Unicorn Foundation

Seeking the cure for Neuroendocrine Cancers

Neuroendocrine tumours:

A guide for patients

unicornfoundation.org.au

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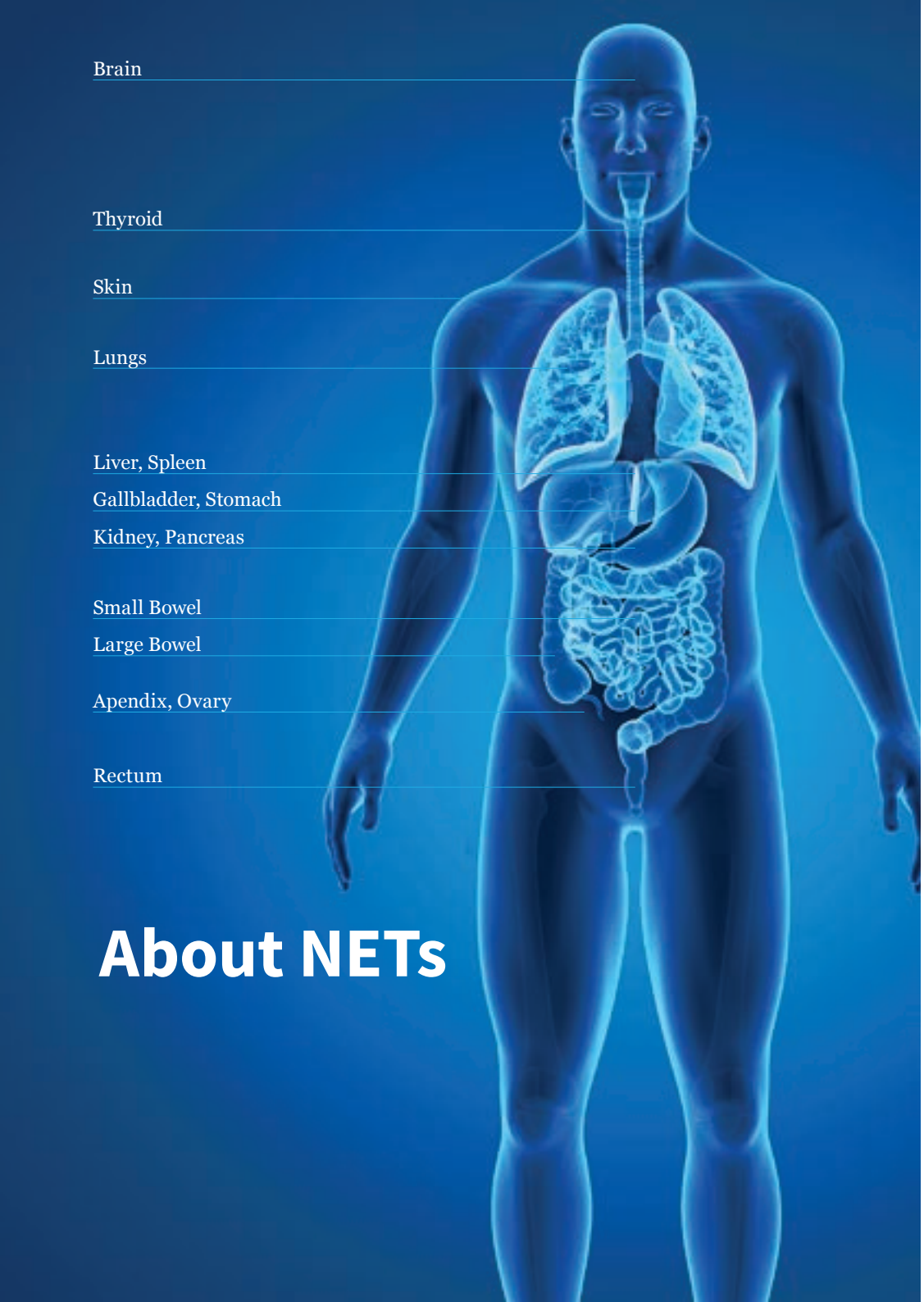
Introduction

This book has been developed for people with neuroendocrine tumours (NETs). It contains information to help you understand diagnosis and treatment options.

This booklet may also help when talking about NETs with family and friends. Everyone's experience is different; therefore, this information may be helpful now or in the future. Its purpose is as a guide to help you understand what is available to you, and for you to use this information to help you make choices.

For more information, and to make sure you stay up to date with the latest developments in NETs, subscribe to the Unicorn Foundation's enews by visiting www.unicornfoundation.org.au.

This booklet was developed by medical professionals with input from NET patients. New treatments and technologies are continually being developed, so this information may change in the future. If you hear of anything not listed in these pages, please ask your healthcare professional for more information.



About NETs

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' (see later in this booklet), 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

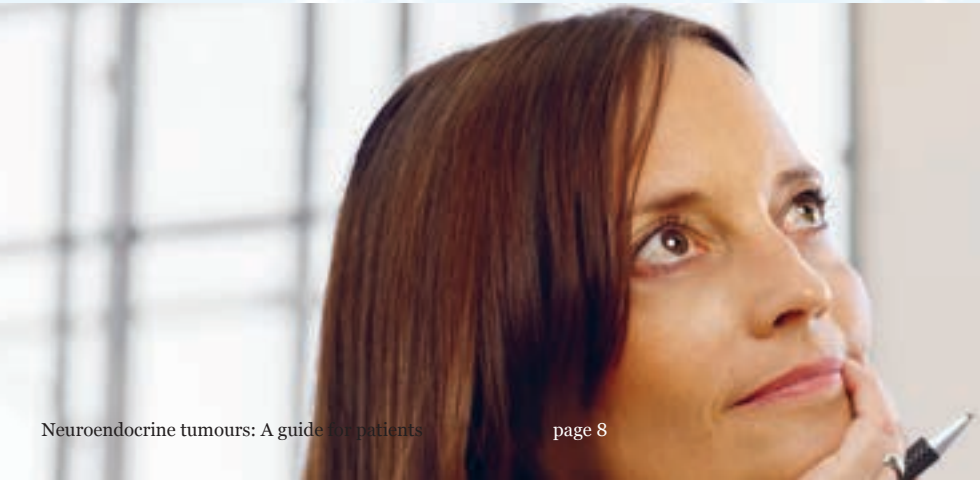
- Colon NETs are rare, can be large, aggressive, and have the potential to spread and cause bowel obstructions and bleeding. If the NET has spread to the liver, the person may have symptoms like wheezing, facial flushing and watery diarrhoea.

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)

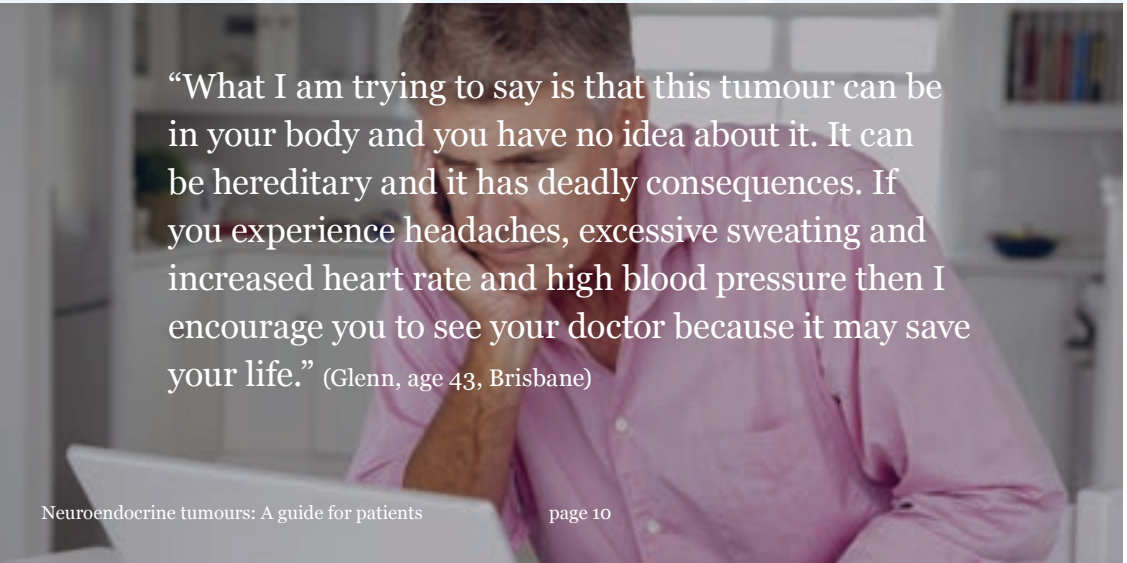
Pancreatic NETs (pNETs): functioning and non-functioning

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 (see later in this booklet).

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.

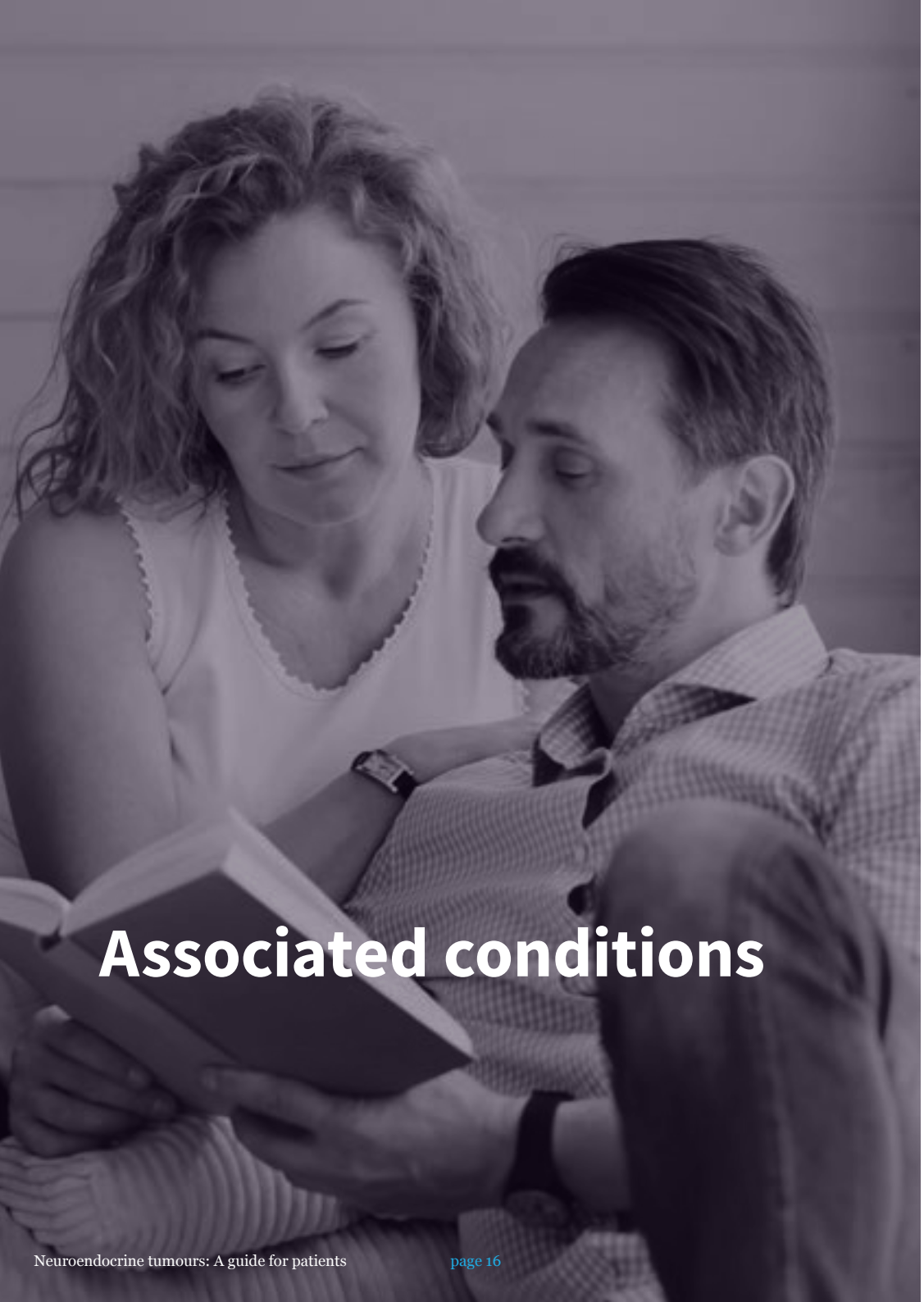
Neuroblastoma

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.



