

Neuroendocrine Cancer of the Lungs



Welcome...

...to your personal guide to living with Neuroendocrine Cancer of the Lung(s). We hope it'll give you some useful and straight forward information.

Whether you want to know every detail of what your diagnosis may mean for you, or would rather your care team just got on with it, there's much to be said for being prepared and being informed.

There is a lot of information within this booklet and some of it may be difficult for you to read right now. You may find it helpful to read just parts of it now, then come back to it later – whenever you feel ready to do so.

You may also prefer to either read it alone or with a friend or family member – whatever feels right for you.

Everyone deals with illness differently.

Some people want to know exactly what's happening, others prefer doctors to keep things as general as possible – and it's completely up to you how you approach your life with Neuroendocrine Cancer.

However, trying to prepare for what is to come, or to understand what is currently happening or being planned – why certain options or treatments are being suggested – can help.

This does not mean you suddenly need to become a scientific expert in your disease. But it does mean that getting your head around some of the facts and potential implications of your diagnosis can put you in a stronger and maybe less stressful position – and help you to make informed decisions about your care.

We hope that many of the questions you may have, are answered in this booklet, but don't be afraid to ask your care team anything that isn't – or contact us.

Further Information

Is available on our website www.neuroendocrinecancer.org.uk or contact us via email admin@nc-uk.org.

Support

NET Nurse Advice-line, NET Natter Groups, On-line groups and our Counselling Service.

There really is no such thing as a stupid question – what is important is that you have information you need, in a way you can understand, at the time you need it.

An important note about your care

When you are diagnosed with a Neuroendocrine Cancer, it's vital to get the best possible advice and treatment from the right team of people – and across the UK there are procedures and specialist centres in place to ensure this happens.

A specialist, accredited, "NET" specific Multi-Disciplinary Team ("NET" MDT) should be involved in reviewing your case on an ongoing basis.

This team will be made up of a range of clinical experts who specialise in Neuroendocrine Cancer.

You may be referred to one automatically, but if that doesn't happen you can ask for a referral to be made.

These teams will work with your lung team to ensure best care.

A list of all UK and European accredited Neuroendocrine Centres of Excellence is available via the Centres of Excellence tab at www.enets.org or visit the Clinical Practice page at www.ukinets.org or give us a call.

Helpline Number

0800 434 6476

Office Number

01926 883487

www.neuroendocrinecancer.org.uk

Changes in terminology occur over time - the specialist societies and services were established during the time when 'NET' was used as the over-arching term.

This is why "NET" is still used in an organisation's name - this does not reflect a lack of knowledge or expertise in ALL forms of Neuroendocrine Cancer.

Neuroendocrine Cancer of the Lung(s)

Before we delve too deeply into what Neuroendocrine Cancer is – and the different types that may occur in the Lungs – let's have a look at the 'normal' anatomy and functions of the lungs.

This can help to understand how Neuroendocrine Cancer may affect normal function, give rise to symptoms and how it can best be identified, diagnosed and treated.

The Lungs: Anatomy

The lungs are a pair of large, spongy organs that fill the chest and are either side of the heart.

Each lung consists of several distinct lobes.

The right lung has 3 lobes — the upper, middle, and lower lobes.

The smaller left lung only has 2 lobes — upper and lower.

Each lobe has a number of segments : Right Upper Lobe (RUL) has 3, Right Middle Lobe (RML) has 2, Right Lower Lobe (RLL) has 5,

Left Upper Lobe (LUL) has 5 and Left Lower Lobe (LLL) has 4.

Neuroendocrine cells are present throughout the respiratory tract (lungs) as part of the normal anatomy (see diagrams).

Each lung is covered by a thin tissue layer called the pleura. The same kind of thin tissue lines the inside of the chest cavity.

A thin layer of fluid acts as a lubricant allowing the lungs to slip smoothly as they expand and contract with each breath.

Typically, a man's lungs can hold more air than a woman's. At rest, a man's lungs can hold around 750 cubic centimetres (about 1.5 pints) of air, while a woman's can hold around 285 to 393 cc (0.6 to 0.8 pints) of air. However, even at maximum exercise intensity, we only use 70% of the possible lung capacity.

Our lungs are how we breathe, taking in oxygen and breathing out carbon dioxide — but they also have several other functions that help maintain health.

Diagram 1: The Lungs

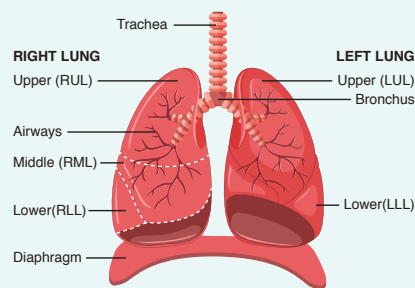
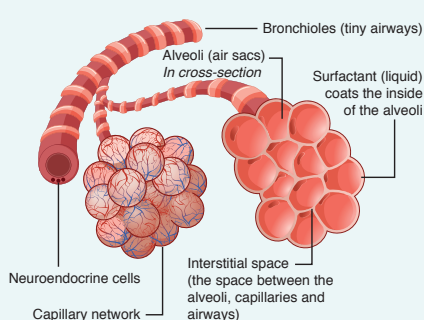


Diagram 2: Cross-section of lung



The Lungs: Functions

Oxygen in and carbon dioxide out (aka Gaseous exchange): When we breathe in, air travels down the throat and into the trachea, also known as the windpipe. The trachea divides into smaller passages called the bronchial tubes, which go into each lung (see diagram 1). The bronchial tubes branch out into smaller subdivisions: the smallest of which are called bronchioles and each bronchiole has an air sac, called alveoli (see diagram 2). The alveoli have many capillary veins in their walls. Oxygen passes through the alveoli, into the capillaries and into the blood. It is carried to the heart and then pumped throughout the body to the tissues and organs. As oxygen is going into the bloodstream, carbon dioxide passes from the blood into the alveoli and then makes its journey out of the body, when we breathe out.

Infection control: To help clear the lungs from inhaled debris or infection, the bronchial tubes are lined with a coating of very small hairs (cilia). These cilia wave back and forth spreading mucus into the throat (Mucus helps to clean out the lungs and rids them of dust, germs, etc...) so that it can be dispelled by the body (cough / sneeze). Within the alveoli and mucus, are substances and cells that help deal with organisms that may cause infection (see diagram 3).

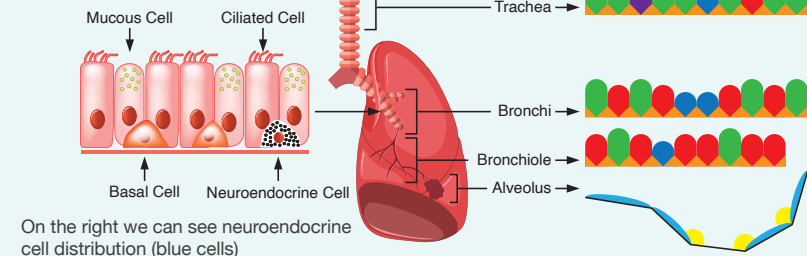
Filtering of blood: Blood entering the right side of the heart passes through the

pulmonary capillaries, before reaching the left side of the heart to be pumped throughout the whole body. As the blood passes through the pulmonary capillaries, large particles such as emboli (clots), air bubbles, cell debris and fat globules can get trapped (because of the small size of the capillaries). This prevents such particles entering the circulation and obstructing the arteries supplying vital organs, such as the brain.

Metabolic (Metabolism is a term that describes all the chemical reactions* in your body. These chemical reactions — keep your body alive and functioning): The lower airways are lined by a large number of neuroendocrine cells responsible for the secretion and release of substances such as bradykinin, prostaglandins, serotonin, substance P, calcitonin gene-related peptide (CGRP), heparin and histamine (see diagram 3). These are released in response to stimuli, such as changes in oxygen level. In addition, the pulmonary tissue is responsible for the conversion and break down of certain substances (e.g. bradykinin and adrenaline), all of this helps maintain normal body function. Waste or by products may be released by the lungs as gases (e.g. acetone — the 'pear-drop' smell of breath in certain diabetic states).

*Chemical reactions — processes in which one or more substances are converted to one or more different substances. For example: how our bodies convert sugar into energy.

Diagram 3: Lung - cell types



Neuroendocrine Cancer: History & Terminology

Neuroendocrine Cancer was first described as a specific disease in the mid-1800's and yet few have heard of it.

In 1907, the term 'Carcinoid' was applied – from the German word for "cancer-like".

This term became very popular amongst the medical community of the time, as it was believed that Neuroendocrine Cancer, though sharing certain characteristics, was not truly a cancer – but cancer-like "karzinoide".

It was also thought that ALL Neuroendocrine Cancers were indolent, that is, very slow growing and unlikely to spread or behave in the same way as other malignancies.

By the 1950's however, it was clear that these 'Carcinoids' could behave like common cancers, and that whilst many may grow slowly, they shared other cancers' ability to spread to other parts of the body, and some could indeed grow as rapidly.

More recently, a new term has been proposed and is now being used, though mostly in medical publications:

Neuroendocrine Neoplasm (neoplasm means new growth) – though in practice, you may still hear 'carcinoid' and NET or Neuroendocrine Tumour mentioned.

Neuroendocrine Neoplasm, or '**NEN**', has been introduced as the new umbrella term to help clarify the differences between all abnormal growths of the neuroendocrine system – benign or malignant.

For example adenomas are benign (non-cancerous growths) but can occur in neuroendocrine cells.

More importantly, this new term was to help distinguish between malignant NENs – that is Neuroendocrine Cancer – NETs and NECs.

NET or **Neuroendocrine Tumour** has a particular appearance under the microscope – the abnormal changes seen are called 'well-differentiated'.

In **NEC** or **Neuroendocrine Carcinoma** – these changes are called poorly differentiated.

