

ULTRASENSITIVE SERUM PROSTATE SPECIFIC ANTIGEN NADIR ACCURATELY PREDICTS THE RISK OF EARLY RELAPSE AFTER RADICAL PROSTATECTOMY

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ABSTRACT

Purpose: Ultrasensitive prostate specific antigen (PSA) assays allow a lower limit of detection (less than 0.01 ng/ml) than standard PSA assays. In this study we examined the ability of ultrasensitive PSA nadir to predict relapse after radical prostatectomy (RP).

Materials and Methods: A total of 906 men treated with RP were followed with PSA measurements at 3, 6 and 12 months, and yearly thereafter. Of the 906 men 545 (60%) with a PSA nadir of less than 0.01 ng/ml or at least 3 followup ultrasensitive PSA measurements underwent analysis and stratification by PSA nadir. Biochemical relapse was defined as 2 consecutive increasing post-nadir PSA measurements of 0.1 ng/ml or greater. The ability of ultrasensitive PSA nadir to predict relapse was assessed by univariate and multivariate analysis.

Results: At a mean followup of 3.1 years 54 of 545 men (9.9%) experienced biochemical relapse with a mean time to relapse of 25.2 months. Relapse rates in men with a PSA nadir of less than 0.01 (423), 0.01 (75), 0.02 (19) and 0.04 or greater ng/ml (28) were 4%, 12%, 16% and 89%, respectively. Men with a nadir of less than 0.01 ng/ml had a significantly lower relapse rate than men with a nadir of 0.01 ($p < 0.01$), 0.02 ($p < 0.025$) or 0.04 or greater ng/ml ($p < 0.01$). Multivariate logistic regression analysis showed that a nadir of 0.01 ($p < 0.05$), 0.02 ($p < 0.05$) and 0.04 or greater ng/ml ($p < 0.01$) independently predicted an increased risk of biochemical relapse compared to a nadir of less than 0.01 ng/ml.

Conclusions: Ultrasensitive PSA nadir accurately predicts the risk of early biochemical relapse following RP. Men who achieve a nadir of less than 0.01 ng/ml have a low likelihood of early relapse. Higher nadir points may identify candidates for early adjuvant or salvage therapies.

KEY WORDS: prostate, prostate-specific antigen, prostatic neoplasms, recurrence, prostatectomy

Radical prostatectomy (RP) is considered by many to be the gold standard treatment for early stage, clinically confined prostate cancer. Since the description of nerve sparing radical prostatectomy by Walsh and Mostwin,¹ several refinements have been made by various groups in an attempt to improve functional and cancer related outcomes. Despite such refinements contemporary RP series of localized disease show relapse in up to 50% of men by 10 years.^{2,3} Preoperative prostate specific antigen (PSA), seminal vesicle invasion, positive margin status and prostatectomy Gleason score have been shown to serve as useful predictors for postoperative relapse.⁴ Men who have relapse are typically offered adjuvant radiotherapy, hormonal therapy or experimental protocols designed to slow progression. The earlier identification of biochemical relapse may be useful to identify men who are at higher risk for such relapse, thereby, allowing earlier intervention.

The clinical use of serum PSA has improved the ability to detect relapse after RP at an earlier interval.⁵ Early diagnosis of relapse following RP is desirable to select candidates for salvage therapies, such as radiation.⁶ Earlier intervention is

desirable to maximize the likelihood of salvage radiotherapy to eradicate residual disease.

Conventional serum PSA assays have a lower limit of detection of 0.1 to 0.4 ng/ml. Therefore, most groups to date have defined biochemical relapse after RP as a measurable PSA of 0.1 to 0.4 ng/ml. Ultrasensitive PSA assays allow a lower limit of detection to less than 0.01 ng/ml, resulting in earlier detection of biochemical relapse.^{7,8} In this retrospective analysis we determined if ultrasensitive PSA nadir after RP accurately predicts the risk of biochemical relapse.

METHODS

Following approval by our institutional review board the medical records of 906 men undergoing RP performed by a single surgeon (HL) between January 1997 and December 2000 were retrospectively reviewed to obtain clinical, pathological and followup data. All data were recorded in completely de-identified fashion for subsequent analysis. Pre-treatment and posttreatment PSA, Gleason score, clinical and pathological stage, and surgical margin status were recorded. Postoperative PSA measurement was performed at 3, 6 and 12 months, and yearly thereafter. Ultrasensitive PSA assays were requested prior to all scheduled followup appointments.

