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ORIGINAL REPORT

Risk of Prostate Cancer Recurrence in Men Treated With Radiation Alone or in Conjunction With Combined or Less Than Combined Androgen Suppression Therapy

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ABSTRACT

Purpose
We determined the risk of recurrence in men enrolled on a randomized trial for prostate cancer who were treated with radiation therapy (RT) alone or in conjunction with combined or less than combined androgen suppression therapy (AST).

Patients and Methods
Between 1995 and 2001, 206 men with localized but unfavorable-risk adenocarcinoma of the prostate were randomly assigned to receive RT or RT and AST, which was defined as 6 months of both a luteinizing hormone-releasing hormone agonist and an antiandrogen. A post–random assignment hypothesis that was generated by multivariable Cox regression analyses was used to evaluate whether the risk of prostate-specific antigen (PSA) recurrence was significantly associated with months of antiandrogen use; regression analysis adjusted for known prognostic factors, comorbidity score, and medications that can elevate liver function tests sufficiently to necessitate discontinuation of the antiandrogen.

Results
After a median follow-up of 8.2 years (interquartile range,7.0 to 9.5 years), 81 men sustained PSA recurrence. An increasing PSA level ($P < .001$); Gleason score of 8, 9, or 10 ($P < .001$); and clinical category T2 disease ($P = .005$) were significantly associated with an increased risk of recurrence. However, recurrence risk was significantly decreased (adjusted hazard ratio, 0.81; 95% CI, 0.72 to 0.92; $P = .001$) with each additional month of antiandrogen use after analysis was adjusted for these known prognostic factors.

Conclusion
Men with localized but unfavorable-risk prostate cancer who were treated with RT and 6 months of planned combined AST appear to have an increased risk of recurrence when treated with less than as compared with 6 months of the antiandrogen.

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INTRODUCTION

Randomized studies[1-5] have documented a prolongation in prostate cancer–specific and/or overall survival when durations of androgen suppression therapy (AST) that range from 4 months to lifelong compared with no AST have been added to external-beam radiation therapy (RT) in the management of men who have clinically localized or locally advanced adenocarcinoma of the prostate. In the studies that evaluated AST durations of 6 months or less[1-3] AST consisted of both a luteinizing hormone-releasing hormone (LHRH) agonist and an antiandrogen, whereas the vast majority of AST use in studies that evaluated long-term AST was an LHRH agonist only.[4-5] Although the use of combined AST compared with AST monotherapy has not been shown to prolong time to death in men with metastatic prostate cancer,[6] this issue remains unaddressed for men with localized prostate cancer. Therefore, we performed a post–random assignment, hypothesis-generating analysis to determine if the risk of recurrence in men enrolled on a randomized trial[3] for prostate cancer and who were treated with RT alone or in conjunction with less than combined AST was higher compared with men who were treated with RT and combined AST, after analysis was adjusted for known prognostic factors.

PATIENTS AND METHODS

Patient Population and Treatment

Between December 1, 1995 and April 15, 2001, 206 men (median age, 72.5 years; range, 49 to 82 years) with

1992 American Joint Commission on Cancer clinical stage[7] T1b-T2bN0M0 but unfavorable-risk prostate cancer were enrolled. Prescription and nonprescription medications under use at the time of random assignment and the reason for their use were prospectively recorded. Prostate needle biopsy specimens underwent central review by a pathologist with expertise in genitourinary pathology. Before study entry, all men signed an institutional review board–approved, protocol-specific informed consent form in accordance with federal and institutional guidelines. This trial has been registered on the National Institutes of Health Web site, http://www.clinicaltrials.gov, as NCT00116220. The eligibility and exclusion criteria, registration, random assignment, stratification, treatment, and quality assurance guidelines for this study have been described previously.[3]

The Adult Comorbidity Evaluation–27

By using detailed information on pre-existing medical conditions and comorbidities that was collected at baseline before random assignment, a comorbidity score was assigned with the Adult Comorbidity Evaluation (ACE)–27, a 27-item, validated comorbidity index for use in patients with cancer.[8] The index was used to assign grades to diseases of specific conditions into one of four levels of comorbidity (grade 0, none; grade 1, minimal; grade 2, moderate; grade 3, severe) according to the severity of the individual organ system decompensation and prognostic impact. The instrument can be found at http://oto.wustl.edu/clinepi/calc.html.

