Validation of a prognostic nomogram in patients undergoing resection for pancreatic ductal adenocarcinoma in a UK tertiary referral centre

E. J. CLARKa, M. A. TAYLORA, S. CONNORA, R. O’NEILLa, M. F. BRENNANb, O. J. GARDENA & R. W. PARKSA

aClinical and Surgical Sciences (Surgery), Royal Infirmary of Edinburgh, Edinburgh, UK and bDepartment of Surgery, Memorial Sloan-Kettering Cancer Centre, New York, NY, USA

Abstract

Introduction. Survival following resection for pancreatic ductal adenocarcinoma (PDAC) remains poor. The aim of this study was to validate a survival nomogram designed at the Memorial Sloan-Kettering Cancer Centre (MSKCC) in a UK tertiary referral centre. Methods. Patients who underwent resection for PDAC between 1995 and 2005 were analysed retrospectively. Standard prognostic factors and nomogram-specific data were collected. Continuous data are presented as median (inter-quartile range). Results. Sixty-three patients were analysed. The median survival was 326 (209–680) days. On univariate analysis lymph node status (node –ve 297 (194–471) days versus node –ve 367 (308–1060) days, \( p=0.005 \)) and posterior margin involvement (margin –ve 210 (146–443) days versus margin –ve 355 (265–835) days, \( p=0.024 \)) were predictors of a poor survival. Only lymph node positivity was significant on multivariate analysis (\( p=0.006 \)). The median nomogram score was 217 (198–236). A nomogram score of 113–217 predicted a median survival of 367 (295–847) days compared to 265 (157–443) days for a score of 218–269, \( p=0.012 \). Conclusion. Increasing nomogram score was associated with poorer survival. However the accuracy demonstrated by MSKCC could not be replicated in the current cohort of patients and may reflect differences in patient demographics, accuracy of pathological staging and differences in treatment regimens between the two centres.

Key Words: pancreatic adenocarcinoma, prognosis, nomogram

Introduction

Long-term survival following potentially curative resection for pancreatic ductal adenocarcinoma (PDAC) remains poor with a median survival of 12–18 months \([1–9]\) and few actual five-year survivors \([1]\). Surgery combined with adjuvant therapies offers the only prospect of long-term cure. Although with the advent of specialised centres the mortality following pancreaticoduodenectomy has fallen to less than 5%, early postoperative morbidity remains high \([10]\) and it takes three to six months for quality of life measures to return to normal \([11,12]\). Therefore, identifying those patients with a poor prognosis and short life expectancy may prove advantageous when counselling patients and their relatives regarding potential therapeutic and non-therapeutic interventions.

Nomograms are mathematical models which utilise prognostic variables in an attempt to calculate percentage survival in the short and long term. They have been used to predict survival in patients with sarcomas, and those with gastric, colorectal, lung and prostate cancer \([13–17]\). A prognostic nomogram for pancreatic cancer (Figure 1) was developed from a large cohort of patients in the Memorial Sloan-Kettering Cancer Centre (MSKCC). The purpose of this nomogram was to determine the probability that patients undergoing resection for PDAC would be alive at one, two and three years postoperatively and to provide more accurate prognostic information than the conventional TNM system, which is non-discriminatory \([18]\).

The aim of the present study was to validate the accuracy of the MSKCC pancreatic cancer nomogram against an independent data series from a UK tertiary referral centre.
Methods

Patients who underwent resection for histologically confirmed PDAC at the Royal Infirmary of Edinburgh from January 1995 to January 2005 were analysed. Exclusion criteria included patients who had died within 30 days of surgery. Patients were identified from a prospective database and data was supplemented by retrospective case note review. Standard prognostic factors and nomogram-specific data were collected including clinical factors (age, sex, weight loss, back pain), operative details (pancreaticoduodenectomy, distal pancreatectomy, splenectomy, portal vein resection) and pathological factors (resection margin status (malignant cells < 1 mm of radial or surgical margin (margin positive (+ve)) or margin negative (−ve)), posterior resection margin status, differentiation, number of nodes with metastatic involvement (node +ve or node −ve), total number of nodes resected, T-stage, tumour size). Weight loss was defined as objective loss of weight as recorded in the database or in clinical correspondence. Outcome data included survival from time of operation and the total nomogram score, calculated for each patient using the MSKCC nomogram [18].

