

Comorbidity, Body Mass Index, and Age and the Risk of Nonprostate-Cancer-Specific Mortality After a Postradiation Prostate-Specific Antigen Recurrence

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BACKGROUND: Some men with a postradiation therapy (RT) prostate-specific antigen (PSA) recurrence will die of noncancer causes before developing metastases. Therefore, our ability to determine who would benefit from salvage hormone therapy (HT) would be enhanced if an individual's risk of nonprostate-cancer-specific mortality were known.

METHODS: Among 206 men with unfavorable-risk localized prostate cancer initially randomized to RT+/-HT, 87 men who experienced PSA recurrence were studied. Fine and Gray's competing risks regression was used to assess whether body mass index (BMI) and the Adult Comorbidity Evaluation-27 comorbidity level at randomization were associated with the risk of nonprostate-cancer-specific mortality after PSA recurrence, adjusting for age at recurrence. **RESULTS:** After a median postrecurrence follow-up of 4.4 years, moderate/severe comorbidity (adjusted hazard ratio [HR] = 3.15; $P = .02$), BMI \geq median (27.4 kg/m²; adjusted HR=2.98; $p=.04$), and increasing age at recurrence (adjusted HR = 1.17; $P = .03$) were significantly associated with an increased risk of nonprostate-cancer-specific mortality. Five-year cumulative incidence estimates of nonprostate-cancer-specific mortality were as follows: 0% (95% confidence interval [CI] [0,0]) for low-risk patients (mild/no comorbidity and age < median [76.2 years] and BMI < median), 18.8% (5.8-31.8) for intermediate-risk patients (mild/no comorbidity and either age \geq median or BMI \geq median); and 37.9% (95% CI, 6.8-68.9) for high-risk patients (moderate/severe comorbidity; $P = .03$ overall).

CONCLUSIONS: After a post-RT PSA recurrence, men with moderate/severe comorbidity and those who are obese or older face a substantial risk of nonprostate-cancer-specific mortality, and they could be considered for surveillance protocols with a plan to initiate salvage HT if the PSA rises rapidly (eg, PSA doubling time <6 months) or the patient develops clinically or radiographically evident disease. *Cancer* 2010;116:610-5. © 2009 American Cancer Society.

KEYWORDS: salvage hormone therapy, prostate cancer, noncancer mortality, body-mass index, comorbidity, ACE-27.

After external beam radiation therapy (RT) for clinically localized prostate cancer, up to 30% of men will experience a PSA recurrence.^{1,2} In this setting, there is no randomized evidence that early initiation of salvage hormone therapy (HT) improves survival, but the use of early salvage HT is common.³

Because the average time between prostate-specific antigen (PSA) failure and clinically evident metastases can be quite prolonged (eg, 8 or more years in postprostatectomy or post-RT series), many men with PSA failure will die of nonprostate cancer causes without developing metastases.^{4,5} For such men, it is unclear whether there is a benefit to initiating salvage HT at the time of PSA recurrence, particularly if their PSA doubling time is long (ie, in excess of 1 year), or if their risk of death from nonprostate cancer causes is high. Therefore, the decision of whether to initiate salvage HT must take into consideration both the likelihood that the PSA recurrence will lead to a clinically evident metastasis and the probability that the patient will live long enough to experience those sequelae.

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While the predictors of prostate-cancer-specific mortality after PSA failure are known, the predictors of nonprostate-cancer-specific mortality have been less well elucidated. Therefore, the purpose of this study is to determine the predictors of nonprostate-cancer-specific mortality in a cohort of men who participated in a trial of radiation alone versus radiation plus HT for localized prostate cancer and experienced a subsequent PSA recurrence.

