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Research Article

A retrospective analysis of neuroendocrine tumour of pancreas: a single institute study

Yogen P. Chheda[1], Deeksha Arora[2]*, Rutul Patel[1]

[1]Department of Surgical Oncology, Gujarat Cancer Research Institute, Ahmedabad, Gujarat, India
[2]Department of General Surgery, Sri Krishna Hospital, Karamsad, Anand, Gujarat, India

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***Correspondence:**
Dr. Deeksha Arora,
E-mail: drdeeksharora@gmail.com

ABSTRACT

Background: The aim of the work was the clinical characteristics and analysis of preliminary results for surgical treatment of pancreatic neuroendocrine tumors (PNETs). This article deals with the classification of the Pancreatic Neuroendocrine Tumors (PNETs) and discusses their presentation, behaviour, treatment and prognosis.
Methods: This was a retrospective study of 70 patients of PNET done over a period of 3 years in The Gujarat Cancer and Research Institute, Ahmedabad. 24 patients who underwent surgical treatment for PNET were further evaluated for surgical outcome, 5yr disease free survival and overall survival.
Results: In this study of 70 patients, 61(87.14%) were non-functional. Approximately 77% of PNETs were advanced on presentation (57% metastatic and 20% locally advanced). 20 patients had disease resectable on presentation (11 NF + 9 F). These 20 patients belong to stage I and II of TNM staging system. Only 4 out of 40 metastatic diseases had locally resectable tumor. Of 24 patients who underwent surgery, 12 underwent pancreatico-duodenectomy, 6 underwent enucleation and 6 underwent distal pancreatectomy.
Conclusions: PNETs are uncommon tumor of pancreatic origin with presentation more commonly in males than females, usually in the 5th decade. Approximately 77% of patients are advanced or metastatic at presentation. Among those resectable, the Overall Survival for FPNETs and NFPNETs was 90% and 94% respectively and 5yr Disease Free Survival for the same was 100% and 84% respectively.

Keywords: Pancreatic neuroendocrine tumour, Distal pancreatectomy, Pancreatico-duodenectomy

INTRODUCTION

Endocrine neoplasms can be divided according to the chemical nature of their secretion products into two groups. Neoplasms that secrete peptide hormones and biogenic amines comprise the first group. The second group includes the tumours that generate steroid hormones. The tumours of the first group are called neuroendocrine neoplasms (NENs) because of the marker proteins that they share with the neural cell system-synaptophysin and neuron specific enolase and others like chromogranins A, B and C and the proprotein convertases PC2 and PC3.[1,2]

The neural cell adhesion molecule CD56 is positive in many NENs, but is not specific for these tumours.[1]

Under the electron microscope the NENs show typical neurosecretory granules. Approximately two-thirds of NETs are found in the gastrointestinal tract, one quarter occurs in the lungs, and the remaining cases arise in other endocrine tissues, such as the thyroid. These tumors account for approximately 2% of all malignancies of the gastrointestinal tract.[3,4] NETS in the gastrointestinal tract occur predominantly in the small intestine (44.7%), followed by the rectum (19.6%), appendix (16.7%), colon (10.6%), and stomach (7.2%).[3,5] Pancreatic NENs

account for less than 1% of all pancreatic carcinomas and less than 3% of all pancreatic neuroendocrine neoplasms.[3,6] The incidence of this tumor appears to be on a rise, which is probably due to improvements and intensification of efforts in diagnostic endoscopy. NENs are heterogeneous in their clinical behavior and require therapies specially tailored according to staging, grading, origin and expression of peptide receptors. The previous World Health Organization (WHO) classifications for NENs of the tubular gastrointestinal tract (WHO, 2000) and pancreas (WHO, 2004) used a hybrid classification system that incorporated both staging and histological grading information into a single prognostic prediction system. The 2010 WHO classification, which was developed along with the European Neuroendocrine Tumor Society (ENETS), uses two separate and complementary.[3,6,7]

METHODS

NET of pancreatic origin referred to GCRI during the period from Jan 2007 to December 2009 were included in this study. Clinical data including gender, age at diagnosis, and anatomic locations, were obtained for all of the GEP-NETs cases. The 2010 WHO NET classification system was applied to all of GEP-NETs, using haematoxylin and eosin-stained slides and the immunohistochemistry (MIB1 monoclonal antibodies against the Ki-67 antigen) cell proliferation index. The pathological diagnoses of the NETs in this series considered the typical morphological findings and the expression of neuroendocrine markers, including chromogranin A and/or synaptophysin.[3,8] Patients with diagnosis of carcinoid tumor were excluded from this study. Patients were classified as localized, locally advanced and metastatic. Overall survival was defined as the time from diagnosis to last follow-up in living patients. 5 year disease free survival was defined by the absence of disease in patients after the treatment till follow up after 5 years.

