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# Relapse and Cure Rates of Prostate Cancer Patients After Radical Prostatectomy and 5 Years of Follow-Up

EVYENIA J.K. VASSILIKOS,[1] HE YU,[2] JOHN TRACHTENBERG,[3] ROBERT K. NAM,[3] STEVEN A. NAROD,[4] IRVING L. BROMBERG,[1,4] and ELEFTHERIOS P. DIAMANDIS[5]

[1]Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada; [2]Department of Medicine, Section for Cancer Prevention, Louisiana State University Medical School, Shreveport, Louisiana, USA; [3]Division of Urology, The Toronto Hospital, Toronto, Ontario, Canada; and [4]The Centre for Research in Women's Health, and [5]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada

**Objectives:** We have compared the ability of an ultrasensitive prostate specific antigen assay and a regular PSA assay to identify relapse and cure rates of prostate cancer patients after radical prostatectomy, during a 5-year follow-up period.
**Design and methods:** We measured PSA by an ultrasensitive assay (detection limit 0.001 ng/mL) and a conventional PSA assay (detection limit 0.1 ng/mL) in serial serum samples obtained from 197 patients who have undergone radical prostatectomy.
**Results:** Based on ultrasensitive PSA analysis, we have identified three groups of patients: 62% of patients did not show any significant changes in serum PSA; 15% of patients demonstrated slow PSA increases over time but none of the measurements exceeded 0.1 ng/mL within 4 years; and 23% of the patients had relatively significant increases of serum PSA and were classified as having 'fast relapse'. The vast majority of these patients were subsequently identified to have relapse by the regular PSA assay. The ultrasensitive PSA assay detected relapse by an average of eighteen months earlier than the conventional PSA method. Fast relapsing patients were associated with other prognostic indicators of the disease including pre-operative PSA, tumor volume, Gleason score, clinical stage, surgical margin positivity, periprostatic tissue involvement, capsular invasion and seminal vesicle invasion. The group with slowly rising PSA had prognosis which was between the patients in remission and fast relapsing patients.
**Conclusions:** The use of ultrasensitive PSA analysis for monitoring patients after radical prostatectomy provides earlier detection of relapse (by 18 months) and identifies three distinct groups of patients. Fast relapsing patients should be good candidates for early therapeutic interventions. Copyright © 2000 The Canadian Society of Clinical Chemists

KEY WORDS: prostate cancer; cancer monitoring; prostate specific antigen; ultrasensitive assay; cancer relapse; cancer cure; tumor markers.

Correspondence: Dr. E.P. Diamandis, Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5, Canada. E-Mail: ediamandis@mtsinai.on.ca

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## Introduction

One of the most important clinical applications of serum prostate specific antigen (PSA) is for detecting prostate cancer recurrence after radical prostatectomy (1–3). Studies have shown that consistent increases in serum PSA after surgical resection of the prostate are indicative of recurrence of the disease (4,5). Since the PSA elevation occurs much earlier than the development of clinical signs and symptoms (6–8), PSA-defined biochemical relapse of prostate cancer has been widely accepted as an early predictor of clinical recurrence. However, because of the limitation of PSA analytical methods to detect minute amounts of PSA, little is known about the actual levels of serum PSA in patients treated with radical prostatectomy and then monitored with conventional PSA assays, which indicate "absence" of this marker from serum. It remains unclear if there are changes in serum PSA concentrations that are undetectable by the regular PSA test and yet detectable by more sensitive assays, and if these changes have any clinical utility. Understanding these issues will help to determine if the PSA-based detection of prostate cancer recurrence can be further optimized and then used for early therapeutic interventions.

In our previous study, we evaluated this issue with use of a highly sensitive immunoassay for PSA (9). The method used had a detection limit of 0.001 ng/mL, which was 100-fold lower than most conventional PSA methods with detection limits ~0.1 ng/mL. Our preliminary results indicated that prostate cancer recurrence, defined by the ultrasensitive PSA assay, was associated with a number of clinical and pathological features that are known to be unfavourable for prognosis of prostate cancer, including positive surgical margins, Gleason score and tumor volume. Our study suggested that changes of serum

PSA at very low levels (under the detection limit of conventional PSA assays) were associated with the risk of prostate cancer recurrence and that by using an ultrasensitive PSA assay to monitor post-radical prostatectomy patients, we could identify prostate cancer recurrence earlier than by using the conventional PSA methods. Our data have been confirmed and are in accordance with other published reports on this issue (10–14).

