Published in final edited form as:

J Urol. 2008 November ; 180(5): 1980–1985. doi:10.1016/j.juro.2008.07.031.

What are the Factors Associated With Short Prostate Specific Antigen Doubling Time After Radical Prostatectomy? A Report From the SEARCH Database Group

Anna E. Teeter, Lionel L. Bañez, Joseph C. Presti Jr., William J. Aronson, Martha K. Terris, Christopher J. Kane, Christopher L. Amling, and Stephen J. Freedland*

Division of Urologic Surgery and Duke Prostate Center, Department of Surgery, Duke University Medical Center (AET, LLB, SJF), Urology Section, Department of Surgery, Veterans Affairs Medical Centers (AET, LLB, SJF) and Department of Pathology, Duke University School of Medicine (SJF), Durham, North Carolina, Department of Urology, Stanford University Medical Center and Urology Section, Department of Surgery, Veterans Affairs Medical Centers, Palo Alto (JCP) and West Los Angeles (WJA), Department of Urology, University of California at Los Angeles Medical Center, Los Angeles (WJA) and Division of Urology, Department of Surgery, University of California at San Diego Medical Center, San Diego (CJK), California, Urology Section, Division of Surgery, Veterans Affairs Medical Centers and Division of Urologic Surgery, Department of Surgery, Medical College of Georgia, Augusta, Georgia (MKT), and Division of Urology, Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama (CLA)

Abstract

Purpose—Short prostate specific antigen doubling time following recurrence after radical prostatectomy portends a poor prognosis in men with prostate cancer. We determined which demographic and clinicopathological variables were predictive of a short prostate specific antigen doubling time in a cohort of men with clinically localized prostate cancer treated with radical prostatectomy.

Materials and Methods—Data on 856 men from the Shared Equal Access Regional Cancer Hospital database who underwent radical prostatectomy for node negative prostate cancer between 1988 and 2003 were included in the analysis. We used logistic regression analysis to determine the independent factors associated with a short prostate specific antigen doubling time of less than 9 months vs a longer doubling time of 9 months or greater, or no recurrence. The variables analyzed were patient age, race, logarithmically transformed preoperative prostate specific antigen, body mass index, year of surgery, pathological Gleason sum, extraprostatic extension, surgical margin status and seminal vesicle invasion.

Results—On multivariate analysis higher preoperative prostate specific antigen (OR 2.20, 95% CI 1.52–3.19, $p < 0.001$), pathological Gleason sum 8–10 (OR 4.70, 95% CI 2.11–10.43, $p < 0.001$) and 7 (OR 2.11, 95% CI 1.09–4.08, $p = 0.026$), tumors with extraprostatic extension and/or positive surgical margins (OR 2.08, 95% CI 1.48–3.91, $p = 0.023$), and seminal vesicle invasion (OR 3.26, 95% CI 1.48–7.21, $p = 0.003$) were independent predictors of a short prostate specific antigen doubling time. Based on these risk factors we developed a table to estimate the risk of recurrence with a prostate specific antigen doubling time of less than 9 months.

Conclusions—The factors that are invariably used to predict overall biochemical recurrence following radical prostatectomy, including high prostate specific antigen, high grade and adverse pathological findings, also predict aggressive recurrence.

Keywords

prostate; prostatic neoplasms; prostate-specific antigen; neoplasm recurrence; local; tumor markers; biological

Early identification of men at high risk for prostate cancer death remains a vital component in the appropriate management of prostate cancer. Studies aimed at identifying prognostic factors have consistently demonstrated that PSADT calculated shortly after primary treatment failure is a robust predictor of cancer specific death.¹⁻³ Unfortunately because current methods used to calculate PSADT require multiple PSA measurements after biochemical recurrence, this valuable information is unknown until men have recurrence. However, it is important to identify men at high risk for aggressive recurrence as early as possible so that they can be monitored and treated appropriately. To date the clinicopathological characteristics predictive of aggressive recurrences have only been studied in cohorts with recurrence.^{4,5} Although 1 study included men without recurrence, only preoperative factors were examined.⁶ Thus, factors that can be used immediately after surgery to predict aggressive recurrence remain unknown.

