VOLUME 27 · NUMBER 35 · DECEMBER 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Evaluating the Combined Effect of Comorbidity and Prostate-Specific Antigen Kinetics on the Risk of Death in Men After Prostate-Specific Antigen Recurrence

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Submitted April 13, 2009; accepted June 26, 2009; published online ahead of print at www.jco.org on October 26, 2009.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/09/2735-6000/$20.00

DOI: 10.1200/JCO.2009.23.6067

ABSTRACT

Purpose
We examined whether time-dependent continuous prostate-specific antigen (PSA) velocity at recurrence was associated with all cause mortality (ACM) adjusting for comorbidity levels among men treated with definitive radiation therapy (RT) alone with or without androgen suppression therapy (AST) in the setting of a randomized controlled trial.

Patients and Methods
From 1995 to 2001, 206 men with localized, unfavorable prostate cancer were randomly assigned to receive RT alone or RT and AST combined. Cox multivariate regression analysis was performed to evaluate the relationship between PSA velocity at recurrence and ACM, adjusting for known prostate cancer prognostic factors, including Adult Comorbidity Evaluation 27 comorbidity level.

Results
With a median follow-up of 8.4 years, 89 biochemical recurrences and 74 ACM deaths occurred. Among all patients, higher PSA velocity was associated with increased ACM (hazard ratio [HR], 1.47; 95% CI, 1.07 to 1.44; $P < .001$) after adjusting for age, treatment arm, comorbidity score, and salvage AST. For 89 patients with biochemical recurrence, increasing PSA velocity at recurrence (HR, 1.60; 95% CI, 1.23 to 2.09; $P \leq .001$) and moderate to severe comorbidity score (HR, 7.94; 95% CI, 1.55 to 40.52; $P = .01$) were associated with increased ACM. PSA velocity at recurrence was associated with significantly higher risk of ACM among patients with no or minimal comorbidity ($P < .001$), but not moderate to severe comorbidity ($P = .12$).

Conclusion
Rapid PSA velocity at recurrence is significantly associated with an increased risk of ACM among patients with no or minimal comorbidity but not moderate to severe comorbidity. These findings support judicious use of salvage AST, particularly in men with moderate to severe comorbidities, where prospective surveillance protocols are needed.

J Clin Oncol 27:6000-6005. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Because of the lack of randomized controlled trials (RCTs), the management of biochemical recurrence of prostate cancer after definitive radiation therapy (RT) is not standardized. Although RCTs have established that androgen suppression therapy (AST) in combination with RT confers an overall survival benefit compared with RT alone in management of unfavorable risk prostate cancer[1,2] in the de novo setting, this question remains to be answered in the recurrent setting.

Because of the unclear benefit of AST in this setting and the potential for AST-related adverse effects, many practitioners have concerns about recommending AST to all patients with biochemical recurrence. Additionally, recent studies suggest that AST administration may be associated with an increased risk of fatal and nonfatal cardiovascular events, particularly among older patients with significant comorbidities.[3,4] These data suggest that the addition of AST to RT in definitive treatment of prostate cancer may lead to an improvement in overall survival only among patients with no or minimal comorbidities.[5]

Therefore, with emerging literature demonstrating the risk of AST-related cardiotoxicity,[3,4] it is increasingly important to factor in both baseline patient comorbidity levels and known prostate cancer prognostic factors when selecting appropriate patients for salvage AST treatment.[5] To that end, several parameters have been found to be associated

with worse prostate cancer–specific survival after biochemical recurrence, including shorter time to prostate-specific antigen (PSA) recurrence, higher Gleason score, and faster PSA doubling time.[6,7] Although previous studies have established a significant association of PSA doubling time as a categoric or continuous covariate in predicting prostate cancer–specific mortality,[6,7] no studies to date have examined PSA kinetics as a time-dependent and continuous covariate and its impact on all cause mortality (ACM).

In this study, we examine whether there is independent prognostic value of time-dependent continuous PSA velocity at recurrence in determining the risk of ACM, adjusting for known prognostic factors and comorbidity level among men treated with definitive RT with or without 6 months of AST in an RCT setting.

