

# TIME TRENDS IN BIOCHEMICAL RECURRENCE AFTER RADICAL PROSTATECTOMY: RESULTS OF THE SEARCH DATABASE

THE SEARCH DATABASE STUDY GROUP: STEPHEN J. FREEDLAND, JOSEPH C. PRESTI, JR, CHRISTOPHER L. AMLING, CHRISTOPHER J. KANE, WILLIAM J. ARONSON, FREDERICK DOREY, AND MARTHA K. TERRIS

## ABSTRACT

**Objectives.** To determine whether in the prostate-specific antigen (PSA) era stage and/or grade migration of patients treated with radical prostatectomy (RP) has occurred. We also examined whether the biochemical recurrence rates after RP have changed with time.

**Methods.** A total of 1654 patients from the Shared Equal Access Regional Cancer Hospital (SEARCH) database were analyzed for time trends in age, preoperative PSA level, clinical stage, biopsy Gleason score, prostatectomy Gleason grade, pathologic stage, margin status, and recurrence rates after RP. Results were stratified into three 4-year blocks of time between 1988 and 2002 for analysis.

**Results.** The preoperative PSA level, patient age, tumor stage, rate of capsular penetration, and lymph node involvement decreased with time. Both biopsy and pathologic Gleason grade steadily increased with time. The positive margin rate and incidence of seminal vesicle involvement remained stable. On multivariate analysis, only serum PSA level ( $P < 0.001$ ) and biopsy Gleason score ( $P < 0.001$ ) were significant independent predictors of the time to recurrence after RP. The year of surgery was not a significant independent predictor of biochemical recurrence after RP in multivariate analysis.

**Conclusions.** Despite lower stage and lower PSA levels with time, we found no improvement in PSA recurrence rates over time. This may reflect lead-time bias in detecting PSA recurrence by the use of more sensitive PSA assays in recent years. UROLOGY 61: 736–741, 2003. © 2003, Elsevier Science Inc.

The Food and Drug Administration approved prostate-specific antigen (PSA) testing to monitor men with prostate cancer in 1986. It quickly

became apparent that PSA measurement was also a valuable tool for the detection of early-stage prostate cancer.<sup>1–3</sup> By the late 1980s, PSA testing was widely used to screen asymptomatic men for prostate cancer, leading to dramatic increases in the incidence of new prostate cancer diagnoses and a dramatic decrease in the incidence of advanced disease.<sup>4–6</sup> Combined with alterations in surgical technique that allowed improved potency preservation,<sup>7</sup> the rates of radical prostatectomy (RP) markedly increased.<sup>4,8</sup> Among men undergoing RP within the PSA era, there has been continued stage migration.<sup>9–12</sup> However, whether this stage migration within the PSA era has resulted in improved biochemical success after definitive therapy such as RP is unclear.<sup>11–13</sup> Moreover, PSA screening resulted in significant controversy as to whether it would result in patients being treated unnecessarily for small, clinically insignificant cancers.<sup>14</sup>

We sought to determine whether in the PSA era stage and/or grade migration has occurred and

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*From the Department of Urology, University of California, Los Angeles, School of Medicine, Los Angeles, California; Department of Urology, Stanford University School of Medicine, Palo Alto, California; Department of Urology, Naval Medical Center, San Diego, California; Department of Urology, University of California, San Francisco, School of Medicine, San Francisco, California; Department of Surgery, Veterans Affairs Greater Los Angeles Health Care System, Los Angeles, California; Department of Biostatistics, University of California, Los Angeles, Los Angeles, California; and Division of Urology, Medical College of Georgia, Augusta, Georgia*

*Reprint requests: Stephen J. Freedland, M.D., Department of Urology, University of California, Los Angeles, School of Medicine, 10833 Le Comte Avenue, 66-124 CHS, Box 951738, Los Angeles, CA 90095-1738*

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whether this has resulted in improvements in PSA control after RP. To examine this, we studied men treated with RP between 1988 and 2002 using a multicenter database of men treated with RP, the Shared Equal Access Regional Cancer Hospital (SEARCH) database. We determined whether there were changes in the clinical and pathologic features or biochemical recurrence rates with time.