RESULTS

Out of the total 70 patients of PNET, patients with localized disease were 16 (88% males and 12% females), locally advanced disease were 14 (71% males and 29% females) and metastatic were 40 (80% males and 20% females). The maximum number of PNET patients belonged to age group 51-60yrs (57%). 57% patients were diagnosed in the IVth stage (Figure 1). 87% of the PNET were functional tumors that is gastrinoma and insulinoma. The most common presentation was abdominal pain (71%). All patients of insulinoma[6] presented with typical symptoms of whipple's triad and weight gain. All patients had fasting blood sugar less than 45 gm% and average insulin level was 14 u/ml. All patients of gastrinoma presented with epigastric pain, vomiting and average serum gastrin level(fasting) was 800 pg/ml. 55% of the functional PNET were located in the tail of pancreas (5 insulinomas out of 9 functional PNET) and 55% of non-functional PNET in head of pancreas (34 out of 61). IHC positivity rate was 95% for chromogranin, 85% for synaptophysin and 82% for neuron- specific enolase (Figure2). Most of the functional PNET were operated by enucleation (55%), rest by distal pancreatectomy and pancreatico-duodenectomy. Whereas, 60% of nonfunctional PNET were operated by pancreatico-duodenectomy, rest by enucleation and distal pancreatectomy. Therefore, overall pancreatico-duodenectomy was the most common surgery done for PNET (50%) (Figure 3). Post operatively, 4 patients were reported to have wound infection, 3 had anastomotic leak and 2 had atelectasis (Figure 4).

Table 1: pTNM classification for endocrine tumors of the pancreas.[9,10]

T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Limited to the pancreas and size <2 cm
T2	Limited to the pancreas and size 2–4 cm
T3	Limited to the pancreas and size >4 cm or invading duodenum or bile duct
T4	Invading the wall of adjacent large vessels (celiac axis or superior mesenteric artery), stomach, spleen, colon, adrenal gland
N	Regional lymph nodes
NX	Regional lymph node status not assessed
N0	Absence of lymph node metastasis
N1	Presence of regional lymph node metastasis
M	Distant metastases
MX	Distant metastasis not assessed
M0	Absence of distant metastases
M1	Distant metastasis

The overall survival for operable patients with PNETs was found to be 100% for insulinomas (6 out of 6) and 94% for NFPNETs (14 out of 15). 1 out of 3 operated patients of gastrinoma expired due to extensive liver metastasis. The disease free survival at 5 yrs for the remaining patients was 100% for FPNETs and 94% for NFPNETs.

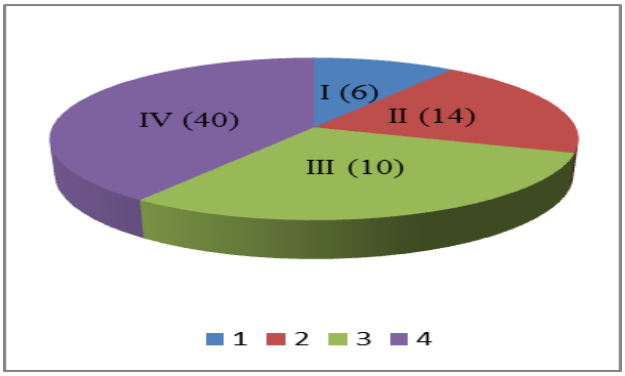

Figure 1: Stage distribution.

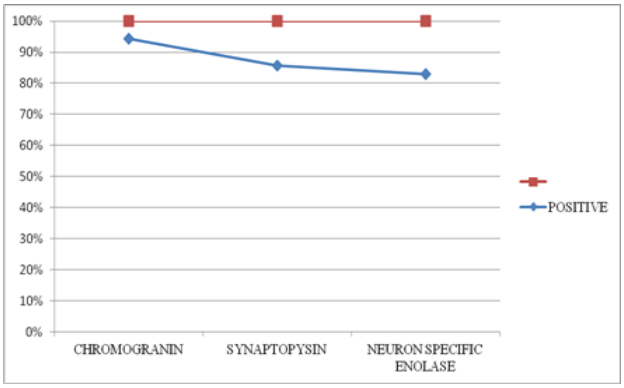

Figure 2: IHC positivity rate.

Table 2: Proposal for a pTNM classification and disease staging for endocrine tumors of the pancreas.[9]

Stage I	T1 N0 M0
Stage IIa	T2 N0 M0
Stage IIb	T3 N0 M0
Stage IIIa	T4 N0 M0
Stage IIIb	any T N1 M0
Stage IV	any T any N M1

DISCUSSION

PNET includes several entities that are divided on the basis of their symptomatology into functioning neoplasms (i.e., with hormonal syndromes such as insulinomas, gastrinomas, glucagonomas, or VIPomas) and non-functioning neoplasms (i.e., without hormonal syndromes). Most of the functioning and non-functioning PETs fall into the category of well-differentiated carcinomas, with the exception of insulinomas.