PATIENTS AND METHODS

Patient Eligibility and Treatment

Between December 1, 1995, and April 15, 2001, 206 patients from six Harvard affiliated hospitals who had been diagnosed using American Joint Committee on Cancer (AJCC, 1992) categories T1b to T2b, NX, M0 for adenocarcinomas of the prostate and who had at least one unfavorable prognostic factor were randomly assigned to receive either 70 Gy three-dimensional conformal radiation therapy alone (n = 104) or in conjunction with 6 months of AST (n = 102). AST included a luteinizing hormone-releasing hormone agonist and the antiandrogen flutamide. Unfavorable prognostic factors considered for trial entry included PSA of more than 10 ng/mL and ≤ 40 ng/mL; a biopsy Gleason score of 7 or higher; radiographic evidence of extracapsular extension; or seminal vesicle invasion on endorectal coil magnetic resonance imaging. The exclusion criteria, registration, randomization, stratification, treatment, and quality assurance guidelines for this study have been previously described.[1]

Adult Comorbidity Evaluation 27

The Adult Comorbidity Evaluation 27 (ACE-27) score is a validated 27-item comorbidity index for cancer patients.[8] Using the ACE-27 index, a comorbidity score was assigned to each patient by one physician (A.V.D.) after thorough review of detailed information of patients' baseline medical conditions and comorbidities, which were collected before trial randomization. The decision to use the ACE-27 index was based on its validation of comorbidities, specifically in the setting of newly diagnosed cancer and the selection of clinically significant comorbidities by experts.[9-11] By applying the ACE-27 index, grades were assigned to diseases of specific conditions according to the degree of organ system decompensation and its prognostic impact (grade 0 = none, grade 1 = minimal, grade 2 = moderate, grade 3 = severe). After classification of the individual comorbid conditions, an overall comorbidity score was assigned based on the highest ranked single ailment. When two or more moderate ailments were present in different organ systems, the overall comorbidity score was designated as severe. Additional information regarding the ACE-27 index can be found at http://oto.wustl.edu/clinepi/calc.html.

Follow-Up

Patients were followed by measuring the PSA level and performing a digital rectal examination every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually thereafter. PSA failure was defined as two consecutive rises of PSA of more than 0.2 ng/mL obtained after a nadir value had been reached. The time of PSA failure was defined as the time of the first PSA rise. At time of PSA failure, patients underwent routine follow-up assessment, computed tomography or magnetic resonance imaging of the pelvis, and a bone scan to evaluate for metastatic disease. On PSA failure, recommendations for PSA levels and follow-up were at the discretion of the treating physician. At PSA levels of approximately 10 ng/mL, salvage AST was recommended for patients in both treatment arms. Patients were followed from the date of random assignment until death or last observation through the prespecified analysis date of January 10, 2008.

Statistical Analysis

The primary end point of the original study was time to PSA failure. However, before the first planned interim analysis, which was to be performed 3 years after completion of accrual, follow-up time was extended to evaluate the prespecified secondary end points of ACM and prostate cancer–specific mortality (PCSM). ACM was analyzed by randomized treatment group. Further stratification by the ACE-27 comorbidity score after random assignment was also analyzed.[8]

Description of Study Cohort at Random Assignment and PSA Recurrence

Descriptive statistics were used to evaluate patient baseline characteristics at study entry. χ^2 analysis was performed to compare the distribution of all but two baseline characteristics for men by comorbidity scores and by treatment arm; Fisher's exact test was used to analyze Eastern Cooperative Oncology Group (ECOG) performance status and AST use.[12] Table 1 summarizes baseline patient and tumor characteristics stratified by treatment arms and comorbidity levels. Nonparametric Wilcoxon test was performed to compare median PSA velocity at recurrence by comorbidity levels and by treatment arm.[13]

Calculation of PSA Velocity

PSA levels were treated with log transformation to ensure normal distribution. For the analysis of all 206 patients, time zero is defined as the date of random assignment. For patients who never experience PSA failure, time-dependent PSA velocity at recurrence is coded as zero for all follow-up time. For patients who develop PSA recurrence, time-dependent PSA velocity at recurrence is defined as the value of PSA velocity obtained using a linear regression of all PSA values during the 12 months before the time of PSA recurrence, which was defined using PSA nadir + 2 ng/mL.[14,14a] From the date of random assignment and before the time of biochemical recurrence, the value of the time-dependent PSA velocity is coded as zero. From the time of PSA recurrence until the end of follow-up for that patient, the value of the time-dependent PSA velocity equals the single value of PSA velocity. Although multiple assessments of PSA are made during follow-up for biochemical recurrence, there is only one value for the variable "time-dependent PSA velocity at recurrence" per patient.