## MATERIAL AND METHODS

After each institution provided institutional review board approval, patients undergoing RP since 1988 at the Veterans Affairs (VA) Health Care Facilities in West Los Angeles, Palo Alto, and San Francisco, as well as the San Diego Naval Hospital, were combined into one database, the SEARCH database.

Patients treated with preoperative androgen deprivation or radiotherapy were excluded. This resulted in a study population of 1684 patients. Patients were grouped into three groups on the basis of the year in which RP was performed. Group 1 was from 1988 to 1991, group 2 from 1992 to 1995, and group 3 from 1996 to 2002. The 1992 TNM staging system was used to classify the stage,<sup>15</sup> and tumors were graded using the Gleason grading system.<sup>16</sup> The clinical stage was unknown in 47 patients (6 in group 1, 38 in group 2, and 3 in group 3); the biopsy Gleason score was unknown in 207 patients (133 in group 1, 54 in group 2, and 15 in group 3); the serum PSA level was unknown in 286 patients (33 in group 1, 14 in group 2, and 240 in group 3); and age was unknown in 18 patients (all group 1).

The RP specimens were sectioned as per the usual routine of each individual institution and analyzed for Gleason score, pathologic stage, and involvement of the surgical margins.<sup>17-20</sup> Patients were followed for up to 164 months to determine PSA recurrence. Patients who received adjuvant radiotherapy or hormonal therapy for adverse pathologic findings with undetectable PSA levels were censored as not having recurrence at the time of treatment. Data from the three VA medical centers were collected retrospectively, and data from the San Diego Naval Hospital was collected prospectively starting in the mid-1990s. Recurrence was defined as a single PSA level greater than 0.2 ng/mL or two values at 0.2 ng/mL. However, the lower limit of detection for the PSA assays at the various institutions decreased over time, with lower limits of detection of up to 1.0 ng/mL at the beginning of the study period. No follow-up data were available for 107 patients (44 in group 1, 17 in group 2, and 48 in group 3). These patients were included for evaluating the difference among the varying periods for preoperative and pathologic characteristics, but not biochemical recurrence.

### STATISTICAL ANALYSIS

Age, biopsy Gleason score, and serum PSA level were examined as continuous variables. Clinical stage was evaluated as an ordinal variable of T1 versus T2-T3. The three groups were evaluated as a categorical variable for comparing the clinical and pathologic variables using an analysis of variance model. Predictors of time to biochemical recurrence were evaluated using a Cox proportional hazards model. For the multivariate analysis, a forward stepwise Cox regression survivorship model was used. A *P* value of less than 0.1 was used to determine which variables should be entered into the model at each step. The period of surgery was evaluated as a categorical variable. Survival curves were estimated using the technique of Kaplan and Meier. Differences in survival curves between the groups were evaluated using a log-rank test for equality of

survivorship. All clinical (age, clinical stage, serum PSA level, biopsy Gleason score) and pathologic (surgical Gleason score, pathologic stage, capsular penetration, surgical margin status, seminal vesicle invasion, and lymph node involvement) variables were similar among the four centers contributing to the SEARCH database. Therefore, the data from all four centers was combined for analysis. All statistical analyses were performed using STATA, version 7.0 (Stata, College Station, Tex).

## RESULTS

The clinical characteristics of the study population are shown in Table I. The annual number of patients undergoing RP steadily increased until 1992 and remained relatively stable since. Over time, the increase in the percentage of patients with clinical T1 tumors was steady and significant. The preoperative serum PSA level and median age at the time of surgery steadily declined with time. A steady rise in biopsy Gleason scores occurred over time. This was largely due to an increase in the number of Gleason score 6 tumors and a decrease in the number of Gleason score 4 and 5 tumors. No differences were found in the percentage of patients who had high-grade tumors (Gleason score 7 or greater) over time (*P* = 0.508).

