Posterior prostate specific antigen determination as prognostic progression factor in prostate cancer treated with radical prostatectomy


ABSTRACT

Objective: To identify whether there is an association between prostate specific antigen levels measured three months after radical prostatectomy and biochemical recurrence.

Methods: Open, comparative, retrospective, cross-sectional study was carried out. Case records of patients with prostate cancer treated with radical prostatectomy at the authors’ institution from January 1991 to May 2010 were reviewed (n = 180 case records). Patients were staged according to prostate specific antigen levels and were then registered if there was biochemical recurrence (prostate specific antigen above 0.40 ng/mL); time of recurrence was recorded. Groups were compared to identify whether there was association between prostate specific antigen levels three months after surgery and biochemical recurrence frequency. Information was registered on a data collection sheet and a database was created on Excel. Descriptive statistics were carried out using STATA statistical package. Chi square test was used to compare the frequencies of biochemical recurrence of patients with different prostate specific antigen levels. There was a significant association between prostate specific antigen levels three months after surgery and biochemical recurrence.

RESUMEN

Objetivo: Identificar si existe asociación entre los niveles del antígeno prostático específico (APE) medido a los tres meses posteriores a la prostatectomía radical y su recurrencia bioquímica.

Métodos: Estudio transversal comparativo, descriptivo, abierto, retrospectivo. Se revisaron los expedientes de pacientes con cáncer de próstata tratados con prostatectomía radical en nuestra institución entre enero de 1991 y mayo de 2010 (n = 180 expedientes). Se estadificaron los pacientes de acuerdo con los niveles de APE. Posteriormente se registró si presentaron recurrencia bioquímica (APE mayor 0.40 ng/mL) y se consignó el tiempo en que se presentó dicha recurrencia. Se compararon los grupos para identificar si existe asociación entre los niveles de APE de los tres meses poscirugía y la frecuencia de la recurrencia bioquímica. Los datos se recogieron en Excel y se realizó estadística descriptiva. Para comparar las frecuencias de recurrencia de acuerdo al nivel de APE se utilizó ji cuadrada. Se utilizó el paquete estadístico STATA.
used to compare recurrence frequency in relation to prostate specific antigen level.

**Results:** Mean age of patients was sixty-four years. Initial rectal examination showed stage T1a in three patients, T1b in six patients, T1c in seventy-three patients, T2a in fifty-five patients, T2b in twenty-four patients, and T2c in nineteen patients. Mean preoperative prostate specific antigen was 13 ng/mL. Mean preoperative and postoperative Gleason score was 6. Risk classification according to D’Amico groups was as follows: seventy-five patients were in low risk group, sixty patients were in intermediate risk group, and forty-five patients were in high risk group. In regard to first postoperative prostate specific antigen value, one hundred and one patients had a value of 0-0.1 ng/mL; thirty-eight patients had a value of 0.11-0.20 ng/mL; nine patients had a value between 0.21-0.30 ng/mL; twelve patients had a value between 0.31-0.39, and twenty patients had prostate specific antigen value ≥ 0.4 ng/mL. Recurrence-free survival was 73% at nineteen years and significant P was 0.0000.

**Conclusions:** Values of first prostate specific antigen determination after radical surgery were useful in determining biochemical recurrence risk in relation to postoperative levels found.

**Keywords:** Prostate cancer, biochemical recurrence, PSA, Mexico.

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**INTRODUCTION**

Between 230,000 and 240,000 men are diagnosed with prostate cancer annually in Europe and the United States. Approximately 40% choose definitive treatment with radical prostatectomy (RP), which is the criterion standard in patients with life expectancy above 10 years. In Mexico in 2003 there were 6536 histological registers of prostate cancer, making it one of the most frequent tumors in the male population. It is second only to lung cancer as cause of death by cancer in men, with 3766 deaths per year and a rate of 11.9 per 100,000 inhabitants. Prostate cancer (CaP) presents more frequently in men over 60 years of age, and men 75 years and older represent half the cases at 47%. According to the 2003 Malignant Neoplasm Histological Report there were 4602 deaths from CaP. Different treatment options include radical prostatectomy, radiotherapy, and hormonal block. Follow-up in all these modalities is the measurement of prostate specific antigen (PSA) in blood.