For the subgroup analysis of 88 patients with biochemical recurrence, time zero is defined as time of recurrence. Since all patients in this subgroup experience a biochemical recurrence, PSA velocity at recurrence was not considered a time-dependent variable.

Time to ACM Analyses

Cox regression analyses were used to determine whether PSA velocity at recurrence was associated with the risk of ACM, adjusting for pretreatment PSA level, highest biopsy Gleason score, AJCC tumor category, age at random assignment, treatment arm, and ACE-27 comorbidity score at the time of random assignment.[15] PSA velocity at recurrence was run as both a continuous variable and a categoric variable (dichotomized as > third quartile *v* ≤ third quartile). Age and pretreatment PSA levels were treated as continuous variables. Gleason score (Gleason 7 *v* Gleason 6 or less, Gleason 8-10 *v* Gleason 6 or less), AJCC tumor category (T2 *v* T1), treatment arm (RT alone *v* RT and AST combined), and comorbidity scores (ACE-27 comorbidity scores 2 and 3 [high] *v* ACE-27 comorbidity scores 0 and 1 [low]) were treated as categoric variables with established clinical cut points. Significant interaction between comorbidity score and treatment arm was identified in a prior secondary analysis of these patients[5]; thus, an interaction term was included in the multivariate model. To adjust for the potential effect of timing of biochemical recurrence, a time-dependent, continuous covariate of time to PSA failure was included within a multivariate model. Additionally, to adjust for the use of AST delivered for PSA failure, the time-dependent covariate AST2 was included. Time-dependent salvage AST was defined as the actual duration of salvage AST; in this case, time zero is defined as the date of initiation of salvage AST. The value of the time-dependent covariate AST2 is coded as zero for any

Table 1. Clinical Characteristics and Treatment Stratification at Random Assignment (N = 206)

Baseline Clinical Characteristic	RT (n = 104)					RT and AST (n = 102)				
	No or Minimal Comorbidity (n = 79)		Moderate or Severe Comorbidity (n = 25)			No or Minimal Comorbidity (n = 78)		Moderate or Severe Comorbidity (n = 24)		
	No. of Patients	%	No. of Patients	%	*P*	No. of Patients	%	No. of Patients	%	*P*
Age, years										
Median	73		74		.52	72		72		.97
Range	51-81		61-81			49-82		61-79		
≤ 60	4	5	0	0	.60	2	3	0		.92
61-70	18	23	7	28		22	28	6	25	
71-75	31	39	10	40		35	45	14	58	
76-80	25	32	6	24		17	22	4	17	
> 80	1	1	2	8		2	3	0		
Baseline PSA, ng/mL										
Median	11.2		10.8		.37	11.5		10.0		.54
Range	3.1-40.0		0.9-24.8			3.1-36.0		1.3-21.1		
Gleason score										
5-6	21	27	6	24	.09	26	33	4	17	.17
7	50	63	11	44		42	54	16	67	
8-10	8	10	8	32		10	13	4	17	
AJCC tumor category										
T1b	1	1	1	4	.54	1	1	1	4	.14
T1c	33	42	8	32		46	59	8	33	
T2a	20	25	6	24		13	17	7	29	
T2b	25	32	10	40		18	23	8	33	
ACE-27 comorbidity score										
0 (none)	68	86	NA		NA	67	86	NA		NA
1 (minimal)	11	14	NA			11	14	NA		
2 (moderate)	NA		22	88		NA		21	88	
3 (severe)	NA		3	12		NA		3	12	
ECOG performance status										
0	76	96	25	100	1.0*	75	96	20	83	.05*
1	3	4	0			3	4	4	17	
Treatment stratification										
PSA of 20-40 ng/mL	11	14	2	8	.75	11	14	1	4	.78
Gleason score of 7-10	47	59	17	68		44	56	20	83	
PSA of 10-20 ng/mL and Gleason score of 5-6	19	24	5	20		22	28	2	8	
Low-risk and endorectal MRI evidence of extracapsular extension or seminal vesicle invasion	2	3	1	4		1	1	1	4	
AST use for PSA failure										
Orchiectomy	4	5	0		1.0*	0		1	4	.15*
LHRH agonist	22	28	4	16		11	14	1	4	

