLUSIONS AND RELEVANCE These results suggest that pre-SRT PSA level may be a prognostic biomarker for outcomes of antiandrogen treatment with SRT. In patients receiving late SRT (PSA >0.6 ng/mL, hormone therapy was associated with improved outcomes. In men receiving early SRT (PSA ≤0.6 ng/mL), long-term antiandrogen treatment was not associated with improved OS. Future randomized clinical trials are needed to determine hormonal therapy benefit in this population.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT00002874

JAMA Oncol. 2020;6(5):735-743. doi:10.1001/jamaoncol.2020.0109
Published online March 26, 2020.

Visual Abstract

Supplemental content

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The use of radical prostatectomy (RP) in men with high-risk localized prostate cancer is increasing.[1] Surgery alone is curative for some men, but a substantial proportion develop a subsequent rising prostate-specific antigen (PSA)—termed *biochemical recurrence*.[2,3] Salvage radiotherapy (SRT) is often indicated in this setting, and although it is effective, not all men are cured.[4] This was the inspiration behind the Radiation Therapy Oncology Group (RTOG) 9601 randomized clinical trial. Men with adverse pathologic analysis results after RP and a detectable postoperative PSA were randomized to either 2 years of a nonsteroidal antiandrogen or placebo, both with SRT. At a median follow-up of 13 years, the addition of the antiandrogen to SRT was associated with improved 12-year overall survival (OS) from 71% to 76%.[5] This seminal trial, however, started accrual more than 20 years ago and many participants received SRT with PSA levels greater than 0.5 ng/mL.

We now know that SRT delivered at lower PSA levels is associated with improved outcomes compared with delayed use.[6,7] As a result, men with lower PSA levels derive less absolute benefit from hormone therapy, even if the relative benefit is the same. Furthermore, advances in molecular imaging have now shown that higher pre-SRT PSA levels are associated with increased probability of harboring extrapelvic metastatic disease.[8] This provides biologic rationale that patients with higher PSA levels may preferentially derive a treatment benefit of hormone therapy for occult distant metastatic disease. Thus, it is unclear whether the survival benefit in the RTOG 9601 trial applies to patients receiving SRT at lower PSA levels.

We therefore performed a subgroup analysis of the RTOG 9601 trial to assess the association of antiandrogen therapy with outcomes using the pre-SRT PSA stratification variable. We hypothesized that those receiving SRT at lower PSA levels would not derive clinical benefit and may experience net harm from long-term high-dose antiandrogen therapy.

Key Points

Question For men with recurrent prostate cancer after radical prostatectomy, can prostate-specific antigen (PSA) level be used to help predict outcomes of long-term antiandrogen treatment added to salvage radiotherapy (SRT)?

Findings In this secondary analysis of the RTOG 9601 trial, pre-SRT PSA level of higher than 1.5 ng/mL was associated with an overall survival benefit with long-term antiandrogen therapy. Patients treated at a PSA of 0.6 ng/mL or less had no overall survival improvement, but had a greater than 3-fold increase in high-grade cardiac and neurologic events and a 2-fold increase in other cause mortality with 2 years of bicalutamide.

Meaning Antiandrogen treatment has morbidity, and pre-SRT PSA can be used to personalize who derives net benefit of hormone therapy with SRT.

Methods

Trial and Treatment Details

All patients initially consented to enroll on RTOG 9601 after local institutional review board approval. This secondary analysis was exempt from institutional review board approval because no identifying patient health information was shared between the National Cancer Institute and the University of Michigan. The trial protocol and analysis plan are available in Supplement 1. The RTOG 9601 trial was a double-blind, placebo-controlled trial of men receiving SRT with or without the addition of a nonsteroidal antiandrogen (150 mg/d bicalutamide for 2 years). All patients received SRT to the prostate bed (64.8 Gy in 1.8 Gy per fraction) only. The trial was sponsored by the National Cancer Institute and conducted through RTOG/NRG Oncology. AstraZeneca supplied drug/placebo, but had no role in collection of data, analysis, or preparation of any report. Approval for analysis was granted by NRG Oncology and the National Cancer Institute through a data-sharing agreement with the senior author (D.E.S.). Herein, antiandrogen therapy refers to bicalutamide, and hormone therapy more generally to either antiandrogen therapy or androgen deprivation therapy (ADT) agents such as luteinizing hormone-releasing hormone (LHRH) agonists and antagonists.

Patients

All patients underwent RP and lymphadenectomy with negative lymph nodes by pathologic analysis. Trial entry criteria included disease confined to the prostate (pathologic T2) with a positive surgical margin or extraprostatic disease (pathologic T3). Patients had a PSA that reached 0.2 to 4.0 ng/mL at least 8 weeks after surgery with no evidence of metastatic disease by standard abdominal and pelvic computed tomography and nuclear medicine bone scan. Patients who received prior long-term hormone therapy, chemotherapy, or pelvic radiotherapy were excluded.

