

A Preoperative Prognostic Score for Resected Pancreatic and Periampullary Neuroendocrine Tumours

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Key Words

Neuroendocrine tumour, periampullary/pancreatic · Resection, tumour · Prognostic factors, neuroendocrine tumours

Abstract

Background/Aims: To identify potential preoperative prognostic factors in resected pancreatic and periampullary neuroendocrine tumours. **Methods:** Clinico-pathological data for 54 consecutive patients with pancreatic or periampullary neuroendocrine tumours referred to our institution over a 10-year period were identified from a prospective database. **Results:** 34 patients underwent pancreatic resection (12 males, 22 females; median age 54 (IQR 44–71) years). There was a single 30-day mortality (3%). Nodal status (log rank, $p = 0.652$), microscopic resection margin involvement ($p = 0.549$) and tumour size ($p = 0.122$) failed to exhibit any prognostic value. Only the presence of malignant tumour characteristics was associated with poorer overall survival ($p = 0.008$). Analysis of preoperative parameters showed that age >60 years ($p = 0.056$), platelet-lymphocyte ratio >300 ($p = 0.008$), alkaline phosphatase levels >125 U/l ($p = 0.042$) and alanine aminotransferase >35 U/l ($p = 0.016$) were adverse prognostic factors. A risk stratification score was generated where each adverse preoperative parameter was allocated a

score of 1. A cumulative score of ≤ 1 was defined as low risk, while a score of ≥ 2 was defined as high risk. Median overall survival in the high-risk group was 10.4 months, while the median survival in the low-risk group was >60 months ($p < 0.001$). **Conclusion:** Significant prognostic information can be gained from routine preoperative biochemistry and haematology results in resected pancreatic and periampullary neuroendocrine tumours. These findings merit further evaluation in a larger patient cohort.

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Introduction

Neuroendocrine tumours account for approximately 2–3% of all pancreatic neoplasms [1, 2] and may be associated with hereditary tumour syndromes such as multiple endocrine neoplasia type 1 and von Hippel-Lindau disease [3]. Although characteristically associated with an indolent clinical course and favourable long-term survival with surgical resection [1, 4], significant heteroge-

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neity in survival outcomes can be observed when comparing different sub-groups of tumour [1, 5]. Several studies have investigated which histological tumour characteristics provide the most prognostic information following resection for pancreatic and periampullary neuroendocrine tumours [6–10]. Tumour differentiation and the presence of distant metastatic disease are consistently reported to represent the most significant prognostic factors in resected cases, while the reported prognostic relevance of tumour size, nodal status and resection margin status differs in these studies.

Few studies have evaluated whether any preoperative factors may also influence survival in resected neuroendocrine tumours. Of the various demographic parameters commonly investigated, increasing patient age is commonly identified as an adverse prognostic factor [8, 11], while some studies have also suggested that gender may also influence survival [8]. Although previous studies have investigated various preoperative haematology and clinical biochemistry parameters as potential prognostic factors in resected pancreatic and periampullary adenocarcinoma [12–14], no previous studies have evaluated whether the same indices may also predict survival in resected neuroendocrine tumours. The objective of this study was to identify whether any routine preoperative haematology and clinical biochemistry results may be of prognostic value in resected pancreatic and periampullary neuroendocrine tumours with a view to constructing a preoperative risk stratification system.

Patients and Methods

Consecutive patients with a diagnosis of pancreatic or periampullary neuroendocrine tumours referred to the Pancreatic Unit at the Royal Liverpool University Hospital over a 10-year period between 1997 and 2007 were identified from a prospective clinical database. Data collected included patient demographics, preoperative blood results, operative details, tumour histology and survival. Histological data included site and classification of the primary tumour, the presence and number of nodal metastases, resection margin involvement, tumour size and differentiation. Tumour differentiation was recorded according to the WHO classification system [15, 16]. Postoperative mortality was defined as death occurring within 30 days of surgical intervention. In the group that did not undergo resection ($n = 20$), a histological diagnosis was made on biopsy results in 12 (60%). In the remaining cases with unresected neuroendocrine tumours, the diagnosis was based on imaging (see below), biochemistry results, clinical presentation and subsequent course.

Computed tomography, magnetic resonance imaging, endoscopic ultrasound, positron emission tomography and somatostatin receptor scintigraphy were routinely utilised to characterise the primary lesion(s) and identify the presence of metastatic

disease in the preoperative setting. Staging laparoscopy with laparoscopic ultrasonography was also used selectively if borderline features for unresectability were present on preliminary imaging. Three of 34 patients underwent pancreatic resection with preoperative radiological evidence suggestive of liver metastases.