Both have variable rates of growth, with NET more likely to show slow to moderate growth and NEC more likely to grow rapidly.

The terminology can be confusing and old wording may still be used, even by experts!

For Lung NENs (NETs & NECs) – this confusion may be even more likely as the term Carcinoid is still in use (see below).

Lung NENs account for up to 20% of all lung cancers. To date, 6 types of Lung NEN have been identified (many medical publications refer to 3-4 types):

- 1 DIPNECH – (Diffuse Idiopathic Pulmonary NeuroEndocrine Cell Hyperplasia) – not a cancer in itself, but **may** lead to TC or AC.
- 2 Typical Carcinoid (TC) low grade neuroendocrine tumour (NET)
- 3 Atypical Carcinoid (AC) mid-grade neuroendocrine tumour (NET)
- 4 Small cell lung cancer (SCLC) is a neuroendocrine carcinoma (NEC) – high-grade
- 5 Large cell neuroendocrine carcinoma (NEC) – high-grade
- 6 MiNEN or mixed cell carcinoma – high-grade.

Lung NENs: Cancer development, genetics, grading and staging

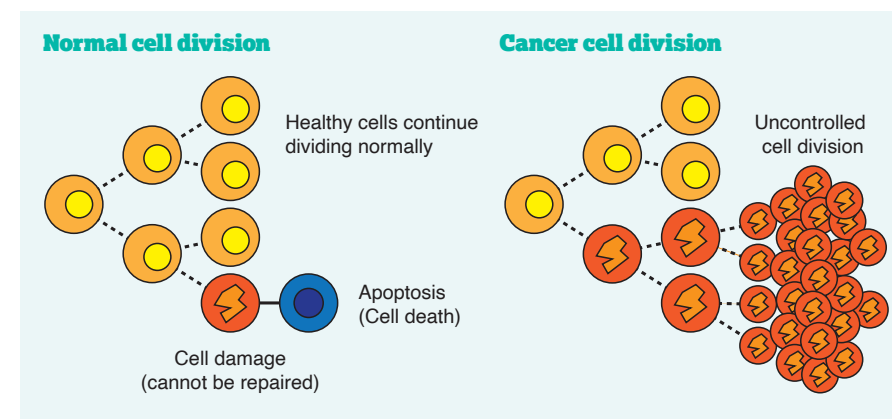
When neuroendocrine cells work well, our bodies work well. But, as in all cancers, problems start when abnormalities occur and the cells start growing and behaving abnormally.

A normal cell:

- Exists in a specific place in the body
- Divides and replicates itself only when necessary
- Has a life cycle, so does its job then dies off
- Repairs or destroys itself if it gets damaged
- Doesn't cause damage to neighbouring cells by growing too large and invading them.

A cancer cell:

- Can detach from the tumour (collection of cancer cells) and travel to other parts of the body
- Keeps dividing and growing – as it doesn't know to stop
- Often grows abnormally, so can't perform a function properly
- Doesn't destroy itself if it gets damaged
- Ignores warnings from neighbouring cells to stop growing and can invade them.



Genotype, Phenotype and Mutation

Genotype is your complete heritable genetic identity but can also refer just to a particular gene or set of genes carried by an individual. It can determine anything from eye and hair colour to certain diseases / conditions or behaviours.

Phenotype is a description of your actual physical characteristics – the visible evidence of your genotype, e.g. brown hair.

However, your phenotype can be altered by environment or external influences – e.g. sun-bleaching of hair.

Mutation is a change that occurs in our DNA sequence, either due to mistakes when the DNA is copied or as the result of environmental factors.

So not all genetic mutations are inherited, some are acquired during a person's lifetime – these are called somatic mutations.

So each of us has a unique identity that can be altered by either a genetic mutation / manipulation or external factor.

Scientific advances have helped to identify certain genes and mutations that lead to the development of certain health conditions such as cancer.

Understanding these, alongside linked external influences has led to improvements in prevention of disease, reductions in incidence and/or better targeted treatments.

However, there is still much to learn and for many cancers, multiple pathway changes or influences may be involved, rather than a single mutation.

In Lung NENs a number of mutations have been identified and what they have in common is their role in cell development and growth – or rather their altered role in this process.

For example one gene may provide instructions for making a specific protein.

This protein may act as a tumour suppressor, which means that it regulates cell growth and keeps cells from dividing too fast or in an uncontrolled way – it also interacts with other proteins to influence cell survival.

When mutated, this can lead to cells grow

out of control – as mentioned above.

However, one mutation alone may not be the sole reason certain cancers occur.

Grading

Grading is based on how cells look under a microscope (differentiation) and how quickly they are dividing to form new, cancerous cells. Your care team will want to grade your NET/NEC so they can plan the best treatment for you.

To understand grading, you need to know about another important part of classification – differentiation.

Differentiation refers to what NET/NEC cells look like compared to healthy cells.

Cells that are well differentiated have some similarities to normal neuroendocrine cells but have started to change in size and shape.

They have also begun to appear irregular in how they are arranged.

Cells that are poorly differentiated have become more abnormal in size and shape, and have a very irregular arrangement.

Expert opinion recommends a slightly different way of grading Lung NENs than that used in other NEN's – and advocates using Mitotic Rate rather than Ki67% as the assessment/measurement tool.

Mitotic Rate is a measure of how fast cancer cells are dividing and growing.

To find the mitotic rate, the number of cells dividing in a certain amount of cancer tissue is counted (preference is 2mm²).

Ki67 is a protein that is present during all of the active stages of the cell cycle – a useful marker of proliferation (cell division and growth).

However, whilst Ki67 has a value in distinguishing low-moderate Lung 'Carcinoids' from high-grade disease, it is

not thought to reliably separate the low to moderate Carcinoids, that is, TC from AC. Though it may play a role in predicting prognosis of TC and AC.

Type	Mitotic Rate	Features	Ki67	NEN Grade equivalent*
Typical Carcinoid	fewer than 2 mitoses/2 mm2	absence of necrosis	Up to 5%	1 - 2**
Atypical Carcinoid	2–10 mitoses/2 mm2	foci of punctate necrosis	Up to 20%	2
Small Cell Lung NEC	more than 10 mitoses/2 mm2	extensive geographic necrosis	50-100%	3
Large Cell Lung NEC	more than 10 mitoses/2 mm2 (usually greater than 50/2 mm2)	extensive geographic necrosis	40-80%	3

*** In other types of NEN – Grade 1 is well-differentiated with a Ki67 <3%, Grade 2 is well-differentiated with a Ki67 of 3-20%, Grade 3 has a Ki67 >20% but is divided into 2 types of differentiation – 3a = well-differentiated, 3b = poorly differentiated*

Staging for lung NEN is complex – more so than for small bowel NEN or other NENs, and is based on a combination of several factors, including:

- The size and location of the tumour
- Whether it has spread to the lymph nodes (and if so where / which side)
- Whether it has spread to other parts of the body.

Staging is usually expressed as a TNM score: where T= tumour, N = Lymph nodes and M = Metastases (where disease has spread to secondary sites).

There are 5 stages for lung NENs: stage 0 (zero) and stages I through to IV (1 through to 4): T0 means there is no evidence of a primary tumour. Nx is where local lymph nodes cannot be assessed. N0 = no lymph nodes involved. M0 = no metastases (secondaries) identified.

Full details of staging can be found in Appendix 1 of this booklet.

Types of Lung NEN – and the symptoms they may cause

1 DIPNECH (Diffuse Idiopathic Pulmonary NeuroEndocrine Cell Hyperplasia) – The cause is unknown and the process of development incompletely understood, but it can arise in healthy lungs, without any pre-existing chronic lung disease – and it is not linked with smoking.

Diagnosis is based on examining cells under a microscope (histological examination): the cells are found to show enlargement of the lung neuroendocrine cells (hyperplasia), multiple tumourlets (<5mm) and associated inflammation and blockage of the smallest airways in the lungs.

DIPNECH is to be suspected if neuroendocrine cell hyperplasia is associated with obliterative bronchiolitis (a.k.a. 'bronchiolitis obliterans' or 'popcorn lung': a disease that results in obstruction of the smallest airways of the lungs (bronchioles) due to inflammation).

It is a fairly indolent disease – often stable over many years, with very little evidence of change on scans, however, given clinical presentation/symptoms, impact on quality of life and potential for development of TC, follow up is recommended.

Symptoms include a dry cough, shortness of breath, wheezing and lethargy/fatigue.

2 Typical Carcinoid (T.C.) low grade growth neuroendocrine tumour (NET) – The cause is unknown.

It can arise in healthy lungs, without any pre-existing chronic lung disease – or on the background of DIPNECH – and is also not linked with smoking.

They are usually sporadic lesions (that is, they are not hereditary); however, rare familial cases have been reported – up to 5% of patients with multiple endocrine neoplasia type 1 (MEN1) develop a T.C.

Histological examination confirms type and likely behaviour : T.C. is a well-differentiated, usually low-grade cancer, usually slow to develop and spread.

They have a low incidence of metastases (approx 15% spread to secondary sites e.g. lymph nodes, liver, bone...) and once removed have a low and slow recurrence risk which is why lifelong surveillance is an expert recommendation.

Symptomatically – they may not cause symptoms for several years in some people, or they may be found when tests are done for other reasons.

When symptoms are present, there is coughing or wheezing and any sputum or phlegm produced through coughing may or may not contain blood.

If the tumour is large enough to cause a blockage of the airway(s) infection and / or wheeze may develop and be the first indication that something is not right.

3 Atypical Carcinoid (AC) mid-grade neuroendocrine tumour (NET) – low to moderate growth neuroendocrine tumour (NET). The cause is unknown.

It can arise in healthy lungs, without any pre-existing chronic lung disease – or on the background of DIPNECH.

They do not seem to be related to smoking, air pollutants, or other chemicals, but as with Typical Carcinoids, people with multiple endocrine neoplasia type 1 (MEN1) may be at slightly higher risk.

