PREOPERATIVE PREDICTIVE MODEL FOR BIOCHEMICAL RECURRENCE IN PATIENTS WITH LOCALIZED PROSTATE CANCER TREATED WITH RADICAL PROSTATECTOMY

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Summary.- OBJECTIVES: To identify pre-prostatectomy clinical prognostic factors for biochemical recurrence (BR) and to create a predictive model for BR based on predictive clinical variables prior to radical prostatectomy (RP).

METHODS: a retrospective case-records study of patients with clinically localized prostate cancer treated with RP as monotherapy pN0-pNx and monitored at least for 12 months between 1996 and 2007. We considered BR the PSA persistence or elevation after RP greater than 0.4 ng/ml. The clinical variables analyzed were PSA, clinical stage and Gleason score from the biopsy (GS). Univariate and multivariate analysis were carried out using the chi squared test and logistic regression to determine the variables associated with BR. In order to estimate BR based on the variables identified we developed a mathematical model and designed an Excel spreadsheet to apply it. Calibration and discrimination were performed using the Hosmer-Lemeshow test and an ROC curve determining the area under the curve.

RESULTS: We included 627 patients. The mean age was 64 years with a mean follow-up of 87 months. The mean PSA was 8 ng/ml. 68.6% of patients had a PSA \leq 10 ng/ml, 53.1% had a GS \leq 6 and 61.7% had a clinical stage of cT1a-c. BR was observed in 204 (32.5%) patients, 39 due to biochemical persistence. The mean time to BR was 28 months with 89.7% of instances occurring in the first 8 years. On the multivariate analysis, PSA and GS were independent predictors of BR (p=0.001), while the cT2c stage had a tendency towards statistical significance (p=0.06). The three variables were included in the equation for the model with different specific weight. Specificity was 93.6%, sensitivity was 36.8% and an overall precision of 75.1%. The model had a predictive capacity of 73% and a p-value < 0.001.

CONCLUSIONS: PSA and GS are independent prognostic clinical variables associated with BR-free survival. The predictive model developed allows the risk of BR to be estimated with 73% reliability.

Keywords: Biochemical recurrence. Predictive model. Radical prostatectomy.
INTRODUCTION

Prostate cancer is the most frequently tumor in men and the second leading cause of oncological death (1). Approximately one third to half of the patients treated with curative intent undergo radical prostatectomy (2,3).

Around 30% of patients following RP experience an increase in serum PSA with no clinical or radiological evidence of metastatic involvement (14). 77% of cases of biochemical recurrence (BR) occur five years following surgery and 4% after 10 years (5).

Multiple predictive factors for BR, both clinical and pathological, have been identified and used to develop nomograms to predict BR following RP (6).

Nomograms are optimized models that use a formula or algorithm to predict the probability of outcome (7). They represent a useful tool for estimating individual risk of recurrence based on clinical and pathological variables. Thereby, allows treatment and clinical decision making to be optimized.

In this work we identify the pre-prostatectomy clinical prognostic factors for BR and create a predictive model for BR based on predictive clinical variables prior to RP.

MATERIALS AND METHODS

We retrospectively analyze the database of patients who underwent RP in the Urology Department at Gregorio Marañón University General Hospital between 1996 and 2007. The update of patients’ monitoring was held in December 2011.

We selected patients with clinically localized disease treated with RP as monotherapy, pN0-pNx, and followed-up at least 12 months. We excluded patients who underwent neoadjuvant or adjuvant therapy and those without PSA, clinical stage or anatomopathological information.

Patients were classified prior to surgery based on D’Amico risk groups (8).

The 2009 UICC TNM classification was used for the pathology stage (9).

The RP was performed by all members of the department, including residents, according to the technique described by Walsh (10). Lymph node dissection was conducted when lymph node risk involvement was > 7%, which included the nodes overlying the external iliac artery and vein, the nodes within the obturator and the nodes medial and lateral to the internal iliac artery (11).
Diagnosis was made by transrectal prostate biopsy guided by ultrasounds, 6 cores when prostate volume was <50 cc and 10 cores when prostate volume was >50 cc or rebiopsy (12).