Statistical Analysis

Median and inter-quartile ranges (IQR) were used to describe the data. Spearman's rank correlation was used to describe the relationship between two continuous variables and logistic regression was used to compare categorical data. Survival data were analysed using the Kaplan-Meier method and survival curves were compared using the log-rank (Cox-Mantel) test. Prognostic factors were primarily analysed as continuous variables where possible in order to reliably describe their association with overall survival [15]. Survival times were calculated from the date of operation in resected cases and those undergoing palliative surgery. The date of diagnosis was used in the remaining unresected cases. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using Statview version 5 and Microsoft Excel 2007.

Results

From September 1997 to July 2007, 54 consecutive patients with pancreatic or periampullary neuroendocrine neoplasms were referred to the Royal Liverpool University Hospital. A total of 34 of these patients had resections for histologically confirmed pancreatic or periampullary neuroendocrine tumours. There were 26 censored cases in this group with a median follow-up time of 31.3 (IQR 15.2–59.9) months. A single patient died within 30 days of surgery (3%). Five patients undergoing resection had multiple endocrine neoplasia type 1 and 2 patients had von Hippel-Lindau disease.

In total, 20 patients did not undergo resection. This was due to the presence of significant distant metastatic disease in 13 cases, locally advanced disease in 5 cases and anaesthetic risk in the remaining 2 cases. The diagnosis of unresectability was made at laparotomy in 6 cases. Figure 1 demonstrates that patients undergoing surgical resection had a significantly more favourable overall survival (median survival >60 months) when compared with unresected cases (median survival 18.1 months; log rank, $p < 0.001$). The presence of distant metastatic disease in unresected cases ($n = 13$) was associated with a median survival of 8.2 months.

Patient demographics of the resected group along with the classification and histological characteristics of the neuroendocrine tumours are outlined in table 1. Twenty-one patients (62%) underwent pancreatoduodenectomy (1 with portal venous resection), 8 (24%) had distal pancreatectomy, 3 (9%) had enucleation and 2 (6%) under-

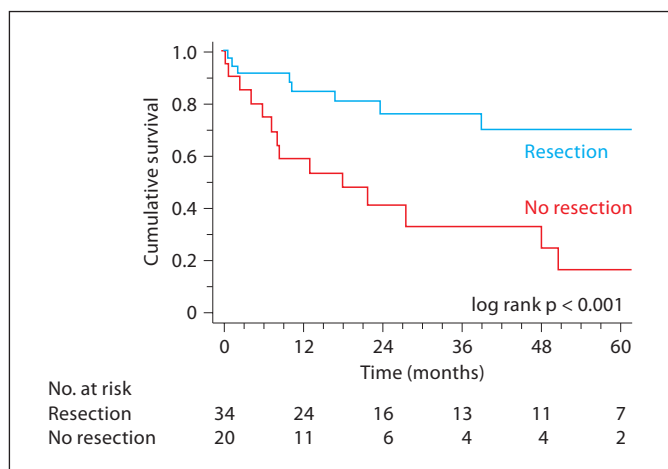


Fig. 1. Kaplan-Meier analysis of survival in pancreatic and periampullary neuroendocrine patients according to resection.

went total pancreatectomy. Neuroendocrine tumour was identified in a peripancreatic lymph node in 1 case undergoing pancreatoduodenectomy, but the location of the primary was not identified in the resected specimen. Twenty-four of the 34 resected cases had non-functioning neuroendocrine tumours, 5 insulinoma, 4 gastrinoma and 1 somatostatinoma.

Prognostic Factors in Resected Cases

Gender had no impact on postoperative survival in the group undergoing resection (log rank, $p = 0.828$). Increasing age was found to be of borderline significance when modelled as a continuous prognostic variable in the resected group (Cox, HR 1.051, 95% CI 0.998–1.108, $p = 0.060$).

Neither tumour size (Cox, HR 1.022, 95% CI 0.994–1.051, $p = 0.122$), resection margin involvement (log rank, $p = 0.549$) nor nodal status (log rank, $p = 0.652$) were found to represent significant prognostic variables. Only tumour differentiation was associated with survival when comparing well-differentiated tumours with benign features against well-differentiated tumours with low-grade malignant features (log rank, $p = 0.008$). The single case exhibiting high-grade malignant tumour features was analysed alongside the low-grade malignant cases for the purposes of this analysis. Increasing tumour size was associated with a trend towards an increased likelihood of malignant tumour characteristics (logistic regression, OR 1.044, 95% CI 0.997–1.094, $p = 0.067$).