Abbreviations: RT, radiation therapy; AST, androgen suppression therapy; PSA, prostate-specific antigen; AJCC, American Joint Committee on Cancer; ACE-27, Adult Comorbidity Evaluation 27; NA, not applicable; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; LHRH, luteinizing hormone-releasing hormone.

*Fisher exact test was performed for ECOG performance status and AST use.

time from the date of random assignment to the date of initiation of salvage AST. In addition, a patient followed for an additional 2 years after salvage AST would have the time-dependent salvage AST covariate coded as 1 month at 1 month after AST initiation, as 6 months at 6 months after AST initiation, and as 2 years at the time of last follow-up, being 2 years in this case. For patients who did not receive salvage AST, time-dependent salvage AST was coded as zero. Unadjusted and adjusted hazard ratios (HRs) were calculated for all covariates using the Cox proportional hazards model with associated 95% CIs and *P* values.

Estimates of ACM

For the purpose of illustration, the impact of PSA velocity on estimates of ACM for each comorbidity subgroup was displayed in Figures 1 and 2. On the basis of a previous study of pretreatment PSA velocity and the risk of ACM following RT,[16] the upper quartile was selected as the cut point for PSA velocity in this study. ACM was calculated from the date of random assignment in the analysis of the entire patient cohort and was calculated from the date of biochemical failure in subgroup analysis of the patients with biochemical recurrence. The Kaplan-Meier method[17] was used to estimate and characterize overall survival, and ACM (%) was defined as 1 minus overall survival (%). The threshold for statistical significance was a two-sided *P* value of less than .05. In estimating ACM stratified by PSA velocity among men stratified by comorbidity levels, a Bonferroni correction was used to adjust for multiple comparisons and thus, a two-sided *P* value of less than .025 was deemed statistically significant for this

Table 2. Summary of Patient Characteristics at Time of Recurrence

Characteristic	Patients No.	Patients %	Median PSA Velocity (log ng/mL/yr)	IQR
Entire patient cohort	89	100	0.65	0.32-1.11
Treatment arm				
RT alone	62	70	0.61	0.28-1.11
RT and AST combined	27	30	0.72	0.37-1.16
Comorbidity score				
Low comorbidity score (0-1)	74	83	0.64	0.31-1.23
High comorbidity score (2-3)	15	17	0.68	0.43-1.05

Abbreviations: PSA, prostate-specific antigen; IQR, interquartile range; RT, radiation therapy; AST, androgen suppression therapy.

analysis.[14,14a] All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Descriptive Characteristics of the Study Cohort at Random Assignment and PSA Recurrence

Between December 1, 1995, and April 15, 2001, 206 patients were enrolled onto the study, including 104 patients assigned to receive RT alone and 102 patients assigned to receive RT and 6 months of AST. The two groups of patients were well balanced with respect to all pretreatment characteristics including age, baseline PSA level, Gleason score, AJCC tumor category, and ECOG performance status. The distribution of comorbidity scores (assigned postrandomization) was also similar between the treatment arms (Table 1). Specifically, at the time of random assignment, 79 (38%) and 78 (38%) patients with low comorbidity scores and 25 (12%) and 24 (12%) patients with high comorbidity scores were randomly assigned to receive RT alone versus RT and AST, respectively.

