Cancer Association of South Africa (CANSA)

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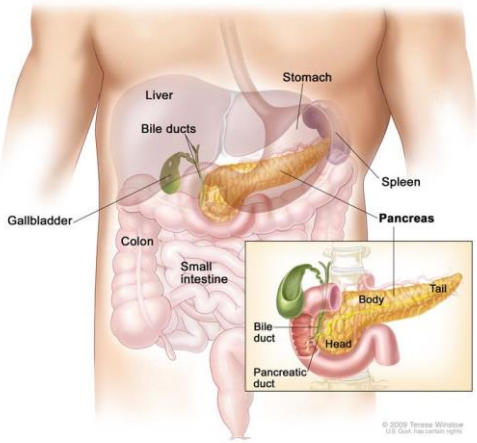
Fact Sheet on Pancreatic Neuroendocrine Tumours

Introduction

The pancreas is a gland about 15cm long that is shaped like a thin pear lying on its side. The wider end of the pancreas is called the head, the middle section is called the body, and the narrow end is called the tail. The pancreas is a soft, lobulated, retroperitoneal organ which lies behind the stomach and in front of lumbar vertebrae 1 & 2 of spine, It is connected to the duodenum (the first part of the small intestine) through a small tube called the pancreatic duct.



[Picture Credit: Pancreatic Neuroendocrine Tumours]

There are two kinds of cells in the pancreas:

- Endocrine pancreas cells make several kinds of hormones (chemicals that control the actions of certain cells or organs in the body), such as insulin to control blood sugar. They cluster together in many small groups (islets) throughout the pancreas. Endocrine pancreas cells are also called islet cells or islets of Langerhans. Tumours that form in islet cells are called islet cell tumours, pancreatic endocrine tumours, or pancreatic neuroendocrine tumours (pancreatic NETs).
- Exocrine pancreas cells make enzymes that are released into the small intestine to help the body digest food. Most of the pancreas is made of ducts with small sacs at the end of the ducts, which are lined with exocrine cells.

Neuroendocrine tumours (NETs) are neoplasms that arise from cells of the endocrine (hormonal) and nervous systems. Many are benign (non-cancerous), while some are malignant (cancerous). The tumours most commonly occur in the intestine, where they are often called carcinoid tumours, but they are also found in the pancreas, lung and the rest of the body.

Although there are many kinds of NETs, they are treated as a group of tissue because the cells of these neoplasms share common features, such as looking similar, having special secretory granules, and often producing biogenic amines and polypeptide hormones.

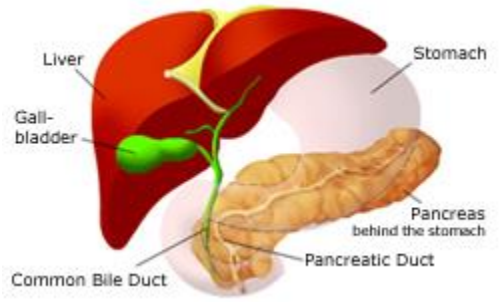
Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Diagnostic Radiographer; Dip Audiometry and Noise Measurement; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Pancreatic Neuroendocrine Tumours

Pancreatic neuroendocrine tumours (pancreatic NETs or PNETs) account for less than 5% of all pancreatic tumours. They may be benign or malignant and they tend to grow slower than exocrine tumours. They develop from the abnormal growth of endocrine (hormone-producing) cells in the pancreas called islet cells. They are sometimes referred to as “islet cell tumours”.

Some of the hormones which islet cells produce include insulin, glucagon and somatostatin. Pancreatic neuroendocrine tumours are either functional (produce hormones) or non-functional (produce no hormones).

Functional neuroendocrine tumours cause the pancreas to overproduce hormones consequently causing hormone-related symptoms. The majority of PNETs are non-functional tumours. Non-functional tumours do not produce any hormones so they do not cause any hormone-related symptoms. As a result, these tumours are typically diagnosed once the tumour is advanced and is causing symptoms such as pain or jaundice.



[Picture Credit: Pancreatic Tumours]

Endocrine tumours of the pancreas are rare tumours that include insulinomas, gastrinomas, VIPomas and non-functioning pancreatic endocrine tumours. Tumours that are small in size and usually benign – such as insulinomas – can frequently be excised through a laparoscopic approach.