End Points

The primary end point was OS. Sample size, randomization, blinding, and interim analysis have been previously described.[5] The present secondary analyses assess the interaction of pre-SRT PSA and antiandrogen treatment association with OS. Secondary end points included distant metastasis (DM) and other-cause mortality (OCM). End points were defined per the trial protocol, including OCM, which was any death not meeting any of these criteria (1) death due to prostate cancer or complications of protocol treatment, (2) death with known progressive metastatic disease while on salvage hormone therapy, or (3) death with a known rising PSA while on salvage hormone therapy. Late toxic effects data was collected per protocol. With a focus of OCM, the current study reports grades 3 to 5 cardiac and neurologic events given the evidence that hormone therapy may be associated with cardiac disease and dementia.[9,10]

Statistical Analysis

Our subgroup analysis was performed in accordance with the credibility criteria proposed by Sun et al.[11] Patients were stratified by pre-SRT PSA levels (0.2-1.5 vs >1.5 ng/mL). Although the trial protocol stated that additional analyses of treatment

Table 1. Baseline Characteristics by PSA Strata and Treatment Assignment

Characteristic	PSA ≤1.5 ng/mL		PSA >1.5 ng/mL	
	Placebo	Bicalutamide	Placebo	Bicalutamide
Patients, No.	313	329	63	55
Age, median (IQR), y	65 (60-69)	65 (59-69)	64 (61-70)	65 (60-69)
KPS				
80	4 (1.3)	5 (1.5)	0	0
90	71 (22.7)	69 (21.0)	21 (33.3)	14 (25.5)
100	238 (76.0)	255 (77.5)	42 (66.7)	41 (74.5)
Pathologic T-stage				
T2	104 (33.2)	113 (34.3)	16 (25.4)	15 (27.3)
T3	209 (66.8)	216 (65.7)	47 (74.6)	40 (72.7)
Gleason score				
2-6	86 (27.5)	94 (28.6)	17 (27.0)	19 (34.5)
7	170 (54.3)	172 (52.3)	31 (49.2)	26 (47.3)
8-10	50 (16.0)	56 (17.0)	12 (19.0)	9 (16.4)
Unknown	7 (2.2)	7 (2.1)	3 (4.8)	1 (1.8)
Surgical margin				
Positive	239 (76.4)	244 (74.2)	42 (66.7)	44 (80.0)
Negative	74 (23.6)	85 (25.8)	21 (33.3)	11 (20.0)
PSA nadir after surgery, ng/mL				
<0.5	289 (92.3)	298 (90.6)	43 (68.3)	40 (72.7)
≥0.5	24 (7.7)	31 (9.4)	20 (31.7)	15 (27.3)
PSA, median (IQR), ng/mL	0.50 (0.33-0.80)	0.56 (0.35-0.80)	2.50 (1.80-2.92)	2.10 (1.80-2.90)
0.20-0.30	74 (23.6)	74 (22.5)	0	0
0.31-0.60	114 (36.4)	127 (38.6)	0	0
0.61-1.50	125 (39.9)	128 (38.9)	0	0
>1.50-4.00	0	0	63 (100.0)	55 (100.0)

Abbreviations: IQR, interquartile range; KPS, Karnofsky performance status; PSA, prostate-specific antigen.

