Preoperative risk factors and their biochemical recurrence implication for locally advanced prostate cancer in patients that underwent radical prostatectomy

Schroeder-Ugalde Iván Mauricio,1 Xochipitécatl-Muñoz Daniel Juan,2 Navarro-Vargas Juan Carlos,1 Velázquez-Macías Rafael.3

ABSTRACT

Background: Radical prostatectomy continues to be the criterion standard for localized prostate cancer treatment. The average positive margin rate is 28% and is related to preoperative factors such as clinical stage, Gleason score, and preoperative PSA. Patients with positive surgical margins have a greater probability of biochemical progression.

Material and methods: In this study we analyzed the preoperative risk factors associated with locally advanced disease in the surgical specimen, the therapeutic options, and their implications in relation to biochemical recurrence.

Results: Seventy-one case records of patients that underwent radical prostatectomy at the advanced specialty hospital, Hospital Central Sur de PEMEX, were reviewed. Sixty-seven patients were included, 29 (43.2%) of which had locally advanced disease. The patients were classified into risk groups and in the PSA and Gleason

Introducción: La prostatectomía radical continúa siendo el estándar de oro para el tratamiento del cáncer de próstata (CaP) localizado. La tasa media de márgenes positivos se sitúa en el 28%, se relaciona con factores preoperatorios como el estadio clínico, el valor de Gleason y el antígeno prostático específico (APE) preoperatorio. Los pacientes con márgenes positivos tienen mayor probabilidad de progresión bioquímica.

Material y métodos: En este estudio analizamos los factores de riesgo preoperatorios asociados con enfermedad localmente avanzada en la pieza quirúrgica, cuáles son las opciones terapéuticas y sus implicaciones en relación con la recaída bioquímica.

Resultados: Se revisaron 71 expedientes de pacientes operados de prostatectomía radical en el Hospital Central Sur de Alta Especialidad (HCSAE) de PEMEX. Se incluyeron 67 pacientes, de los cuales 29 (43.2%) se encontraron con enfermedad localmente avanzada. Se clasificó a los pacientes en grupos de riesgo y se realizó un análisis
score groups there was no statistical significance with a p>0.05. There was statistical significance in the clinical stage group with a p < 0.05. Of the 11 patients with locally advanced disease that were kept under surveillance, 8 (72.7%) did not present with biochemical recurrence, with a mean follow-up of 39 months. The incidence increase in locally advanced disease in relation to the risk groups according to PSA and Gleason score could not be corroborated.

Conclusions: The low recurrence incidence in the patients that were kept under surveillance was an interesting result. Further studies are needed to clarify doubts as to the precise moment adjuvant treatment should be initiated in an effort to increase patient survival.

Keywords: Prostate, radical prostatectomy, locally advanced prostate cancer, Mexico.

INTRODUCTION

Prostate cancer (CaP) is the most frequent non-cutaneous cancer and the second cause of death by cancer in men in the United States. In Mexico, CaP ranks in first place (17%) in regard to cancers that affect men. Unfortunately, up to 60% of the cases that are first-time diagnoses are in clinically advanced stages, making curative treatment an impossibility for those patients. With the onset of the prostate specific antigen (PSA) era and opportune CaP detection, this percentage has been decreasing and the diagnosis rate of localized cancer has been increasing. Radical prostatectomy continues to be the criterion standard for localized CaP treatment and the retropubic approach is the most common. Its main advantage is that it offers the possibility of cure with a minimum of side effects. It is a well-tolerated procedure with a low morbidity rate and a general mortality rate of 0.2%. Compared with other treatments for localized disease, the potential disadvantages are the need to be hospitalized and the amount of recovery time, the possibility of incomplete resection, and the risk of erectile dysfunction and urinary incontinence. The average rate of positive margins in the surgical specimens of radical prostatectomy is 28%, with ranges that vary from 0 to 53%. The possibilities of there being positive margins are related to clinical stage, tumor volume, the percentage of cancer in the biopsy, Gleason score, preoperative PSA value, the anatomopathologic processing of the surgical specimen, neoadjuvant therapy, early cancer diagnosis possibilities, and also the experience of the surgeon. Patients with positive margins have a greater probability of biochemical progression, and it appears that they also have more probabilities of response to adjuvant and rescue treatment with radiotherapy. Even though from an overall perspective 50% of the patients with positive margins present with biochemical recurrence at five years, not all positive margins necessarily have the same behavior.

The aim of this study was to analyze the preoperative risk factors that are associated with a histopathologic result of locally advanced disease in the surgical specimen and to analyze the therapeutic options and their implications in relation to biochemical recurrence. In addition a descriptive study was carried out on other variables related to the characteristics and progression of the group of patients that underwent radical prostatectomy.