In this work, we have followed up a cohort of 197 patients who have undergone radical prostatectomy about 5 years ago and attempted to establish their outcomes. Unique in our study was the use of a highly sensitive PSA immunoassay with a detection limit of 0.001 ng/mL. The high sensitivity of this assay allowed us to categorize these patients into three distinct groups. (a) Those who did not show any significant change in serum PSA, as determined by the highly sensitive PSA monitoring. We consider these patients as being 'cured' from the disease. (b) Those who show a detectable but relatively slow PSA increase over time. We consider these patients as 'biochemically relapsing'. (c) Those who show relatively rapid and consistent increases in serum PSA shortly after radical prostatectomy and who are destined to relapse clinically.

The early identification and classification of these patients into the three distinct groups may help physicians to optimize the management of these patients at an early stage.

## Methods

### Patients and serum specimens

Prostate cancer patients who were followed by serial serum PSA analysis after radical prostatectomy and whose serum PSA concentration was under the detection limit of a regular PSA assay (<0.1 ng/mL) in the first post-surgical specimen, were the initial recruiting criteria for our study. During February 1993 through November 1994, a total of 347 patients who met the criteria were consecutively identified at the Prostate Centre of The University Health Network, Ontario, Canada. Sequential serum specimens subsequently drawn for PSA testing from these patients were continuously collected until May 1998. Of the 347 patients, 197 had three or more sequential serum specimens collected during the study period. Our study has been approved by the Ethics Committees of The University Health Network and the University of Toronto.

The results of this study are based on the 197 patients who had at least three serial specimens. More than 87% of patients had 4 or more serial serum samples, 67% had 5 or more, 46% had 6 or more, 33% had 7 or more and 24% had 8 or more serial samples (maximum 17 samples). The median duration between surgery and collection of the first serial sample was 7 months, and the median duration between surgery and collection of the last serial sample was 60 months. The median time for collecting these samples, that is, the time interval between the first and last collection of these samples, was 48 months.

Of the 197 patients, 8 (4.1%) had radical prostatectomy before 1990, 15 (7.6%) in 1990, 35 (17.8%) in 1991, 42 (21.3%) in 1992, 63 (32.0%) in 1993 and 30 (15.2%) in 1994. Four patients (2%) had no information on their surgery date. The age of the patients ranged from 45 to 73 years and the mean was 63. For the 169 patients who had information on follow-up time, the mean follow-up (identical to median) was 52.5 months (SD = 20.4) and the range was between 7 and 108 months. Clinical and pathological information available for the study included preoperative PSA, tumor volume, clinical stage, histological grade (Gleason score), surgical margin involvement, apical margin involvement, periprostatic tissue involvement, capsular invasion, seminal vesicle invasion, bladder neck invasion and nodal involvement.

Among the 197 patients, 194 had PSA recurrence status determined by our ultrasensitive PSA test and 171 had PSA recurrence status determined by the regular PSA test. Patient relapse based on ultrasensitive PSA monitoring was considered, based on the following arbitrary criteria, as defined previously (9,15). (a) At least 2 consecutive PSA concentration increases after the baseline sample. Baseline sample was considered the first available sample after surgery. (b) The two consecutive increases should at least double the baseline PSA concentration.

Patients who met the above criteria for relapse were further classified into two categories; fast relapse and slow relapse, as follows: Fast relapse patients changed their serum PSA rapidly, crossing the cutoff level of 0.1 ng/mL (100 ng/L) earlier than 4 years post-surgery. Slow relapse patients had detectable increases of serum PSA over time which either never crossed or crossed the 0.1 ng/mL cutoff more than 4 years post-surgery.

The definition of relapse determined by the conventional PSA test was as follows, based on the criteria used at the Prostate Center of The University Health Network. A PSA value >0.2 ng/mL on at least 2 consecutive occasions, which occurred at least 3 months apart or a value greater than 1.0 ng/mL at any time post-surgery.

The ultrasensitive PSA assay used in this study has been described in detail in our previous papers (16,17). Briefly, the assay is an immunofluorometric method using two monoclonal anti-PSA antibodies. After forming a sandwich between PSA and the capture and detection antibody, the detection antibody, conjugated with biotin, further reacted with alkaline phosphatase-conjugated streptavidin. The substrate for the alkaline phosphatase was diflunisal phosphate, which, after being hydrolyzed by the enzyme, generated long-lasting fluorescence with a distinct wavelength in the presence of $Tb^{3+}$ and EDTA (18). The fluorescence was measured in a time-resolved mode to minimize non-specific back-

ground signal. The assay has a detection limit of 0.001 ng/mL. The precision of the assay for both within- and between-run was between 5–13% (coefficient of variation) within the measurement range. All specimens were measured in triplicate. Serial samples from the same patient were measured within the same microtiter plate to minimize the variation between plates and runs.