The pathologic characteristics of the study population are shown in Table I. A small, but steady, increase in the percentage of patients who had organ-confined (pT2 or less) tumors was noted. Conversely, the rate of capsular penetration and the incidence of lymph node involvement steadily decreased over time. No association was found between the time of RP and the incidence of either positive surgical margins or seminal vesicle invasion. As with the biopsy Gleason scores, the pathologic Gleason scores from the surgical specimens steadily increased over time. This was largely a result of an increase in the number of Gleason score 6 tumors in the prostatectomy specimens and a decrease in the number of patients with Gleason score 4 or 5 tumors, mirroring the trend seen with biopsy. However, a trend was noted for an increasing percentage of patients with high-grade tumors (Gleason 7 or greater) over time (*P* = 0.078).

With a mean follow-up of 44 months (median 35), the overall biochemical recurrence rate was 25%. Using a log-rank analysis, the period in which RP was performed was a significant predictor of the time to biochemical recurrence, with more recent patients having higher PSA failure rates (*P* = 0.006, Fig. 1). Using a Cox proportional hazards model, group 2 (*P* = 0.001) and group 3 (*P* = 0.019) patients had higher biochemical recurrence rates than did group 1 patients (Table II). No difference was found in the time to biochemical recurrence between group 2 and group 3 patients (*P* = 0.589).

**TABLE I. Clinical and pathologic characteristics of men undergoing radical prostatectomy**

Characteristic	1988–91	1992–95	1996–02	P Value*
Patients (n)	314 (19)	534 (32)	836 (50)	
Clinical stage (n)				<0.001
T1a/b	23 (7)	11 (2)	12 (1)	
T1c	28 (9)	142 (29)	423 (51)	
T2	254 (82)	336 (68)	393 (47)	
T3	2 (1)	7 (1)	5 (1)	
Preoperative PSA (ng/mL)				<0.001
Mean ± SD	11.8 ± 18.1	11.2 ± 9.7	8.9 ± 7.6	
Median	6.2	8.4	6.8	
Age (yr)				<0.001
Mean ± SD	66.1 ± 6.2	64.6 ± 6.2	61.2 ± 6.5	
Median	67	65	62	
Biopsy Gleason score (n)				<0.001
2	9 (5)	8 (2)	4 (0)	
3	9 (5)	4 (1)	1 (0)	
4	37 (20)	80 (17)	48 (6)	
5	43 (24)	113 (24)	111 (14)	
6	31 (17)	115 (24)	399 (49)	
7	37 (20)	111 (23)	194 (24)	
8	10 (6)	35 (7)	48 (6)	
9	4 (2)	12 (3)	16 (2)	
10	1 (1)	2 (0)	0 (0)	
Mean ± SD	5.4 ± 1.6	5.8 ± 1.4	6.1 ± 1.0	
Pathologic stage (n)				0.028
≤T2	199 (67)	359 (68)	613 (74)	
T3	91 (31)	145 (28)	203 (24)	
T4	7 (2)	21 (4)	18 (2)	
Pathologic Gleason score				<0.001
2	1 (1)	1 (0)	0 (0)	
3	10 (6)	8 (2)	1 (0)	
4	23 (14)	33 (6)	9 (1)	
5	43 (25)	133 (26)	79 (10)	
6	26 (15)	112 (22)	327 (41)	
7	41 (24)	177 (34)	313 (39)	
8	11 (7)	30 (6)	34 (4)	
9	12 (7)	26 (5)	35 (4)	
10	1 (1)	0 (0)	1 (0)	
Mean ± SD	5.9 ± 1.6	6.2 ± 1.3	6.5 ± 0.9	
Positive surgical margins (n)	83 (27)	176 (34)	244 (29)	0.113
Capsular penetration (n)	91 (31)	131 (25)	182 (22)	0.010
Seminal vesicle invasion (n)	29 (9)	55 (10)	63 (8)	0.183
Positive lymph nodes (n)	12 (4)	17 (3)	8 (1)	0.009

KEY: PSA = prostate-specific antigen.  
 Numbers in parentheses are percentages.  
 \* Analysis of variance.

In multivariate analysis using a stepwise Cox proportions hazard analysis, only serum PSA ( $P < 0.001$ ) and biopsy Gleason score ( $P < 0.001$ ) were independent predictors of the time to biochemical failure (Table II). The period of surgery was not a significant independent predictor of the time to biochemical recurrence after RP in multivariate analysis. Moreover, when each center was examined separately, the period of surgery was not a significant predictor of biochemical recurrence after RP on multivariate analysis ( $P > 0.1$  for all analyses).