The results of a univariate Cox proportional hazards analysis of various preoperative blood results as potential

Table 1. Patient demographics and histological distribution of 34 resected pancreatic and periampullary tumours

Gender	
Males	12
Females	22
Median age (IQR), years	54 (44–71)
Tumour location	
Pancreas	25
Head	11
Neck/body	6
Tail	8
Duodenum	5
Ampulla	3
Periampullary lymph node	1
Tumour histology	
Median tumour size (IQR), mm	20 (14–38)
Differentiation (n = 34)	
Well differentiated	33
Benign behaviour	14
Low-grade malignancy	19
Poorly differentiated	1
Nodal status (n = 30)	
Positive	17
Negative	13
Resection margin status (n = 31)	
Positive	11
Negative	20

clinical prognostic markers in the resected pancreatic and periampullary neuroendocrine tumours are shown in table 2. Preoperative albumin, alanine aminotransferase and platelet-lymphocyte ratio were all significantly associated when analysed as continuous variables. Elevated alkaline phosphatase levels were associated with poorer survival when using a cut-off value of 125 U/l (log rank, $p = 0.042$), but this was not significant when analysed as a continuous variable (Cox, $p = 0.187$). There was a significant association between lower albumin levels and poorer survival using continuous values (Cox, $p = 0.047$), but not when dichotomising between high or low (≤ 33 g/l) albumin levels (log rank, $p = 0.332$). Only two of 16 resected cases with preoperative serum CA19-9 levels had elevated levels (>37 kU/l). Only one patient was jaundiced at the time of resection (bilirubin level 47 $\mu\text{mol/l}$). Bilirubin levels ($p = 0.439$), γ -glutamyl transferase ($p = 0.628$) and CA19-9 ($p = 0.847$) were not found to have any prognostic value on univariate Cox analysis. Multivariate Cox survival analysis in the resected patient group was not performed due to the limited number of events (i.e. deaths) [18].

