USEFULNESS OF THE MEMORIAL SLOAN KETTERING CANCER CENTER NOMOGRAM IN THE PROGNOSIS OF PATIENTS TREATED WITH RADICAL CYSTECTOMY FOR INVASIVE BLADDER CANCER

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Summary.- OBJECTIVES: To evaluate the usefulness of the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram for prediction of recurrence probability in our series of patients who have undergone radical cystectomy for bladder cancer.

METHODS: 397 patients underwent radical cystectomy for bladder cancer between 1986 and 2005. 165 patients were excluded: 21 due to exitus in the immediate postoperative period, 32 due to previous radiation therapy, 6 due to neoadjuvant chemotherapy, 5 due to inability to complete follow-up, 15 that did not undergo lymphadenectomy and 86 who were alive at the time of review with less than 5 years of follow-up. Patients were classified into recurrence risk groups: organ-confined tumors (pT0-2 pN0), extra-bladder involvement (pT3-4 pN0) and lymph node involvement (pN+). Survival analysis was performed using the Kaplan-Meier method. Five-year recurrence-free survival by risk groups in our series was compared with the one estimated using the MSKCC nomogram using a ROC curve.

RESULTS: We analyzed 232 patients. Follow-up in patients who died of cancer was 25 ± 25 months. For alive patients and those who died of other causes, follow-up was 120 ± 39 months. Pathology studies revealed 42.7% organ-confined tumors, 33.2% with extra-bladder involvement and 24.1% with lymph node involvement. The five-year recurrence free survival analysis according to the Kaplan-Meier method stratified by risk groups was: pT0-2 76%, pT3-4 51%, pN+ 31%. The probability of recurrence free survival according to the MSKCC nomogram in the same risk groups was: 85% ± 5%, 62% ± 10% and 25% ± 13%, respectively. The area under the ROC curve was 0.795 (95% CI 0.739-0.852).

CONCLUSION: In our series, the MSKCC nomogram constitutes a useful tool for predicting 5-year cancer free survival in patients who undergo radical cystectomy.

Keywords: Nomogram. Radical cystectomy. Recurrence.

Resumen.- OBJETIVO: Valorar la utilidad del nomograma del Memorial Sloan Kettering Cancer Center (MSKCC) para predecir la probabilidad de recidiva en nuestra serie de pacientes sometidos a cistectomía radical por cáncer de vejiga.
INTRODUCTION

Bladder cancer is the 5th most common neoplasm in men and the 17th most common in women, corresponding globally to the 9th most common tumor. It has a higher incidence in North America and Eastern Europe (1). Approximately 75% of tumors present as non-muscle-invasive tumors and 25% as muscle-invasive tumors. In the case of superficial tumors, 20-30% are considered high risk for recurrence and progression (2).

Radical cystectomy with ilio-obturator lymph node dissection is the treatment of choice for patients with muscle-invasive tumors and high-risk non-muscle invasive tumors that are refractory to endovesical therapy or in cases in which the risk of progression is high despite not infiltrating the muscle layer (3).

The risk of disease recurrence and progression following cystectomy has classically been determined by the pathological stage of the disease, creating heterogeneous risk groups that do not allow for calculation of the risk for individual patients.

Nomograms are optimized models that use a formula or algorithm to predict the probability of the outcome (4). They currently are a useful tool for estimating the risk of recurrence and cancer-specific mortality on individual patients, based on the most relevant pathological clinical variables, allowing for individualization of treatment and clinical decision making.

The aim of this paper is to evaluate the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram to estimate the bladder cancer free survival in the series of patients who have undergone radical cystectomy at Gregorio Marañon University General Hospital in Madrid.

MÉTODOS: Un total de 397 pacientes fueron sometidos a cistectomía radical por carcinoma vesical entre los años 1986 y 2005 ambos inclusive. Excluimos 165 pacientes: 21 por exitus en el postoperatorio inmediato, 32 por radioterapia previa, 6 por quimioterapia neoadyuvante, 5 por imposibilidad de seguimiento, 15 en los que no se realizó linfadenectomía y 86 vivos en el momento de la revisión con un seguimiento inferior a cinco años.