Associated conditions

Von Hippel–Lindau syndrome (VHL) (a syndrome is a group of symptoms that commonly occur together)

Von Hippel Lindau (VHL) is an inherited cancer syndrome caused by mutations of the VHL gene. It affects both sexes equally, About one in every 30,000 to 40,000 people get this syndrome.

VHL causes retinal (eye) haemangiomas, cerebellar and spinal cord haemangioblastomas, renal cell carcinomas (RCC) and pheochromocytomas.

Cystic masses in the pancreas are common and 10–15% of VHL patients develop islet cell neuroendocrine tumours.

Neurofibromatosis type 1

Neurofibromatosis type 1 is a relatively common inherited disorder that affects 1 in every 3000 people.

Patients usually have a particular skin pigmentation (‘café au lait spots’), neurofibromas (nodules on the skin) and bone deformities, including scoliosis of the spine, and are at risk of bone fractures due to osteoporosis.

Patients with neurofibromatosis type 1 are prone to developing both benign and malignant tumours. These tumours include:

- brain and eye tumours (glioma)
- tumours of the nerves
- gastrointestinal stromal tumours (GIST)
- pheochromocytoma
- small bowel (duodenal) NET
- breast cancer, leukaemia, sarcomas.
- pancreatic tumours

Tuberous sclerosis

Tuberous sclerosis (TS) is an inherited condition characterised by benign growths in the skin, brain, kidneys, lungs and heart, which can affect how these organs function.

People with TS may be at risk of developing insulinomas—a neuroendocrine tumour of the pancreas.

Symptoms and signs

(clinical presentation)

NETs are often small and slow-growing. Depending on where they are in the body, they can produce a variety of symptoms or in some cases no symptoms.

The symptoms can be vague (e.g. extreme tiredness) or similar to those of conditions such as irritable bowel syndrome, Crohn disease, peptic ulcer disease, other stomach/digestive disorders, asthma and facial flushing similar to that associated with menopause.

Most doctors are unfamiliar with NETs. They are therefore unlikely to suspect a NET when they first see a patient with NET.

Quick guide to symptoms of GEP-NETs and bronchial NETs

Intestinal NETs	Watery diarrhoea Cramping, intermittent abdominal pain Flushing; asthma-like wheezing Bowel obstruction
Pancreatic NETs	Epigastric or back pain Peptic ulcer disease Diarrhoea Intermittent hypoglycemic episodes (low blood sugars) Diabetes Rash
Bronchial NETs	Wheezing Cough Bloody sputum Recurrent chest infections/pneumonia

Carcinoid syndrome

When GEP-NETs spread (metastasise), the most common site for secondary tumours to grow is in the liver. They can also spread to the bones, the lungs and the lymphatic system.

Many GEP-NETs have an associated syndrome (a collection of symptoms related to a disease or disorder). The most common is carcinoid syndrome, which can occur in up to one in three patients. It is caused when an excess of hormones such as serotonin is produced due to the NETs.

The symptoms of carcinoid syndrome vary between people with NETs. Typical symptoms include:

- Flushing: usually a red/purple flush of the face, neck and upper chest, which may be related to triggers such as alcohol, certain foods, exercise and emotions.
- Diarrhoea: usually presents as watery diarrhoea occurring without warning, which includes night-time episodes. It usually does not respond to anti-diarrhoea medications or other treatments prescribed for irritable bowel syndrome.
- Wheezing: affects about one in five patients with carcinoid syndrome and may be associated with facial flushing. Unlike asthma, wheezing of carcinoid syndrome may not be triggered by colds/flus, exercise, allergens or cold air.
- Abdominal pain: often colicky (intermittent) and cramping. It is often not relieved by going to the toilet.
- Carcinoid heart disease: up to one in five NET patients have carcinoid heart disease at diagnosis. The right side of the heart is more likely to be affected, with leaking of the tricuspid and pulmonary valves causing shortness of breath and swelling (oedema) of the legs.
- Fatigue.
- Skin changes: a small number of patients have skin changes such as telangiectasia (red/purple spots of face, neck and chest).
- Some patients with NETs develop a condition known as pellagra (niacin deficiency), which presents as a rash, dark pigmentation on skin, swollen mouth and bright red tongue, vomiting and diarrhoea, headache, fatigue, depression, disorientation or confusion, memory loss.

Not everyone with NETs will have carcinoid syndrome, even if their disease has spread.

Carcinoid crisis

Sometimes people with NETs have a particularly bad episode of carcinoid syndrome triggered by stress, general anaesthetic or certain treatments. This is called 'carcinoid crisis'.

Symptoms include intense flushing, diarrhoea, abdominal pain, wheezing, palpitations, low or high blood pressure, altered mental state and, in extreme cases, coma.

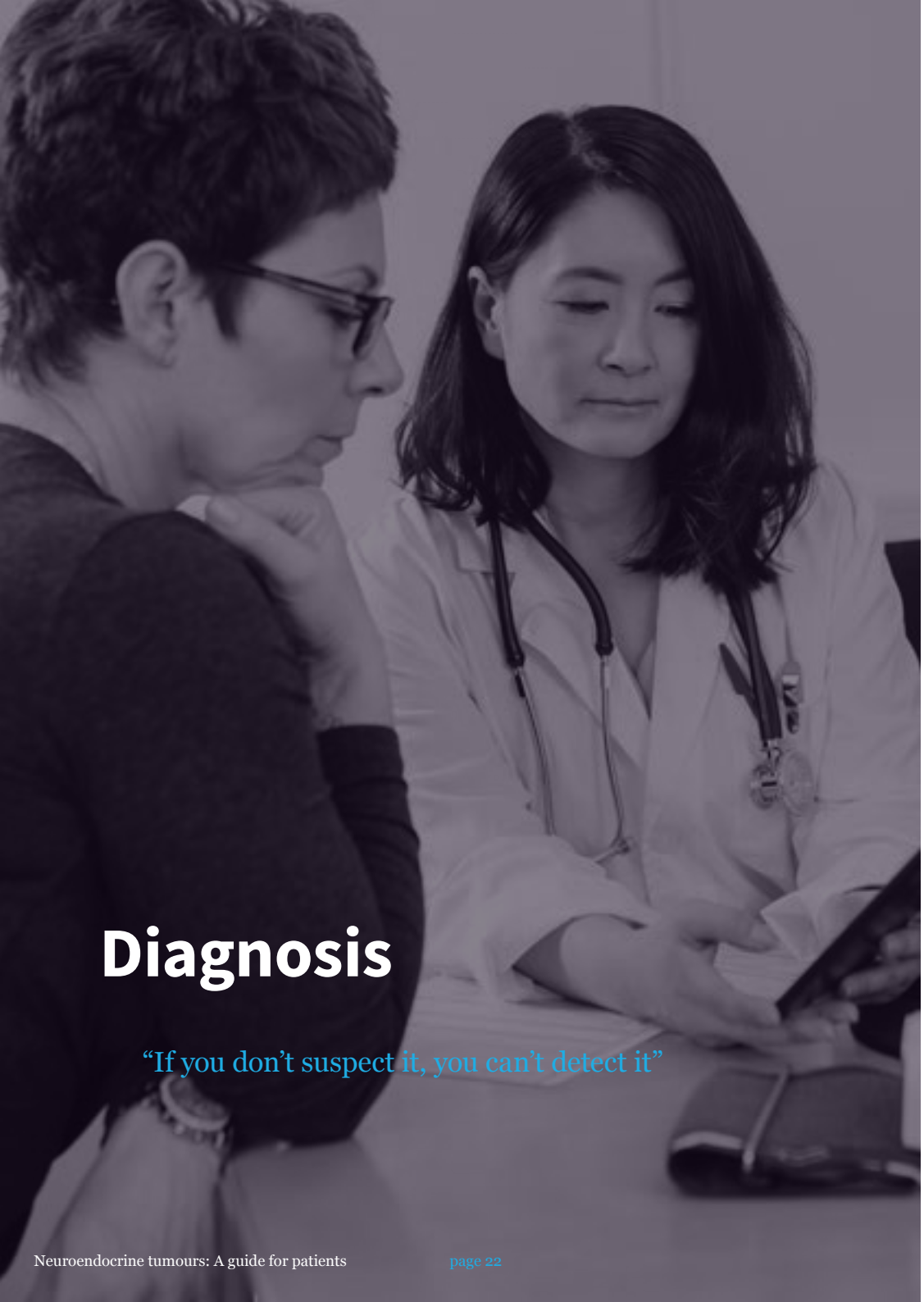
Your NET specialist will ensure you are monitored during a procedures (including dental work and anaesthetics), in which you may be susceptible to these symptoms and may give you medication to prevent such a crisis occurring (e.g. an infusion of a somatostatin (octreotide) analogue). **A wallet sized card is available on the Unicorn Foundation website for patients to carry to alert health professionals to Carcinoid Crisis and management of this.**

Carcinoid heart disease

Some NETs secrete the hormone serotonin. This can affect the heart by causing thick 'plaques' within the heart muscle. The valves on the right side of the heart are also affected and may become 'leaky', causing symptoms such as breathlessness, fatigue, enlarged liver and swollen ankles.

Up to one in five patients with carcinoid syndrome have carcinoid heart disease and may eventually develop heart failure. Whilst carcinoid heart disease cannot be reversed, treatment can prevent further deterioration. This usually consists of treatments to decrease hormone production (SSAs, liver-directed therapy, or even debulking surgery). Patients may be referred to see a cardiologist and there may be medications to help preserve heart function. Ultimately, some patients with carcinoid heart disease may be advised to have heart surgery to replace the leaking valves.

As the above treatments are more effective in treating early carcinoid heart disease, and valve damage is irreversible, echocardiography should be considered regularly in NET patients, particularly those with functional NET or known carcinoid heart disease.



