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# Surgical resection for neuroendocrine tumors of the pancreas: a fourteen years single institutional observation

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**Abstract. – OBJECTIVE: Pancreatic neuroendocrine tumors (PNETs) are a rare entity that can present with symptoms of hormone overproduction with surgical resection being the only chance for cure despite the poorly defined tumor behavior. Their management involves a variety of therapies which require a well coordinated multidisciplinary team with the effort to optimize outcomes.**

**PATIENTS AND METHODS: A retrospective analysis of 25 consecutive patients was performed by means of our single institution prospectively maintained database. All patients' files from 1999 to 2013, with histologically proven neuroendocrine tumors of the pancreas, were reviewed for clinical presentation, functional status, treatment, postoperative morbidity and mortality.**

**RESULTS: Of 25 patients a total of 22 patients (11 females, 11 males, average age 49.7 years) underwent surgery with curative intent. We had 3 female patients that underwent palliative surgery because of unresectable disease. Nineteen of the 25 were not functional tumor. For the resected patients the overall morbidity was 38.8%. The 30-day mortality rate was zero. The overall median length of hospital stay was 10.4 days (range 4-23 days)**

**CONCLUSIONS: Surgical resection with regional lymph node dissection is the only potentially curative therapy for patients with localized PNETs with the exceptions of most insulinomas where simple enucleation may be the standard of treatment. The anatomic considerations for determining the resecability are the same as those for pancreatic adenocarcinomas. Careful follow-up after surgery is essential because up to 50% of patients who undergo complete resection develop metachronous liver metastasis. Distant metastatic disease should be resected if possible.**

*Key Words:*
Neuroendocrine tumors, Pancreas, Surgical resection, Survival.

## Introduction

Neuroendocrine tumors of the pancreas are the most common abdominal endocrine neoplasms. They account for 2%-4% of all pancreatic neoplasms and are roughly divided into functional and non-functional, single and multiple, sporadic and associated with hereditary syndromes (MEN-1, VHL, Tuberous Sclerosis, Neurofibromatosis-1). Functional tumors secrete ectopic hormones (e.g., insulin, gastrin, glucagon, vasoactive intestinal peptide, corticotropin) that can cause distinct clinical syndromes[1].

The first functional pancreatic neuroendocrine tumor, an islet cell neoplasm, was described in 1902 by Nicholls[2]. More than eighty years ago William J. Mayo, MD, performed the first operation for a pancreatic endocrine neoplasm on a physician who had self-diagnosed hypoglycemia and was found to have a malignant insulinoma with liver metastases. Shortly thereafter, in 1929, Howland et al[5] reported the first surgical cure for a functional pancreatic endocrine neoplasm with enucleation of a benign insulinoma located in the body of the gland. Since then, surgery has continued to remain the gold standard for PNETs and the only known curative treatment. For decades these neoplasms have remained rare, with practically all of those diagnosed being functional neoplasms (mostly insulinomas) and very few nonfunctioning neoplasms. Indeed erroneously, functional neoplasms have previously been shown to comprise up to 85% of PNENs[6,7].

Thus, the vast majority of pancreatic neuroendocrine tumors are nonfunctional (80%), and they are generally not diagnosed until symptoms develop from a mass effect or from metastatic disease in those tumors that are malignant. In many patients, the tumor is noted serendipitously on an abdominal imaging study and the patients are asymptomatic[1]. Patients with neuroendocrine pancreatic cancers have a significantly better prognosis than those with the more common counterpart, ductal pancreatic adenocarcinoma, but the two pathological entities may be impossible to distinguish preoperatively[8-11]. As with ex-



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ocrine cancers, resection is the only chance for cure, and the type of resection that is required depends on the location of the tumor. To evaluate the experience with these uncommon neoplasms, the Authors conducted a retrospective review of the patients treated at the Surgical Oncology Unit, Garibaldi-Nesima Hospital, Catania, who underwent resection for pancreatic neuroendocrine tumors over the last 14 years.