The conventional PSA assay used in this study was the Abbott IMx, Abbott Diagnostics, (Chicago, IL, USA) with a detection limit of 0.1 ng/mL.

### Statistical analysis

Clinical and pathological features were compared between patients with and without PSA recurrence using analysis of variance (ANOVA) for means, Wilcoxon rank sum test for medians and chi-square test or Fisher's exact test for categorical data. Associations of PSA recurrence with clinical/pathological features of the patients were analyzed using the Cox proportional hazards regression model (19). Survival time was defined as the time interval between the date of surgery and the date of disease recurrence or the date of the last serum specimen collected in the study for PSA test. The survival analysis was performed univariately only, because the purpose of the analysis was to compare the associations of known prognostic features with different survival outcomes determined by either a regular PSA test or the ultrasensitive PSA test, instead of assessing the prognostic value of these features. Most of the clinical and pathological features analyzed in the Cox regression model as independent variables are well-established prognostic markers for prostate cancer. They included continuous variables (pre-operative PSA and tumor volume), ordinal categorical variables (clinical stage and Gleason score) and dichotomous categorical variables (surgical margin involvement, apical margin involvement, periprostatic tissue involvement, capsular invasion, seminal vesicle invasion and bladder neck invasion). Since only three patients were found to have metastatic lesions in lymph nodes, the variable of nodal involvement was not included in the analysis. All $p$ values were derived from two-sided statistical tests.

## Results

### Regular PSA recurrence versus ultrasensitive PSA recurrence

Among the 197 patients in the study, 194 had PSA recurrence status determined by our ultrasensitive PSA assay. Of the 194 patients, 120 (62%) were in remission, 44 (23%) had fast recurrence and 30 (15%) had slow recurrence. Three patients did not have sufficient ultrasensitive PSA results to determine their relapse status. Examples of patients with fast recurrence are shown in Figures 1 and 2, patients with slow recurrence are shown in Figure 3 and patients in remission, in Figure 4. The status of

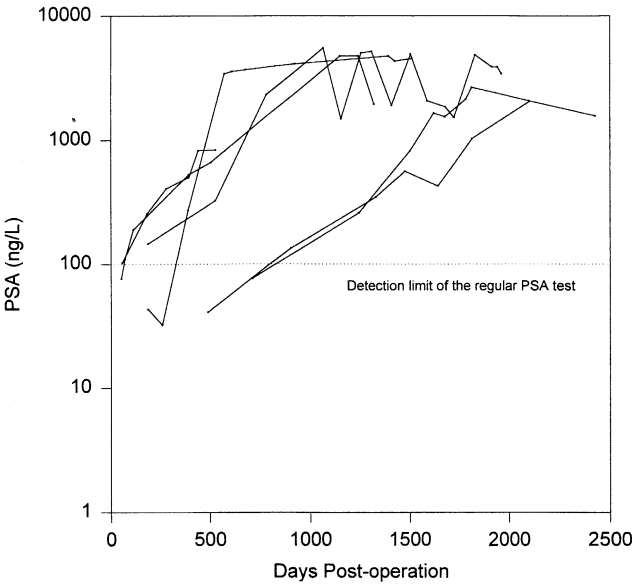


Figure 1 — Changes of serum PSA over time, as determined by the ultrasensitive PSA assay. Examples of patients who relapsed quickly (<2 years) after radical prostatectomy.

recurrence determined by the regular PSA test could be found in 171 patients, of whom 134 (78%) were in remission and 33 (19%) had recurrent disease. There were four patients whose post-operative PSA levels never went below the detection limit of the regular PSA assay (0.1 ng/mL). These patients were not included in the data analysis.