Parbhu, S.K. & Adler, D.G. 2016.

“Pancreatic neuroendocrine tumors (PNETs) are neoplasms that arise from the hormone producing cells of the islets of Langerhans, also known as pancreatic islet cells. PNETs are considered a subgroup of neuroendocrine tumors, and have unique biology, natural history and clinical management. These tumors are classified as 'functional' or 'non-functional' depending on whether they release peptide hormones that produce specific hormone- related symptoms, usually in established patterns based on tumor subtype.”

Man, D., Wu, J., Shen, Z. & Zhu, X. 2018.

BACKGROUND: Neuroendocrine tumors (NETs) are a group of heterogeneous cancers arising from a variety of anatomic sites. Their incidence has increased in recent years. This study aimed to analyze the prognosis of NETs originating from different anatomic sites.

METHODS: We identified 73,782 patients diagnosed with NETs from the Surveillance Epidemiology and Ends Results (SEER) database from 1973 to 2014. Clinical data were compared between patients with different primary tumor sites using the chi-squared test. Differences in survival among NET patients with different tumor sites were compared by Kaplan-Meier analysis. Cox proportional hazard models were performed to identify the prognostic factors of overall survival.

RESULTS: In this cohort, the lung/bronchus was the most common site of NETs, accounting for 30.6%, followed by the small intestine (22.2%), rectum (16.2%), colon (13.4%), pancreas (10.8%), and stomach (6.8%). Totally, 73,782 patients were selected for this cohort from 1973 to 2014. The median survival duration was 41 months. The 1-, 3-, 5-, and 10-year overall survival rates for patients with NETs were 72.8%, 52.7%, 39.4%, and 18.1%, respectively. Patients with NETs located in the

rectum had the best prognosis, followed by those with NETs in the small intestine (HR, 1.660, 95% CI, 1.579, 1.744), lung/bronchus (HR, 1.786, 95% CI, 1.703, 1.874), stomach (HR, 1.865, 95% CI, 1.755, 1.982), and colon (HR, 1.896, 95% CI, 1.799, 1.999). Patients with NETs in the pancreas had the highest risk of mortality (HR, 2.034, 95% CI, 1.925, 2.148).
CONCLUSION: Significant differences in survival were found among various primary tumor sites. NETs in the rectum had the best prognosis, while those in the pancreas had the worst. Primary tumor sites might be one of the most useful outcome predictors in patients with NETs.

Incidence of Pancreatic Neuroendocrine Tumours in South Africa
The National Cancer Registry (2014) does not provide any information on the incidence of Pancreatic Neuroendocrine Tumours.

Signs and Symptoms of Pancreatic Neuroendocrine Tumours
When one has neuroendocrine tumours (NETs), one can get a lot of different symptoms, from shortness of breath to headaches to cramps in one's belly. Why the variety? It is all about location. The tumours can show up in lots of places, and where they are growing makes a big difference to how one feels.

The trouble with finding NETs is they often do not cause symptoms at first. Because some of these tumours can be so slow growing, they may actually not cause problems for a long time. If something grows slowly, the other tissues and cells around it have time to accommodate it.

Even if one does feel like something is not right, one might not connect it with NETs. The symptoms can be vague, so the tumour is often missed for a long time.

Pain of pancreatic origin in acute pancreatitis, chronic pancreatitis, and pancreatic cancer is felt in the epigastrium and bores into the back; it is aggravated when lying down and may be relieved by sitting and bending forwards. Transmitted aortic pulsations can be seen and felt in pancreatic masses (tumours and cysts) as the pancreas lies on the aorta.

Diagnosis of Pancreatic Neuroendocrine Tumours
Because the recognition of hormonal hypersecretion syndrome requires considerable clinical experience and the symptoms of non-functioning PNETs are nonspecific, the diagnosis of PNET is often delayed. Endocrine testing, imaging, and histological evidence are all required to accurately diagnose PNETs. A complete diagnosis should establish the PNET nature, assess the tumour grade, identify the primary and metastatic loci, and determine whether the tumour is functioning. If hormonal hypersecretion syndrome is suspected, appropriate biochemical testing is performed to determine hormonal hypersecretion and followed by imaging, endoscopy, and biopsy.

