



Unicorn
Foundation

*Seeking the cure for
Neuroendocrine Cancers*

Neuroendocrine tumours: A guide for healthcare professionals



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First edition: 2015

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Contents

Introduction	7
About NETs	8
What are NETs?	8
Epidemiology.....	9
Gastroenteropancreatic NETs (GEP-NETs)	9
Gastric NETs	9
Small bowel NETs.....	10
Large bowel NETs.....	10
Rectal NETs	10
Pancreatic NETs (pNETs): functioning and non-functioning	11
Bronchopulmonary (lung) NETs	11
Thymic NETs	12
Testicular NETs	12
Ovarian and endometrial NETs	12
Multiple endocrine neoplasias (MEN syndrome).....	12
Pheochromocytoma	14
Paraganglioma	14
Medullary thyroid carcinoma	14
Adrenocortical carcinoma (ACC).....	14
Merkel cell carcinoma (neuroendocrine tumour of the skin)	14
Neuroblastoma.....	14
Associated conditions	15
Von Hippel–Lindau syndrome (VHL).....	15
Neurofibromatosis type 1	15
Tuberous sclerosis.....	15
Clinical presentation	16
Carcinoid syndrome	17
Carcinoid crisis.....	17
Carcinoid heart disease	18
Diagnosis	19
Tests.....	19
Classification, staging and grades of NET	22
Clinical management	23
The role of NET multidisciplinary teams (NET MDT)	23
Surgical management	24
Curative surgery.....	24

Palliative surgery.....	24
Cardiac and thoracic surgery.....	24
Perioperative and anaesthetic management of NET patients.....	24
Medical management.....	24
Somatostatin analogues.....	24
Sandostatin LAR® (depot preparation of octreotide).....	25
Somatuline® Autogel (depot preparation of Lanreotide).....	25
Chemotherapy.....	25
Targeted molecular therapies.....	25
Peptide receptor radionuclide therapy (PRRT).....	26
Liver directed therapies.....	26
Symptom control.....	27
No treatment.....	27
Clinical trials.....	27
The experience of having a neuroendocrine tumour.....	28
First chapter: Something feels wrong.....	28
Second chapter: Diagnosis.....	28
Third chapter: Transition.....	30
Fourth chapter: Living with a NET.....	31
The NET specialist.....	32
Questions to ask during the consultation.....	32
Patient support.....	34
Clinical trials.....	34
Complementary (alternative) therapies.....	34
Diet.....	35
Resources.....	38
Websites.....	38
Acknowledgements.....	38
About the Unicorn Foundation.....	38
Glossary: What does that word mean?.....	39

*“I will never forget the complete and utter shock,
fear and sadness that engulfed me when I was told
I had NET cancer.”* (Jamie, age 37, Adelaide)

Introduction

This book has been developed for healthcare professionals to improve understanding and knowledge about neuroendocrine tumours (NETs). It contains information to help you understand diagnosis and treatment options. This booklet may also help when explaining this complex diagnosis to a patient's family and friends.

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.

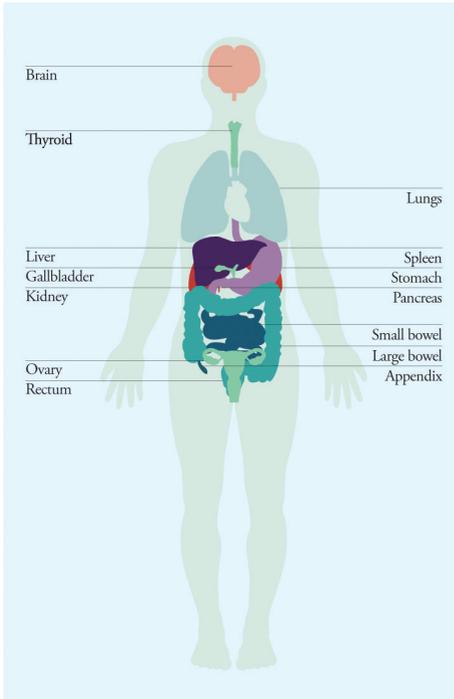
This booklet was developed by medical professionals with input from NET patients. New treatments and technologies are continually being developed, so this information may change in the future.

Neuroendocrine tumours were first described over 100 years ago by the German pathologist, Siegfried Oberndorfer (1876–1944), who was the first to characterise the nature of the tumours and refer to them as 'benign carcinomas'. He named them 'karzinoide' ('carcinoma-like'), emphasising in particular their benign features. Oberndorfer later amended his classification to include the possibility that these small bowel tumours could be malignant and also metastasise.

Unfortunately, for more than 50 years there have been many medical misconceptions and much misunderstanding about NETs. Fortunately, over the last 10 years, there has been significant improvement in the diagnosis, management and understanding of neuroendocrine tumours .

About NETs

What are NETs?



NETs are a complex group of tumours that develop predominantly in the digestive or respiratory tracts, but can occur in other areas of the body. These tumours arise from neuroendocrine cells. The main function of neuroendocrine cells in the body is to create, store and secrete a variety of peptides (little proteins) and hormones for normal bodily functions.

Like all cancers, NETs develop when these neuroendocrine cells undergo changes, causing them to divide uncontrollably and grow into a tumour (an abnormal tissue mass).