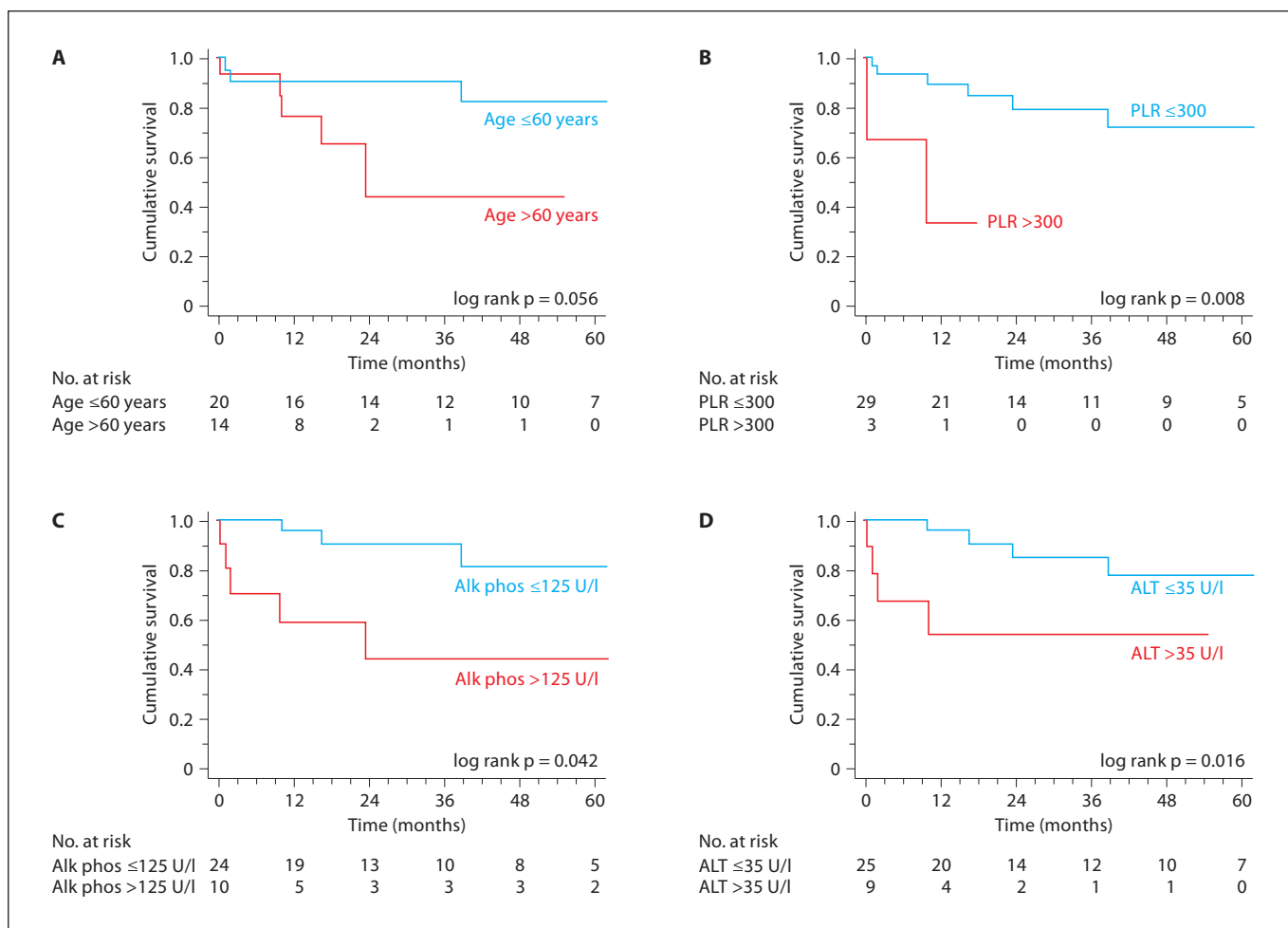


Fig. 2. Kaplan-Meier analysis of survival in resected neuroendocrine tumours stratified by patient age and preoperative blood results.

Table 2. Univariate Cox proportional hazards analysis of patient age and preoperative blood results as prognostic factors in resected pancreatic and periampullary neuroendocrine tumours

	n	Median (IQR)	Univariate Cox proportional hazards analysis		
			χ^2	Hazard ratio (95% CI)	p
Age, years	34	54 (44–71)	3.531	1.051 (0.998–1.108)	0.060
Albumin, g/l	34	42 (39–44)	3.944	0.906 (0.823–0.999)	0.047
Alkaline phosphatase, U/l	34	95 (69–134)	1.743	1.002 (0.999–1.006)	0.187
Alanine aminotransferase, U/l	34	24 (16–38)	4.008	1.011 (1.000–1.023)	0.045
Platelet-lymphocyte ratio	32	157 (104–186)	4.246	1.004 (1.000–1.008)	0.039

Hazard ratios for continuous prognostic data reflect the increased relative hazard for each incremental unit increase in the prognostic variable. Preoperative haematology data were unavailable in 2 cases.

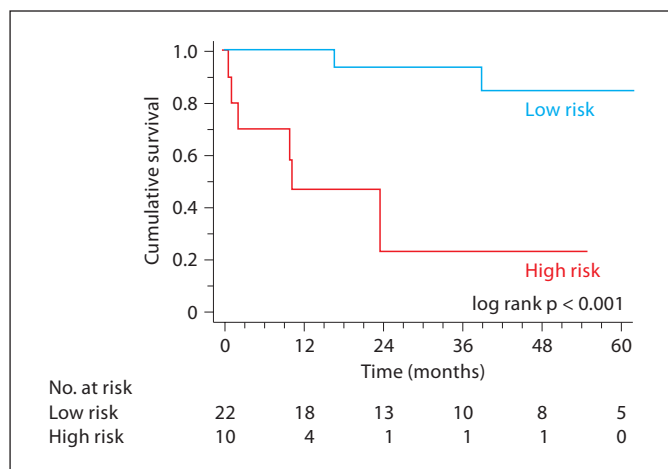


Fig. 3. Kaplan-Meier survival analysis of preoperative prognostic risk stratification in resected pancreatic and periampullary neuroendocrine tumours.

Patient age, platelet-lymphocyte ratio, alkaline phosphatase and alanine aminotransferase (ALT) were used to construct a preoperative prognostic score. The individual Kaplan-Meier analyses to illustrate the survival trends for each variable are shown in figure 2. Cut-off values were selected on the basis of the normal reference range for ALT (>35 U/l) and alkaline phosphatase (>125 U/l) or the value for which the maximum survival difference was recorded (>60 years for patient age and >300 for the platelet-lymphocyte ratio). Table 3 demonstrates the cumulative points allocation used to generate the prognostic score. A total score of 0 or 1 was defined as low risk and a score of 2 or greater was defined as high risk. Median overall survival for the high-risk group (n = 10) was recorded as 10.4 months, while median survival for the low-risk group was not reached but was greater than 60 months. Figure 3 demonstrates that this risk stratification system was superior to any individual prognostic parameter (log rank, p < 0.001). There was no significant association between an increasing preoperative prognostic score and the likelihood of malignant tumour features (logistic regression, OR 1.950, 95% CI 0.871–4.367, p = 0.104), tumour size (Spearman's ρ = 0.225, p = 0.306), nodal status (logistic regression, OR 1.026, 95% CI 0.540–1.948, p = 0.937) or resection margin status (logistic regression, OR 1.219, 95% CI 0.616–2.413, p = 0.569).