Fasting levels of pancreatic polypeptide (PP), gastrin, proinsulin, insulin, glucagon, and vasoactive intestinal peptide (VIP) are worth measuring because they are the hormones most frequently produced by functioning PNETs. False positive results are common, especially for CGA, because it is often elevated in patients taking anti-acids or in those with atrophic gastritis.

Anatomical computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis is important to evaluate the pancreatic, liver, lymph node, and peritoneal metastases. Nuclear imaging with octreotide should be performed at least once to determine if the tumours have a high affinity for somatostatin and if there are occult tumours not detected by anatomical imaging.

FDG-PET is not usually indicated because most PNETs are negative; however, FDG-PET can ascertain the overall tumour burden in high-grade PNETs. Recently, PET with gallium 68–labelled octreotide has been demonstrated to be extremely sensitive at detecting small and extra-hepatic PNET metastases but is not widely available.

Liver masses are typically biopsied transcutaneously with ultrasound or CT guidance, and pancreatic masses are biopsied with endoscopic ultrasound guidance. Tumour biopsy is critical for PNET diagnosis, not only to demonstrate the neuroendocrine nature of the tumour but also to preliminarily grade the tumour and to perform immunocytochemical staining for hormones and islet markers, which is useful for determining the pancreatic origin of liver metastases. Currently, the best predictor of PNET behaviour is tumour grade; therefore, the cytologic examination of the biopsied tumour sample should classify the tumour as a well-differentiated endocrine tumour (low grade of malignancy), a well-differentiated endocrine carcinoma (intermediate grade), or a poorly differentiated endocrine carcinoma (high grade).
(Ro, *et al.* 2013).

Singhi, A.D. & Klimstra, D.S. 2018.
"With increasing accessibility and advancements in abdominal imaging modalities, the incidence of pancreatic neuroendocrine neoplasms has increased steadily during the past few decades. By definition, neuroendocrine neoplasms of the pancreas show neuroendocrinedifferentiation, but they represent a broad and heterogeneous group of neoplasms with diverse clinical and pathological characteristics. The majority of pancreatic neuroendocrine neoplasms can be classified as well-differentiated pancreatic neuroendocrine tumours (PanNETs) or poorly differentiated pancreatic neuroendocrine carcinomas (PanNECs). While PanNETs and PanNECs are distinct entities with respect to clinical presentation, outcome and therapeutic approach, they may exhibit overlapping histopathological features. Moreover, the frequent modifications in nomenclature and prognostic grading systems over the years of not only pancreatic neuroendocrine neoplasms, but neuroendocrine neoplasms from other organ sites, has created confusion for both pathologists and clinicians as to the appropriate use of terminology and grading when evaluating these neoplasms. This review examines the current concepts and issues of nomenclature and grading of PanNETs and PanNECs. In addition, considering the morphological overlap between high-grade (G3) PanNETs and PanNECs, we discuss an integrative and practical diagnostic approach to aid in discriminating challenging cases."

Sun, H., Zhou, J., Liu, K., Shen, T., Wang, X. & Wang, X, 2018.
PURPOSE: Predictive factors of lymph node metastasis (LNM) in pancreatic neuroendocrine tumors (pNETs) are not well established. We sought to identify the value of MR imaging features in preoperatively predicting the lymph node metastasis of pNETs.
MATERIALS AND METHODS: In this study, we enrolled 108 consecutive patients with pNETs between January 2009 and June 2018. MR morphologic features and quantitative data were evaluated. Predictors of LNM were evaluated using univariate and multivariate logistic regression models.

RESULTS: A total of 108 patients with pNETs were finally enrolled, including 82 LNM-negative and 26 LNM-positive patients. Features significantly related to the LNM of pNETs at univariate analysis were tumor size > 2 cm (P = 0.003), Ki-67 > 5% (P = 0.002), non-enhancement pattern (P < 0.001), apparent diffusion coefficient value (P < 0.001), main pancreatic duct dilation (P < 0.001) and pancreatic atrophy (P = 0.032) and extrapancreatic tumor spread (P = 0.001), CNRs during arterial, portal and delay phase (P = 0.005, 0.047, and 0.045, respectively), and histological classification (P = 0.006). At multivariate analysis, non-enhancement pattern (P = 0.019; odds ratio, 6.652; 95% CI 1.369, 32.321) and main pancreatic duct dilation (P = 0.018; odds ratio, 6.745; 95% CI 1.379, 32.991) were independent risk factors for predicting the LNM of pNETs.
CONCLUSION: The non-enhancement characteristic and main pancreatic duct dilation appear to be linked with LNM in pNETs. These radiological predictors can be easily obtained preoperatively, and may help to avoid missing pNETs with a high risk of LNM.

