
Identifying Men Diagnosed With Clinically Localized Prostate Cancer Who are at High Risk for Death From Prostate Cancer

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Purpose: We identified factors at diagnosis that are significantly associated with time to prostate cancer specific mortality following radical prostatectomy or external beam radiation therapy.

Materials and Methods: The study cohort included 1,453 men treated with radical prostatectomy (1,095) or external beam radiation therapy (358) for localized prostate cancer between 1989 and 2002. Cox regression multivariate analysis was used to evaluate whether prostate specific antigen, prostate specific antigen velocity, biopsy Gleason score and clinical tumor category at diagnosis were significantly associated with time to prostate cancer specific mortality following radical prostatectomy or external beam radiation therapy.

Results: In addition to increasing prostate specific antigen ($p \leq 0.04$) and biopsy Gleason score 8 to 10 disease ($p \leq 0.02$), prostate specific antigen velocity more than 2 ng/ml yearly was significantly associated with shorter time to prostate cancer specific mortality in patients treated with radical prostatectomy (adjusted HR 12, 95% CI 3 to 54) and external beam radiation therapy (adjusted HR 12, 95% CI 3 to 54) compared with that in men with prostate specific antigen velocity 2 ng/ml yearly or less ($p \leq 0.001$). Despite low risk disease 7-year estimates of prostate cancer specific mortality were 5% to 19% in patients in whom prostate specific antigen increased by more than 2 ng/ml during the year before diagnosis compared with less than 1% in those with a prostate specific antigen increase of 2 ng/ml or less.

Conclusions: Despite prostate specific antigen level less than 10 ng/ml and Gleason score 6 cancer a prostate specific antigen increase of more than 2 ng/ml during the year before diagnosis places a man at high risk for prostate cancer death following radical prostatectomy or external beam radiation therapy.

Key Words: prostate, prostatic neoplasms, risk, mortality, prostate-specific antigen

While PSA recurrence is not unusual following RP or RT performed to treat clinically localized prostate cancer, PCSM is a much less common event in this patient population.¹ This discrepancy is due to the advanced age of men at diagnosis and competing causes of mortality, in particular cardiovascular disease and second cancers.

Studies have shown that the factors significantly associated with PSA failure following RP or RT are also significantly associated with PCSM.^{2,3} These factors are high baseline PSA, particularly more than 20 ng/ml, and biopsy Gleason score 8 to 10 disease. Tumor category has become relatively less important as a prognostic factor because most patients diagnosed today have nonpalpable disease as result of increased PSA screening and the resultant stage migration toward earlier stage disease.⁴⁻⁷

Concomitant with stage migration, median PSA at presentation has also decreased, such that PSA greater than 10 ng/ml at diagnosis has become infrequent.⁴ Moreover, be-

nign prostatic hyperplasia increases serum PSA and it is commonly seen in men of prostate cancer bearing age. As a result, the prognostic significance of any single PSA value below 10 ng/ml is becoming more limited.

Despite decreasing PSA values at presentation the information obtained from serial PSA values in the form of PSA velocity has been shown to be significantly associated with tumor stage,⁸ grade,⁸ time to PSA failure⁹ and time to PCSM following RP.¹⁰ Specifically based on secondary analysis of a prospective screening study¹⁰ we observed that a PSA increase of more than 2 ng/ml during the year before diagnosis is significantly associated with PCSM despite RP. Therefore, a determination of which patient with PSA 4.0 ng/ml at presentation has good vs poor prognosis disease may be made based on whether PSA during the prior year was closer to 3.5 or 1.5 ng/ml, respectively. To better define the patient at high risk we evaluated whether PSA, PSA velocity, biopsy Gleason score and clinical tumor category at diagnosis are significantly associated with time to PCSM following RP or RT.

PATIENTS AND METHODS

Patient Selection, Staging and Treatment

Pretreatment and followup information were compiled on 480 men treated with RT at the Harvard Medical School

Study received institutional review board approval.

