NeuroEndocrine Cancer Australia

About NETS

Brain
Thyroid
Skin
Lungs
Liver, Spleen
Gallbladder, Stomach
Kidney, Pancreas
Small Bowel
Large Bowel
Appendix, Ovary
Rectum

What are NETs?

NETs are tumours that usually develop in the digestive or respiratory tracts, but can occur in other areas of the body. These tumours arise from cells called neuroendocrine cells. Neuroendocrine cells create, store and secrete proteins hormones for normal body functions.

NETs develop when these neuroendocrine cells undergo changes, causing them to divide uncontrollably and grow into a mass (called a tumour).

Neuroendocrine tumours can be very slow-growing or can be more aggressive. While they were once thought to be non-cancerous (benign), we now know that these tumours can be cancerous.

While these tumours are may be simply called neuroendocrine tumours (or NETs), the location of the tumour may be added to the name: for example, lung NET, bowel NET or pancreatic NET.

How common are NETs?

Previously considered to be rare, NETs are increasing in incidence in Australia (7 people per 100,000 / per year). This is about the same as testicular cancer, cervical cancer, multiple myeloma, Hodgkin lymphoma and cancers of the central nervous system.

People with some genetic conditions such as multiple endocrine neoplasia (MEN), Von Hippel–Lindau (VHL) disease and neurofibromatosis (NF) have an increased risk of developing NETs.

Gastroenteropancreatic NETs (GEP-NETs)

Gastric NETs (NETs of the Stomach)

There are four types of gastric NET:

- Type I is the most common. These are associated with atrophic gastritis and an overproduction of gastrin (hypergastrinaemia). These are small polyps (less than 1–2 cm) that are sometimes found during a gastroscopy. These polyps may not be cancerous, but they may recur. They can be removed and a regular follow-up plan put in place. Long-term use of proton pump inhibitors (anti-acid medications) for gastric reflux or dyspepsia may increase risk of this type of NETs.
- Type II: These are uncommon and may occur as part of an inherited condition known as multiple endocrine neoplasia type 1 (MEN 1): when excessive secretion of the hormone gastrin by a tumour (gastrinoma) causes over-production of stomach acid. This is known as Zollinger–Ellison syndrome. These tumours in the stomach are often small and are often simply monitored with endoscopic ultrasound.
- Type III: These uncommon tumours are often larger (>2 cm) and can spread to other parts of the body (metastasise). They need to be surgically removed.
- Type IV is a very rare type of gastric NET and is the most difficult to treat. Tumours are often large and may have spread (metastasised) at diagnosis.

Duodenal NETS

- Duodenal NETs produce many hormones and peptides such as serotonin, calcitonin and gastrin somatostatin. Patients may present with ‘carcinoid syndrome’, pain in the abdomen or fatigue due to anaemia.

Small bowel NETs

- Jejunum and ileum NETs are often slow-growing and small and cause no symptoms. This can make them difficult to diagnose in the early stages. Often, when the diagnosis is made, the tumour is larger and may have metastasised. The person may have pain in the abdomen, a bowel obstruction or carcinoid syndrome.

Large bowel NETs

- Colon NETs are rare, can be large, aggressive, and have the potential to spread and cause bowel obstructions and bleeding. If the NET has spread to the liver, the person may have symptoms like wheezing, facial flushing and watery diarrhoea.

Appendiceal NETS

- Appendiceal NETs are often found during surgery for appendicitis. If the tumours are less than 1 cm in size, further surgery is often not required.
- Goblet cell carcinomas have 'goblet' shaped cells when viewed under a microscope. They may be found when the person seeks treatment for acute appendicitis, pain in the abdomen or a mass in the abdomen. Women with this type of NETs may also have metastases on the ovary.

Rectal NETs

These NETs are often found 'by accident' such as during an endoscopy. Patients may present with symptoms such as rectal bleeding or change in bowel habit, but often have no symptoms. If it doesn't cause symptoms, the cancer may spread before it is found.

"Googling tumours on the pancreas and liver was not at all what anyone wants to read about, so I didn't."