Diagnosis

"If you don't suspect it, you can't detect it"

NETs are difficult to detect for a number of reasons:

- They are often very small.
- They can occur almost anywhere in the body.
- Symptoms can vary widely and some patients have no symptoms at all.
- There are many types of NETs and the diagnosis requires a series of tests, which may include blood tests, imaging (CT/MRI), endoscopy, nuclear medicine scans (PET scans) and biopsies to prove the diagnosis.

Patients who are diagnosed with a NET have often seen many different doctors (general practitioners and specialists) over many years and had many tests before the correct diagnosis is made.

On average it takes 4 to 7 years for this diagnosis. This is because NETs often present with similar symptoms to other common conditions. There is also a widespread lack of awareness of the disease among doctors.

You will be advised to have a number tests and scans that will tell your doctor about your disease, its spread and the rate of growth.

Tests

For your records it is useful to obtain copies of your tests to keep with your records. Some of the tests you might have are listed below.

Biopsy

This involves taking a piece of tissue from the suspected tumour and having it analysed in the a pathology laboratory.

Tissue biopsies are usually taken during medical tests (e.g. an endoscopy) or during operations. Doctors can sometimes tell from biopsies where in the body a cancer has started. Tissue can also be obtained using a fine needle biopsy, where a needle is inserted into a tumour (e.g. in the liver) to obtain a small sample of the cells. This is usually done under local anaesthetic, and an ultrasound is often used to help locate the correct area.

The pathology report is critical for oncologists to decide on the treatments that will best manage your NET.

Blood tests

Doctors will be looking for NET biomarkers for evidence of a rise in certain peptides and hormones in the blood. You may need special preparation, often including fasting, for some of these blood tests. Your pathology blood collection centre will tell you whether it will be advisable to make an appointment and any special preparation needed.

Common blood tests

These may include:

- kidney function test (urea and electrolytes)
- liver function tests
- thyroid function tests
- pituitary hormone screen (e.g. adrenocorticotrophic hormone (ACTH), prolactin, growth hormones and cortisol)
- serum calcium, parathyroid hormone levels (as a simple screening test for MEN-1 syndrome)
- hormone assays,

You may also be asked to give an extra blood sample for use in research studies. You should always be informed of this and asked to sign a consent form.

Chromogranin A (CgA)

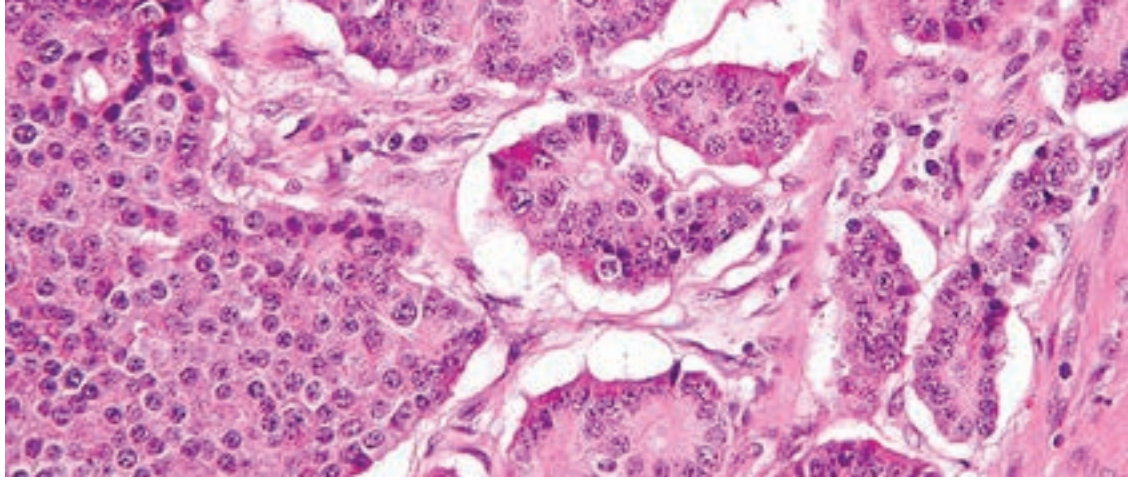
Chromogranin A is produced and released into the bloodstream by some neuroendocrine cells. It is a 'marker', or indicator that there is a NET in the body. Not all patients with NETs will have elevated CgA.

Chromogranin A blood levels can relate to the activity of the tumour in your body. They are often used for monitoring the disease or response to treatments.

Different laboratories use different methods (test kits or assays) to measure chromogranin A. It is important to go to the same laboratory company so that changes in the levels can be interpreted correctly.

Certain conditions can cause higher chromogranin A levels, especially:

- anti-acid medication especially the proton-pump inhibitors (omeprazole, esomeprazole, pantoprazole)
- kidney and liver diseases
- prostate cancer
- atrophic gastritis.



Plasma Metanephrines

Testing for plasma metanephrines is to diagnose or rule out a rare adrenal tumour called a pheochromocytoma or a rare similar tumour located elsewhere in the body called a paraganglioma; these tumors produce excess hormones called catecholamines, which are broken down to metanephrines. Refer to **Unicorn Foundation Fact Sheet** for the procedure for this test. Studies have shown that plasma testing is more sensitive than the more traditional 24-hour urine catecholamines testing. Refer to **FACT Sheet on UF Website** for procedure instruction.

Urine tests

When serotonin breaks down in the body it produces 5-HIAA (5-hydroxyindole-3-acetic acid), which is excreted into the urine.

To test for 5-HIAA in the urine, you will be asked to provide urine samples that have been collected over a 24-hour period. Keep the urine sample cold during the collection period.

Higher than normal levels of serotonin, produced by NET tumours, show up as raised levels of 5-HIAA in urine. Some foods are very high in serotonin/tryptophan and you will be asked to avoid them before and during the test: including chocolate, olives, bananas, pineapple, all tomato products, plums, eggplant, avocado, kiwi fruit, walnuts, brazil nuts, cashew nuts, tea, coffee and alcohol. You will also be asked to avoid certain cough, cold and flu remedies 3 to 7 days before the test.

Endoscopy

Gastroscopy and colonoscopy

This is a way of examining parts of the gut using a flexible fibre-optic tube called an endoscope. The tube can either be inserted down the back of the throat and into the stomach (gastroscopy) or into the colon via the rectum (colonoscopy). During the endoscopy, suspicious lesions in the large bowel and rectum, oesophagus and stomach can be biopsied.

You would usually have these procedures under sedation as a hospital outpatient.

Wireless capsule endoscopy ("Pill Cam")

This involves swallowing a small capsule (the size of a large vitamin pill), which contains a colour camera, battery, light source and transmitter. The camera takes two pictures every second for eight hours, transmitting images to a data recorder about the size of a portable CD player that patients wear around the waist. This system allows your doctor to see the small bowel but is unable to take biopsies.

Endoscopic ultrasound

This is usually done under sedation and involves looking at the digestive tract with a flexible camera with ultrasound capabilities. This test is sensitive for detection of NETs in the stomach, duodenum, pancreas and rectum. Ultrasound guided biopsies can also be performed. The test can help pick up small tumours that might not be clearly visible on other scans.

Bronchoscopy

If you have a suspected lung NET, the doctor may suggest a bronchoscopy. This test looks at the inside of the airways. A doctor puts a narrow, flexible tube called a bronchoscope down your throat and into the airway to see the trachea and bronchus and also take biopsies.

You can usually have this procedure under sedation as a hospital outpatient.

Radiological imaging

CT scans

A multi-slice spiral (CT) scan can rapidly take fine slice (millimetres thick) images of the body with computer reconstruction providing a three-dimensional picture of the inside of the body.

The scan usually takes about 5 minutes. Depending on the scan, you need to arrive earlier in order to drink about a litre of oral contrast material (which outlines the bowel). Sometimes you will also have a drip inserted into your vein so you can have intravenous contrast. This helps to produce good images so a doctor can see the tumours or other abnormalities.

You may be advised to have a blood test prior to the scan to ensure normal kidney function.

If liver images are needed, it is important that a multi-phase liver scan is requested (non-contrast - arterial phase, portal venous and delayed). If this not requested often it is difficult to detect NETs in the liver.

MRI scans

The magnetic resonance imaging (MRI) scans use magnetic fields to create a signal that is processed into an image. MRI scans are safe; however, if you have any metal parts in your body (e.g. a pacemaker), you cannot have an MRI.

MRI scans take longer to perform than CT scans and are noisy (you can use ear plugs). Some people can feel claustrophobic when in the MRI tunnel and may require some sedation to tolerate the scan.

MRI can add further information to the results of CT scans.

Ultrasound scans

Ultrasound imaging (sonography) uses high-frequency sound waves to produce pictures of the inside of the body. Ultrasound scans are non-invasive and the images are captured in 'real time'. They can show the structure and movement of your body's internal organs, as well as blood flowing through blood vessels.

Nuclear imaging (functional imaging)

Nuclear imaging techniques use radiolabelled compounds (small radioactive particles connected to small proteins or peptides) that are injected into the blood stream. These compounds are then taken up by the tumour cells or bind to receptors (somatostatin receptors) on the surface of the tumour, which are then detected by monitors (cameras). Nuclear imaging techniques are very sensitive and specific in detecting NETs and their metastases.

It is important for these scans to be done during the initial assessment stage of any NET patient, and as a part of the ongoing follow-up and management.

PET (positron emission tomography) scan

A PET scan can show how body tissues are working, as well as what they look like. PET scanners are very expensive and only a few hospitals have one. This means that you may have to travel to another hospital for your scan. Increasingly, PET scans are being combined with CT scans to provide more detailed images. These types of scanners are known as PET/CT scanners.

With a PET scan, you first have an injection of a small amount of a low dose radioactive drug (radiotracer) which only stays in the body for a few hours.

PET scans usually take a few hours and are performed as an outpatient procedure.

Gallium-68 (Ga68) PET scan

This test can help reveal the site of NET tumours. This test is essential for any patient with a NET. As this may show tumours that don't appear on any other scans

18F-FDG PET ([18 fluorine] fluoro-D-glucose)

18F-FDG is a glucose analogue with the attached radiotracer 18fluorine. This compound is taken up by cells that rapidly metabolise glucose, which occurs in many different types of cancer including types of NETs.

This test can help to show whether there are cells, like cancer cells, that rapidly take up glucose in the body. Some NETs, particularly faster growing ones, may show up on this type of scan. If you have this test, you will need to fast beforehand and remain still before the test.