Assessment of Flutamide Usage, Toxicity, and Dose Modification

AST consisted of 6 months of either leuprolide or goserelin acetate and 6 months of the nonsteroidal antiandrogen flutamide. The number of days that each patient took flutamide during the 6-month treatment period was monitored and recorded by the site investigator's protocol team. Liver function tests (LFTs) were obtained during AST every 2 weeks for 1 month and then monthly thereafter, according to the national standard. These tests included aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total billirubin levels. In the event that either the aspartate aminotransferase or alanine aminotransferase reached two times the upper limit of normal, flutamide was discontinued and LFTs were obtained weekly until they were at or below the upper limit of normal. Once normal levels occurred, flutamide was restarted orally at 125 mg three times a day, and LFTs then were obtained every 2 weeks for 1 month and then monthly. If the aspartate aminotransferase or alanine aminotransferase levels were elevated to at least twice the upper limit of normal again, flutamide was permanently discontinued, and LFT's were drawn monthly until they were at baseline or at or less than the upper limit of normal. If a patient was taking aspirin and experienced an increase in the LFTs that necessitated the discontinuation of flutamide, aspirin use was continued. Dose adjustments for leuprolide and goserelin were not specified in the protocol. All men received 6 months of one of these drugs.

If a patient experienced gastrointestinal discomfort that consisted of cramps, diarrhea, or uncontrolled nausea, flutamide was held until the side effects subsided; it then was restarted orally at a dose of 250 mg once daily, and the dose was increased at 3-day intervals to 250 mg twice daily and then to 250 mg three times a day as tolerated. If the patient could not tolerate flutamide after it was reintroduced orally at the full dose, then a half dose (125 mg three times a day) was attempted and was increased to 250 mg three times a day and then to 375 mg three times a day every 3 days. If the patient was unable to tolerate the half dose, flutamide was discontinued permanently.

Follow-Up

Follow-up started on the day of random assignment and concluded on June 1, 2007, or on the date of death, whichever came first; no patient was lost to follow-up. Patients were seen every 3 months for 2 years, every 6 months for an additional 3 years, and annually thereafter. At each follow-up, a history and physical examination, including a digital rectal examination, was performed in addition to a serum PSA level before the digital rectal examination. At the time of PSA failure, a pelvic computed tomography scan or a magnetic resonance imaging scan and a bone scan were obtained in addition to the routine follow-up assessment. Salvage AST administration for PSA failure was recommended when the PSA level reached 10 ng/mL.

Statistical Methods

Primary end point. The primary end point of the original randomized[3] study was the time to PSA recurrence. PSA recurrence was defined as a PSA greater than 1.0 ng/mL and a PSA that increased by greater than 0.2 ng/mL at two consecutive visits after treatment. In the current study, which is a retrospective and hypothesis-generating study, the primary end point also was the time to PSA recurrence. All men in this study had the opportunity to achieve at least a 2-ng/mL increase in the PSA level above the nadir before the initiation of AST for PSA failure, because the protocol required that salvage AST would be recommended as the PSA level approached 10 ng/mL. Therefore, we were able to use the 2006 American Society of Therapeutic Radiology (ASTRO) consensus definition of a PSA value that exceeds the PSA nadir by 2 ng/mL[9] to define PSA recurrence in the current study.