Neuroendocrine tumours can be indolent (very slow-growing) or can be more aggressive. In 1907, when neuroendocrine tumours

were first classified, they were named 'carcinoid' (meaning 'cancer-like') as they seemed to grow slowly and were therefore not thought to be truly cancerous. The use of 'carcinoid' is being phased out in medical literature, as we now know that these tumours can be malignant.

Current terminology is simply neuroendocrine tumours (or NETs) or with the primary location of the tumour added: for example, lung NET, bowel NET or pancreatic NET.

Over the last two decades there has been a significant increase in the incidence of NETs, with most of them being sporadic (not related to another disease or inherited). However, in patients with genetic conditions such as multiple endocrine neoplasia (MEN), Von Hippel–Lindau (VHL) disease and neurofibromatosis (NF), there is an increased risk of developing these tumours.

Other neuroendocrine tumours are found outside the gastrointestinal or respiratory system, such as:

- in the adrenal glands—pheochromocytoma and adrenocortical carcinoma
- in the nervous system—paragangliomas
- in the skin—Merkel cell tumours
- in the thymus—thymic NET
- in the testes and ovaries
- in the thyroid gland—medullary thyroid cancer
- neuroblastoma (a neuroendocrine cancer in children).

Although NETs share common cellular features, their behaviour is highly dependent on the cells that make up the tumour (as seen under the microscope). The cells can be classified into well-differentiated (low and intermediate grade) or poorly differentiated (high grade), which characterises their growth pattern (slow growing to aggressive) and gives an indication of prognosis and the appropriate treatments (see later in this booklet for grading systems).

Epidemiology

Previously considered to be rare, NETs are increasing in incidence (3–4/100,000) in Australia—equivalent to testicular cancer, cervical cancer, multiple myeloma, Hodgkin lymphoma and cancers of the central nervous system.

Prevalence (35/100,000) is much higher than incidence due to five-year survival rates of approximately 50–60%.

The prevalence of gastroenteropancreatic NETs (GEPNET) is second only to colorectal cancers and is higher than most other gastrointestinal cancers, including pancreatic, gastric, oesophageal and hepato-biliary carcinomas.

Gastroenteropancreatic NETs (GEP-NETs)

Traditionally, these NETs were classified by the site of origin as:

- foregut—stomach, duodenum, pancreas, bronchus (lung)
- midgut—small bowel and beginning of large bowel, including appendix
- hindgut—most of large bowel, rectum and genitourinary system (testes, ovaries).

Now, the term **gastroenteropancreatic (GEP-NET)** is used.

Gastric NETs

Gastric NETs represent less than 1% of all gastric cancers; however, their detection has increased due to the increased use of gastroscopy.

There are four types of gastric NET:

- **Type I** is the most common and represents about 70–80% of all gastric NETs. These are associated with atrophic gastritis and an overproduction of gastrin (hypergastrinaemia). Typically, these are small polyps (less than 1–2 cm) and are 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.

There is a potential association with hypergastrinaemia induced by long-term use of proton pump inhibitors (anti-acid medications) used to control gastric reflux or dyspepsia.

- **Type II** accounts for around 5% of gastric NETs. These 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. The tumours in the stomach are often quite small and can be managed conservatively with regular monitoring including endoscopic ultrasound.
- **Type III** accounts for 15–20% of gastric NETs. These tumours are often larger (>2 cm) and can metastasise. They are not related to over-production of gastrin and need to be surgically removed.
- **Type IV** is a very rare type of gastric NET and is the most difficult to manage. Tumours are often large and metastatic at diagnosis.

Small bowel NETs

There are many different types of **duodenal NET**. These NETs produce many hormones and peptides such as serotonin, calcitonin and gastrin somatostatin.

Patients may present with carcinoid syndrome (see later in this booklet), abdominal pain or fatigue due to anaemia.

Jejunum and ileum NETs are often asymptomatic, slow-growing and small, which makes diagnosis in the early stages difficult. Often, when the diagnosis is made, the tumour is larger and may have metastasised—at which time the patient may present with abdominal pain, carcinoid syndrome or a bowel obstruction.

Large bowel NETs

Appendiceal NETs are usually discovered incidentally—quite often during surgery for a suspected appendicitis. If the tumours are less than 1 cm in size, curative surgery is often performed.

Another group of tumours that arise from the appendix are the **goblet cell carcinomas**, so named because they have ‘goblet’ shaped cells when viewed under a microscope. Patients often present late with acute appendicitis, abdominal pain or abdominal mass and a significant proportion of females also have metastases on the ovary at the time of diagnosis.

Colon NETs are rare and can be large, aggressive, have the potential to spread and may present with bowel obstruction and bleeding. If the NET has already metastasised to the liver, other symptoms classic of carcinoid syndrome—e.g. wheezing, facial flushing, watery diarrhoea—may also be present.

Rectal NETs

These account for about 27% of all NETs in the gastrointestinal tract and 16% of all NETs. In around half of the cases, the tumour is discovered incidentally. Patients may present with symptoms such as rectal bleeding or change in bowel habit, but often they are asymptomatic. Patients may present with metastatic disease due to a lack of symptoms.