Los pacientes fueron clasificados según grupos de riesgo de recidiva: tumor órganoconfinado (pT0-T2 N0), localmente avanzado (pT3-T4 N0) y afectación ganglionar (pN+). Realizamos un análisis de supervivencia mediante el método Kaplan-Meier y comparamos mediante una curva ROC la supervivencia libre de recidiva a cinco años por grupos de riesgo de nuestra serie, con la estimada mediante el nomograma del MSKCC.

RESULTADOS: Analizamos 232 pacientes. El 90% fueron varones y la edad media 62,5 años. El estudio anatomopatológico reveló 99 (42,7%) tumores órganoconfinados, 77 (33,2%) con afectación extravesical y 56 (24,1%) con afectación ganglionar. El seguimiento en los pacientes muertos por cáncer fue de 25 ± 25 meses, con una mediana de 17. En los pacientes vivos o muertos por otras causas el seguimiento fue de 120 ± 39 meses, y la mediana 115,5. La mortalidad cáncer específica fue del 59,5%. La supervivencia libre de recidiva a cinco años estimada y estratificada por grupos de riesgo fue: pT0-2 76%, pT3-4 51%, pN+ 31%. La supervivencia libre de recidiva según el nomograma del MSKCC en los mismos grupos fue: 85% ±5% en tumores órganoconfinados, 62% ± 10% en casos de afectación extravesical, y 25% ± 13% en pacientes con metástasis ganglionares. El área bajo la curva ROC obtenida fue 0.795 (IC 95% 0.739-0.852).

CONCLUSIÓN: En nuestra serie, el nomograma del MSKCC constituye una herramienta útil para predecir la supervivencia libre de recidiva a 5 años en los pacientes sometidos a cistectomía radical.

Palabras clave: Nomograma. Cistectomía radical. Recidiva.

MATERIALS AND METHODS

We did a retrospective analysis of the series of patients who underwent radical open cystectomy for bladder cancer in Gregorio Marañon University General Hospital in Madrid between 1986 and 2005, both inclusive.

A total of 397 medical records from patients who underwent cystectomy were reviewed, with 165 patients being excluded from the study for the following reasons: 86 patients were alive at the time of review and had less than five years of follow-up, 32 patients received previous treatment with radiation therapy with intent to cure, 21 patients died in the immediate postoperative period, 15 cases did not have a lymph node dissection, 6 patients underwent neoadjuvant chemotherapy and 5 patients could not be followed in our center.
Cystectomy was performed using the routine anterograde technique with lymph node dissection being done following cystectomy. The minimum limits for lymph node dissection were the genitofemoral nerve laterally, the bladder medially, the femoral canal caudally, the bifurcation of the common iliac vessels cranially and the obturator fossa posterolaterally. Surgery was performed staff members and by residents in the urology department.

All patients had a histological diagnosis and local staging by transurethral resection of the bladder. In addition, we performed an extension study in all cases using contrast CT of the thorax, abdomen and pelvis. Patients with evidence of metastatic involvement in solid organs were treated with other therapeutic strategies than radical cystectomy.

The pathological staging of the cystectomy specimen was established according to the 1997 AJCC TNM classification. The histological grade was established according to the 1973 WHO classification. The surgical specimen was processed according to the routine protocol of our center’s pathology department.

Patients were stratified into three risk groups according to the histological analysis of the cystectomy specimen in organ-confined tumors (pT0-pT2), locally advanced tumor or extra-bladder involvement (pT3-pT4) and tumor with lymph node metastasis (pN+).

We compare five-year recurrence free survival following cystectomy of the patients in our series using the MSKCC nomogram estimation stratified by risk groups. The data were obtained using a computer program from the MSKCC web site. The factors included in the predictive model are: age, gender, delay until cystectomy since TUR, cellular grade, tumor stage and tumor origin.

We did a descriptive study of the variables analyzed using routine statistics for quantitative and qualitative variables. We used the Kaplan-Meier method to analyze recurrence free survival. Comparison between the survival observed in the series and the survival estimated by the nomogram by risk groups was performed using an ROC (Receiver Operating Characteristic) curve and measurement of the area under the curve. An area under the curve of 0.50 is equal to a null discrimination capacity. When it reaches 0.70, the discrimination capacity is acceptable. If it is 0.80, we consider it good and perfect when it reaches 1 (6). Statistical significance was defined as p < 0.05. All calculations were performed using the Spanish version of SPSS version 15.0.