Different publications have shown that the curative benefit of this procedure is linked to adequate patient selection and greater benefit has been found for patients with well-differentiated tumors, PSA ≤ 20 ng/mL, and localized disease. Results have not been satisfactory in locally advanced disease or in patients presenting with risk factors (PSA ≥ 20 ng/mL, clinical stage T3, perineural permeation, Gleason score ≥ 7). D’Amico proposed grouping cases together according to PSA, clinical stage, and biopsy Gleason score in order to predict biochemical recurrence risk. Control rates for localized disease are high. Twenty to thirty percent of patients present with recurrence that initially is demonstrated with an increase in PSA with no clinical or radiological evidence of metastasis.

This biochemical recurrence indicates the presence of epithelial prostatic tissue and is assumed to be cancer. The course of biochemical recurrence varies. Some patients present with clinical progression for metastasis, while others have no major problems.
Biochemical recurrence does not replace clinical progression or specific mortality of CaP and is probably an associated event. Determining an increase in PSA that represents local or systemic disease is an important factor in patients at risk for clinical progression. Management of patients with elevated PSA is based on clinical progression risk, life expectancy, and determining if increase is due to local or systemic disease.

Biochemical recurrence is defined as any detectable PSA level after radical prostatectomy or an increase in PSA after a period of time in which it has not been detectable. Mean PSA life is 3.1 days and after radical prostatectomy it should be reduced to undetectable levels after 4 weeks. Periodic PSA testing after radical prostatectomy is the cornerstone of postoperative surveillance for recurrent disease. Definitions in the literature include single or multiple PSA values of 0.2-0.6 ng/mL. The most commonly used limit is PSA ≥ 0.2 after radical prostatectomy and two consecutive values of ≥ 0.2 is accepted by the European Urological Association (EUA) as a basis for beginning treatment.

Seventy-nine percent of men with PSA ≥ 0.4 ng/mL show evidence of clinical progression, and therefore PSA ≥ 0.4 ng/mL has been accepted as the minimum for biochemical recurrence one month after surgery, followed by subsequent PSA level equal to or greater than the first measurement. Two successive increases of PSA ≥ 0.4 is the optimum biochemical recurrence definition that predicts significant clinical events. However, the first PSA determination and its association with biochemical recurrence has not been specifically studied, even in patients with levels below 0.40 ng/mL that can be considered disease-free, and so this is the objective of the present work.

**OBJECTIVE**

To identify whether an association exists between first PSA determination after radical prostatectomy and biochemical recurrence.

To compare biochemical recurrence frequency according to different PSA cut-off points in the first determination after radical prostatectomy.

**METHODS**

An open, retrospective, comparative, cross-sectional study was carried out. Case records of patients that underwent radical prostatectomy at the authors’ institution between January 1991 and May 2010 were reviewed (n=180 case records).

Patients were staged according to PSA levels and if they presented with biochemical recurrence (PSA above 0.40 ng/mL) it was registered along with time of recurrence. Groups were compared to determine if there was an association between the first postoperative PSA quantification and biochemical recurrence frequency.

Data was registered on a data collection sheet, a database was developed using Excel, and descriptive statistics were carried out. Chi square test was used and statistical significance was considered when P ≤ 0.05. STATA statistical package was used.

**Inclusion criteria:** Case records of patients with CaP treated with radical prostatectomy and whose PSA levels were determined within the first three postoperative months.

**Exclusion criteria:** Patients treated with radiotherapy or hormone therapy.

**RESULTS**

Case records of 180 patients were reviewed and the following age groups were established: 2 patients were under 50 years of age; 50 patients were between 51-60 years of age; 104 patients were between 61-70 years of age; and 24 patients were above 71 years of age. Mean age was 64 years at the time of radical prostatectomy.

Mean initial preoperative PSA was divided into levels of 0-4 ng/mL, 4-10 ng/mL, 10.1-19.9 ng/mL, and ≥ 20 ng/mL. Ten patients had PSA of 0-4ng/mL; 86 patients had PSA between 4-10 ng/mL; 58 patients had PSA between 10.1-19.9 ng/mL; and 26 patients had PSA ≥ 20 ng/mL. Mean preoperative PSA was 13 ng/mL.