## Patients and Methods

### *Data Collection*

The medical records of 25 patients referred at the Surgical Oncology Unit, Garibaldi-Nesima Hospital, Catania between July 1, 1999, and December 30, 2013 with histologically proven neuroendocrine neoplasm of the pancreas, were reviewed. twenty-two patients out of twenty-five (22/25) underwent resection of the tumor at the same institution. The review included patient demographics (age and sex), surgical data (type of resection/palliation, operative blood loss, and duration of surgery), pathological diagnosis, postoperative morbidity and mortality rates and length of hospital stay. Tumors of patients with appropriate signs, symptoms, and laboratory evidence of hormonal excess were considered functional and were classified by their respective clinical syndromes: insulinoma, glucagonoma, gastrinoma and ACTHoma. Tumors of patients without a recognizable clinical syndrome and with normal serum hormone levels were classified as nonfunctional (neuroendocrine carcinomas and benign islet cell neoplasms), independent of immunohistochemistry of the tumor specimen. Pre-operative radiological assessment included a thoracic, abdomen and pelvis computed tomography (CT) and in selected cases magnetic resonance imaging (MRI) of the pancreas as well as of the liver if metastases or suspicious liver lesions were detected on CT. In addition, an endoscopic ultrasound scan (EUS) and somatostatin receptor scintigraphic scanning (OctreoScan®) were performed in selected cases to further characterize the primary lesion and localize metastatic disease. Postoperative mortality was defined as death occurring in the first 30 postoperative days or prior to discharge from the hospital. For morbidity analysis, complication were defined according to internationally accepted criteria as per the International Study Group of Pancreatic Surgery (ISGPS)[12]. A pancreatic fistula was defined as drainage of any measurable amount of amylase-rich fluid per 24 hours, with at least 3 times the upper normal limit of serum amylase concentration after the third postoperative day[13]. Delayed gastric emptying (DGE) was defined as intolerance to oral intake and need for nasogastric decompression after the seventh postoperative day. Other complications were categorized and defined as any of the following: intra-abdominal abscess (fluid requiring drainage and with positive bacterial culture results); wound infection (purulent drainage requiring open packing); postoperative bleeding (requiring transfusion or endoscopic or operative intervention); bile leak (bilious drainage from intraoperatively placed drains or bile collection requiring drainage); biliary stricture (requiring stenting and/or late reoperation); cardiac (myocardial infarction or new-onset arrhythmia requiring intervention); pulmonary (pneumonia, effusion requiring drainage, or reintubation); sepsis (fever, leukocytosis, or bacteremia requiring medical and/or surgical intervention); and reoperation in the first 30 postoperative days or prior to discharge from the hospital. Surgical resection with intent to cure involved the complete tumor resection of all identified disease at operation, including the primary tumour, hepatic metastases and other intra-abdominal disease, if needed. The only 3 palliative surgeries consisted of bypass procedures. Histopathological analysis was based on the WHO classification of pancreatic NET[14].

## Results

During the study period, 22 of the 25 patients with malignant PNETs underwent surgery with curative intent. The median age at diagnosis was 49.7 years (range: 17-70) and the male to female ratio was 1. The other 3 females patients with median age of 73 years (range 65-81) had advanced disease not amenable of resectability with curative intent, thus they were managed by palliation. 19 of the 25 were not functional tumor. The functional PNETs consist of 3 Insulinoma, 2 Gastrinoma and 1 ACTHoma.

Based on tumor site and size, and relationship to the pancreatic duct, performed curative surgeries consisted of 8 standard Whipple procedures, 6 pylorus-preserving pancreaticoduodenectomy (one with portal vein resection and reconstruction), 2 laparoscopic enucleations, 5 distal pancreatectomies with splenectomy and 2

laparoscopic DP (one with splenic vessels preservation). All of the enucleations were performed for insulinomas. In one case there was the need to perform aggressive en-bloc surgery to pursue tumor-free margins by means of a total gastrectomy plus distal pancreatectomy, splenectomy and resection of the left colonic flexure.

