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Pancreatic neuroendocrine tumor: A multivariate analysis of factors influencing survival

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Abstract

Background: The outcomes of pancreatic neuroendocrine tumors are extremely diverse, and determining the best strategy, optimal timing of therapy and the therapeutic results depend on understanding prognostic factors. We determined the clinical, radiological and histological factors associated with survival and tumor recurrence for patients with pancreatic neuroendocrine tumor.

Methods: From January 1, 1991 to December 31, 2011, 127 patients with pancreatic neuroendocrine tumor underwent pancreatectomy. The variables including clinical characteristics, surgical data and pathological findings were examined by univariate and multivariate analyses.

Results: There were 103 patients with non-functional tumors (81%). Sixty-four patients (50%) underwent left pancreatectomy, 51 (42%) patients underwent pancreatico-duodenectomy, 12 (9%) patients underwent enucleation and 2 patients (1%) underwent central pancreatectomy. Forty-eight patients (38%) had synchronous liver metastases. Six patients (5%) required portal vein resection, and 19 (15%) patients required enlarged "en-bloc" resection of adjacent organs. The overall morbidity and mortality rates were 48% and 2.3%, respectively. The 1-, 3- and 5-year overall survival rates were 94%, 84%, and 74%, respectively. In multivariate analyses, synchronous liver metastases ($p = 0.02$) and portal vein resection ($p < 0.01$) were independent prognostic factors of survival.

Conclusions: Synchronous liver metastases and portal vein resection were found to be independent factors influencing survival.

Keywords: Neuroendocrine tumor; Pancreatic surgery; Liver metastases; Prognostic factor; Survival

Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms with a long-term evolution. The estimated incidence is approximately 1 per 100,000 persons per year in the general population, and PNETs represent 1–2% of all pancreatic neoplasms.[1,2] PNETs are functional or non-functional (35–50% of PNETs)[3,4] tumors and represent a heterogenous group of neoplasms with an extremely variable clinical behavior that depends on histologic features and disease staging. Furthermore, incidentaloma PNETs have increased in overall incidence in recent years because of fortuitous diagnosis on CT scans.[5]

Patients with PNETs have a better prognosis than those with the more common ductal pancreatic adenocarcinoma.

Abbreviations: PNET, pancreatic neuroendocrine tumor; PD, pancreatico-duodenectomy; LP, left pancreatectomy; PVR, portal vein resection; POPF, Post-operative pancreatic fistula.

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Approximately 20–40% of patients diagnosed with PNETs are eligible for complete surgical resection.[5–7] Resection remains the only curative therapy and provides a 5-year overall survival exceeding 60%.[8–10] The natural evolution of PNETs could lead to regional lymph node, liver, pulmonary, and bone metastases that reduce overall 5-year survival below 30%.[4,10–14] The treatment of patients diagnosed with liver metastases arising from PNETs is controversial and varies from observation[9–11,15–17] to "aggressive" resection. Thus, the management of patients diagnosed with synchronous hepatic metastasis from a PNET is still a challenge for oncologists.[18] A variety of therapeutic options has been evaluated, including medical treatment (somatostatin analogs, interferon, chemotherapy), local therapy (external radiotherapy, hepatic artery chemoembolization), and surgery (hepatectomies, radiofrequency ablation, liver transplantation) to reduce the tumor burden and its related hormonal secretion activity.

The outcome of PNETs is extremely diverse, which makes the individual assessment of prognostic factors critical. Determining the best therapeutic strategy, the proper timing of therapy and the therapeutic results requires the knowledge of prognostic factors.

We conducted a retrospective multicenter review of patients who underwent resection for PNETs over the last 20 years to identify factors influencing survival. The prognostic factors affecting post-operative long-term survival and PNET recurrence were examined by performing univariate and multivariate analyses.

Materials and methods

Data collection

From January 1, 1991 to December 31, 2011, 127 patients with PNET underwent pancreatectomy at Institut Paoli-Calmettes, Hôpital Nord and Hôpital de la Conception (Marseille, France). All patient data were entered retrospectively into clinical databases approved by the Institut Paoli-Calmettes, Hôpital Nord and Hôpital de la Conception Institutional Review Boards. Patients with signs, symptoms and biochemical evidence of hormonal excess were considered to have functional tumors and were classified by their respective clinical syndrome. Patients with no recognizable clinical syndrome and normal serum hormone levels were considered to have non-functional tumors. Patients were considered to have synchronous hepatic disease when the liver metastases and primary tumor were identified simultaneously. Metachronous liver disease was defined as the earliest radiologic evidence of new hepatic recurrence after complete resection or new neoplasm growth after incomplete resection.

Patients with adenocarcinoma of the pancreas, intraductal papillary mucinous adenocarcinoma, carcinoma of the duodenum, distal common bile duct, or ampulla of Vater were excluded.

Preoperative work-up, surgical procedures and pathological analysis

Preoperative tumor staging was performed by computed tomography (CT) and/or magnetic resonance (MR), endoscopic ultrasound, and somatostatin receptor scintigraphy at the surgeon's discretion. All surgical indications were discussed by a multidisciplinary pancreatic tumor board consisting of surgeons, radiologists, pathologists, oncologists and gastroenterologists. According to the period of treatment, liver metastases were assessed by both angio-CT scans and magnetic resonance imaging (MRI). The liver volume was calculated in bilobar disease to determine the appropriate strategy. A PNET diagnosis was based on conventional histology and immunohistochemistry (chromogranin A, synaptophysin and Ki67). All cases were reviewed and classified according to the WHO 2010 (World Health Organization) classification and assigned an ENETS (European Neuroendocrine Tumor Society)/TNM-based stage and grading score.[19,20]

All patients underwent pancreatectomy (i.e., pancreatico-duodenectomy (PD), left pancreatectomy (LP), central pancreatectomy (CP) or enucleation (EN)) to remove their primary PNET. In patients with synchronous liver metastasis, pancreatectomy was associated with a) one stage (major hepatectomy, segmentectomy, metastasectomy, radiofrequency ablation) or b) two stage ("cleaning of the left lobe" (metastasectomies, radiofrequency ablation), followed by right portal vein embolization and finally right hepatectomy) liver treatment based on liver involvement. Patients with metachronous liver metastasis underwent the same liver strategies.

To achieve PD, the duodenum (pylorus-preserving procedure) or the stomach (classic procedure) was transected, followed by transection of the pancreatic neck, uncinate process, and jejunum distal to the ligament of Treitz. According to center/surgeon preference, reconstruction was undertaken with a pancreaticojejunostomy (duct-to-mucosa or invaginated anastomosis) or pancreaticogastrostomies, followed by an end-to-side choledochojejunostomy and either antecolic or retrocolic end-to-side duodenojejunostomy or gastrojejunostomy.

To achieve LP, splenic vessels were electively ligated and sectioned after transection of the pancreatic neck. The spleen was routinely removed, and a total clearance of peripancreatic lymph nodes was performed.

Enucleation was defined as the excision of affected parenchyma with a minimal resection margin, which was performed when the tumor was not close to the main pancreatic duct. If enucleation was not possible for tumors of the neck and body of the pancreas, then CP was performed if the remnant pancreas was at least 5–7 cm long. In this setting, the proximal remnant was evaluated after elective ligation of the main pancreatic duct. Reconstruction of the distal pancreas was performed by end-to-side pancreaticogastrostomy.