Ultrasensitive Assay of Prostate-Specific Antigen Used for Early Detection of Prostate Cancer Relapse and Estimation of Tumor-Doubling Time After Radical Prostatectomy

He Yu, Eleftherios P. Diamandis, Anthony F. Prestigiacomo, and Thomas A. Stamey

We used an ultrasensitive prostate-specific antigen (PSA) assay with a detection limit of 0.02 µg/L for long-term monitoring of PSA changes in 5 patients who were cured by radical prostatectomy and in 10 patients who had failed prostatectomies; 5 patients who underwent cystoprostatectomy were also evaluated with one sample after surgery. Relapse-free periods, determined on the basis of criteria designed specifically for the ultrasensitive assay or proposed for other currently available PSA assays, were calculated for the patients with failed prostatectomies. Tumor-doubling times were also calculated, postoperatively, according to a model that assumes exponential tumor growth over time. We found that prostate cancer relapse, on average, could be diagnosed 420 or 883 days earlier with the ultrasensitive assay than with assays having detection limits of 0.1 or 0.3 µg/L, respectively. Tumor-doubling times, calculated after radical prostatectomy, ranged from 67 to 568 days among the 10 patients. We also present evidence that even more sensitive PSA assays might be able to further reduce the relapse-free periods in ~50% of the prostate cancer patients who ultimately relapse.

Indexing Terms: monitoring therapy/fluorescence immunoassay/ tumor markers

The incidence rate of prostate cancer, the most common cancer of men in North America, continues to increase (1, 2). Part of the rise in incidence is attributed to improvements in diagnostic techniques, which can identify more patients with cancer at an early stage (3). The number of patients treated with radical prostatectomy is also increasing (4). There being no effective way to prevent this cancer, it is important to improve the management of affected patients after surgery.

Prostate-specific antigen (PSA), a 33-kDa single-chain glycoprotein produced by the epithelial cells of the prostate gland, is present in prostatic tissue, seminal plasma, and serum, making it a valuable marker for the management of prostate cancer. The serum concentration of PSA is measured to aid the diagnosis of prostate cancer, to assess therapy, and to monitor recurrence or metastasis (5, 6).

Studies have shown that an increase of serum PSA after radical prostatectomy indicates recurrent or metastatic cancer and that serial evaluation of PSA concentrations after radical prostatectomy is a simple, inexpensive, and effective way to identify these recurrences (7–12). However, questions about the efficiency of monitoring remain (12–14). The least amount of PSA that can be detected by commercially available PSA methods is ~0.1 µg/L. In most postoperative patients, PSA concentrations in serum decrease to well below this value if no residual prostatic tissue is left after surgery (5, 6, 15, 16).

We and others have postulated that cancer relapse could be diagnosed earlier if PSA were accurately monitored postsurgically at <0.1 µg/L. Analytical methods with such capabilities have recently become available and used in preliminary studies to monitor prostate cancer patients (12, 16–19). Here we demonstrate that using an ultrasensitive time-resolved fluorometric PSA assay to monitor patients after radical prostatectomy allowed us to identify patient relapse many months or years earlier than could assays for which detection limits are ≥0.1 µg/L. In addition, we were able to calculate the doubling times for cancer cells, which could be used as an indicator of the aggressiveness of the cancer and could help in selecting appropriate therapy at an early stage after radical prostatectomy.

Materials and Methods

PSA assay. The newly developed ultrasensitive PSA assay described in detail elsewhere (16) was used for the analysis of all serum samples. In brief, the assay uses one monoclonal anti-PSA capture antibody immobilized in white polystyrene microtitration wells, one biotinylated polyclonal anti-PSA detection antibody, and alkaline phosphatase-conjugated streptavidin. The activity of alkaline phosphatase (EC 3.1.3.1) is measured through the hydrolysis of a substrate, difluorosyl phosphate (DFP), the dephosphorylated form of which further reacts with Tb3+ and EDTA to form a highly fluorescent ternary complex. After laser excitation, the fluorescence of the complex is quantified in a time-resolved mode, so that the background signal can be reduced to a minimum. This assay can accurately quantify PSA concentrations in the range 0.02–10 µg/L.