As of January 10, 2008, 89 (43%) of 206 patients developed biochemical recurrences, including 62 patients randomly assigned to receive RT alone and 27 patients assigned to receive RT and AST combined. The median age at PSA failure was 76.2 years (range, 57.5 to 87.8 years). There was no significant difference in median PSA velocity at recurrence by comorbidity levels ($P = .95$) or by treatment arm ($P = .29$). In total, 43 (48%) of these patients subsequently received salvage AST. Table 2 summarizes median PSA velocity of the 89 patients at recurrence with respect to treatment arm and comorbidity levels.

Time to ACM Analyses

With a median follow-up of 8.4 years (interquartile range, 7.2 to 10.2 years), there were 74 deaths (36%) among the 206 men. A higher PSA velocity at recurrence remained significantly associated with increased ACM (HR, 1.47; 95% CI, 1.24 to 1.75; $P < .001$) after adjusting for advanced age (HR, 1.06; 95% CI, 1.003 to 1.11; $P = .04$), random assignment to the RT alone arm (HR, 2.37; 95% CI, 1.18 to 4.76; $P = .02$), high comorbidity score (HR, 12.73; 95% CI, 5.91 to 27.41; $P \leq .001$), and treatment with salvage AST at recurrence (HR, 1.24; 95% CI, 1.07 to 1.44; $P = .004$; Table 3). As demonstrated in earlier studies,[5] there was a significant interaction between treatment arm and comorbidity score ($P = .007$). For the 89 patients with biochemical failure, only increasing PSA velocity at recurrence (HR, 1.60; 95% CI, 1.23 to 2.09; $P < .001$) and moderate to severe comorbidity score (HR, 7.94; 95% CI, 1.55 to 40.52; $P = .01$) remained significantly associated with an increased risk of ACM (Table 4).

Estimates of ACM Stratified by PSA Velocity and Comorbidity Scores

Among patients with low comorbidity scores, men with a PSA velocity in the upper quartile had significantly higher rates of ACM

Table 3. Risk of All Cause Mortality Based on Clinical Factors at Random Assignment and at the Time of PSA Recurrence (N = 206)

Clinical Factor	Unadjusted HR	95% CI	P	Adjusted HR	95% CI	P
Age, years (at random assignment, continuous)	1.07	1.02 to 1.13	.006	1.06	1.003 to 1.11	.04
Treatment arm						
RT and AST	1.00	—		1.00	—	
RT alone	1.62	1.02 to 2.58	.04	2.37	1.18 to 4.76	.02
Log PSA	1.31	0.92 to 1.86	.132	1.12	0.80 to 1.57	.51
Gleason score						
≤ 6	1.00	—		1.00	—	
7	1.23	0.70 to 2.18	.48	0.80	0.43 to 1.49	.48
8-10	2.90	1.49 to 5.65	.002	1.52	0.74 to 3.13	.25
Tumor category						
T1	1.00	—		1.00	—	
T2	1.47	0.92 to 2.34	.11	0.98	0.59 to 1.62	.94
ACE-27 comorbidity score						
No or minimal	1.00	—		1.00	—	
Moderate to severe	3.53	2.22 to 5.61	< .001	12.73	5.91 to 27.41	< .001
Treatment arm comorbidity*	0.15	0.06 to 0.40	< .001	0.17	0.06 to 0.48	< .001
Time-dependent PSA velocity	1.59	1.38 to 1.82	< .001	1.47	1.24 to 1.75	< .001
Time-dependent salvage AST	1.38	1.22 to 1.56	< .001	1.24	1.07 to 1.44	.004

Abbreviations: PSA, prostate-specific antigen; HR, hazard ratio; RT, radiation therapy; AST, androgen suppression therapy; ACE-27, Adult Comorbidity Evaluation 27.
*Interaction term.