To evaluate accurately the ability of ultrasensitive PSA nadir to predict relapse only men with a minimum of 3 ultrasensitive PSA measurements during followup were included in the analysis. Because men were allowed to elect the most convenient laboratory in which to obtain followup PSA,

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many did not obtain an ultrasensitive measurement prior to every visit. Additionally, many ultrasensitive measurements were performed by different assays. To stratify properly men according to a nadir point of less than 0.01, 0.01, 0.02, or 0.04 or greater ng/ml we limited our analysis to PSA measurements by the Immulite Ultrasensitive Assay (DPC, Los Angeles, California), an assay with a lower limit of detection of (less than 0.01 ng/ml). Only men with a nadir measurement of less than 0.01 ng/ml or a minimum of 3 ultrasensitive measurements by this assay were included in the analysis. Measurements by other assays were excluded from analysis. Relapse was defined as 2 consecutive increasing post-nadir serum PSA measurements of 0.1 ng/ml or greater.

The 2-sample Student t test was used to compare followup time, time to nadir and time to relapse in the less than 0.01 ng/ml PSA nadir group against those in the other 3 subgroups. Pearson chi-square analysis was used for comparisons between pairs of the 4 PSA nadir groups. Finally, multivariate logistic regression analysis predicting relapse or no relapse was performed with the 4 PSA nadir groups, in addition to prostatectomy Gleason 7 or greater, preoperative PSA ng/ml or greater, positive surgical margin, and pathological stages T3A/B and T3C/4A. The Student t and chi-square tests were performed using SPSS v11.01 software (SPSS, Chicago, Illinois) and logistic regression was performed using Stata 8.0/SE software (StataCorp., College Station, Texas).

RESULTS

The charts of 906 men were retrospectively evaluated. Men were grouped according to a PSA nadir of less than 0.01, 0.01, 0.02, or 0.04 or greater ng/ml. Of the 906 men 545 (56%) were identified with a PSA nadir within these defined grouping criteria. Table 1 lists the clinical, pathological and demographic characteristics of the 4 groups. Individuals with a PSA nadir of 0.04 ng/ml or greater more often had a pretreatment PSA of 10 ng/ml or greater, Gleason score 8 or greater, clinically palpable disease and seminal vesical invasion. In-

dividuals with a nadir of less than 0.01, 0.01 and 0.02 ng/ml had similar baseline disease characteristics. Men with a nadir of 0.02 ng/ml or greater more often had positive surgical margins and extracapsular disease.

Men were followed a mean of 3.1 years. Surprisingly many men did not achieve a PSA nadir at the first postoperative measurement. Mean time to ultrasensitive PSA nadir was 10.4 months. Of the 545 men 54 (9.9%) experienced biochemical relapse. Relapse rates in men with a PSA nadir of less than 0.01 ng/ml (423), 0.01 ng/ml (75), 0.02 ng/ml (19) and 0.04 ng/ml or greater (28) were 4%, 12%, 16% and 89%, respectively (table 2). Mean time to relapse in men in the PSA nadir groups less than 0.01, 0.01, 0.02 and 0.04 or greater ng/ml was 31.1, 28.7, 16.0 and 19.7 months, respectively. Men with a PSA nadir of 0.04 ng/ml or greater were the only group to have a significantly shorter time to relapse than men with a PSA nadir of less than 0.01 ng/ml.

Chi-square analysis demonstrated that men with a PSA nadir of less than 0.01 ng/ml had a significantly lower rate of biochemical relapse than men with a nadir of 0.01 ng/ml ($p < 0.01$), 0.02 ng/ml ($p < 0.025$) and 0.04 ng/ml ($p < 0.01$). There was no significant difference in relapse prevalence between the PSA nadir 0.01 and 0.02 ng/ml groups but the relapse prevalence in these 2 groups was significantly smaller compared to that in the 0.04 ng/ml or greater nadir group (each $p < 0.01$).

Multivariate logistic regression analysis revealed that the PSA nadirs 0.01 ng/ml ($p = 0.045$), 0.02 ng/ml ($p = 0.048$) and 0.04 or greater ng/ml ($p < 0.001$) served as independent predictors of an increased risk of biochemical relapse compared with a PSA nadir of less than 0.01 ng/ml (table 3). In addition, preoperative PSA 10 ng/ml or greater ($p < 0.001$), pathological stage T3C or greater ($p = 0.001$), positive surgical margin ($p < 0.001$) and pathological Gleason score 7 or greater ($p = 0.004$) were also found to be independent predictors of biochemical relapse. Organ confined disease (pT2) was used as the reference variable in the analysis with pathological stage.