Of the 167 patients who had information on PSA recurrence by both methods, 80% of the patients were shown to have agreement on their recurrence status, which included 105 patients in remission

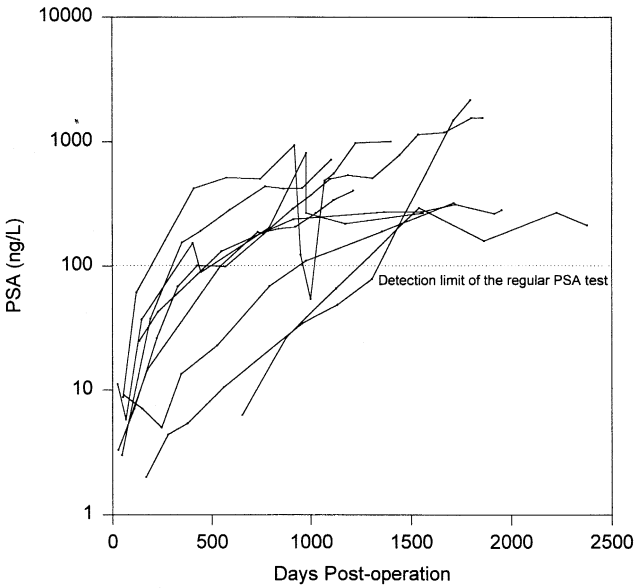


Figure 2 — Changes of serum PSA over time, as determined by the ultrasensitive PSA assay. additional examples of patients who were classified to have 'fast relapses', based on the criteria outlined in the text.

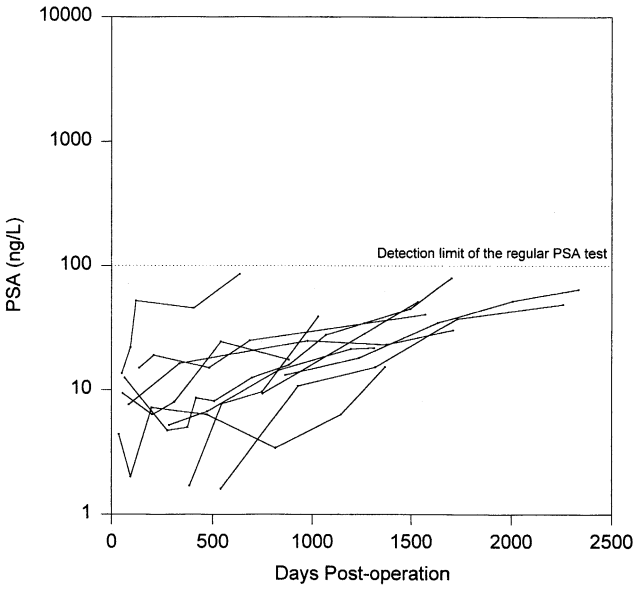


Figure 3 — Changes of serum PSA over time, as determined by the ultrasensitive PSA assay. Examples of patients who were classified to have 'slow relapses', based on the criteria outlined in the text.

and 31 with recurrent disease determined by both methods (Table 1). Of the additional 31 patients who were in remission by the regular PSA test, 26 (84%) were in slow recurrence and 5 (16%) were in fast recurrence, as determined by the ultrasensitive PSA assay. Overall, using the ultrasensitive PSA test, 31 patients (30%) who were considered in remission by a regular PSA test would be reclassified as having recurrence (Table 1).

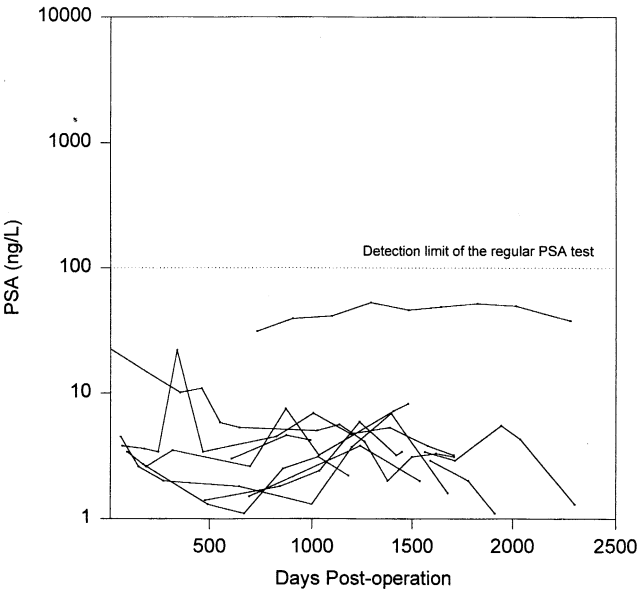


Figure 4 — Changes of serum PSA over time, as determined by the ultrasensitive PSA assay. Examples of patients who were classified as being in remission or cured, based on the criteria outlined in the text.

TABLE 1
Classification of 167 Patients into Various Groups by the Regular PSA and Ultrasensitive PSA Test

| Status by Regular PSA Test | Ultrasensitive PSA Test | | |
|---|---|---|---|
| | Remission | Slow Relapse | Fast Relapse |
| Remission ($n$ = 136) | 105 | 26 | 5 |
| Recurrence ($n$ = 31) | 0 | 0 | 31 |

$n$ = number of patients.

