Clinical implications of the rise and fall of prostate specific antigen after laser prostatectomy

M.P. van IERSEL, C.M.G. THOMAS*, W.P.J. WITJES, R. de GRAAF†, J.J.M.C.H. de la ROSETTE and F.M.J. DEBRUYNE

Objective To characterize the serum kinetics of prostate specific antigen (PSA) after visual laser ablation of the prostate (VLAP).

Patients and methods The PSA values of 45 patients were measured at 24 h and at 1, 4, 12, 26 and 52 weeks after VLAP and the changes assessed in relation to symptom scores, urinary flow rates and prostate size.

Results After an initial rise immediately after VLAP, the serum PSA level declined. At 24 h, the PSA value reached a mean level 23 times higher than the PSA level before VLAP and then took a mean of 78 days to reach a new baseline. The mean decrease of the subsequent baseline value relative to that before treatment was 1.7 ng/mL. The prostatic size and energy applied correlated positively with the rise in PSA 24 h after VLAP. The rise in maximal urinary flow after VLAP, the decrease in the symptom score and residual urine volume did not correlate with the rise in PSA level 24 h after VLAP or with the time to reach a value halfway between the level at 24 h and the new baseline value.

Conclusions The pattern of the increase in serum PSA level and decline after VLAP was not predictive of the clinical outcome of therapy.

Keywords Prostate specific antigen, benign prostatic enlargement, laser treatment

Introduction

PSA is secreted by prostatic epithelial cells into the lumina of the prostate ducts; the concentration of PSA in prostatic secretions is about 10^6 of that in serum [1]. Normal prostatic epithelial cells are separated from the capillary and lymphatic system by an intact basal cell layer and basement membrane [2]. When the basal membrane of the prostatic epithelium is disrupted, PSA in the lumen can leak into the serum and increase the serum PSA concentration. Invasive treatments like TURP cause a rapid rise in the level of serum PSA [3–6]; acini rich in PSA are transected during the operation for BPE and the enzymes are released into the fossa where they are absorbed by the irrigating fluid. After an invasive treatment for BPE, the PSA level increases and the value cannot be used to differentiate reliably between BPE and prostatic cancer until the PSA level attains a new baseline value. In a patient who is considered a candidate for visual laser ablation of the prostate (VLAP), the presence of prostatic carcinoma should be excluded, as during VLAP no tissue is obtained for histopathological examination and consequently it is uncertain whether foci of prostatic cancer are present. After VLAP, prostatic cancer can develop in the remaining prostatic tissue. Because the heterogenicity of the TRUS image increases after VLAP, the predictive value of TRUS is decreased, as it is after TURP [7].

During this post-operative period, possible prostate cancer can be detected largely by determining the serum PSA level and by a DRE. The interpretation of elevated serum PSA levels after VLAP is only possible if the kinetics of serum PSA are known. Moreover, an awareness of the incidence of false-positive findings from PSA after VLAP could reduce unnecessary anxiety in the patient, and the need for prostate biopsies.

The serum kinetics of PSA after VLAP for BPE have not been characterized sufficiently and the potential prognostic significance for the clinical outcome of variables describing the changes in PSA after VLAP are uncertain. To address these issues, we evaluated the changes in the serum PSA levels of patients with BPE after they had been treated with VLAP.

Patients and methods

The study group consisted of 45 patients, all considered clinically to have BPE as assessed by a symptom score.
Results

After an initial rise caused by VLAP, the serum PSA level declined (Table 1); the times at which PSA was determined varied slightly from the intended times. The similarity in the values at 12 and 26 weeks suggests that the value attained a new baseline and was no longer decreasing. This was confirmed by measurements taken in six patients at 52 weeks, where only two showed a slight increase in PSA level compared with the values at 12 and 26 weeks, and for all six the increase was not significant (Wilcoxon signed rank test). Analysis of the residual errors showed that the PSA values were fitted best by a double-exponential model and the model chosen was:

\[
\text{serum PSA} = C \times \exp(\exp(A - B \times (t - 1)))
\]

where \( t \) denotes the time in days after VLAP with \( t \geq 1 \), \( C \) is the asymptotic value of the baseline reached after VLAP, \( A \) determines the value at \( t = 1 \) and \( B \) is the rate of the decrease in PSA 24 h after VLAP. The rate of decrease is greater in the first few days after VLAP than in the succeeding weeks and thus the ‘half-life’ is not constant but increases steadily. The parameters \( A \), \( B \) and \( C \) were fitted for each of the 45 patients using a weighting inversely proportional to the square of the PSA values, with a zero dose plus 3 \( \text{ng/mL} \) used for the baseline determination. The fitted estimates of the parameters were used to calculate different characteristics of the fitted curve.