TABLE 1. Characteristics of men undergoing RP according to PSA nadir groups

Characteristic	PSA Nadir (ng/ml)			
	Less Than 0.01	0.01	0.02	0.04 or Greater
No. pts	423	75	19	28
Age:				
Median	60	60	58	61.5
Mean	59.74	60.36	57.89	61.21
Preop PSA (ng/ml):				
Median	5.7	5.8	6.6	7
Mean	6.66	6.9	7.94	10.2
No. less than 4 (%)	72 (17.0)	8 (10.7)	2 (10.5)	2 (7.1)
No. 4–10 (%)	296 (70.0)	57 (76.0)	14 (73.7)	18 (64.3)
No. greater than 10 (%)	55 (13.0)	10 (13.3)	3 (15.8)	8 (28.6)
No. biopsy Gleason score (%):				
4–5	47 (11.1)	4 (5.3)	3 (15.8)	3 (10.7)
6–7	365 (86.3)	70 (93.3)	16 (84.2)	18 (64.3)
8 or Greater	11 (2.6)	1 (1.3)	0	7 (25.0)
No. clinical stage (%):				
T1	349 (82.5)	65 (86.7)	16 (84.2)	17 (60.7)
T2	74 (17.5)	10 (13.3)	3 (15.8)	11 (39.3)
T3	0	0	0	0
No. pathological stage (%):				
T2	336 (79.4)	54 (72.0)	13 (68.4)	12 (42.9)
T3A–B	75 (17.7)	14 (18.7)	5 (26.3)	11 (39.3)
T3C	8 (1.9)	7 (9.3)	0	5 (17.9)
T4A	4 (0.9)	0	1 (5.3)	0
No. RP Gleason score (%):				
4–5	59 (13.9)	7 (9.3)	0	1 (3.6)
6–7	340 (80.4)	66 (88.0)	17 (89.5)	15 (53.6)
8 or Greater	24 (5.7)	2 (2.7)	2 (10.5)	12 (42.9)
No. surgical margin (%):				
Pos	64 (15.1)	11 (14.7)	7 (36.8)	11 (39.3)
Neg	359 (84.9)	64 (85.3)	12 (63.2)	17 (60.7)

TABLE 2. Biochemical relapse rates in PSA nadir groups

	PSA Nadir (ng/ml)				
	All	Less Than 0.01	0.01	0.02	0.04 or Greater
No. pts	545	423	75	19	28
No. relapses	54	17	9*	3*	25*
% Relapse	9.91	4.02	12.00	15.79	89.29
Mean followup \pm SD (yrs)	3.1 \pm 1.2	3.2 \pm 1.2	2.9* \pm 1.2*	2.7 \pm 1.2*	1.6 \pm 1.5*
Mean mos to nadir \pm SD	10.4 \pm 11.0	10.9 \pm 11.4	8.8 \pm 9.4	8.8 \pm 10.9	7.4 \pm 8.1
Mean mos to relapse \pm SD	25.2 \pm 16.1	31.1 \pm 15.3	28.7 \pm 16.9	16.0 \pm 6.9	19.7 \pm 16.6*

* Vs nadir group less than 0.01 ng/ml $p < 0.05$.

TABLE 3. Multivariate logistic regression analysis of prediction of biochemical relapse

Independent Variable	Logistic Regression Coefficient	95% CI	p Value
Preop PSA 10 ng/ml or greater	1.685	0.839–2.531	<0.001
Pathological stage:			
T2	Referent	Referent	
T3A/B	0.186	–0.706–1.078	0.683
T3C/T4A	2.271	0.984–3.557	0.001
Pathological Gleason 7 or greater	1.704	0.549–2.859	0.004
Pos margin	1.653	0.733–2.574	<0.001
Nadir PSA (ng/ml):			
Less than 0.01	Referent	Referent	
0.01	1.135	0.278–2.242	0.045
0.02	1.429	0.010–2.848	0.048
0.04 or Greater	6.345	4.513–8.178	<0.001

DISCUSSION

In the last decade predicting RP outcome using preoperative variables and surgical pathology has received significant attention. The ability to stratify the risk of relapse is useful for the proper selection of candidates for surgery as well as conventional and experimental adjuvant therapies. Polascik et al have previously proposed a nomogram to predict pathological stage based on preoperative PSA, clinical stage and biopsy Gleason score.⁹ Preoperative and postoperative variables have subsequently been integrated into predictive models, resulting in the development of nomograms that can be used to predict biochemical recurrence based on clinical and pathological data at followups as long as 10 years.^{10,11}

The ability to detect relapse after RP has been greatly enhanced by serum PSA monitoring. Biochemical relapse often predates clinical relapse by several years. This application of serum PSA has allowed a greater understanding of the true curative potential of surgery for prostate cancer and allowed earlier intervention with salvage radiotherapy. The definition of relapse after RP has been arbitrarily determined at several institutions. At our institution we have used a definition of 2 consecutive, increasing post-nadir serum PSA measurements of 0.1 ng/ml or greater. This is based on the observation that at our institution crossing the threshold of 0.1 ng/ml has consistently predicted a further PSA increase at early followup after RP (unpublished data).