Grading and Staging of Pancreatic Neuroendocrine Tumours
When a doctor plans to treat a neuroendocrine tumour (NET), a key part of the strategy is figuring out whether the NET is advanced or just starting. To do that, he/she needs to understand two important words: stage and grade. The stage tells whether the disease has spread from its original spot, and where in the body it has moved to. The grade describes how it looks under a microscope compared to normal cells. That is important because it can show whether it is likely to spread slowly or quickly.

Pancreatic NETs - the stages for this type are the same as the ones for pancreatic cancer. It is based on where the tumour is located.

Treatment of Neuroendocrine Tumours and Pancreatic Neuroendocrine Tumours
In caring for a person with a tumour, different types of doctors often work together to create a patient's overall treatment plan that combines different types of treatments. This is called a multidisciplinary approach. Cancer care teams also include a variety of other health care professionals, including physician assistants, oncology nurses, social workers, pharmacists, counsellors, dietitians, and others.

Descriptions of the most common treatment options for a neuroendocrine tumour are listed below. Treatment options and recommendations depend on several factors, including:

- The type of neuroendocrine tumour
- If it is cancerous and the stage
- Possible side effects
- The patient's preferences and overall health

The prognosis of these neuroendocrine tumours is often much better than for pancreatic adenocarcinoma with good cure rates depending on the type of tumour. There is an association of neuroendocrine tumours with genetic mutations which can cause several members of the same family to have these types of tumours.

The rarity of these tumours makes the care of these patients challenging and a multidisciplinary approach by experts in the field is important for patients to obtain the best care and treatment

possible. The Multidisciplinary Endocrine Tumour Program is composed of endocrinologists, endocrine surgeons, radiologists, nuclear medicine specialists and oncologists who specialise in the diagnosis and treatment of these rare pancreatic endocrine tumours.

Types of pancreatic neuroendocrine tumours:

Insulinoma - insulin is produced by beta cells which are organised into islands of cells in the pancreas. The primary function of insulin is to regulate the metabolism and storage of sugar in the body. Insulinomas are neuroendocrine tumours which produce insulin and are the most common type of functional neuroendocrine tumours. As these tumours grow they produce large amounts of insulin which can cause low blood sugar. When the blood sugar gets too low patients can experience symptoms which include dizziness, confusion, abnormal behaviour and even loss of consciousness. Several tests are required to confirm the diagnosis of an insulinoma because there are several other reasons for low blood sugar. Once the diagnosis is confirmed with blood tests, imaging studies such as CT scan or ultrasound are used to localise the tumour. The primary treatment is surgical removal of the insulinoma which provides excellent cure rates.

Gastrinoma - a gastrinoma is a neuroendocrine tumour which produces the hormone gastrin. The function of gastrin is to stimulate the stomach to produce acid to aid in the digestion of food. Normally when there is enough acid in the stomach to digest a meal the production of gastrin is turned down and the stomach acid level slowly returns to a level needed for an empty stomach. Gastrinomas continuously produce gastrin which leads to very high levels of stomach acid which can then lead to ulcer formation in the stomach and small intestine (also called Zollinger-Ellison Syndrome). Patients may complain of abdominal pain from these ulcers which may improve with antacid medications. Blood tests to measure the level of gastrin can be falsely elevated if patients are taking antacid medications during the test and these should be discontinued prior to testing. After the diagnosis of gastrinoma is confirmed with blood tests, imaging studies including CT scan and ultrasound can help to localise the tumour prior to surgical removal.

Glucagonoma - the alpha cells of the pancreas produce the hormone glucagon which acts to counter the effects of insulin. Normally when a person has not eaten for several hours, the blood sugar drops and glucagon is released. This causes breakdown of sugar stored in the form of glucagon which quickly brings the blood sugar back up to normal. Glucagonomas continuously produce glucagon which can cause continuously elevated blood sugar and symptoms typically seen with diabetes. Surgical removal of the tumour is the primary treatment after imaging studies are completed.