The only 3 palliative procedures consisted of explorative laparotomy and tumor biopsy associated with a gastrojejunal bypass in one case and with an hepaticojejunostomy plus gastrojejunostomy in the other case. In these patients we did not embarked in debulking procedures since the patients were asymptomatic from an endocrine point of view at the time of diagnosis with exception of gastric outlet syndrome and jaundice. No mortality nor complications occurred within this subgroup of patients and the median length of stay was 5 days (range 4-6 days).

Partial or complete control of endocrine-related symptoms was achieved in all patients that received R0 resection. For the resected patients the overall morbidity was 38.8% and consisted of one wound dehiscence and portal vein graft thrombosis in a patient that underwent PPPD with portal vein resection and reconstruction; one postoperative bleeding treated with relaparotomy; one biliary leak and delayed gastric emptying spontaneously subsided; one wound infection and one transient ischemic attack. The 30-day mortality rate was zero. The overall median length of hospital stay was 10.4 days (range 4-23 days) with a significant statistical difference between the two groups of patients treated with PD vs. DP, being the LoS 13.3 (range 7-23) vs. 7.5 days (range 4-12), respectively.

PNETs account for 2% to 4% of pancreatic tumors and may occur sporadically or as part of a hereditary syndrome. Patients may present with symptoms related to locally advanced or metastatic nonfunctional tumors or with symptoms related to hormone secretion. Pancreatic neuroendocrine tumors, form a fascinating issue not only from the standpoint of genetics, tumor biology and diagnostic methodology, but also from the technical view of the surgeon. The management of localized PNETs is surgical resection that remains the mainstay of therapy. Complete tumor excision offers the only opportunity for cure and provides symptomatic relief for functional PNETs. Most of these tumors are malignant, with the exception of most insulinomas, and resection should follow oncologic principles such as pancreaticoduodenectomy, distal pancreatectomy or total pancreatectomy with associated regional lymphadenectomy[15,16].

Nonfunctional PNETs are often locally advanced at time of diagnosis, though, rates of resecability and survival are improved compared with adenocarcinoma[17].

The reported median survival was of 7 to 10 years for patients undergoing resection for locoregional disease in experienced centers[18,19].

Patients who present with unresectable disease in absence of distant metastases require an individualized therapeutic strategy to provide optimal palliation. Occasionaly, these patients may require palliative bypasses to relieve biliary or intestinal obstruction rather than debulking or R2 resection of the primary tumor, that results in unnecessary morbidity.

Hepatic metastases occur in greater than 50% of patients and their management involves a variety of therapies which require a well coordinated multidisciplinary with the effort to optimize outcomes because they are an important determinant of survival[20-21].

## Conclusions

The surgeon plays an important role for the cure of PNETs but because of the hetereogeneity of the disease with hereditary, unresectable and diffuse metastatic forms, many experienced clinicians involved in the nonsurgical disciplines that may offer another optional treatment concept to the afflicted patient, ant this differente approach represent a challenge in this era[22-23].

### Conflict of Interest

The Authors declare that they have no conflict of interests.

## References

1) Jensen RT, Norton JA. Endocrine neoplasms of the pancreas. In: Yamada T, ed. Textbook of Gastroenterology. Vol 2. 2nd ed. Philadelphia, Pa: JB Lippincott, 2003; pp. 2108-2146.
2) Nicholls AG. Simple adenoma of the pancreas arising from an island of Langerhans. J Med Res 1902; 8: 385-395.
3) Wilder RM, Allan FN, Power MH, Robertson HE. Carcinoma of the islets of the pancreas: hyperinsulinism and hypoglycemia. JAMA 1927; 89: 348-355.