MATERIALS AND METHODS

Patient Selection

At academic (Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center) and community-based (St Anne's Hospital, Metrowest Medical Center, and Suburban Oncology Center) medical centers in Massachusetts, between December 1, 1995, and April 15, 2001, 206 men (median age, 72.5 years; range, 49-82 years) with 1992 American Joint Commission on Cancer (AJCC) Clinical Stage T1b to T2bN0M0 adenocarcinoma of the prostate and at least 1 unfavorable prognostic factor (PSA >10 ng/mL, biopsy Gleason score \geq 7, or endorectal MRI evidence of T3 disease) were randomized to receive 70Gy of RT alone or in combination with 6 months of HT. HT comprised a luteinizing-hormone-releasing hormone agonist and the antiandrogen flutamide. A complete compilation of pre-existing medical conditions and comorbidities was ascertained by the treating physician and recorded at baseline before randomization to satisfy the inclusion criterion that the patient have at least a 10-year life expectancy excluding death from prostate cancer and an Eastern Cooperative Oncology Group performance status of 0 or 1.

Among the men in the randomized trial, 89 developed a PSA recurrence, but 2 were missing information on baseline body mass index (BMI), and so 87 men composed the final cohort of the current study. PSA recurrence in the randomized study was initially defined as a PSA greater than 1.0 ng/mL and a PSA that increased by greater than 0.2 ng/mL at 2 consecutive visits after treatment. However, in the current study, we reclassified PSA failure according to the standard 2006 American Society of Therapeutic Radiology (ASTRO) consensus definition, in which PSA failure is scored on the day that the PSA value exceeds the PSA nadir by 2 ng/mL.⁶ It was possible to do this because the protocol recommended salvage HT only as the PSA level approached 10 ng/mL, and, therefore, all men in this study had had the opportunity to achieve at least a 2 ng/mL increase in the PSA level above

the nadir before salvage HT. Before study entry, all men signed an institutional review board-approved, protocol-specific, informed consent form in accordance with federal and institutional guidelines.

Adult Comorbidity Evaluation-27

By using detailed information on pre-existing medical conditions and comorbidities collected at baseline before randomization, a comorbidity score was assigned by the principal investigator (A.V.D.) using the Adult Comorbidity Evaluation-27 (ACE-27), a 27-item validated comorbidity index for use in patients with cancer.⁷ The ACE-27 instrument was selected because the clinically relevant comorbid ailments used to obtain the comorbidity score were selected based on prior research by experts. In addition, the ailments were validated specifically for the case of the newly diagnosed patient with cancer. The index was used to assign grades to diseases of specific conditions into 1 of 4 levels of comorbidity (grade 0 [none], grade 1 [mild], grade 2 [moderate], or grade 3 [severe]) according to the severity of the individual organ system decompensation and prognostic impact. Once a human's individual comorbid conditions were classified, an overall comorbidity score was assigned based on the highest ranked single ailment. For the case in which 2 or more moderate ailments occur in different organ systems, the overall comorbidity score was designated as severe. An example of the scoring in the case of the cardiovascular system is that a prior history of myocardial infarction (MI) within 6 months, more than 6 months, or an old MI by electrocardiogram only (age undetermined) would be scored as severe, moderate, and mild comorbidity, respectively. The instrument can be found at <http://oto-wustl.edu/clinepi/calc.html>.

Follow-Up

Follow-up started on the day of PSA failure and concluded on the date the patient was last observed or the date of death through the prespecified analysis date of January 10, 2008, whichever came first. The median for the date of last follow-up in living men was January 26, 2007 (range, October 14, 2001- January 10, 2008). Patients were observed every 3 months for 2 years, every 6 months for an additional 3 years, and then 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 in addition to the routine follow-up assessment, computed tomography or MRI of the pelvis and a bone scan were also obtained. As

noted, salvage HT administration for PSA failure was recommended when the PSA level reached 10 ng/mL.

Determination of the Cause of Death

The primary outcome of the study was nonprostate-cancer-specific mortality. The attending oncologist who followed the patient until death determined the cause of death. To record a death as due to prostate cancer, there had to be documented hormone refractory metastatic prostate cancer and evidence that the PSA level was increasing at the time of the last follow-up visit despite the use of second-line hormonal maneuvers or cytotoxic chemotherapy before death. All other deaths were considered nonprostate-cancer-related deaths.

Statistical Methods

Baseline characteristics

The baseline characteristics of the study cohort at the time of randomization and at the time of PSA recurrence were enumerated using descriptive statistics in a tabular format.