(Katie, age 41, Sydney)

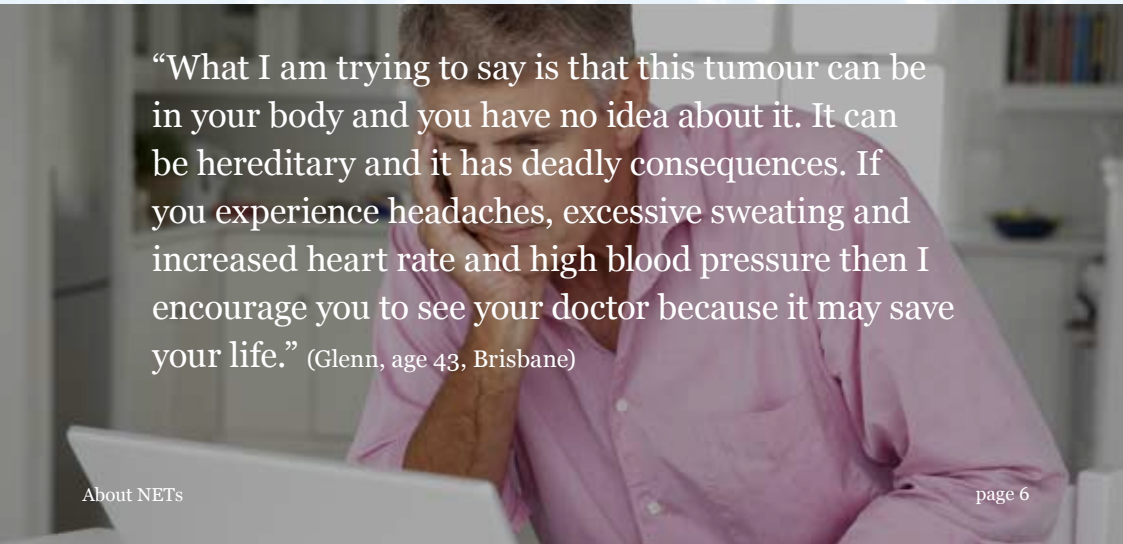
Pancreatic NETs (pNETs): functioning and non-functioning

Pancreatic NETs are divided into two groups: functioning and non-functioning.

Functioning pNETs produce symptoms due to excessive hormone production:

- Insulinomas are tumours that secrete insulin causing low blood sugar and symptoms such as disorientation, confusion, sweating, trembling and heart palpitations.
- Gastrinoma are tumours that secrete gastrin, which stimulates the stomach to produce too much acid, causing symptoms such as dyspepsia, stomach ulcers, nausea, diarrhoea and weight loss.
- Glucagonoma are tumours that secrete glucagon, which raises blood sugar (hyperglycaemia). This can cause fatigue, frequent urination, dry mouth, nausea, blurred vision, weight loss, anaemia and depression. These tumours can cause a red rash (migratory erythema) in the groin.
- Somatostatinoma are tumours that secrete somatostatin, which causes symptoms of diabetes, diarrhoea, steatorrhoea (fatty pale bowel motions) and weight loss.
- VIPoma are tumours that secrete vasoactive intestinal peptide, which causes severe watery diarrhoea, which may lead to electrolyte imbalances in the blood such as low potassium (hypokalaemia) and low chloride (hypochorhydria), weakness and fatigue.

The **non-functioning pNETs** may also produce ineffective hormones and peptides which don't cause physical effects. As a result, patients often present late when symptoms such as abdomen or back pain have occurred due to the growing tumour.



"What I am trying to say is that this tumour can be in your body and you have no idea about it. It can be hereditary and it has deadly consequences. If you experience headaches, excessive sweating and increased heart rate and high blood pressure then I encourage you to see your doctor because it may save your life." (Glenn, age 43, Brisbane)

Bronchopulmonary (lung) NETs

About one in four NETs start in the lung. These can cause recurrent pneumonia from airway obstruction, chest pain on breathing, coughing blood (haemoptysis) and shortness of breath or wheezing.

Patients with MEN1 have an increased risk of developing bronchopulmonary NETS.

There are four types of NETs of the lungs:

1. Typical carcinoid (TC)
2. Atypical carcinoid (AC)
3. Large cell neuroendocrine carcinoma (LCNEC)
4. Small cell lung cancer (SCLC)

The typical carcinoid types are the most common to occur. These NETs can be more aggressive (grow quickly) than the other listed types of NETs. Lung NETs can affect people of all ages.

Some bronchial NETs produce groups of symptoms (syndromes) related to hormone overproduction: carcinoid syndrome (serotonin), Cushing syndrome (ACTH) and acromegaly (growth hormone).

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare disorder and can occur before lung NETs.

Thymic NETs

NETs of the thymus are uncommon. Most don't cause symptoms until they have grown big enough to press on structures in the chest (trachea, large veins). Thymic NETs can be aggressive. Treatment includes surgical removal and chemotherapy. A very small number of patients with MEN1 can develop thymic NETs.