We identified demographic and clinicopathological factors predictive of aggressive recurrence using the multicenter SEARCH database of men treated with RP to identify those at high risk for aggressive recurrence and, thus, those who are at increased risk for PCSM who would be good candidates for clinical trials.

MATERIALS AND METHODS

Clinical and Pathological Variables

After obtaining institutional review board approval from each institution to abstract and combine data, data on patients undergoing RP at the Veterans Affairs Medical Centers in West Los Angeles and Palo Alto, California; Augusta, Georgia; and Durham, North Carolina were entered into the SEARCH database.⁷ Patients treated with preoperative androgen deprivation or radiation therapy were excluded from study. BMI was calculated as weight in kg divided by height in m². Biochemical recurrence was defined as a single PSA measurement of greater than 0.2 ng/ml, 2 measurements of 0.2 ng/ml or secondary treatment for increased/increasing postoperative PSA. Men who received adjuvant treatment with undetectable PSA were censored as not having had recurrence at the time of treatment. PSADT was calculated by dividing the natural log of 2 (0.693) by the slope of the linear regression line of the natural log of PSA with time.⁸ PSADT was calculated in all patients meeting the recurrence definition who had a minimum of 2 PSA values available that were separated by at least 3 months and within 2 years after recurrence. All PSA measurements within the first 2 years after recurrence were used to calculate PSADT. In patients starting salvage hormone or radiation therapy within this time only PSA measurements before salvage therapy were used. The 45 patients with a PSADT of 0 or less, ie a decrease/no change in PSA, or a long PSADT of more than 100 months were assigned a value of 100 months for ease of calculation.

Study Population

Our primary goal was to identify risk factors for aggressive disease. A priori we defined aggressive disease as recurrence with a PSADT of less than 9 months based on high PCSM

in a prior study.³ Nonaggressive disease was defined as recurrence with a PSADT of 9 months or greater, or no evidence of recurrence since these men are at low risk for prostate cancer death.⁹ A total of 77 men lacking followup data and 226 with recurrence and unknown PSADT were unable to be classified and were excluded.

A total of 472 men without recurrence but with limited followup (less than 36 months) remained at risk for recurrence with a short PSADT and could not be reliably classified. Thus, they were excluded from study. Because men who underwent surgery after 2003, ie those with less than 36 months of maximum potential followup, could only be included if they had recurrence and early recurrence is more likely to be aggressive, their inclusion would have resulted in a potential selection bias. Therefore, all 19 men treated after 2003 who otherwise met the inclusion criteria were excluded from study. Because men with node positive disease are likely to harbor aggressive disease and are at high risk for prostate cancer death, these 13 were excluded from study. We also excluded 40, 21, 14 and 3 men who were missing data on preoperative PSA, postoperative Gleason sum, margin status and extraprostatic extension, respectively, resulting in a study population of 856.

Statistical Analysis

We explored differences in the distribution of demographic and clinicopathological characteristics between aggressive and nonaggressive groups using the Mann-Whitney test for continuous variables (age, PSA, percent of positive cores, prostate weight and surgery year) and the chi-square test for categorical variables (race, BMI, postoperative Gleason sum, extraprostatic extension, margin status and SV invasion). BMI was stratified as less than 25, 25 to 29.9, 30 to 34.9 and 35 kg/m² or greater. Pathological findings, including positive surgical margins, extraprostatic extension and SV invasion, were initially examined individually for the risk of aggressive recurrence. Because positive surgical margins and extraprostatic extension connoted similar risks of overall recurrence in a prior SEARCH study¹⁰ and in the current study for aggressive recurrence, we grouped pathological findings as a 3-tiered categorical variable, that is 1) organ confined and negative margins, 2) positive margins and/or extraprostatic extension with-out SV invasion and 3) SV invasion.