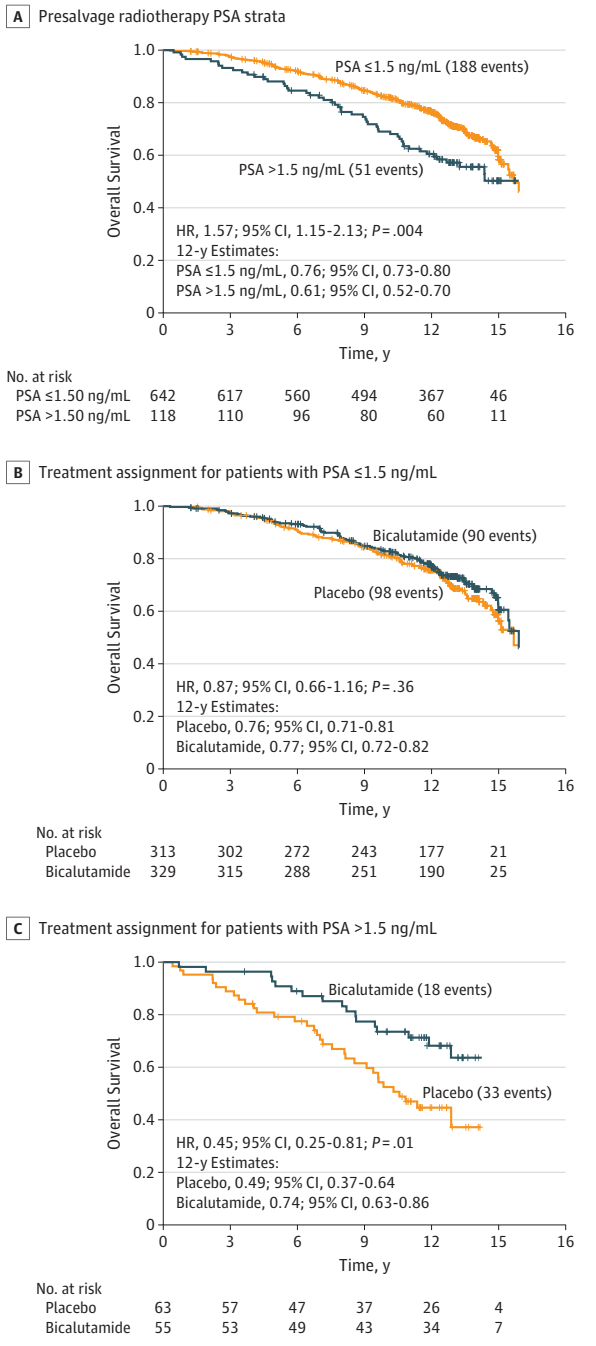
effect would include modifying factors such as age, race, and other characteristics, it did not prespecify hypotheses or direction of effects. We therefore developed an a priori statistical plan to analyze end points by the baseline stratification factor of PSA levels of 1.5 ng/mL or lower. Post hoc, we also analyzed the subgroup of PSA levels of 1.5 ng/mL or lower split by the median PSA levels of the trial of 0.6 ng/mL, given current recommendations for early SRT. We further analyzed the subgroup of patients with the lowest PSA levels (0.2-0.3 ng/mL) based on the proposed benefits of early SRT at first detection of biochemical recurrence.[6,7] This PSA level is relevant, because it represents the median PSA (0.3 ng/mL) in 2 other clinical trials evaluating hormone therapy with SRT.[12,13] In sensitivity analysis, we analyzed PSA cut points by quintile along with nonlinear PSA treatment effect interaction.

Follow-up was calculated by the standard reverse Kaplan-Meier method. Treatment effects on OS are reported using the hazard ratio (HR) from Cox regression models along with absolute differences in Kaplan-Meier event probability estimates.[14,15] For DM and OCM, Fine-Gray subdistribution hazard (sHR) models are reported along with cumulative incidence of events.[16,17] For OCM, cause-specific models are also reported to explore whether OCM differences are driven by differential competing risk of death from prostate cancer.[18,19] Formal interaction tests between treatment and pre-SRT PSA were performed using Cox regression for OS, and Fine-Gray regression for DM and OCM. For the toxic effects analyses, the date of event was not provided by the NCI, so time-to-event analyses could not be performed. Binary logistic regression analyses were performed to calculate the odds ratio (OR) of grades 3 to 5 cardiac or neurologic events by study assignment. To explore whether an increase in cardiac/neurologic events from bicalutamide were potentially owing to differing survival times, a sensitivity analysis investigating other toxic end points not commonly linked to hormone therapy was performed (eg, gastrointestinal (GI) and genitourinary (GU). Analyses used R statistical software (version 3.5.1, R Foundation for Statistical Computing). Two-sided $P < .05$ was deemed statistically significant. Analysis was performed between March 4, 2019, and December 20, 2019.

Results

Between 1998 and 2003, 760 patients were enrolled and comprise the final cohort. Most (n = 642/760, 85%) were in the pre-SRT PSA stratum of 1.5 ng/mL or lower. Age, performance status, pathologic T-stage, Gleason score, margin status, post-RP PSA nadir status, and pre-SRT PSA level were all similar between the control and investigational assignment in this stratum (**Table 1**). The median follow-up of surviving patients was 13 years (13.1 and 13.0 months for bicalutamide and placebo assignments, respectively).

Figure 1. Overall Survival Outcomes by Presalvage Radiation Therapy Prostate-Specific Antigen (PSA)



HR indicates hazard ratio. Overall survival by presalvage radiotherapy PSA strata (A) and by treatment assignment for patients with PSA levels of 1.5 ng/mL or lower (B) and PSA levels higher than 1.5 ng/mL(C).