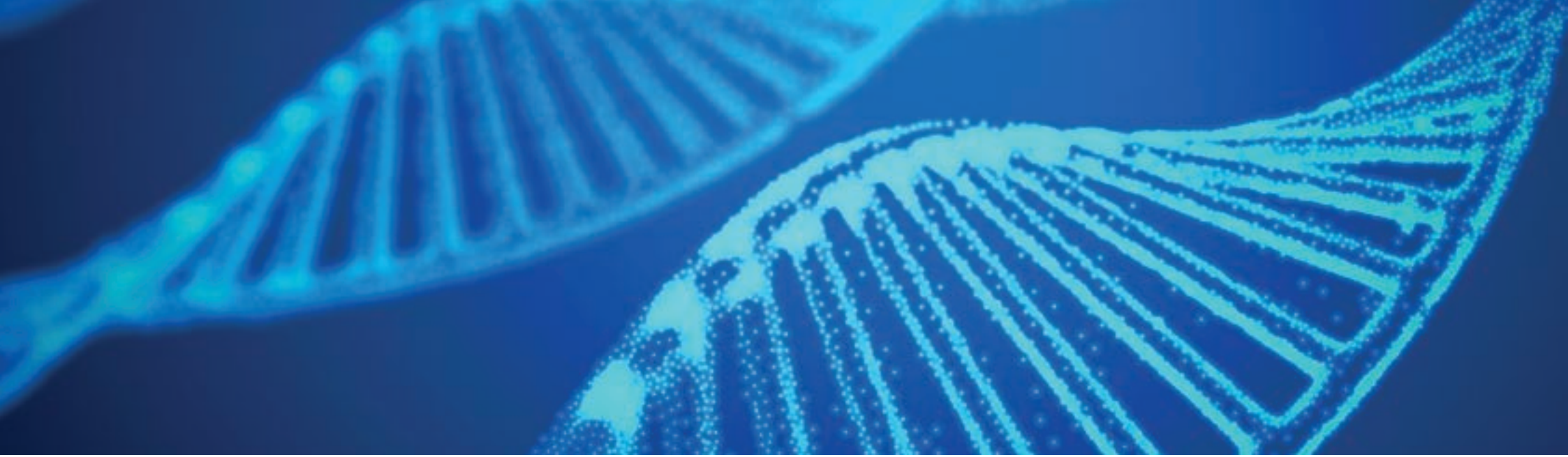
MIBG scan

This scan can help find NETs in the body.

Your doctor may ask you to stop taking certain medications a few days before this test. Your doctor may suggest taking iodine tablets to help protect the thyroid gland during the test. This investigation usually involves taking separate scans over two consecutive days and most patients are allowed home in between.

Bone scan

You may have a bone scan to see if cancer cells have spread to bone in your body. You will have a small injection of radioactive tracer into the vein and images taken by the camera 2 to 4 hours later. There are very few side effects or risks involved with nuclear medicine bone scans and you can usually have it as an outpatient or day-only procedure.



‘Grading’ the NET

NETs, like all cancer, are ‘graded’ into The European Neuroendcorine Tumour Society (ENETS) and World Health Organisation (WHO) system, low (G1), intermediate (G2) or high (G3). The grade represents the aggressiveness of the tumour—the higher the grade, the faster growing it is. Grading the tumour helps your doctors work out the best treatments for you.

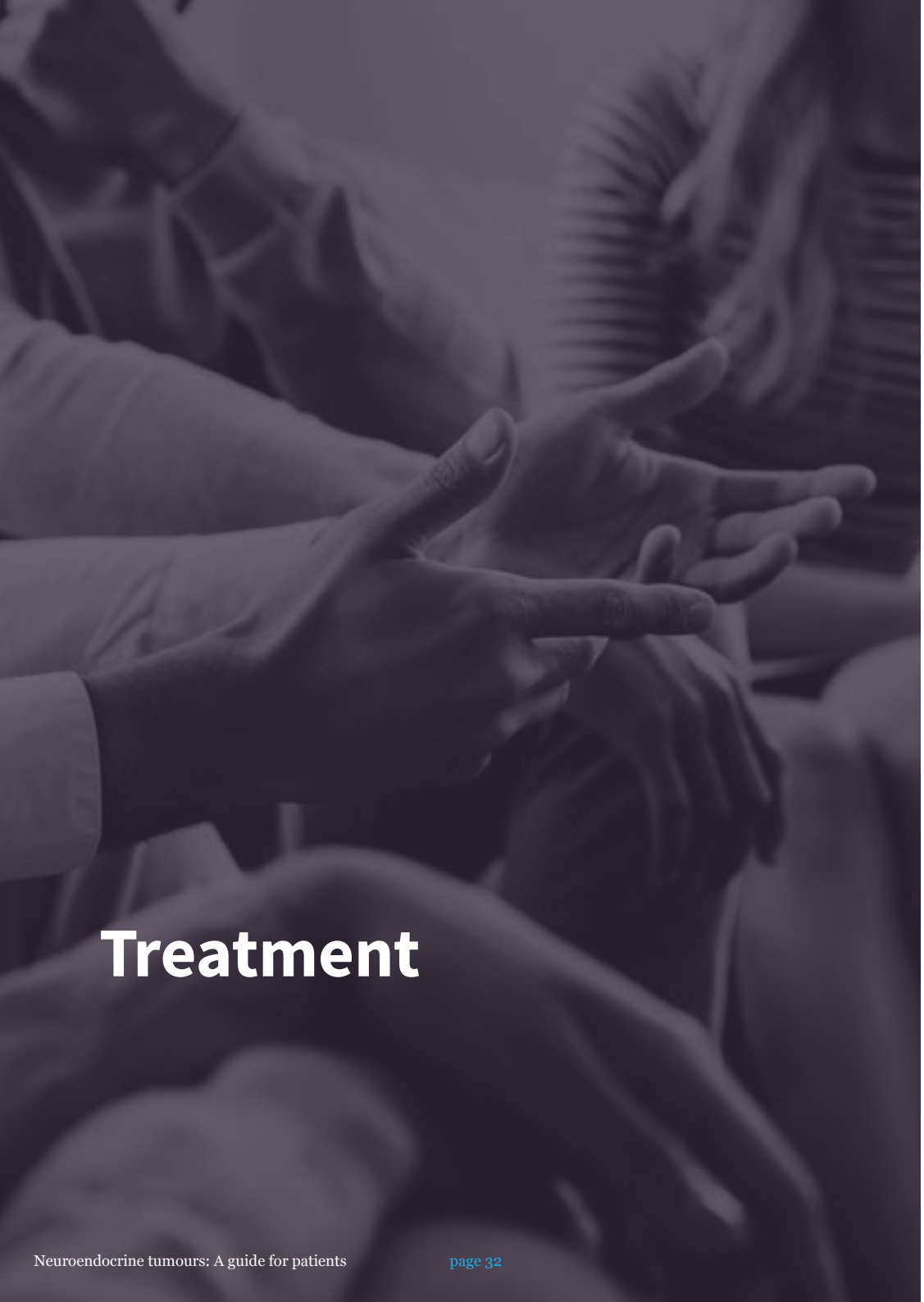
Well Differentiated Neuroendocrine Neoplasms	**Ki67**	**Mitotic**
Neuroendocrine Tumours (NET) G1	<3%	< 2/10 HPF
Neuroendocrine Tumours (NET) G2	3-20%	2-20/10 HPF
Neuroendocrine Tumours (NET) G3	>20%	>20/10 HPF
Poorly Differentiated Neuroendocrine Neoplasms		
Neuroendocrine Carcinomas (NEC) G3 • Small cell type • Large cell type	>20%	>20/10 HPF

Monitoring

There are no established protocols for monitoring NETs with CTs or PET scans.

For those who have no evidence of disease (e.g. after resection of NET), recent guidelines recommend relatively infrequent CT scans (e.g. every 2 years) for a longer time (10 years or even longer) compared to other tumours. There is no agreement amongst NET experts as to how often PET scans should be done (if at all) in this setting.

For patients who have known and present NET disease, imaging may consist of a mix of scans, pathology and other tests. PET scans are particularly helpful at particular times (for example, when a patient is being considered for PRRT, or when there is concern about more aggressive disease). Scans might be performed every 3-6 months, but this could be increased to every 12 months for patients with very stable/slow-growing disease.



Treatment

Being diagnosed with cancer can be a confusing and frightening time for you and your loved ones. Although your healthcare team will do their best to support you, medical appointments can be stressful and it is worth finding ways to get the most out of each appointment. The information in this section will help you to work out what questions to ask.

Each person with NETs should have an individualised treatment plan. This is because there are a number of treatment options available, depending on the type and location of the tumour, your general health and individual preferences. You may find it helpful to download your Wellness and Treatment plan from the Unicorn Foundation website to help you keep on track.

Multidisciplinary teams

The care of NETs can be complex. Your journey may involve not only a whole host of emotions, but also a whole range of investigations, treatments and healthcare professionals.

The fact that there is often not just one treatment option at diagnosis and throughout the journey means that those involved in your care need to consult with each other to work out the best treatment for you. This is called an MDT (multidisciplinary team). MDTs are used across the world in the care of cancer patients and are particularly important for a complex cancer such as NET.

With an MDT, patients can feel more confident that all aspects of their care have been discussed and that the best possible treatment plan will be formulated.

Members of a NET MDT may include:

- Oncologist
- Radiologist
- Pain team
- Gastroenterologist
- Respiratory Physician
- Counselling staff
- Surgeon
- General practitioner/Practice nurse
- Clinic staff
- Endocrinologist
- Nurse specialist
- Cardiologist
- Nuclear medicine specialist
- Dietitian
- Clinical Trials staff
- Palliative care team
- Pathologist

Surgery

People with NETs often have surgery to remove the tumours. The goal of surgery depends on the type of NET cancer, its location in the body and size and whether it has spread from where it began.

Different surgeons may be involved with NETs depending on their expertise and training (e.g. endocrine, colorectal, hepatobiliary, pancreatic and cardiothoracic surgeons).

Surgery for NETs should be done in facilities which have NET specialist units where the surgeons work as part of a team including anaesthetists, oncologists, gastroenterologists, nurses, radiologists and other doctors with expertise in NET cancers.

Curative surgery

This is surgery used when the cancer has not metastasised (spread outside the organ or area where it started). If the tumour can be removed whole and intact with a surrounding margin of clear, healthy tissue, then the surgery will potentially cure the cancer and no other treatment may be necessary.

A follow-up plan will be needed after surgery.

Palliative surgery

When the tumour or tumours have spread or become too large to remove completely, then surgery may be considered to 'de-bulk' the tumour. This will relieve symptoms caused if the tumour is affecting other organs or producing excessive amounts of hormones.

Cardiac and thoracic surgery

Thoracic surgery may be indicated for patients with pulmonary NETs and cardiac surgery for patients with carcinoid heart disease who may need cardiac valve replacement.

Perioperative and anaesthetic management of NET patients

Patients with NET may be at risk of 'carcinoid crisis' in the perioperative period or during surgery. The NET specialist should discuss this with the anaesthetist before surgery.

Medical management

Somatostatin analogues (SSA)

Daily (short acting) or monthly (long acting) injections of somatostatin analogues (Sandostatin, Lanreotide) are available to control some symptoms caused by NETs.

Short acting Octreotide may be given several times a day to control symptoms for 2 to 3 days until a correct dose of long lasting SSA can be prescribed. Sometimes the short acting SSA may be included to reduce symptoms despite the use of the long acting SSA until a treatment regime can be ordered.

Somatostatin analogues are versions of the naturally occurring somatostatin, which is a hormone produced in the brain and digestive tract. Somatostatin regulates the release of several other hormones and chemicals from our internal organs.

Injections of these analogues can stop the overproduction of hormones (e.g. serotonin) that cause symptoms such as flushing and diarrhoea. There is evidence that these injections also slow down rate of growth of tumours.