11

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 by the tumours:

- **Insulinoma**—these 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 insulin causing low blood sugar and symptoms such as disorientation, confusion, sweating, trembling and heart palpitations.
- **Glucagonoma** are tumours that secrete glucagon that can raise blood sugar (hyperglycaemia) causing fatigue, frequent urination, dry mouth, nausea, blurred vision, weight loss, anaemia and depression. Characteristic of this tumour is a red rash (migratory erythema) localised in the groin.
- **Somatostatinoma** are tumours that secrete somatostatin, which causes symptoms of diabetes, diarrhoea, steatorrhoea (fatty pale stools) and weight loss.
- **VIPoma** are tumours that secrete vasoactive intestinal peptide, which causes severe watery diarrhoea, which leads to electrolyte imbalances in the blood such as low potassium (hypokalaemia) and low chloride (hypochlorhydria), weakness and fatigue.

The **non-functioning pNETs** still produce hormones and peptides but with no embolisation syndrome and often present late due to local symptoms (abdominal pain, back pain) due to a growing mass.

“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)

Bronchopulmonary (lung) NETs

The lung is the primary site for about 25% of NETs, which 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 bronchial NETs.

There are four types of lung NETs:

- i) Typical carcinoid (TC)
- ii) Atypical carcinoid (AC)
- iii) Small cell lung cancer (SCLC)
- iv) Large cell neuroendocrine carcinoma (LCNEC).

Around 70% of patients will have the atypical type. Atypical bronchial NETs behave more aggressively than typical ones, although metastases develop in up to 20% of patients with typical bronchial NETs. NETs of the lung can occur at all ages.

A small proportion of bronchial NETs produce various symptoms related to hormone overproduction: carcinoid syndrome (serotonin), Cushing syndrome (ACTH) and acromegaly (growth hormone).

One other presentation is diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). This is a rare disorder and information on DIPNECH is limited, especially with regard to its management and prognosis. It has generally become accepted that DIPNECH is a precursor lesion to lung NETs.

Thymic NETs

NETs of the thymus are uncommon, accounting for 5% of all thymic tumours. Most are asymptomatic until they have grown to a size that causes local compression of structures in the chest (trachea, large veins). Thymic NETs can be aggressive and treatment options include surgical removal and chemotherapy. Two to five per cent of patients with MEN1 develop thymic NETs.

Testicular NETs

Testicular NETs are rare tumours and are responsible for 1% of all testicular cancers. They can be primary or a metastasis and all patients must be investigated for NETs elsewhere in the body. They present as a painless scrotal mass and do not commonly produce symptoms of 'carcinoid syndrome'. Surgical removal (orchidectomy) is the treatment of choice, and long-term follow-up is indicated because of the potential for metastases.

Ovarian and endometrial NETs

NETs of the ovary and endometrium are rare. Unfortunately most are diagnosed late and have metastasised. Patients can present with symptoms related to carcinoid syndrome and carcinoid heart disease.

“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)

Multiple endocrine neoplasias (MEN syndrome)

Multiple endocrine neoplasia (MEN) is characterised by the occurrence of tumours involving two or more of the endocrine glands. There are four major forms of MEN and these may be inherited (autosomal dominant) or sporadic.

13

- **MEN 1:** Ninety-five per cent of patients develop parathyroid tumours (hyperparathyroidism), which is the most common feature of MEN 1; 40% develop pNETs; and 30% develop anterior pituitary tumours. Other tumours associated with MEN 1 are adrenocortical tumours, thymic NETs and gastric NETs. Patients and families need to have genetic testing (MEN1 gene) and should be managed by an expert multidisciplinary team.
- **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 pheochromocytomas and neuromas of the skin and intestine. It is an aggressive form of MEN.
 - **Familial medullary thyroid carcinoma** (MTC) does not have the other tumours that are associated with MEN 2.

“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)

Pheochromocytoma

Pheochromocytomas (PH) are rare neuroendocrine tumours with an incidence of one to four new cases per million/year. They arise from the adrenal (adrenal medulla) glands, which lie atop the kidneys. Sixty per cent of these tumours produce excessive amounts of catecholamines (adrenaline and noradrenaline), which produce symptoms such as:

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

Forty per cent do not secrete these hormones and are asymptomatic, remaining undiagnosed for many years. Pheochromocytomas affect men and women equally with a peak age at diagnosis between 40–50 years, but 20% of all pheochromocytomas are found in children and adolescents.

Paranganglioma

Paranganglia are groups of cells that are 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. A tumour involving the paranganglia is known as a paranganglioma.

Parasympathetic parangangliomas are mainly located in the head and neck, usually do not secrete hormones and rarely metastasise. Sympathetic paranganglioma are found in the thorax, abdomen and pelvis, secrete hormones such as adrenaline or noradrenaline, and metastasise in 20% of cases. Over the last 10 years the understanding of parangangliomas has improved. More than a third of patients with paranganglioma have a hereditary predisposition for the disease. Surgery is the only curative treatment for parangangliomas, but chemotherapy and peptide receptor radionuclide therapy (PRRT) have roles in the management of parangangliomas.

Medullary thyroid carcinoma

Medullary thyroid cancer (MTC) is a rare form of cancer of the thyroid gland in the neck. When there is no family history of the disease and MTC occurs as an isolated case, it is called sporadic MTC. In 25% of all cases, MTC occurs as part of the inherited multiple endocrine neoplasia type 2 (MEN2) syndrome.