Histological examination confirms type and likely behaviour: A.C. is a well-differentiated, low-moderate grade cancer and therefore may grow faster than Typical Carcinoids and there is a greater chance that they will spread (metastases) within and beyond the lungs – which is why lifelong surveillance is an expert recommendation.

Symptomatically – they may not cause symptoms for months to years in some people, or they may be found when tests are done for other reasons.

When symptoms are present, usually there is coughing or wheezing and any sputum or phlegm produced through coughing may or may not contain blood.

If the tumour is large enough to cause a blockage of the airway(s), infection and / or wheeze may develop and be the first indication that something is not right.

In contrast to typical and atypical carcinoids, LCNEC and SCLC are not closely related to each other in regards to certain characteristics, they are distinct/separate types of Lung Neuroendocrine Cancer... and unlike 'lung carcinoids', no precursor lesions (as seen in DIPNECH) are known for SCLCs and LCNECs.

4 Small Cell Lung Cancer (SCLC) a neuroendocrine carcinoma that accounts for almost 20% of all Lung NENs.

Smoking is the single biggest risk factor with additional risks including exposure to radon and asbestos.

SCLC are more likely to occur centrally – that is within the bronchus /main upper airway(s).

Histological examination confirms type and likely behaviour – SCLC is predominantly poorly-differentiated, high-grade cancer – indicating a more aggressive behaviour.

Spread within the lungs and to distant sites (metastases) may already have occurred at the time of diagnosis.

If no metastases are seen and early stage disease is confirmed as operable, surgery may be considered, however first-line treatment is usually chemotherapy and/or radiation.

Symptomatically – common symptoms resulting from local tumour growth include cough (that may produce blood stained sputum) and/or dyspnoea (shortness of breath).

Due to the central position of tumour in the main bronchus or upper airways, additional symptoms related to position or growth of tumour may include Superior Vena Cava (SVC) obstruction, voice hoarseness – due to compression of one of the laryngeal nerves, dysphagia (difficulty swallowing) – due to oesophageal compression, stridor (a harsh vibrating, sometimes high pitched, noise when breathing) – due to compression of the major airways.

Carcinoid and/or specific paraneoplastic syndromes may occur: such as hypercalcaemia, Eaton-lambert syndrome, Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) secretion, and others.

5 Large Cell Neuroendocrine

Carcinoma (NEC or LCNEC) are rare tumours of the lung: the incidence of pulmonary LCNECs appears to be around 4%.

Unlike TCs and ACs, LCNECs can be associated with smoking. LCNECs are more likely to occur peripherally – that is away from the bronchus /main upper airway(s).

Histological examination confirms type and likely behaviour – LCNEC is predominantly poorly-differentiated, high-grade cancer – indicating a more aggressive behaviour.

Spread (metastases) to lymph nodes (>60%) or other sites (>40%) may already be present at the time of diagnosis.

Chemotherapy and close monitoring of effect (on both the tumour and overall health) is usually first-line treatment – unless early stage disease is identified (Stage I-II – with no evidence of spread): In this instance, surgery may be considered plus or minus pre and/or post surgery chemotherapy.

Symptomatically – they may not cause immediately obvious symptoms – e.g.cough, wheeze, blood in sputum and / or infection – though these can occur.

A non-painful nodule or chest pain, nonspecific flu-like symptoms, shortness of breath and / or night sweats may be more commonly experienced/seen.

Rarely, Carcinoid and/or paraneoplastic syndromes may occur.

6 MiNEN (Mixed Neuroendocrine/ Non-Neuroendocrine Cancer)

are tumours that contain both a neuroendocrine and non-neuroendocrine component (e.g. a mix of neuroendocrine cancer and another cancer). This is the rarest form of Lung NEN.

Expert histological examination is essential to ensure accurate diagnosis and reveals evidence of both neuroendocrine cancer and another lung cancer cell type.

It has been proposed that each type must make up at least 30% of the lesion to be recognised as true MiNEN, however, this cutoff has not been universally accepted.

It is a high-grade cancer and therefore is similar symptomatically to high-grade NEC and may be treated by conventional lung cancer therapies and/or SCNEC/LCNEC specific treatment – depending on which cell type has a higher presence within the tumour.

Syndromes associated with Lung NEN

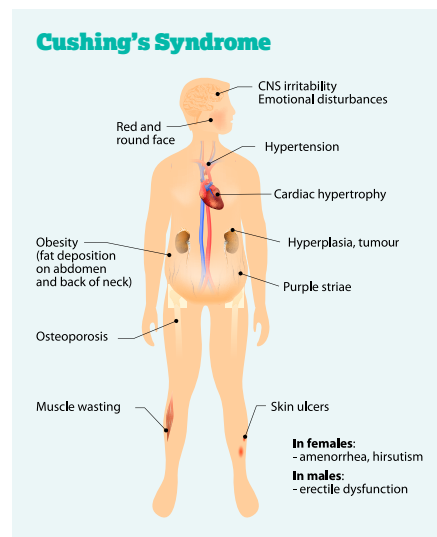
MEN1 (Multiple Endocrine Neoplasia type 1) is distinct amongst syndromes that can be associated with Lung NEN, in that it is a condition that may pre-date the development of a Lung NEN, rather than develop as a result of a Lung NEN.

Multiple Endocrine Neoplasia Type 1 (MEN1), also known as Wermer's Syndrome, is one of a group of genetic disorders under the name Multiple Endocrine Neoplasia. They are inherited disorders, which can be passed down in families and which may cause more than one gland of the body's endocrine (gland) system to develop growths – in MEN1 the sites are usually the 3 'P's: pituitary, parathyroid and / or pancreas. However, up to 5% of all MEN1 patients may also develop neuroendocrine tumours in the chest or stomach area, lipomas (benign tumours of fat cells), benign thyroid tumours and benign tumours of the outer layer of the adrenal gland (adreno-cortical adenomas).

Further information about MEN1 can be found at www.amend.org

Carcinoid Syndrome is seen in up to 5% of all lung NENs and occurs when abnormal neuroendocrine cells release a higher than normal amount of hormones or peptides into the bloodstream (as described in Functions of the Lungs). The most common substance is serotonin, others include histamine, tachykinins and vasoactive peptides. You're more likely to experience symptoms of Carcinoid Syndrome if your primary is in the bowel, lung or ovary or if you have secondary disease in the liver. Typical symptoms of carcinoid syndrome include: Flushing: reddening, usually of

the chest and face – though some people may experience a whole body flush. It is usually "dry" – so not usually associated with sweating (as seen in menopausal flushing) – may be accompanied by a fast heart rate or "palpitations", abdominal cramps, bloating and "wind", diarrhoea, loss or reduction of appetite, wheezing and/or carcinoid heart disease (where fibrous deposits, related to excess serotonin release, sometimes build up and engulf the heart valves. This can stop the valves from opening and closing normally, disrupting blood flow and potentially causing breathlessness and severe tiredness).



Cushing's Syndrome is seen in up to 5% of all lung NENs and occurs when a hormone called ACTH is

over-produced (hyper-secreted) by abnormal neuroendocrine cells. This causes the adrenal glands to make too much cortisol (a steroid hormone) and other hormones, causing symptoms of muscle weakness, weight loss, hypertension (high blood pressure), excessive hair growth, and osteoporosis, hypokalaemia (low potassium levels) and hyperglycaemia (raised blood sugars).

Paraneoplastic Syndrome are a group of clinical disorders that are associated with malignant diseases and are not directly related to the physical effects of the primary or metastatic tumours.

They can include Hypercalcaemia (raised calcium levels), Eaton-lambert syndrome, Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) secretion, Trousseau's syndrome and/or SVC obstruction

Hypercalcaemia (high calcium) There are two main causes of hypercalcaemia. The first is associated with the presence of bone metastasis and how these can affect calcium levels. This process accounts for approximately 20% of cases in lung cancer particularly where bone metastasis are present. The second most common cause, also known as humoral hypercalcaemia of malignancy (HHM), is related to the abnormal secretion of parathyroid-related hormone.

Both causes can be confirmed by measuring calcium levels in the blood.

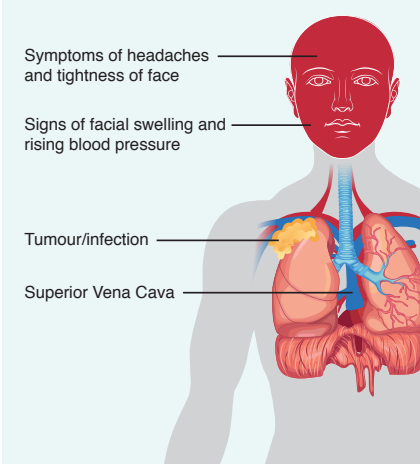
Lambert-Eaton myasthenic syndrome (LEMS) is a very rare condition that may occur as a paraneoplastic disorder in association with cancer (CA-LEMS), notably small cell carcinoma of the lung. It affects the signals sent from the nerves to the muscles, which means that the muscles are unable to tighten (contract) properly, resulting in muscle weakness and a range of other symptoms.

Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) occurs

due to the excessive production of antidiuretic hormone (ADH), which causes hypervolemia (also known as fluid overload) leading to hyponatremia where sodium (salt) levels within the blood are lowered and total body fluid is increased. Approximately 10% of patients who have SCLC exhibit SIADH with symptoms including confusion, seizure, reduced consciousness and coma.

Trousseau's syndrome is an acquired blood clotting disorder that results in migratory thrombophlebitis (inflammation of a vein due to a blood clot). Approximately 50% of patients with Trousseau syndrome have an associated cancer.