Main side effects of Somatotstatin analogues are:

- loss of appetite
- feeling sick
- feeling bloated
- stomach pain
- tiredness (fatigue)
- increased diarrhoea (this is rare)
- soreness at the injection site

You might have raised or lowered blood sugar levels. If you are a diabetic you need to check your blood sugar more often. You might also need fewer diabetic tablets and less insulin.

Having octreotide over many months can cause gallstones. So you might have an ultrasound scan of your gallbladder before you start treatment, and then every 6 to 12 months. Between 10 and 50 out of 100 people (10 to 50%) develop gallstones while they are having octreotide. Most people have no symptoms from the gallstones.

Sandostatin LAR® (depot preparation of octreotide)

Long Acting Octreotide (an analogue of the naturally occurring somatostatin) is the active ingredient in Sandostatin LAR®. Sandostatin LAR® blocks the somatostatin receptors and can slow the tumour growth and treat the symptoms of NETs. Sandostatin LAR must be mixed immediately prior to injection. It is usually given by a health professional however some patients and / or carers give the injection. There is a home program available whereby a nurse can administer it in the patients home or when traveling around Australia.

Somatuline® Autogel (depot preparation of Lanreotide)

Lanreotide (an analogue of the naturally occurring somatostatin) is the active ingredient in Somatuline® LA. Lanreotide may be used instead of somatostatin because it is more potent, lasts longer in the body and is given as a monthly injection. Somatuline® Autogel blocks the somatostatin receptors and can slow the NET tumour growth and treat the symptoms of NETs. Lanreotide comes premixed and is usually given by a health professional, however, some patients can self-inject or receive injection by carer.

Chemotherapy

Chemotherapy may be an option, especially for NET patients with pancreatic, bronchial or high-grade (G2/G3) NETs. Not all NETs respond equally to chemotherapy, so your doctor may or may not recommend it as part of your treatment.

Many chemotherapy treatments involve intravenous drugs that are given in hospital as a day procedure; however, there are also oral chemotherapy agents—your NET doctor or MDT will discuss the best option with you. Chemotherapy, either oral or intravenous, will cause side effects and special care is required to prevent and or minimise these side effects. You will be given specific information relevant to the treatment you will be receiving from your treatment team.

The histology of the tumour (i.e. how it looks under the microscope after biopsy or operation) may help determine the type of treatment you receive.

Chemotherapy may sometimes be recommended after surgery (adjuvant therapy) for high grade NETS. You may be asked if you would like to join a clinical trial researching chemotherapy for different types of NET cancer.

Targeted molecular therapies

Sunitinib (Sutent) is a medication that comes in capsule form. It is mainly used in patients with pancreatic neuroendocrine tumours. It works mainly by blocking a process called angiogenesis (the process of making new blood vessels). Tumours need a good blood supply to grow and Sutent helps stop that process. The drug comes under an umbrella group of drugs known as tyrosine kinase inhibitors.

Everolimus (Affinitor®) is another medication for patients with pancreatic, lung and gastrointestinal neuroendocrine tumours – however funding has not been approved for all these NETs at time of publication. It also comes in a capsule form and is a type of drug that interferes with the mTOR enzyme in cells that regulates growth and metabolism. Blocking the action of this enzyme has been shown to slow the growth of neuroendocrine tumour cells in patients with progressive disease.

Peptide receptor radionuclide therapy (PRRT) or Lutate

PRRT is an outpatient therapy that is effective for some patients with NETs.

Lutetium-177 Octreotate Therapy (Lutate) is primarily used to treat people with NETs when other types of treatment, such as surgery or chemotherapy, are not suitable or are ineffective. This may be due to the size, location and number of tumours present. Lutetium-177 Octreotate is a very specific therapy that can only be used when tumours express a large number of somatostatin receptors. Most NETs show an increase in somatostatin receptors. Other tumours such as head and neck cancers, non-small cell lung cancer, small cell lung cancer and Merkel cell cancer may also express somatostatin receptors. If this therapy is being considered, a diagnostic scan is performed (Gallium 68 PET scan) to distinguish if the tumours are positive for somatostatin receptors

If having this treatment, you may have a dose of chemotherapy to prepare or sensitise the tumour cells for the PRRT. You will also have an infusion of amino acids to help protect your kidneys.

Depending on the treatment regimen, PRRT is given as an induction course of four treatments separated by 6 to 8 weeks. You may have more PRRT later: your doctor will advise you about this.

You may have nausea, fatigue, some hair loss (not baldness), risk of carcinoid syndrome flare and minor changes in the production of your blood as side effects of this treatment. You should contact your treatment team if you do experience any of these side effects as these side effects can be managed.

Liver directed therapies

Hepatic artery embolization (HAE)/ transcatheter arterial chemoembolisation (TACE)

If the NET tumour has spread to the liver, you may be offered hepatic artery embolisation (HAE), which will aim to block the blood supply to the tumours in the liver.

You will have local anaesthetic (and sedation). The radiologist will access an artery in the groin and then direct a catheter, with the help of x-ray imaging, into the main supply of the liver (hepatic artery) and into the artery that supplies blood to the NET tumours in the liver. Tiny particles called microspheres are then injected through the catheter into the artery. These particles block the blood supply to the tumour, which can cause the tumour to shrink or even die.

This procedure may be combined with the injection of chemotherapy or the use of microspheres that contain chemotherapy. This is called transcatheter arterial chemoembolisation (TACE). For this procedure, you will probably be admitted to hospital overnight. The side effects can include fatigue, nausea, vomiting and pain especially around the liver.

Selective internal radiation therapy (SIRT)

This is the use of radiotherapy to treat liver metastases that cannot be removed with surgery.

It is similar to hepatic artery embolisation. An experienced interventional radiologist will insert a catheter into the hepatic artery supplying blood to the NET tumours and tiny beads containing a radioactive substance will be injected. These interfere with the tumour cell DNA and slow tumour growth.

Radiofrequency ablation (RFA)

This is a treatment for metastatic or primary NET and is done by a radiologist. Using ultrasound or CT guidance, a needle (under local anaesthetic and sedation) is inserted through the abdominal wall and into the liver tumour. Once the needle is localised within the tumour, a generator is used to deliver a rapidly alternating current (radiofrequency energy) producing high temperatures (heat) that destroy the cancer cells (necrosis).

Symptom Management

Telotristat etipirate (Xermelo)

Telotristat is a novel oral drug. It inhibits an enzyme that is responsible for the production of serotonin. Excessive blood levels of serotonin cause carcinoid syndrome (diarrhoea, flushing, abdominal pain); therefore, decreasing its production can reduce these symptoms. The recent TELESTAR trial enrolled patients with carcinoid syndrome and 4+ bowel movements per day. The patients who received telotristat reported significantly fewer bowel movements. It is worth noting, however, that telotristat improved bowel motions by approximately 1/day over placebo i.e. patients on telotristat may still have multiple bowel movements

per day. Urinary 5-HIAA (reflecting serotonin production) was also reduced with telotristat. This is a promising option for treatment of patients who have diarrhoea from carcinoid syndrome despite SSAs.

This drug does not act on the tumours to control their growth.

Watchful Waiting

No treatment, or watchful waiting, may be the best option for some NET patients especially if the NET is not causing symptoms or problems, the disease is stable, or the tumour is low grade (G1).

For some people, poor general health or complications secondary to treatments may also make further NET treatment inadvisable.

Clinical trials

Clinical trials are medical research trials involving patients. They are done to try to find new and better treatments. Clinical trials are the only sure way to find out if a new approach to cancer care is better than the standard treatment currently available. They are heavily regulated to ensure that results are meaningful and reliable. For further information refer to

https://www.tga.gov.au/community-qa/clinical-trials-information-consumers or https://www.australianclinicaltrials.gov.au/consumers

www.unicornfoundation.org.au

www.clinicaltrials.gov

Palliative Care

Involving Palliative Care team members as part of the multidisciplinary team is extremely beneficial from diagnosis onward as this can improve the patient's and family's quality of life psychologically and physically. Palliative care is care that helps people live their life as fully and as comfortably as possible and provide services which can meet the individual needs by –

- Relief of pain and other symptoms e.g. vomiting, shortness of breath
- Resources such as equipment needed to aid care at home
- Assistance for families to come together to talk about sensitive issues
- Links to other services such as home help and financial support
- Support for people to meet cultural obligations - Aboriginal and Torres Strait Islander (ATSI), Cultural and Linguistic Diverse (CALD) populations and preferences
- Support for emotional, social and spiritual concerns
- Counselling and grief support
- Referrals to respite care services

Please refer to **www.palliativecare.org.au** for further information

Prognosis

Many patients have an excellent prognosis from NET. If low-grade disease is completely cut out (resected), there is a good chance that it will not come back. However, these patients may need follow-up over a long period to monitor for recurrence.

Even for patients with advanced (unresectable) disease, there can be a wide range of outcomes. The average outcome is quite dependent on the histological (tissue-based) grade of the NET. Patients with low-grade (Grade 1) disease may survive for many (even 10+) years. Patients with high grade (grade 3) disease that is aggressive have an average survival time measured in the range of many months to a few years, despite best treatment.

It is important to realise two things about prognosis:

1. There is a big variation in prognosis - there is a lot of variation in outcomes and no "magic number" for a particular patient. Some patients find discussion of ranges in prognosis (best case/worse case/expected scenarios) very helpful.
2. New treatments and insights can improve care and hence prognosis for all NET patients. Therefore, prognoses based on the available information are a rough estimate.

Living with a NET

The experience of living with an uncommon cancer, such as a NET, is not fully appreciated by most people in the medical and general community. Many patients have a physical and an emotional journey.

For most patients with NETs, their story can be divided into four chapters.

First chapter: Something feels wrong

This is the phase of knowing, or feeling, that something is wrong with their health. You may have periods of feeling well punctuated with episodes of symptoms or have symptoms that become more frequent. You visit their general practitioner many times with the vague symptoms of fatigue or 'feeling just not right'. Your doctor may discuss irritable bowel; flushing/rashes or asthma, which mimic common conditions but actually are due to NET.

On average, NET patients see four to six different doctors (including specialists) over 4 to 7 years before the correct diagnosis is made.

Because of repeated misdiagnoses, patients may feel frustrated, confused, and at times depressed. Some lose faith in the medical system altogether. You may have spent considerable time and money seeking the correct diagnosis. Tragically, because NET patients visit their doctors on so many occasions, some are labelled as being mentally unstable or 'hypochondriacs'.

Second chapter: Diagnosis

This is when a diagnosis of NET is finally made. Patients experience a range of emotions at this point.

- relief that the correct diagnosis has been finally made
- anger at the medical community for the delays and misunderstanding in the diagnosis
- confusion
- fear and hopelessness about what the future holds.

The treating doctors can present a confusing picture of NETs to patients. The word cloud (see image) captures many of the ways the medical community currently views NETs.

This time can be very difficult. Despite the fact that they have a diagnosis, many patients are inadequately treated, mismanaged and given incorrect information by doctors who do not understand NETs. This is understandable given that NETs are an uncommon cancer and many doctors would not have seen a patient with NET in their practice before and may not know where or who are the 'experts' in treating this uncommon cancer.