### ASSOCIATION OF PSA RECURRENCE WITH CLINICAL AND PATHOLOGICAL FEATURES

The recurrence status determined by the regular PSA test was significantly associated with the following clinical and pathological features: high preoperative PSA ($p < 0.001$), large tumor volume ($p < 0.001$), high Gleason score ($p = 0.001$), positive surgical margin ($p = 0.001$), periprostatic tissue involvement ($p = 0.001$), capsular invasion ($p = 0.003$), seminal vesicle invasion ($p = 0.001$) and advanced disease stage ($p = 0.020$) (Table 2). No significant differences were found for apical margin involvement ($p = 0.27$) and bladder neck invasion ($p = 0.23$). Patients with and without recurrence had similar age at diagnosis ($p = 0.29$) and follow-up time ($p = 0.88$).

The same associations were also found for patients who had ultrasensitive PSA recurrence. Table 3 shows that the ultrasensitive PSA recurrence was significantly associated with high preoperative PSA ($p < 0.001$), large tumor volume ($p \leq 0.001$), high Gleason score ($p < 0.001$), positive surgical margin ($p = 0.001$), periprostatic tissue involvement ($p = 0.001$), capsular invasion ($p = 0.058$) and seminal vesicle involvement ($p = 0.005$). In addition, advanced clinical stages were significantly associated with recurrence ($p = 0.0001$). Similar to regular PSA recurrence, no relationship was found for apical margin involvement ($p = 0.73$), bladder neck invasion ($p = 0.23$), patient age ($p = 0.52$) or length of follow-up time ($p = 0.11$).

Although fewer patients with slow PSA recurrence had unfavourable clinical and pathological features, compared to patients with fast PSA recurrence, the group with slow recurrence still had a higher percentage of unfavourable clinical and pathological features than those in remission. The dose-response effect between patients in remission, slow recurrence and fast recurrence could be seen for the variables of pre-operative PSA, mean Gleason score, clinical stage, surgical margin positivity, periprostatic tissue involvement and capsular invasion (Table 3).

### TIME DIFFERENCE IN DETECTING RECURRENCE BETWEEN REGULAR AND ULTRASENSITIVE PSA

There were 31 patients who had PSA recurrence determined by both the regular and ultrasensitive

TABLE 2
Association of Clinical and Pathological Features of Prostate Cancer Patients with Remission or Recurrence, as Determined by the Regular PSA Test

| Variables | Remission | Recurrence | *p* Value |
|---|---|---|---|
| *No. of patients* | *134* | *33* | |
| Mean age (yrs.) | 62 | 64 | 0.29[a] |
| Mean follow-up (months) | 53 | 53 | 0.89[a] |
| *(No. of patients)* | *(133)* | *(33)* | |
| Median Pre-op PSA (ng/ml) | 5.9 | 11.0 | <0.001[b] |
| *(No. of patients)* | *(132)* | *(32)* | |
| Median tumor volume (%) | 20 | 38 | <0.001[b] |
| *(No. of patients)* | *(117)* | *(28)* | |
| Median Gleason score | 7 | 7 | <0.001[b] |
| Mean Gleason score | 6.3 | 7.2 | 0.001[a] |
| *(No. of patients)* | *(134)* | *(32)* | |
| Clinical stage (%) | | | |
| *(No. of patients)* | *(134)* | *(33)* | |
| T1a, T1b, T1c | 42.3 | 21.2 | |
| T2a, T2b, T3a, T3b | 56.7 | 78.8 | 0.020[d] |
| Gleason score (%) | | | |
| *(No. of patients)* | *(134)* | *(32)* | |
| <6/10 | 20.9 | 6.3 | |
| 6/10 | 23.1 | 9.4 | |
| 7/10 | 46.3 | 50.0 | |
| 8/10+ | 9.7 | 34.4 | 0.001[d] |
| Surgical margin (%) | | | |
| *(No. of patients)* | *(132)* | *(32)* | |
| Negative | 75.0 | 37.5 | |
| Positive | 25.0 | 62.5 | 0.001[d] |
| Apical margin (%) | | | |
| *(No. of patients)* | *(131)* | *(33)* | |
| Negative | 64.9 | 54.6 | |
| Positive | 35.1 | 45.4 | 0.27[d] |
| Periprostatic tissue involvement (%) | | | |
| *(No. of patients)* | *(132)* | *(32)* | |
| Negative | 59.1 | 18.8 | |
| Positive | 40.9 | 81.2 | 0.001[d] |
| Capsular invasion (%) | | | |
| *(No. of patients)* | *(133)* | *(32)* | |
| Negative | 36.1 | 9.4 | |
| Positive | 63.9 | 90.6 | 0.003[d] |
| Seminal vesicle invasion (%) | | | |
| *(No. of patients)* | *(133)* | *(33)* | |
| Negative | 92.5 | 63.6 | |
| Positive | 7.5 | 36.4 | 0.001[c] |
| Bladder neck invastion (%) | | | |
| *(No. of patients)* | *(133)* | *(33)* | |
| Negative | 94.7 | 87.9 | |
| Positive | 5.3 | 12.1 | 0.23[c] |