## COMMENT

The introduction of PSA testing has had a dramatic impact on the incidence and treatment of prostate cancer. The incidence of localized disease and thus the number of men who are candidates for curative treatments, including RP, increased significantly. This gave rise to concern that many men who had clinically insignificant tumors would be subjected to potentially morbid and unnecessary treatments. We found that during the PSA era, the average age of men undergoing RP decreased sig-

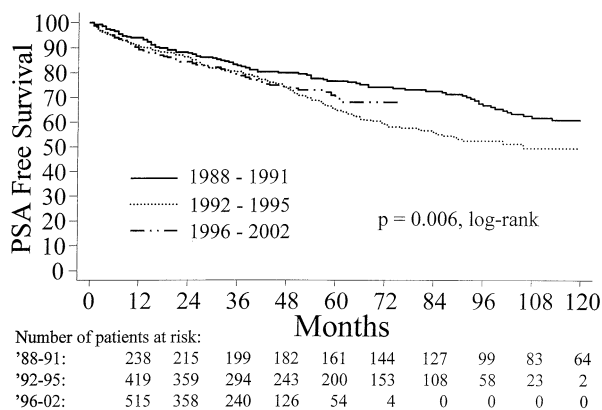


FIGURE 1. Kaplan-Meier survival curves of patients undergoing radical prostatectomy separated by the period of surgery. P value was computed using log-rank survivorship analysis.

nificantly. Although a steady increase in the incidence of organ-confined disease and a concomitant decrease in the incidence of adverse pathologic findings at the time of RP occurred, a trend was noted for a greater percentage of men to have high pathologic Gleason scores (7 or greater). Combined with lead-time bias for detecting biochemical recurrence by the use of PSA assays with a lower threshold of detection in more recent years, a greater PSA recurrence rate was found among the more recently treated men in univariate analysis. However, after controlling for serum PSA level, biopsy Gleason score, and clinical stage, the period of surgery was not a significant independent predictor of the time to biochemical failure after RP.

Adverse pathologic findings are often used as a surrogate of advanced disease. Indeed, much effort has been put into preoperatively predicting the pathologic findings at the time of RP.<sup>21</sup> We found that over time, the incidence of lymph node involvement and extracapsular disease steadily decreased. Similarly, the rate of organ-confined disease increased. These findings are in agreement with several prior studies.<sup>9-12,22</sup> However, Soh *et al.*<sup>13</sup> found that over time no differences were found in the pathologic stage of men undergoing RP, although there was a decrease in the incidence of advanced disease (established extraprostatic extension with a positive surgical margin, seminal vesicle invasion, or lymph node metastases). The increased percentage of patients with organ-confined disease in the current report was less than that previously reported.<sup>10,11</sup> This was likely because the current series included only patients treated since 1988 as opposed to the prior studies that also included patients treated before the introduction of PSA screening.

In the current study, a steady increase occurred in both biopsy and pathologic Gleason scores over time. This was largely due to an increased inci-

dence of Gleason score 6 tumors and a decreased incidence of Gleason score 4 and 5 tumors. Other studies found similar results.<sup>11,13,23</sup> Whether this reflects a changing natural history of prostate cancer or systematic upgrading over time remains to be determined.<sup>24</sup> However, given that Epstein<sup>25</sup> recently recommended that a diagnosis of Gleason score 2 to 4 should not be made on a needle biopsy, it is likely that this trend for a decreased incidence of lower Gleason scores will continue.