The prostatectomy pieces were processed according to the standard procedure established by the Pathology Service, maintained during the study period.

Postoperative follow-up consisted in PSA measurement 3 months after RP, then every 6 months until the 5th year and annually thereafter.

We consider BR to be persistence or increase in PSA greater than 0.4 ng and increasing on the subsequent measurement after RP (13).

Time to BR was defined as the interval in months from surgery until the appearance of BR or until the date of the last review. Patients with biochemical persistence were assigned with 0 months time until BR.

Follow-up time was defined as the interval in months between the date of the prostatectomy and death or until the date the last PSA level was measured.

Clinical variables analyzed were PSA, clinical status and Gleason score from the biopsy (GS). After data collection, the records were turned anonymous in compliance with Organic Law 15/1999 on the Protection of Personal Data (14).

Statistical analysis

We conducted a descriptive analysis of the variables being analyzed using routine statistics for quantitative variables (mean, standard deviation, median, etc.) and qualitative variables (absolute frequencies, etc.). Univariate and multivariate analysis were carried out using a logistic regression. Statistical significance was considered as p <0.05. All calculations were performed using SPSS version 18.0 in Spanish.

Individual probability of BR was calculated according to the general equation (logistic function) (15, 16).

\[
P(Y = 1) = \frac{1}{1 + \exp(-\alpha - \beta_1 X_1 - \beta_2 X_2 - \ldots - \beta_k X_k)}
\]

Where:

- \( Y \) is the dependent variable (biochemical recurrence yes).
- \( X_1, X_2, X_3, \ldots, X_k \) are the independent variables identified.
- \( \alpha, \beta_1, \beta_2, \beta_3, \ldots, \beta_k \) are the model’s parameters.
- \( \exp \) is the simplified exponential function. Corresponds to raising the number e (2.718) to the power contained in parenthesis.

We designed a calculation sheet in Excel to facilitate calculating the estimation of biochemical recurrence with clinical data in daily clinical practice (Figure 1).

Validation of the predictive model

Calibration (level by which the predicted probability coincides with that observed) was
calculated using the Hosmer-Lemeshow test. In this test, if the chi-squared test has not statistical significance, indicates that there was a high level of coincidence between the observed and expected results, representing a “good adjustment” of the model.

Discrimination (level by which the model distinguishes between individuals in which the event occurs and those that it does not) was calculated by constructing a ROC (Receiver Operating Characteristic) curve, calculating the area under the curve, as well as the sensitivity and specificity (17). Internal validation was made with 1000 bootstrapping resamples.

RESULTS

Analysis of the sample

We included 627 patients. Mean age was 63.5 ± 5.9 (43-78) years with a median of 64 years. Mean PSA was 9.4 ± 6.6 (0.8-69) ng/ml with a median of 8 ng/ml.

The mean follow-up time for the series was 91.2 ± 39.6 (12-190) months with a median of 87.

Table I. Clinical characteristics of the series.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Número (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA:</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 10</td>
<td>430 (68.6%)</td>
</tr>
<tr>
<td>10.01 – 20</td>
<td>168 (26.8%)</td>
</tr>
<tr>
<td>≥ 20</td>
<td>29 (4.6%)</td>
</tr>
<tr>
<td><strong>Gleason score:</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>333 (53.1%)</td>
</tr>
<tr>
<td>7</td>
<td>192 (30.6%)</td>
</tr>
<tr>
<td>≥ 8</td>
<td>102 (16.3%)</td>
</tr>
<tr>
<td><strong>Clinical stage (cT):</strong></td>
<td></td>
</tr>
<tr>
<td>T1a-c</td>
<td>387 (61.7%)</td>
</tr>
<tr>
<td>T2a-b</td>
<td>206 (32.9%)</td>
</tr>
<tr>
<td>T2c</td>
<td>54 (8.4%)</td>
</tr>
<tr>
<td><strong>D’Amico risk group:</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>237 (37.8%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>256 (40.8%)</td>
</tr>
<tr>
<td>High</td>
<td>134 (21.4%)</td>
</tr>
</tbody>
</table>

68.6% of patients had a PSA ≤ 10 ng/ml, 53.1% had a GS ≤ 6 and 61.7% had a clinical status of cT1a-c (Only four patients had T1a-b stage). 40.8% of patients were classified in the intermediate risk group for recurrence (Table I).