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affiliate St. Anne's Hospital, Fall River, Massachusetts and on 1,804 treated with RP at Barnes Jewish Hospital from January 1, 1989 to December 1, 2002 for clinical categories T1c (nonpalpable) and T2 (palpable) prostate cancer. A total of 689 and 44 men who had only a single measurement of PSA before RP and RT, respectively, were excluded from study, as were 78 in whom pre-RT PSA measurements were spaced less than 6 months apart. In addition, 20 patients received adjuvant RT and were excluded. The remaining 1,095 RP treated and 358 RP treated men comprised the study cohort. No patient undergoing RT received neoadjuvant, concurrent or adjuvant hormonal therapy. Each man provided written informed consent before study entry and the institutional review board approved the study. Median age at initial therapy was 71.2 years (range 43.2 to 83.5) in RT treated patients and 65.4 years (range 43.3 to 83.5) in RP treated patients. Table 1 shows the clinical characteristics of the men before treatment, stratified by pretreatment risk group. Pre-therapy staging has been previously described.^{2,10}

Treatment consisted of radical retropubic prostatectomy or, from 1994 to 2002, 3-dimensional and conformal radiation therapy with computerized tomography based treatment planning. Before 1994 shaped blocks were used and treatment planning involved transferring computerized tomography defined volumes onto plain x-rays of the pelvis. A 4-field box technique was used to treat the prostate and seminal vesicles to 45 Gy in 25 cases using 1.8 Gy fractions

followed by a boost to the prostate of 22 Gy in 11 and 2.0 Gy fractions using a 1.5 cm margin throughout. All doses were prescribed to the planning target volume and 95% normalization was used, so that the minimum dose received by the prostate was 70.35 Gy. The seminal vesicles were not treated in patients with low risk disease, ie those with PSA less than 10 ng/ml, biopsy Gleason score 6 or less and clinical tumor category 1c or 2a, but the total prostate gland dose was the same.

Followup of Surgically Treated Patients

Median followup was 5.1 years (range 0.5 to 13.1). Followup started on the day of RP and concluded on September 1, 2003 or the date of death, whichever was first. No patient was lost to followup. Before disease recurrence, as defined by 2 consecutive detectable PSA values greater than 0.2 ng/ml after RP, men generally underwent serum PSA measurement every 6 months and digital rectal examination annually. After recurrence PSA was measured a median of every 4 months (range 1 to 12). At recurrence biopsy of the anastomosis was not routinely performed. Overall there were 84 deaths, including 27 from prostate cancer. If PSA was always detectable after RP, the time of recurrence was defined as time zero.

Followup of Radiation Treated Patients

Median followup was 4.0 years (range 0.2 to 13.5). Followup started on the last day of RT and concluded on March 1, 2005 or the date of death, whichever was first. No patient was lost to followup. Before PSA defined recurrence, as specified by the American Society for Therapeutic Radiology and Oncology consensus definition,¹¹ patients underwent serum PSA measurement a median of every 6 months and digital rectal examination annually. After PSA recurrence PSA was measured at a median of 4 months (range 1 to 12). Patients with PSA recurrence were started on salvage hormonal therapy at a PSA of approximately 10 ng/ml. Overall there were 79 deaths, including 30 from prostate cancer.

Cause of Death Determination

Determination of the cause of death was made from death certificates in all cases. To record a death as being due to prostate cancer there had to be documented hormone refractory metastatic prostate cancer and evidence that PSA was increasing at the last followup visit before death.

Statistical Methods

Calculation of PSA velocity. Using the PSA value closest in time to diagnosis (median 1 month, range 0.5 to 3), and all prior PSA values that were within 1 year of diagnosis and separated by at least 6 months from the PSA value at diagnosis, PSA velocity during the year before diagnosis was calculated using linear regression analysis.¹² A minimum of 2 and a maximum of 3 PSA values were used to calculate PSA velocity.

Assessment of recurrence and mortality. Cox regression analysis¹² was used to test whether PSA velocity before diagnosis, and PSA, biopsy Gleason score and clinical tumor stage at diagnosis were significantly associated with time to post-RP or post-RT PCSM. For Cox regression multivariate analysis purposes PSA velocity was considered a categorical

TABLE 1. Pretreatment clinical characteristics in 1,453 study patients, stratified by pretreatment risk group and treatment

