What is (Primary) Neuroendocrine Cancer?

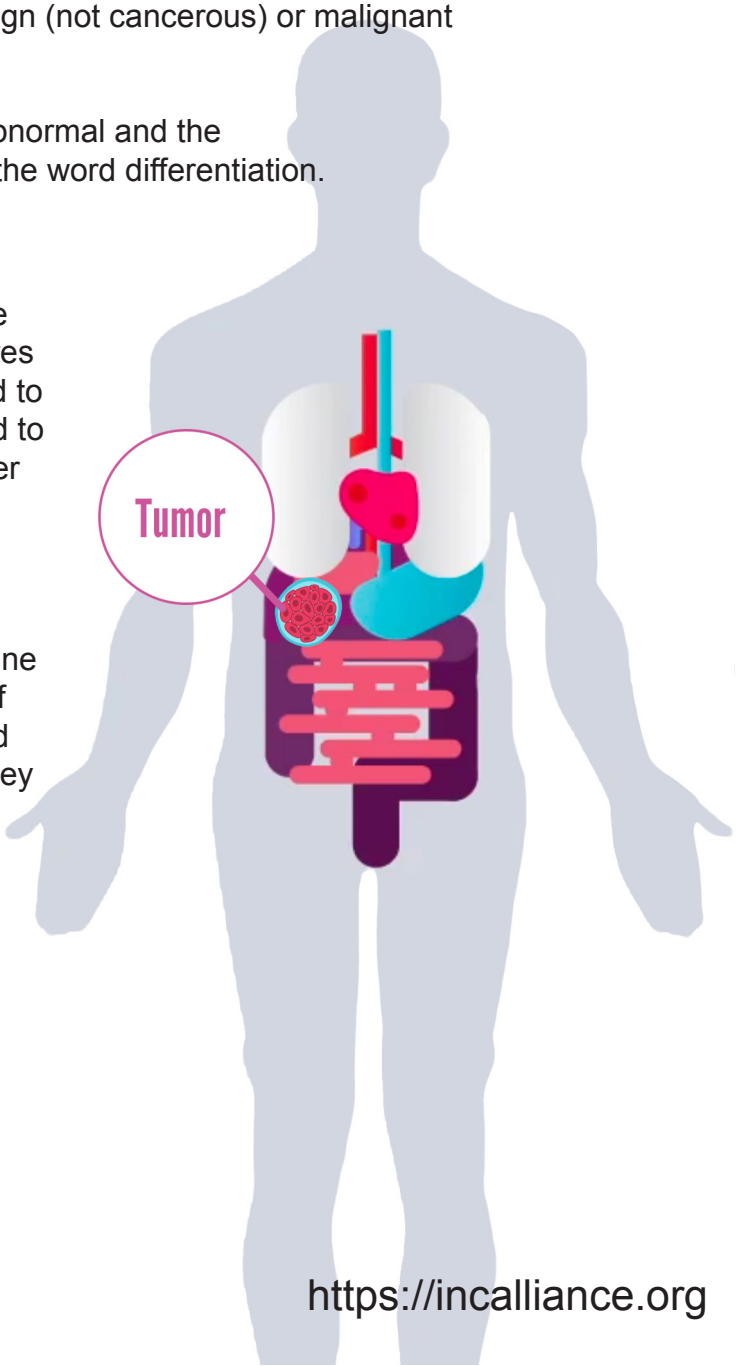
Neuroendocrine tumor (NET) is a label that has been used as an umbrella term for a group of tumors that start in neuroendocrine cells. However, the terminology, or naming, is constantly being updated as we learn more about them. For example, you may hear them described as 'carcinoid' – a term originating over a hundred years ago, meaning 'cancer-like'. The latest terminology is neuroendocrine neoplasms or NEN: 'neoplasm' = means new (abnormal) growth.

Neuroendocrine neoplasms include all new and abnormal growths found to start in neuroendocrine cells – whether benign (not cancerous) or malignant (cancerous).

Malignant neuroendocrine cells look abnormal and the degree of abnormality is described by the word differentiation.

- Well-differentiated neuroendocrine cancer cells still have some features of the original cell but have started to change shape and size. They tend to grow slower than we expect cancer cells to grow, however some may grow rapidly.

- Poorly-differentiated neuroendocrine cancer cells have lost almost all of the features of the original cell and have changed shape and size. They tend to grow as rapidly as we see other, more common, cancer cells grow.