Superior Vena Cava Obstruction (SCVO)



Superior Vena Cava Obstruction (SCVO) The superior vena cava (SVC) is a big vein in the middle of the chest. It carries blood from the upper body to the heart. SCVO is usually caused by a lung cancer near this vein and less commonly other types of cancer. The cancer may be pressing on the SVC or affecting lymph nodes in the chest and this blocks or affects the flow of blood along this vein.

Diagnosis

Before and after you're diagnosed, tests become a regular part of your life. Here's what's likely to happen and why.

Diagnosis isn't straightforward.

NET/NEC is often small, starting out the size of a grain of sand and often not visible to the most accurate scans until it gets to about half a centimetre across or the size of a pea, so finding them and identifying where they started can, on occasion, be difficult.

Because of this, you may well have a number of tests before your diagnosis is confirmed – including specialist tests to ensure the evidence is conclusive.

Once you have a diagnosis, some of the tests you have undergone will be used to monitor your health and the effects of your treatment.

Blood / Urine Tests

- Full blood count
- (B12 + serum Iron)
- Liver and kidney function
- Chromogranin A (and B)
- Urinary 5-HIAA
- CEA
- Calcium
- Glucose
- If Cushing syndrome present/suspected: serum cortisol, urinary cortisol and ACTH
- If MEN1 present/suspected: calcium, PTH and consider genetic studies

Endoscopy

Scans take pictures of your insides from outside your body. As detailed as they are, they don't always give a full view of what's happening inside the hollow organs of the body – for example if doctors want to see inside your airways. In situations like that, endoscopies and endoscopic ultrasounds can be very useful.

- Bronchoscopy
- Endoluminal Bronchoscopic Ultrasound (EBUS).

Scans and other investigations

- Chest x-ray
- Contrast or High Resolution chest CT or CAT scan
- CT / CAT scan abdomen/pelvis to exclude secondary disease – or confirm primary if lung tumour is a secondary (metastasis).
- Gallium-Dotatate PET/CT (SRS SPECT/CT if Dotatate PET n/a)*
- FDG-PET *– if High Grade / rapidly progressing disease.

**You might also hear these called 'functional' scans. Substances, called radioactive labelled tracers or isotopes are used, that have attractions to certain tumour cells, to create images that can help diagnose and monitor NET/NEC.*

Gallium-Dotatate identifies octreotide sensitive receptors often found on the surface of well-differentiated Neuroendocrine Cancers of all grades – these areas are highlighted on the scan.

FDG identifies areas of increase energy consumption – which correlate with rapidly

growing cancers – such as poorly-differentiated neuroendocrine cancers and more common forms of lung cancer.

Both types of functional scans can produce false positive or negative results – for example, areas of acute infection may show up positively – but in conjunction with other tests, these scans can be conclusive in diagnosis.

- Echocardiogram : an ultrasound examination of the structure of the heart including examination of heart valves. It is undertaken if there is a history of heart disease and / or if you have Carcinoid Syndrome and have evidence of raised U5HIAA and / or elevated NT-Pro-BNP +/- clinical signs of heart valve impairment/R sided heart failure

Carcinoid heart disease, (which can affect up to 60% of people diagnosed with Carcinoid Syndrome), is where fibrous deposits sometimes build up and engulf the heart valves.

This can stop the valves from opening and closing normally, disrupting blood flow and potentially causing breathlessness and severe tiredness. In this situation, heart surgery may be required to replace damaged valves.

n.b. Less than 20% of those with a primary lung neuroendocrine cancer will have or develop Carcinoid Syndrome.

- Lung/Respiratory Function Tests : these are undertaken to assess your breathing including your lung capacity.

This can assist your medical team in assessing the degree to which your cancer may be affecting your lung function.

It can also be useful in assessing your potential for surgery including ability to tolerate and recovery from a general anaesthetic.

Pathology

To monitor your treatment or a suspected NET/NEC, your care team might want to take a small piece of tissue, a collection of cells or some fluid from your tumour so it can be studied for the presence of cancer and activity of cells under a microscope.

If you have had surgery to remove a Lung tumour – this will be sent for pathology review.

Studying tissue under a microscope is often the only way to be absolutely sure of a cancer diagnosis. It can give clues about where a cancer started, what kind of cancer cells exist and how quickly they are multiplying.

It may also allow for mutation analysis of your cancer.

This knowledge can help doctors to recommend the best treatment.

- Differentiation and cellular morphology
- Synaptophysin
- Chromogranin
- Ki67 / Mitotic rate (2mm2)
- CD56
- Cytokeratins
- TTF1
- (TTF1, CDX2, Islet1 may be useful to distinguish between primary and secondary lung NET disease.)

Treatment decision making: the MDT and Informed Consent

There is consensus agreement that all Neuroendocrine Cancer patients should be reviewed by a Specialist Neuroendocrine Cancer MDT.

A MDT (MultiDisciplinary Team) is made up of disease specific experts including physicians, surgeons, radiologists, histopathologists, oncologists, clinical nurse specialists, allied health professionals (e.g. dietician) , a multidisciplinary team coordinator and has a designated lead clinician.

They meet to review all investigations, tests and patient relevant information (signs, symptoms, health and family history and current status).

Factors that affect MDT treatment decision – Histology (Cell type, Grade/ Mitotic rate), Stage (0-IV), Functional imaging results (Gallium/Octreotide or FDG PET results), Associated Syndromes (presence or absence of NET related syndromes or para-neoplastic syndrome) and Performance Status (how well / active you are).

Your care team will discuss your treatment options with you – giving you both written and verbal information – to help you make an informed choice.

Together you can agree on the most appropriate treatment for you.

The next stage is for you to give your consent to treatment.

You may be asked to sign a consent form, which you should not do unless you agree with and feel confident in the proposed plan of care.

You have control here and it has to be a decision you feel sure of making – so take

some time to think everything through before signing the form, and if you've got any questions, ask.

Informed consent relies on you being given the information you need to make an informed choice.

This information shouldn't cover just the treatment itself, but should also look at any preparation needed and any side-effects or longer term consequences that may occur.

It can be helpful to discuss your beliefs and preferences too.

For example, are alternatives available to blood transfusion during surgery? How quickly do you need to have the treatment – can you put it back to a different date?

Sometimes talking with someone who has had the same treatment may help.

Being shown round the unit or ward you may stay in can be useful too.

Remember though, that everyone experiences cancer and cancer treatment differently.

Remember – you can say no to a treatment.

Your care team must respect your choice and you don't have to give a reason, although it can be useful for your care team to understand your decision so they can plan future treatments with you.

Questions it may be helpful to have answered :

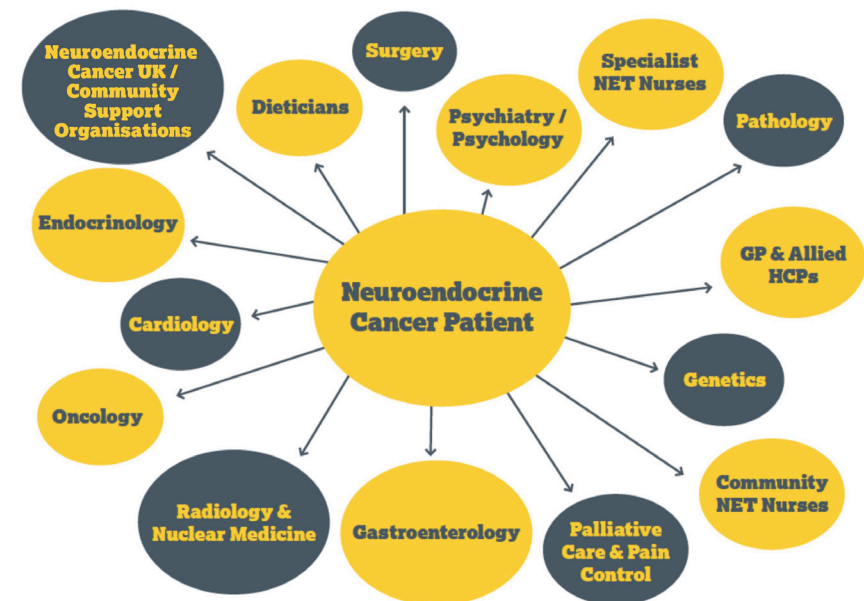
- What exactly does the treatment involve?
 - How likely is it to be effective? Could other treatments be more effective?
- How long does it take? e.g. outpatient,

day case or will I need to be hospital? If I need to be admitted to hospital – how long will I need to stay? Is there anything I can do to prepare for this treatment?

- Where will treatment take place?
- What are the advantages and disadvantages of the treatment? Could there be side effects? Will these be short- or long-term? What can I do to reduce the impact of any side effects or consequences of treatment?
- What impact will it have on my everyday life? Will I need to take time of work?

How long? Will there be limitations or restrictions to what I can do? For how long?

- Will I need someone to look after me or my family? What if I'm a carer, parent, or have pets or neighbours who rely on me? What assistance / help is available?
- Do you have any written information I can take away with me? Who do I contact if I have any further questions after this consultation? What information will be provided to my GP/primary care team? What follow up would be required?



Treatments and potential side-effects

This section concentrates on the treatment of primary lung NEN

For further information on treatments used in Neuroendocrine Cancer visit the website www.neuroendocrinecancer.org.uk or call 0800 434 6476.

Please note that whilst we have listed potential risks and side-effects here, that does not mean that you will experience them or that if you do they will be severe enough to affect or stop ongoing treatment.

Most effects, if they occur can be managed without disrupting therapy or, importantly, your quality of life.

Therefore it is vitally important that should you start to feel unwell or experience any of the effects noted here, you let your care team know as soon as possible.

Lung surgery

Surgery is usually the first option considered as it is the only currently available treatment with the potential for cure. If you have a single tumour, with no evidence of secondary disease (no lymph nodes or metastases) and it can be completely removed, then surgery may be a potentially curative treatment.