Table 4. Risk of All Cause Mortality Based on Clinical Factors at Randomization and the Time of PSA Recurrence for 89 Men Who Experienced PSA Recurrence

Clinical Factor	Adjusted HR	95% CI	*P*
Age, years (at time of PSA failure, continuous)	1.01	0.93 to 1.10	.81
Treatment arm			
RT and AST	1.00	—	
RT alone	2.09	0.74 to 5.92	.16
Log PSA	1.08	0.59 to 1.98	.80
Gleason score			
≤ 6	1.00	—	
7	1.26	0.42 to 3.75	.68
8-10	2.67	0.78 to 9.17	.12
Tumor category			
T1	1.00	—	
T2	1.15	0.50 to 2.65	.74
ACE-27 comorbidity score			
No or minimal	1.00		
Moderate or severe	7.94	1.55 to 40.52	.01
Treatment arm comorbidity*	0.17	0.02 to 1.31	.09
Time to PSA failure (continuous)	1.21	0.89 to 1.65	.22
PSA velocity (continuous)	1.60	1.23 to 2.09	< .001
Time-dependent salvage AST	1.09	0.79 to 1.49	.60

Abbreviations: PSA, prostate-specific antigen; HR, hazard ratio; RT, radiation therapy; AST, androgen suppression therapy; ACE-27, Adult Comorbidity Evaluation 27.
*Interaction term.

compared with patients with a lower PSA velocity ($P < .001$; Fig 1). In contrast, among patients with high comorbidity scores, there was no significant difference in ACM in patients with a PSA velocity in the upper quartile compared with patients having a lower PSA velocity level ($P = .12$; Fig 2).

DISCUSSION

Using data from a large, multicenter, prospective RCT with long-term follow-up, we found that an increasing PSA velocity at recurrence is

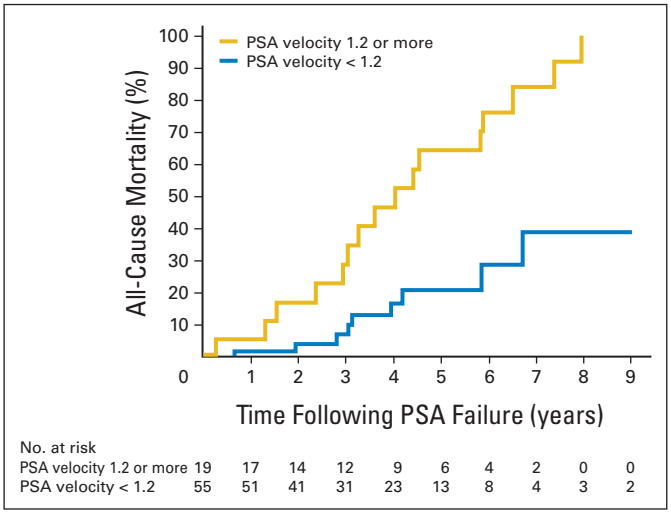

Fig 1. Estimates of all cause mortality stratified by the prostate-specific antigen (PSA) velocity value at the time of PSA recurrence in men with no or minimal comorbidity. Statistical significance is defined as $P < .025$.

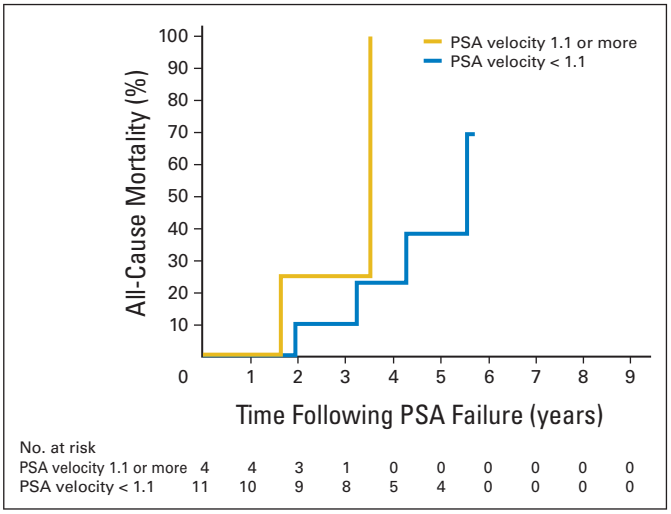

Fig 2. Estimates of all cause mortality stratified by the prostate-specific antigen (PSA) velocity value at the time of PSA recurrence in men with moderate or severe comorbidity. Statistical significance is defined as $P < .025$.

significantly associated with a higher risk of ACM (HR, 1.47; 95% CI, 1.24 to 1.75; $P < .001$) among patients with unfavorable risk prostate cancer treated with definitive RT; moreover, the statistical and clinical significance of this finding is seen only in men with no or low comorbidities. Although previous studies had established shorter PSA doubling time as a significant predictor of higher PCSM,[6,7] this is the first study to demonstrate that time-dependent PSA velocity at recurrence is a predictor for ACM after adjusting for known prostate cancer prognostic factors. By examining PSA velocity stratified by patient comorbidity levels, this study provides evidence that PSA velocity at time of recurrence is prognostic in men with a low comorbidity score ($P < .001$) but not in men with a high comorbidity score ($P = .12$).