Characteristics	No. Surgery (%)	No. Radiation (%)
<i>Low risk cohort</i>		
PSA (ng/ml):		
4.0 or Less	370 (45)	23 (18)
Greater than 4.0-10.0	452 (55)	102 (82)
Biopsy Gleason score 6 or less	822 (100)	125 (100)
Clinical T category:		
1c	631 (77)	72 (58)
2a	191 (23)	53 (42)
Age:		
Younger than 50	5 (1)	1 (1)
50-59	183 (22)	6 (5)
60-69	456 (55)	41 (33)
70-79	177 (22)	73 (59)
80 or Older	1 (0.1)	4 (3)
<i>Higher risk cohort</i>		
PSA (ng/ml):		
4.0 or Less	96 (35)	11 (5)
Greater than 4.0-10.0	118 (43)	107 (46)
Greater than 10.0-20.0	42 (15)	75 (32)
Greater than 20.0	17 (6)	40 (17)
Biopsy Gleason score:		
6 or Less	94 (34)	67 (29)
7	133 (49)	137 (59)
8-10	46 (17)	29 (12)
Clinical T category:		
1c	148 (54)	85 (36)
2a	76 (28)	61 (26)
2b	45 (16)	50 (21)
2c	4 (1)	37 (16)
Age:		
Younger than 50	0	1 (0.5)
50-59	39 (14)	11 (5)
60-69	159 (58)	58 (25)
70-79	75 (27)	152 (65)
80 or Older	0	11 (5)

Percents may not total 100% due to rounding (low risk—PSA less than 10 ng/ml, Gleason score 6 or less and clinical tumor category 1c or 2a and higher risk—all others).

TABLE 2. AHR and unadjusted HR for PCSM risk in study patients treated with RP and RT

Covariate	No. Men	Median Followup (yrs)	No. Events	Univariate Analysis		Multivariate Analysis	
				Unadjusted HR (95% CI)	p Value	AHR (95% CI)	p Value
PSA velocity (ng/ml/yr):							
2 or Less (ng/ml/yr)	833	4.8	3	1.0 (referent)	—	1.0 (referent)	—
Greater than 2	262	5.3	24	20.4 (6.2–67.9)	<0.001	9.8 (2.8–34.3)	<0.001
PSA/unit increase (ng/ml)	1,095	5.1	27	1.08 (1.06–1.1)	<0.001	1.02 (1.06–1.1)	0.001
Gleason score:							
6 or Less	916	5.1	14	1.0 (referent)	—	1.0 (referent)	—
7	133	4.3	6	4.6 (1.7–12.2)	0.05	2.1 (0.7–5.8)	0.17
8–10	46	4.8	7	11.5 (4.2–31.4)	0.003	3.4 (1.2–9.8)	0.02
Tumor stage:							
T1c	779	4.6	4	1.0 (referent)	—	1.0 (referent)	—
T2	316	5.4	23	9.1 (3.1–26.7)	0.82	7.4 (2.4–22.4)	<0.001
PSA velocity (ng/ml/yr):							
2.0 or Less	208	4.5	2	1.0 (referent)	—	1.0 (referent)	—
Greater than 2	150	3.3	28	24 (5.7–102)	<0.0001	12 (3–54)	0.001
PSA/unit increase (ng/ml)	358	4.0	30	1.03 (1.02–1.04)	<0.0001	1.01 (1.006–1.03)	0.04
Gleason score:							
6 or Less	192	4.1	8	1.0 (referent)	—	1.0 (referent)	—
7	137	3.8	13	4.8 (1.8–13)	0.002	3.1 (1.2–8.4)	0.02
8–10	29	4.2	9	19 (6–65)	<0.0001	10.8 (3.3–35)	<0.0001
Tumor stage:							
T1c	157	3.8	6	1.0 (referent)	—	1.0 (referent)	—
T2	201	4.3	24	2.6 (1.1–6.5)	0.04	1.2 (0.5–3.2)	0.70

variable (more than 2 vs 2 ng/ml yearly or less). PSA at diagnosis was evaluated as a continuous variable, whereas biopsy Gleason score and clinical tumor category were analyzed as categorical variables, defined as Gleason 8 to 10 vs 7 vs 6 or less and as T2 vs T1c, respectively. The covariate of patient age on the day of RP or at the end of RT was evaluated as a continuous variable in analyses of all cause mortality. Time zero was defined as the day of RP or the last day of RT.

For all categorical variables the cutoff points selected were made before examining the data, based on established¹³ or recently defined¹⁰ strata. In all Cox regression analyses the assumptions of the proportional hazards model were tested and met. All statistical tests were 2-sided. The HR for PCSM with the associated 95% CI was calculated for all covariates using the proportional hazards model. Illustrations of estimates of time to PCSM following RP or RT were made using a cumulative incidence¹⁴ plot in men with low risk prostate cancer.