Risk of PSA Recurrence

Post–random assignment, hypothesis-generating, multivariable Cox regression analyses[10] were used to evaluate whether the risk of PSA recurrence

Table 1. Distribution of Patient and Tumor Characteristics at Random Assignment for the 206 Men With Localized but Unfavorable-Risk Prostate Cancer Who Comprised the Study Cohort

Clinical Characteristic	Distribution	
	No. of Patients	%
Treatment		
RT and 6 months of both LHRH agonist and antiandrogen	73	35
RT and 6 months of LHRH agonist and < 6 months of antiandrogen	29	14
RT	104	50
PSA, ng/mL		
≤ 4	9	4
4-9.99	72	35
10-19.99	91	44
≥ 20	34	17
Gleason score		
≤ 6	57	28
7	119	58
8-10	30	15
1992 AJCC clinical T category[7]		
T1b	4	2
T1c	95	46
T2a	46	22
T2b	61	30
Aspirin use		
Yes	86	42
No	120	58
Atorvastatin use		
Yes	77	37
No	129	63
Age at random assignment, years		
< 70	60	29
70-75	89	43
> 75	57	28
ACE-27 comorbidity score[8]		
None (0)	135	66
Minimal (1)	22	11
Moderate (2)	43	21
Severe (3)	6	3

NOTE. Unfavorable risk factors included a prostate-specific antigen (PSA) level > 10 ng/mL (maximum 40 ng/mL), biopsy Gleason score of 7 to 10, cancer, or radiographic evidence of extracapsular extension and/or seminal vesicle invasion by using endorectal magnetic resonance imaging.

Abbreviations: RT, radiation therapy; LHRH, luteinizing hormone-releasing hormone; AJCC, American Joint Commission on Cancer; T, tumor; ACE, Adult Comorbidity Evaluation.

was significantly associated with months of antiandrogen use after adjustment for known prognostic factors, the comorbidity score, and the use of other medications (ie, baby aspirin, atorvastatin) that could cause LFT elevation and could necessitate the early discontinuation of the antiandrogen. Prognostic factors included PSA level, Gleason score, and clinical tumor (T) category. To account for the influence on LFT levels of a duration of flutamide and other medication use that was not known on the date of random assignment, these covariates were treated as time dependent.[11] To assess whether an interaction between the duration of medication use that can elevate LFTs and flutamide use existed, interaction terms were included in the multivariable model. For categoric variables, cut points were determined before the analysis and were based on established, clinically relevant strata.[12] The PSA level was log-transformed to ensure that it followed a normal distribution and was treated as a continuous variable, whereas Gleason score and T category were considered categoric variables. Baseline groups were defined as a Gleason score of 6 or less and the clinical category T1. The assumptions of the Cox model were tested, and no evidence that these assumptions were violated was found. Unadjusted and adjusted hazard ratios (HRs)[13] for PSA recurrence with associated 95% CIs and *P* values were calculated for each covariate.

Estimates of PSA Recurrence

For the purpose of illustration, estimates of time to PSA recurrence stratified by months of antiandrogen use (0, >0 to <6, 6) in all men were displayed graphically. Estimates of PSA recurrence were obtained by calculating the fraction of men who were PSA failure–free with the method of Kaplan and Meier[14] and then by subtracting this fraction from 1 and multiplying the result by 100. Comparisons of these estimates were performed with a log-rank test. A two-sided *P* value $<.05$ was considered statistically significant, and adjustments were made for multiple comparisons by using a Bonferroni correction.[15] SAS version 9.1.3 (SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

Description of the Study Cohort

In the original report,[3] a statistically significant improvement in overall survival was noted for the 102 men randomly assigned to receive RT and AST compared with the 104 men randomly assigned to RT. In the current study, of the 104 and 102 men treated with RT versus RT and AST, respectively, 51 (49%) and 35 (34%), respectively, were taking baby aspirin, and 45 (43%) and 32 (31%), respectively, were taking atorvastatin. In addition, 29 (29%) of the 102 men randomly assigned to RT and AST discontinued flutamide before 6 months. Of these 29 men, 24 (24%), two (2%), one (1%), one (1%), and one (1%) discontinued the flutamide because of LFT elevation, patient request, anemia, photosensitivity reaction, and diarrhea, respectively. In these 29 men, the median duration of flutamide was 4.2 months (interquartile range, 3.3 to 5.5 months). Descriptive statistics were used to characterize the clinical and tumor characteristics at random assignment of the 206 men who comprised the study cohort, and these characteristics are listed in Table 1.

