



High-Grade Neuroendocrine Tumours

NET Patient Foundation



High-Grade Neuroendocrine Tumours (NETs)

This booklet is intended to provide patients and their carers with information relating to the diagnosis, treatment and management of high-grade neuroendocrine tumours.

High-grade NETs are a type of carcinoma (or cancer), which is a fast-growing and aggressive cancer. Unlike some other types of neuroendocrine tumours, high-grade NETs are always malignant and metastatic (i.e. can spread to other organs in the body). Treatment options for these kinds of tumours usually include chemotherapy.

What are Neuroendocrine Tumours?

Neuroendocrine Tumours (NETs) are relatively uncommon and are a group of tumours that have benign (not cancerous) and malignant potential. You may hear them referred to as GEP NETs, because they often arise in the cells of the stomach (gastro), intestines (entero) and the pancreas (pancreatic). Other common sites of origin include the rectum (back passage) and lungs. There are a number of different types of NET. Below are some examples:

- ✦ Carcinoids
- ✦ Non-Functioning Pancreatic Tumours
- ✦ Functioning Pancreatic Tumours;
Gastrinomas
Insulinomas
Glucagonomas
- ✦ Pheochromocytomas/Paragangliomas
- ✦ Vipomas
- ✦ Multiple Endocrine Neoplasias

What is Cancer?

The body is made up of hundreds of millions of living cells. Normal body cells grow, divide, and die in an orderly way. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out, damaged, or dying cells.

Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of this out-of-control growth of abnormal cells.

Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells keep on growing and form new cancer cells. They also have the ability to travel to other parts of the body and bed in to form secondary cancers. These cancer cells can grow into (invade) other tissues, something that normal cells cannot do. Being able to grow out of control and invade other tissues is what makes a cell a cancer cell.

In most cases the cancer cells form a tumour. But some cancers, like leukaemia, rarely form tumours. Instead, these cancer cells are in the blood and bone marrow. Tumours can be benign or malignant. In this booklet 'tumour' refers to a malignant non-functioning pancreatic neuroendocrine cancer.

When cancer cells get into the bloodstream or lymph vessels, they can travel to other parts of the body. There they begin to grow and form new tumours that replace normal tissue. This process is called metastasis.

No matter where a cancer may spread, it is always named for the place where it started. For instance, breast cancer that has spread to the liver is still called breast cancer, not liver cancer. Likewise, prostate cancer that has spread to the bone is called metastatic prostate cancer, not bone cancer.

Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their own kind of cancer.

What are High-Grade Neuroendocrine Tumours?

The World Health Organisation (WHO) classification scheme puts neuroendocrine tumours into three categories:

- well-differentiated neuroendocrine tumours, further subdivided into tumours with benign and those with uncertain behaviours
- well-differentiated (low grade) neuroendocrine carcinomas with low-grade malignant behaviour
- poorly differentiated (high grade) neuroendocrine carcinomas, which are the large cell neuroendocrine and small cell carcinomas

It is to this last group that high grade NETs belong. High-grade NETs arise most commonly in the intestine, lung and pancreas, but can also occur in other parts of the body.

NETs are classified using three terms that describe important aspects of the cancer:

The stage, the differentiation, the functionality and the grade.

Stage: the extent of disease

Stage is a measure of how far a tumour has spread. Health organisations around the world use slightly different classification systems for NETs.

The WHO classification uses 4 stages (I through IV), with a higher number indicating more widespread disease.

The following example shows the stage descriptions for a NET of the small intestine:

Stage I tumour is less than 1 cm in size and has not spread to the lymph nodes or other parts of the body.

Stage II tumour is greater than 1 cm in size and has started to spread beyond the original location, but has not spread to the lymph nodes or other parts of the body.

Stage III is any size tumour that has spread to nearby areas of the body and also to 1 lymph node.

Stage IV is any size tumour that has spread to 1 or more lymph nodes and has also spread to other, more distant areas of the body (for example, to the liver).

Please note that the stage descriptions may also vary depending on the type of NET you have. For example, stages for a NET of the lung can differ from stages for a NET of the pancreas.

The European Neuroendocrine Tumour Society (ENETS) have recently proposed a new classification called the TNM staging.

T - primary tumour (this is split into 5 main areas: stomach, small intestine, pancreas, appendix and colon/rectum)

N - disease in the lymph nodes

M - metastatic spread

They also proposed looking at the speed in which the tumours are growing and grading that.

These different ways of staging NET cancers are used in conjunction with one another in order to gain a full picture.