Adrenocortical carcinoma (ACC)

Adrenocortical cancer (ACC) is often known simply as adrenal cancer and affects one to two people per million per year, making it a rare form of cancer. ACC occurs in the outer part (cortex) of the adrenal gland. In adults, it most commonly occurs in the fourth or fifth decades of life. In children, the disease may be less aggressive and so treatment differs from that of adults.

Merkel cell carcinoma (neuroendocrine tumour of the skin)

Merkel cell carcinoma (MCC) is a rare but aggressive skin cancer and presents as a solid purplish coloured 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 presence of Merkel cell polyoma virus. Surgical resection and local radiotherapy are the mainstays of current treatment.

Neuroblastoma

Neuroblastoma is the most common solid tumour of childhood. It is a neuroendocrine tumour, arising from any neural crest element of the sympathetic nervous system. It most frequently originates in one of the adrenal glands, but can also develop in nerve tissues in the neck, chest, abdomen or pelvis. It is almost exclusively a childhood cancer occurring most commonly up to the age of five years.

Associated conditions

Von Hippel–Lindau syndrome (VHL)

Von Hippel–Lindau syndrome (VHL) is an inherited cancer syndrome caused by mutations of the VHL gene on chromosome 3p25. It affects both sexes equally and has an incidence of 1/30,000–40,000 people.

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 (NF1 tumour suppressor gene) disorder that affects 1/3000 people.

Patients usually have 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 benign and malignant tumours in the body. 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.

Tuberous sclerosis

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

There is evidence that these patients may be at risk of developing insulinomas—a neuroendocrine tumour of the pancreas.

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 produce no symptoms.

The symptoms can be vague and non-specific (e.g. lethargy) or similar to those of other, more common conditions such as irritable bowel syndrome, Crohn disease, peptic ulcer disease, other gastrointestinal/digestive disorders, asthma and facial flushing associated with menopause.

The majority of doctors are unfamiliar with NETs and therefore less likely to suspect a NET cancer in their initial investigations.

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 metastasise, the most common site for metastatic tumours ('secondaries') is the liver. Other areas of spread can include the bones, the lungs and the lymphatic system.

Many GEP-NETs have an associated syndrome caused when the neuroendocrine cells over-produce hormones. The most common is **carcinoid syndrome**, which can occur in up to 35% of patients and is caused when an excess of hormones such as serotonin, histamine, somatostatin and chromogranin A are produced.

The symptoms of carcinoid syndrome vary and can often be highly individual.

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:** can occur in up to 20% of patients with carcinoid syndrome and may be associated with facial flushing. Unlike asthma, wheezing of carcinoid syndrome may not be triggered by colds/flu, 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:** 10–20% of NET patients have carcinoid heart disease at diagnosis. The right side of the heart is mostly 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).
- Rarely, some patients with NETs develop a condition known as **pellagra (niacin deficiency)**, which presents as brown patches on the skin, beefy red tongue and mental changes.

Not everyone with NETs will have this collection of symptoms, even if their disease has spread.

Carcinoid crisis

Sometimes patients may suffer a particularly bad episode of carcinoid syndrome triggered by stress, general anaesthetic or certain treatments. Symptoms include intense flushing, diarrhoea, abdominal pain, wheezing, palpitations, low or high blood pressure, altered mental state and, in extreme cases, coma.

Carcinoid heart disease

18

The hormones released by the NETs into the bloodstream (serotonin) can affect the heart by causing thick 'plaques' within the heart muscle. The heart valves (tricuspid and pulmonary) on the right side of the heart are also affected and become 'leaky', causing symptoms such as breathlessness, fatigue, enlarged liver and swollen ankles. Up to 20% of patients with carcinoid syndrome present with carcinoid heart disease and without treatment can develop right heart failure. With somatostatin analogues, the progression of carcinoid heart disease is significantly slowed and other symptoms of heart failure can be managed with diuretics. Some patients with carcinoid heart disease may be suitable for cardiac surgery to replace the leaking valves.

ECG and chest x-ray may provide clues to the diagnosis of carcinoid heart disease but the most sensitive test is echocardiography of the heart. Echocardiography should be performed regularly to monitor the function of the heart in patients with neuroendocrine tumours.

Diagnosis

“If you don’t suspect it, you can’t detect it.”

Neuroendocrine tumours 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 with many tests performed before the diagnosis is made.

On average it takes 4 to 7 years for this diagnosis because NETs often present with symptoms that are associated with common conditions and also there is a widespread lack of awareness of the disease in the medical community.

Patients need numerous tests and scans to obtain information about the disease, its spread and the rate of growth.

Tests

Tests include:

- **Biopsy**
- **Blood tests** (NET biomarkers particularly chromogranin A (CgA) and for evidence of a rise in certain peptides and hormones in the blood).
- **Full blood count**
 - 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.
- **Chromogranin A (CgA)** A glycoprotein that is produced and released into the bloodstream by neuroendocrine cells. It is a sensitive and specific marker, with blood levels of chromogranin A more than twice the reference range usually indicating the presence of a NET. Chromogranin blood

levels can correlate with tumour burden and activity and are often used for monitoring the disease or response to treatments. It is important to use the same laboratory so that changes in the levels can be interpreted consistently. Certain conditions can cause elevation in the blood chromogranin A levels, especially:

- anti-acid medication especially the proton-pump inhibitors (omeprazole, esomeprazole, pantoprazole).
 - kidney and liver diseases.
 - prostate cancer.
 - atrophic gastritis.
- **Urine tests:** for 5-HIAA (5-hydroxyindole-3-acetic acid), which is excreted into the urine. Patients should be advised to avoid foods very high in serotonin/tryptophan (chocolate, olives, bananas, pineapple, all tomato products, plums, eggplant, avocado, kiwi fruit, walnuts, brazil nuts, cashew nuts, tea, coffee and alcohol), and certain cough, cold and flu remedies 3 to 7 days before the test.
 - **Endoscopic procedures:**
 - Gastroscopy and colonoscopy
 - Wireless capsule endoscopy
 - Endoscopic ultrasound
 - Bronchoscopy.
 - **CT:** When looking at the liver images, a multi-phase liver scan must be requested (non-contrast-arterial phase, portal venous and delayed). If this is not requested, often it is difficult to detect NETs in the liver.
 - **MRI**
 - **Ultrasound:** Remember that good ultrasound examinations are dependent on the skill of the sonographer.
 - **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 routinely performed during the initial assessment stage of any NET patient, and as a part of the ongoing follow-up and management.
 - **PET:** Increasingly, PET scans are being combined with CT scans to provide more detailed images.
 - **Gallium-68 (Ga⁶⁸) PET:** This test can help reveal the site of NET tumours. Most NETs have somatostatin receptors on their cell surfaces. Gallium-68 is a radiotracer which, when combined with a peptide (DOTATATE), binds to

these somatostatin receptors on NET tumours. This PET scan, when combined with CT—known as Ga68 PET/CT—is highly sensitive (90%) and specific (82%) for determining the location and biological activity of NETs. This test is essential in the assessment of any patient with a NET.

- **¹⁸F-FDG PET** ([¹⁸F-fluorine] fluoro-D-glucose): ¹⁸F-FDG is a glucose analogue with the attached radiotracer ¹⁸F-fluorine. This compound is taken up by cells that rapidly metabolise glucose, which occurs in many different types of cancer including types of NETs. Patients are required to fast beforehand to minimise the natural blood glucose and insulin levels and after injection of the ¹⁸F-FDG they must remain quiet and still so that the tracer is taken up preferentially by the cancer cells rather than normal tissues like muscle. ¹⁸F-FDG PET/CT should be combined with the Gallium-⁶⁸ PET/CT for staging of NET disease.
- **Octreotide scan:** The Octreoscan® uses octreotide combined with radiotracer Indium-111 (Indium¹¹¹) and then injected via a vein in the arm, it binds to the somatostatin receptors on the tumour surface. The tumours are then detected using a gamma camera, 'lighting up' on the screen as radioactive 'hot spots'. In Australia, the more sensitive Gallium-⁶⁸ PET/CT scan combined with an ¹⁸F-FDG PET/CT is the 'gold standard' for detecting NET primaries or metastases and should replace the octreotide scan.
- **MIBG:** This is another nuclear medical scan in which the radiotracer iodine-23-meta-iodobenzylguanidine (MIBG) is injected into the vein and then the whole body is scanned using a 'gamma camera'. This scan is used to detect pheochromocytoma and neuroblastomas and NETs. It is important for patients to stop taking certain medications a few days before this test, and often iodine tablets are prescribed to help protect the thyroid gland from taking up too much of the radiotracer. This investigation usually involves taking separate scans over 2 consecutive days and most patients are allowed home in between.
- **Bone scan**

“Because of the length of time before being diagnosed, my small intestine NETs metastasised to the liver. A bad case of menopause was the common answer from the range of specialists that I saw.” (Kathy , Adelaide)



PET/CT Scanner (Siemens)

Classification, staging and grades of NET

The European Neuroendocrine Tumour Society (ENETS) and Union for International Cancer Control (UICC) guidelines divide NETs into three grades: low (G1), intermediate (G2) and high (G3). The grade represents the aggressiveness of the tumour.

Grade	ENETs and UICC Differentiation	grading of NETs		
		Proliferation rate by mitotic rate (per 10/HPF)	Proliferation rate by Ki-67 index (%)	Biologic aggressiveness of the tumour
Low grade (G1)	Well differentiated	<2	≤2	Relatively indolent
Intermediate grade Grade 2 (G3)	Well differentiated	2-20	3-20	Moderately aggressive; less predictable
High grade Grade 3 (G3)	Poorly differentiated	>20	>20	Extremely aggressive

To determine the grades of the NET cells, an experienced pathologist reviews the slides under a microscope to see how many cells are dividing (mitotic figures) in a number of high power fields (HPF = 2mm²). The tissues are also stained for neuroendocrine markers (e.g. chromogranin, synaptophysin) and particularly the MIB antibody that is used for the Ki-67 index.

Clinical management

Patients should ideally be treated by a specialist multidisciplinary team (MDT). Each patient will have an individualised treatment plan. There are a number of treatment options available, depending on the type and location of the tumour, and the general wellbeing of the patient.

The role of NET multidisciplinary teams (NET MDT)

The care of NETs can be complex, and for the patient the journey can encompass 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 patient journey means that there has to be a collaboration between all key healthcare professional groups involved in recommending treatment for individual patients. This collaboration has been termed 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.

A MDT is a very important aspect for care when striving to achieve the best quality of life and the best outcome for NET patients. 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.

Studies have shown that NET patients who are managed by a NET MDT have better outcomes and quality of life compared to patients who do not have access to such groups.

