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Prognostic factors and survival after surgical resection of pancreatic neuroendocrine tumor with validation of established and modified staging systems☆

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ABSTRACT

Background: Pancreatic neuroendocrine tumors (PNETs) display wide heterogeneity with highly variable prognosis. This study aimed to identify variables related to survival after surgical resection of PNET.
Methods: A total of 143 patients were identified from a prospectively maintained database. Patient characteristics were analyzed and prognostic factors for overall survival and progression-free survival were evaluated. The WHO, ENETS and AJCC scoring systems were applied to the cohort, and their ability to predict patient outcomes were compared.
Results: Multivariate analysis found that female gender, lymph node metastases and increasing WHO 2010 grade to be independently associated with reduced overall survival ($P < 0.05$). Patients requiring multi-visceral resection or debulking surgery found to be associated with shortest survival. ROC analysis found the ENETS and AJCC scoring systems to be similarly predictive of 5-year overall survival. Modified Ki67 significantly improved its accuracy in predicting 5-year overall survival (AUROC: 0.699 vs 0.605; $P < 0.01$).
Conclusions: Multi-visceral or debulking surgery is associated with poor outcomes. There seems to be no significant difference between enucleation and anatomical segmental resection. Available scoring systems have reasonable accuracy in stratifying disease severity, with no system identified as being superior. Prognostic stratification with modified grading systems needs further validation before applied in clinical practice.

Introduction

Pancreatic neuroendocrine tumors (PNETs) are uncommon, representing 1–2% of all pancreatic tumors [1] and are diverse in terms of their physiological and pathological behavior. As well as typical pathological variables, such as tumor size, nodal or distant metastases, there are further variables which can affect outcome, including Ki67 index and whether tumors are functional or non-functional, based on their ability to produce biological active peptides [2,3].

The World Health Organization (WHO) 2010 classified PNETs into three groups according to the tumor cell proliferation activity. In addition, the European Neuroendocrine Tumor Society (ENETS) 2006 and the American Joint Committee on Cancer (AJCC) 2010 7th edition staging systems stratify disease severity [4]. Several reports have correlated prognostic factors such as size, grade, functional status, distant metastases with survival and tumor recurrence [5–8].

Due to the heterogeneity of these tumors, limited data are available on the indications, the surgical approach and the extent of surgical resection upon survival. Surgery is the choice of treatment for localized primary lesions. Although multi-visceral resection for locally advanced disease, or debulking of the majority of the tumor mass for limited metastatic disease may be recommended, data from the literature are unclear as to the impact of these strategies upon survival [2,3,9,10].

☆ Part of these data have been presented in the Association of Upper Gastrointestinal Surgeons (AUGIS) Congress, Brighton, UK on September 18–19, 2014.

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This study aimed to review the patient, surgical and pathological variables that are related to survival following surgical resection of PNETs. We also compared the ENETS and AJCC systems on the same patient cohort.

Methods

All patients ($n = 143$) with functioning or non-functioning PNETs undergoing surgical exploration with intention to treat in our unit between January 1988 and December 2013 were identified from a prospectively maintained database. The study was approved by the institutional ethics committee. Demographic details, surgical treatment (enucleation, anatomic resection, multi-visceral resection plus metastasectomy and debulking surgery), pathological variables and follow-up information regarding survival and disease status were evaluated. Functional and hereditary lesions were diagnosed on the basis of the distinct clinical syndromes, serum elevation and positive immunohistochemistry of the relevant hormones. Computed tomography, magnetic resonance imaging, somatostatin receptor scintigraphy and endoscopic ultrasound were used for preoperative assessment of tumor location as deemed necessary.

Scoring/staging systems

Tumors were classified according to WHO 2010 classification [4,11] and staged according to ENETS and the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM systems [12,13]. Ki67 grading was also considered, with Ki67 $\leq$ 2% classified as grade 1, 3–20% as grade 2 and >20% as grade 3 [11]. In addition, two modified scores were calculated, the "modified ENETS", a four stage version of the score, and "modified Ki67", which included Ki67 < 5% in grade 1, 5–20% in grade 2 and >20% to grade 3, as proposed by Scarpa et al. [14]. A four stage version of the AJCC, which excluded the letters from the stages, was also considered to make a fairer comparison with the modified ENETS staging.