So, we have 2 main types of 'malignant 'NENs – or "neuroendocrine cancers":

- neuroendocrine tumors (NETs) are well differentiated
- neuroendocrine carcinomas (NECs) are poorly differentiated

Neuroendocrine cancers, whether NETs or NECs, occur when neuroendocrine cells start to change shape and begin to grow abnormally: they may also show changes in their normal function.

What are neuroendocrine cells?

Neuroendocrine cells exist throughout the body and are there to produce hormones and other chemicals to ensure our bodies function normally. These cells make up a coordinated system – the neuroendocrine system – a network of communication to control and regulate that hormone and chemical release.

What is cancer?

Cancer is a condition where cells within the body start to grow and reproduce uncontrollably. These cells can invade and destroy surrounding healthy tissue, including organs and some can spread to other parts of the body (metastasize).

How are neuroendocrine cancers formed?

For some cancers we have identified particular risks or causes –

- Internal: for example, a faulty gene – as seen in breast cancer and BRCA gene.
- External: for example, exposure to a carcinogen (cancer-causing agent) such as smoking or exposure to certain chemicals.

For neuroendocrine cancers, we have not identified a definite cause or risk. Most occur without any obvious or genetic (that is inherited) cause or risk.

However, there is a very small number of people who may have a neuroendocrine cancer **related** genetic condition. Please note that having the genetic condition does not mean you will definitely develop a neuroendocrine cancer – but that you may have a lifetime risk of developing one.

Neuroendocrine cancer related genetic conditions are very rare and include:

- Multiple endocrine neoplasia disorders
- Inherited pheochromocytoma & paraganglioma syndromes
- Neurofibromatosis 1
- Von Hippel Lindau

INCA International Neuroendocrine Cancer Alliance

What is (Primary) Neuroendocrine Cancer?

In terms of cancer development, normal cells have a set of rules that regulate growth and behavior, in cancer the control signals go wrong and the rules are forgotten!

Normal cells:

- develop and grow in a controlled manner
- do what they are programmed to do, then die off to be replaced by new cells
- if damaged - try to repair themselves or die off when they can't
- tend not to separate and travel to other parts of the body
- if they do grow too big for where they are – tend to push against neighboring cells, rather than through them

Cancer cells:

- have an uncontrolled development and growth
- forget what they are programmed to do, do not die off and new cells continue to develop
- have a lack of cell repair and replacement / death, so abnormal cells continue to grow
- can break away from where they start to grow and travel to other parts of the body and settle (metastasize)
- when they do grow too big for where they are, will invade (grow through) neighboring cells and structures

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What are the different types of neuroendocrine cancer?

The difference in type of neuroendocrine cancer can be broken down into a number of ways, for example, site.

Site – where in the body it occurs – e.g. lung, small bowel, pancreas, skin, etc. Site can be broken down into primary or secondary

- **Primary -** refers to where the cancer starts
- **Secondary -** refers to where the cancer has spread to

For example: a small bowel neuroendocrine cancer, is a neuroendocrine cancer that has started in the small bowel. If this cancer has spread (metastasized) to the liver – it is still small bowel neuroendocrine cancer (as that it where it started) but the liver is the secondary site.

Stage – tells us whether the cancer is localized (limited to the area in which it arises) or disseminated (has spread to other places in the body). Staging is usually assessed by scans. Commonly, there are 4 stages:

- 1 = confined to the area in which it starts
- 2 = has spread to surrounding cells or tissue
- 3 = has spread beyond surrounding tissues and to nearby lymph nodes
- 4 = has spread to another place within the body, including lymph nodes.

Grade – the rate at which it grows – this is an assessment, using a microscope, to examine cells to see how many are actively replicating and growing. You might see 'Ki67' or 'Mitotic Index' mentioned in your clinic letters or medical reports alongside a Grading - G1, G2 or G3.

'Mitotic rate' (MiB1) or Ki67 are the measurements used to assess the rate at which your cancer is growing. 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) - often expressed as a percentage (%)

- **NET Grade 1** is where the Ki67 is less than 3% and cells are 'well-differentiated'
- **NET Grade 2** is where the Ki67 is between 3 and 20% and cells are 'well-differentiated'
- **NET Grade 3** is where the Ki67 is above 20% and the cells are 'well-differentiated'
- **NEC Grade 3** is where the Ki67 is above 20% but the cells are 'poorly-differentiated'

Differentiation – the degree of abnormality of the cancer cell:

- Well-differentiated refers to abnormal cancer cells that retain some similarity to their original cell.
- Poorly differentiated cells have lost most, if not all, similarity.