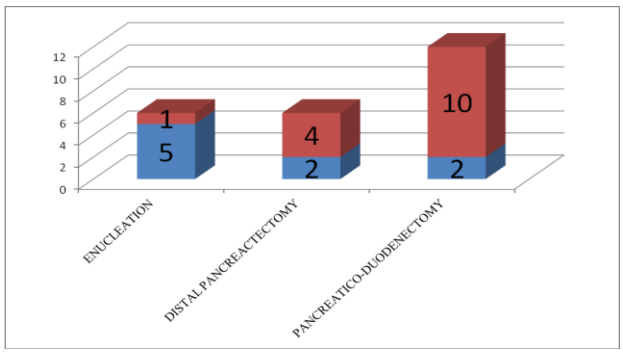

Figure 3: Surgery for pet.

Insulinoma

These tumors are located in the pancreas or are directly attached to it and present as solitary red brown, mostly soft, well-demarcated tumors with a size between 0.5 and 2 cm. Histologically, they show either solid or trabecular, gland-like tumor growth.[9,11,12] The tumor cells are usually bland, and cells with large, pleomorphic nuclei are rare. If they occur, they are not predictive of malignancy. A special finding in insulinomas is the deposition of amyloid that can be immunostained for amylin.[9,13] Immunohistochemically, they stain for insulin and proinsulin. In addition there may be cells expressing glucagon, somatostatin, pancreatic polypeptide or other hormones.[14] The vast majority of insulinomas are benign at the time of diagnosis. This may be due in part to their early detection, as they already become symptomatic at a small size (Figure 5A).[15] Malignant insulinomas occur in an older age group and are rare in children. Tumors producing a hypoglycaemic syndrome are usually larger than 1 cm; micro adenomas (below 0.5 cm in diameter) are functionally silent. Approximately 4–7% of patients with insulinomas suffer from MEN1.[16]

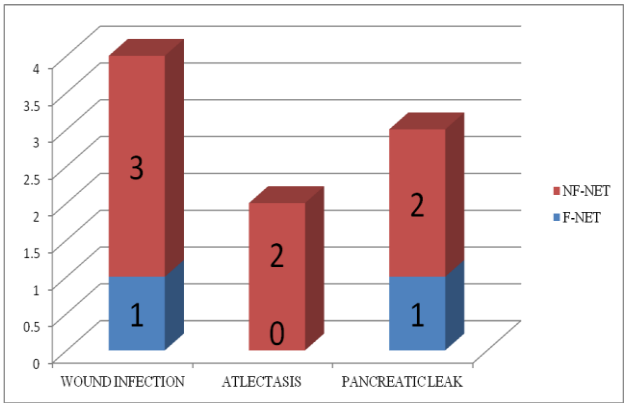

Figure 4: Post-op complications.

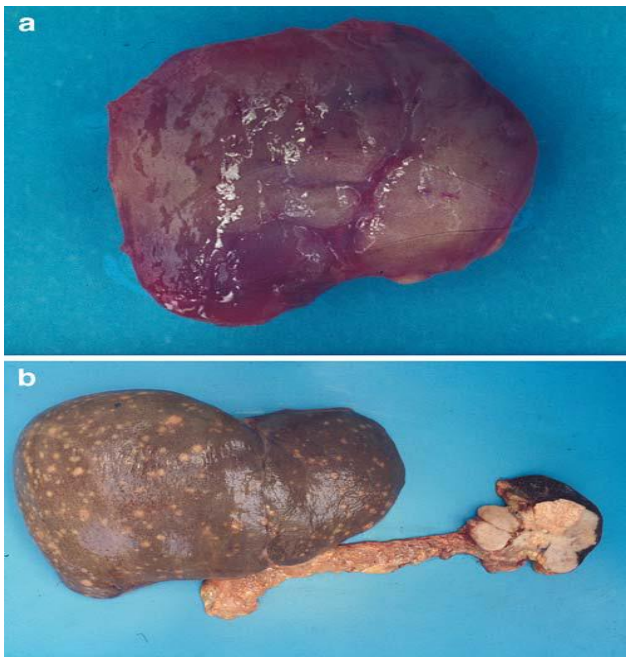

Figure 5: Pancreatic neuroendocrine tumors: A. tumor with a diameter less than 2 cm (insulinoma without metastases). B. large tumor (>2 cm) in the tail of the pancreas with multiple liver metastases (malignant insulinoma).