Our study also demonstrates that because of competing risks, men with high comorbidity scores were less likely than men with low comorbidity scores to develop PSA failure (32% *v* 47%, respectively). If however, men with high comorbidity scores were to develop PSA failure, their PSA velocity was found to be no different than that in men with low comorbidity scores (0.68 *v* 0.64; $P = .95$), confirming that aggressiveness of prostate cancer at time of recurrence is unrelated to the patient's comorbidity at random assignment.

These findings support the growing body of literature that highlights the importance of baseline patient comorbidity assessment in estimating an individual's risk of biochemical recurrence and life expectancy from prostate cancer and/or competing causes of death. Accurately identifying individuals who have sufficient life expectancy to warrant aggressive prostate cancer treatment can help in development of an optimal prostate cancer treatment plan for the individual patient.[5,18] In patients diagnosed with cancers with a long natural history, as in prostate cancer, competing causes of death need to be considered, especially for patients with moderate and severe comorbidities.

In 2008, D'Amico et al[5] demonstrated that among men with moderate to severe comorbidity, there was no significant difference in ACM between those randomly assigned to RT compared with those randomly assigned to RT and AST combined (13 *v* 19 deaths; HR, 0.54; 95% CI, 0.27 to 1.10; $P = .08$) potentially due to the significant

interaction between comorbidity score and treatment. In combination with other recent studies that provide evidence of increased risk of myocardial infarction in older patients with AST administration,[3,4] these findings by D'Amico et al suggest that pre-existing comorbid conditions may potentially increase the risk of treatment-related, and particularly AST-related, complications.[5] Our current results build on these earlier findings and provide evidence of the importance of comorbidity evaluation in determining ACM in the recurrent setting.

The clinical significance of our findings is that men with high comorbidity scores who experience PSA failure may be excellent candidates for surveillance studies with regular PSA and radiologic imaging because of the high risk of competing causes of death, low risk of prostate cancer–related death, and the potential for increased toxicity from AST use. In contrast, in men with low comorbidity scores, higher PSA velocity at recurrence is predictive of increased risk of ACM. Along with higher Gleason score and shorter time to PSA failure, which have been shown in prior studies to be associated with greater PCSM,[6,7] patients with no to minimal comorbidities who present with high PSA velocity at recurrence should be considered for aggressive salvage therapy, including potential addition of AST.

This study has several potential limitations. First, because this study was a secondary analysis of a prospective randomized trial, our results are hypothesis-generating and should be confirmed in a large randomized trial. That trial would assesses the impact of salvage AST on ACM among patients with biochemical recurrence following definitive treatment using a prerandomization stratification powered to examine the effect of salvage AST on low- and high-comorbidity-level subgroups where comorbidity is defined using a validated index such as the ACE-27. Second, more studies are needed to better delineate which specific comorbidities are most significantly associated with shortened life expectancy in men receiving AST. Finally, studies should be performed to explore health-related quality of life outcomes, which are particularly relevant among patients who may potentially receive salvage AST with a lack of definite improvement in outcome.

In conclusion, our study demonstrates that rapid PSA velocity at recurrence is significantly associated with an increased risk of ACM among patients with low comorbidity scores but not among patients with high comorbidity scores because there is a substantial risk of competing causes of death. These findings support judicious use of salvage AST, particularly in men with moderate to severe comorbidities, where prospective surveillance protocols are needed. In addition, further study in the setting of prospective RCTs with prerandomization stratification by comorbidity level that are powered to evaluate the impact of salvage AST on ACM in each of these comorbidity subgroups is needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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