Although biochemical-free survival among men undergoing RP during the PSA era has improved relative to men treated before widespread PSA testing, several studies failed to find continued improvement in recurrence rates during the PSA era.<sup>11,13</sup> The current study, encompassing only patients treated during the PSA era, found that the period of RP was not a significant independent predictor of biochemical recurrence. This is in contrast to a recent report by Ung *et al.*<sup>12</sup> who found biochemical recurrence rates have decreased during the PSA era. Given that more recent patients had lower incidences of advanced pathologic findings and higher rates of organ-confined disease in the current study, it is unclear why this did not translate into improved PSA-free survival rates. One possible explanation is the higher Gleason scores among more recently treated men. However, whether these increased Gleason scores truly reflect disease differences or systematic upgrading is unknown.<sup>24</sup> The most likely explanation for a lack of improved PSA-free survival among more recently treated patients is lead-time bias in the detection of biochemical recurrence by the use of PSA assays with greater sensitivity to detect low levels of PSA. The use of PSA testing with lower levels of detection results in the detection of biochemical recurrence as much as 18 months earlier.<sup>26,27</sup> In the current study, the PSA recurrence definition was a single value greater than 0.2 ng/mL or two values at 0.2 ng/mL. Therefore, a patient with a PSA value of 0.21 ng/mL by ultrasensitive PSA testing was considered to have recurrence. However, with a less sensitive PSA assay, this would equate to a single PSA level of 0.2 ng/mL, which would not be considered recurrence until a second PSA value at 0.2 ng/mL, which might be several months later. Moreover, in the early 1990s, the lowest threshold of PSA detection was greater than 1.0 ng/mL. As a result, men whose serum PSA values were greater than 0.2 but less than 1.0 ng/mL, and who thus should have been considered to have recurrence, had an undetectable PSA value and were considered to not have recurrence. Another possible reason for the lack of a reduction in the PSA recurrence rates over time is that our patient populations were clinic based rather than a screening population. One may be

**TABLE II. Cox proportional hazards analysis of factors predicting time to biochemical recurrence after radical prostatectomy**

	HR	95% CI	P Value
Univariate analysis			
Biopsy Gleason score	1.29	1.19–1.40	<0.001
Serum PSA	1.03	1.02–1.03	<0.001
Clinical stage	1.18	0.95–1.46	0.144
Age	1.00	0.99–1.02	0.904
Time period (continuous variable)	1.17	1.02–1.34	0.030
1992–95 (relative to 1988–91)	1.54	1.18–2.01	0.002
1996–02 (relative to 1988–91)	1.42	1.06–1.91	0.019
1996–02 (relative to 1992–95)	0.94	0.74–1.19	0.589
Multivariate analysis			
Serum PSA	1.02	1.01–1.02	<0.001
Biopsy Gleason score	1.24	1.14–1.36	<0.001

KEY: HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen.

more likely to see a difference in PSA recurrence in a screening population with aggressive screening such that patients diagnosed more recently would be expected to have much lower stage and PSA values.

The limitations to the current study were that it was retrospective and the mean follow-up was relatively short. Furthermore, because all four centers in the SEARCH database are equal access medical centers in California, the current findings may not apply to patients at non-equal access medical centers.

## CONCLUSIONS

During the PSA era and among our patient population, a steady shift was found for men to undergo surgery at younger ages and for earlier stage disease. However, the mean Gleason scores increased over time. Despite this stage migration, we found no improvement in PSA recurrence rates with time. This may reflect lead-time bias in detecting PSA recurrence by the use of more sensitive PSA assays.

## REFERENCES

1. Cooner WH, Mosley BR, Rutherford CL Jr, *et al*: Clinical application of transrectal ultrasonography and prostate specific antigen in the search for prostate cancer. *J Urol* 139: 758–761, 1988.
2. Catalona WJ, Smith DS, Ratliff TL, *et al*: Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 324: 1156–1161, 1991.
3. Catalona WJ, Smith DS, Ratliff TL, *et al*: Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. *JAMA* 270: 948–954, 1993.
4. Newcomer LM, Stanford JL, Blumenstein BA, *et al*: Temporal trends in rates of prostate cancer: declining incidence of advanced stage disease, 1974 to 1994. *J Urol* 158: 1427–1430, 1997.
5. Hankey BF, Feuer EJ, Clegg LX, *et al*: Cancer surveillance series: interpreting trends in prostate cancer—part I:

evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. *J Natl Cancer Inst* 91: 1017–1024, 1999.

6. Dennis LK, and Resnick MI: Analysis of recent trends in prostate cancer incidence and mortality. *Prostate* 42: 247–252, 2000.

