Nomogram application in Mexico for bladder cancer in patients at the Hospital General “Dr. Manuel Gea González”


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Abstract
Background: Bladder cancer is the most common neoplasia of the urinary tract. Seventy-five percent of the tumors are noninvasive and 25% are invasive. There is a 50%-70% recurrence and progression rate, and at 5 years it is 10%-15%. Sixty percent of the patients die after 5 years despite treatment.

Aims: To determine whether the published predictive nomograms for bladder cancer are accurate for the Mexican population.

Methods: The case records of patients diagnosed with bladder cancer within the time frame of 2007-2013 were analyzed and 6 different bladder cancer nomograms were applied. The predictive nomogram results were compared with patient progression.

Results: Sixty patients were included in the study; 36% presented with invasive tumors and 64% with superficial tumors. Twelve of the patients had recurrence during the follow-up at a mean of 3.3 years. The nomogram predicted a recurrence rate at 5 years of 52%. The disease progression prediction at 5 years was 17% and in our patients it was 22%. The nomogram predicted an overall survival of 70% at 5 years and in our case series, there was a 4.5% mortality rate at 3.1 years.

Conclusions: The nomograms studied do not appear to function with precision within the population studied, which may be due to ethnic differences, dissimilarity in the initial clinical stages and in the access to healthcare, or due to the retrospective study design.
Introduction

Bladder cancer is the most common malignant urinary tract neoplasia. It is also the seventh most common cancer in men and the seventeenth in women. Worldwide incidence is 9 per 100,000 men and 2 per 100,000 women. 1 In Latin America, bladder cancer has an incidence of 5.6 per 100,000 inhabitants; in Mexico it corresponds to 14.4% of the genitourinary cancers and is the fourth most frequent. 2 Mortality in men is 3 per 100,000 and in women it is 1 per 100,000 with a very high geographic variation due to unequal healthcare service access. 1 The incidence of bladder cancer and its mortality rate have decreased in the last few years due to reduced exposure to causal agents such as smoking and to health system improvements. 3-5 Smoking is the most important risk factor for bladder cancer and is present in 50% of the cases. 6,7 Tobacco contains aromatic amines, aromatic polycyclic hydrocarbons, and chlorinated hydrocarbons that are excreted by the kidneys. Occupational exposure to aromatic amines, aromatic polycyclic hydrocarbons, and chlorinated hydrocarbons corresponds to 10% of the cases of bladder cancer and they are present in the paint, metal, and oil industries. 8 Other risk factors for developing bladder cancer include exposure to ionizing radiation, the use of cyclophosphamide and pioglitazone, as well as presenting with schistosomiasis. 1

Approximately 75% of the patients present with bladder cancer confined to the mucosa (T1a, CIS) or submucosa (T1). These presentations are grouped into a category known as non-muscle-invading bladder cancer. 3

The non-muscle-invading tumors can be managed through photodynamic therapy. There is a 50%-70% recurrence of these tumors and the risk for progression is 10%-15% at 5 years. Up to 50% of the patients with muscle-invading tumors have distant metastasis within the first 2 years and 60% die at the fifth year despite treatment. Disease progression to a measurable metastatic state occurs at a mean 1.2 years after radical cystectomy and is fatal in the majority of the patients, despite a high initial response to chemotherapy rate. 11,12

It is necessary to have a way of accurately estimating the possibility of treatment success, complication rates, and long-term morbidity in order to adequately counsel the patient and make decisions supported by the best possible information. 13

Decisions are traditionally made based on the experience of the attending physician, but this manner of decision-making is not impartial and is liable to subjective and objective factors that can compromise the decision at each of the treatment phases. 14-17

In an attempt to resolve these limitations and obtain more precise and reliable predictions, prognostic and predictive tools have been developed based on statistical models. In general, these predictive models have been shown to be equal to or better than clinical judgment for predicting disease results. Nevertheless, the physician’s opinion is still very important for measuring the variables that are used within the predictive models, as well as for applying the models and interpreting the results. 19

Strictly defined, a nomogram is a graphic calculation method that can be based on any type of function, such as a logistic regression or Cox regression model. 20,21 The nomogram usually incorporates continuous or categorical variables. The effect of the variables in the result of interest is represented in the form of axes, and agreement points are attributed to the prognostic or predictive importance of the variable of interest (fig. 1).

