Cancer Association of South Africa (CANSA)

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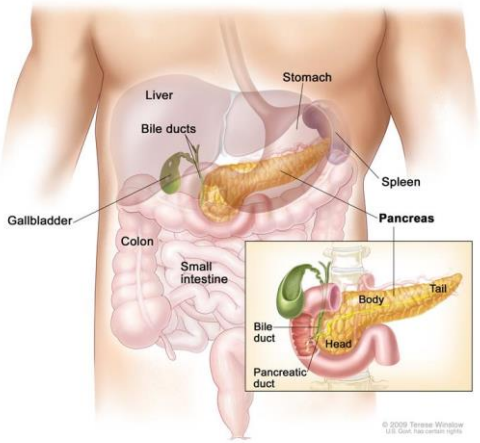
Fact Sheet on Pancreatic Neuroendocrine Tumours

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.

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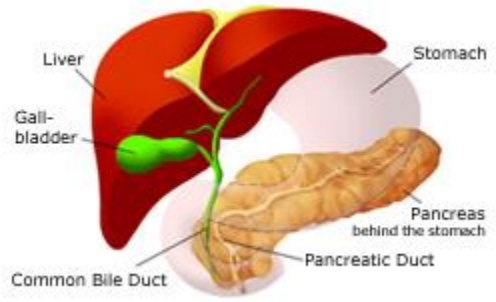
Pancreatic Neuroendocrine Tumours

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.

Ma, Z.Y., Gong, Y.F., Zhuang, H.K., Zhou, Z.X., Huang, S.Z., Zou, Y.P., Huang, B.W., Sun, Z.H., Zhang, C.Z., Tang, Y.Q., Hou, B.H. 2020.
"Pancreatic neuroendocrine tumors (pNETs) are a heterogeneous group of tumors with complicated treatment options that depend on pathological grading, clinical staging, and presence of symptoms related to hormonal secretion. With regard to diagnosis, remarkable advances have been made: Chromogranin A is recommended as a general marker for pNETs. But other new biomarker modalities, like circulating tumor cells, multiple transcript analysis, microRNA profile, and cytokines, should be clarified in future investigations before clinical application. Therefore, the currently available serum biomarkers are insufficient for diagnosis, but reasonably acceptable in evaluating the prognosis of and response to treatments during follow-up of pNETs. Surgical resection is still the only curative therapeutic option for localized pNETs. However, a debulking operation has also been proven to be effective for controlling the disease. As for drug therapy, steroids and somatostatin analogues are the first-line therapy for those with positive expression of somatostatin receptor, while everolimus and sunitinib represent important progress for the treatment of patients with advanced pNETs. Great progress has been achieved in the combination of systematic therapy with local control treatments. The optimal timing of local control intervention, planning of sequential therapies, and implementation of multidisciplinary care remain pending."

Scott, A.T. & Howe, J.R. 2019. Pancreatic neuroendocrine tumors are a diverse group of neoplasms with a generally favorable prognosis. Although they exhibit indolent growth, metastases are seen in roughly 60% of patients. Pancreatic neuroendocrine tumors may produce a wide variety of hormones, which are associated with dramatic symptoms, but the majority are nonfunctional. The diagnosis and treatment of these tumors is a multidisciplinary effort, and management guidelines continue to evolve.

Incidence of Pancreatic Neuroendocrine Tumours in South Africa

The National Cancer Registry (2017), known for under reporting, does not provide any information on the incidence of Pancreatic Neuroendocrine Tumours.

According to the outdated National Cancer Registry (2017), known for under reporting, the following number of pancreatic cancer cases was histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	231	1:627	0,58%
Asian males	7	1:921	0,72%
Black males	54	1:1 785	0,41%
Coloured males	29	1:460	0,60%
White males	141	1:224	0,67%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	219	1:937	0,53%
Asian females	13	1:608	1,01%
Black females	59	1:2 689	0,32%
Coloured females	37	1:544	0,81%
White females	110	1:323	0,55%

The frequency of histologically diagnosed cases of pancreatic cancer in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	0	0	3	15	55	81	52	9
Asian males	0	0	0	2	1	4	0	0
Black males	0	1	3	9	14	17	9	0
Coloured males	0	0	1	4	6	14	4	0
White males	0	0	2	11	24	46	39	9

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	0	1	5	20	65	72	39	17
Asian females	0	0	0	1	5	3	3	1
Black females	0	1	2	8	25	16	4	3
Coloured females	0	0	2	3	10	13	7	2
White females	0	0	1	8	25	40	25	11

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

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).