Members of a NET MDT may include:

Oncologist	Radiologist	Pain Team
Gastroenterologist	Physician	Counselling Staff
Surgeon	General Practitioner/ Practice Nurse	Clinic Staff
Endocrinologist	Nurse Specialist	Palliative Care Team
Nuclear Medicine	Dietitian	Pathologist

Surgical management

Patients with NETs often undergo surgical procedures to remove the tumours.

The goal of surgery depends on the type of NET cancer, its location and size and whether there is a spread distant from the primary site. Different surgeons may be involved with NET cancers depending on their expertise and training (e.g. endocrine, colorectal, hepatobiliary and pancreatic, and cardiothoracic surgeons).

Most planned surgery for NET cancers should be carried out in 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 is potentially curative 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 to relieve symptoms caused by the tumour compressing or altering the function of 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 are at risk of 'carcinoid crisis' in the perioperative period or during surgery. The specialist should discuss this with the anaesthetist before surgery.

Medical management

Somatostatin analogues

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

Somatostatin analogues are synthetic 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 now evidence that these injections also slow the rate of growth of tumours. Somatostatin analogues are the mainstay of medical treatment for most NETs.

Sandostatin LAR® (depot preparation of octreotide)

Octreotide (an analogue of the naturally occurring somatostatin) is the active ingredient in Sandostatin LAR®. Octreotide is used instead of somatostatin because it is more potent, lasts longer in the body and is usually given as a monthly injection. Sandostatin LAR® blocks the somatostatin receptors and can slow the tumour growth and treat the symptoms of NETs.

Somatuline® Autogel (depot preparation of Lanreotide)

Lanreotide (an analogue of the naturally occurring somatostatin) is the active ingredient in Somatuline® LA. Lanreotide is 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.

Chemotherapy

This may be an option, especially for NET patients with pancreatic, bronchial or high-grade (G2/G3) NETs. Not all NETs respond equally to chemotherapy, therefore careful selection of patients is imperative so as to improve the chance of response and avoid unnecessary side effects and toxicity.

Many chemotherapy treatments involve intravenous drugs that are given in hospital as a day procedure; however, there are also oral chemotherapy agents. The NET doctor will discuss the most appropriate option with the patient.

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

Some of the current chemotherapeutic drugs used in the treatment of NETs include streptozotocin, 5-fluorouracil, etoposide, carboplatin, cisplatin, temozolamide and capecitabine.

Chemotherapy may sometimes be recommended after surgery (adjuvant therapy). Patients may be asked to be involved with current clinical trials looking into the different combinations of chemotherapy agents that are most appropriate 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. Angiogenesis is 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 (Afinitor®) is another medication for patients with pancreatic neuroendocrine tumours. 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)

Peptide receptor radionuclide therapy (PRRT) uses radiolabelled somatostatin analogues linked to peptides which target and bind to somatostatin receptors on the tumour cells.

The radionuclides commonly used in PRRT for neuroendocrine tumours are indium-111 (^{111}In), lutetium-177 (^{177}Lu) and yttrium-90 (^{90}Y). As the radionuclides 'decay' they emit radiation (high-energy particles) that cause disruption to the DNA of the tumour cells. The damage caused by these radionuclides is targeted to the tumour cells (within millimetres) and spares normal tissues that do not have the somatostatin receptor on their cell surface.

PRRT can be considered in both non-functioning and functioning NETs with positive somatostatin receptor (seen on Gallium-68 PET) status, irrespective of the primary tumour site.

The basis for patient selection for PRRT is the evidence of somatostatin receptors seen with Gallium-68 PET scan or the Octreoscan®.

PRRT is an outpatient therapy. Patients attend the clinic and are often given a dose of chemotherapy which prepares or sensitises the tumour cells for the radionuclide. They are also given an infusion of amino acids which help protect the kidney function.

Depending on the treatment regime, PRRT is given as an induction course of four treatments separated by 6 to 8 weeks. Further maintenance doses of PRRT may be administered after the induction course, but the NET specialist and the NET MDT determine this.

The side effects of PRRT are mild and usually limited to nausea, fatigue and minor changes in the production of blood.

Liver directed therapies

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

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

For this procedure, an experienced interventional radiologist using local anesthetic (and sedation) accesses an artery in the groin and then directs 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. 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 is also combined with the injection of chemotherapy or the use of microspheres that contain chemotherapy; in this setting the therapy is called transcatheter arterial chemoembolisation (TACE).

For this procedure, patients are usually admitted to hospital overnight. The side effects include fatigue, nausea, vomiting and pain especially around the liver.

Selective internal radiation therapy (SIRT)

This is a new way of using radiotherapy to treat liver metastases that cannot be removed with surgery.

In a process similar to hepatic artery embolisation, the interventional radiologist inserts a catheter into the hepatic artery supplying blood to the NET tumors and tiny beads (SIR-spheres) containing the radioactive substance yttrium-90 (^{90}Y) are injected. These SIR-spheres emits radiation (high energy particles), interfering with the tumour cell DNA and slowing tumour growth.

Radiofrequency ablation (RFA)

This is a treatment for metastatic or primary NET and is performed by an interventional 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 control

Telotristat etipirate (Telestar®)

Telotristat is a new oral drug undergoing trials. Its action blocks 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 should minimise these symptoms. This drug does not act on the tumours to control their growth.