All lung surgery should be carried out by a specialist respiratory, thoracic or cardio-thoracic surgeon – who have expertise and experience in safe techniques that minimise complication risk and reduce post-operative pain (incision type, nervesparing techniques, appropriate anaesthesia and peri-operative analgesia).

It's possible to have keyhole surgery of

the lung, which is usually done through a procedure called video-assisted thoracoscopy (or VATS).

However, you may need to have open surgery – either a thoracotomy (which involves an open cut being made in the chest) or a sternotomy (when a cut is made through the breastbone) – to ensure complete removal of tumour and/or nearby lymph nodes.

There are a number of possible surgical options, which will be decided by where your NET/NEC is. Options include:

- **Metastectomy**, which involves a small lung tumour being 'scooped' out of the lung.
This is usually done to treat secondary tumours that have spread from elsewhere.
- **Wedge resection**, which involves the removal of a 'wedge' of lung that contains the tumour.
- **Segmentectomy**, which involves the removal of the segment(s) of lung that contains the tumour.
- **Lobectomy**, which involves the removal of one or more lobes.
- **Sleeve resection**, which involves the removal of an upper lobe along with part of the main airway. The remaining lung is then attached to the remaining airway.
- **Pneumonectomy**, which involves the removal of an entire lung.

Surgery for secondary disease (metastases) related to a lung primary will be dependent on several factors including site, position,

amount of disease, aim of surgery and your general health and symptoms.

Surgery for secondary lung disease (lung metastases) would depend on primary site and type of NEN.

Potential side-effects of lung surgery – immediate, short-term and long-term:

- **hypothermia** – during surgery – may be due to the temperature of the theatre, certain anaesthetic medications and / or length of time lungs are exposed during surgery (internal body heat loss).
- **syndrome related** – Carcinoid Syndrome -> Carcinoid Crisis. Cushings -> adrenal insufficiency / blood clots (DVT - legs, PE - lungs)
- **bleeding** – during and after surgery
- **blood clot(s) in leg or lung** – during and after surgery – linked with immobility and Cushings
- **infection** – post surgery – short-term risk.
- **pain** – post surgery – this may be an immediate, short-term or longer-term issue.

Interventional radiology / Endobronchial therapy

(treatment delivered via bronchoscopy)

Ablation is a treatment that involves inserting a probe or needle into your cancer then trying to destroy it using heat or cold.

It can be used in combination with, or as an alternative to surgery.

This can be done by passing the probe/needle through either the chest wall or via a bronchoscope:

- **RadioFrequency Ablation (RFA)** uses heat from radio-frequency waves to target and kill cancer cells.
- **Microwave ablation (MWA)** is similar to RFA but uses heat from microwaves rather than radio waves to destroy cancer cells

Endobronchial therapies:

- **Bronchial stent insertion** A stent is a hollow tube that may be placed in your airway to open an area of narrowing.
If one of the bronchi is narrowed a stent can be used to improve that narrowing and hence improve your breathing.
The aim is to make your breathing easier though it will not cure the disease causing the narrowing.
- **Laser therapy** uses light energy to destroy tissue through thermal activity (heat). Thermal activity is generated as a result of the transfer of light energy to tissue.
- **Brachytherapy** refers to the use of radiation treatment delivered via bronchoscopy – and is only used in specific circumstances and where specialised facilities exist.

Other therapies you may hear or read about include:

- **Electrocautery** uses the flow of electricity to generate heat. Electrical current flows from the probe into the target tissue adjacent to the tip of the probe.
- **Argon Plasma Coagulation (APC)** works similarly to electrocautery. Less commonly used.
- **Cryotherapy** is a way of killing cancer cells by freezing them. It is also called cryosurgery or cryo-ablation.
- **Photodynamic therapy** is a treatment that uses a drug, called a photosensitizer or photosensitizing agent, and a particular type of light.
When photosensitizers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells.
Potential risks and side effects are rare but can include: damage to the airways – by

the bronchoscope or probe, bleeding, respiratory infection and/ or respiratory failure.

Targeted therapy

- **Everolimus** (which is also marketed as Afinitor) is a daily tablet to treat well to moderately-differentiated, non-syndromic pancreatic, gastrointestinal and lung NETs, that cannot be removed by surgery and showing signs of progression (that is, further growth and / or spread). It works by blocking a particular protein, called mTOR, that causes cancer cells to grow.

Everolimus may also stop cancer cells from developing blood vessels.

Without a blood supply, cells are starved of oxygen and nutrients and so can't grow. Suitable for TCs and ACs.

The pharmaceutical company that produces Everolimus have listed the following as possible side effects: Mouth ulcers, increased risk of infection, coughing and feeling short of breath, nausea, reduced appetite and weight loss, diarrhoea and / or constipation, changes in blood sugar levels, fever, feeling tired and/or a red rash.

- **Peptide Receptor Radionuclide Therapy (PRRT)** is a type of very targeted radiotherapy, it is administered in the Nuclear Medicine Department (where you may already have had an Octreotide, Gallium-Dotate or FDG-PET scan).

It involves injecting a substance (*Lutetium, Yttrium 90 or MiBG) that travels directly to NET cells, binds to receptors on those cells and then releases a high dose of radiation designed to kill the cells.

Potential side-effects of PRRT include : pain after treatment, feeling and/or being sick (usually only associated with the amino acid infusion given at the time of therapy), diarrhoea, feeling tired, increased risk of infection, kidney damage (though this is rare)

and / or low platelet levels.

- **External Beam Radiotherapy** is the use of high-energy rays (such as x-rays) or radioactive particles to kill cancer cells.

Treatment is much like getting an x-ray, but the radiation dose is stronger.

The procedure itself is painless.

Each treatment lasts only a few minutes, but the setup time – getting you into place for treatment – usually takes longer.

Most often, radiation treatments are given five days a week for several weeks, but this can vary based on the reason it's being given.

External beam radiotherapy side-effects can be related to the site targeted and so may include : general weakness and fatigue, dry, red, itchy or peeling skin at target site, shortness of breath, swallowing difficulties, sore throat, shoulder stiffness, radiation pneumonitis (coughing, fever and a sensation of fullness in the chest that can occur several weeks or months after radiation therapy) and / or radiation fibrosis (lung scarring).

Cytotoxic chemotherapy

Chemotherapy can be used before, alongside or after other treatments. When considering whether chemotherapy is right for your NET/NEC, your care team will consider :

- Tumour cell type
- Tumour rate of growth (grading) – Ki67% and/or Mitotic Rate
- Functionality – is your tumour visible on Octreotide /Gallium-Dotate imaging (usually low-moderate grade Lung NEN TC/AC) or FDG-PET (usually high-grade disease – SCLC/LCNEC)?
- Aim of treatment – e.g. to try to shrink tumour to allow for surgery, to try to stop further growth and/or alleviate symptoms

- Use as a post surgery treatment

Chemotherapy kills rapidly-dividing cells in a variety of ways, depending on the drug.

Since there are many different types of cancers that all grow differently, many chemotherapy drugs have been developed to target these various growth patterns.

Each drug has a different way of working and is effective at a specific time in the life cycle of the cell it targets.

There may also be particular cell mutations that may have been identified within your tumour that may make it more sensitive to specific types of chemotherapy.

Chemotherapy is usually used in SCLC, LCNEC and occasionally AC – depending on Mitotic Rate and disease behaviour.

The most commonly, but not only, used regimens of chemotherapy used in Lung NEN are :

- Platinum based chemotherapy e.g. Cisplatin/Carboplatin + Etoposide
- Temozolomide/Capecitabine

Potential side-effects of chemotherapy – these may depend on which drugs / regimens are used – but can include:

Feeling tired (this can carry on for several months after your treatment ends), feeling and being sick, altered taste/appetite, weight loss, diarrhoea and/or constipation, increased risk of infection, hair thinning or loss (not all drugs/regimens), dry skin and skin rashes – particularly on the hands and feet, brittle or dry nails and / or numbness or tingling in the hand and feet.

Somatostatin Analogues

Somatostatin is a substance that occurs naturally in the body.

It helps to control the release of hormones into the bloodstream, including those released by Neuroendocrine Cancers.

Somatostatin analogues are drugs created to mimic the behaviour of somatostatin.

By helping to control hormone levels, they can reduce symptoms of Carcinoid Syndrome, like diarrhoea, flushing and wheezing.

There is also trial evidence within certain types of NEN (low to moderate grade) that Octreotide (Sandostatin LAR) and Lanreotide (Somatuline Autogel), both somatostatin analogues, interfere with tumour growth rate – either stabilising or slowing down further tumour growth.

The pharmaceutical companies that manufacture somatostatin analogues (which include drugs like lanreotide and octreotide) list the potential side effects as: loss of appetite, feeling and being sick, feeling bloated, stomach pain and/or cramping, diarrhoea and/or steatorrhoea, soreness where you're injected, alterations in blood sugars and/or gallstones.

IFN-2Alpha

Interferons are made naturally by the body as part of the immune system. They prompt cells to respond to – or 'interfere' with – problems like viruses and bacteria.

Interferon Alpha is a manmade substance designed to mimic interferons.

It stimulates immune system cells to attack cancer cells, it interferes with the development of cancer cells, and it causes cancer cells to produce chemicals that attract immune cells.

Alpha-interferon is given to reduce the symptoms of tumours that have spread, often when other treatments aren't working. And it's sometimes given in combination with a somatostatin analogue.

Potential effects of Interferon Alpha include: pain, redness, itching or swelling where you've had the injection, thinning hair (this is

more likely after a high dose or long course of Interferon), dizziness, loss of appetite, changes in the way things taste, increased risk of infection, feeling tired and breathless, feeling weak, flu-like symptoms, diarrhoea, tummy pain, feeling sick, experiencing emotional changes, including depression, struggling to sleep, headaches, weight loss, itchy skin or rashes and /or coughing.