BR Characteristics

BR was observed in 204 (32.5%) patients. In 39 (19.1%) cases, this was due to biochemical persistence.

The mean time until BR was 35.1 ± 32.6 (0-132) months with a median of 28 months. Excluding patients with biochemical persistence, the mean was 44.6 ± 30.6 (5-132) with a mean of 36 months.

80.4% of BR occurred in the first 5 years of follow-up and 89.7% in the first 7 years.

We did not find any significant differences (p = 0.39) in the elapsed time until BR based on D’Amico recurrence risk group.

We did not find any significant differences in the age of patients without BR and patients who presented BR (p = 0.34).

Statistical correlation between clinical variables and BR

On the univariate analysis, PSA, GS and clinical stage were associated with biochemical recurrence with statistical significance (p < 0.001).

All the above variables were included in the multivariate analysis. PSA and GS behaved as independent predictors of biochemical recurrence after bootstrap (p = 0.001), while the clinical stage did not have a statistically significant association with recurrence (p = 0.16), except for the cT2c stage which had a strong tendency towards statistical significance (p = 0.06) (Table II).

Development of the predictive model for calculating the probability of BR with the clinical variables

The probability of BR can be estimated using the following formula based on the variables analyzed:

$$P(RB = S_i) = \frac{1}{1 + e^{-\text{exp}}}$$

exp=-1.758+0.927(PSA=10-20)+2.097(PSA=20) +0.795 (Gleason=7) + 1.616(Gleason=8) +0.127 [clinical stage = cT2a-b] + 0.776 (clinical stage=cT2c)
Validation of the predictive model

Calibration was performed using the Hosmer-Lemishow test. The chi-squared test was 1.318 (p = 0.971), there was not statistical significance.

Discrimination was evaluated by constructing an ROC curve and calculating the area under the curve. Specificity was 93.6% sensitivity was 36.8% and the overall precision was 75.1%.

The model has an area under the curve of 73% (95%CI 68.6-77.4) and statistical significance (p) <0.001 (Figure 2).

DISCUSSION

The classical stratification into risk groups proposed by D'Amico and cols8 in 1998 has enjoyed great diffusion until now for predicting BR within 5 years despite not being a mathematical model, nor presenting internal or external validity parameters, which makes a very rough prediction of the likelihood of biochemical recurrence.

Nowadays the use of mathematical models allows to calculate the probability of individual BR according to certain clinical characteristics that relate statistically significant in multivariate analysis with recurrence (18). Most commonly used nomograms based on pre-surgical variables are the Kattan (19), Stephenson (20) and Cooperberg (21). The Stephenson model is an updated 10-year prediction version of the Kattan nomogram which predictability was up to 5 years. In the model proposed by Cooperberg et al prediction is performed up to 5 years. Our mathematical model allows the prediction of BR up to 7 years, time when 90% of BR took place in our series.

These three models use common variables such as PSA, GS, clinical stage. and the percentage of cylinders affected by the tumor at biopsy although this last fact slightly increases the predictability of the model. Our model include the statistically significant variables in the multivariate analysis: PSA and GS. The clinical stage was included as in the other nomograms due to the tendency towards significance of the cT2c stage.

The internal discrimination capacity measured in the area under the ROC curve was 66%, 76% and 76% for the Cooperberg, Kattan and Stephenson nomograms, respectively. In our model it was 73%.

As with our series, patients with PSA ≤ 10 ng/ml predominate in the preoperative nomograms. PSA is the independent variable with the greatest influence on score in the Cooperberg nomogram, reaching up to 4 points rate if their value exceeds 30 ng/ml.