We used a forward stepwise logistic regression model to determine the characteristics most predictive of aggressive disease with $p < 0.15$ as the primary entry criterion. Variables at $p \geq 0.1$ were successively deleted until only significant variables remained. The variables considered for entry were patient age, BMI, preoperative PSA, race, pathological Gleason sum, surgery year, percent of positive cores, prostate weight and pathological stage grouping. Because PSA and prostate weight were not normally distributed, these variables were examined after logarithmic transformation. The association between BMI and disease aggressiveness was not statistically significant, although there was a suggestion that, when categorized as less than 30 vs 30 kg/m² or greater, obese patients were more likely to have aggressive recurrences ($p = 0.12$). Similarly there was a modest but not significant association between larger prostate weight and a lower risk of aggressive disease ($p = 0.10$). However, given that neither association was statistically significant, and BMI and prostate weight data were missing on 131 men (15%), neither was considered for entry into the final models. Finally, when analysis was limited to 623 men (73%) with data available on the percent of positive cores and 6 or greater biopsy cores obtained, the percent of cores predicted aggressive recurrence in significant and independent fashion ($p = 0.03$). However, in these 623 men adding the percent of cores to the model resulted in a modest and clinically insignificant improvement in predictive accuracy (AUC 0.77 vs 0.75). Thus, combined with the fact that 27% of the cohort had missing data or fewer than 6 cores obtained, the percent of positive cores was not considered for entry into the final model.

Using the final multivariate logistic model we developed a table to predict the probability of aggressive disease based on clinicopathological parameters with $p < 0.05$ considered significant. Data were similar among all sites and were combined for analysis. All statistical analysis was performed using statistical software.

Sensitivity Analysis

In men with recurrence the association between time to recurrence and PSADT at recurrence is on a continuum.⁹ Therefore, to test alternate cutoffs of the minimum followup needed in men without recurrence to classify them as being at high risk we repeated our analysis with the minimum followup required of 12, 24, 48 and 60 months. Because these analyses had differing entry criteria, the number of patients in each subanalysis differed. The number of patients in the 12, 24, 48 and 60-month sensitivity analyses was 1,124, 990, 740 and 629, respectively.

RESULTS

Clinicopathological Characteristics

There were no significant differences between men with aggressive vs nonaggressive disease in age, race, year of surgery or BMI. However, men in the aggressive group had higher PSA, more positive cores, higher pathological grade disease and more adverse pathological findings (table 1).

Of the 779 men in the nonaggressive group 207 had recurrence with a PSADT of 9 months or greater and 572 had no recurrence. Men without recurrence had a median 75-month followup, while those with recurrence with a PSADT of 9 months or greater had a median time to recurrence of 35 months. In the 77 men with aggressive recurrence the median time to recurrence was 9 months. Median PSADT in the aggressive recurrence group was 5.2 months vs 23 in the nonaggressive group.

Factors Associated With Aggressive Recurrence

On multivariate analysis higher PSA ($p < 0.001$), higher pathological grade disease and adverse pathological results were significantly associated with aggressive recurrence (table 2). Specifically a pathological Gleason sum of 7 ($p = 0.026$) and 8–10 ($p < 0.001$) relative to Gleason 2–6 tumors significantly correlated with a short PSADT. There was no notable difference in the predictive value of a pathological Gleason sum of $3 + 4 = 7$ vs $4 + 3 = 7$ and, thus, they were combined for simplicity. Extraprostatic extension and/or positive margins ($p = 0.023$) and SV invasion ($p = 0.003$) were associated with an increased likelihood of aggressive recurrence relative to that of organ confined, margin negative disease. PSA was categorized using standard cutoffs of less than 10, 10 to 19.9 and 20 ng/ml or greater.¹¹ Stratified PSA remained significantly predictive of aggressive recurrence after adjustment for grade and stage (table 2).