Predictors of Time to Nonprostate-Cancer-Specific Mortality

Fine and Gray's competing risks regression was used to assess whether BMI and ACE-27 comorbidity level at randomization were significantly associated with the risk of nonprostate-cancer-specific mortality after PSA recurrence adjusting for age at the time of PSA recurrence.⁸ Covariates included in the model were age at PSA failure (continuous), BMI at randomization (categorical as BMI \geq median vs BMI<median), ACE-27 comorbidity level (categorical as moderate/severe vs no/mild comorbidity), Gleason score (categorical defined as 8-10 vs 7 vs the baseline of Gleason 6 or less), baseline PSA (continuous), clinical stage (categorical defined as T2 vs T1), and treatment arm (RT vs RT+/-HT). For the purposes of analysis, the PSA level was log transformed to ensure that the values were normally distributed. For all regression analyses, the assumptions of the Fine and Gray regression model were tested and no evidence that these assumptions were violated was found. Adjusted hazard ratios (HRs) for all-cause mortality with associated 95% confidence intervals (CIs) and *P* values were calculated for each covariate from the Fine and Gray regression model.

Estimates of Nonprostate-Cancer-Specific Mortality Within Subgroups

The significant predictors of time to nonprostate-cancer-specific mortality were used to generate subgroups

of patients at low, intermediate, and high risk of nonprostate-cancer-specific mortality based on the hazard ratios from the multivariable model. The cumulative incidence of nonprostate-cancer-specific mortality was calculated for each risk group, and *k* sample *P* values were used to compare the estimates of survival.⁹⁻¹¹ All *P* values were 2-sided. A level of significance *P* < .05 was used for all statistical tests. R version 2.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all calculations pertaining to Fine and Gray's regression and Gray's *k* sample test. All other analyses were done in SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

The baseline characteristics at randomization and at the time of PSA recurrence of the patient cohort are displayed in Table 1. The median BMI at randomization was 27.4 kg/m². The median time to PSA failure was 3.7 years, and the median age at PSA failure was 76.2 years. Of the 87 men, 63 (72%) had no ACE-27 comorbidity, 9 (10%) had mild comorbidity, 14 (16%) had moderate comorbidity, and 1 (1%) had severe comorbidity. The median postrecurrence PSA doubling time was 13.2 months (interquartile range, 7.5 to 26.6 months).

Predictors of Nonprostate-Cancer-Specific Mortality

After a median follow-up of 4.4 years after PSA recurrence (interquartile range, 2.1-6.3), there were 15 nonprostate-cancer-specific deaths and 16 prostate-cancer-specific deaths. Table 2 displays the results of the Fine and Gray analysis for time to nonprostate-cancer-specific mortality. Factors significantly associated with an increased risk of nonprostate-cancer-specific mortality were moderate or severe comorbidity (adjusted HR = 3.15; *P* = .02), a BMI \geq median value of 27.4 (adjusted HR = 2.98; *P* = .04), and increasing age at PSA recurrence (adjusted HR = 1.17; *P* = .03).

Estimates of Nonprostate-Cancer-Specific Mortality by Risk Group

The 3 significant factors associated with time to nonprostate mortality were used to divide patients into 3 categories at varied risk of dying from nonprostate causes, as shown in Figure 1. Construction of the groups was guided by the relative magnitude of the hazard ratios from the multivariable regression. Low risk

Table 1. Baseline Characteristics of Study Cohort at Randomization and at the Time of PSA Recurrence (N=87)

Characteristics at Randomization	
Age, median (IQR)	72.1 (68.9-75.0)
ACE-27 comorbidity level	
None	63 (72%)
Mild	9 (10%)
Moderate	14 (16%)
Severe	1 (1%)
BMI	
Median (IQR)	27.4 (25.5-30.2)
<25	16 (18%)
25 to <30	49 (56%)
30+	22 (25%)
Gleason Score	
5-6	24 (28%)
7	50 (57%)
8 to10	13 (15%)
AJCC tumor category	
T1b	0 (0%)
T1c	33 (38%)
T2a	20 (23%)
T2b	34 (39%)
Baseline PSA, median (IQR)	12.2 (8.0, 19.2)
Baseline PSA in ng/mL	
≤4	4 (5%)
>4-10	24 (28%)
>10-20	40 (46%)
>20	19 (22%)
Assigned treatment	
RT	60 (69%)
RT+HT	27 (31%)
Characteristics at PSA recurrence	
Age at PSA failure, median (IQR)	76.2 (71.8-79.2)
Interval to PSA failure, median (IQR)	3.7 (2.2, 5.1)
Age at PSA failure	
≤60	1 (1%)
61 to70	26 (30%)
71to 75	37 (43%)
76 to 80	20 (23%)
>80	3 (3%)
PSADT	
Median (IQR)	13.2 (7.5, 26.6)
<3.0 mo	6 (7%)
3.0-6.0 mo	10 (11%)
6.0-12.0 mo	23 (26%)
>12 mo	48 (55%)