Clinical Trials

Your care team might suggest participating in a clinical trial, as a treatment option. Clinical trials are voluntary research studies conducted in people and designed to answer specific questions about the safety or effectiveness of drugs, vaccines, other therapies, new ways of using existing treatments, or a combination of new and existing therapies.

If you are interested in participating in a clinical trial, talk with your neuroendocrine cancer team.

Alternatively, if you would rather look for yourself, having information about your particular neuroendocrine cancer may help you to narrow down your search.

Trials will always have a list of eligibility or inclusion/exclusion criteria.

This is a list of characteristics that all patients must have to be accepted onto the study.

Types of eligibility criteria can include: age, previous medical history +/- medications +/- previous treatment(s) and current health status but may also include disease specific criteria, such as type and site, functioning or non-functioning/syndromic or non-syndromic, grade (Ki67% or mitotic rate) and whether the cancer is well or poorly-differentiated.

If you find a trial you think you may be eligible for you can discuss it with your clinical team.

A medical referral is the only way to join a clinical trial. Your doctor can refer you to trials

appropriate for you.

They will also be able to contact the team running the trial and find out more information about it.

Your doctor will be able to review the information about the trial with all of the things they know about you, your current health and previous treatments.

Being under a specialist neuroendocrine team, or having access to that team ensures that experts on your particular care and pathway are looking after you, but also they will be involved in specific neuroendocrine cancer research so will be able to answer questions you may have about clinical trials.

Patients who want to volunteer for a clinical trial can search **ClinicalTrials.gov** to find suitable studies in their geographic area.

After finding a study on the website that looks like a good fit, the patient can contact the study investigators directly for more information on how to take part.

This database is not the easiest to use and we, at Neuroendocrine Cancer UK, are working with the iCancer team and INCA to find an easier solution to engaging more patients in clinical trials and to make the information about that trial easier to find and understand.

New treatments are being developed and tested everyday and existing treatments are being reviewed and retested in different combinations.

Research into cancer and cancer treatments is moving forward all the time, so don't be surprised if you're offered a treatment or trial that's not listed on the current trials list.

Further information is available via the Research page on our website **www.neuroendocrinecancer.org.uk**.

Surveillance

If your NET/NEC is stable, in remission, isn't causing symptoms or is growing very slowly, your care team may recommend that the best response is to monitor it – rather than starting treatment that may have side effects. There are various terms used to describe the process of monitoring cancer rather than starting a course of treatment.

Your care team might call it 'active surveillance', 'active monitoring', 'watchful waiting' or 'wait and see'.

This can seem odd or unnerving. It's natural to think that if you have a tumour you should do something about it.

But active surveillance doesn't mean doing nothing. It means monitoring your cancer and health – how it is affecting you, but not putting you through any treatments that might not be necessary and could cause side effects, which could affect your quality of life.

Timing of surveillance will be guideline based but adapted to take into account your Lung NEN type, symptoms and overall wellbeing/general health.

Supportive therapy & Self-management strategies :

Discovering you have cancer, undergoing diagnostic tests, cancer treatments and living with the effects of all of these factors can put a lot of extra strain on you, both physically and psychologically.

The whole process of being diagnosed with and treated for cancer is abnormal.

No one expects the sudden shift to a life of tests, treatments and unfamiliar medical language, and however realistic we are about our lives not lasting forever, being confronted with our mortality through a cancer diagnosis isn't something that's easy to deal with.

Whilst your care team can make recommendations for treatment – the

decision about what treatments you receive is yours.

Which all sounds very clear cut, however, how you feel about this may be far from that precise – and there may be times when life feels very uncertain – giving rise to anxieties and fears.

We discuss emotional well-being on pages 28-29 and further sources of support can be found on our website **www.neuroendocrinecancer.org.uk**.

How much healthcare involvement you have will depend upon your particular type of NET or NEC and the decisions you make about your care.

So what can help?

Letting your care team know about your overall and long-term health, along with how you're feeling now, is a vital part of getting the right diagnosis and care.

It helps to ensure the right tests are done, and can guide decisions not only about which treatments are right for you, but also about whether you need treatment at a particular time.

It's really important that you tell your doctors as much information as possible about your health – especially if anything changes.

Equally important is to discuss your wishes, preferences and any concerns you may have related to your cancer and the impact it is having on you – mentally, emotionally and socially (e.g. family/relationships, work, lifestyle and finances).

In our handbook there are dedicated sections to aspects of living with Neuroendocrine Cancer that might be helpful – such as Understanding Neuroendocrine Cancer, Effects of Neuroendocrine Cancer and Treatments, Diet & Nutrition, Looking after Yourself and Practical issues.

Here we'll concentrate on some of the specifics to life with Lung NENs – in particular getting the best of symptom management, improving and maintaining lung health, pre and post surgical care and support.

Optimising symptom management

Alongside some of the treatments you may be offered to treat your cancer, there may be other therapies and/or medications that may be prescribed for you to help reduce or

relieve symptoms – for example analgesia to alleviate pain.

External beam radiotherapy has been used both as a treatment for lung primary cancer and also for alleviating pain related to bone metastases (single site e.g. rib).

There may even be medications offered to reduce the side or after effects of treatment, such as anti-sickness medicines (anti-emetics) to help reduce chemotherapy-related nausea.

If you do have symptoms, or side/after effects of treatment, it is important to discuss these, and how they are affecting you, with your care team.

It may help to write down any symptoms you may be experiencing, in order of importance to you.

It can help your team to identify the best way of helping you if you can describe the symptom, for example, breathlessness – is it all the time? Only going up and down stairs or during/after a long walk? Can you lie down flat? Do you need pillows – how many? Does anything make it better or worse?

Write things down – and take this note along with you.

It can sometimes be difficult to talk as freely as you might want to – busy clinic, unfamiliar healthcare staff, nervousness or anxiety felt by you, uncertainty... all of these things can influence how well or poorly a consultation may go.

But, this is your time and each consultation should be a two-way discussion, involving you in every decision.

Your doctor or nurse may need blood, scan

and other investigation or monitoring results to tell them what's happening with your cancer and overall health, but only you can tell them how it's affecting you.

Improving and maintaining lung health

In 2019, the European Society of Thoracic Surgeons & Enhanced Recovery After Surgery (ERAS) Society published Guidelines for enhanced recovery after lung surgery.

Much of the advice in these guidelines relates to pre-surgery: the key being that optimising health before surgery occurs, helps to reduce complications (e.g. infection) and encourages earlier recovery.

Importantly, the guidelines can also be used as helpful advice for anyone affected by lung cancer or disease, even if surgery is not the treatment for you.

We have also looked at information for people post surgery and living with Lung NEN.

Pre-habilitation and Rehabilitation

Pre-habilitation is a process through which healthcare professionals can work with patients, and the people close to them, to prepare for and manage the impact of cancer and its treatments before, during and after treatment.

It also can be useful for those who are not having acute treatment – for example active monitoring and / or supportive care.

Rehabilitation is the process of assisted recovery. Healthcare professionals, working with patients and the people close to them, to help restore or adjust to life following an illness or medical intervention.

Recovery to a good level of health is often possible, however there are circumstances in which regaining your usual level of health and activities may not be possible – either immediately or ever.

A key factor for both is **information and**

education. But, as we have said in our introduction, everyone deals with illness differently.

Some people want to know exactly what's happening, others prefer doctors to keep things as general as possible – and it's completely up to you how you approach your life with a Neuroendocrine Cancer.

However, trying to prepare for what is to come can help. Being prepared for treatments, for instance, can help you know what to expect, what is usual and what's not – for example what side effects could happen and how to deal with them, if they occur.

Many areas of healthcare (oncology, dietician, radiology, etc.) have their own information leaflets or factsheets about certain treatments and procedures – it can help to have this written information as well as verbal explanations.

If you have sight or hearing problems or language difficulties, ask if they have this information in a format you would find easier to use e.g. large print, braille, 'talking books', other languages, videos or podcasts.

Sometimes something as simple as a basic diagram, picture or drawing can help.

What's important is that you get the information you need to understand what's happening, so you can make the right choices about your treatment and/or ongoing care.

Some healthcare providers have established ERAS* or PREPARE** programmes they can offer you when considering surgery.

The following is based on the aspects and activities both of these programmes cover – though maybe not in the same order!

*ERAS is Early Recovery After Surgery.

**PREPARE stands for Physical activity, Respiratory exercise, Eat well, Psychological well-being, Ask about medications, Remove bad habits and Enhanced recovery.

Nutrition

Although there is no one specific diet suitable for everybody who has NET/NEC, there may be adjustments you need to make to what you eat in general or at certain times.

You may need to add things to your diet based on your general health, your treatment, the type of NET/NEC you have or if you're losing weight.

Being diagnosed with a neuroendocrine cancer (be it a NET or NEC) can put you at risk of having a poor nutritional status or even malnutrition.

This may be due to :

- unintentional weight loss,
- reduced food intake before diagnosis
- reduced food intake since diagnosis
- and / or due to where your cancer is.

You may also be experiencing a reduced ability to process food normally, for example, if you have Carcinoid Syndrome or Pancreatic Enzyme Insufficiency (P.E.I – this has been linked to somatostatin analogue therapy).

Surgery and some other treatments, like chemotherapy, can increase the risk of reduced nutrition – either in the short or long term.

Post-operative complications and increased length of stay in hospital have both been linked to malnutrition.

Side-effects such as sore mouth, taste changes and / or nausea can also affect appetite and limit food intake.

Being undernourished can weaken the immune system, which can contribute to complications such as a chest infection or prolonged wound healing.

On its own or alongside anaemia, it can also cause tiredness and/or depression, which can lead to decreased mobility and can make recovery more difficult and prolonged.

Obtaining adequate nutrition and correcting any nutritional deficiencies (such as anaemia) is therefore vitally important for a number of reasons.

Some symptoms can be managed by eating a healthy and appropriate diet.