Outcomes

Pancreatic fistula were graded according to the International Study Group on Pancreatic Fistula criteria (ISGPF) [15]. The above criteria were applied retrospectively for the diagnosis of fistula in the pre-ISGPF era on the basis of clinical or biochemical findings. All previous pancreatic fistula definitions applied to our study group were reviewed and re-classified accordingly. All patients had regular clinical follow-up and cross sectional imaging according to the clinical condition of each patient.

The primary end points were the overall survival (OS) and progression free survival (PFS) from the date of surgical resection of the primary lesion. For the PFS, progression was classified as radiologically proven recurrence, increase in the tumor size or presence of a new lesion in unresectable disease.

Statistical analysis

The data were analyzed by a medical statistician (HJ) using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY) and Stata 14 (Stata Corp., TX). OS and PFS rates were calculated using the Kaplan–Meier methodology, with comparisons across factors made using log-rank tests.

The accuracy of the staging systems to predict 5-year OS and PFS was assessed using ROC curves. Patients who did not have the potential of 5-year follow-up, namely those who were lost to follow-up after less than five years, or those who died and had follow-up starting less than five years from the end of the study period, were excluded from this analysis. In each case, comparisons between the areas under the ROC (AUROC) curves for the systems were performed using the "roccomp" command in Stata [16].

Multivariate analysis was then performed using a Cox regression model, with a forward stepwise entry method, to identify independent predictors of OS and PFS. Statistical significance was defined as P values less than 0.05 throughout.

Table 1
Demography and clinical characteristics of the entire cohort ($n = 143$).

Characteristics	Data
Age (yr)	53.5 ± 16.0
Male	57 (39.9%)
Functioning tumor	54 (37.8%)
Insulinoma	43 (30.1%)
Gastrinoma	4 (2.8%)
Somatostatinoma	3 (2.1%)
VIPoma	2 (1.4%)
Glucagonoma	1 (0.7%)
PP	1 (0.7%)
Tumor site	
Head	76 (53.1%)
Body-tail	61 (42.7%)
Multicentric	6 (4.2%)
Hereditary status	
Sporadic	127 (88.8%)
MEN 1	10 (7.0%)
VHL	5 (3.5%)
Neurofibrimatosis	1 (0.7%)
Operation	
Anatomic resection (Whipple-DP-TP-CP)	78 (54.5%)
Enucleation	33 (23.1%)
Multi-visceral	19 (13.3%)
Debulking	13 (9.1%)
Size (cm)	2.8 (0.6–21.0)
<2	48 (33.6%)
2–4	45 (31.5%)
>4	50 (35.0%)
Lymph nodes status	
Negative	94 (65.7%)
Positive	49 (34.3%)
Positive margins*	18/130 (13.8%)
Follow-up (mon)	72 (0–290)
Hospital stay (d)	8 (1–96)

Data were presented as mean ± SD or number (percentage) or median (range).\
* margins exclude patients undergoing debulking surgery. MEN 1: multiple endocrine neoplasial 1; VHL: Von Hippel – Lindau; DP: distal pancreatectomy; TP: total pancreatectomy; CP: central pancreatectomy.

Results

Patient demographics and clinical characteristics

Of the 143 patients analyzed, the age at surgery was 53.5 ± 16.0 years, and 60.1% (86/143) were female. Key demographics, surgical and pathological characteristics are summarized in Table 1. Nineteen patients (13.3%) underwent multi-visceral resections, including liver resection for metastases ($n = 14$), hemicolectomy ($n = 5$), adrenalectomy ($n = 1$), small bowel resection ($n = 1$) and subtotal gastrectomy ($n = 1$). Thirteen patients (9.1%) underwent non-curative debulking surgery of the primary tumor.

Predictors of survival: patient factors

The median follow-up, based on the Kaplan–Meier estimate of potential follow-up, was 72 months, with a maximum of 290 months. The actuarial 1-, 3-, 5- and 10-year OS rates were 90.1%, 83.9%, 78.1% and 64.9%, respectively. Univariate analysis found increasing age, tumor size, and positive lymph nodes to be associated with significantly shorter OS (Table 2). The type of surgery was also a significant predictor of OS ($P < 0.01$). The shortest survival

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