The mean (sd) PSA level 24 h after VLAP was 103 (59) \text{ng/mL}, which was 23 (sd 15) times greater than the pre-operative value. The mean (sd) value of \( T/2 \) was 5.6 (2.3) days and the mean (sd) value of \( T_{10\%} \) was 78 (49) days; the mean (sd) level of the new baseline was 1.7 (2.7) ng/mL below the level before VLAP.

Table 2 shows the relationship between the characteristics of the PSA curves and the clinical features of the patients. In patients with a large prostate, the rise in PSA level was generally greater and the new baseline

| Table 1 | Serum PSA of 45 patients before and after VLAP |
|---|---|---|---|---|---|---|
| | Before VLAP | After VLAP | 1 | 4 | 12 | 26 |
| PSA level ng/mL | 6.2 | 107.8 | 30.9 | 9.1 | 5.0 | 4.8 | 3.4 |
| Mean | 6.2 | 107.8 | 30.9 | 9.1 | 5.0 | 4.8 | 3.4 |
| Range | <1.0-14.5 | 9.7-290 | 1.5-92.0 | <1.0-31.0 | <1.0-16.0 | <1.0-20.0 | <1.0-5.4 |
| n | 45 | 45 | 45 | 44 | 44 | 38 | 6 |

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was reached sooner. The energy given during VLAP correlated moderately with the rise in PSA 24 h after VLAP but there was no significant correlation between the characteristics of the PSA curves and the rise in maximum urinary flow rate after VLAP, the decrease in the IPSS or the decrease in residual urine volume. There was a weak correlation (r = 0.45) between the decline in serum PSA level at the new baseline compared with the PSA value before VLAP and with the reduction in prostate volume as measured with TRUS 26 weeks after VLAP.

Table 2 Relationships between parameters describing the changing PSA level after VLAP and the clinical parameters

<table>
<thead>
<tr>
<th></th>
<th>ΔPSA</th>
<th>ΔPSAr</th>
<th>T/2</th>
<th>ΔPSAb</th>
<th>T10%</th>
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<tr>
<td>Prostate volume</td>
<td>0.40</td>
<td>-0.31</td>
<td>-0.25</td>
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<td>-0.46</td>
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<td>-0.06</td>
<td>0.00</td>
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<td>-0.03</td>
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<td>0.24</td>
<td>0.21</td>
<td>0.20</td>
<td>0.16</td>
</tr>
<tr>
<td>ΔVolume</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>SPC</td>
<td>-0.20</td>
<td>-0.12</td>
<td>-0.18</td>
<td>-0.15</td>
<td>-0.51</td>
</tr>
</tbody>
</table>
| Means (so) and P values according to Student’s t-tests

Cavity
- Yes (n = 25): 109 (69); 27 (17); 6.1 (2.6); 1.7 (2.4); 95 (56)
- No (n = 18): 97 (46); 17 (9); 4.6 (1.7); 1.5 (1.2); 52 (21)

Infection
- Yes (n = 21): 91 (61); 22 (12); 4.8 (1.8); 1.5 (2.2); 67 (43)
- No (n = 24): 114 (57); 24 (18); 6.2 (2.6); 1.9 (3.2); 88 (52)

△PSA, PSA at 24 h after VLAP minus the initial value. ΔPSAr, PSA level 24 h after VLAP relative to the initial value. T/2, the time to reach a PSA level halfway between the value at 24 h and at the new baseline. ΔPSAb, the initial PSA level minus that at the new baseline. T10%, the time for the PSA level to reach a value within 10% of the new baseline. Energy, the amount of energy delivered to the prostate during VLAP. ΔVolume, the reduction in prostate volume at 26 weeks after VLAP. SPC, duration of suprapubic catheterization. Cavity, the presence of a cavity on TRUS. Infection, post-operative urinary infection. ns = not significant (P > 0.05)