Using these 3 variables we developed a table to estimate the likelihood of aggressive recurrence in a patient within 3 years after recurrence (table 3). The AUC of this table for predicting aggressive recurrence was 0.79.

Sensitivity Analysis

We performed sensitivity analyses using alternate cutoffs of 12, 24, 48 and 60 months to define the minimum time needed before a patient without recurrence could be classified as having nonaggressive disease. On all sensitivity analyses the same factors, ie higher PSA, higher grade disease and adverse pathological findings, with similar point estimates were associated with aggressive recurrence, as in the 36-month threshold model (data not shown).

DISCUSSION

PSADT is a well-known predictor of outcome in patients with recurrence after RP but it cannot be calculated until a patient has recurrence and has undergone several subsequent PSA measurements. We identified variables that could be used earlier in the disease course to stratify men by the risk of aggressive recurrence and the subsequent risk of prostate cancer specific death. Therefore, we examined various demographic and clinicopathological factors to determine the characteristics most predictive of aggressive recurrence, defined as recurrence with a PSADT of less than 9 months, in 856 men who underwent RP. The cutoff of less than 9 months was based on prior studies showing that men who experience recurrence with PSADT less than 9 months are at high risk for prostate cancer specific and overall mortality.^{3,12} Men who had recurrence with a PSADT of 9 months or greater were grouped with men who did not have recurrence based on their similar low risk for PCSM.⁹

Given recent data suggesting that adjuvant radiation therapy decreases the recurrence risk and possibly metastasis,¹³ efforts are warranted to identify men at high risk as early as possible. Also, while to our knowledge the role of adjuvant chemotherapy is currently unknown, it is being actively investigated. Given the potential toxicity associated with chemotherapy, adjuvant therapy could only be justified in patients who are at high risk for aggressive recurrence. Current methods to screen for patients at high risk rely on the risk of any PSA recurrence. However, not all recurrences are fatal, although recurrences with a short PSADT often are. In 1 series patients who experienced recurrence with a PSADT of less than 9 months were at 70% all cause mortality risk within 15 years after recurrence with greater than 90% of deaths attributable to prostate cancer.¹² Thus, models should be developed to predict aggressive recurrence, not just any recurrence, which allows the early identification of men at high risk for mortality so that they may be enrolled in clinical trials, while sparing men at low risk the toxicity of adjuvant therapy.

To this end groups have examined clinical and pathological predictors of aggressive recurrence.^{4,5} While these prior studies were limited due to the inclusion of only recurrent cases, it was found that Gleason sum,^{4,5} pathological stage^{4,5} and time to recurrence⁵ predicted short PSADT. Although our study differed by including nonrecurrent cases, our conclusions were similar. Specifically we found that PSA, pathological Gleason sum and pathological stage grouping were significantly associated with the risk of aggressive recurrence and the resulting model had an AUC of 0.79 for estimating aggressive recurrence. This is similar to or better than prior models for predicting outcomes less strongly linked with mortality, such as PSA recurrence.¹⁴ These results require external validation but after they are validated providers can use this table to identify men at low risk for aggressive recurrence who can be safely monitored as well as men at high risk who are candidates for adjuvant therapy trials. Our model is designed specifically to predict aggressive recurrence within 3 years after surgery. Our sensitivity analysis suggests that this model would be similar if a 5-year cutoff were used and recurrences after 5 years are rarely aggressive.

Of note, a prior study included nonrecurrent cases, although the investigators only examined preoperative variables.⁶ Thus, the valuable pathological data that become available after surgery were not included. As in the current study, those investigators found that stage and grade (clinical stage and biopsy grade) predicted disease aggressiveness. They also found that preoperative PSA velocity predicted aggressive recurrence. We were unable to include this because this information was missing for most men in our series.