Subgroup Analysis by Pre-SRT PSA Stratification Variable

The PSA stratification variable was significantly prognostic for OS (**Figure 1**A). Men with PSA levels of 1.5 ng/mL or lower randomized to bicalutamide had no significant improvement in OS (hazard ratio [HR], 0.87; 95% CI, 0.66-1.16; *P* = .36) (Figure 1B) compared with placebo with a similar estimate in multivariable analysis (HR, 0.86; 95% CI, 0.65-1.15; *P* = .32) (eTable 1 in Supplement 2**)**. In this group, men had a lower hazard of DM (subdistribution HR [sHR], 0.72; 95% CI, 0.51-1.01; *P* = .06) (eFigure 1 in Supplement 2) that was statistically significant on multivariable analysis (sHR, 0.67; 95% CI, 0.47-0.95; *P* = .03). For men with PSA levels higher than 1.5 ng/mL, bicalutamide was associated with improved OS (HR, 0.45; 95% CI, 0.25-0.81; *P* = .01) (Figure 1C). There was also lower hazard of DM (sHR, 0.36; 95% CI, 0.15-0.84; *P* = .02) (eFigure 2 in Supplement 2).

The interaction test between pre-SRT PSA as a continuous variable and bicalutamide treatment effect was significant for both OS (HR, 0.69; *P* = .02) and DM (HR, 0.68; *P* = .03), suggesting that the bicalutamide treatment effect varied with pre-SRT PSA level (eTable 2 in Supplement 2). The interaction remained significant after multivariable adjustment for age, Gleason score, T-stage, surgical margin, and nadir PSA.

Post Hoc Analyses by Additional PSA Thresholds

Pre-SRT PSA remained prognostic across additional PSA subgroups (eFigure 3 in Supplement 2). As suggested by the significant interaction test, there was also differing relative benefit and potential harm of antiandrogen therapy (eFigure 3 in Supplement 2).

Early SRT (pre-SRT PSA 0.2-0.6 ng/mL)

The median pre-SRT PSA for the entire RTOG 9601 cohort was 0.6 ng/mL, and a total of 389 men had a PSA between 0.2 and 0.6 ng/mL (eTable 3 in Supplement 2). There was no significant difference in OS between men who received bicalutamide or placebo (HR, 1.16; 95% CI, 0.79-1.70; *P* = .46) (**Figure 2**). Men randomized to antiandrogen therapy had a 2-fold increased hazard of OCM (sHR, 1.94;[95% CI, 1.17-3.20; *P* = .01). The estimated increase in OCM with bicalutamide at 12-year was 9.4% (95% CI, 2.2%-16.7%). Similar OCM hazard estimates were derived from a cause-specific model (HR, 1.85; 95% CI, 1.12-3.07; *P* = .02). On multivariable analysis, there was no significant difference in OS or DM between treatment assignment. Men treated with antiandrogen therapy had significantly higher OCM (sHR, 1.84; 95% CI, 1.11-3.07; *P* = .02; **Table 2**) and similar findings were confirmed in a cause-specific model (HR, 1.72; 95% CI, 1.03-2.87; *P* = .04).

The primary increase in OCM was noted in those with the lowest PSA. A total of 148 men had entry PSA of 0.2 to 0.3 ng/mL. This subgroup had a 4-fold increased rate of OCM with bicalutamide (sHR, 4.14; 95% CI, 1.57-10.9; *P* = .003) (**Figure 3**). The 12-year OS was 13.3% lower (70.9%; 95% CI, 60.5%-82.9% vs 84.2%; 95% CI, 76.0%-93.2%; *P* = .06; eFigure 4 in Supplement 2). The interaction test between pre-SRT PSA and OCM, however, did not yield statistically significant results.

Late SRT (PSA 0.61-1.5)

A total of 253 men had entry PSA levels of 0.61 to 1.5 ng/mL. Similar to patients with PSA levels greater than 1.5 ng/mL, patients receiving bicalutamide had significant improvement in OS (HR, 0.61; 95% CI, 0.39-0.94; *P* = .02) with an associated reduction in DM, although not reaching statisical signifi-

cance (HR, 0.69; 95% CI, 0.43-1.12; P = .14; eFigure 5 in Supplement 2). Sensitivity analysis of PSA cut points by quintile and using continuous PSA demonstrated similar findings of PSA as a predictive biomarker (eFigures 6 and 7 in Supplement 2).