**RESULTS**

A total of 232 patients were included for the study, being men 90% of cases (209). Mean age was 62.5 ± 10 years with a median age of 65 years.

Medium time since diagnosis to cystectomy was 46±8 days, with a median of 44 days.

Practically all tumors had a high histological grade G3 (94%), no G1 was found in the series.

Transitional cell carcinoma of the bladder represented 89% of all tumors, while squamous cell carcinoma and adenocarcinoma represented 8% and 3% respectively.

Medium number of lymph node obtained in cystectomy specimens was 13 (8-22).

The majority of cystectomy pieces corresponded to the organ-confined tumor group (42.7%). The remaining risk groups are detailed in Table I.

The overall follow-up time for the series was 64 ± 56 months with a median of 41 months. Follow-up of patients who died of bladder cancer was 25 ± 25 months with a median of 17. Follow-up of live pa-

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Nº of Cases (%)</th>
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<tbody>
<tr>
<td>Organ-confined (pT0-pT2N0M0)</td>
<td>99 (42,7%)</td>
</tr>
<tr>
<td>Extra-bladder involvement (pT3-pT4N0M0)</td>
<td>77 (32,3%)</td>
</tr>
<tr>
<td>Lymph node involvement (pN+M0)</td>
<td>56(24,1%)</td>
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Table I. Number of patients in each risk group.
tients or patients who died of causes other than cancer was 120 ± 39 months with a median of 115.5 months.

Cancer-specific mortality for the series was 59.5% (138 patients), mortality due to other causes was 5.2% (12 patients), with 35.3% of patients (82 cases) alive at the time of review.

Recurrence in our series stratified by risk groups was 24% for the organ-confined group, 49% for the group with extra-bladder involvement and 69% for patients in the lymph node involvement group.

The probability of recurrence at five years for the same groups calculated by the MSKCC nomogram was 15% ± 5%, 38% ± 10% and 75% ± 13%, respectively (Table II).

We analyzed the discrimination capacity of the MSKCC model using a ROC curve and calculating the area under the curve which was 0.795 (95%CI 0.739-0.852) (Figure 1).

**DISCUSSION**

There are currently two nomograms available for calculating the probability of recurrence following radical cystectomy, being the MSKCC nomogram the widely used. It has the advantage of being available online on the center’s web site, allowing for calculation of recurrence probability from the consultation room (5).

This predictive model was developed from the data collected from 12 prestigious oncology surgery centers in the United States and included a total of 9064 patients (5).

On the multivariate analysis, the independent variables that were associated with tumor recurrence that were statistically significant and collected on the nomogram were: pathological stage, lymph node involvement, gender, cellular grade, histological type, and involvement and time transpired until cystectomy (5).

These data coincide with those obtained in the review by Monzo et al (7), in which the main independent factors for recurrence were analyzed from the main radical cystectomy series published to date. These were the two most constant factors with the highest statistical association in different studies analyzed in the pathology staging (pT) and lymph node involvement (pN). In the series of Shariat et al (8) on 958 patients treated with in their series of 958 patients treated with radical cystectomy in three different prestigious oncology surgery centers in the United States, advanced pathological state and lymph node involvement were statistically associated on multivariate analysis with worst oncological prognosis (p<0.001). In the MSKCC nomogram 38, 3% of

<table>
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<th>Risk Group</th>
<th>5 Year Recurrence HGUGM</th>
<th>5 Year Recurrence MSKCC</th>
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<tbody>
<tr>
<td>Organ-confined</td>
<td>24%</td>
<td>15% ±5%</td>
</tr>
<tr>
<td>Extra-bladder involvement</td>
<td>49%</td>
<td>38% ±10%</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>69%</td>
<td>75% ±13%</td>
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**Figure 1.** ROC curve that demonstrates that the model’s level of discrimination in our series.
the patients had organ-confined tumors, 37.6% locally-advanced tumors and 17.1% lymph node involvement, similiar to our series with 42.7%, 32.3% and 24.7% respectively.