Good nutrition can promote healing, prevent deficiencies and help you to maintain a healthy weight.

It can help improve both quality of life and muscle function.

Pre-surgery, “carb-loading” may be advised. Research has shown that you can lose more glycogen (a form of carbohydrates stored in your muscles for energy), during surgery than while training 2.5 hours for a race!

And that carb-loading can reduce not only hunger, thirst and anxiety before a surgery but also nausea, vomiting, pain and even your length of stay in the hospital following surgery.

Therefore, to help support your recovery, eat more complex carbohydrates before and after surgery.

Examples include: beans, oatmeal, wholewheat bread, quinoa, barley, potatoes, and sweet potatoes.

These foods are also naturally rich in vitamins, minerals, and phytochemicals*.

**Phytochemicals are naturally occurring compounds in plant foods, that have been found to have certain positive benefits to human health.*

Further information and links can be found on our website:

www.neuroendocrinecancer.org.uk



Further information on the Eatwell Guide can be found at www.nhs.uk

Physical activity

You don't need to suddenly take up marathon running or jogging, but gentle activities like swimming, walking, gardening, stretching exercises, yoga and tai chi can all help your body to get stronger.

If you have issues that affect your mobility, such as arthritis, simple armchair exercises can help too. And you might find that exercise gives your mood a boost.

With walking you can start with a short 5 minute stroll, building up your time in 5 minute increases a day, until you are walking for 1-2 miles a day (other health considerations and mobility allowing). You should be able to walk and talk at the same time. If you are unable to do this or become quite breathless – cut back slightly in time and distance.

Swimming and cycling are also excellent ways to exercise, however if you have had surgery – it is best to wait until your wound has completely healed before re-starting or taking up either of these activities. This can take up to 6-8 weeks.

If you are on chemotherapy or any other medication or treatment that may lower your normal immunity (white cell count) – it is best to avoid swimming until your therapy has completed and white cell count has recovered.

Upper body exercises

Alternate arm lifts: starting with your right arm, raise it as if asking the teacher if you can speak! then lower it. Repeat 10 times, then do the same with your left. (n.b. this is also a useful exercise post lung surgery – where you concentrate slightly more on the side you have had your op).

Hand-Leg slide: start by standing straight (comfortably), bend slightly over to the right, sliding your hand down your leg as you do so. Return to the standing position and do the same again, but this time bending to the left. Repeat 10 times.

Chair turn: Sit upright in a chair. Put your hands on your shoulders : Right hand left

shoulder, Left hand right shoulder. In this position turn your upper body to the right, then to the left. Keep your elbows at shoulder height and your back straight. repeat 10 times.

Breathing exercises

Breathing control: Rest your hand lightly on your stomach. Breathe in and out, quietly and gently through your nose, if you can. As you breathe in, your stomach should rise.

Deep breaths: Take a long, slow deep breath – in through your nose and out gently through your mouth. Try to breathe right down to the bottom of your lungs, expanding your ribcage. Aim to do 3-4 deep breaths before returning to Breathing control.

The Huff (useful if you need to clear phlegm – but you may need to go a couple of cycles of Breathing control and Deep breaths before doing The Huff!): A huff is similar to a cough but you are aiming to keep your mouth and throat open – imagine holding a mirror to your face and trying to 'steam' it with your breath. Take a deep breath in and then breathe out as forcefully as you comfortably can, keeping your mouth open. If you wheeze as you breathe out – you may be huffing too hard!

Cough: Following a huff you may need to do a good strong cough – especially if it has loosened any phlegm. If you have had surgery – to your lung or abdomen – it may help to use a pillow or rolled up towel to support your wound. Coughing can be uncomfortable but it can help to clear phlegm and therefore prevent infection.

Following surgery or interventional radiology some shortness of breath is to be expected and is normal. When you first get home and start pottering about, you may feel breathless but this is ok – initially. Returning to your usual level of fitness can take some time – it could be weeks or months. Occasionally, however, due to the extent of surgery and whether you had any complications, some degree of breathlessness may persist.

Psychological well-being

A cancer diagnosis doesn't only affect

your body. It can have a big impact on your emotions, your relationships, your job, your bank balance and many other parts of your life.

We can't tell you that everything is going to be OK or that your life won't change.

Or that relationships and emotions won't sometimes get messy as you adjust to life with a NET or NEC.

Important aspects of your life – your relationships, work life and social life – will be affected to some degree.

There will be times when life feels great, of course. Many people live well for years, following a NET or NEC diagnosis and we very much hope this will be the case for you.

But living well can depend on many things:

- Your physical health and disease status (type, grade, treatments, etc.),
- Your emotional health (worry, concern, anxiety, how you react/cope with challenges/stress), and
- Your social and familial health (those around you – family and friends, work colleagues/ employers/ employees – how much support you have and how much others depend on you).

How we think and feel is often influenced by our memories, experiences, relationships, beliefs, those around us, as well as our hopes for and concerns about the future.

Being diagnosed, having treatment for and living with cancer can throw our thoughts and emotions into chaos. It's completely natural to experience a whole range of different feelings – often at the same time – and trying to work out how you feel, or how you think you should feel, can be distressing.

One thing that can help is to try to identify and name the emotions you're feeling.

Separate out and name the emotions you are feeling. Just as with physical health, where identifying the symptom and cause can help

treatment – in emotional health, identifying the feeling and why you feel that way can help in dealing with it.

Most thoughts and feelings are helpful, but some can become harmful and may negatively affect our decision-making and quality of life.

In general, it's a good idea to find someone you feel completely at ease with, and who will let you speak openly and honestly, without judging what you say or immediately jumping in with unhelpful advice or attempts to 'fix' things.

Sometimes, however, you might not want to talk to those closest to you.

Help and support is available.

You can arrange to talk to your specialist nurse, care team or GP, over the phone or during an appointment: it may help to explain why you want an appointment when you book it, or ask for a double appointment, to ensure you are given time to talk, rather than a routine 5 or 10 minute slot..

You may find it helpful to talk to other people with Neuroendocrine Cancer – at support groups (including our "Natter"s) and / or online.

We have several online support groups and links, including Neuroendocrine Cancer UK Support (a closed Facebook group – that requires membership with our charity to join – nb membership is free!).

You can call our Helpline – available Monday-Friday 9am-5pm: calls are answered by either one of our Neuroendocrine Cancer nurses or an experienced member of staff.

All calls to this number are confidential.

We also offer a free telephone counselling service which is available to anyone affected by a Neuroendocrine Cancer; patients, family and friends.

Further information about how we can support you (and other helpful links) are available through our website: www.neuroendocrinecancer.org.uk or you can call us free on 0800 434 6476.

Follow-up for Lung:

As per national and international expert and evidence-based guidelines. n.b. guideline advice may be tailored to you and your particular disease, your overall health and your informed choice.

Follow up is dependent on type, tumour extent (Staging), histological differentiation, proliferative activity (Grading) and / or treatment.

Primary Lung NENs :

DIPNECH :

No current consensus, but given clinical presentation, impact on quality of life and potential for development of TC, follow up is recommended.

Clinical review and interval chest x-ray / CT scan as symptoms/general health status dictate.

Typical Carcinoid:

Following surgery: review at 3, 6 and 12 months for 1st 2 years, then annually (life-long) with Chest X-ray (and bronchoscopy as indicated).

CT every 3 years (more frequently if R1 or node positive resection or as clinically indicated).

Functional imaging* at 1 year post op, then only if suspicion of recurrence.

EndoBronchial UltraSound (EBUS) can be used if there is suspicion of local recurrence, and may be used 5-10years as surveillance.

Atypical Carcinoid:

Closer monitoring required.

Review at 3 months then every 6 months for first 5 years, with CT, then annually (lifelong) if all stable/disease free.

Functional imaging* at 1 year post op, then only if suspicion of recurrence.

NB in high grade disease FDG-PET may be more accurate than Gallium-Dotatate as functional scan.

EBUS can be used if there is suspicion of local recurrence, and may be used 1-3 years as surveillance.

If on ongoing therapy: 3 monthly review - If local progression suspected for EBUS.

For High Grade Disease (Small Cell / Large Cell / MiNEN):

Following surgery: CT every 3-6 months for first 3 years then 6-12 monthly.

In inoperable / advanced disease:

CT every 2-3 months if on therapy. Repeat biomarkers – if elevated at diagnosis.

**Gallium-PET for well-differentiated disease, FDG-PET for poorly-differentiated.*

Appendix: Lung staging in detail

Stage 0 (TisN0M0)

This is called in situ disease, meaning the tumour is “in place” and has not grown into nearby tissues and spread outside the lung.

Stage I (Diagram 1) is divided into two sub-stages based on the size of the tumour:

Stage IA tumours are 3cm or less in size – can be further divided into:

IA1 (T1aN0M0) The tumour is up to 1cm across and has not reached the membranes that surround the lungs, and it does not affect the main branches of the bronchi.

IA2 (T1bN0M0) The tumour is between 1-2cm across. It has not reached the membranes that surround the lungs, and it does not affect the main branches of the bronchi.

IA3 (T1bN0M0) The tumour is between 2-3cm across. It has not reached the membranes that surround the lungs, and it does not affect the main branches of the bronchi.

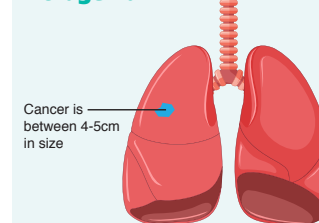
Stage IB (T2aN0M0) The tumour is between 3-4cm across AND has grown into a main bronchus, but is not within 2cm of

the carina (the point where the windpipe splits into the left and right main bronchi) AND/OR has grown into the visceral pleura (the membranes surrounding the lungs) AND/OR is partially clogging the airways.