No treatment

No treatment, or watchful waiting, may be suitable 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).

In some circumstances, 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 carried out to try to find new and better treatments. Carrying out clinical trials is the only sure way to find out if a new approach to cancer care is better than the standard treatments currently available.

The experience of having a neuroendocrine tumour

The experience of living with an uncommon cancer, such as a neuroendocrine cancer, is not fully appreciated by most people either in the medical or general community. For many patients it is an emotional journey.

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

First chapter: Something feels wrong

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

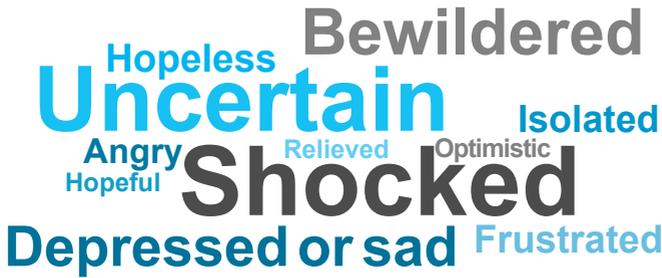
On average, NET patients see four to six different doctors (including specialists) over 4 to 7 years before the correct diagnosis is made.

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

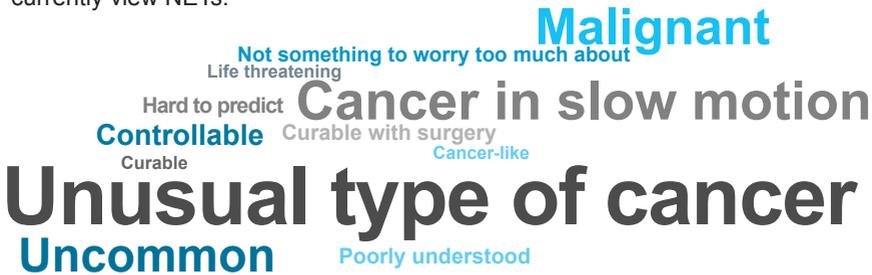
Second chapter: Diagnosis

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 and they have not been malingering or crazy
- 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 many in the medical community currently view NETs.



This period is very difficult for many NET patients. 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 each patient’s NET requires assessment and review of all the patient’s 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 NET multidisciplinary team (NET 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.

Many NET patients feel uncomfortable asking their 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.

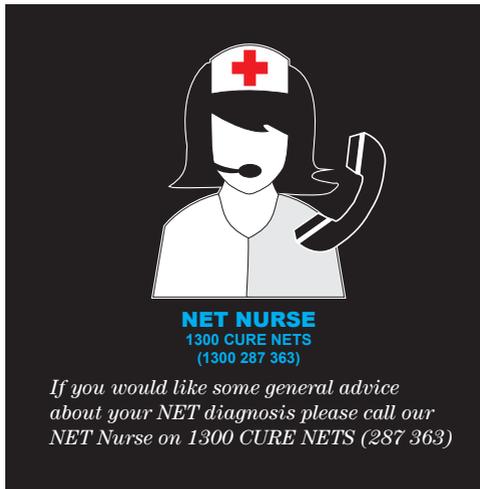
To help Australian patients find a NET Specialist, the Unicorn Foundation has developed a register of NET specialists and NET MDTs to which patients can be referred (www.unicornfoundation.org.au).

Third chapter: Transition

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

This is an extremely difficult and stressful period of adjustment. The patient is facing untold emotional and physical challenges in ‘coming to grips’ with their situation and this is compounded and magnified by the reactions of loved ones, family and friends, who are trying to help but may not understand the cancer.

Support and comfort during this time can be found in the many ‘patient and carer’ focused services that the Unicorn Foundation can provide, such as NET nurse support, telephone support service and our 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 but often do not have expertise in NETs.



“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 NET nurse who could help understand NET issues has been one of the most powerful experiences of my NET years.” (Deborah, Camperdown)

“I have used the service 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. She calls me back after I have a concern and has been a great support to me as a country patient.” (Dorothy, NSW)

Fourth chapter: Living with a NET

This is the adjustment period, when a NET patient, after years of misdiagnosis and the shock of being told they have a cancer, receives expert treatment and advice and begins to comprehend the notion of ‘living with a NET’.

Living with a NET is challenging and can have a significant 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. Even though the NET specialist and team will be focused on managing the disease and patient physical wellbeing, it is important to also recognise and manage the patient’s emotional and social wellbeing.

Unlike the more common cancers, such as breast, bowel, prostate, skin and lung cancer, the journey is less well defined for NETs. 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 to look well, they are struggling with many of these symptoms and need to be supported during such times.

It is important for patients to develop a ‘working’ relationship with their NET specialist, allowing the specialist to guide their 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 their NET specialist and allow them to share this burden, which will free up time for the patient to pursue things in life that empower and give joy, such as family, hobbies and holidays.

The 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 are 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.

This advice can help patients make the most of their appointments:

- Take all recent pathology (blood tests) and radiology results to the appointment.
- Regularly take notes on how you are feeling and take these notes to the appointment.
- Write down questions that you want to ask before the consultation. If you do not understand the answers, don't be embarrassed to ask for the answer to be repeated or rephrased.
- Keep a diary of all your symptoms, 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.
- 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 companion may help to make sure your concerns are raised.