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Patients. A total of 20 patients were studied. Five patients undergoing operations for bladder carcinoma had their prostates removed along with their urinary bladders (cystoprostatectomy). The prostates of these patients were examined histologically in 3-mm step sections and found to be free of prostate cancer. We used samples from these patients to evaluate baseline serum PSA concentrations in male patients without prostate tissue. Serum was sampled once from each patient at 307, 405, 665, 847, or 995 days after surgery. Another five patients who had small, organ-derived prostate tumors (Gleason grade 1–3) were also used as controls. These patients had no clinical signs of cancer relapse after radical prostatectomy and were monitored frequently for PSA over long periods (from at least 1535 to 2854 days after surgery); five sequential sera were available from each of these patients (total 25 sera).

Finally, we also studied 10 patients with histologically confirmed prostate cancer who underwent radical prostatectomy and whose PSA decreased to <0.3 µg/L by the Yang assay (19) (detection limit, 0.3 µg/L). These patients represent failed prostatectomies; their PSA concentrations ultimately increased to well above 0.3 µg/L. At least 5 consecutive sera were available for each patient, with maximum follow-up times between 551 and 2555 days; in all, 73 serum samples were analyzed for these 10 patients. All sera were stored at −70°C and were analyzed in duplicate in the same run to avoid the contribution of random errors from between-run assay variation. The study was approved by the Ethics Committee at Stanford.

Data interpretation. For purposes of evaluating the limited number of serum samples in these patients, we arbitrarily selected a set of interpretative criteria for cancer relapse, based on PSA changes over time after radical prostatectomy. PSA values were reported with three decimal points. Any PSA value <0.020 µg/L was considered nonquantifiable by the assay because the precision at lower values was >20% (data not shown). A significant change in PSA concentration was considered a change ≥0.010 µg/L. Cancer relapse was considered when the patient had two consecutive increases in PSA concentrations that would at least double his initial PSA measurement. Thus, for all patients whose PSA was ≤0.020 µg/L at least 8 weeks after surgery (baseline PSA, seven patients), a concentration of ≥0.040 µg/L, after two consecutive increases in baseline PSA, was taken as an indication of relapse. For the three patients with PSA >0.020 µg/L after surgery, a doubling of the initial PSA concentration after two consecutive PSA increases was considered an indication of relapse.

To compute “relapse-free” (relapse undetected) periods and doubling times for the tumors, we have assumed that tumor cells proliferate exponentially and that PSA concentration changes according to the equation:

\[ [\text{PSA}]_t = [\text{PSA}]_0 \cdot e^{Kt} \]

where \([\text{PSA}]_t\) is the concentration of PSA at any time \(t\), \([\text{PSA}]_0\) is the baseline PSA concentration after surgery, and \(K\) is a constant. Doubling times \((t_d)\) were calculated as \(\ln 2/K\), where \(K\) is the slope of the plot of \(\ln([\text{PSA}])\) vs time, calculated experimentally. Only samples with PSA concentrations increasing over time were included in the linear semilogarithmic regression. A similar approach for calculating doubling times has also been used in previous studies (20).

The relapse-free periods for the ultrasensitive assay were calculated as the time between surgery and the measurement of PSA at 0.040 µg/L (for patients with postoperative PSA ≤0.020 µg/L) or as the time between surgery and the measurement of a PSA value double the postoperative PSA value (when the latter was >0.020 µg/L). For comparison, relapse-free periods were also calculated as the times from surgery to measurements of PSA concentrations of 0.1 µg/L or 0.3 µg/L—detection limits of first-generation PSA assays now being widely used for monitoring prostate cancer.

Results

Figure 1 presents changes in PSA concentrations over time for the five control patients who had been successfully cured by radical prostatectomy (I–V) and for the patients who had failed prostatectomies (I–10). These data were obtained with our ultrasensitive time-resolved immunofluorometric procedure. Table 1 lists the PSA concentrations for all the control samples and for the cystoprostatectomy patients (evaluated once, long after surgery). According to the criteria we devised for detection of relapse, none of the five control patients fell into the relapse category. Although there was some variation in PSA concentrations with time (Fig. 1), no significant consecutive increases of PSA were observed in any of the five control patients.