Testicular NETs

Testicular NETs are rare. There may be a painless mass in the scrotum. These NETs do not usually produce symptoms of carcinoid syndrome. Removal with surgery (orchidectomy) is currently considered the best treatment.

Prostate NETs

Primary Prostate NETs are also rare and account for less than 5% of prostate cancers. More frequently, small sections of neuroendocrine carcinoma occur within the far more common adenocarcinoma form. Treatment options for prostate cancer are active surveillance; Radical prostatectomy, External beam radiotherapy, Brachytherapy (internal radiotherapy); and Hormonal therapy.

Ovarian and endometrial NETs

NETs of the ovary and endometrium are rare. Most are found late, after they have spread. Patients can present with symptoms related to carcinoid syndrome and carcinoid heart disease.

Multiple endocrine neoplasia (MEN syndrome)

In Multiple Endocrine Neoplasia (MEN) there are tumours in two or more of the endocrine glands. There are four major forms of MEN. They may be inherited (autosomal dominant) or sporadic.

- **MEN 1:** Most people with MEN 1 develop parathyroid tumours (hyperparathyroidism; others develop pancreatic NETs or tumours in the pituitary gland. Other MEN 1 tumours include adrenocortical tumours, thymic NETs and gastric NETs. Patients and their families are advised to have genetic testing (MEN1 gene).
- **MEN 2** is a rare genetic (RET gene) syndrome that has three categories: 2A, MEN2B and medullary thyroid carcinoma (MTC).
  - MEN2A is characterised by the development of medullary thyroid carcinoma (MTC), pheochromocytoma and parathyroid adenomas.
  - MEN 2B patients develop MTC earlier in life, develop pheochromoctyomas and neuromas of the skin and intestine. It is an aggressive from of MEN.
  - Familial medullary thyroid carcinoma (MTC) does not have the other tumours that are associated with MEN 2.

Pheochromocytoma

Pheochromocytomas (PH) are rare NETs which start in the adrenal glands on top of the kidneys. Most produce excessive amounts of hormones resulting in symptoms such as:

- high blood pressure and rapid heart rate (palpitations)
- sweating
- severe headaches
- anxiety and feelings of rapid heart rate
- loss of weight

The remainder have no symptoms and are often undiagnosed for many years.

They mostly affect adults however can also affect children and adolescents.

Paraganglioma

Paraganglia are groups of cells found near nerve cell bundles called ganglia. These ganglia are located in the head, neck, thorax, abdomen or pelvis and are classified as either parasympathetic or sympathetic, depending on which nerves they are associated with. A tumour involving the paraganglia is known as a paraganglioma.

- Parasympathetic paragangliomas are mainly found in the head and neck, usually do not secrete hormones and rarely metastasize.
- Sympathetic paraganglioma are found in the thorax, abdomen and pelvis, secrete hormones such as adrenaline or noradrenaline, and metastasize in one in five cases.

More than a third of patients with paraganglioma have inherited mutations.

The main treatment modalities are surgery, embolization, radiation therapy and stereotactic radiosurgery. People with these NETs may also be offered chemotherapy and peptide receptor radionuclide therapy (PRRT).

Medullary thyroid carcinoma

Medullary thyroid cancer (MTC) is a rare form of cancer of the thyroid gland in the neck.

Adrenocortical carcinoma (ACC)

Often known simply as adrenal cancer, this NET affects one to two people per million per year, which means it is very rare. ACC occurs in the outer part (cortex) of the adrenal gland. In adults, it most commonly occurs in middle age.

The disease may be less aggressive in children, who have different treatment from adults.

Neuroblastoma

Neuroblastoma most commonly starts in one of the adrenal glands, but can also develop in nerve tissues in the neck, chest, abdomen or pelvis. It mostly affects children, usually under the age of five.

Merkel cell carcinoma (neuroendocrine tumour of the skin)

Merkel cell carcinoma (MCC) is a rare but aggressive skin cancer. The first symptom may be a solid purple nodule in the skin, especially in sun-exposed skin areas (e.g. head and neck). Risk factors for the disease are sun exposure, old age, previous cancers and the Merkel cell polyoma virus.

Surgery and radiotherapy are commonly used to treat these NETs. Immunotherapy has come to the fore in recent years with several major trials and gained approval in some countries.

"Something changed in the way I approached my MEN 1 diagnosis as time has gone on. I decided that I was not going to be defined by this condition. It is a small part of me; I am NOT part of it."

(Michelle, age 54, Brisbane)

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