Functional – refers to the hormone and chemical production and release by these cells.

- Non-functioning neuroendocrine cancer cells usually retain their ability to release normal amounts of hormone or chemicals.
- Functioning neuroendocrine cancer cells produce and release abnormal amounts of the hormone or chemical they are usually responsible for.

How is it diagnosed?

There are a number of tests that can be carried out to confirm a diagnosis of neuroendocrine cancer. These include blood and urine tests, as well as scans and other investigations, such as a biopsy (taking a sample of the cancer to examine it under a microscope).

The type of test you have depends on the type of neuroendocrine cancer that is suspected. Alternatively, neuroendocrine cancer may not be suspected, but diagnosed while undergoing tests or treatments for something else.

You will be asked about your:

- general health – fitness, lifestyle, social situation
- any symptoms you may be experiencing
- your previous medical history
- any medications you are taking – prescribed and non-prescribed, herbal, homeopathic and/or legal/illegal
- your family medical history
- and whether you have any allergies or not

It is important to be as open and honest as you can, during this consultation, so that your overall well-being can be assessed and an accurate diagnosis made.

How is neuroendocrine cancer treated? Can it be cured?

As with more common cancers, early diagnosis offers the best chance of cure.

Treatment will depend on the type (grading, functionality, etc.), position and size of your neuroendocrine cancer – and whether (or to where) it has spread.
It will also depend on whether you have any other health concerns and / or illnesses and your general health and fitness.

There is global consensus agreement that all neuroendocrine cancer patients should be reviewed by a specialist neuroendocrine cancer MDT to ensure best care.

There are certain types of neuroendocrine cancer, where if diagnosed early, often incidentally, cure through surgery, is possible. For example, diagnosis of a small, localized Grade 1 NET at the tip of the appendix, with no evidence of local or distant disease – only found after surgery for suspected appendicitis.

The current reality, however, is that due to a number of reasons, at least half of those diagnosed with neuroendocrine cancer will have secondary disease at the time of diagnosis. This means that cure may not be possible, however, this is not the same as being told you have a terminal illness.

No cure (incurable) is NOT the same as ‘terminal’, and many people living with neuroendocrine cancer are doing just that – living. Many people are living long and well, with the support of their families, support network and specialist neuroendocrine cancer team.

The key aim of treatment, therefore, should be to help you have the best possible quality of life – as well as best life expectancy.

There is global consensus agreement that all neuroendocrine cancer patients should be reviewed by a specialist neuroendocrine cancer team to ensure the best care.
An important part of meeting with the specialist team (doctors, specialist nurses and allied healthcare professionals), is to make sure you understand what’s being discussed, so that you can make informed choices about your care.

One or more of the approaches below may be suggested:

- Removal of all or part of the cancer
- Control of disease, by slowing or stopping the growth of cancer
- Monitoring or surveillance
- Palliation, or easing of, symptoms

Therefore, treatment options may include: surgery, medications, interventions, trial therapy and / or symptom control – alongside emotional and social support.

Please see our selection of factsheets for further information about the types of treatment you may be offered for your type of neuroendocrine cancer.

There may be variations in access to the treatments available depending on the country.

What happens after diagnosis and treatment?

There are expert agreed guidelines regarding how and when follow up should occur, however, in practice this varies and often with good reason. Follow up should be determined by an expert and based on evidence and research, but also tailored to you and what is appropriate for your best care.

Resources

- **International Neuroendocrine Cancer Alliance (INCA)**
  www.incalliance.org
- **The Carcinoid Cancer Foundation**
  www.carcinoid.org
- **Neuroendocrine Tumor Research Foundation**
  www.netrf.org
- **Neuroendocrine Cancer UK**
  www.neuroendocrinecancer.org.uk
- **Neuroendocrine Cancer Australia**
  https://neuroendocrine.org.au
- **Canadian Neuroendocrine Tumour Society (CNETS)**
  https://cnets.ca

For the full list of INCA members: **https://incalliance.org/full-members/**

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