The relapse-free periods and doubling times for the 10 patients who had failed prostatectomies are presented in Table 2. The baseline PSA value (after radical

![Fig. 1. Changes in serum PSA concentration over time in 10 patients who underwent radical prostatectomy and ultimately relapsed (I–10; solid lines) and 5 patients who underwent radical prostatectomy for small, low-grade tumors and stayed in remission (I–V; broken lines).](image-url)
Table 1. Mean PSA concentrations after radical prostatectomy or cystoprostatectomy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>n¹</th>
<th>Days after surgery</th>
<th>Mean</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control I</td>
<td>5</td>
<td>188–1826</td>
<td>0.006</td>
<td>0.002</td>
</tr>
<tr>
<td>Control II</td>
<td>5</td>
<td>94–1535</td>
<td>0.021</td>
<td>0.011</td>
</tr>
<tr>
<td>Control III</td>
<td>5</td>
<td>290–1892</td>
<td>0.038</td>
<td>0.014</td>
</tr>
<tr>
<td>Control IV</td>
<td>5</td>
<td>936–2854</td>
<td>0.020</td>
<td>0.004</td>
</tr>
<tr>
<td>Control V</td>
<td>5</td>
<td>744–2462</td>
<td>0.007</td>
<td>0.001</td>
</tr>
<tr>
<td>Cystoprostatectome</td>
<td>5²</td>
<td>307–995</td>
<td>0.031</td>
<td>0.018</td>
</tr>
</tbody>
</table>

¹ Number of sequential sera from each patient available for analysis.
² Five different patients contributed one serum sample each at days 307, 405, 665, 847, and 995 after cystoprostatectomy.

prostatectomy) was ≤0.020 μg/L in seven patients and >0.020 μg/L in three patients. In one patient (patient 3) the PSA concentration at 92 days after radical prostatectomy was 0.053 μg/L, decreasing to 0.006 μg/L at 183 days; thus in some patients, complete clearance of PSA after surgery may be delayed beyond 3 months. The time it took for PSA concentrations to double in the 10 relapsed patients ranged from 67 days (patient 6) to 568 days (patient 9); the mean ± SD for all 10 was 277 ± 144 days. Another patient (patient 8) had a doubling time of 450 days; the doubling times for the remaining seven patients fit within a somewhat narrower range, i.e., between 162 and 311 days. The graphs of Ln[PSA] vs time were practically linear in all cases (Fig. 2).

Discussion

PSA is one of the most valuable tumor markers, having been used successfully for diagnosis, screening, and postsurgical management of prostate cancer patients (5–7). Recently, PSA has also been proposed as a prognostic marker for breast carcinoma (21, 22). The commercially available PSA assays in current use have detection limits between 0.1 and 0.3 μg/L, but second-generation ultrasensitive PSA assays (12, 16–19) are now capable of measuring PSA concentrations well below 0.1 μg/L. The potential usefulness of such newer assays for the management of prostate cancer patients after radical prostatectomy has been reviewed (23).

Fig. 2. Plot of Ln[PSA] vs time in the 10 patients who relapsed after radical prostatectomy.

Only the time periods during which PSA was increasing are plotted. The slope of the curve, K, was used to calculate the tumor-doubling time reported in the text (see Table 2).

Table 2. Relapse-free intervals and doubling times for 10 patients with failed prostatectomies.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline PSA, μg/L ¹</th>
<th>Baseline</th>
<th>Days</th>
<th>Relapse-free period determined at PSA cutoff (μg/L) of 0.04</th>
<th>0.1</th>
<th>0.3</th>
<th>Tumor-doubling time, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.011</td>
<td>85</td>
<td></td>
<td>558</td>
<td>798</td>
<td>1304</td>
<td>215</td>
</tr>
<tr>
<td>2</td>
<td>0.025</td>
<td>70</td>
<td></td>
<td>555</td>
<td>922</td>
<td>1373</td>
<td>311</td>
</tr>
<tr>
<td>3</td>
<td>0.006</td>
<td>183</td>
<td></td>
<td>948</td>
<td>1278</td>
<td>1714</td>
<td>260</td>
</tr>
<tr>
<td>4</td>
<td>0.008</td>
<td>85</td>
<td></td>
<td>972</td>
<td>1226</td>
<td>2066</td>
<td>288</td>
</tr>
<tr>
<td>5</td>
<td>0.020</td>
<td>613</td>
<td></td>
<td>955</td>
<td>1094</td>
<td>1375</td>
<td>178</td>
</tr>
<tr>
<td>6</td>
<td>0.020</td>
<td>75</td>
<td></td>
<td>159</td>
<td>228</td>
<td>333</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>0.080</td>
<td>89</td>
<td></td>
<td>249</td>
<td>–</td>
<td>414</td>
<td>162</td>
</tr>
<tr>
<td>8</td>
<td>0.020</td>
<td>333</td>
<td></td>
<td>686</td>
<td>1130</td>
<td>2436</td>
<td>450</td>
</tr>
<tr>
<td>9</td>
<td>0.018</td>
<td>729</td>
<td></td>
<td>1033</td>
<td>1805</td>
<td>3546</td>
<td>568</td>
</tr>
<tr>
<td>10</td>
<td>0.061</td>
<td>79</td>
<td></td>
<td>362</td>
<td>–</td>
<td>666</td>
<td>269</td>
</tr>
</tbody>
</table>