METHODS

The case records were reviewed of 71 patients that underwent radical prostatectomy due to adenocarcinoma of the prostate at the Hospital Central Sur de Alta Especialidad (HCSAE) de PEMEX within the time frame of April 2004 to February 2011. Only cases...
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A total of 67 patients were included in the study and their mean age was 60 years with a range of 42 to 71 years. Of the enrolled patients, 26 (38.8%) had no associated comorbidities, 21 (31%) had a past medical history of smoking, five patients (7.4%) were diabetic, and 22 (32.8%) had high blood pressure (HBP). The mean PSA was 10.9 ng/mL (2.85 to 29 ng/mL range). Preoperative Gleason score was 2 in three patients (4.5%), nine patients (13.4%) had a Gleason score of 3, three patients (4.5%) had a Gleason score of 4, three patients (4.5%) had a Gleason score of 5, 22 patients (32.8%) had a Gleason score of 6, 16 patients (23.9%) had a Gleason score of 7, six patients (9%) had a Gleason score of 8, and three patients (4.5%) had a Gleason score of 9. In accordance with clinical stage, two patients (3%) had stage T1B, 38 patients (56.7%) had stage T1C, 16 patients (23.9%) had stage T2A, and 10 patients (14.9%) had stage T2B (Table 1). Neoadjuvant hormone therapy was used in 19 patients (28.4%), of which eight (42%) presented with locally advanced disease. In relation to the histopathologic result, the previous Gleason score was under-staged in 35 patients (52%), over-staged in 10 patients (6.7%), and it remained the same in 20 patients (29.8%). Thirty-eight patients (56.7%) presented with organ-confined disease, 18 patients (26.8%) had positive surgical margins, eight patients (11.9%) had positive vesicles, and three patients (4.4%) had positive margins and vesicles. In total, 29 patients (43.2%) presented with locally advanced disease (Figure 1). Patients were classified into risk groups for preoperative PSA, Gleason score, and clinical stage (Figures 2 to 4). After statistical analysis, no statistically significant results were found in the PSA and Gleason score groups, but there was statistical significance in the clinical stage group (Table 2). PSA value was also analyzed separately, the use of previous androgen blockade was evaluated, as was the increase in Gleason score in the surgical specimen with respect to preoperative data. There was statistical significance in relation to PSA (Table 3). Of the 29 patients with locally advanced disease, 13 were sent to radiotherapy to determine the histopathologic result, five were given immediate hormone therapy, and 11 were kept under surveillance. Of the 11 patients under surveillance, eight (72.7%) of them, with a mean 39-month follow-up (11 to 71 month range), did not present with biochemical recurrence, three patients were classified as low-risk, three as intermediate-risk, and two as high-risk patients (Figure 5). Of the 38 patients with a histopathologic result of organ-confined disease, 17 (44%) presented with biochemical recurrence at a mean of 17 months, with a 3 to 65 month range. Mean blood loss was 1460 mL, with a range of 300 to 4500 mL. The mean surgery duration

### RESULTS

Table 1. clinical characteristics of the total group of patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patient total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60 (42 - 71)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>HBP</td>
<td>22 (32.8%)</td>
</tr>
<tr>
<td>DM</td>
<td>5 (7.4%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>21 (31.3%)</td>
</tr>
<tr>
<td>PSA</td>
<td>10.93 (2.85 - 29)</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td>3</td>
<td>9 (13.4%)</td>
</tr>
<tr>
<td>4</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td>5</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td>6</td>
<td>22 (32.8%)</td>
</tr>
<tr>
<td>7</td>
<td>16 (23.9%)</td>
</tr>
<tr>
<td>8</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>9</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>T1B</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>T1C</td>
<td>38 (56.7%)</td>
</tr>
<tr>
<td>T2A</td>
<td>16 (23.9%)</td>
</tr>
<tr>
<td>T2B</td>
<td>10 (14.9%)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>67</td>
</tr>
</tbody>
</table>

HBP: high blood pressure; DM: diabetes mellitus; PSA: prostate specific antigen

of organ-confined cancer were included and four cases with preoperative stage T3 or higher were excluded. Age, associated comorbidities, previous androgen blockade use, previous PSA, diagnostic Gleason score, and clinical stage according to the D’Amico criteria were evaluated in the 67 patients included in the study. A multivariate analysis was carried out for a result of locally advanced disease defined as extracapsular invasion, positive surgical margins, and/or seminal vesicle invasion in the surgical specimen. Postoperative treatment and progression of patients with locally advanced disease were analyzed and in the group with organ-confined disease, PSA values at three, six, 12, and 36 months and the time of biochemical recurrence were evaluated. The SPSS version 15 program for Windows was used for the statistical analysis (Student’s t test, Mann-Whitney U test, and chi-square test). Intraoperative bleeding, surgery duration, hospital stay, and late complications were analyzed as independent variables.
was 175 minutes, with a 90 to 300 minute range. Mean hospital stay was nine days, with a 5 to 32 day range. Of the 67 patients, 28 (41.8%) did not present with late complications, 22 (32.8%) presented with erectile dysfunction, nine (13.4%) presented with stricture, and four (6%) with urinary incontinence (Figure 6).