Grade 3-5 Cardiac and Neurologic Events

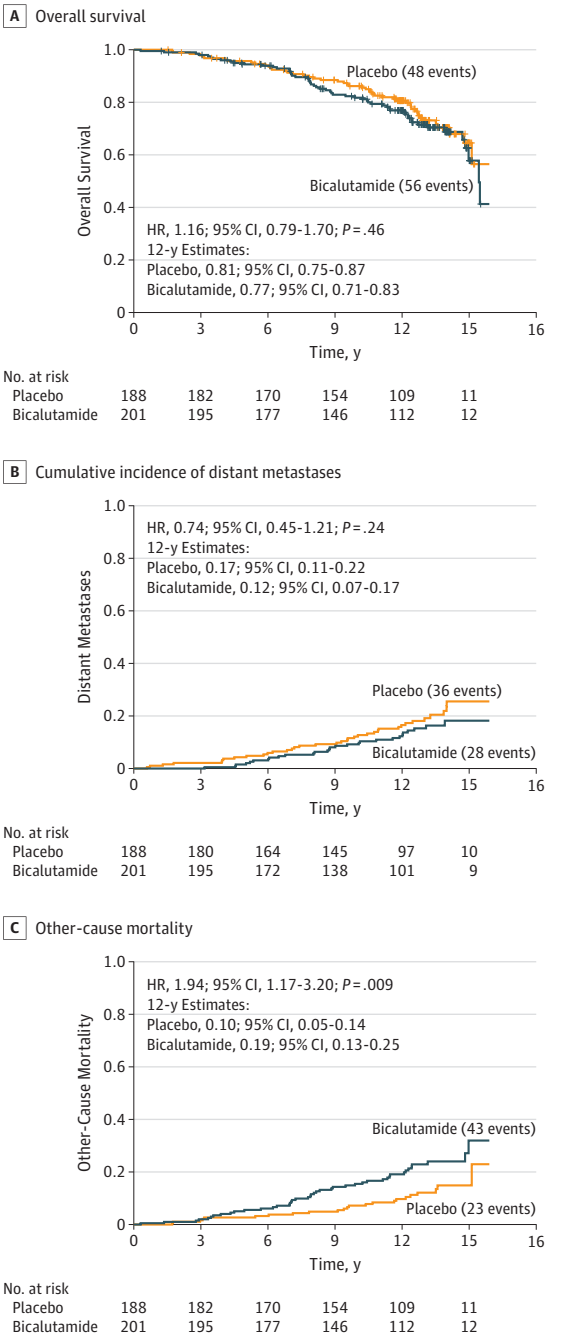
In the total cohort, 23 grades 3 to 5 cardiac events and 12 neurologic events were observed during follow-up; 17 of 389 (4.6%) vs 6 of 373 (1.6%) cardiac events and 8 of 387 (2.1%) vs 4 of 373 (1.1%) neurologic events occurred in the bicalutamide vs placebo treatment assignments, respectively. Two patients assigned bicalutamide had grade 5 cardiac toxic effects, although attribution is not known. The odds of combined grades 3 to 5 cardiac and neurologic events were significantly increased in the bicalutamide assignment for the overall cohort (OR, 2.48; 95% CI, 1.16-5.74; P = .02), the PSA of 1.5 ng/mL or higher stratum (OR, 2.96; 95% CI, 1.22-8.26; P = .02), and those receiving early SRT at PSA levels of 0.6 ng/mL or lower (OR,3.57; 95% CI, 1.09-15.97; P = .05). Other grades 3 to 5 toxic effects, including late GI or GU toxic effects, were not significantly different by treatment assignment (eFigure 8 in Supplement 2).

Discussion

The RTOG 9601 trial enrolled 760 patients with biochemically recurrent prostate cancer and demonstrated that the addition of 2 years of high-dose bicalutamide improved OS compared with placebo. In this report, we demonstrate that pre-SRT PSA was both prognostic for OS and predictive of net benefit of long-term antiandrogen therapy. In the large subgroup of men in the PSA stratum of 1.5 ng/mL or lower, there was not a statistically significant OS benefit with near identical between-group 12-year estimates. In subsequent post hoc analyses, those with PSA levels of 0.6 ng/mL or lower did not appear to benefit from antiandrogen therapy with the suggestion of worse OCM.

Caution is warranted with any subgroup analysis, planned or unplanned, because they may be underpowered with bias resulting toward the null. Sun and colleagues[20] developed updated criteria to assess the credibility of subgroup analyses. When the RTOG 9601 clinical trial was designed, it was less common for subgroups to have formalized statistical hypotheses stating the direction of effect. For this reason, 2 of the 10 criteria (a priori hypotheses and direction of effect) will not be met for any subgroup analyses of the RTOG 9601 clinical trial. The current subgroup analysis met all other 8 criteria. In design, PSA was measured at baseline prior to randomization, was a stratification variable, and this subgroup was 1 of a small number of hypotheses tested. In analysis, there was a significant interaction test for OS, the effect was independent of other variables, and the size of the subgroup was large (85% of participants). In context, there was significant interaction test for closely related end points (DM) that can explain the benefit observed. Moreover, the interaction has been demonstrated across other studies. In the GETUG-16 trial, a relative and absolute difference in progression-free survival (PFS) benefit of ADT was noted by pre-SRT PSA.[12] There is also indirect evidence that supports a biologically rational explanation for the observed association; men with a higher pre-SRT PSA have a higher probability of harboring both regional and distant metastatic disease, a disease state in which hormone therapy has proven benefit.[21] Thus, the credibility of this subgroup analysis should not be dismissed.