Calabrò D, Argalia G, Ambrosini V. 2020.

"Pancreatic neuroendocrine neoplasms (panNENs) are heterogeneous neoplasms with neuroendocrine differentiation that show peculiar clinical and histomorphological features, with variable prognosis. In recent years, advances in knowledge regarding the pathophysiology and heterogeneous clinical presentation, as well as the availability of different diagnostic procedures for panNEN diagnosis and novel therapeutic options for patient clinical management, has led to the recognition of the need for an active multidisciplinary discussion for optimal patient care. Molecular imaging with positron emission tomography/computed tomography (PET/CT) has become indispensable for the management of panNENs. Several PET radiopharmaceuticals can be used to characterize either panNEN receptor expression or metabolism. The aim of this review is to offer an overview of all the currently used radiopharmaceuticals and of the new upcoming tracers for pancreatic neuroendocrine tumors (panNETs), and their clinical impact on therapy management. [^{68}Ga]Ga-DOTA-peptide PET/CT (SSA-PET/CT) has high sensitivity, specificity, and accuracy and is recommended for the staging and restaging of any non-insulinoma well-differentiated panNEN cases to carry out detection of unknown primary tumor sites or early relapse and for evaluation of in vivo somatostatin receptors expression (SRE) to select patient candidates for peptide receptor radiometabolic treatment (PRRT) with ^{90}Y or ^{177}Lu and/or cold analogs. SSA-PET/CT also has a strong impact on clinical management, leading to a change in treatment in approximately a third of the cases. Its role for treatment response assessment is still under debate due to the lack of standardized criteria, even though some semiquantitative parameters seem to be able to predict response. [^{18}F]FDG PET/CT generally shows low sensitivity in small growing and well-differentiated neuroendocrine tumors (NET; G1 and G2), while it is of utmost importance in the evaluation and management of high-grade NENs and also provides important prognostic information. When positive, [^{18}F]FDG PET/CT impacts therapeutical management, indicating the need for a more aggressive treatment regime. Although FDG positivity does not exclude the patient from PRRT, several studies have demonstrated that it is certainly useful to predict response, even in this setting. The role of [^{18}F]FDOPA for the study of panNET is limited by physiological uptake in the pancreas and is therefore not recommended. Moreover, it provides no information on SRE that has crucial clinical management relevance. Early acquisition of the abdomen and premedication with carbidopa may be useful to increase the accuracy, but further studies are needed to clarify its utility. GLP-1R agonists, such as exendin-4, are particularly useful for benign insulinoma detection, but their accuracy decreases in the case of malignant insulinomas. Being a whole-body imaging technique, exendin-PET/CT gives important preoperative information on tumor size and localization, which is fundamental for surgical planning as resection (enucleation of the lesion or partial pancreatic resection) is the only curative treatment. New upcoming tracers are under study, such as promising SSTR antagonists, which show a favorable biodistribution and higher tumor-to-background ratio that increases tumor detection, especially in the liver. [^{68}Ga]pentixafor, an in vivo marker of CXCR4 expression associated with the behavior of more aggressive tumors, seems to only play a limited role in detecting well-differentiated NET since there is an inverse expression of SSTR2 and CXCR4 in G1 to G3 NETs with an elevation in CXCR4 and a decrease in SSTR2 expression with increasing grade. Other tracers, such as [^{68}Ga]Ga-PSMA, [^{68}Ga]Ga-DATA-TOC, [^{18}F]SiTATE, and [^{18}F]AlF-OC, are also under investigation."

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.

Johnstone 2nd, M.E., Carter, M.M., Wilson, G.C., Ahmad, S.A. & Patel, S.H. 2020.
"Pancreatic neuroendocrine tumors (PanNETs) are the second most common malignancy of the pancreas, and their incidence is increasing. PanNETs are a diverse group of diseases which range from benign to malignant, can be sporadic or associated with genetic mutations, and be functional or nonfunctional. In as much, the treatment and management of PanNETs can vary from a "Wait and See" approach to orthotopic liver transplantation (OLT). Despite this, surgical resection is still the primary treatment modality to achieve cure. This review focuses on the surgical management of PanNETs."

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/

Medical Disclaimer

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