Because of the different types of NETs—functioning or non-functioning, their location and grade (e.g. slow growing or aggressive), the hormones that they may secrete and whether they have spread—the medical and surgical options for managing each patient's NET are specific to that patient.

A treatment plan that is clinically suitable for your NET requires assessment and review of your medical history by a NET specialist with access to a NET multidisciplinary team.

Many clinical studies demonstrate that NET patient care and long-term outcomes are improved when managed by a specialised neuroendocrine multidisciplinary team (MDT). It is critical for NET patients to have access to such people and teams to ensure that they are being managed appropriately and receiving the best available treatments.

You may feel uncomfortable asking your doctors for a 'second opinion' to be provided by a NET specialist; however, doctors are usually agreeable to this because they appreciate the fact that making an effective treatment choice can be very challenging. If getting a second opinion through your treating doctor is not possible, you can get a referral from any doctor, including your general practitioner. To help Australian patients find a NET Specialist, the Unicorn Foundation has developed a register of NET specialists and NET MDTs to which patients can be referred (www.unicornfoundation.org.au).

Third chapter: Transition

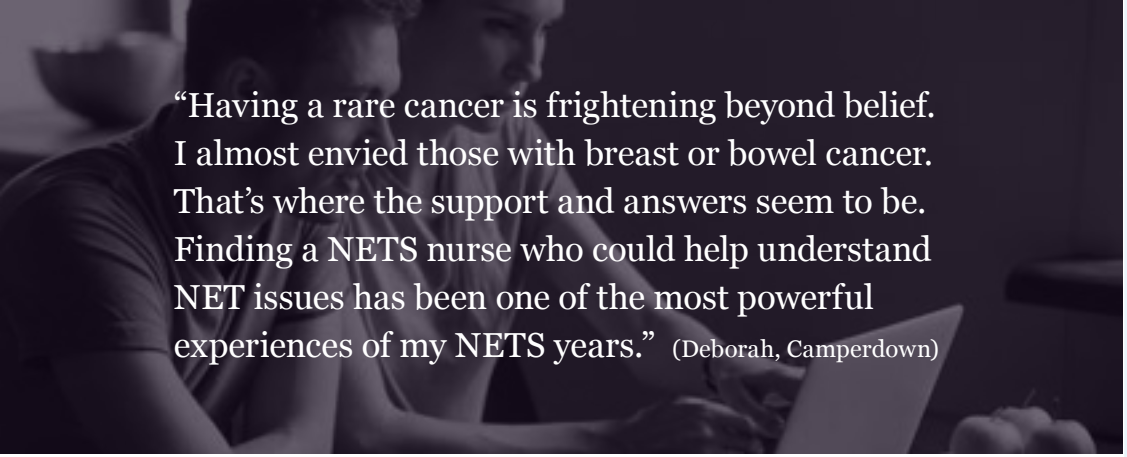
During this time, many patients are commenced on treatments and/or receive surgery for their NET.

This is can be an extremely difficult and stressful period of adjustment. You may face untold emotional and physical challenges in 'coming to grips' with your situation and this can be compounded and magnified by the reactions of loved ones, family and friends, who are trying to help but may not understand the cancer.

You can get support and comfort during this time from the Unicorn Foundation whose services includes NET nurse support, telephone support service and a private Facebook community where many patients converse in a safe, supportive and non-threatening forum. Other services, such as the Cancer Council helplines, can give general advice and support which includes legal and financial assistance.

"I have used the service that the NET nurse provides on many occasions. Just recently I had my first treatment of Lutate and she was very helpful to me during this time explaining that my reaction to it was a good sign. Explaining that it was a sign that the tumours had been hit hard by the treatment"

(Dorothy, Sydney)



"Having a rare cancer is frightening beyond belief. I almost envied those with breast or bowel cancer. That's where the support and answers seem to be. Finding a NETS nurse who could help understand NET issues has been one of the most powerful experiences of my NETS years." (Deborah, Camperdown)

Fourth chapter: Living with a NET

This is the adjustment period, when, perhaps years of misdiagnosis and the shock of being told you have a cancer, you receive expert treatment and advice and begin to comprehend the notion of 'living with a NET'.

Living with a NET is challenging and can have a considerable impact on activities of daily life, and many NET patients need to make significant adjustments. There are so many things to think about that it can be overwhelming.

Questions about what will happen 'next' are at the forefront of every patient's thoughts and actions and for many people the impact on their physical, mental and emotional health is significant.

Generally, most people with NETs describe themselves as having 'good health' but that often hides the reality of symptoms of fatigue, muscle weakness, intermittent abdominal pain, diarrhoea, skin rashes, headaches, anxiety and depression. It is important for caregivers, family, friends and work associates to understand that although the NET patient appears well, they are struggling with many of these symptoms and need to be supported during such times.

It is important for you to develop a 'working' relationship with your NET specialist, allowing them to guide your treatment.

Many NET patients describe feeling that their identity has been 'stolen' and replaced by an overwhelming focus on their disease. Therefore, it is vital to develop trust in your NET specialist and allow them to share this burden, which will free up time for you to pursue things in life that empower and give joy, such as family, hobbies and holidays.

Seeing your NET specialist

NET patients see their NET specialist and many other members of the NET team, including their general practitioner, on a regular basis. These appointments can be stressful as there are often many issues to discuss, questions to ask, and explanations to be given within a limited time in the consultation room or outpatient clinic.

It is vital to prepare for these consultations in order to get the most out of the time spent with your doctor.

- Take all recent pathology (blood tests) and radiology results to the appointment if you have them.
- Before the consultation, write down questions that you want to ask. If you do not understand the answers, don't be embarrassed to ask for the answer to be repeated or rephrased.
- Regularly take notes and keep in a diary of all your symptoms to take to your appointment, how you are feeling even if they seem minor or unrelated to your NET, including triggers for the symptoms, their frequency and severity, and factors that may relieve the symptoms. Some doctors are very happy for patients to email these notes through, ahead of the appointment, so they are aware of what needs to be covered. **The Unicorn Foundation website has a Treatment and Wellness Plan which can be downloaded to assist in keeping a comprehensive record of the type of NET, tests, treatments, management and care.**
- Take a trusted friend or family member with you to the appointment. If you are feeling anxious, you may not hear everything that is said, or ask all the questions you wanted to. It helps to have additional ears there to listen, and your guest may help to make sure your concerns are raised.
- Many doctors are happy for people to record their consultation on a smart phone or electronic voice recorder. This can enable you to listen back later, and provide to carers who may not be able to attend. Check with your doctor beforehand.

Deciding on a treatment strategy can be difficult, so getting a second opinion is quite common. You have the right to know as much about your condition and prognosis as you wish and you have the right to know the overall treatment strategy, including what options are available to you if initial treatments are not successful in stabilising your disease.

You have the right to make decisions for yourself, even if the decision is against having medical treatment or is to end medical treatment.

Questions to ask during the consultation

General:

- What type of NET do I have?
- Where is the NET located? Has it spread to other parts of my body?
- What are the risk factors for NETs?
- Is my NET likely to be caused by genetic factors? Are any other members of my family at risk of developing a NET?
- Are you a NET specialist? How many NET patients do you treat a year?
- Are you able to consult with or refer me to a NET specialist?
- Are you involved with or have access to a NET multidisciplinary team?
- Where can I find out more information about my NET?
- How could it have spread when the margins were clear from surgery?

Tests

- What type of histology is my NET (the description of the NET as it looks under the microscope)? Did an experienced NET Pathologist review the tumour?
- What other tests do I need to have? (Refer to the diagnosis section. Tests may include blood tests such as chromogranin A (CgA); 24-hour urine tests (5-HIAA); functional nuclear medicine scans (Gallium-68 PET scan, FDG scan,); triple phase CT of the liver; MRI; and echocardiography of the heart.

Staging

- What is the grade and staging of my NET? What does this mean?
- Based on my grade and staging, what is my prognosis?

Management

- What are my management options?
- What is the expected timeline for my management plan? Do I need to be treated immediately?
- Which treatments, or combination of treatments, do you recommend? Why?
- What is the goal of the treatment you are recommending?
- Can I have long overseas holidays whilst on treatment?

Treatments

- What will be done during the treatment and how will it affect me?
- How often do I need this treatment? (Treatment schedule)
- Is there a home support program for this treatment, so I can have this at (or closer to) home?
- Will I need to be hospitalised for a treatment, or is this treatment done as an outpatient?
- What are the side effects or risks (short term and long term) of this treatment?
- How can I best prepare myself for this treatment?
- What should I avoid or not do while having this treatment?
- How will this treatment affect my daily life? Will I be able to work, exercise and do my usual activities?
- Does this treatment treat my symptoms of NET?
- What are the costs for my NET treatments? Are my treatments covered by Medicare, Pharmaceutical Benefits scheme (PBS) or my insurance?

Clinical trials

- What are clinical trials?
- Are there any relevant clinical trials for my NET?
- What are the benefits and risks of participating in a clinical trial?
- How will I be monitored while participating in a clinical trial?
- What are my responsibilities during a clinical trial?
- Are there any costs associated with being in the clinical trial?
- Where can I learn more about clinical trials for NET?

Support

- What supports are available to me? To my family?
- Who should I call with questions or concerns out of hours?
- May I contact you or the nurse to talk about additional information I find?
- Do you know of any support groups or resources for NET patients?
- I am concerned about managing the costs related to my NET care: who can help me with these concerns?
- Am I eligible for any benefits if I cannot work?

Patient support

The Unicorn Foundation operates face-to-face NET support group meetings in most Australian capital cities six times per year. NET patients and carers can also access a 'closed' forum on Facebook as well as obtain information and support with our specialist NET nurse on **1300 287 363** or **netnurse@unicornfoundation.org.au**

It is very important for all Australian NET patients to contact the Unicorn Foundation (**unicornfoundation.org.au**) or join the mailing list to remain updated on current issues related to NET in Australia.

Clinical trials

You can find out more about current NET trials at:

- Australian and New Zealand Clinical Trials Registry www.anzctr.org.au
- Cancer Australia www.australiancancertrials.gov.au
- Australian National Health and Medical Research Council www.australianclinicaltrials.gov.au
- United States National Health Institutes Clinical Trials (includes international and Australian trials) www.clinicaltrials.gov
- Current Australian NET Clinical Trials - www.unicornfoundation.org.au

Complementary (alternative) therapies

Complementary therapies are also known as natural or traditional therapies and can be divided into three main categories:

- 'natural' therapies: herbal and naturopathic compounds, Chinese medicines, homeopathy, etc.
- mind-body (mindfulness) techniques: meditation, relaxation, support groups, counselling, music or art therapy, hypnotherapy, aromatherapy, etc.
- physical therapies: massage, yoga, tai chi, acupuncture, reflexology, Pilates, Alexander technique, etc.

It should be noted that such therapies are not subject to the same strict regulations as evidence based therapies. Studies have shown that more than 50% of patients with cancer have used some form of complementary therapies in addition to their conventional medical treatments. For many NET patients, taking a 'holistic' approach to their health improves their quality of life by addressing their dietary, physical, emotional and spiritual needs.