Rectal examination revealed stage T1a in 3 patients, T1b in 6 patients, T1c in 73 patients, T2a in 55 patients, T2b in 24 patients, and T2c in 19 patients.

In regard to preoperative Gleason score pattern, 1 patient had Gleason score of 2; 5 patients had Gleason score of 3; 23 patients had Gleason score of 4; 17 patients had Gleason score of 5; 96 patients had Gleason score of 6; 26 patients had Gleason score of 7; 9 patients had Gleason score of 8; and 3 patients had Gleason score of 9. Mean preoperative Gleason score was 6.

Risk classification according to D’Amico groups was: 75 patients in low risk group; 60 patients in intermediate risk group; and 45 patients in high risk group.

Postoperative Gleason score was: 2 patients with Gleason score of 2; 2 patients with Gleason score of 3; 10 patients with Gleason score of 4; 14 patients with Gleason score of 5; 86 patients with Gleason score of 6; 40 patients with Gleason score of 7; 17 patients with Gleason score of 8; 8 patients with Gleason score of 9; and 1 patient with Gleason score of 10. Mean Gleason score after radical prostatectomy was 6.

First postoperative PSA taken within three months after surgery resulted in 101 patients with PSA between 0-0.1 ng/mL; 38 patients with PSA between 0.11-0.20
ng/mL; 9 patients with PSA between 0.21-0.30 ng/mL; 12 patients with PSA between 0.31-0.39 ng/mL; and 20 patients with PSA ≥ 0.4 ng/mL. Kaplan-Meier curves were used to show these results (Image 5).

Recurrence presented in 47 of the 180 patients (26%) and there was a mean 12 months between surgery and recurrence. Seventy-four percent of patients were recurrence-free at 19 years.

In relation to preoperative stage, recurrence presented in 1 patient that had stage T1a (1.49%); in 1 patient that had T1b (1.49%); in 18 patients that had T1c (35.8%); in 12 patients that had T2a (31.3%); in 6 patients that had T2b (14.9%); and in 9 patients that had T2c (14.9%) (Image 6).

In regard to first postoperative PSA value only 10 patients (10%) of the 101 patients with PSA levels between 0-0.10 ng/mL presented with biochemical recurrence; 17 patients (44%) of the 38 patients with PSA levels between 0.11-0.20 ng/mL presented with recurrence; 8 patients (88.8%) of the 9 patients with PSA levels between 0.21-0.30 ng/mL had recurrence; 12 patients (100%) of the 12 patients with PSA levels between 0.31-0.39 ng/mL had recurrence; and the 20 patients with PSA levels of 0.40 ng/mL were considered to have immediate recurrence or failed treatment. Kaplan-Meier curves were used to represent results (Image 7 and 8).

In regard to patients with PSA levels between 0-0.10 ng/mL that presented with recurrence, 1 patient had stage T1a; 5 patients had T1c, 2 patients had T2a; 1 patient had T2b, 1 patient had T2c; 2 patients had Gleason score of 5; 2 patients had Gleason score of 6; 2 patients had Gleason score of 7; 3 patients had Gleason score of 8; 1 patient had Gleason score of 9. Mean recurrence was 17 months.

In regard to patients with PSA between 0.11-0.20 ng/mL, 1 patient had stage T1b; 6 patients had T1c; 5 patients had T2a, 1 patient had T2b, 4 patients had T2c. One patient had Gleason score of 4; 3 patients had Gleason score of 5; 5 patients had Gleason score of 6; 3 patients had Gleason score of 7; 4 patients had Gleason score of 8; and 1 patient had Gleason score of 9. Mean recurrence was 16 months.

In patients with PSA levels between 0.21-0.30 ng/mL, 4 patients had stage T1c; 2 patients had T2a; and 2 patients had T2c. Three patients had Gleason score of 6; 4 patients had Gleason score of 7; and 1 patient had Gleason score of 10.