Differentiation: what cancer cells look like

Differentiation is the word used to describe a NET or other cancer in terms of how it looks under a microscope. This includes how different the NET cells look compared to the healthy cells around it.

A NET can be described as being “well-differentiated”, meaning it looks similar to surrounding tissue. Well-differentiated NETs are considered to be either grade 1 or grade 2. These NETs may be called “low grade” or “intermediate grade.” A “poorly differentiated” NET means that the tumour cells look very abnormal - that is, very different to the surrounding tissue. These NETs are more dangerous and are categorised as grade 3, or “high grade,” neuroendocrine carcinomas.

Grade: how dangerous the cancer is

The “grade” of a NET is an estimation of how fast the cancer cells are dividing to form new cells. The grade of a NET is related to its differentiation. There are several systems for grading NETs, including a new WHO system introduced in 2010, which is shown here.

Grade	Differentiation
NET Grade 1	Well-differentiated tumor with a low number of cells actively dividing
NET Grade 2	Well-differentiated tumor, but with a higher number of cells actively dividing
Neuroendocrine carcinoma (NEC) Grade 3	Poorly differentiated, malignant carcinoma (most aggressive form of NET)

By using information about stage, differentiation, and grade together, your doctor can decide how best to manage your NET.

Although your doctor may not talk about grade and differentiation with you, he or she may talk about how serious or aggressive your NET is, which refers to how quickly or how much it may grow or spread. Be sure to ask questions if you are unsure about something or want to better understand your disease.

How are NETs diagnosed?

If a neuroendocrine tumour is suspected you can expect to face numerous, regular tests and scans that will provide your doctor with important information about your disease. These can include:

Biopsy

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

Ki67 (MIB1) is an important marker of cell-proliferation, and helps to show how quickly the cancer is growing - this is done by looking at the biopsy tissue under a microscope.

Blood tests

You will be asked to have a fasting gut hormone blood test. This will involve you fasting for six hours prior to the test. Blood will be tested for certain tumour markers, particularly chromogranin A and B (nearly all NETs express abnormally high levels of chromogranin A). The tests will also find out if you have high levels of other hormones and peptides (Pancreatic Polypeptide, Gastrin, Vaso Intestinal Peptide, Neurotensin, insulin, Somatostatin and Glucagon).

Chromogranin A is a useful marker: doctors will be interested in seeing the trend over a period of time to see whether the levels are rising or falling. Other blood tests will look at the functioning of your liver and kidneys and other organs such as the thyroid. A full blood count will provide information on various components in the blood such as red and white cells, and platelets.

Urine tests (5HIAA)

When certain hormones are broken down by the liver, it is excreted as a substance called 5-hydroxyindoleacetic acid (5HIAA) in the urine. Higher than normal levels of serotonin produced by carcinoid patients show up as raised levels of 5HIAA in their urine. You may be asked to do a urine collection over a 24 hour period so that your 5HIAA levels can be checked.

You will be asked to avoid certain foods prior to and during the test including chocolate, olives, bananas, pineapple and its juice, all tomato products, plums, aubergine, 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 prior to the test. This is because they contain substances that might artificially raise your serotonin levels and give a false test result.

Endoscopic ultrasound

Endoscopic ultrasound (EUS) is a technique that uses a special endoscope that has an ultrasound probe attached. Endoscopy refers to the procedure of inserting a long flexible tube via the mouth or the rectum to see the digestive tract. Using the EUS scope, doctors can obtain a very detailed image of the deeper layers of the GI tract, surrounding lymph nodes, blood vessels, and organs. Biopsies can also be taken at the same time. EUS is performed under sedation in the endoscopy unit.

CT scan

A computerised tomography (CT) scan provides a three dimensional picture of the inside of the body. It can be used to determine the position and size of tumours, and regular scans are useful to find out more about the rate of tumour growth and how your tumour is responding to treatment. When you arrive at the clinic you will probably be asked to drink a litre of fluid containing a contrast agent that helps to highlight tumours, and you may also have a cannula inserted through which a special contrast dye is administered during the scan. These both help your specialists to 'read' the scans more clearly as the tumours are highlighted.

MRI scan

Magnetic resonance imaging (MRI) scans can help reveal where tumours are positioned. It uses magnetism rather than X rays to take pictures of inside the body. Scans can take up to one hour to complete and you have to lie very still inside the scanner lying on a couch. These scans are often used in addition to CT scans.