Before starting any complementary medicines or therapies it is important to understand:

- How the therapy works.
- Will the therapy cause harm, have side effects or interact with other medications or tests?

There is no conclusive scientific evidence for that natural therapies can successfully treat cancers; however, there is anecdotal evidence for mind-body techniques and physical therapies to assist in improving pain management, sleep, stress relief, depression, anxiety and general quality of life.

It is vitally important to tell your NET specialist about any 'natural' medicines or complementary therapies you are using or intend to use. They can potentially have a negative impact on the disease or interact with other NET treatments and diagnostic tests.

Diet

Why diet is important

There are a number of reasons why focusing on diet and healthy eating is important for NETs patients.

Eating well can:

- Help you cope better with treatment
- Assist in healing. This is important after surgery, chemotherapy, radiotherapy or other medical treatment
- Improve your body's immune system, its natural defense
- Help you maintain your weight and feel better in yourself. This is important even if you are not having treatment.

For those who are not losing weight, have symptoms controlled well and are otherwise well on no other prescribed diet, their focus should be to follow a healthy eating diet. This should be high in foods such as fruit, vegetables and wholegrains but low in nutrients such as salt, saturated fat an added sugar. Choose from a range of natural colours; at least three vegetable and two fruit portions a day.

Some NETs patients may need to seek advice about the right foods. Patients with pancreatic NETs in particular may have more complex needs and should seek guidance from an experienced nutritionist. See the Unicorn Foundation website for our **Nutrition Booklet**.

Carcinoid trigger foods

For some patients certain foods and drinks can trigger symptoms such as abdominal pain, diarrhea and flushing. The types of foods/drinks that cause this reaction vary. The most reliable method of identifying them is with a food and symptom diary. The diary is completed over a 2 -4 week period and includes foods eaten, medications and any symptoms experienced afterwards. If you identify a 'trigger food', try reducing the portion size. If this does not help, you may need to

exclude it completely from your diet. Possible common triggers include:

- Size of meal
- Fat content
- Spice and alcohol
- Meals moderate to high in amines (e.g. aged cheese, smoked/salted fish & meat)

Common issues and strategies

Weight loss

It is important not to ignore loss of weight. Progressive loss of weight may be as a result of a number of problems, so you should discuss this with your doctor, nurse specialist and dietitian.

General tips to boost your intake:

- Eat "little and often"
- Small frequent meals and snacks may be easier for you to manage rather than the traditional three meals per day
- Have snacks in between your meals
- Eat when you feel hungry
- Use convenience foods (ready meals, canned foods, frozen foods) if you are too tired to prepare meals.

Tips to increase your protein and energy intake:

- Eat foods rich in protein, meat, poultry, fish, eggs, dairy products (milk, yoghurt, chees) pulses and nuts
- Have foods rich in energy, oils, nuts, butter, margarine, and any other foods high in fat and sugar. Use full-fat dairy products (e.g. whole milk, full fat cheese, full cream yoghurt, double cream)
- Have fortified milk: add 3 -4 tablespoons of skimmed milk powder to 1 pint of milk. Use in the same way that you would ordinary milk
- When having breakfast: use fortified milk or neutral flavoured supplement drinks. Try adding dried fruit, nuts, sugar, honey, yoghurt, evaporated milk or cream
- Stews or casseroles; add noodles, lentils or beans. Stir in cream or sour cream
- Soups or sauces; make with fortified milk or add grated cheese, double cream, butter or oil
- Desserts; add ice cream, cream, evaporated milk, condensed milk, jam, honey, golden syrup, lemon curd, dried fruit, nuts or chocolate
- Use fortified milk to make milky desserts (e.g. custard)
- Sandwiches, toast, plain biscuits or jacket potatoes; add butter, margarine, mayonnaise, cheese, peanut butter, olives or avocado
- Vegetable; add grated cheese, oil, butter or margarine
- Salads; use oil, mayonnaise, salad cream, salad dressing, Greek yoghurt, nuts or seeds
- Try using fortified milk in hot chocolate, smoothies or other high energy drinks
- If necessary, your dietitian may advise you to get a prescription of supplement drinks

> "Regular exercise such as walking has been shown to reduce muscle wasting and fatigue, as well as nausea and vomiting, and can help some people sleep better"
>
> (NET Specialist)

Diarrhoea

Diarrhoea may be a result of many things in NETs including the tumour-secreting hormones, treatment, intolerance to food or an infection. Here are some things to try;

- If you have diarrhoea and you have not started a new treatment, see your doctor as you may have an infection
- Eat little and often
- Reduce insoluble fibre (e.g. bran, wheat germ) but increase soluble fibre in diet (oats, apricots, high fruit jams)
- Cook and peel fruit and vegetables
- Juice 'without bits' rather than whole products / smoothies
- Non-dairy, multi-strain probiotics (check with your doctor if you are on chemotherapy)

Wind and bloating

This problem can accompany diarrhea and constipation. Here are some tips to help;

- Avoid gas-forming foods (e.g. onions, garlic, cabbage, pulses, cauliflower broccoli, nuts and spicy foods)
- Trial a low fibre diet

- Avoid fizzy drinks and chewing / bubble gum
- Skipping meals is more likely to cause wind, therefore eat regular meals
- Chew your food well to reduce the amount of air swallowed
- Monitor bowel movements and speak to your doctor or nurse if the problem persists

How do I know if I am not absorbing fat appropriately?

If you have diarrhoea and/or your stools appear pale, oily, float or are hard to flush, then this might indicate that you are not absorbing fat as you should. Talk to your doctor, nurse or dietitian if your stools appear different or if you have diarrhoea. If your doctor or dietitian thinks you may have problems absorbing fat, they may recommend you take pancreatic enzyme tablets to help with this. Creon is a common brand of pancreatic enzymes and is taken at the beginning of meal times. – refer to the Vitamin / Dietary Fact Sheet on the Unicorn Foundation website.

Nausea and vomiting

You may feel nauseous or vomit for several reasons. Please tell your treatment team so they can investigate possible causes.

- Eat small, frequent meals throughout the day to avoid feeling full
- Take little sips of nutritious drinks between meals rather than with them
- Avoid cooking smells if possible
- Cold food and drinks usually have less smell than hot cooked foods
- Seek out tart flavours (e.g. citrus juices, sorbets and lemon curd) and salty and minty flavours
- Eat plain biscuits, crackers or dry toast
- Avoid greasy or fatty foods
- Try ginger extract in foods or drinks (e.g. crystalised stem and fresh ginger in stir fries / juices / grated onto salads)

When to ask for help

It is important to note that this is only a basic guide. It is important to discuss your needs with your treatment team, particularly if you have weight loss, diarrhea or any other prolonged symptoms.

Financial Advice & Assistance

Support and information directory

A wide range of organisations and health professionals can help you manage the financial impact of cancer.

Financial help

- Financial Counselling Australia Information about financial counselling and help to find a counsellor. **- 1800 007 007 - financialcounsellingaustralia.org.au or debtselfhelp.org.au**
- MoneySmart Free financial tips and safety checks from the Australian Securities and Investments Commission (ASIC). **- 1300 300 630 - moneysmart.gov.au**
- Financial Information Service (FIS) Free, confidential service from the Department of Human Services to help with investment and financial decisions. **- 132 300 (say 'Financial Information Service') - humanservices.gov.au (type 'FIS' in the search box)**
- Financial Planning Association of Australia (FPA) Information about financial planning and help to find a financial planner. **- 1300 626 393 - fpa.com.au**
- Cancer Council Pro Bono Program Program that can connect you with a financial planner or accountant; free assistance for eligible clients. **- 13 11 20**

Government benefits

- Department of Human Services Includes Centrelink and Medicare; financial support for people in need. **- 132 717 (Centrelink) - 132 011 (Medicare) - humanservices.gov.au**
- Pharmaceutical Benefits Scheme (PBS) Help with cost of prescription medicines. **- 1800 020 613 - pbs.gov.au**

Bankruptcy

- Australian Financial Security Authority (AFSA) Information about bankruptcy and personal insolvency agreements. **- 1300 364 785 - afsa.gov.au**
- Dispute resolution Financial Ombudsman Service (FOS) Free, independent service for resolving disputes with financial services. **- 1800 367 287 - fos.org.au**
- Credit and Investments Ombudsman (CIO) Free, independent service for resolving disputes with financial services. **- 1800 138 422 - cio.org.au**

- Telecommunications Industry Ombudsman (TIO) National independent dispute resolution scheme for complaints about phone or internet services. **- 1800 062 058 - tio.com.au**

Legal advice

- National Association of Community Legal Centres (NACLC) The peak national body for Australia's community legal centres, which provide free legal services. **- 02 9264 9595 - naclc.org.au**
- Cancer Council Pro Bono Program Program that can connect you with a lawyer if you need legal advice; free assistance for eligible clients. **- 13 11 20**
- No Interest Loan Schemes NILS - Good Shepherd Microfinance Information about NILS providers. **- 13 NILS (13 64 57) - nils.com.au**

Taxation Australian

- Taxation Office Tax information. **- 13 28 65 - ato.gov.au**

Psychological Tips

Addressing your psychological well-being can help you feel more relaxed and in control, cope better during treatment, overcome anxiety and depression, and enjoy life.

Tips to help you improve your psychological well-being:

- Focus on what you can change, not on what you can't change.
- Cancer means something different to each individual. Everyone experiences cancer differently. so remember your experience is unique to you.
- Talk about your feelings. Reach out to family and friends, other cancer patients
- Make healthy lifestyle choices. Pay attention to your needs for rest, nutrition, exercise and private time.
- Seek professional counselling, including individual, couple, family and/or group therapy and support groups.
- Try mind-body techniques, such as relaxation therapies, laughter therapy, stress management interventions

The Cancer Council have a comprehensive library of patient information booklets which address psychological matters, including assistance for carers in caring for someone with cancer. Refer **www.cancer.org.au**

Travel Assistance

Patients attending consults and / or receiving treatment away from home are entitled to some financial assistance. There is a website at https://www.medistays.com.au which provides information on registering and applying for travel and accommodation assistance.

Even when you are receiving treatment, you are able to travel nationally and internationally. Travel insurance can be obtained; here are some websites which can assist you-

https://fastcover.com.au/travel-insurance/can-you-get-travel-insurance-if-you-have-cancer#NewsLetter

https://www.allcleartravel.com.au/travel-insurance/cancer/

https://www.tga.gov.au/travelling-medicines-and-medical-devices

https://www.humanservices.gov.au/individuals/services/medicare/travelling-overseas-pbs-medicine

Resources

Websites

www.netpatientfoundation.org.au

www.incalliance.org

www.cancer.org.au

www.unicornfoundation.org.au

www.prostate.org.au

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About the Unicorn Foundation

The Unicorn Foundation was formed in 2009 by Simone Leyden (CEO and co-founder) and Dr John Leyden (Chair and co-founder) due to the experience they had with their sister Kate's diagnosis with pancreatic neuroendocrine cancer. The Foundation is an independent medical not-for-profit charity directed towards improving the outcomes of patients with NETs.