VIPoma - Vasoactive Intestinal Polypeptide (VIP) is a hormone produced in the pancreas and in other locations throughout the body. Neuroendocrine tumours called VIPomas will cause symptoms including profuse watery diarrhoea, dehydration and electrolyte disturbances. These tumours are extremely rare and blood tests and imaging studies are needed to confirm the diagnosis. Patients are treated with medication to decrease symptoms and often require intravenous fluid to treat dehydration before proceeding to surgery.

Non-functional neuroendocrine tumours - some tumours that arise from endocrine cells of the pancreas do not produce hormones and, therefore, do not produce any of the symptoms which are

described above. These types of tumours are often detected incidentally on CT scan or other imaging studies obtained to work-up another medical problem. Some of these tumours may grow quite large and cause upper abdominal discomfort as they compress surrounding structures. The challenge in the diagnosis of these types of tumours is to distinguish them from pancreatic adenocarcinoma which has a worse prognosis. Surgery is the primary treatment for non-functional neuroendocrine tumours after blood tests and imaging studies are complete.

Zandee, W.T., Brabander, R., Blaževic, A., Kam, B.L.R., Teunissen, J.J.M., Feelders, R.A., Hofland, J. & de Herder, W.W. 2018.

PURPOSE: Peptide receptor radionuclide therapy (PRRT) with the radiolabeled somatostatin analogue [Lutetium-177-DOTA0-Tyr3]octreotate (177Lu-DOTATATE) is widely applied for inoperable metastatic small intestinal and non-functioning pancreatic neuroendocrine tumors(pNETs). The aim of this study is to describe the safety and efficacy of the treatment of functioning pNETs.

METHODS: Patients were treated with up to four cycles of 177Lu-DOTATATE with an intended dose of 7.4 Gbq per cycle. Radiological (RECIST 1.1), symptomatic and biochemical response were analyzed retrospectively for all patients with a functioning pNET (insulinoma, gastrinoma, VIPoma and glucagonoma) treated with 177Lu-DOTATATE. Quality of life (QOL) was assessed with the EORTC QLQ-C30 questionnaire.

RESULTS: Thirty-four patients with a metastatic functioning pNET (ENETS grade 1 or 2) were included: 14 insulinomas, 5 VIPomas, 7 gastrinomas and 8 glucagonomas. Subacute hematological toxicity, grade 3 or 4 occurred in 4 patients (12%) and a hormonal crisis in 3 patients (9%). PRRT resulted in partial or complete response in 59% of patients and the disease control rate was 78% in patients with baseline progression. 71% of patients with uncontrolled symptoms had a reduction of symptoms and a more than 80% decrease of circulating hormone levels was measured during follow-up. After PRRT, median progression-free survival was 18.1 months (IQR: 3.3-35.7) with a concurrent increase in QOL.

CONCLUSION: Treatment with 177Lu-DOTATATE is a safe and effective therapy resulting in radiological, symptomatic and biochemical response in a high percentage of patients with metastatic functioning pNETs. Hormonal crises occur relatively frequent and preventive therapy should be considered before and/or during PRRT.

Ramage, J., Naraev, B.G. & Halfdanarson, T.R. 018.

"^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) is now approved for patients with advanced gastroenteropancreatic neuroendocrine tumors (NET), and it is therefore important to understand the efficacy and safety of PRRT in this patient population. PRRT efficacy and safety outcomes have frequently been summarized for patient populations with gastroenteropancreatic NET, but not specifically in patients with pancreatic NET (panNET). The pivotal phase 3 trial of ^{177}Lu-DOTATATE PRRT in NET was restricted to patients with a midgut primary site. No phase 3 trial data on PRRT treatment outcomes are currently available for the panNET patient population. This review presents the available evidence for panNET treatment outcomes with PRRT and demonstrates that the available data favor PRRT as a modality for this NET primary site. However, several other therapies for advanced panNET are currently available, and the sequencing and combination of PRRT with these other therapies is set to become the big challenge for the future of panNET management. Patient, tumor, and logistical factors (tumor burden, expression of somatostatin receptors, availability of PRRT, patient preferences, and concerns over long-term toxicity) need to be taken into consideration when selecting therapy."

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The *South African National Clinical Trials Register* provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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