The factors useful for predicting aggressive recurrence, ie stage, grade and PSA, are the classic prostate cancer prognostic triad. Interestingly but perhaps not surprisingly these

factors are identical to the variables used in the Kattan postoperative nomogram for predicting overall recurrence,¹⁴ the D'Amico criteria for risk stratification¹¹ and the Partin tables for predicting pathological stage.¹⁵ Thus, it appears the factors predicting overall recurrence also predict aggressive recurrence.

While some studies have suggested that PSA may not be an important prognostic variable in contemporary men,¹⁶ others found that PSA remains a valuable clinical tool in the current era.^{17,18} Our results lend further support to the importance of PSA. Gleason sum has been used to grade prostate tumors since the 1960s.¹⁹ Biopsy and pathological Gleason sum are used to guide therapy and predict outcomes.^{11,14,15} Moreover, in studies of recurrent cases pathological Gleason sum has predicted prostate cancer specific³ and overall¹² survival. Prior studies also showed that pathological stage is an important predictor of recurrence,¹⁴ metastasis⁸ and prostate cancer specific survival.²⁰ Adverse pathological findings have also been linked to shorter PSADT in men with recurrence after prostatectomy.¹² Our findings corroborate the importance of pathological stage for postoperative risk stratification.

In our study there was a suggestion that prostate weight and BMI could be useful for predicting aggressive recurrence, although neither attained statistical significance. Whether this reflects their modest predictive ability or the limited number with these data is unclear. We used PSADT as a study end point based on data linking a PSADT of less than 9 months to an increased risk of prostate cancer death.³ To our knowledge whether this cutoff is optimal is unknown. At the equal access centers of SEARCH we found that race did not predict aggressive recurrence, although it may possibly be predictive in other populations. While the percent of cores significantly predicted aggressive recurrence, its addition to the final model in men with available data did not dramatically improve risk stratification. Whether its addition in an expanded data set would justify the added complexity of the table requires further study. Finally, the number of men with aggressive disease was modest. Therefore, larger studies in different populations are needed to confirm these results.

CONCLUSIONS

In the current study PSA, pathological Gleason sum and pathological stage predicted aggressive recurrence following RP. Using these variables we created a table to estimate the risk of aggressive recurrence. After this table is validated it may be used to risk stratify men and identify men at high risk for aggressive recurrence who are good candidates for adjuvant therapy trials.

Acknowledgments

Supported by the Department of Veterans Affairs, Department of Defense, National Institutes of Health, Georgia Cancer Coalition, American Urological Association Foundation/Astellas Rising Star in Urology Award and a Duke Roadmap Scholarship (TCI RH 024126).

Abbreviations and Acronyms

BCR	increasing PSA
BMI	body mass index
EPE	extraprostatic extension
PCSM	prostate cancer specific mortality
PSA	prostate specific antigen
PSADT	PSA doubling time

RP	radical prostatectomy
SEARCH	Shared-Equal Access Regional Cancer Hospital
SV	seminal vesicle

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Table 1
Demographic, clinical and pathological characteristics in 856 men undergoing RP in SEARCH database, stratified by disease aggressiveness