Other variables such as cytological grade, gender and age were only statistically significant in some studies. However, there was no unanimity about their relevance to tumor recurrence.

The presence of a histological type other than transitional cell carcinoma, such as squamous cell carcinoma or adenocarcinoma, is common in countries where the prevalence of schistosomiasis is high, such as in Egypt. In the study published by Rogers et al (9), the presence of a variant other than transitional cell carcinoma was significantly associated with a higher probability of death and progression (p < 0.001) in patients treated with cystectomy. In the MSKCC 74% of the tumors were transitional cell carcinoma, 21% squamous cell carcinoma and 5% adenocarcinoma. In our series urothelial carcinoma was more frequent (89%) and the others less common (8 and 3% respectively). These differences are probably caused due geographic and poblational differences between the series.

The influence on recurrence and cancer-specific survival of the time between histological diagnosis and the time of the cystectomy was demonstrated in the studies by Chang et al (10) and Sanchez-Ortiz et al (11). These studies found a significant increase in the presence of extra-bladder disease in the cystectomy piece (81% versus 51%) in patients with a delay in radical treatment greater than 3 months. This was associated with an increase in cancer-specific mortality, the rate of local recurrence and in the rate of cancer in the superior urothelium.

The influence of cellular grade on cancer recurrence was demonstrated in the studies by Shariat et al (8) corresponding to independent risk factor in multivariate analysis (p<0.01). In our series like in Shariat study G3 incidence was 94%. In the MSKCC this factor is included as a variable, but the incidence is not available.

This nomogram allows for calculation of the probability of tumor recurrence in the first five years following radical cystectomy, the time period in which the majority of recurrences happen. The study by Volkmer et al (12), revealed that the majority of recurrences take place in the first 20 months after cystectomy, with 25% occurring in the first year and 3% from the third year onward. Cancer mortality is the norm in tumor recurrence with a median survival of 8 to 14 months despite chemotherapy treatment. Five-year survival is 3%.

The fundamental limitation of this model is the limited information on lymph node involvement which only refers to tumor invasion or no tumor invasion. The data has shown that this is important for the oncology prognosis, as are the number of pathological lymphadenopathies and the ratio between the number of lymph nodes affected by the tumor (13). The total number obtained on lymph node dissection are not included in the model.

The MSKCC model allows the probability of tumor recurrence following cystectomy to be predicted with 75% reliability. This is 7% improvement over the prediction using the TNM classification (68%) (14).

The other most commonly used nomogram was developed by Karakiewicz et al. (15) in 2006 in a multisite study with 728 patients. This nomogram allows for the probability of tumor recurrence to be calculated 2, 5 and 8 years after radical cystectomy. In this model, the variables included are the same as the MSKCC nomogram; age, cellular grade, T and N tumor stages, as well as lymphovascular invasion, presence of carcinoma in situ and use of neoadjuvant and adjuvant chemotherapy and radiation therapy. This nomogram has a reliability of 78%. However, because it does not include the histological type, its use cannot be extended to other regions where other tumor variants are common. In addition, this nomogram is not available online, making it difficult to apply in routine daily practice in the clinic.

The use of nomograms can make up part of routine clinical practice when said model can be applied to our environment, taking into account that the majority of cases are seen in oncology specialty centers. For this reason, it would be necessary to evaluate the discrimination capacity of these models in our own patients.

When we use the MSKCC nomogram in our series of patients who have undergone radical cystectomy, we observe that the level at which the model distinguishes between individuals in which the event occurs and those in which it doesn’t occurs, corresponds to an area under the ROC curve of 0.795.

Our work shows the limitations of being a retrospective historical, the exclusion of a important number of patients, and surgical specimens have not been analyzed by the same pathologist.

**CONCLUSION**

In our series of patients who have undergone radical cystectomy, the MSKCC nomogram constitu-
tes a useful tool in predicting tumor recurrence with a discrimination capacity of 79%.

REFERENCES AND RECOMMENDED READINGS
(*of special interest, **of outstanding interest)

4. Diccionario de la Real Academia Española de la Lengua. XXIª Edición