7. Walsh PC, and Donker PJ: Impotence following radical prostatectomy: insight into etiology and prevention. *J Urol* 128: 492–497, 1982.

8. Xia Z, Jacobsen SJ, Bergstralh EJ, *et al*: Secular changes in radical prostatectomy utilization rates in Olmsted County, Minnesota, 1980 to 1995. *J Urol* 159: 904–908, 1998.

9. Jhaveri FM, Klein EA, Kupelian PA, *et al*: Declining rates of extracapsular extension after radical prostatectomy: evidence for continued stage migration. *J Clin Oncol* 17: 3167–3172, 1999.

10. Amling CL, Blute ML, Lerner SE, *et al*: Influence of prostate-specific antigen testing on the spectrum of patients with prostate cancer undergoing radical prostatectomy at a large referral practice. *Mayo Clin Proc* 73: 401–406, 1998.

11. Han M, Partin AW, Piantadosi S, *et al*: Era specific biochemical recurrence-free survival following radical prostatectomy for clinically localized prostate cancer. *J Urol* 166: 416–419, 2001.

12. Ung J, Richie J, Chen M, *et al*: Evolution of the presentation and pathologic and biochemical outcomes after radical prostatectomy for patients with clinically localized prostate cancer diagnosed during the PSA era. *Urology* 60: 458–463, 2002.

13. Soh S, Kattan MW, Berkman S, *et al*: Has there been a recent shift in the pathological features and prognosis of patients treated with radical prostatectomy? *J Urol* 157: 2212–2218, 1997.

14. Montie JE: Controversies in the early detection of prostate cancer. *In Vivo* 8: 407–411, 1994.

15. Beahrs OH, Henson DE, and Hutter RVP: *American Joint Committee on Cancer Manual for Staging Cancer*. Philadelphia, JB Lippincott, 1992.

16. Gleason DF: Classification of prostatic carcinomas. *Cancer Chemother Rep* 50: 125–128, 1966.

17. Terris MK: Sensitivity and specificity of sextant biopsies in the detection of prostate cancer: preliminary report. *Urology* 54: 486–489, 1999.

18. Borirakchanyavat S, Bhargava V, Shinohara K, *et al*:

Systematic sextant biopsies in the prediction of extracapsular extension at radical prostatectomy. *Urology* 50: 373–378, 1997.

19. Freedland SJ, Jalkut M, Dorey F, *et al*: Race is not an independent predictor of biochemical recurrence after radical prostatectomy in an equal access medical center. *Urology* 56: 87–91, 2000.

20. Borboroglu PG, Comer SW, Riffenburgh RH, *et al*: Extensive repeat transrectal ultrasound guided prostate biopsy in patients with previous benign sextant biopsies. *J Urol* 163: 158–162, 2000.

21. Partin AW, Kattan MW, Subong EN, *et al*: Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. *JAMA* 277: 1445–1451, 1997.

22. Arai Y, Egawa S, Tobisu K, *et al*: Radical retropubic prostatectomy: time trends, morbidity and mortality in Japan. *BJU Int* 85: 287–294, 2000.

23. Schwartz KL, Grignon DJ, Sakr WA, *et al*: Prostate cancer histologic trends in the metropolitan Detroit area, 1982 to 1996. *Urology* 53: 769–774, 1999.

24. Smith EB, Frierson HF Jr, Mills SE, *et al*: Gleason scores of prostate biopsy and radical prostatectomy specimens over the past 10 years: is there evidence for systematic upgrading? *Cancer* 94: 2282–2287, 2002.

25. Epstein JI: Gleason score 2-4 adenocarcinoma of the prostate on needle biopsy: a diagnosis that should not be made. *Am J Surg Pathol* 24: 477–478, 2000.

26. Vassilikos EJ, Yu H, Trachtenberg J, *et al*: Relapse and cure rates of prostate cancer patients after radical prostatectomy and 5 years of follow-up. *Clin Biochem* 33: 115–123, 2000.

27. Takayama TK, Vessella RL, Brawer MK, *et al*: The enhanced detection of persistent disease after prostatectomy with a new prostate specific antigen immunoassay. *J Urol* 150: 374–378, 1993.