The mission of the Unicorn Foundation is:

- to assist and support patients and carers, through support groups and access to networks of expertise
- to lobby for access to new and appropriate investigations and treatments
- to raise awareness and knowledge of neuroendocrine cancers within the medical community and general public
- to encourage and support Australian based research in the area of neuroendocrine cancers.

If you would like to know more about the Unicorn Foundation or get involved please visit our website **www.unicornfoundation.org.au** or email **info@unicornfoundation.org.au**. All donations are most welcomed as we continue our work to improve the outcomes of NET patients.

Glossary

What does that word mean?

Use this glossary to find the meanings of important terms that are highlighted in this brochure.

Adrenal gland: A gland near the top of the kidney that creates hormones, like adrenaline and cortisol. Your body has 2 adrenal glands.

Adrenocorticotropic hormone (ACTH): is a hormone produced in the front of the pituitary gland in the brain. Its function is to regulate levels of steroid hormone cortisol which is released from the adrenal gland

Aggressive: A term used to describe the speed or extent to which a tumour grows and spreads.

Atrophic gastritis: Chronic inflammation of the stomach mucous membrane that leads to decreased acid secretion, increased gastrin levels andenlargement of enterochromaffin-like (type of neuroendocrine cell) cells resulting in increased CgA levels and histamine production.

Biomarkers: a measurable indicator of the severity or presence of some disease state.

Biopsy: A procedure where a small amount of tissue is removed from the body and examined under a microscope or using other tests to find out if there is a tumour, its type an extent.

Calcitonin: A 32-amino acid peptide hormone produced by thyroid C cells that modulates blood calcium levels by opposing the effects of parathyroid hormone, which causes release of calcium from the bone. Calcitonin functions to lower blood calcium levels by inhibiting osteoclast limiting bone cell activity and reducing absorption and reabsorption of calcium in the intestine and kidney, respectively. Calcitonin is also secreted by medullary carcinomas of the thyroid and occasionally by other neuroendocrine tumours.

Carcinoid: Has the same meaning as NET or GEP-NET (see below). The words may be used in place of one another.The term carcinoid is an older term used before NET or GEP-NET

Carcinoid crisis: A potentially life-threatening heart-lung condition caused by sudden release into the systemic circulation of hormones from a NET. It may occur as a result of an event (e.g food, alcohol, exercise, or a drug administration) or during a diagnostic test. Liver directed therapies may increase the risk of carcinoid crisis An intravenous somatostatin analogue (such as Octreotide) and appropriate heart and

blood support is often needed to address dangerous changes in heart and blood function.

Carcinoid syndrome: A set of symptoms that occur when a functioning NET releases the hormone serotonin. The symptoms may be wheezing, flushing, diarrhea etc and can be sudden or severe.

Carcinoma: Cancer that starts in the skin or in tissues that line or cover internal organs.

Chemotherapy: The use of drugs to destroy cancer cells.

Chromogranin A (CgA): Detection of elevated plasma levels of CgA has be shown to be a sensitive biomarker for neuroendocrine tumours.

Chronic atrophic gastritis type A: Chronic inflammation of the stomach usually caused by an autoimmune response associated with loss of parietal cells of foci of endocrine cell (ECL) enlargement

Cushing syndrome: Excess secretion of cortisol from the adrenal cortex, which may be secondary to hypersecretion of ACTH from the pituitary, resulting in rapid weight gain, particularly of the trunk and face with sparing of the limbs (central obesity), growth of fat pads along the collar bone and back of the neck (buffalo hump) and a round face often referred to as a `moon face'. Other symptoms include excess sweating, thinning of the skin and bruising, fatigue, osteoporosis, and diabetes. Cushing was a pioneer in the management of pituitary tumours.

Differentiation/differentiated cells: In tumour cells, differentiation refers to how developed the cells are. Differentiated tumour cells look more like normal cells. Undifferentiated or poorly differentiated tumour cells don't have the structure of normal cells, and don't work the way normal cells do. Poorly differentiated tumour cells usually have a greater chance of being faster growing and more likely to spread

Duodenum: The first part of the small intestine, connected to the stomach. The duodenum gets enzymes from the pancreas and chemicals from the liver and the gallbladder to help with digestion.

Endocrine system: A group of glands and organs that control different body functions by producing and releasing hormones.

Functional NET: A NET that releases hormones and may cause many different symptoms. Also called a secretory NET.

Gastrin: A hormone released by the pancreas that tells the stomach to produce digestive acids and enzymes.

Gastrinoma: A neuroendocrine tumour coming from gastric mucosa, mainly (60%) occurring the duodenum, that overproduces and secretes gastrin, thereby giving rise to the respective gastrinoma. The typical symptoms of a gastrinoma include peptic ulceration and excessive acid production (e.g. indigestion acid reflux symptoms, abdominal pain, gastrointestinal bleeding, and duodenal perforation). Secretory diarrhoea is also caused due to high gastric output in the duodenum that neutralises the pancreatic enzymes.

Gastroenteropancreatic NET (GEP-NET): A NET that most often starts in the gastrointestinal tract or pancreas

Gastrointestinal (GI) tract: Another name for the digestive system. It includes the mouth, throat, oesophagus, stomach, small intestine, large intestine, rectum and anus.

Glucagon: A hormone released by the pancreas that raises glucose (sugar) levels in the blood.

Glucagonoma: A pancreatic NET derived predominantly from alpha cells of the pancreas that secrete glucagon. The inappropriate glucagon secretion by the tumour cells can cause diabetes, mellitus, cachexia, anaemia, venous thrombosis, migratory necrolytic erythema, diarrhoea, and neuropsychiatric symptoms.

Grade: A system of classifying tumour cells. The cells are graded based on how they look under a microscope and how quickly the tumour is likely to grow and spread. Low-grade tumours (grades 1 and 2) look like the tissue around them. They are less aggressive. High-grade tumours (grades 3 and 4) do not look like the tissue around them. They are more aggressive.

Hormone: A substance, usually a protein, that is released and travels through the bloodstream to different organs. Hormones help control how some of the organs in the body work.

Hyperglycaemia: Having high levels of glucose (sugar) in the blood. Symptoms include dry mouth, thirst, frequent urination (including at night) blurry vision, and dry, itchy skin.

Hypoclorydria: Having low levels of hydrochloric acid in the stomach. Symptoms include halitosis (bad breath), heartburn, bloating or belching, gas right after eating, and indigestion.

Hypoglycaemia: Low levels of glucose (sugar) in the blood. Symptoms include dizziness, headache, tiredness and confusion.

Hypokalemia: Low levels of potassium in your blood. It may be caused by diarrhoea. Low levels can cause muscle weakness, cramp, twitch and if severe paralysis. It can also cause abnormal heart rhythms.

Insulin: A hormone released by the pancreas that lowers glucose (sugar) levels in the blood.

Insulinoma: A pancreatic NET derived predominantly from beta cells of the pancreas that is benign in 90% of cases. The tumour oversecretes insulin, causing intermittent symptoms of hypoglycaemia (I.e., visual disturbance, irritability, bizarre behaviour, sweating, headache, tachycardia, anxiety, somnolence, paraesthesia, etc.). In more severe cases, seizures, stupor, coma and even permanent brain damage may occur.

Lesions: Areas of abnormal tissue that may or may not be cancerous.

Metastasise: To spread from one part of the body to another. The words `localised', `regional', and `distant' are sometimes used to describe how much a NET has spread.

Multiple Endocrine Neoplasia syndrome type 1: MEN1 is a hereditary condition associated with tumours of the endocrine (hormone producing) glands. It is associated with an increased risk of developing multiple cancerous and non-cancerous tumours in glands such as the parathyroid, pituitary, and pancreas. This disorder affects approximately 1 in 30000 people.

Non-functional NET: A NET that doesn't release hormones. This type of NET may only cause symptoms when it grows. Also called a non-secretory NET.

Pancreas: An organ that produces hormones and enzymes that help your body digest food.

Pellagra: A condition caused by low levels of niacin (a B vitamin) in the blood. Symptoms include rash, dark pigmentation on skin, swollen mouth and bright red tongue, vomiting and diarrhoea, headache, fatigue, depression, disorientation or confusion, memory loss.

Proteins: The basic building blocks of tissue and other structures in the body. An enzyme is a kind of protein that causes chemical changes in the body.

Radiation: A form of therapy used to kill cancer cells by damaging their DNA. Radiation can damage normal cells too, so treatment should be carefully planned to decrease side effects.

Radiology: The use of radiation to treat or diagnose disease.

Radiotherapy: The use of high-energy radiation to destroy cancer cells and shrink tumours. The radiation may come from a machine outside the body or from radioactive material that is placed in the body near cancer cells.

Serotonin: A hormone made by certain types of cells in the body, mostly in the gastrointestinal tract. Serotonin helps with various functions, including digestion.

Somatostatin: A hormone that stops the release of other hormones, including gastrin, insulin, glucagon, and serotonin (see definitions for these hormones in this glossary).

Somatostatin analogues: Synthetic analogues of the peptide hormone somatostatin that have a longer half-life in circulation and can be used for imaging or as therapeutic agents.

Specialised cells: Cells that have specific jobs in the body. They start as unspecialised cells, also known as stem cells, which are present in babies still in the womb. Unspecialised cells can turn into any kind of cell. The DNA in the cell determines the kind of cells they will become. The cells then grow and change shape, becoming specialised cells.

Syndrome: A set of symptoms that occur together. A syndrome may be a sign of a certain disease or it may mean there's an increased chance of developing the disease. For example hypoglycaemia syndrome may be caused by a type of NET called an insulinoma, and Zollinger Ellison syndrome may be caused by a type of NET called gastrinoma.

Thymus: An organ near the base of the neck that produces infection-fighting cells.

Thyroid: A small gland in the neck, just under the skin below the Adam's apple. It produces thyroid hormones which control metabolism.

Tumour: An abnormal growth or mass in the body caused when cells grow out of control or don't die when they are supposed to. A tumour may be non-cancerous (benign) or cancerous (malignant).

Tumour burden: The number of cancer cells, size of a tumour, or the amount of cancer in a person's body.

Ulcer: A round sore on an external or internal surface of the body, caused by breakdown in the skin or mucous membrane which fails to heal.

Unspecialised cells: Also known as stem cells. These cells are present in babies still in the womb. They can turn into any kind of cell. The DNA in the cell determines the kind of cells they will become. The cells then grow and change shape, becoming specialised cells with specific jobs in the body.

Vasoactive intestinal peptide (VIP): A substance released by the pancreas that causes watery diarrhoea if levels are too high.

Von Hippel-Lindau syndrome: An inherited genetic disorder associated with renal angioma, renal cell carcinoma and pheochromocytoma (a neuroendocrine tumour of the medulla of the adrenal glands). The disorder is caused by mutations of VHL tumour suppressor gene on the short arm of chromosome 3.

Wheezing: A whistling sound made during breathing that happens when airways become partially blocked. Some tumours can squeeze an airway and cause the blocking. It can also be caused by the action of some hormones

Zollinger Ellison Syndrome: A disorder caused by excess secretion of gastrin from a duodenal or pancreatic neuroendocrine tumour resulting in excessive secretory diarrhoea and intractable peptic ulcers.

Unicorn Foundation

Seeking the cure for Neuroendocrine Cancers