PSA indicates prostate-specific antigen; IQR, interquartile range; ACE, Adult Comorbidity Evaluation-27; BMI, body mass index; AJCC, American Joint Commission on Cancer; PSADT, prostate-specific antigen doubling time.

was defined as age < median and BMI < median and no/mild comorbidity. Intermediate risk was defined as no/mild comorbidity and either age ≥ median or BMI ≥ median, and high risk was defined as moderate or

severe comorbidity. The 5-year estimates of the cumulative incidence of nonprostate-cancer-specific mortality for each group were as follows: 0% (95% CI, 0-0) for low-risk patients; 18.8% (95% CI, 5.8-31.8) for intermediate-risk patients; and 37.9% (95% CI, 6.8-68.9) for high-risk patients (overall $P = .03$).

DISCUSSION

In this study, we examined a cohort of men who experienced PSA recurrence after external beam radiation therapy with or without 6 months of HT for unfavorable localized prostate cancer in the context of a randomized controlled trial. We found that the 3 significant factors that were associated with an increased risk of nonprostate-cancer-specific mortality after recurrence were moderate to severe comorbidity, increasing age at recurrence, and a BMI greater than the median value of 27.4 kg/m² (for reference, the National Institutes of Health cutoff for overweight is BMI ≥25 kg/m²).¹² By using these 3 factors, we defined clinically useful groups of men with various risks of nonprostate-cancer-specific mortality 5 years after recurrence, ranging from 0% in the low-risk group to 38% in the high-risk group.

The clinical significance of this study is that this information can be used alongside the known risk factors for prostate-cancer-specific mortality to select men for entry onto surveillance protocols after a PSA recurrence. Currently, there is no randomized data to address the specific question of the optimal timing and use of salvage HT for men who have an asymptomatic PSA-only relapse and no clinical evidence of disease. Therefore, a reasonable approach to therapy would be to weigh the risk that a patient will develop metastases and die of prostate-cancer against the competing risk that he will die of nonprostate cancer-specific mortality before developing a symptomatic metastasis. The risk factors for prostate-cancer-specific mortality are known and include a short PSA doubling time, a short interval to PSA recurrence, and a Gleason score of 8-10.^{4,5,13-16} For patients with these risk factors and an otherwise normal life expectancy, early initiation of salvage HT may be warranted. On the other end of the spectrum, for patients without such prostate-cancer-specific mortality risk factors who have a high risk of nonprostate-cancer-specific mortality, entry into a surveillance protocol would be warranted. For example, men with a PSA doubling time greater than 1 year, Gleason 7 or less disease, and an interval to PSA recurrence of greater than 2 to 3 years could be considered for surveillance if they fall into the “intermediate-risk” or “high-risk”

Table 2. Risk of Nonprostate-Cancer-Specific Mortality Based on the Fine and Gray Multivariable Regression Analysis

	Adjusted Hazard Ratio	95% Confidence Interval	P
BMI ≥ median (27.4kg/m ²) vs < median	2.98	1.04-8.53	.04
Moderate/severe comorbidity vs no/mild	3.15	1.16-8.54	.02
Age at PSA recurrence	1.17	1.01-1.34	.03
RT vs RT+HT	1.53	0.49-4.84	.47
Log (PSA)	1.92	0.70-5.26	.21
Gleason 7 vs 6	0.91	0.27-3.02	.87
Gleason 8-10 vs 6	0.57	0.10-3.35	.54
Clinical T2 vs T1	0.31	0.09-1.02	.054

BMI indicates body mass index; PSA, prostate-specific antigen; RT, radiation therapy; HT, hormone therapy.