[a]Analysis of variance.
[b]Wilcoxon rank sum test.
[c]Fisher's exact test.
[d]Chi-square test.

PSA analysis (Table 1). The time intervals from surgery to recurrence, determined by the two methods were compared among 29 patients who had complete collection of postoperative serum samples. The results of the analysis are shown in Table 4. The mean time intervals were 20.5 months for ultrasensitive PSA and 38.4 months for regular PSA. The time of recurrence determined by ultrasensitive PSA was significantly shorter than regular PSA ($p < 0.001$). On average, using the ultrasensitive PSA test, we could detect prostate cancer relapse about 18 months earlier than by using the regular PSA test.

### SERUM LEVELS OF PSA AMONG PATIENTS WITHOUT PSA RECURRENCE

Among the 103 patients who had no recurrence, as defined by both methods, there were only 25 (23%) patients whose serum PSA was consistently undetectable in their serial serum samples by the ultra-

TABLE 3
Association of Clinical and Pathological Features of Prostate Cancer Patients with Remission or Recurrence, as Determined by the Ultrasensitive PSA Test

| Variables | Remission | Recurrence | | *p* Value |
|---|---|---|---|---|
| | | Slow | Fast | |
| *No. of patients* | *120* | *30* | *44* | |
| Mean age (yrs.) | 63 | 62 | 62 | 0.52[a] |
| *(No. of patients)* | *(119)* | *(29)* | *(44)* | |
| Mean follow-up (months) | 54 | 45 | 52 | 0.11[a] |
| *(No. of patients)* | *(108)* | *(26)* | *(35)* | |
| Median Pre-op PSA (ng/ml) | 4.8 | 6.4 | 10.0 | <0.001[b] |
| *(No. of patients)* | *(111)* | *(28)* | *(41)* | |
| Median tumor volume (%) | 20 | 15 | 35 | <0.001[b] |
| *(No. of patients)* | *(93)* | *(25)* | *(30)* | |
| Median Gleason score | 7 | 7 | 7 | <0.001[b] |
| Mean Gleason score | 6.2 | 6.9 | 7.3 | <0.001[a] |
| *(No. of patients)* | *(115)* | *(28)* | *(44)* | |
| Clinical stage (%) | | | | |
| *(No. of patients)* | *(108)* | *(27)* | *(36)* | |
| T1a, T1b, T1c | 47.2 | 33.3 | 13.9 | |
| T2a, T2b, T3a, T3b | 52.8 | 66.7 | 86.1 | 0.001[d] |
| Gleason score (%) | | | | |
| *(No. of patients)* | *(115)* | *(28)* | *(44)* | |
| <6/10 | 23.5 | 14.3 | 2.3 | |
| 6/10 | 26.1 | 14.3 | 13.6 | |
| 7/10 | 46.1 | 46.4 | 47.7 | |
| 8/10+ | 4.4 | 25.0 | 36.4 | <0.001[d] |
| Surgical margin (%) | | | | |
| *(No. of patients)* | *(107)* | *(26)* | *(35)* | |
| Negative | 76.6 | 61.5 | 42.9 | |
| Positive | 23.4 | 38.5 | 57.1 | 0.001[d] |
| Apical margin (%) | | | | |
| *(No. of patients)* | *(105)* | *(27)* | *(36)* | |
| Negative | 63.8 | 55.6 | 61.1 | |
| Positive | 36.2 | 44.4 | 38.9 | 0.73[d] |
| Periprostatic tissue involvement (%) | | | | |
| *(No. of patients)* | *(106)* | *(27)* | *(35)* | |
| Negative | 59.4 | 55.6 | 22.9 | |
| Positive | 40.6 | 44.4 | 77.1 | 0.001[d] |
| Capsular invasion (%) | | | | |
| *(No. of patients)* | *(107)* | *(27)* | *(35)* | |
| Negative | 35.5 | 33.3 | 14.3 | |
| Positive | 64.5 | 66.7 | 85.7 | 0.058[d] |
| Seminal vesicle invasion (%) | | | | |
| *(No. of patients)* | *(107)* | *(27)* | *(35)* | |
| Negative | 90.7 | 92.6 | 68.6 | |
| Positive | 9.3 | 7.4 | 31.4 | 0.005[d] |
| Bladder neck invastion (%) | | | | |
| *(No. of patients)* | *(107)* | *(27)* | *(36)* | |
| Negative | 94.4 | 96.3 | 86.1 | |
| Positive | 5.6 | 3.7 | 13.9 | 0.23[c] |