And finally, in the group of patients with PSA levels between 0.31-0.39 ng/mL, 3 patients had T1c; 3 patients had T2a; 4 patients had T2b; and 2 patients had T2c. Two patients had Gleason score of 5; 4 patients...
had Gleason score of 6; 2 patients had Gleason score of 7; 2 patients had Gleason score of 8; and 2 patients had Gleason score of 9 (Table 1).

**DISCUSSION**

The majority of articles base their follow-up on PSA, and 0.40 ng/mL is the accepted cut-off point for biochemical recurrence; a PSA of 0.2 ng/mL is debatable. Biochemical recurrence is defined as any PSA level detectable after radical prostatectomy. Mean PSA life is 3.1 days and should go down to undetectable levels after 4 weeks. In the present study 26% of patients presented with biochemical recurrence during follow-up, despite having PSA under 0.40 ng/mL. Study group analysis showed that 10% of patients with PSA between 0-0.10 ng/mL, that could be considered cured, had biochemical recurrence within the first 17 months. All patients in the group with PSA levels between 0.31-0.39 ng/mL presented with biochemical recurrence, regardless of pathological stage and risk group, prompting the following questions: should a postoperative PSA level of 0.40 ng/mL define biochemical recurrence or should support be lent to the opinion that a PSA level of 0.2 ng/mL is the cut-off point for biochemical recurrence? And how should one proceed when the first PSA determination does not fall within optimum levels (0.0 ng/mL)? In the present study, biochemical recurrence took place at a mean 12 months, taking into account all PSA cut-off points used. A second PSA determination could be carried out or adjuvant treatment begun.

In a series carried out by Eisenberg, postoperative PSA levels were measured within 1-3 months after surgery in 525 patients and there was a biochemical recurrence-free rate of 86% in those patients that had undetectable PSA (≤ 0.05 ng/ml) compared with 67% of patients that had detectable PSA. The present authors found that more than 50% of patients had recurrence when PSA did not fall below 0.2 ng/mL. Most striking was the fact that in the group of patients with PSA levels between 0.31-0.39 ng/mL, mean initial PSA was 31 ng/mL, making PSA a very important predictive factor in biochemical recurrence.
First PSA determination values after radical surgery were useful for determining risk for biochemical recurrence in patients in relation to their postoperative values. Patients with first postoperative PSA determination above 0.2 ng/mL had early biochemical recurrence. PSA continues to be the most important predictive factor in treatment failure. Biochemical failure should be considered to exist in those patients that have PSA level ≥ 0.2 ng/mL. First determination is important for attempting to predict or identify patients at risk for biochemical recurrence or perhaps to evaluate when early adjuvant treatment should be initiated. A larger sample needs to be studied in order to corroborate the present results.

### Table 1. General distribution of cases based on PSA level.

<table>
<thead>
<tr>
<th>PSA (ng/mL)</th>
<th>N° patients</th>
<th>Initial PSA</th>
<th>Gleason score</th>
<th>Recurrence (mean in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 0.10</td>
<td>10</td>
<td>12.9</td>
<td>low: 4</td>
<td>17</td>
</tr>
<tr>
<td>0.11 - 0.20</td>
<td>17</td>
<td>11.9</td>
<td>low: 9</td>
<td>16</td>
</tr>
<tr>
<td>0.21 - 0.30</td>
<td>8</td>
<td>11.3</td>
<td>intermediate: 3</td>
<td>21</td>
</tr>
<tr>
<td>0.31 - 0.39</td>
<td>12</td>
<td>31.7</td>
<td>high: 4</td>
<td>5</td>
</tr>
</tbody>
</table>

### CONCLUSIONS

First PSA determination values after radical surgery were useful for determining risk for biochemical recurrence in patients in relation to their postoperative values. Patients with first postoperative PSA determination above 0.2 ng/mL had early biochemical recurrence. PSA continues to be the most important predictive factor in treatment failure. Biochemical failure should be considered to exist in those patients that have PSA level ≥ 0.2 ng/mL. First determination is important for attempting to predict or identify patients at risk for biochemical recurrence or perhaps to evaluate when early adjuvant treatment should be initiated. A larger sample needs to be studied in order to corroborate the present results.

### BIBLIOGRAPHY