Gastrinoma

Pancreatic gastrinomas are less common than duodenal gastrinomas .They are associated with the sporadic form of ZES and only very rarely with the MEN1-associated form of ZES.[17] They are usually located in the pancreatic head, where they present as solitary tumors that usually have a diameter of more than 2 cm. The anatomical area comprising the head of the pancreas, the superior and ascending portion of the duodenum, and the relevant lymph nodes has been called the "gastrinoma triangle," as it harbors the vast majority of these tumors.[18] Histologically, they predominantly show a mixed trabecular and solid pattern with some pseudo glandular structures. Immunohistochemically, they are positive for gastrin but may also show some glucagon, somatostatin, or pancreatic polypeptide cells. The risk of liver metastases increases with tumor size. Metastases to other organs are rare. In general, the progression of gastrinomas is slow. Patients with complete tumor resection have 5- and 10-year survival rates of 90–100%, respectively.

Table 3: Proposal for the stratification of gastroenteropancreatic neuroendocrine tumours into three treatment groups based on growth features, TNM stages.[1]

Prognosis	Histological type	Grade	Stage	Potential treatment
Localized tumour				
Very low risk of metastasis	Well differentiated	G1	T1	Endoscopic resection
Low risk	Well differentiated	G1	T2	Surgery
Intermediate risk	Well differentiated	G2	T1	Surgery
High risk	Well differentiated	G1/2	T2	Surgery
High risk	Poorly differentiated	G3	T1/2/3	Surgery, a.t.
Nodal metastases				
Slow growth	Well differentiated	G1	T1/2/3 N1	Surgery
Intermediate growth	Well differentiated	G2	T1/2/3 N1	Surgery, a.t.
Fast growth	Poorly differentiated	G3	T1/2/3 N1	Surgery, a.t.
Nodal and haematogenous metastases				
Slow growth	Well differentiated	G1	Any T N1M1	Surgery, a.t.
Intermediate growth	Well differentiated	G2	Any T N1M1	Surgery, a.t.
Fast growth	Poorly differentiated	G3	Any T N1M1	Chemotherapy

a.t.: additional treatment, including biotherapy and/or chemotherapy.

Glucagonoma

These are NETs that produce glucagon and are associated with a syndrome consisting of skin rash (necrolytic migratory erythema), mild glucose intolerance, anaemia, weight loss, depression, diarrhoea, and a tendency to develop deep-vein thrombosis. They are usually large, solitary tumors with a diameter less than 7 cm commonly found in the tail of the pancreas. Extra pancreatic glucagonomas are rare. Histologically, they display a mixed trabecular and solid pattern, and immunohistochemically; they stain for glucagon or proglucagon-derived peptides. Approximately 60–70% of glucagonomas are metastatic at the time of diagnosis.[19] Malignant glucagonomas grow slowly and patients may survive for many years.

VIPoma

These are associated with the Verner–Morrison syndrome or WDHA syndrome- watery diarrhoea, hypokalaemia, hypochlorhydria, alkalosis, glucose intolerance, and anaemia. These symptoms are caused by inappropriate secretion of VIP and peptide histidine methionine (PHM). The tumors are usually located in the tail of pancreas. They are large and solitary tumors. Histologically, they show a solid or trabecular growth pattern. Immunohistochemically, they stain for VIP and PHM and also sometimes for pancreatic polypeptide and other hormones.[20] Most VIPomas present with metastasis in the regional lymph nodes and the liver at the time of diagnosis. The 5-year survival rate is about 59% for patients with metastases and 94% for those without metastases.[1]

Non-functioning PENs

These PENs are either incidental findings or become clinically apparent because of size, invasion of adjacent organs, or the occurrence of metastases. Historically, most of these tumors were large when detected and usually malignant. Large non-functioning PETs are found to occur most frequently in the head of the pancreas where they produce symptoms of cholestasis in this location. In general, the presenting symptoms are mostly non-specific and may consist of nausea, vomiting, or

diarrhoea. Immunohistochemically, these tumors stain for synaptophysin and chromogranin A and show a wide range of positivity for hormones including glucagon, somatostatin, and pancreatic polypeptide. The elevated hormone levels in the blood (e.g., glucagon, somatostatin, or pancreatic polypeptide) in some of these tumors reflect the hormonal immunoreactivity in the tumor.

Among the many therapeutic options for PNENs, surgery is the treatment of choice. A variety of surgical options are available to reduce load of tumor and improve survival. The extent of surgical resection depends on the tumor size and origin. Radiofrequency ablation or TACE is usually adopted to treat liver involvement. Besides surgery, other therapeutic options such as chemotherapy, biological therapy and targeted therapy can be used.

CONCLUSION

PETs are uncommon tumor of pancreatic origin with presentation more commonly in males than females, usually in the 5th decade. Approximately 75% of patients are advanced or metastatic at presentation Chromogranin > synaptophysin > NSE as tumor marker for PETs. Early stage (I, II), younger age, functional tumor are associated with good prognosis. In the absence of randomized control trial and prospective studies based on PNETs, we hope this case series will help to guide the management of NET pancreas.

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