RESULTS

PSA Velocity as a Predictor of Recurrence and Death

Median PSA velocity in radiation treated patients was 1.5 ng/ml yearly (IQR 0.74 to 3.8) with 2.0 ng/ml yearly representing the 58th percentile. In the 125 and 233 patients at low and higher risk 2.0 ng/ml yearly represented the 77th and 48th percentiles, respectively. In surgically treated patients median PSA velocity was 1.0 ng/ml yearly (IQR 0.5 to 2.0). Of 30 prostate cancer deaths observed in RT treated patients 28 occurred in men in whom PSA velocity was greater than 2.0 ng/ml yearly. Similarly 24 of 27 prostate cancer deaths in surgically treated patients occurred in men with PSA velocity greater than 2.0 ng/ml yearly.

In addition to increasing PSA and biopsy Gleason score, PSA velocity more than 2 ng/ml yearly was significantly associated with shorter time to PCSM in patients treated with RP (AHR 9.8, 95% CI 2.8 to 34.3, $p < 0.001$) and RT

(AHR 12, 95% CI 3 to 54, $p = 0.001$) compared with that in men with PSA velocity 2 ng/ml yearly or less (table 2). Despite low risk disease 7-year estimates of PCSM approached 20% in RT treated patients in whom PSA velocity exceeded 2 ng/ml yearly compared to 0% in those with PSA velocity 2 ng/ml yearly or less.

Recurrence and Mortality Estimates Stratified by PSA Velocity and Risk Group

Figures 1 and 2 show a significant difference between the cumulative incidence estimates of PCSM in patients treated with RP and RT ($p = 0.0003$ and 0.0007 , respectively), as stratified by pretreatment PSA velocity greater than 2 vs 2 ng/ml yearly or less in men with low risk disease. Men treated with RP who presented with low risk disease and

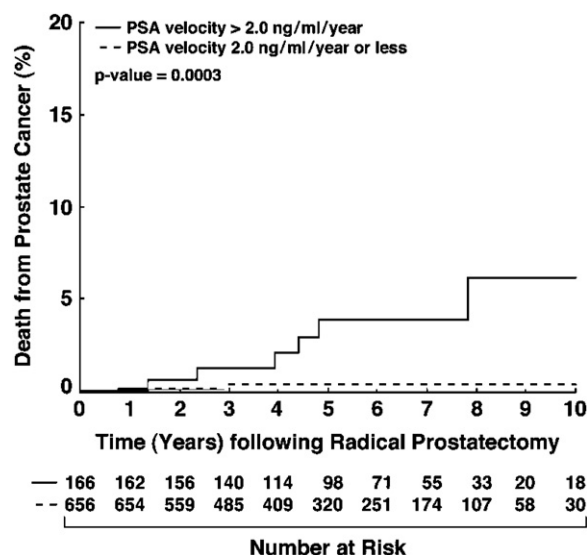


FIG. 1. PCSM cumulative incidence estimates stratified by pretreatment PSA velocity in surgically treated men with low risk disease (log rank $p = 0.0003$).

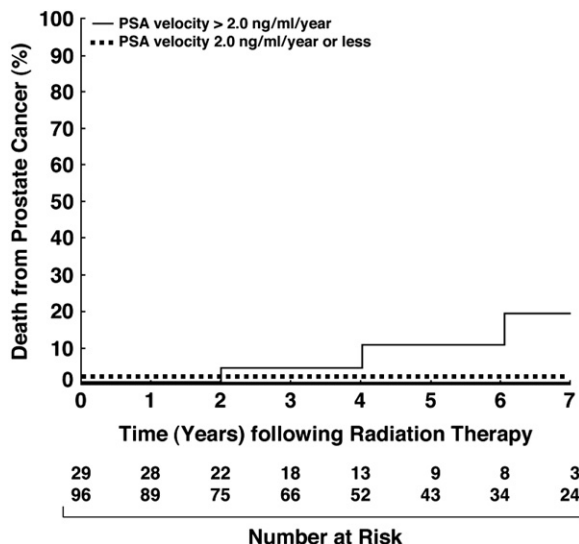


FIG. 2. PCSM cumulative incidence estimates stratified by pretreatment PSA velocity in radiation treated men with low risk disease (log rank $p = 0.0007$).