Deciding on a treatment strategy can be difficult, so choosing to get a second opinion is quite common.

Patients should be assured that they have the right to know as much about their prognosis as they wish and have the right to know the overall treatment strategy, including what options are available if initial treatments are not successful in stabilising the disease.

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

Questions to ask during the consultation

Encourage patients to ask questions of their healthcare professionals, such as the following.

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?

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, PET-CT 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?

Treatments

- What will be done during the treatment and how will it affect me?
- How often do I need this treatment? (Treatment schedule)
- 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 deal directly 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
- Australian Cancer Trials 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

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.

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 patients should understand:

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

Currently there is no conclusive scientific evidence for the use of natural therapies to 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 that patients tell their NET specialist about any 'natural' medicines or complementary therapies as they can potentially have a negative impact on the disease or interact with other NET treatments.

Diet

Why diet is important

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

35

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 defence.
- Help you maintain your weight and feel better in yourself. This is important even if you are not having treatment.

For those people 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 and added sugars. Choose from a range of natural colours: at least three vegetable and two fruit portions a day.

Some NET 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.

Carcinoid trigger foods

For some patients, certain foods and drinks can 'trigger' symptoms such as abdominal pain, diarrhoea 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 the meal
- fat content
- spice and alcohol
- meals moderate to high in amines (e.g. aged cheese, alcohol, smoked/salted fish and 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:

- Foods rich in protein: meat, poultry, fish, eggs, dairy products (milk, yoghurt, cheese), pulses and nuts.
- 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 yoghurts, double cream).
- Fortified milk: add 3–4 tablespoons of skimmed milk powder to 1 pint of milk. Use in the same way that you would use ordinary milk.
- Breakfast cereals: 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 deserts (e.g. custard).
- Sandwiches, toast, plain biscuits or jacket potatoes: add butter, margarine, mayonnaise, cheese, peanut butter, olives or avocado.
- Vegetables: 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 foods 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.

- Juices ‘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 diarrhoea 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 your bowel movements and speak to your doctor or nurse if the problem persists.

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. crystallised 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 very basic guide. It is important to discuss your needs with your treatment team, particularly if you have weight loss, diarrhoea or any other prolonged symptoms.

This chapter was adapted from: Whyand, T., Davies, P. and Caplin, M. (2014), Food and Neuroendocrine Tumours (NETs), Royal Free Hospital Neuroendocrine Tumour Unit, European Neuroendocrine Tumour Society Centre of Excellence, Royal Free London, NHS Foundation Trust, London.

Resources

Websites

www.netcancerday.org

www.netpatientfoundation.org.au

www.incalliance.org

38

Acknowledgements

The Unicorn Foundation gratefully acknowledges the support given by the following organisations without pre-condition and editorial input:

- Novartis Australia
- Pfizer Australia
- IPSEN Australia
- The Wilson HTM Foundation
- Medicare Local Foundation Ranges and North Western Melbourne.

About the Unicorn Foundation

The Unicorn Foundation was formed in 2009 by Dr John Leyden (Chair and co-founder) and Simone Leyden (CEO 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.

“If I hadn’t discovered the Unicorn Foundation I can honestly say I would be lost. The support and friendship I have received is priceless.” (Kay, Adelaide)

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.

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

Atrophic gastritis: Chronic inflammation of the stomach, especially the fundus, characterised by atrophic mucosa, decreased acid secretion, increased gastrin levels and hyperplasia of enterochromaffin-like cells resulting in increased CgA levels and histamine production.

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.

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.

Carcinoid crisis: A potentially life-threatening heart-lung collapse caused by sudden release into the systemic circulation of vasoactive amines and peptides 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 provocative study such as a pentagastrin or certain tests. Hepatic embolisation may engender this event subsequent to massive tumour infarction. An intravenous somatostatin analogue 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 sudden or severe.

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

Catestatin: A bioactive peptide fragment of chromogranin A (amino acids 352-2372) that inhibits catecholamine release from adrenal chromaffin cells and stimulates histamine release from mast cells, thereby regulating blood pressure.

Chemotherapy: The use of drugs to destroy cancer cells, usually by affecting their ability to grow.

Chromogranin A (CgA): Detection of elevated plasma levels of CgA has been 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) hyperplasia.

Cushing syndrome: Hypersecretion 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 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 malignant.

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 causes a secretory NET.

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

Gastrinoma: A G-cell derived neuroendocrine tumour, mainly (60%) occurring the duodenum, that overproduces and secretes gastrin, thereby giving rise to the respective gastrinoma. The typical symptoms of a gastrinoma are related to peptic ulceration and excessive acid production (e.g. dyspepsia, 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.

Growth hormone-releasing factor (GRF): A chemical released by the brain that tells the pituitary gland to produce growth hormone.

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.

Hypoclorhydria: 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 (salt) in your blood. It may be caused by diarrhoea.

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.

Metastasis: 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: An inherited genetic disorder caused by germ-line mutations in the MEN-1 gene. It (menin) is on chromosome 11q13 that 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 diarrhoea, scaly skin rash, mental confusion, change in skin colour and inflamed mucus membranes.

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 where the lining of the stomach or duodenum has been eaten away by stomach acid and digestive juices.

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.

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.

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.

“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 since my NET diagnosis.” (Deborah Burdett, Sydney)



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Neuroendocrine Cancers*