Octreotide scan or Octreoscan

This is a common scan for NET patients. It can help to detect tumours that might be not be seen on other conventional scans. Octreotide is a somatostatin analogue, a substance that mimics the action of naturally occurring somatostatin. When octreotide is combined with a mildly radioactive agent and then injected via a vein in the arm, it sticks to somatostatin receptors on the tumour surface and the tumours 'light up' on the screen as hot spots. This is a useful test to find out more about your tumours, where they are positioned, and also whether you would be suitable for certain treatments that use octreotide or another chemical called lanreotide as a 'carrier agent'. It may also be used to decide if you can be treated with a treatment form of this chemical

Positron emission tomography (PET) and/or PET CT

PET scans are a nuclear medicine imaging technique that produces a three-dimensional image or picture of functional processes in the body. A ¹⁸F FDG-PET scan can be helpful in some patients with high-grade NETs. Some centres are also able to offer a new scan called a Gallium dotatate scan.



What does a diagnosis of a high-grade NET mean?

The team looking after you may feel that they need to start on treatment a little quicker for someone with high grade NET. The treatment you get is more likely to be a chemotherapy based treatment as chemotherapy is known to act well on faster growing cells. There are however other treatment options now available.

Treatment

The decision about treatment is determined by your own particular disease and needs, so the treatments described below provide an outline of possible options but your specialist will discuss your own individual treatment plan with you prior to starting treatment.

The best option will depend on where the cancer has spread to, the extent of cancerous cell growth, and the level of damage to the body. It will also depend on other features of the cancer, such as its drug receptor status and its aggressiveness.

The initial goal maybe to stabilise the disease. To accomplish the treatment goal, it is important for the doctor to consider each individual's health and treatment history.

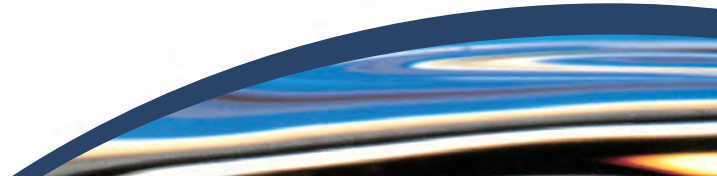
There are a few treatment categories.

Systemic therapies affect the entire body instead of just focusing on the location of the metastases. These therapies are intended to kill all cancerous cells, including microscopic cancerous cells circulating in the blood system that can travel to, and grow in, distant parts of the body. Examples of these therapies are chemotherapy, radionuclide therapy and immunotherapies.

Local therapies including radiation, surgery, RFA, cryotherapy and embolisation and can be used to target cancerous cells in very specific areas of the body. Surgery is generally performed to remove a cancerous growth; however, surgery can also be performed to relieve symptoms. The type of surgery chosen will depend on the size of a tumour and its location. A tumour may be operated on to relieve some of the pressure caused by either a painfully pressed nerve, such as one pressing on the spinal cord, or by the expansion of an organ, such as the liver. Doctors may also need to remove a part of the affected organ. Some tumours cannot be operated on due to size, formation or location as they may be attached to a vital part of the body, such as a main artery that does not allow for removal.

Clinical Trials can be an opportunity to receive treatment that you could not get outside the trial. If you are interested in taking part in a clinical trial, you should speak to your doctor or nurse.

Alternative therapies also referred to as complementary and holistic therapies look at the healing of an individual's body, as well as the mind and spirit. None of these alternative therapies offer a cure, but practices such as yoga, acupuncture and homeopathy may help to improve your sense of well-being.



Treatment of High-Grade NET

Surgery

You may have had an operation to find or remove the high grade NET. Sometimes a further exploratory operation may be needed.

Chemotherapy

This is a drug treatment which acts by attacking the tumour cells and trying to shrink the tumour. There are various types of drugs which may be used according to the type of tumour you have, and how aggressive this is. Chemotherapy can either be given intravenously (through a drip) or in tablet form which you can take at home. Once your specialist has decided upon the most appropriate treatment for you, you will be given more detailed information.

For high-grade NETs, combined chemotherapy treatments are likely to be used.

For example:

- Cisplatin + etoposide
- Carboplatin + etoposide
- Temozolomide + capecitabine
- Temozolomide + bevacizumab

For high-grade lung NETs, available chemotherapy regimens include combination of 5-FU and interferon α , streptozotocin-based combinations, the etoposide-cisplatin regimen or chemotherapy combining cyclophosphamide, doxorubicin and vincristine.