Clinical Factors Associated With an Increased Risk of PSA Recurrence

After a median follow-up of 8.2 years (interquartile range, 7.0 to 9.5 years), 81 men sustained PSA recurrence. As listed in Table 2, an increasing PSA level ($P < .001$); a Gleason score of 8, 9, or 10 ($P < .001$); and clinical category T2 disease ($P = .005$) were significantly associated with an increased risk of recurrence. However, recurrence risk was significantly decreased (adjusted HR, 0.81; 95% CI, 0.72 to 0.92; $P = .001$) with each additional month of antiandrogen use after analysis adjustment for these known prognostic factors. Although increasing aspirin use in months was significantly associated with an increase risk of recurrence on univariable analysis, significance for this time-dependent covariate was not reached on multivariable analysis after adjustment for known prognostic factors (PSA level, Gleason score, and T category) and for the months of antiandrogen received.

Table 2. Univariable and Multivariable Cox Regression[10] Analyses of the Relative Risk of Recurrence According to Patient and Tumor Characteristics at Randomization for the 206 Men in the Study Cohort

	Univariable Analysis			Multivariable Analysis		
	Relative Risk			Relative Risk		
Covariate	No.	95% CI	*P*	No.	95% CI	*P*
Log PSA level per unit increase	2.07	1.4 to 3.1	< .001	2.3	1.6 to 3.4	< .001
Gleason score						
≤ 6	1.0		—		1.0	—
7	1.4	0.8 to 2.4	.26	1.6	0.9 to 2.9	.13
8-10	3.2	1.7 to 6.0	< .001	3.4	1.7 to 6.7	< .001
Tumor stage						
T1	1.0		—	1.0		—
T2	1.9	1.2 to 3.0	.005	1.6	1.02 to 2.6	.04
ACE-27 comorbidity score[8]						
None or minimal	1.0		—	1.0		—
Moderate or severe	1.1	0.7 to 1.8	.73	0.8	0.5 to 1.4	.52
Treatment						
Antiandrogen use (time) per month increase	0.83	0.76 to 0.90	< .001	0.81	0.72 to 0.92	.001
Medications that can elevate LFTs						
Aspirin use (time) per month increase	1.02	1.01 to 1.03	.001	1.01	0.996 to 1.02	.15
Atorvastatin use (time) per month increase	0.998	0.987 to 1.009	.76	1.00	0.985 to 1.01	.86
Interaction terms						
Aspirin use (time) × antiandrogen use (time)	1.003	0.99 to 1.006	.11	1.003	1.0 to 1.007	.09
Atorvastatin use (time) × antiandrogen use (time)	1.00	0.99 to 1.00	.77	1.00	0.99 to 1.00	.80

Abbreviations: PSA, prostate-specific antigen; ACE, Adult Comorbidity Evaluation; LFTs, liver function tests.