Using the nomogram a score was determined for each patient and the median nomogram score was calculated for the cohort of Edinburgh patients. The predicted versus actual survival, based on the median nomogram score, was then calculated.

Statistical analysis was performed using Statview software (version 5.0.1). All data are presented as median (inter-quartile range). Kaplan-Meier survival curves were created. Uni- and multivariate analysis were performed using the log rank test and Cox proportional hazards method, respectively to identify independent prognostic factors. The significance of differences between actual versus predicted survival were assessed using the Chi-squared test or Fisher exact test where appropriate. A p-value of < 0.05 was deemed significant.

Results

Sixty-three patients (37 male, 26 female) with a median age of 65 (59–71) years were included in the study. In three patients, the presence or absence of weight loss was not recorded and in one patient the presence or absence of back pain was not recorded. In these cases the median nomogram score was inputted in place of missing data points rather than excluding patients as this was found to have no effect on the total

Table I. Demographics of MSKCC/Edinburgh patients.

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<thead>
<tr>
<th></th>
<th>MSKCC (n = 555)</th>
<th>Edinburgh (n = 63)</th>
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<tbody>
<tr>
<td>Mean age</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>Male gender</td>
<td>50%</td>
<td>59%</td>
</tr>
<tr>
<td>Portal vein resection</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Resection margin positive</td>
<td>21%</td>
<td>38%</td>
</tr>
<tr>
<td>Pancreatic head resection versus other</td>
<td>89%</td>
<td>98%</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>28%</td>
<td>48%</td>
</tr>
<tr>
<td>Posterior resection margin positive</td>
<td>14%</td>
<td>32%</td>
</tr>
<tr>
<td>Back pain</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>54%</td>
<td>83%</td>
</tr>
<tr>
<td>Mean number of positive lymph nodes</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Mean number of negative lymph nodes</td>
<td>16.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Tumour diameter = 2 cm</td>
<td>Not reported</td>
<td>22%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Not uniform</td>
<td>One patient</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>2.8%</td>
<td>4.7%</td>
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nomogram score. Sixty-two patients (98%) underwent pancreaticoduodenectomy and one patient (2%) underwent a distal pancreatectomy and splenectomy. No portal vein resections were performed. The demographic data for Edinburgh patients in comparison to MSKCC patients is shown in Table I. The median survival was 326 (209–680) days with the longest survivor having lived 1330 days (three years and seven months approximately).

Twenty patients (32%) had positive posterior resection margins and 45 patients (69%) were lymph node positive. On univariate analysis, lymph node status (node +ve 297 (194–471) days versus node –ve 367 (308–1060) days, \( p = 0.005 \) and posterior margin involvement (posterior margin +ve 210 (146–443) days versus posterior margin –ve 355 (265–835) days, \( p = 0.024 \) were predictors of a poor survival (Figure 2 and Figure 3). However on multivariate analysis only lymph node status remained an independent predictor of survival (\( p < 0.006 \) (Table II). A nomogram score of less than 217 predicted a median survival of 367 (295–847) days compared to 265 (157–443) days for a nomogram score of 218 or greater, \( p = 0.012 \) (Figure 4).

The actual survival of Edinburgh patients at 12, 24 and 36 months was plotted against predicted survival based on the median nomogram score (217) of the group (Figure 5). Edinburgh patients were found to have a shorter survival than predicted by the nomogram. Taking the median score of 217, the nomogram predicted that 63% of Edinburgh patients would have survived at one year but only 44% actually survived \( (p = 0.021) \). At two years the nomogram predicted that 28% would survive but only 24% actually survived \( (p = 0.23) \). At three years the nomogram predicted that 15% of patients would survive but only 8% actually survived \( (p = 0.04) \).