Figure 2. Outcomes for Men at or Below the Median Presalvage Radiotherapy Prostate-Specific Antigen (PSA) Level of 0.60 ng/mL by Treatment Arm



HR indicates hazard ratio. A, Overall survival; B, cumulative incidence of distant metastasis; and C, other-cause mortality for patients at or below the median trial PSA levels by treatment arm.

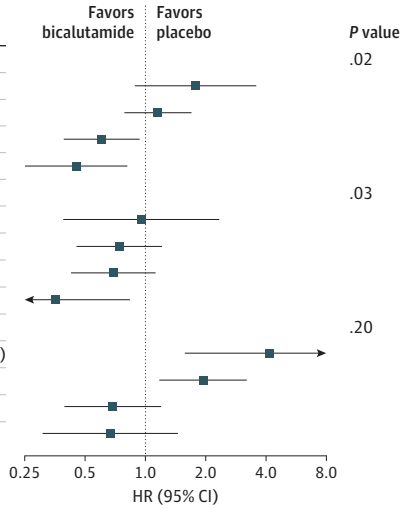
Table 2. Multivariable Analysis for Overall Survival, Distant Metastasis, and Other-Cause Mortality for Patients With PSA Levels of 0.2 to 0.6 ng/mL

	Overall survival (n = 383)		Distant metastasis (n = 383)		Other-cause mortality (n = 383)	
Variable	HR (95% CI)	*P* Value	sHR (95% CI)	*P* Value	sHR (95% CI)	*P* Value
Bicalutamide vs placebo	1.07 (0.72-1.59)	.73	0.69 (0.43-1.13)	.14	1.87 (1.12-3.12)	.02
Age	1.10 (1.06-1.13)	<.001	1.00 (0.96-1.04)	.91	1.12 (1.07-1.16)	<.001
Gleason score						
7 vs ≤6	1.09 (0.68-1.75)	.71	1.47 (0.75-2.87)	.26	0.86 (0.49-1.49)	.59
8-10 vs ≤6	1.91 (1.09-3.34)	.02	2.68 (1.27-5.64)	.01	0.77 (0.38-1.58)	.48
T2 vs T3	0.91 (0.58-1.43)	.69	0.71 (0.37-1.38)	.31	1.20 (0.71-2.03)	.49
Margin, positive vs negative	1.02 (0.64-1.65)	.92	0.47 (0.26-0.82)	.01	1.24 (0.67-2.32)	.49
Nadir PSA, <0.5 vs ≥0.5 ng/mL	1.74 (0.63-4.83)	.29	1.88 (0.64-5.57)	.25	2.80 (1.11-7.08)	.03

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen; sHR, subdistribution hazard ratio.

Figure 3. Forest Plot of Overall Survival, Distant Metastasis, and Other-Cause Mortality by Presalvage Radiotherapy PSA Level

End point, PSA	Bicalutamide incidence/N	Placebo incidence/N	12-Year absolute difference bicalutamide vs placebo (CI 95%)	HR (95% CI)	*P* value
Overall survival					.02
0.20-0.30	20/74	13/74	-0.13 (-0.27 to 0.01)	1.78 (0.88-3.57)	
0.20-0.60	56/201	48/188	-0.04 (-0.12 to 0.05)	1.16 (0.79-1.70)	
0.61-1.50	34/128	50/125	0.09 (-0.03 to 0.20)	0.61 (0.39-0.94)	
≥1.51	18/55	33/63	0.25 (0.07 to 0.42)	0.45 (0.25-0.81)	
Distant metastasis					.03
0.20-0.30	9/74	10/74	0.01 (-0.10 to 0.13)	0.95 (0.39-2.34)	
0.20-0.60	28/201	36/188	-0.04 (-0.12 to 0.03)	0.74 (0.45-1.21)	
0.61-1.50	28/128	37/125	-0.10 (-0.21 to 0.01)	0.69 (0.43-1.12)	
≥1.51	7/55	20/63	-0.18 (-0.33 to -0.03)	0.36 (0.15-0.84)	
Other-cause mortality					.20
0.20-0.30	17/74	5/74	0.18 (0.06 to 0.31)	4.14 (1.57-10.89)	
0.20-0.60	43/201	23/188	0.09 (0.02 to 0.17)	1.94 (1.17-3.20)	
0.61-1.50	21/128	29/125	-0.03 (-0.13 to 0.08)	0.69 (0.39-1.20)	
≥1.51	10/55	15/63	-0.09 (-0.23 to 0.06)	0.67 (0.31-1.45)	



HR indicates hazard ratio; PSA, prostate-specific antigen.