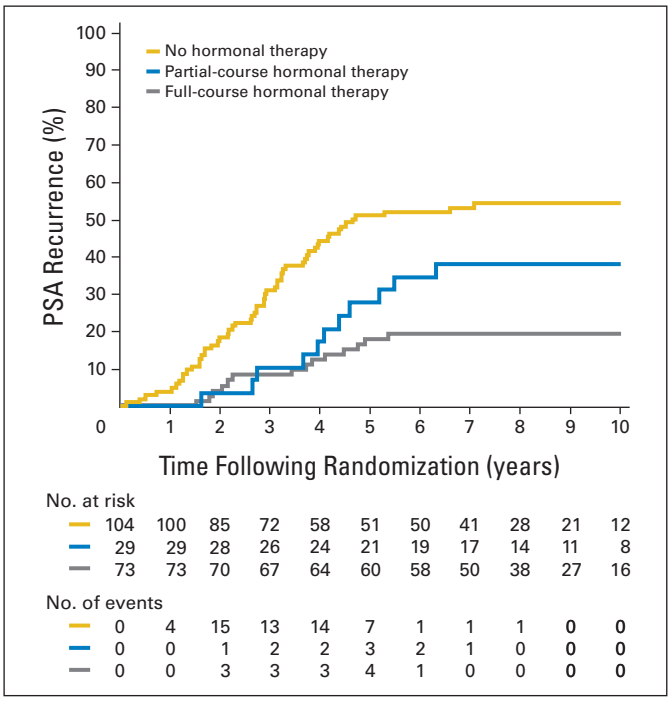

Fig 1. 1 Kaplan and Meier estimates[14] of prostate-specific antigen (PSA) failure–free survival for the 206 men in the study cohort whose treatment was stratified by the duration of flutamide use and was analyzed with log-rank, pairwise *P* values. A significant *P* value[15] was $< .05 \div 3$ (.017). *P* value for 6 versus 0 months, $< .001$; for 6 versus < 6 months, .06; for < 6 versus 0 months, .07. Partial-course hormonal therapy is 6 months of leuprolide or goserelin acetate and < 6 months of flutamide. Full-course hormonal therapy is 6 months of leuprolide or goserelein acetate and 6 months of flutamide.

Estimates of PSA Recurrence

Estimates of PSA recurrence were significantly lower ($P < .001$) in men who received 6 months of flutamide compared with those who received no AST. Similarly, estimates of PSA recurrence also were lower in men who received flutamide for 6 months compared with those who received less than 6 months of AST and were lower in men who received less than 6 months of AST compared with those who received no AST. The latter two comparisons approached, but did not reach, statistical significance, with *P* values of .06 and .07, respectively. These data are illustrated in Figure 1, in which estimates of PSA recurrence at 10 years were 19% (95% CI, 12% to 30%), 38% (95% CI, 23% to 58%), and 54% (95% CI, 45% to 64%) in men who received 6 months of flutamide, less than 6 months of flutamide, and no flutamide, respectively.

DISCUSSION

The results of this study revealed that recurrence risk was significantly decreased with each additional month of antiandrogen use after adjustment for known prognostic factors. Although a hypothesis-generating study, because this is a post–random assignment analysis, this is the first study, to our knowledge, to report an association between the extent of AST received and the recurrence risk in men who undergo RT for localized prostate cancer. This observation identifies the need for prospective study of monotherapy versus combined AST (preferably with bicalutamide, because of its widespread use). Specifically, although the use of combined therapy compared with monotherapy has not been shown to prolong the time to death in men with metastatic prostate cancer,[6] this issue remains unaddressed for men with localized prostate cancer.

Several points require further consideration. First, the primary end point of this study was the time to PSA recurrence and not prostate cancer–specific mortality, because a limited number of prostate cancer–specific deaths occur in men who undergo RT and AST. However, because PSA failure was defined with the 2006 American Society for Therapeutic Radiology and Oncology consensus definition[9] that has been shown to be significantly associated with a greater risk of metastases and cancer death, there is a high likelihood that many of the PSA failure events observed in this study will translate into metastases and cancer death. Second, although PSA doubling time has been suggested as a surrogate for prostate cancer–specific mortality after RT,[16] it was not selected as an end point in this study, because collection of serum testosterone levels during follow-up were not mandated by the protocol and because PSA levels can rise after AST completion as the testosterone level rebounds towards normal. Therefore, without follow-up serum testosterone levels, we could not ascertain whether the increasing PSA levels reflected cancer recurrence or testosterone-driven PSA rebound, which would make it difficult to know when to start using follow-up PSA values to estimate a doubling time. The lack of complete testosterone data in a prior report[17] may also explain why it remains unclear whether the PSA doubling time can act as a surrogate for prostate cancer–specific mortality in men who are treated with RT and AST. Third, the observation that LFT elevation led to administration of less than 6 months of flutamide and the association of this with a greater risk of recurrence may have important implications on any medication that can cause LFT elevation. In addition, it is possible that LFT elevation that results from the use of antiandrogen therapy may be a marker of more aggressive cancer biology or may be a negative predictor of response to treatment. These hypotheses require further study. Finally, because only known prognostic factors (ie, PSA level, Gleason score, and T category) and the comorbidity level could be adjusted in our time-to-recurrence analysis of the evaluated duration of flutamide use, the possibility that unknown or unmeasured confounding factors (eg, pretreatment PSA velocity[18]) could have influenced the time to recurrence remains.