Discussion

The results of this study confirm the poor prognosis associated with PDAC even after potentially curative resection. Well-established prognostic factors in patients undergoing resection for PDAC include tumour differentiation, resection margin status, tumour size and nodal involvement [2–7] although in the current cohort of patients only lymph node positivity remained significant on multivariate analysis. This was also found to be a highly significant prognostic factor by the MSKCC group.

An increasing nomogram score was shown to be associated with poorer survival (Figure 4). However, the accuracy of the nomogram reported by the MSKCC group could not be replicated in the current cohort of patients. This may have been due to the relatively small sample size. The overall actual survival of Edinburgh patients was found to be consistently less than the predicted survival using the nomogram, based on the median nomogram score of 217 for the group (Figure 5). There are several possible explanations for this. Although the patient groups appear different at baseline with more patients having positive resection margins, poorly differentiated tumours and weight loss at presentation (Table I), all of these factors are included in the nomogram and therefore it is unlikely that these account for the results.

It should be noted that some pathological definitions may differ slightly between the USA and the UK and this may lead to inaccurate nomogram scoring. For example, the posterior resection margin is also variously known as the mesenteric, uncinate or retroperitoneal margin [19–22]. In the USA, the posterior resection margin has been defined as the adipose tissue dorsal and lateral to the superior mesenteric artery [22–25]. However, the UK pathological guidelines define the posterior resection margin as the tissue immediately posterior to the head of the pancreas and also describe the medial pancreatic (or superior mesenteric vein) margin [19]. Although the definitions of the posterior resection margin are essentially similar, they could be misinterpreted, justifying pleas for standardisation of pathological reporting for resected tumours in the head of pancreas [21,26,27]. Invasion specifically of the posterior resection margin has previously been identified as an adverse prognostic factor [8,9,20] and so differences in pathological reporting may have affected the
nomogram results. It is important that reporting of such prognostic factors is standardised to allow accurate comparison between centres.

Although it would appear that the surgery performed at MSKCC may have been more extensive with a higher number of portal vein resections performed and an increased median number of nodes per specimen identified (Table I), it is recognised that lymph node count is often related to the quality of pathological reporting. This is important as the Edinburgh patients may have been understaged which would result in a worse actual survival compared with predicted survival.

However, perhaps the most important difference between the patient groups was in the use of adjuvant therapies. Only one patient in the current series received adjuvant chemotherapy, as it was not a standard practice in the UK during the time period of the study, whereas a greater proportion of the MSKCC patients received some form of adjuvant therapy. The optimal use of adjuvant therapy is still to be defined. In Europe, chemotherapy has now been adopted subsequent to the ESPAC trial [28], whereas in the USA, chemoradiotherapy is the standard adjuvant therapy [29,30]. Although debate is ongoing, it has become clear that adjuvant therapy is beneficial. This may be a rational explanation for the difference in survival between the two groups of patients.

In conclusion, although an increasing nomogram score is associated with poorer survival, the accuracy demonstrated by MSKCC could not be replicated in the current cohort of patients. This may reflect differences in patient demographics, accuracy of pathological staging and differences in treatment

<table>
<thead>
<tr>
<th>Table II. Analysis of prognostic variables.</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Positive lymph nodes Yes</td>
</tr>
<tr>
<td>Positive lymph nodes No</td>
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<tr>
<td>Posterior resection margin positive Yes</td>
</tr>
<tr>
<td>Posterior resection margin positive No</td>
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<tr>
<td>Resection margin positive Yes</td>
</tr>
<tr>
<td>Resection margin positive No</td>
</tr>
<tr>
<td>Tumour size =2 cm Yes</td>
</tr>
<tr>
<td>Tumour size =2 cm No</td>
</tr>
<tr>
<td>Poorly differentiated Yes</td>
</tr>
<tr>
<td>Poorly differentiated No</td>
</tr>
<tr>
<td>Median nomogram score ≤217</td>
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<tr>
<td>Median nomogram score &gt;217</td>
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regimens between the two centres. This emphasises the importance of national development of nomograms for the practice patterns of an institution or a country. The MSKCC nomogram has been successfully validated in another US institution [31] although this is the first study evaluating the nomogram in a tertiary referral centre in the UK.

References