**DISCUSSION**

In Mexico, radical prostatectomy is the most widely used treatment method for localized CaP in patients with a life expectancy of 10 years or more, and is considered to be the criterion standard. Nevertheless, in some patients (2.5 to 40%) the histopathologic result shows extraprostatic disease with no evidence of metastasis, which has been named locally advanced CaP or clinical stage T3N0M0.6,7 In this case series, the percentage of locally advanced disease was higher than that reported in the medical literature and so the decision was made to analyze the risk factors that affected this result. According to the international literature, the variables with the most influence on the result of locally advanced disease after radical prostatectomy are Gleason score, preoperative PSA, and clinical stage. These were the variables studied in detail in a multivariate analysis that produced only one statistically significant relation in the clinical stage group, showing that patients with stage T2B had a greater risk for locally advanced disease compared with those patients that had stages T1C-T2A. Factors such as the time of diagnosis and treatment, correct surgical indication, and a careful and refined surgical technique5 are also related to the incidence of locally advanced disease. These factors were not analyzed in this study and could have had an influence on the results.

Another of the variables that was analyzed and that has been widely studied in the medical literature is androgen deprivation prior to radical prostatectomy. Soloway MS et al. published the results of neoadjuvant androgen ablation in stage T2B CaP and found that androgen deprivation reduced the positive surgical
Another associated factor is the increase in the Gleason score of the surgical specimen. Up to 40% of patients that underwent radical prostatectomy have been reported to have an increase in Gleason score with respect to biopsy scores, and our case series produced a similar result, with an increase in Gleason score in 52% of the patients. Kojima reported that up to 47% of the patients with a PSA value above 10 ng/mL tended to have an increase in Gleason score, as well as 32% of the patients with PSA values between 4 and 10 ng/mL. The affirmation that a higher Gleason score in the surgical specimen is directly correlated with a greater possibility of extraprostatic disease was not able to be corroborated in our study in which 52.8% of the patients had organ-confined disease and 47.2% had locally advanced disease.

Other authors have had interesting results in their studies of other factors with respect to surgical technique. Ward JF et al. observed that neurovascular band-sparing was not a factor in risk for positive margins, and Gaker DL et al. reported that positive margins in the prostatectomy surgical specimens had no relation to the sparing or non-sparing of continence mechanisms at the level of the bladder neck and apex.

Oncologic control varies from 75 to 90% for the first five years and from 65 to 70% at 15 years. PSA elevation is usually the earliest evidence of tumor recurrence after radical prostatectomy. By consensus, disease recurrence is considered to exist if the PSA level is 0.4 ng/mL or higher, eight or more weeks after the procedure. Of the patients who will definitely present with biochemical recurrence, in approximately 50% it will be within the first three years, in 80% it will be the first five years, and in 99% it will be the first 10 years. Non-progression rates vary according to pathologic and clinical risk factors. Clinical risk factors are tumor stage, Gleason score, preoperative PSA, and the time lapse between diagnosis and treatment. Poor outcome factors include perineural or lymphovascular invasion, extracapsular extension, positive margins, seminal vesical invasion, and metastasis to lymph nodes.

Pérez-Becerra et al. published results from a study of 185 patients, detecting biochemical recurrence in 33% of the patients at 17 months, similar to the results of our case series in which biochemical recurrence presented in 44% at a mean of 17 months. Just as in this study, patients with locally advanced disease are omitted because they are generally given adjuvant treatment without knowing if or when they would present with biochemical recurrence. A direct relation between locally advanced disease and biochemical recurrence is described in the medical literature. In a case series of 255 patients, Ojea-Calvo et al. reported that of the patients with negative surgical margins, 55 (24.4%) had biochemical recurrence and 170 (75.6%)
did not, and of the patients with positive surgical margins, 30 (46.2%) had biochemical recurrence and 35 (53.8%) did not ($p=0.001$). These data showed that the probability of five-year recurrence-free disease in the patients with negative surgical margins was 71% vs 44% of the patients with positive surgical margins ($p<0.001$).

