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Survival prognostic factors of gastro-enteric-pancreatic neuroendocrine tumors after primary tumor resection in a single tertiary center: Comparison of gastro-enteric and pancreatic locations

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Abstract

Aim: This study aimed to evaluated prognostic factors of patients with GEP-NETs after primary tumor resection comparing pancreatic and gastro-enteric locations.
Methods: Patients undergone surgery for primary GEP-NETs between 01/2000 and 03/2012 were considered. All specimens were reclassified according to the WHO 2010 scheme.
Results: A total of 83 patients were considered: 37 pancreatic NETs (pNET) and 46 gastroenteric NETs (GE-NET). The two groups were similar in terms of age, sex and tumors size. A higher rate of patients with pNETs had Ki67 score $\geq$3 (64.8% vs. 39%, p = 0.027) while the rates of Mitotic Index $\geq$2x10HPF (62% pNET vs. 50% GE-NET, p = 0.374) and diagnosis of neuroendocrine carcinoma NEC (16.2% pNET vs. 17.3% GE-NET, p = 0.100) were similar. The rates of distant metastases (GE-NETs 30.4% vs. p-NETs 29.7%, p = 0.944) and liver metastases (19.5% GE-NET vs. 27% pNET, p = 0.421) were comparable. Radical resection was achieved in a similar proportion in both groups [33 patients (89.1%) pNET vs. 36 (78.2%) GE-NET, p = 0.393]. After a median follow-up of 47.1 months overall 3, 5 and 10-years survival rates of whole patients were 88.1%, 81.2% and 76.7%. There was not difference on 5-years overall survival between pNET (81.4%) and GE-NET (81%, p = 0.901). At multivariate analysis age $\geq$70 [OR 4.177 (CI 95% 1.26–13.8), p = 0.019] and NEC [OR 5.932 (CI 95% 1.81–19.40), p < 0.001] were negative prognostic factors of survival.
Conclusion: Overall survival of GEP-NET after resection of primary tumors seems to be correlated to patient's age and WHO 2010 staging system but not to primary tumor site.

Keywords: Pancreatic neuroendocrine tumors; Gastro-enteric neuroendocrine tumors; Surgery; Overall survival

Introduction

Following the growing interest on neuroendocrine tumors (NETs), several studies have been published evaluating prognostic factors for Gastro-Entero-Pancreatic (GEP) NETs.[1–9] Many of these papers showed primary pancreatic location of NETs (pNET)[1,3,4,6] as important negative prognostic factor. Nevertheless data on prognostic factors of GEP-NET come from studies including both resected and not-resected patients. Recent comprehensive guidelines for the diagnosis and treatment of GEP-NETs published by ENETS[10] and NANETS[11] defined surgical resection as the only curative option for NET patients. In this perspective,

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post-resection prognostic staging is mandatory to determine the optimal treatment strategy for GEP-NETs. This study aimed to evaluated prognostic factors of patients with GEP-NETs after primary tumor resection, with special attention paid to the impact of primary tumor site comparing pancreatic and gastro-enteric locations.

Patients and methods

All patients undergoing surgery for primary GEP-NETs between 01/2000 and 03/2012 were considered. According to the primary NET site, patients were divided into two groups: pancreatic NETs (pNET) and gastro-enteric NETs (GE-NET).

Patients that underwent only endoscopic procedure for their primary tumor (submucosal dissection or electroexcision) were excluded. Patients with distant metastases at diagnosis were included, even if metastasis resection was not performed (R2 resections).

Staging and surgical management

Preoperative work-up consisted of blood examinations and Thoraco-Abdominal Computed Tomography (CT) scan. In cases of pancreatic NETs, endoscopic ultrasound and Magnetic Resonance Imaging (MRI) were also performed. If a NET is suspected, staging included somatostatin receptor scintigraphy (Octreoscan). Laboratory investigations included chromogranin A (CgA) level determination in all patients. Depending on clinical symptoms, other markers were measured such as urinary 5HIAA for the carcinoid syndrome, gastrin for the Zollinger–Ellison syndrome and insulin/pro-insulin for the hypoglycemic syndrome. CgA levels in blood were measured using commercial kits (CIS bio International, France) (normal range: 19.4–98.1 ng/mL). In the case of postoperative NET diagnosis, staging was completed with evaluation of CgA levels and octreotide scirntigraphy or FDG-PET, according to the grade of differentiation. All patients were classified according to the 7th American Joint Council on Cancer (AJCC) TNM staging system.[12] The extent of surgical resection depended on the tumor size and primary location, according to the ENETS guidelines. Pancreaticoduodenectomy was performed according to the Whipple technique. Reconstruction was undertaken with pancreaticojejunostomy (duct-to-mucosa or invaginated anastomosis), followed by an end-to-side choledochojejunostomy and either antecolic or retrocolic end-to-side gastro-jejunostomy. To achieve spleno-pancreasectomy, splenic vessels were electively ligated and sectioned after transection of the pancreatic neck. Spleen was routinely removed and a total clearance of peripancreatic lymph nodes was performed. An extended lymphadenectomy was systematically associated. Patients with liver metastases synchronous with primary GEP-NETs were systematically considered for simultaneous primary tumor and hepatic resection. Resection of the tumor was defined R0 if tumoral lesions were entirely removed with pathologically tumor-free margins, R1 in case of microscopic tumor infiltration and R2 in presence of macroscopic residual tumor.

Pathologic data

All specimens were reviewed by pathologists with wide experience in GEP-NET diagnosis (MM, MP) and were re-evaluated and classified according to the WHO 2010 scheme for neuroendocrine tumors.[13] The diagnosis was supported by the identification of synaptophysin and/or chromogranin A in tumor cells. The proliferative activity was assessed by means of Ki67 (clone MIB1, Dako Cytomation, Glostrup, Denmark).

Follow-up

After resection, patients entered a six month follow-up, consisting of CgA level measurement and imaging procedures including abdominal ultrasonography, thoraco-abdominal CT or MRI with intervals between one and two years. Octreotide scintigraphy was performed yearly or at the appearance of new lesions. Postoperative follow-up was performed by outpatient clinics or by contacting the family doctors of single patients and it was updated to September 2013.

Statistical analysis

Continuous variables were reported as mean (±SD), unless otherwise stated, and compared by Student t-test. Categoric variables were compared by χ-square test or Fisher exact test, as appropriate. The Kaplan–Meier method was used to estimate survival probabilities, which were compared using the Log-rank test. Overall survival (OS) was calculated from the date of the primary tumor resection to the last follow-up contact. Multivariate analysis was performed using a Cox proportional hazard model to identify independent prognostic factors of OS after primary tumor resection. Multivariate analysis was completed for factors with a p value ≤ 0.05 in the univariate analysis. A p-value < 0.05 was considered significant for all tests.

Results

Patients groups

A total of 83 patients with a diagnosis of GEP-NETs were included in the study. According to the primary NET site, patients were divided into two groups: pancreatic NETs (n = 37) and gastro-enteric NETs (n = 46). The mean characteristics of both groups were reported in Table 1.

Among GE-NETs, the sites of origin were appendix (15, 32.6%), small intestine (12, 26%), duodenum/jejunum (10,