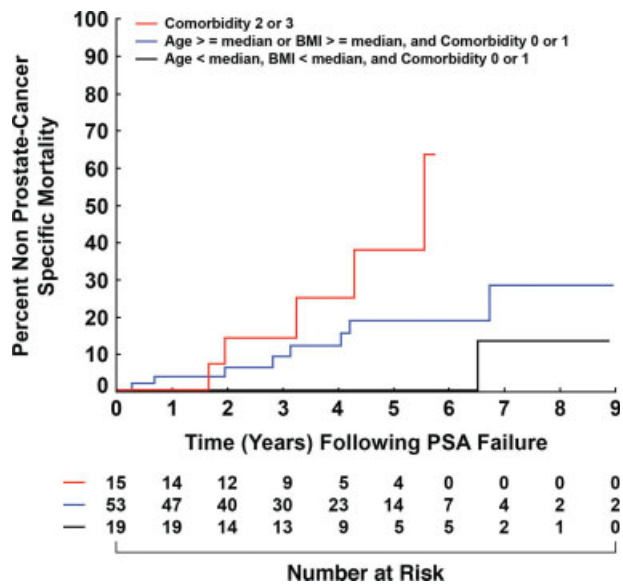


Figure 1. Illustrated is the cumulative incidence of nonprostate-cancer-specific mortality after prostate-specific antigen recurrence, stratified by risk group determined by comorbidity level, BMI, and age at recurrence (*P* log rank = .03).

groups for nonprostate-cancer-specific mortality as identified in this study (ie, moderate to severe comorbidity, or advanced age at recurrence [aged >76.2 years], or high baseline BMI (>27.4 kg/m²). Such a protocol might entail PSA checks every 6 months and imaging as warranted, and salvage HT would be withheld until the PSA began to rise rapidly (eg, doubling time <6 months), or the patient developed clinically or radiographically evident disease.^{17,18} Clinicians may also consider such an approach off-protocol for patients at high risk of nonprostate-cancer-specific mortality (ie, moderate/severe comorbidity) who have otherwise favorable prostate cancer features.¹⁹

Such a surveillance protocol would help to either delay or prevent men from being exposed unnecessarily to

the side effects of hormonal therapy, including hot flashes, loss of libido, decreased muscle mass, mild anemia, osteoporosis, and the potential for metabolic changes as well as adverse cardiovascular consequences.²⁰⁻²²

This analysis does have potential limitations; the small number of patients in certain subgroups limits the accuracy of the point estimates for survival. In particular, as shown in Figure 1, the high-risk group contained only 15 patients and 5 nonprostate-cancer-specific death events. Therefore, these results should be validated in other series as well. In addition, the median follow-up from the time of PSA recurrence was 4.4 years, so we were not able to make reliable projections about the risk of nonprostate-cancer-specific mortality beyond 5 years, which also has relevance as the time from PSA recurrence to clinically evident metastases can be many years.^{4,5} Also, the BMI and comorbidity level used for analysis in this study were acquired at the time of randomization, and given the average 3.7 year interval from randomization to PSA failure, it is possible that these variables could have been slightly different at the time of PSA failure, as comorbidities and weight tend to increase as men age. It should also be noted that in the multivariable analysis (Table 2), having clinical T2 versus T1 disease was near significantly associated with a decreased risk of nonprostate-cancer-specific mortality, possibly reflecting a higher competing risk of prostate-specific mortality among that group of patients.

In summary, we found that comorbidity level, BMI, and age at recurrence could be used to predict the risk of nonprostate-cancer-specific mortality for men who experience a PSA recurrence after definitive radiation therapy. For men at intermediate risk or high risk of nonprostate-cancer-specific mortality (19% and 38% at 5 years, respectively), who have long PSA doubling times and other favorable features, close surveillance with a plan to

initiate salvage HT only if the PSA doubling time drops below 6 months or if the patient develops clinically or radiographically evident disease may be reasonable. These findings will need to be validated in other series.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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