[a]Analysis of variance.
[b]Kruskal-Wallis test.
[c]Fisher's exact test.
[d]Chi-square test.

sensitive PSA assay (*i.e.*, <0.001 ng/mL). The majority of the patients (>75%) who were in remission had measurable, but very low, serum PSA concentrations which ranged between 0.001 and 0.01 ng/mL. Very few patients without recurrence had PSA levels between 0.01 and 0.1 ng/mL. Examples of patients who had detectable but not consistently changing PSA, at very low concentrations, are shown in Figure 4.

### TIME OF RELAPSE, DETERMINED BY ULTRASENSITIVE PSA

Among the 44 patients who suffered fast relapse, based on the ultrasensitive monitoring, we have

TABLE 4
Time Interval From Surgery to Recurrence as Determined by Regular and Ultrasensitive PSA Monitoring

| Method | Mean (SD), months | Range, months | *p* Value |
|---|---|---|---|
| Regular PSA | 38.4 (16.3) | 9.2–66.0 | |
| Ultrasensitive PSA | 20.5 (13.6) | 7–51.4 | <0.001 |

established the serial sample which provided the first evidence of relapse and then, the sample with which confirmation of relapse was established, based on the outlined criteria. In 36/44 patients, the relapse was evident in the first sample after baseline and the relapse was confirmed in the following (second) sample. In 4 patients, the relapse was evident in the second sample after baseline and in 3 of them, the relapse was confirmed in the subsequent (third sample), and in one patient in the fourth sample. From the remaining 4 patients, 2 were suspected to have relapse in the third serial sample and 2 in the fourth. All relapses were confirmed by the fifth consecutive sample.

**Discussion**

There is no question that monitoring of prostate cancer patients after radical prostatectomy with PSA measurements in serum is an effective means of detecting relapse. Currently, the clinical practice is to treat patients who demonstrate consistent increases in serum PSA, after radical prostatectomy, without waiting for these patients to clinically relapse. Consequently, the end point for comparison selected in this study (*i.e.*, failure of prostatectomy when the PSA rises above 0.2 ng/mL by conventional PSA analysis), is justifiable and is currently in routine use. In this article, we refer to this as 'regular PSA' relapse. Ultrasensitive PSA assays have recently been developed and evaluated (10–17). There are now a few commercially available assays that qualify as 'ultrasensitive', *i.e.*, detection limits ≤0.01 ng/mL. Although these assays have been shown to be superior to regular PSA assays for monitoring prostate cancer patients after radical prostatectomy (10--17), their widespread use has not as yet been realized. Partially, this is due to the fact that clinical studies demonstrating superiority of ultrasensitive PSA monitoring versus regular PSA monitoring in relation to patient outcomes do not as yet exist. Our previous article (9), as well as the work of others (10–14), has shown that ultrasensitive PSA analysis is associated with earlier detection of relapse and appears to be clinically significant. We found associations between relapses detected in the ultrasensitive PSA regime and clinicopathological variables of poor patient prognosis, including positive margins, Gleason score, and tumor volume (9). These data have been confirmed by others (10–14).

The purpose of this article was to examine relapse and cure patterns of prostate cancer patients after radical prostatectomy. The patients were monitored with ultrasensitive and regular PSA assays for about 5 years. In Figures 1 through 4, we demonstrate that there are three distinct clinical groups of patients: (a) those who did not show any consistent PSA changes in the ultrasensitive regime over the 5 years of follow-up (62%); (b) another group of patients show demonstrable PSA changes in the ultrasensitive regime over time but these changes are relatively slow and PSA never crosses the cut-off limit of 0.1 ng/mL within 4 years postsurgery; and ( c) the third group of patients (23%) demonstrates rapid changes of serum PSA shortly after radical prostatectomy and PSA crosses the 0.1 ng/mL cut-off earlier than 4 years postsurgery.