Discussion

The fitted parameters from the curve for each patient were used for the analysis, rather than the absolute values, thus partly correcting for any variation in the actual sampling time, and explaining the differences in the increase in PSA level at 24 h after VLAP between
the model and the values in Table 1. The 23-fold increase 24 h after VLAP indicates that the tissue was extensively damaged. This rise is comparable with the 14-fold (so 4) increase of PSA 24 h after transurethral ultrasound-guided laser-induced prostatectomy (TULIP) found by Bosch et al. [9]. However, it is much higher than the 5.9 ng/mL increase 18–24 h after TURP reported by Oesterling et al. [3]. Using the Yang assay, Stamey et al. [4] reported a 53-fold rise in PSA concentration in six patients immediately after TURP for BPE; Vesey et al. [5] reported that PSA levels rose ninefold immediately after TURP. Price et al. [6] measured PSA levels at 1, 3, 5 and 42 days after TURP; PSA levels were elevated on days 1, 3 and 5 among patients with BPE and gradually decreased to below the baseline value by 42 days. Comparing the rise of PSA after TURP with the rise after laser ablation of the prostate, Kabalin et al. [10] reported similar peak levels after both procedures; however, the peak value occurred immediately after TURP, in the recovery room, but 24 h after laser ablation. The difference between TURP and VLAP in the time taken to reach the peak PSA level, and the different impact on prostatic tissue, might explain the different responses in PSA level post-operatively reported by these authors.

According to Stamey et al. [12] and Vesey et al. [5], a dramatic rise in serum PSA immediately after TURP implies BPE rather than prostate cancer, as they found insignificant or much smaller increases in serum PSA in the latter after TURP. Vesey et al. [5] suggested that this difference could be caused by a more easily extractable store of PSA in the dilated acinar spaces of hyperplastic tissue, containing pooled prostatic secretions rich in PSA.

In the present study, the decrease in the PSA level after VLAP followed a double-exponential curve. In this model, the 'half-life' is not constant but increases steadily, which could be explained by an initial sharp decline in PSA level caused by the disappearance of the sequestered PSA that leaked into the blood during VLAP, after which there was less but persistent leakage of PSA from damaged prostatic tissue. The half-life of serum PSA has been calculated by Oesterling et al. [11] to be 3.15 days, using the Tandem-R PSA assay, and by Stamey et al. [12] to be 2.2 days, using the Pros-Check PSA assay. The 'half-life' of 5.6 days 24 h after VLAP is considerably longer and supports the hypothesis that the decrease in PSA after VLAP is influenced by damaged prostatic tissue. The attainment of a new (lower) mean (sd) baseline at 78 (49) days after VLAP is comparable with that found by Bosch et al. [9] after TULIP. However, it is considerably longer than the median time required for the serum PSA value to return to a stable level after TURP, as found by Oesterling et al. [13] (18 days, range 12–30+). This also agrees with Kabalin et al. [10] who found that PSA levels decreased more slowly after laser prostatectomy than after TURP. A possible explanation could be the altered architecture of the prostate after VLAP, with necrotic tissue remaining in situ rather than being immediately resected as in TURP. The lower level of PSA at the new baseline after VLAP compared with the level before treatment may reflect the ablation of PSA-producing tissue during VLAP. As necrotic tissue remains in the prostate for a long time after treatment with high-intensity focused ultrasound, transurethral needle ablation and transurethral microwave thermotherapy, the time necessary for serum PSA levels to reach a new baseline after these procedures should be comparable with that after VLAP.

In the present study, the T10% of a high proportion of the patients was reached within 4 months; if the PSA level does not decline to a new baseline 4 months after VLAP, further management of the patient will depend on the decisions of the individual clinician and such patients may represent a high-risk group for prostate cancer. Because serum PSA values vary within an individual, measurements must be repeated to confirm any suspicious increase. We recommend that biopsies are taken when the PSA is consistently and significantly above the pre-operative level during this period. An alternative approach is to keep these patients under prospective review, using DRE, PSA measurements and TRUS at 6-monthly intervals. If a new baseline PSA value is reached and the serum PSA starts to rise again after VLAP, the percentage PSA increase with time (PSA slope) may be used to distinguish patients with carcinoma. Oesterling et al. [13] found that a rise of >20% per year indicated carcinoma. Accordingly, Feneley et al. [7] reported that serial measurements of PSA in patients with incidental carcinoma found after TURP allowed the disease activity to be monitored and a PSA slope >20% per year was the most accurate marker to predict biopsy-proven residual disease. Although no malignancy was found in the present patients with increasing PSA levels one year after VLAP, the PSA slope might be helpful in diagnosing prostate carcinoma after VLAP.

In conclusion, because of the effects of VLAP on serum PSA, levels decreased more slowly after laser prostatectomy than after TURP. A possible explanation could be the altered architecture of the prostate after VLAP, with necrotic tissue remaining in situ rather than being immediately resected as in TURP. The lower level of PSA at the new baseline after VLAP compared with the level before treatment may reflect the ablation of PSA-producing tissue during VLAP. As necrotic tissue remains in the prostate for a long time after treatment with high-intensity focused ultrasound, transurethral needle ablation and transurethral microwave thermotherapy, the time necessary for serum PSA levels to reach a new baseline after these procedures should be comparable with that after VLAP.