PSA velocity greater than 2.0 ng/ml yearly had 7-year estimates of PCSM of 5% (95% CI 4 to 6) compared to 0.5% (95% CI 0 to 1) in men in whom PSA velocity was 2.0 ng/ml yearly or less. This value was 19% (95% CI 2 to 39) vs the 0% rate in RT treated patients.

DISCUSSION

While PSA failure is considered to represent treatment failure, the time course to prostate cancer death following PSA failure can be protracted and it is associated with PSA doubling time.^{1,15} Therefore, when identifying patients who are eligible for phase III studies of the role of chemotherapy in addition to standard therapy for newly diagnosed prostate cancer, a cohort of men at high risk for PCSM and not simply for PSA failure should be identified. While evidence exists to support a significant association between PSA at diagnosis and the biopsy Gleason score with time to PCSM following RP² or RT,^{2,3} the role of PSA velocity before diagnosis for defining high risk disease is evolving.¹⁰

As previously shown, in the current study increasing PSA and Gleason score were significantly associated with an increasing risk of PCSM following RP or RT. In addition, evidence is provided to support that a PSA increase of more than 2.0 ng/ml during the year before diagnosis is also associated with a significantly higher PCSM rate following RP or RT. Specifically the 24 of 27 RP treated and 28 of 30 RT treated patients who were observed to die of prostate cancer had PSA velocity exceeded 2 ng/ml yearly. This translates into an approximately 10-fold increase in the rate of prostate cancer death after adjusting for known prognostic factors at diagnosis in men with PSA velocity greater than 2.0 ng/ml compared to that in all others.

The clinical significance of this study is that a PSA increase of more than 2.0 ng/ml during the year before diagnosis places a patient in a high risk category for cancer death despite RP or RT and despite apparent low risk disease. This increased risk of PCSM is presumably derived from occult micrometastatic disease that is present at diagnosis. Specifically despite low risk disease men with a PSA

increase exceeding 2 ng/ml during the year before diagnosis had a significantly higher likelihood of PCSM whether they were initially treated with RP or RT (figs. 1 and 2). Therefore, these men should be considered for enrollment in randomized clinical trials evaluating whether docetaxel, which has been shown to prolong survival in men with hormone refractory metastatic prostate cancer,^{16,17} may also prolong survival when administered in conjunction with local therapy.

Moreover, the current standard of practice in men with high risk prostate cancer is RT and AST based on the survival benefit reported in 2 prospective, randomized trials.^{18,19} Therefore, in otherwise healthy men with low risk disease and pre-RT PSA velocity greater than 2.0 ng/ml yearly who are planning to undergo RT and are not interested in enrolling in a clinical trial, offering RT and AST could be viewed as a reasonable option.

There are several points in this study that require clarification. 1) Not all men who had PSA velocity greater than 2.0 ng/ml yearly experienced recurrence and PCSM. Therefore, while men who experienced a PSA increase of more than 2 ng/ml during the year before diagnosis were at an average approximate 10-fold risk for PCSM, the risk in any individual can vary, as noted by the large 95% CI (table 2). 2) While observation in patients with PSA velocity greater than 2.0 ng/ml yearly would not appear to be warranted, whether observation would lead to shorter survival than in patients offered RP, RT or RT and AST remains an unresolved issue. To answer this requires a randomized study, such as the Prostate Cancer Intervention vs Observation Trial.²⁰ 3) PSA velocity in men diagnosed with prostate cancer has been shown to increase with time.⁶ As a result, using PSA values dating back several years the calculated value of PSA velocity can be less than the actual value at diagnosis, which more accurately reflects the clinical scenario at the time that management decisions and counseling are occurring. Therefore, when estimating PSA velocity, it is important to use information from the year before diagnosis with PSA values spaced approximately 6 months apart. Otherwise baseline variation in the PSA assay may produce an erroneous result. For these reasons in this study we used a minimum of 2 and a maximum of 3 PSA values that were within 1 year of diagnosis but separated by 6 months. In conclusion, despite PSA less than 10 ng/ml and Gleason score 6 cancer a PSA increase of more than 2 ng/ml during the year before diagnosis places a man at high risk for prostate cancer death following RP or RT.

Abbreviations and Acronyms

AHR	=	adjusted HR
AST	=	androgen suppression therapy
PCSM	=	prostate cancer specific mortality
PSA	=	prostate specific antigen
RP	=	radical prostatectomy
RT	=	external beam radiation therapy

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