In this study we determined if the nadir of ultrasensitive PSA measurements after RP accurately predicted the risk of relapse. We found that a nadir of less than 0.01 ng/ml predicted a significantly lower risk of relapse than any higher nadir point. Additionally, of men achieving a nadir of less than 0.01 ng/ml those who had relapsed experienced a longer interval prior to relapse (mean 31.1 months) than those with a higher nadir. Each increment of 0.01 ng/ml in PSA nadir demonstrated an increasing risk of recurrence with a shorter interval to relapse.

Based on our findings we have proposed that men with a PSA nadir of less than 0.01 ng/ml in year 1 of followup subsequently only need to undergo annual measurement of serum PSA. To date the relapse rate in men with a nadir point of greater than 0.04 ng/ml is 89%. We believe that these individuals should be considered for adjuvant therapy at an

early point in postoperative followup. Because the mean time to nadir in our series was less than 1 year, one might consider adjuvant or salvage therapy in any individual not achieving a PSA nadir of less than 0.04 ng/ml within year 1 of followup. The decision about salvage radiotherapy in this instance should be based on a combination of preoperative variables, surgical pathology and PSA velocity.

Doherty et al have previously reported that a PSA nadir of less than 0.01 ng/ml served as a good prognostic indicator for biochemical disease-free survival.¹² Although this study had a shorter followup (median 1.3 vs 3 years) and used a different definition of biochemical relapse (3 consecutive PSA increases) the conclusions of the 2 studies are consistent. In addition to validating the findings of Doherty et al, we found that absolute PSA nadir can provide risk stratification with regard to biochemical relapse. Our analysis confirmed that the 3 levels of detectable PSA nadir tested in our study serve as independent prognostic indicators of relapse.

In the current study positive surgical margins, seminal vesicle invasion, preoperative PSA and prostatectomy Gleason score were found to be significant independent predictors of relapse. Ultrasensitive PSA provided additional prediction of relapse when performing multivariate analysis incorporating these factors. When using a multivariate logistic regression model that did not incorporate ultrasensitive PSA nadir, the model had 31% sensitivity for the prediction of biochemical relapse. Upon the addition of ultrasensitive PSA nadir to the multivariate model, sensitivity improved to 53%. Moreover, the percent correct prediction of the latter model improved to 94.3% with the addition of ultrasensitive PSA nadir.

An important implication of our multivariate data is that the inclusion of ultrasensitive PSA nadir in postoperative nomograms would improve the ability of such nomograms to select candidates for adjuvant or salvage therapies. Such a nomogram might be implemented 1 year after surgery because PSA nadir was achieved at a mean followup of 10.4 months.

Because of the retrospective nature of our study, there are inherent limitations. Only 56% of the men in our study met inclusion criteria, primarily because of poor compliance with obtaining ultrasensitive PSA measurements. Although our

study group included 545 men, subgroup sizes varied considerably from 423 in the less than 0.01 ng/ml nadir group to 19 in the 0.02 ng/ml nadir group. Ultimately a larger number of men during followup may allow us to create predictive nomograms more effectively. Of the 906 men in the original database 33% did not have enough ultrasensitive PSA measurements to meet inclusion criteria. We do not believe that the exclusion of these men created significant bias in our study group since we observed no significant difference in relapse rate, Gleason score, margin status or stage between men who were excluded vs included. Finally, many men who met inclusion criteria had followup data performed with a conventional PSA assay. This could have masked the true patient nadir if it was lower than those measured by ultrasensitive assay.

Another significant potential limitation of our study is the relatively short patient followup (mean 3.1 years). It is conceivable that the absolute differences in relapse rate observed between PSA nadir stratiles may be lost with longer followup. This is particularly feasible given the delayed interval to relapse observed to date in patients at low risk. If this were the case, PSA nadir may simply be a surrogate measure of time to relapse rather than risk of relapse. Further followup with repeat analysis will allow us to determine this.

CONCLUSIONS

Ultrasensitive PSA nadir serves as an independent prognostic indicator for early biochemical failure following RP. Men with a lower nadir are less likely to have relapse and, when relapse occurs, it does so at a later interval. Individuals who achieve a nadir of less than 0.01 ng/ml by the ultrasensitive assay have an extremely low likelihood of early relapse. We believe that these men may require less frequent followup after RP. Individuals with a nadir of greater than 0.04 ng/ml have an extremely high likelihood of relapse, suggesting that they may be good candidates for early adjuvant or salvage intervention. Our study suggests that the incorporation of ultrasensitive PSA nadir into postoperative predictive nomograms may allow more accurate prediction of the risk of relapse after RP.

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