¹ The postsurgical serum PSA value assessed at the various times after surgery shown in the table.
² In these patients, whose baseline PSA exceeded 0.020 μg/L, the relapse-free period was calculated as the period between surgery and the time at which their PSA was double their baseline concentration. Thus, for patients 7 and 10, the time between baseline PSA value and 0.1 μg/L PSA was not calculated.
After demonstrating that ~50% of prostate cancer patients who have undergone radical prostatectomy have serum PSA <0.01 μg/L (24), we postulate that monitoring these patients for PSA concentrations well below 0.1 μg/L may allow earlier detection of relapse. In addition, PSA changes could also be used to calculate tumor-doubling time, as an indicator of tumor proliferative potential. Such information may be useful for determining which patients should be treated early and which patients should be monitored without administration of adjuvant therapy.

Here we report our findings for 15 patients who were monitored frequently over relatively long periods after their radical prostatectomy. Five, who had had removed low-histological grade (Gleason grade 1–3) small tumors localized in the prostate, were monitored for 50–95 months. None of these patients had any clinical signs of relapse or fulfilled the criteria we have set for relapse, and none of the five serum samples available for each patient graphically represented as sequential results in Fig. 1 revealed any consistent PSA increases over time. The mean PSA values for the five control prostate cancer patients and the five patients with cystoprostatectomy (Table 1) revealed that three of the control patients had PSA ≤0.020 μg/L, two had PSA >0.020 μg/L, and the mean PSA concentration in the cystoprostatectomy group was 0.031 μg/L. These data suggest that the traces of PSA, circulating in the serum of patients without prostate tissue or evidence of prostate cancer, and which did not change with time, were released by nonprostatic tissue, which is capable of synthesizing PSA, as previously described (25, 26).

Ten patients who had histologically confirmed prostate cancer, and who were treated with radical prostatectomy but ultimately relapsed, were also studied. PSA changes monitored over long periods in all patients are presented in Fig. 1. McNeal et al. have previously suggested that prostate tumors grow exponentially over time and that PSA concentration also changes exponentially (20, 27). A near-linear relationship would then be expected to exist between \( \ln(\text{PSA}) \) and time, and this has been confirmed in our study (Fig. 2). Using these plots, we calculated tumor-doubling times as described above, and calculated relapse-free periods based on the criteria we established for our ultrasensitive assay and on the criteria previously used with commercially available kits having detection limits of 0.1–0.3 μg/L. These data are presented in Table 2.

In the 10 patients who underwent radical prostatectomy, baseline PSA values were ≤0.020 μg/L in 7 and >0.020 μg/L in 3, in accordance with previous reports by our group (16, 24). One patient (patient 3, Fig. 1) did not seem to clear his preoperative PSA even after 3 months after the surgery. However, we could not exclude the possibility that this patient might have tumor cells in his circulation, producing PSA. Such cells could cause a subsequent increase in serum PSA if they were to be successfully implanted. As determined with our ultrasensitive assay, the relapse-free periods for the 10 patients (Table 2) ranged from 159 to 1033 days (mean 640 days, median 607 days). When we use a PSA cutoff of 0.1 μg/L to calculate relapse-free periods, the mean was 1060 days and the median was 1112 days; at a cutoff of 0.3 μg/L, the corresponding values were 1523 and 1374 days. With the ultrasensitive assay, we could diagnose relapse by an average of 420 days or 883 days earlier, in comparison with commercial kits having detection limits of 0.1 or 0.3 μg/L, respectively. Earlier diagnosis of relapse by 185 to 581 days was previously demonstrated when the PSA cutoff value was decreased from 0.3 to 0.1 μg/L (19). The present study clearly demonstrates the additional benefit of using lower cutoff values, which is now possible with ultrasensitive assays.