Somatostatin analogue injections

Daily, fortnightly or monthly injections of somatostatin analogues are available, which may help to control some of the symptoms produced by the tumours. Somatostatin analogues are synthetic versions of somatostatin, a naturally occurring hormone produced in the brain and digestive tract that inhibits the release of several other hormones and chemicals from our internal organs. The two most commonly used are octreotide and lanreotide but there are clinical trials with a new drug called pasireotide. These drugs are less likely to be used in high grade NETs as they are more effective in less aggressive cancers

Radionuclide targeted therapy

Also called peptide receptor radionuclide therapy (PRRT) or hormone-delivered radiotherapy. This treatment involves a similar strategy as that applied in an octreotide scan, but the dose of radiation is high enough to stabilise the tumour and potentially to shrink the tumour. Radioactive substances are chemically combined with hormones that are known to accumulate in a NET. This combination is injected into the patient: the hormones will enter the tumour, and the attached radiation will kill the tumour cells. The benefits of this treatment are the ability to deliver radiotherapy directly to the cancer tissue with minimal damage to normal tissue and it is extremely well tolerated with only minor side effects for the majority of patients. There are a number of different radioactive agents available.

New anti-cancer drugs

New anti-cancer drugs - Sunitinib and Everolimus are two drugs which have recently been shown to be beneficial for patients with certain types of pancreatic neuroendocrine tumours. These drugs are given in tablet form. They work by interfering with the development of blood vessels to the tumour and they also disrupt the ability of the tumour cells to grow. Your consultant will advise whether these drugs may be suitable for you.

Embolisation/irradiation

If the tumours are causing pain or other symptoms, they may be treated with palliative intent by appropriate local options such as embolisation for liver metastases and irradiation treatment for brain and bone deposits. These treatments are carried out by a specialist radiologist. The aim is to block the blood supply to the part of the liver containing tumour; this cuts off the oxygen and nutrient supply, and the tumour may stop growing or even shrink for a period of time.

Cryotherapy

This treatment uses extreme cold produced by liquid nitrogen to destroy cancerous cells. It can be used to treat tumours on the skin and tumours inside the body.

Radiofrequency Ablation

This is a procedure that uses radio waves and heat to destroy cancerous cells.

Multidisciplinary teams

The care of NET cancers 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 very 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 among all key healthcare professional groups, who are making clinical decisions for individual patients.

This collaboration has been termed an MDT (multidisciplinary team). This is a formula that is now being used across the world in the care of cancer patients.

An MDT will usually be formed by a particular specialist with expertise and interest in NET cancers and other adrenal tumours. This specialist is commonly an endocrinologist or oncologist.

A patient may see some or all of the following people:

- Oncologist
- Surgeon
- Endocrinologist
- Radiology staff
- Nuclear medicine physician
- Dietitian
- Nurse Specialist
- Palliative Care Team
- Pain Team
- General Practitioner/Practice Nurse
- Counselling Staff
- Various Technicians
- Clinic Staff
- Hospital Staff
- Hospice Team

Patients can feel more confident in the knowledge that all aspects of their care have been discussed and that the best possible treatment plan will be formulated. A well coordinated and disciplined MDT is a very important aspect for care when striving to achieve the best quality of life and the best outcome for NET cancer patients.

Effective Communication with the Health Care Team

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 worthwhile to be reminded of ways to get the most out of each appointment.

A few things to keep in mind:

- The most important part of your healthcare team is YOU
- YOU know more about YOU than anyone else does
- Your doctor can help you more if you are an active partner in your treatment
- If you are dissatisfied with the care that you receive, and discussion with your doctor does not resolve the situation, you can ask for a second opinion - how you feel about the care you receive is the most important thing

Tips:

Bring a trusted friend or family member with you to the appointment if you can. If you are feeling anxious, you may not hear everything that's 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 brought up.

Try to get into the practice of taking notes on how you are feeling, and take these notes into your appointments.

Write down a list of questions you want to ask. If you don't understand the answers to any of your questions, don't be embarrassed to ask for the answer to be repeated or rephrased. Make sure you know who your point of contact is and how to get hold of them, in case you have questions later.

Deciding on a treatment strategy can be difficult so choosing to get a second opinion is quite common. Physicians are usually very open to this because they appreciate the fact that making an effective treatment choice can be very challenging.

If getting a second opinion through your specialist is not possible, you can get a referral from any of your physicians, including your general practitioner.

You have the right to know as much about your own 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 do not work to stabilise your disease.

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

You can find out more about current trials at:

Current Controlled Trials

This website allows users to search, register and share information about randomised controlled trials. Covers multiple registers, including England, Scotland and the US.