The total point axis is used to estimate the combined effect of all the variables in the result probability. The format of the nomogram is unique because it allows the combination of multiple variables, whether continuous or categorical, in a single model. The concordance index quantifies the ability of the nomogram to identify which of 2 randomly selected patients will present with recurrence first. A 0.5 index means distinction is impossible and a 1.0 value represents perfect distinction. 19

Objetivo: Determinar si los nomogramas predictivos publicados para cáncer de vejiga, pueden ser aplicados de manera certera en nuestra población.

Material y método: Se analizaron los expedientes con diagnóstico de cáncer de vejiga del 2007-2013 y se aplicaron 6 diferentes nomogramas de cáncer de vejiga. Se compararon los resultados predichos por el nomograma y la evolución del paciente.

Resultados: Se incluyeron sesenta pacientes con cáncer de vejiga. El 36% con tumores invasores y 64% superficiales. Doce pacientes tuvieron recurrencias en seguimiento con promedio a 3.3 años, y el nomograma predijo una recurrencia a 5 años de 52%. Se predijo una progresión de 17% a 5 años, y en nuestros pacientes se presentó en 22%. La sobrevida global según el nomograma era de 70% a 5 años, y en nuestra serie hubo mortalidad de 4.5% a 3.1 años.

Discusión: Los nomogramas estudiados parecen no funcionar de manera exacta dentro de esta población, lo cual puede ser por diferencias étnicas, en las etapas clínicas iniciales y en el acceso a la salud o por tratarse de un estudio retroactivo.
The predictive precision is the most important value to study in a nomogram and it should be evaluated and validated outside of the population the nomogram was created with. No predictive model is perfect and the accepted accuracy generally varies from 70% to 80%.

A predictive model should be able to be generalized, given that the characteristics of the model and the patient can vary, making the model less precise. External validation should be carried out on patients with characteristics different from those of the patients used to produce the model. Before employing a nomogram, the physician should decide whether it applies to his or her patient, depending on the characteristics used. Nomogram generalization limitations can be related to differences in population characteristics, or due to migrations of status or grade, as well as to differences in inclusion and exclusion criteria. The majority of nomograms are created using populations from a single hospital, and thus cannot be generalized.

The first nomogram for bladder cancer was published in 2005 in a multinational study. The authors developed a nomogram that estimated the risk for recurrence and progression of non-muscle-invading tumors, with a precision of 0.848 for evaluating generalized recurrence, and set the stage for the development of the nomograms to follow.

The tools for adequately predicting the progression of bladder cancer patients are extremely important because they can affect the decision to use multimodal therapy. Due to the large number of predictive models, it is important to understand the mechanisms by which they work and the advantages and disadvantages of each one. Unfortunately there are no randomized prospective studies that clearly show that nomogram use improves patient treatment. However, until such studies are conducted, nomograms are the best option in the doctor/patient decision-making process.

The aim of this article was to determine whether the published international predictive nomograms for bladder cancer are an accurate instrument in the Mexican population.

### Methods

The case records were reviewed of patients diagnosed with urothelial bladder cancer within the time frame of 2003 to 2013, including patients with muscle-invading and non-muscle-invading tumors. The data of these patients was put in a total of 6 different nomograms, and the nomogram predictions were compared with the actual evolution of the patient. Recurrence and progression of non-muscle-invading tumors at 1 and 5 years were evaluated, along with the risk for locally advanced disease in radical cystectomy, the risk for lymph node metastasis in radical cystectomy, the risk for recurrence at 5 years, specific cancer mortality at 5 years, and the total mortality in patients with muscle-invading tumors. Means, medians, and percentages were used in making the comparisons.