	Aggressive Disease	Nonaggressive Disease	p Value
No. pts	77	779	
Mean $\pm$ SD age at surgery	62.9 $\pm$ 6.5	62.0 $\pm$ 6.4	0.23 (Mann-Whitneytest)
Median surgery yr	1996	1997	0.13 (Mann-Whitneytest)
No. race (%):			0.79 (chi-square test)
White	43 (56)	425 (55)	
Black	27 (35)	296 (38)	
Other	7 (9)	57 (7)	
No. BMI (%):			0.19 (chi-square test)
Less than 25 kg/m ²	17 (29)	189 (28)	
25–29.9 kg/m ²	21 (36)	310 (46)	
30–34.9 kg/m ²	17 (29)	123 (18)	
35 kg/m ² or Greater	3 (5)	45 (7)	
PSA (ng/ml):			<0.001 (Mann-Whitney test)
Mean $\pm$ SD	18.3 $\pm$ 18.0	9.3 $\pm$ 7.2	
Median (IQR)	13.1 (7.1–23.9)	7.3 (5.0–10.8)	
No. Pathological Gleason sum (%):			<0.001 (chi-squaretest)
2–6	14 (18)	387 (50)	
7	44 (57)	333 (43)	
8–10	19 (25)	59 (8)	
Prostate wt (gm):			0.30 (Mann-Whitneytest)
Median (IQR)	39.0 (26.0–49.3)	39.0 (30.7–50.8)	
Mean $\pm$ SD	41.2 $\pm$ 21.2	44.5 $\pm$ 23.7	
% Pos cores:			<0.001 (chi-squaretest)
Median (IQR)	33.5 (16.7–50.0)	47.4 (27.5–66.7)	
Mean $\pm$ SD	33.5 $\pm$ 0.21	47.4 $\pm$ 0.26	
No. extraprostatic extension (%)	35 (45)	168 (22)	<0.001 (chi-squaretest)
No. pos surgical margins (%)	50 (65)	312 (40)	<0.001 (chi-squaretest)
No. SV invasion (%)	19 (25)	59 (8)	<0.001 (chi-squaretest)

	Aggressive Disease		Nonaggressive Disease		p Value (chi-squaretest)
No. pathological stage grouping (%):					<0.001
Organ confined, neg margin	16	(21)	403	(52)	
EPE +/-or pos margin	42	(55)	317	(41)	
SV invasion	19	(25)	59	(8)	

Aggressive and nonaggressive disease defined as PSADT less than 9 months and 9 months or greater, respectively.

Table 2

Multivariate analysis of factors predicting PSADT less than 9 months in men undergoing RP

	OR	95% CI	SE	p Value
<i>Model 1 (PSA as continuous variable)</i>				
logPSA	2.20	1.52–3.19	0.41	<0.001
Pathological Gleason				
sum:				
2–6	Referent			
7	2.11	1.09–4.08	0.71	0.026
8–10	4.70	2.11–10.43	1.91	<0.001
Pathological stage				
grouping:				
Organ confined, neg margin	Referent			
Extraprostatic extension +/- or pos margins	2.08	1.48–3.91	0.67	0.023
SV invasion	3.26	1.48–7.21	1.32	0.003
<i>Model 2 (PSA as categorical variable)</i>				
PSA (ng/ml):				
Less than 10	Referent			
10–19.9	2.33	1.30–4.19	0.70	<0.001
20 or Greater	5.67	2.91–11.07	1.93	<0.001
Pathological Gleason				
sum:				
2–6	Referent			
7	2.10	1.08–4.08	0.70	0.028
8–10	4.80	2.14–10.80	1.98	<0.001
Pathological stage				
grouping:				
Organ confined, neg margin	Referent			
Extraprostatic extension +/- or pos margin	2.07	1.10–3.90	0.67	0.024
SV invasion	3.17	1.43–7.01	1.28	0.004

Table 3

Likelihood of aggressive cancer (recurrence with PSADT less than 9 months) within 36 months after surgery

PSA (ng/ml)	% Pathological Gleason Sum (95% CI)		
	2-6	7	8-10
Less than 10:			
Organ confined, neg margin	2 (1-3)	4 (2-7)	8 (4-16)
Extraprostatic extension +/- positive margins	4 (2-7)	7 (4-12)	15 (8-26)
SV invasion	5 (2-12)	11 (5-20)	21 (11-38)
10 or Greater-less than 20:			
Organ confined, neg margin	4 (2-8)	8 (4-15)	17 (8-32)
Extraprostatic extension +/- positive margins	8 (4-15)	15 (10-23)	29 (18-45)
SV invasion	12 (5-24)	22 (12-35)	39 (23-57)
20 or Greater:			
Organ confined, neg margin	9 (4-19)	18 (9-31)	33 (16-56)
Extraprostatic extension +/- positive margins	17 (8-32)	31 (19-45)	50 (31-70)
SV invasion	24 (11-45)	40 (24-59)	61 (39-79)