<http://www.controlled-trials.com/>

ClinicalTrials.gov

This is a register of federally and privately supported clinical trials conducted in the United States and around the world.

clinicaltrials.gov

You can also search for research trials available to patients in the UK and Europe on these websites:

www.macmillan.org.uk

www.cancerhelp.org.uk

www.ctu.mrc.ac.uk (The Medical Research Council Clinical Trials Unit)

www.ncrn.org.uk (National Cancer Research Network)

www.eortc.be/ (European Organisation for Research and Treatment of Cancer)

Further support



NET Patient Foundation

From diagnosis, throughout treatment and beyond, our services are here every step of the way. Here is an overview of all the services we offer to people living with and beyond NET cancer.

Helpline - 0800 434 6476

Our free, confidential helpline is here for anyone who has questions about NET cancers (neuroendocrine tumours). Your call will be answered by one of our nurses or trained staff members with experience of NET cancer. Whatever your concern, you can be confident we will understand the issues you might be facing, and that the information you receive is clear and up-to-date. We will also let you know where else you can go for further support. The helpline is open 10am-2pm Monday to Friday. We also operate a call-back service for those who wish to leave a message out of hours.

Website - www.netpatientfoundation.org

We know how important it is to understand as much as possible about your NET cancer. Our website is here round-the-clock giving you instant access to information when you need it. As well as clinical information, you'll find real life experiences and access to the largest online NET cancer community in the UK, so you can share your questions or concerns with other people in a similar situation.

Discussion forums

Through our discussion forums you can exchange tips on coping with the side effects of treatment, ask questions, share experiences and talk through concerns online. Our dedicated areas for popular topics should make it easy for you to find the information you're looking for. The discussion forums are easy-to-use. If you're feeling anxious or just need to hear from someone else who's been there, they offer a way to gain support and reassurance from others in a similar situation to you.

Ask the nurse

If you find it difficult to talk about your cancer, we can answer your questions by email instead. Our 'ask the nurse' service is available on the website - complete a short form that includes your question and we'll get back to you with a confidential, personal response.

Information and support sessions

We run information and support sessions for people living with NET cancer. These meetings include talks from some of the country's top NET specialists, invaluable Question & Answer sessions, as well as an opportunity to meet other NET patients. For information about meetings in your area, please see our website or call our helpline.

Information resources

Our free information resources are for anyone affected by NET cancer. They are here to answer your questions, help you make informed decisions and ensure you know what to expect. All of our information is written and reviewed regularly by healthcare professionals and people affected by NET cancer, so you can trust the information is up-to-date, clear and accurate. You can order our publications by sending us an email or calling the helpline. All our publications can also be downloaded from our website.

Other organisations

Macmillan Cancer Support

89 Albert Embankment London SE1 7UQ
General enquiries: 020 7840 7840
Helpline: 0808 808 0000
Website: www.macmillan.org.uk
Textphone: 0808 808 0121 or Text Relay
Macmillan Cancer Support provides practical, medical, emotional and financial support to people living with cancer and their carers and families. Over the phone, its cancer support specialists can answer questions about cancer types and treatments, provide practical and financial support to help people live with cancer, and are there if someone just wants to talk. Its website features expert, high-quality information on cancer types and treatments, emotional, financial and practical help, and an online community where people can share information and support. Macmillan also funds expert health and social care professionals such as nurses, doctors and benefits advisers.

The NET Patient Foundation incorporating Living with Carcinoid was formed at the start of 2006 and has Charity Commission status.

The Foundation has the following aims:

- ✚ To provide accurate and up-to-date information for people living with, or affected by, NET cancers
- ✚ To provide support for patients and others affected by NET cancers
- ✚ To provide education for healthcare professionals in the treatment and care of NET patients
- ✚ To raise awareness of NET cancers within the medical community, and amongst the general public
- ✚ To improve access to care for NET patients
- ✚ To raise funds, which will help to support research around the UK & Ireland

Did you know?

- 50% of patients are diagnosed when the cancer has already spread
- Early diagnosis significantly improves outcomes for patients
- Help us to make a difference. Donate now at www.netpatientfoundation.org

Why the moth?

We have chosen the moth as our logo to symbolise this 'camouflaged' condition. We aim to encourage medical professionals to consider an uncommon alternative when symptoms persist (i.e. a NET rather than IBS).

"When you see an insect beating its brightly patterned wings against your window, don't assume it's a butterfly. It could be a moth."

It is thanks to the incredible generosity of the Walsh and Cripps and Dawson families that we were able to produce this booklet.

If you'd like to know how you can help us to continue our work, please call us on 0800 434 6476



This booklet has been compiled with the assistance of:

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NET Patient Foundation

incorporating Living with Carcinoid
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The NET Patient Foundation supports people diagnosed with
neuroendocrine tumours and their families.

For further information and to make contact telephone 0800 434 6476
or visit our website:
www.netpatientfoundation.org

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