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F.M.J. Debruyne, MD, PhD, Urologist.

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Department of Urology, *Laboratory of Endocrinology and Reproduction and †Department of Medical Statistics, University Hospital of Nijmegen ‘St Radboud’, The Netherlands

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Conclusions The pattern of the increase in serum PSA level and decline after VLAP was not predictive of the clinical outcome of therapy.

Keywords Prostate specific antigen, benign prostatic enlargement, laser treatment

Introduction

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PSA LEVELS AFTER LASER PROSTATECTOMY

After an initial rise caused by VLAP, the serum PSA level declined (Table 1); the times at which PSA was determined varied slightly from the intended times. The similarity in the values at 12 and 26 weeks suggests that the value attained a new baseline and was no longer decreasing. This was confirmed by measurements taken in six patients at 52 weeks, where only two showed a slight increase in PSA level compared with the values at 12 and 26 weeks, and for all six the increase was not significant (Wilcoxon signed rank test). Analysis of the residual errors showed that the PSA values were fitted best by a double-exponential model and the model chosen was:

\[
\text{serum PSA} = C \times \exp \left( \exp \left( A - B \times (t - 1) \right) \right)
\]

where \( t \) denotes the time in days after VLAP with \( t \geq 1 \), \( C \) is the asymptotic value of the baseline reached after VLAP, \( A \) determines the value at \( t = 1 \) and \( B \) is the rate of the decrease in PSA 24 h after VLAP. The rate of decrease is greater in the first few days after VLAP than in the succeeding weeks and thus the ‘half-life’ is not constant but increases steadily. The parameters \( A, B \) and \( C \) were fitted for each of the 45 patients using a weighting inversely proportional to the square of the PSA values.

Correlations between these variables and various other clinical indices were determined using Pearson’s method (or Spearman’s, for the duration of catheterization). The relationship of these variables with the presence of a laser-induced cavity as seen on TRUS and with the presence of post-operative urinary infection was analysed using Student’s \( t \)-tests for two samples.

<table>
<thead>
<tr>
<th>PSA level (ng/mL)</th>
<th>Before VLAP</th>
<th>After VLAP 24 h</th>
<th>1</th>
<th>4</th>
<th>12</th>
<th>26</th>
<th>52</th>
</tr>
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<tr>
<td>Mean</td>
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<td>107.8</td>
<td>30.9</td>
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<td>3.4</td>
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<td>1.5–92.0</td>
<td>&lt;1.0–31.0</td>
<td>&lt;1.0–16.0</td>
<td>&lt;1.0–20.0</td>
<td>&lt;1.0–5.4</td>
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<td>( n )</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>44</td>
<td>44</td>
<td>38</td>
<td>6</td>
</tr>
</tbody>
</table>

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**Discussion**

The fitted parameters from the curve for each patient were used for the analysis, rather than the absolute values, thus partly correcting for any variation in the actual sampling time, and explaining the differences in the increase in PSA level at 24 h after VLAP between

### Table 2 Relationships between parameters describing the changing PSA level after VLAP and the clinical parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APSA</th>
<th>APSAr</th>
<th>T/2</th>
<th>APSAb</th>
<th>T(_{10%})</th>
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<td>Prostate volume</td>
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<td>6.1 (2.6)</td>
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<td></td>
</tr>
<tr>
<td>Yes (n = 21)</td>
<td>91 (61)</td>
<td>22 (12)</td>
<td>4.8 (1.8)</td>
<td>1.5 (2.2)</td>
<td>67 (143)</td>
</tr>
<tr>
<td>No (n = 24)</td>
<td>114 (57)</td>
<td>24 (18)</td>
<td>6.2 (2.6)</td>
<td>1.9 (3.2)</td>
<td>88 (152)</td>
</tr>
<tr>
<td>P</td>
<td>ns</td>
<td>ns</td>
<td>0.05</td>
<td>ns</td>
<td>ns</td>
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</table>