Preoperative Blood Results and Metastatic Disease

In the overall patient group (including resected and unresected cases) none of the preoperative biochemistry

Table 3. Points allocation used to construct preoperative prognostic score (n = 32)

	Points
Age	
≤60 years	0
>60 years	1
Alkaline phosphatase	
≤125 U/l	0
>125 U/l	1
ALT	
≤35 U/l	0
>35 U/l	1
Platelet-lymphocyte ratio	
≤300	0
>300	1

The cumulative score for the four parameters was used to stratify patients into high- or low-risk groups: a total score of 0 or 1 was defined as low risk (n = 22), and a total score of 2 or more was defined as high risk (n = 10).

or haematology parameters were significantly associated with the presence of metastatic disease. There was a non-significant trend, however, for elevated alkaline phosphatase levels in metastatic cases (median alkaline phosphatase levels = 180 (IQR 93–278) vs. 96 (IQR 71–136) U/l, respectively; Mann-Whitney, p = 0.079). This was also observed for γ -glutamyl transferase (median levels = 123 (IQR 63–328) vs. 28 (IQR 19–75) U/l, respectively; Mann-Whitney, p = 0.081).

Discussion

Malignant primary tumour characteristics and distant metastases are the most important prognostic factors for pancreatic and periampullary neuroendocrine tumours [4, 6–10]. Other histological tumour characteristics, however, such as nodal involvement, tumour size and resection margin status appear to be of lesser significance [4, 6–10]. A recent large study [19] using pooled data from the US National Cancer Database demonstrated that patient age, tumour differentiation and distant metastases were the most significant prognostic factors in resected cases while gender, ethnicity, socioeconomic status, tumour size, nodal status, resection margin status and histological tumour type were not predictive of survival. This study did not analyse any potential preoperative prognostic factors other than patient demographics.

No other previous studies have reported any system of preoperative risk stratification in the specific context of resected pancreatic and periampullary neuroendocrine tumours. In the present study, the finding that amongst the histological prognostic factors only tumour grade was associated with a significantly poorer survival is consistent with the US National Cancer Database study [19].

The present study suggests that significant prognostic information can be obtained prior to surgical intervention for this patient group and that resection of pancreatic and periampullary neuroendocrine neoplasms is characteristically associated with favourable survival outcomes [20, 21]. Despite this, a sub-group of cases exists for whom poorer survival is seen, notably in older patients [10, 13, 21]. The median age of the patient cohort in the present study (54 (IQR 44–71) years) is comparable with the median age in the patient series reported by Bilimoria et al. [19] (56 (IQR 45–67) years).

Lower serum albumin levels were also shown to be associated with poorer survival as previously reported for inoperable pancreatic adenocarcinoma [22] as well as other malignancies [23]. This may reflect the significance of nutritional status in determining early survival outcomes for these patients. The one previous study that investigated the prognostic value of any preoperative biochemistry in neuroendocrine malignancy suggested that elevated alkaline phosphatase levels were associated with poorer survival in patients with metastatic neuroendo-

crine tumours of both gastrointestinal and pulmonary origin [24]. The results of the present study also indicate that the platelet-lymphocyte ratio has prognostic value in resected pancreatic and periampullary neuroendocrine tumours, similar to that observed for pancreatic ductal adenocarcinoma [25].

When using patient age, alkaline phosphatase levels, ALT and the platelet-lymphocyte ratio to generate a preoperative prognostic score, it was possible to identify a high-risk patient group undergoing resection with a median survival of only 10.4 months. These findings suggest that routine preoperative biochemistry and haematology results might provide significant prognostic information for patients undergoing resection for pancreatic and periampullary neuroendocrine tumours. No details regarding disease-specific mortality were prospectively collected and insufficient clinical data were available to make a reliable retrospective assessment of cause of death for all patients who died during the follow-up period. Therefore, no attempt to investigate disease-specific survival in this patient group was possible. The validity of the preoperative prognostic score for different sub-groups of neuroendocrine tumours (e.g. non-functioning vs. functioning) could also not be reliably assessed due to the limited number of patients included in the present study. However, if validated in a larger patient cohort, the proposed preoperative risk score may be of potential use alongside existing post-resection prognostic scores in risk stratification of patients for future clinical trials.

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