Despite these considerations, men with localized but unfavorable-risk prostate cancer who are treated with RT and 6 months of AST appear to have an increased risk of recurrence when treated with less than 6 months compared with 6 months of antiandrogen. Prospective evaluation of the extent of AST delivered and its impact on survival is needed in men with localized but unfavorable-risk prostate cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Denham J, Steigler A, Lamb DS, et al: Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: Results from the Tran-Tasman Radiation Oncology Group 96.01 randomised controlled trial. Lancet Oncol 6:841-850, 2005

2. Pilepich MV, Winter K, John MJ, et al: Phase III Radiation therapy Oncology Group (RTOG) 8610 of Androgen Deprivation Adjuvant to Definitive Radiotherapy in Locally Advanced Carcinoma of the Prostate. Int J Radiat Oncol Biol Phys 50:1243-1252, 2001

3. D'Amico AV, Manola J, Loffredo M, et al: Six-month androgen suppression plus radiation therapy vs. radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. JAMA 292:821-827, 2004

4. Bolla M, Collette L, Blank L, et al: Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomized trial. Lancet 360:103-106, 2002

5. Pilepich MV, Winter K, Lawton CA, et al: Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma: Long-term results of phase III RTOG 8531. Int J Radiat Oncol Biol Phys 61:1285-1290, 2005

6. Eisenberger MA, Blumenstein BA, Crawford ED, et al: Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 339:1036-1042, 1998

7. Beahrs OH, Henson DE, Hutter RVP, et al: American Joint Committee on Cancer Staging Manual (ed 4). Philadelphia, PA, Lippincott, 1992, pp 181-186

8. Piccirillo JF, Tierney RM, Costas I, et al: Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 291:2441-2447, 2004

9. Roach M III, Hanks G, Thames H Jr, et al: Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 65:965-974, 2006

10. Cox DR: Regression models and life tables. J R Stat Soc B 34:187-220, 1972

11. Klein JP, Moeschberger ML: Refinements of the semiparametric proportional hazards model, in Klein JP, Moeschberger ML (eds): Survival Analysis: Techniques for Censored and Truncated Data (ed 2). New York, NY, Springer, 2003, pp 295-328

12. D'Amico AV, Whittington R, Malkowicz SB, et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 280:969-974, 1998

13. Neter J, Wassermann W, Kutner M (eds): Simultaneous inferences and other topics in regression analyses-1, in Applied Linear Regression Models. Homewood, IL, Irwin Professional Publishing, 1983, pp 150-153

14. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-500, 1958

15. Agresti A: In, Agresti A (ed): An Introduction to Categorical Data Analysis (ed 2). New York, NY, John Wiley & Sons, 2002, pp 16-52

16. D'Amico AV, Moul J, Carroll P, et al: Surrogate marker for prostate cancer specific mortality following radical prostatectomy or radiation therapy. J Natl Cancer Inst 95:1376-1383, 2003

17. Valicenti RK, Desilvio M, Hanks GE, et al: Post-treatment prostatic-specific antigen doubling time as a surrogate endpoint for prostate cancer-specific survival: An analysis of Radiation Therapy Oncology Group Protocol 9202. Int J Radiat Oncol Biol Phys 66:1064-1071, 2006

18. D'Amico AV, Loffredo M, Renshaw AA, et al: Six-month androgen suppression plus radiation therapy compared with radiation therapy alone for men with prostate cancer and a rapidly increasing pretreatment prostate-specific antigen level. J Clin Oncol 24:4190-4195, 2006

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