\(\Delta PSA\), PSA at 24 h after VLAP minus the initial value. \(\Delta PSA_r\), PSA level 24 h after VLAP relative to the initial value. T/2, the time to reach a PSA level halfway between the value at 24 h and at the new baseline. \(\Delta PSA_b\), the initial PSA level minus that at the new baseline. T\(_{10\%}\), the time for the PSA level to reach a value within 10% of the new baseline. Energy, the amount of energy delivered to the prostate during VLAP. ΔVolume, the reduction in prostate volume at 26 weeks after VLAP. SPC, duration of suprapubic catheterization. Cavity, the presence of a cavity on TRUS. Infection, post-operative urinary infection. ns = not significant (\(P > 0.05\))
the model and the values in Table 1. The 23-fold increase 24 h after VLAP indicates that the tissue was extensively damaged. This rise is comparable with the 14-fold (so 4) increase of PSA 24 h after transurethral ultrasound-guided laser-induced prostatectomy (TULIP) found by Bosch et al. [9]. However, it is much higher than the 5.9 ng/mL increase 18–24 h after TURP reported by Oesterling et al. [3]. Using the Yang assay, Stamey et al. [4] reported a 53-fold rise in PSA concentration in six patients immediately after TURP for BPE; Vesey et al. [5] reported that PSA levels rose ninefold immediately after TURP. Price et al. [6] measured PSA levels at 1, 3, 5 and 42 days after TURP; PSA levels were elevated on days 1, 3 and 5 among patients with BPE and gradually decreased to below the baseline value by 42 days. Comparing the rise of PSA after TURP with the rise after laser ablation of the prostate, Kabalin et al. [10] reported similar peak levels after both procedures; however, the peak value occurred immediately after TURP, in the recovery room, but 24 h after laser ablation. The difference between TURP and VLAP in the time taken to reach the peak PSA level, and the different impact on prostatic tissue, might explain the different responses in PSA level post-operatively reported by these authors. According to Stamey et al. [12] and Vesey et al. [5], a dramatic rise in serum PSA immediately after TURP implies BPE rather than prostate cancer, as they found insignificant or much smaller increases in serum PSA in the latter after TURP. Vesey et al. [5] suggested that this difference could be caused by a more easily extractable store of PSA in the dilated acinar spaces of hyperplastic tissue, containing pooled prostatic secretions rich in PSA.

In the present study, the decrease in the PSA level after VLAP followed a double-exponential curve. In this model, the 'half-life' is not constant but increases steadily, which could be explained by an initial sharp decline in PSA level caused by the disappearance of the sequestered PSA that leaked into the blood during VLAP, after which there was less but persistent leakage of PSA from damaged prostatic tissue. The half-life of serum PSA has been calculated by Oesterling et al. [11] to be 3.15 days, using the Tandem-R PSA assay, and by Stamey et al. [12] to be 2.2 days, using the Pros-Check PSA assay. The 'half-life' of 5.6 days 24 h after VLAP is considerably longer and supports the hypothesis that the decrease in PSA after VLAP is influenced by damaged prostatic tissue. The attainment of a new (lower) mean (sd) baseline at 78 (49) days after VLAP is comparable with that found by Bosch et al. [9] after TULIP. However, it is considerably longer than the median time required for the serum PSA value to return to a stable level after TURP, as found by Oesterling et al. [13] (18 days, range 12–30+). This also agrees with Kabalin et al. [10] who found that PSA levels decreased more slowly after laser prostatectomy than after TURP. A possible explanation could be the altered architecture of the prostate after VLAP, with necrotic tissue remaining in situ rather than being immediately resected as in TURP. The lower level of PSA at the new baseline after VLAP compared with the level before treatment may reflect the ablation of PSA-producing tissue during VLAP. As necrotic tissue remains in the prostate for a long time after treatment with high-intensity focused ultrasound, transurethral needle ablation and transurethral microwave thermotherapy, the time necessary for serum PSA levels to reach a new baseline after these procedures should be comparable with that after VLAP.

In the present study, the T10% of a high proportion of the patients was reached within 4 months; if the PSA level does not decline to a new baseline 4 months after VLAP, further management of the patient will depend on the decisions of the individual clinician and such patients may represent a high-risk group for prostate cancer. Because serum PSA values vary within an individual, measurements must be repeated to confirm any suspicious increase. We recommend that biopsies are taken when the PSA is consistently and significantly above the pre-operative level during this period. An alternative approach is to keep these patients under prospective review, using DRE, PSA measurements and TRUS at 6-monthly intervals. If a new baseline PSA value is reached and the serum PSA starts to rise again after VLAP, the percentage PSA increase with time (PSA slope) may be used to distinguish patients with carcinoma. Oesterling et al. [13] found that a rise of >20% per year indicated carcinoma. Accordingly, Reneney et al. [7] reported that serial measurements of PSA in patients with incidental carcinoma found after TURP allowed the disease activity to be monitored and a PSA slope >20% per year was the most accurate marker to predict biopsy-proven residual disease. Although no malignancy was found in the present patients with increasing PSA levels one year after VLAP, the PSA slope might be helpful in diagnosing prostate carcinoma after VLAP.

In conclusion, because of the effects of VLAP on serum PSA it is not useful to measure PSA for the 4 months after VLAP. The kinetics of serum PSA level after VLAP provided no useful information to predict the clinical outcome.

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