Doubling time is an important tumor characteristic that can be used to distinguish tumors with potential to metastasize and grow faster. Therapeutic decisions based on tumor-doubling times and other criteria have been proposed (12, 17, 20). In a previous detailed study on doubling times in patients who did not receive any treatment, the tumors with short doubling times were associated with late stage, metastasis, and Gleason score ≥7; tumors with long doubling times were associated with early stage, organ-confined disease, and Gleason score ≤6 (20). In that study, the doubling times varied considerably, from <2 to >48 months. In our study of 10 patients who underwent radical prostatectomy, 1 (patient 6) had a doubling time of 67 days, 2 had doubling times of 162 and 178 days, 5 had doubling times between 215 and 311 days, and 2 patients had doubling times of 450 and 568 days. Larger studies involving more patients will be needed to determine whether these doubling times define subgroups for whom specific treatment strategies should be developed. Our mean doubling time for the 10 patients was 277 ± 144 days, in close agreement with previously reported values of 213 ± 240 days (12) and 260 ± 207 days (17).

Throughout this paper, we have assumed that tumor doubling times are the same as PSA doubling times. Although the experimental data fit well the exponential model proposed, several factors may affect the direct relationship between tumor cell number and serum PSA concentration or even the exponential tumor growth with time: tumor cell death, inflammatory response, variable diffusion of PSA from the tumor to the circulation, and neovascularization and tumor angiogenesis.

Doubling times are difficult to calculate preoperatively because once the tumor is diagnosed, it should be treated as early as possible. Our data suggest that doubling times can be assessed during postoperative patient monitoring, and possibly used for further therapeutic decisions. Could even more sensitive PSA assays further help physicians to diagnose relapse earlier than the periods shown in Table 2? We suggest that PSA assays with detection limits near 0.001 μg/L should be developed and critically examined, in light of...
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the following findings. Among all the patients studied who underwent radical prostatectomy, ~30% had baseline PSA values >0.020 μg/L [see data presented here and elsewhere (24)]. Because these patients must have had PSA released from residual tumor tissue or from nonprostatic tissue, their monitoring with more-sensitive PSA assays will not result in any additional benefit in terms of earlier detection of relapse. PSA released from proliferating tumor tissue must reach concentrations similar to those from nonprostatic tissue before it becomes easily detectable. However, in ~70% of these patients, PSA was ≤0.020 μg/L after radical prostatectomy (Table 2) and <0.010 μg/L in 50% of the cases (16, 24). In those patients, the postsurgical PSA concentration, which cannot be accurately determined with present assays, may well be <0.005 μg/L. Thus, a method that could accurately monitor PSA in the range of 0.001-0.02 μg/L might detect earlier relapse and calculate doubling times earlier in ~50% of the postsurgical patients. If the PSA cutoff were 0.020 μg/L instead of the 0.040 μg/L used in this study, the relapse would be detected one doubling time earlier than that given in Table 2. The development of such a third-generation assay is currently under investigation and may have other potential utility, i.e., the detection of PSA in women’s sera for breast cancer diagnosis and monitoring (21, 24).

In summary, by using an ultrasensitive assay that can reliably measure PSA concentrations of at least 0.020 μg/L, one can detect relapse by an average of 14 or 29 months earlier than can be done with PSA assays having detection limits of 0.1 or 0.3 μg/L, respectively. Earlier detection of relapse and determination of tumor-doubling times would allow physicians to make more rational decisions as to when and how aggressively to treat the prostate tumor relapse. Given that small tumors respond better than larger tumors and require lower doses of adjuvant therapy, we expect that the information made available from ultrasensitive assays would improve patient morbidity and mortality after radical prostatectomy.

However, because current adjuvant therapy is not very helpful in treating recurrent prostate cancer, our proposals must await the development of new, more-effective chemotherapeutic regimens before full realization in practice.

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References