### Results

A total of 60 patients diagnosed with bladder cancer were found. Mean age at the time of diagnosis was 62 years; 78% of the patients were men and 22% were women. Thirty-six percent of the patients presented with muscle-invading tumors and 64% with superficial tumors (table 1). A total of 12 patients (20%) had recurrence during the follow-up and the mean presentation time was 3.3 years; four of those patients had received BCG therapy. The nomogram (EORTC) had predicted a mean recurrence at 5 years of 52%. The non-muscle-invading tumor progression prediction was 17% at 5 years, and it was 22% in our patients. The nomogram prediction of risk for locally advanced disease in radical cystectomy was accurate when the risk was above 90%, but there was no correlation in values under 50%. The ability of the nomograms to predict the risk for lymph node metastasis was not accurate because positive metastasis presented in only one patient, despite the fact that the mean risk for disease was 16.3%. Cancer-specific survival at 5 years in patients that had been operated on was calculated by the nomograms as 78% at 5 years and overall survival at 5 years as 70%; in our series the overall cancer-specific mortality rate was 4.5% at a mean 3.1 years in patients that had been operated on (table 2).

### Discussion

In 2005, Shariat et al. proposed a probability nomogram in over 2,000 patients, studying recurrence-free survival and
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progression-free survival with 87% accuracy, but only with internal validation. 27

In 2006, Karakiewicz et al. published a probability nomogram in patients managed with radical cystectomy, predicting stages T and N in the pathologic result and recurrence-free survival with 78% accuracy and internal validation. 29

In 2006, Bochner et al. published a probability nomogram for patients managed with radical cystectomy in over 9,000 patients with 76% accuracy and internal validation, and an attempt was made to predict recurrence-free survival at 5 years. 30

In 2007, Bassi et al. published an artificial neural network nomogram, the last large nomogram, in 369 patients managed with radical cystectomy, evaluating the recurrence-free survival at 5 years with 76% accuracy and internal validation 31 (table 3).

We can see that in the majority of the published nomograms, only internal validation was carried out and often with populations from a single hospital center or region of the country.32-35 Nuhn et al.36 externally validated a nomogram produced in the United States and applied it to a multinational and multi-institutional population. The models were applicable to the 2,501 patients studied, but the predictions underestimated the real results, the same as in our study.

The heterogeneity of the patient populations (for example, ethnic, racial, genetic, environmental differences, and different risk factors) or differences in hospital strategies, attending physicians, or follow-up protocols can cause poor calibration of the nomogram in question. In order to use nomograms created in the United States and Europe, they must first be validated and calibrated in different types of populations, preferably prospectively and with patients of all racial and ethnic groups.

It should also be noted that the majority of nomograms studied herein and those applied in the majority of the urology departments in Mexico, do not take into account the new, recognized risk factors that can have an impact on patient outcome, such as the time lapse between diagnosis

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<tr>
<td>Parameter</td>
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<tr>
<td>Recurrence at 5 years</td>
<td>52% (31%-78%)</td>
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<tr>
<td>Progression at 5 years</td>
<td>17% (1%-45%)</td>
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<tr>
<td>Risk for N+</td>
<td>16% (6.5%-45%)</td>
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<tr>
<td>Cancer-specific survival at 5 years</td>
<td>78% (39%-92%)</td>
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<td>Overall survival at 5 years</td>
<td>70% (46%-87%)</td>
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<th>Table 3</th>
<th>Bladder cancer nomograms</th>
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<td>Reference</td>
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NMI: non-muscle-invading; EGFR: epidermal growth factor receptor; LVI= lymphovascular invasion; TURP: transurethral resection of the prostate; CIS: carcinoma in situ.
and surgery, tumor size, hydronephrosis, surgical margin status, number of lymph nodes removed, and lymph node density. Nomograms are not valid for non-urothelial tumors and so cannot be applied to this type of tumor; new nomograms need to be created that include them. The application of new technologies and molecular discoveries should be introduced into nomograms that then must be validated.

A limitation of our study is its retrospective design and the long amount of time the patients were studied, during which there have been modifications in staging and in the surgical techniques used, which can also change the results. Nevertheless, the aim of this study was to reflect a real-world setting and the daily practice of urology in Mexico in which nomograms play an important role in decision-making.

Conclusions

In our series, the nomograms studied did not appear to function adequately in this population, which could be due to the ethnic differences between our population and that in which the models were developed, or to differences in the initial clinical stages, in the access to healthcare services, or also because the study was a retrospective one. However, it lays the foundation for a necessary joint prospective validation study or for the development of prediction models appropriate for and adjusted to the Mexican population.

Conflict of interest

The authors declare that there is no conflict of interest.

Financial disclosure

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References