4) van Heerden JA, Churchward MM. Dr Dickinson Ober-Wheelock. A case of sporadic insulinoma or multiple endocrine neoplasia type 1. Mayo Clin Proc 1999; 74: 735-738.

5) Howland G, Campbell WR, Maltby EJ, Robinson WL. Dysinsulinism convulsions and coma due to islet cell tumor of the pancreas, with operation and cure. JAMA 1929; 93: 674-679.

6) Berretta M, Cappellani A, Di Vita M, Berretta S, Nasti G, Tirelli U, Canzonieri V. Biomarkers in neuroendocrine tumours. Front Biosci S2, 2010; 1: 332-342.

7) Broder LE, Carter SK. Pancreatic islet cell carcinoma, I: clinical features of 52 patients. Ann Intern Med 1973; 79: 101-107.

8) Phan GQ, Yeo CF, Hruban RH, Lillemoe KD, Pitt HA, Cameron JL. Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. J Gastrointest Surg 1998; 2: 472-482.

9) Matthews BD, Heniford BT, Reardon PR, Brunicardi FC, Greene FL. Surgical experience with nonfunctioning neuroendocrine tumors of the pancreas. Am Surg 2000; 66: 1116-1122.

10) Evans DB, Skibber JM, Lee JE, Cleary KR, Ajani JA, Gagel RF, Sellin RV, Fenoglio CJ, Merrell RC, Hickey RC. Nonfunctioning islet cell carcinoma of the pancreas. Surgery 1993; 114: 1175-1182.

11) Dralle H, Krohn SL, Karges W, Boehm BO, Brauckhoff M, Gimm O. Surgery of resectable nonfunctioning neuroendocrine pancreatic tumors. World J Surg 2004; 28: 1248-1260.

12) Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP, Vollmer CM Jr. Clinical and economic validation of the International Study Group of Pancreatic Surgery (ISGPS) classification scheme. Ann Surg 2007; 245: 443-451.

13) Bassi C, Falconi M, Molinari E, Salvia R, Butturini G, Sartori N, Mantovani W, Pederzoli P. Reconstruction by pancreatico-jejunostomy vs pancreaticogastrostomy following pancreatectomy. Ann Surg 2005; 242: 767-773.

14) Kloppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. Ann N Y Acad Sci 2004; 1014: 13-27.

15) Fendrich V, Bartsch DK. Surgical treatment of gastrointestinal neuroendocrine tumors. Langenbecks Arch Surg 2011; 396: 299-311.

16) Kouvaraki MA, Solorzano CC, Shapiro SE, Yao JC, Perrier ND, Lee JE, Evans DB. Surgical treatment of nonfunctioning pancreatic islet cell tumors. J Surg Oncol 2005; 89: 170-185

17) Hodul PJ, Strosberg JR, Kvols LK. Aggressive surgical resection in the management of pancreatic neuroendocrine tumors: when is it indicated? Cancer Control 2008; 15: 314-321

18) Grant CS. Surgical management of malignant islet cell tumors. World J Surg 1993; 17: 498-503.

19) Schurr PG, Strate T, Rese K, Kaifi JT, Reichelt U, Petri S, Kleinhans H, Yekebas EF, Izbicki JR. Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. Ann Surg 2007; 245: 273-281.

20) Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. Clin Cancer Res 2008; 14: 7798-7803.

21) Tomassetti P, Campana D, Piscitelli L, Casadei R, Santini D, Nori F, Morselli-Labate AM, Pezzilli R, Corinaldesi R. Endocrine pancreatic tumors: factors correlated with survival. Ann Oncol 2005; 16: 1806-1810.

22) Berretta M, Di Francia F, Tirelli U. The new oncologic challenges in the 3RD millennium. WCRJ 2014; 1: e133.

23) Berretta M, Tirelli U. Elderly cancer patients in the 3rd millenium: between hope and reality. Anticancer Agents Med Chem 2013; 13: 1299.