The GETUG-16 randomized clinical trial tested whether addition of a short-term LHRH agonist (subcutaneous injection of goserelin for 6 months duration) to SRT is associated with improved outcomes.[12] Although the primary end point was PFS, sample size was expanded (n = 743) to increase power to detect a treatment effect on OS. There are notable differences between the GETUG-16 and RTOG 9601 clinical trials,[22,23] with more patients at favorable risk in the former. All patients in the GETUG-16 trial had an undetectable PSA post-RP, whereas 44% of those in the RTOG 9601 clinical trial had a nadir PSA level higher than 0.1 ng/mL. The upper limit of PSA in the GETUG-16 trial was 2.0 ng/mL compared with 4.0 ng/mL in the RTOG 9601 trial; approximately 20% in the GETUG-16 trial had an entry PSA level higher than 0.5 ng/mL compared with 60% in the RTOG 9601 trial. Despite these differences, our analysis of the RTOG 9601 trial of men within the PSA level of 1.5 ng/mL or lower stratum demonstrates consistent results with the GETUG-16 trial. The recent GETUG-16 trial update showed a metastasis-free survival (MFS) improvement with ADT.[24] Although MFS data was retrospectively collected in GETUG-16, the effect size on DM (HR, 0.73; 95% CI, 0.54-0.98) was very similar to our results in men with PSA levels of 1.5 ng/mL or lower (HR, 0.72; 95% CI, 0.51-1.01). Yet neither trial demonstrated a significant improvement in OS for patients with PSA levels of 2.0 or lower and 1.5 ng/mL or lower in the GETUG-16 and RTOG 9601 trials, respectively. Thus, there is evidence from more than 1400 patients from 2 randomized clinical trials with 9 to 13 years of follow-up that neither short- or long-term hormone therapy improves OS with early SRT. The RTOG 0534 trial was also recently presented in abstract. With shorter follow-up (5 years), no significant improvement in DM or OS from the addition of short-term ADT to SRT (n = 1159 in arms 1 and 2) is evident to date.[13]

Pre-SRT PSA is not only a predictive biomarker to identify benefit from antiandrogen therapy, but it also is useful in a discussion of potential harm. The RTOG 9601 trial has the longest follow up of any randomized clinical trial of SRT with

or without hormone therapy. We found that not only was there an increase in combined cardiac and neurologic grades 3 to 5 events, but there was also an increased risk of OCM in those assigned to early SRT with antiandrogen therapy. Although this may be specific to high-dose, long-term antiandrogen treatment (150 mg bicalutamide), LHRH agonist treatments have also been associated with cardiac events, dementia, metabolic syndrome, and fracture risk.[9,25,26] In localized prostate cancer, a Spanish randomized clinical trial[27] demonstrated that 28 months vs 4 months of LHRH agonist treatment was associated with increased cardiac events at a median follow-up of 5 years. In men receiving early SRT, a population that appears to derive minimal oncologic benefit from hormone therapy, the morbidity of long-term antiandrogen treatment may have been more apparent given the mature follow-up of the RTOG 9601 trial.

This report is timely. The American Urological Association/American Society for Radiation Oncology guidelines previously reserved endorsement of hormone therapy use with SRT until an OS benefit was identified.[28] The recently updated guidelines provide grade A recommendation to offer hormone therapy for patients receiving SRT based on evidence available through 2017, while acknowledging that ongoing (and then as yet unpublished) research may help personalize this guideline.[29,30] The present analysis and the subsequent update of the GETUG-16 clinical trial suggest that hormone therapy does not improve OS when early SRT is employed. We recommend including these additional findings in the shared decision-making discussion of benefits and potential risks of hormone treatment in these patients.

Limitations

This study is not without limitations. Although our study meets nearly all credibility criteria proposed by Sun et al,[11] subgroup analyses can be underpowered and remain subject to potential bias, particularly where subgroups have fewer than 250 patients per group. Yet, pre-SRT PSA as a continuous variable has strong association with treatment effect. To provide confirmatory evidence, especially in patients with PSA levels of of 0.2 to 0.3 ng/mL, we encourage other investigators to evaluate hormone therapy treatment effects in planned subsets, such as in the GETUG-16, RTOG 0534, and the as yet unreported Radiotherapy and Androgen Deprivation in Combination after Local Surgery (NCT00949962) randomized clinical trials.[31] Although the odds of clinically important cardiac and neurologic toxic effects were increased with bicalutamide, we did not have access to time-to-event data, which limits firm conclusions. In addition, the other cause of death was unknown in a substantial percentage of men, so specific causality cannot be addressed. Moreover, it is unknown whether these results apply to men receiving lower doses or shorter durations of bicalutamide, other types of hormone therapy (such as LHRH agonists/antagonists), or next-generation androgen-signaling inhibitors. Finally, molecular imaging tests now provide a more sensitive assessment of disease status in patients with a detectable PSA level after definitive treatment.[32] Future trials are needed to define the benefit of radiation and hormone therapy based on the location and extent of disease.