In our study, PSA level was an independent predictor of BR in the multivariate analysis (p =0.001) and included in the model.

PSA density in relation to prostate volume has also been studied in several papers and conflicting data exist about its usefulness in predicting biochemical recurrence. According to Radwan et al (22) this parameter is more useful than the PSA to estimate the risk of recurrence. Freedland and colleagues (23) in a study of 552 patients concluded that PSA density is an independent predictor of RB but not statistically significantly increases the predictive ability of PSA as a predictor of the RB.

In the experience of Kotb et al (24) PSA density does not add function to the value of PSA in patients with PSA> 10 ng / ml, which is important in determining the risk of RB in patients with PSA <10 ng/ml.

In our work, like at the most important preoperative nomograms PSA density is not included in the analysis. The controversy over the usefulness of this parameter and doubts about its calculation using the ultrasound or the real gland volume, are factors
that make this factor not to be considered in these great series.

In our study the most common clinical stage, was cT1 while cT2 was the most frequent in the nomograms by Kattan and Stephenson. One possible explanation for this difference is that a portion of the RPs were performed in the era prior to wide use of PSA in these studies, with tumors being diagnosed only when they were palpable. This data is not comparable with the Cooperberg nomogram because it analyzed stages T1 and T2 together, making up 98% of cases.

In the Cooperberg model, the clinical stage is not a predictive factor for BR (p = 0.33), except if there is extracapsular involvement (cT3a) in which case it adds one point to the score. In the Stephenson and Kattan models, the clinical stage is significantly associated (p < 0.001) with the risk of BR. In all models this variable is included in the nomogram.

In our model, the clinical stage does not constitute an independent predictor of BR, though the cT2c stage does have a clear tendency towards statistical significance (p = 0.06) and we included it as a variable in the predictive model.

Freeland et al (25) found no statistically significant differences in BR-free survival at ten years in patients with stage cT2b and cT2a. Armatys et al (26) demonstrate in their series that patients with clinical stage cT1c have more favorable anatomopathological findings in the prostatectomy specimen that patients with cT2c, although without differences in BR-free survival.

In our series the most common GS was ≤ 6 as in the preoperative nomograms. In this models the GS constitutes an independent predictor for BR as in our model in the (p =0.001). We group patients together according to a Gleason score ≤ 6, 7 or ≥ 8, not distinguishing between primary and secondary pattern (because our series is historical, we do not have a pathologist and this datum was only given to us recently).

The work of Briganti et al (27) which analyzes the influence of the number and percent of cores in the likelihood of developing RB in their series over 3000 patients, concludes that even if there is a statistically significant association with the RB, this data does not significantly increase the predictive capacity of biopsy SG in the development of RB. In all three models the percentage of cylinders affected by neoplasia is analized, concluding that increases the information but not the predictability of the nomogram.

According to the clinical guidelines of the European Association of Urology (28) tumor involvement of