We have investigated the agreement between ultrasensitive monitoring and regular PSA monitoring regarding remission and relapse rates of these patients. In Table 1, we demonstrate that there is an excellent agreement between the two methods. All recurrences detected by the regular PSA assay were also identified by the ultrasensitive PSA assay. However, the ultrasensitive PSA assay detected an additional 5 patients with fast recurrence and another 26 patients with slow recurrence who, by the regular PSA assay, were shown to be in remission. Although the regular PSA assay is clearly capable of detecting recurrences, the difference between regular PSA and ultrasensitive PSA monitoring is in the timing of relapse detection. For those patients who relapsed, as indicated by both methods, the ultrasensitive PSA assay detected the relapse by an average of 18 months earlier. This prolonged lead time, provided by the ultrasensitive assay, may ultimately lead to better patient outcomes by administration of treatments at an earlier stage, when the tumor is small and probably localized and likely more sensitive to lower doses of therapeutic interventions. These proposals are supported by reports indicating that earlier intervention, in patients who demonstrate isolated PSA increases post-therapy, may lead to better survival outcomes (20,21). Clearly, more studies will be necessary to demonstrate not only the superiority of ultrasensitive PSA assays in detecting earlier relapse but also, the better clinical outcomes when earlier treatments are administered.

Our classification of relapsing patients into 'fast relapsing' and 'slow relapsing' groups parallels similar classifications by others which are also based on the rate of PSA increases over time (11). In our previous article (9), we have calculated PSA doubling-times and Patel *et al.* (22) have calculated slopes of PSA changes over time. These almost equivalent classifications have been shown to have clinical importance (9,22). The definition proposed here is simpler than the calculation of doubling-times and may be preferred.

We have indicated that prostate cancer relapses detected by the ultrasensitive as well as the regular

PSA assays are closely associated with other clinical and pathological features of unfavourable prognosis (23–35). These data are presented in Tables 2 and 3. While the association between relapses detected by the regular PSA assay and fast relapses detected by the ultrasensitive PSA assay have been shown in Table 1, a critical question remains if the patients demonstrating slow recurrences, as detected by ultrasensitive PSA analysis, constitute a distinct group with different prognosis. The data of Table 3 indicate that there is a dose-response relationship between various clinicopathological variables in patients who are in remission, slow recurrence or fast recurrence, respectively. For example, preoperative PSA is progressively higher in patients who are in remission, to patients who are in slow recurrence, to patients who are in fast recurrence. The same trends are seen for clinical stage, Gleason score, surgical margin positivity, periprostatic tissue involvement and capsular invasion. These data suggest that the prognosis of patients with 'slow recurrence' probably lies between those who are in remission and those who demonstrate fast recurrence.

Examination of the patients who experienced fast relapse after radical prostatectomy revealed that the vast majority of them (36/44) demonstrated increases in serum PSA in the first sample post-baseline analysis. Relapse was then confirmed, based on our criteria, in the subsequent (second) sample. These data support the view that the patients who are destined to suffer a fast relapse can be identified very early after radical prostatectomy (within 2 years). Additionally, patients who do not show any changes in serum PSA, long after radical prostatectomy (*e.g.*, 5 years in this study), may be considered as being in long-term remission or as being cured from the disease. Based on our findings, only 2 patients who had non-changing PSA after 2 years of ultrasensitive monitoring, relapsed biochemically with increasing PSA after longer monitoring.

In conclusion, we here provide evidence that ultrasensitive PSA analysis can better define the patterns of prostate cancer relapse after radical prostatectomy in comparison to conventional PSA analysis. A very significantly prolonged lead time (by 18 months) is provided with ultrasensitive analysis. Furthermore, ultrasensitive monitoring allows for the identification of patients who have minimal or no risk for recurrence after radical prostatectomy (62% of the patients), another group which demonstrates detectable but slowly rising serum PSA over time (15% of the patients) and a third group which demonstrates fast PSA increases over time (23%), and fulfills the criteria for relapse by conventional analysis. Longer monitoring will further determine if the patients who are now in remission have been cured from their disease and if the patients who have slow recurrence will ever develop clinical relapse. The group with fast recurrence can be identified by ultrasensitive PSA analysis shortly after radical prostatectomy (within 2 years) and they should be excellent candidates for early therapies aiming to treat relapsing disease. The realization on the capabilities of ultrasensitive PSA assays in monitoring prostate cancer patients, after radical prostatectomy, may ultimately lead to better clinical outcomes and to the identification of patients who have been cured.

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