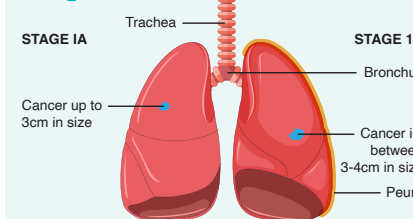
Stage II is divided into 2 substages:

Stage IIA (T2bN0M0) The tumour is between 4-5cm AND has grown into a main bronchus, but is not within 2cm of the carina (the point where the windpipe splits into the left and right main bronchi) AND/OR has grown into the visceral pleura (the membranes surrounding the lungs) AND/OR is partially clogging the airways (and is larger than 4cm but not larger than 5cm across).

Stage Ila



Stages Ia and Ib



Stage IIB describes either a tumour that is up to 3cm across and has not grown into the membranes that surround the lungs, and does not affect the main branches of the bronchi.

It has also spread to lymph nodes within the lung and/or around the area where the bronchus enters the lung (hilar lymph nodes). These lymph nodes are on the same side as the cancer (T1a/b/cN1M0).

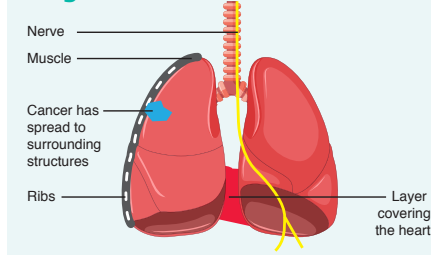
OR, (T2a/bN1M0) the tumour is between 3-5 cm across and has grown into a main bronchus, but is not within 2cm of the carina (the point where the windpipe splits into the left and right main bronchi) AND/OR has grown into the visceral pleura (the membranes surrounding the lungs) AND/OR is partially clogging the airways.

It has also spread to lymph nodes within the lung and/or around the area where the bronchus enters the lung (hilar lymph nodes).

These lymph nodes are on the same side as the cancer.

OR, (T3N0M0) the tumour is between 5-7cm across and has grown into the chest wall, the inner lining of the chest wall (parietal pleura), the phrenic nerve, or membranes of the sac surrounding the heart (parietal pericardium) AND/OR there are 2 or more separate tumour nodules in the same lobe of a lung.

Stage IIb



Stage III are classified as either stage IIIA, IIIB, or IIIC. The stage is based on the size of the tumour and which lymph nodes the cancer has spread to.

Stage III cancers have not spread to other distant parts of the body.

IIIA (T1a/b/cN2M0) The cancer is no larger than 3cm across, has not grown into the membranes that surround the lungs, and does not affect the main branches of the bronchi, but has spread to lymph

nodes around the carina (the point where the windpipe splits into the left and right bronchi) or in the space between the lungs (mediastinum).

These lymph nodes are on the same side as the main lung tumour.

OR (T2a/bN2M0) the tumour is between 3-5cm across and has grown into a main bronchus, but is not within 2cm of the carina (the point where the windpipe splits into the left and right main bronchi) AND/OR has grown into the visceral pleura (the membranes surrounding the lungs) AND/OR is partially clogging the airways.

The cancer has spread to lymph nodes around the carina (the point where the windpipe splits into the left and right bronchi) or in the space between the lungs (mediastinum).

These lymph nodes are on the same side as the main lung tumour.

OR (T3N1M0) where the tumour is between 5-7cm AND/OR has grown into the chest wall, the inner lining of the chest wall (parietal pleura), the phrenic nerve, or membranes of the sac surrounding the heart (parietal pericardium) AND/OR there are 2 or more separate tumour nodules in the same lobe of a lung.

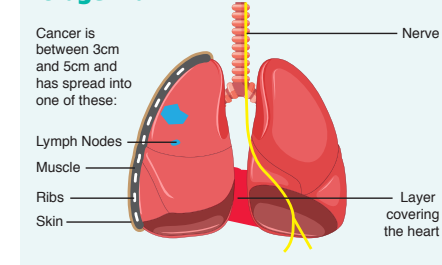
The cancer has also spread to lymph nodes within the lung and/or around the area where the bronchus enters the lung (hilar lymph nodes) and these lymph nodes are on the same side as the cancer.

OR (T4 N0/1M0) where the tumour is >7cm across AND/OR has grown into the space between the lungs (mediastinum), the heart, the large blood vessels near the heart (such as the aorta), the windpipe (trachea), the tube connecting the throat to the stomach (oesophagus), the thin muscle separating the chest from the abdomen (diaphragm), the backbone, or the carina AND/OR there are 2

or more separate tumour nodules in different lobes of the same lung.

The cancer may or may not have spread to lymph nodes within the lung and/or around the area where the bronchus enters the lung (hilar lymph nodes). Any affected lymph nodes are on the same side as the cancer.

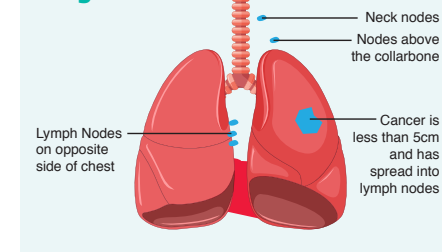
Stage IIIa



IIIB (T1a/b/cN3M0) as above T1 tumour, and the cancer has spread to lymph nodes near the collarbone on either side of the body, and/or has spread to hilar or mediastinal lymph nodes on the other side of the body from the main tumour.

OR (T2a/bN3M0) as above T2a/b tumour, and the cancer has spread to lymph nodes near the collarbone on either side of the body, and/or has spread to hilar or mediastinal lymph nodes on the other side of the body from the main tumour or (T3N2M0) as above T3 tumour and the cancer has spread to lymph nodes around the carina

Stage IIb

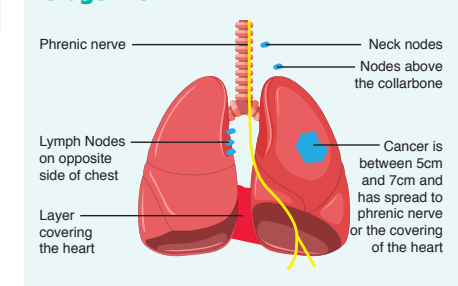


(the point where the windpipe splits into the left and right bronchi) or in the space between the lungs (mediastinum). These lymph nodes are on the same side as the main lung tumour.

OR (T4N2M0) as above T4 tumour and the cancer has spread to lymph nodes around the carina (the point where the windpipe splits into the left and right bronchi) or in the space between the lungs (mediastinum).

These lymph nodes are on the same side as the main lung tumour **IIIC (T3N3M0)** as above T3 tumour and N3 lymph node status or (T4N3M0) as above T4 tumour and N3 lymph node status.

Stage IIc



Stage IV means the lung NET has spread to more than 1 area in the other lung, the fluid surrounding the lung or the heart, or distant parts of the body through the bloodstream.

Therefore, it is possible for a patient to have distant metastases away from the site of a lung primary, even when other areas of the lungs remain metastases free.

Stage IV is divided into 2 substages:

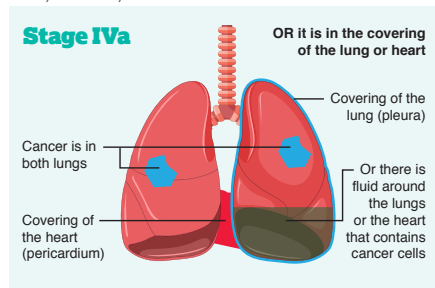
Stage IVA (AnyT AnyN M1a) The cancer can be any size and may or may not have grown into nearby structures.

It may or may not have reached nearby lymph nodes. In addition, has spread to

the other lung AND/OR the fluid around the lung (called malignant pleural effusion) AND/OR fluid around the heart (called malignant pericardial effusion).

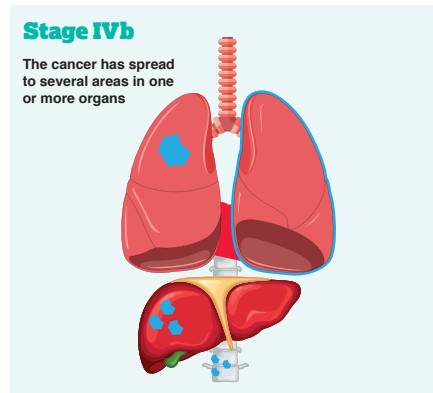
OR (AnyT AnyN M1b) the cancer can be any size and may or may not have grown into nearby structures.

It may or may not have reached nearby lymph nodes. It has spread as a single tumour outside of the chest, such as to a distant lymph node or an organ such as the liver, bones, or brain.



Stage IVB (AnyT AnyN M1c) The cancer can be any size and may or may not have grown into nearby structures. It may or may not have reached nearby lymph nodes.

It has spread as more than one tumour outside the chest, such as to distant lymph nodes and/or to other organs such as the liver, bones, or brain.



References

- Caplin et al. (2015) Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids [published online February 2, 2015]. *Ann Oncol*. Accessed via <https://academic.oup.com/annonc/article/26/8/1604/247409> July 2019.
- Fasano et al (2015) Pulmonary Large-Cell Neuroendocrine Carcinoma – From Epidemiology to Therapy. *J Thorac Oncol.*: 10(8): 1133–1141.
- Garcia-Carbonera et al: ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. *Neuroendocrinology* (2016) 103(2): 186-94.
- Gustafsson et al (2008) Bronchopulmonary neuroendocrine tumors. *Cancer*: 113:5–21.
- Hendifar et al (2017) Neuroendocrine Tumors of the Lung: Current Challenges and Advances in the Diagnosis and Management of Well-Differentiated Disease. *J Thorac Oncol*: Vol. 12 No. 3: 425-436.
- Öberg et al (2012) Neuroendocrine bronchial and thymic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up PLUS e-Update (2016) eUpdate – Neuroendocrine Tumours Treatment Recommendations accessed from www.esmo.org July 2019.
- Pavel et al: ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology* (2016)103(2):172-85.