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>Relative Risk (HR)</th>
<th>IC95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA:</td>
<td></td>
<td></td>
<td></td>
<td>0,001</td>
</tr>
<tr>
<td>• ≤ 10</td>
<td>1,00</td>
<td></td>
<td>Referencia</td>
<td></td>
</tr>
<tr>
<td>• 10,1 – 20</td>
<td>0,927</td>
<td>2,52</td>
<td>1,69-3,76</td>
<td>0,001</td>
</tr>
<tr>
<td>• &gt; 20</td>
<td>2,097</td>
<td>8,14</td>
<td>3,17-20,87</td>
<td>0,001</td>
</tr>
<tr>
<td>Score Gleason:</td>
<td></td>
<td></td>
<td></td>
<td>0,001</td>
</tr>
<tr>
<td>• ≤ 6</td>
<td>1,00</td>
<td></td>
<td>Referencia</td>
<td></td>
</tr>
<tr>
<td>• 7</td>
<td>0,795</td>
<td>2,21</td>
<td>1,45-3,37</td>
<td>0,001</td>
</tr>
<tr>
<td>• ≥ 8</td>
<td>1,616</td>
<td>5,03</td>
<td>2,98-8,48</td>
<td>0,001</td>
</tr>
<tr>
<td>Clinical Stage:</td>
<td></td>
<td></td>
<td></td>
<td>0,17</td>
</tr>
<tr>
<td>• cT1a-c</td>
<td>1,00</td>
<td></td>
<td>Referencia</td>
<td></td>
</tr>
<tr>
<td>• cT2a-b</td>
<td>0,127</td>
<td>1,13</td>
<td>0,75-1,70</td>
<td>0,55</td>
</tr>
<tr>
<td>• cT2c</td>
<td>0,776</td>
<td>2,17</td>
<td>0,93-5,07</td>
<td>0,06</td>
</tr>
<tr>
<td>Constant</td>
<td>-1,758</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B – parâmetro estimado
more than 15% of the cylinders is associated with adverse pathologic anatomy in the prostatectomy specimen with increased positive margins, capsular invasion and extraprostatic involvement. In our work this data was not analyzed by the contradictions in the literature about this factor.

At present, the growing interest in genetic markers carried Morote et al (29) to include KLK2, SULT1A1 and TLR4 genes in their predictive model which includes clinicopathologic variables, increasing with statistically significantly the ability to predict the RB.

In our opinion, the study suffers from the following limitations:

1. It is a retrospective study which introduces problems in analyzing the data.
2. The biopsies and surgical pieces have not been analyzed by the same pathologist.
3. As this is a historical series and, as our group has already published, we have observed a migration from high Gleason scores at the start of the series towards moderate and low Gleason scores (30). This effect not only can be attributed to earlier diagnosis, but also to a learning effect on the part of pathologists.
4. Though the number of patients is large according to the data published in the Spanish literature, it is significantly lower than previously published models.
5. We have not done external validation of our model. Therefore, we cannot offer its use in a population that is different than ours.

**CONCLUSIONS**

The PSA and GS of the biopsy are the independent prognostic clinical variables associated with BR-free survival, clinical stage cT2c presents statistical trend towards significance.

The predictive model developed with clinical variables allows to estimate the risk of BR with a reliability of 73%. External validation of the model built will allow the application to other different populations and the creation of an aplication for mobile tecnology.

The inclusion of genetic markers may improve the predictive capability of the model, although its routine use is still complex.

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**Table III. Clinical variables of the main preoperative models for biochemical recurrence.**

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Kattan (19)</th>
<th>Cooperberg (21)</th>
<th>Stephenson (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≤ 10</td>
<td>689 (70,1%)</td>
<td>1174 (81%)</td>
<td>No disponible</td>
</tr>
<tr>
<td>• 10,01 – 20</td>
<td>187 (19,0%)</td>
<td>209 (15%)</td>
<td></td>
</tr>
<tr>
<td>• ≥ 20</td>
<td>107 (10,9%)</td>
<td>56 (4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Score Gleason:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≤ 6</td>
<td>671 (68,3%)</td>
<td>1068 (74%)</td>
<td>378 (54,4%)</td>
</tr>
<tr>
<td>• 7</td>
<td>213 (21,7%)</td>
<td>239 (17%)</td>
<td>206 (29,7%)</td>
</tr>
<tr>
<td>• ≥ 8</td>
<td>99 (10,1%)</td>
<td>132 (9%)</td>
<td>109 (15,7%)</td>
</tr>
<tr>
<td><strong>Clinical stage:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• T1</td>
<td>231 (21,5%)</td>
<td>1410 (98%)</td>
<td>803 (41%)</td>
</tr>
<tr>
<td>• T2</td>
<td>694 (70,6%)</td>
<td>Suma T1-T2</td>
<td>1088 (55%)</td>
</tr>
<tr>
<td>• T3</td>
<td>58 (5,9%)</td>
<td>29 (2%)</td>
<td>88 (4%)</td>
</tr>
</tbody>
</table>
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