Conclusions

Patients with pre-SRT PSA levels higher than 1.5 ng/mL derived a large OS benefit from the addition of 2 years of antiandrogen therapy to SRT, and hormone therapy should be standard of care for these men. In subgroup analysis by the PSA stratification variable, we could not identify a statistically significant improvement in OS from antiandrogen therapy in the PSA levels of 1.5 ng/mL or lower stratum. This was most striking for men with PSA levels of 0.6 ng/mL or lower, where significant improvement in OS was not observed. These men had a more than 3-fold increase in odds of grades 3 to 5 neurologic and cardiac events and a 2-fold increased hazard of OCM from long-term antiandrogen treatment. Pre-SRT PSA can serve as both a prognostic and predictive serum biomarker to guide hormone therapy use with SRT. Randomized clinical trials are ongoing to determine if molecular biomarkers can further help personalize hormone therapy use in men receiving early SRT (NCT03371719).

ARTICLE INFORMATION

Accepted for Publication: January 9, 2020.

Published Online: March 26, 2020. doi:10.1001/jamaoncol.2020.0109

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Obtained funding: Shipley, Spratt.
Administrative, technical, or material support: Dess, Den, Hall, Gharzai, Jaworski, Schaeffer, Lee, Rosenthal, Michalski, Dignam, Feng, Spratt.
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Conflict of Interest Disclosures: Dr Kishan received honoraria and consulting fees from Varian Medical Systems, Inc, ViewRay, Inc, and Intelligent Automation, Inc. Dr Kishan has also served on an advisory board for Janssen, Inc, and received research funding from the Prostate Cancer Foundation. Dr Zumsteg reported personal fees from EMD Serono and Scripps Proton Therapy Center outside the submitted work. Dr Den reported grants from GenomeDx during the conduct of the study and personal fees from Alpha Tau outside the submitted work. Dr Hall reported institutional research support from Elekta AB, Stockholm, Sweden outside the submitted work. Dr Sartor reported personal fees from Advanced Accelerator Applications and Astellas; grants and personal fees from AstraZeneca and Bayer; personal fees from Bellicum, Blue Earth Diagnostics, Inc; personal fees from Bravarin Nordic, Bristol Myers Squibb, Clovis, and Constellation; grants and personal fees from Dendreon, personal fees from EMD Serono, personal fees from Myriad, personal fees from Noxopharm, personal fees from Progenics, grants and personal fees from Jennsen, personal fees from Myovant, personal fees from Pfizer, grants and personal fees from Sanofi, grants from Endocyte, Innocrin, Invitae, and SOTIO outside the submitted work; in addition, Dr Sartor had a patent to 7 166 691 issued and licensed. Dr Nguyen reported grants and personal fees from Bayer, personal fees from Boston Scientific, grants and personal fees from Janssen, personal fees from Dendreon, personal fees from Ferring, personal fees from Cota, grants and personal fees from Astellas, personal fees from Blue Earth, and personal fees from Augmenix outside the submitted work. Dr Michalski reported grants from NCI funded RTOG/NRG grant during the conduct of the study; personal fees from Merck, inc; and personal fees from Boston Scientific, inc; outside the submitted work. Dr Zietman reported a stipend as editor in chief of *International Journal of Radiation Oncology Biology Physics* from Elsevier publishers. Dr Sandler reported personal fees from Janssen and stock interests in Radiogel outside the submitted work; and Former chair, NRG Oncology GU Cancer Committee Member, ASTRO Board of Directors. Dr Efstathiou reported personal fees from Blue Earth Diagnostics, Taris Biomedical, Boston Scientific, AstraZeneca, Bayer Healthcare, Genentech/Roche, and EMD Serono/Pfizer, and personal fees from Janssen outside the submitted work. Dr Feng reported personal fees from Janssen, Sanofi, Blue Earth Diagnostics, Astellas, Clovis, Genentech, Bayer, and Celgene, nonfinancial support from PFS Genomics, Nutcracker Therapeutics, and Serimmune outside the submitted work. Dr Spratt reported personal fees from Janssen and personal fees from Blue Earth outside the submitted work. No other disclosures were reported.

Disclaimer: All analyses and conclusions in this manuscript are the sole responsibility of the authors and do not necessarily reflect the opinions or views of the clinical trial investigators, the NCTN, or the NCI.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank the Prostate Cancer Foundation (DES), the Prostate Cancer NIH SPORE (DES, P50CA186786), and the Department of Defense (DES, PC151068). Additionally, we are thankful for the support of the NCI in conducting this randomized clinical trial, U10CA180868 (NRG Oncology Operations), and U10CA180822 (NRG Oncology Statistics and Data Management Center).

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