A positive surgical margin in a prostatectomy surgical piece leads us to four possible scenarios: the first is that there is limited residual cancer at the prostatic surgical site; the second is that there is no residual cancer; the third is that there is residual cancer at the prostatic surgical site and microscopic distant metastasis; and the fourth is that there is no residual cancer at the prostatic surgical site and there is distant metastasis. Only in the first of these situations is it possible to offer a curative intent benefit to the patient. It can be in the form of adjuvant radiotherapy immediately after surgery or as rescue radiotherapy that is delayed until biochemical recurrence appears. However, there are currently no phase III studies that validate one therapeutic modality or the other, or that evaluate the role of hormonal therapy in those patients.19-21 The most appropriate PSA level for initiating hormonal therapy is not known.4 Hachiya T et al. compared adjuvant hormonal therapy and surveillance in patients with positive surgical margins after radical prostatectomy. The percentage of patients free from biochemical recurrence at five years was 85.9% in the hormonal therapy group and 80% in the surveillance group, with no statistically significant difference.22 Interestingly, the results of that study were similar to those of our case series in which 72.7% of the patients that were kept under surveillance and with a follow-up of 39 months did not present with biochemical recurrence. Guidelines from the European Association of Urology propose, as a type A recommendation, that all patients that present with biochemical failure, but that do not have an elevation above 1.5 ng/mL, can be under conservative surveillance and have a life free from disease that is almost equal to that of low-risk patients,23 without specifying whether this declaration can be applied to patients with locally advanced disease.

In regard to radiotherapy and its correct application time, Kamat AM et al. reported that a Gleason score ≥7 and a preoperative PSA greater than 10.9 ng/mL were the strongest predictive factors for biochemical recurrence after postoperative adjuvant radiotherapy, even if PSA prior to radiotherapy has been undetectable.24

However, international studies coincide in stating that the patient should receive adjuvant treatment, whether with radiotherapy alone or together with hormonal blockade.25 In a case series of 66 patients with locally advanced disease and a mean follow-up of 74 months, Andrade-Platas et al. reported an overall survival rate of 97%, showing that a result of locally advanced disease in the surgical specimen did not result in a high mortality rate. However, they found an elevated biochemical recurrence rate in the patients that had only undergone surveillance (77%).26

Therefore, an effort has been made to normalize the criteria to be followed in deciding on the treatment of choice in this type of patient and the appropriate time at which to carry it out. According to Ojea-Calvo et al. in an international literature review, the guideline for action could be established as follows: adjuvant radiotherapy treatment for patients with positive surgical margins due to extraprostatic extension with a preoperative PSA under 10 ng/mL and a Gleason score ≤6; hormonal treatment for patients with positive surgical margins due to extraprostatic extension with a preoperative PSA greater than 10 ng/mL or a Gleason score ≥7; and surveillance for patients with positive unifocal rounded surgical margins ≤4 mm and due to capsular incision.5

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Figure 5. Adjuvant treatment

Figure 6. Late complications

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Finally, the late complications described in the medical literature are bladder neck contracture or stricture in 0.5 to 10% of the patients, incontinence after 24 months in 8%, and erectile dysfunction in 12 to 30%.\textsuperscript{22,23} The general surgical complication rate ranges from 5 to 7% and advanced age is the most frequent factor associated with complications.\textsuperscript{24,25} In a case series of 78 patients, Costilla-Montero A et al. compared the late complication rate with various international case series and obtained similar percentages, with incontinence in 3.2% of patients, erectile dysfunction in 33%, and stricture in 16%.\textsuperscript{30} These results were also similar to ours, which were incontinence in 6% of the patients, erectile dysfunction in 32.8%, and stricture in 13.4%.

CONCLUSIONS
Radical prostatectomy continues to be the treatment of choice for localized CaP. However, its performance in high risk patients is a controversial topic and therefore there are nomograms that predict the possibility of extraprostatic disease. These results in more adequate patient selection that in turn reduces the incidence of locally advanced disease.

The management of biochemical recurrence status is still a theme of debate and no consensus has been reached for determining treatment and its adequate initiation. Although there are recommendations for deciding upon surveillance, hormonal therapy, and radiotherapy in accordance with risk groups, there are still no studies with results that can be applied to patients with locally advanced disease.

Radical prostatectomy continues to be the criterion standard and the procedure with which new treatments are compared. The favorable aspect of this procedure is that it has the capacity to achieve biochemical curative rates of up to 60% at eight years without the need for complementary treatments, especially in patients whose cancer is confined to the surgical specimen.

REFERENCES