Neuroendocrine tumours: a Guide for nurses

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Foreword

This guide has been written for nurses who care for patients affected by neuroendocrine tumours (NETs). Whether you care for only two patients with NET or as many as a hundred, a sound understanding of this disease is vital to ensure that your patients receive the best possible care.

This guide has been produced to fill a gap that exists in the provision of nurse education material on NETs. The guide provides a detailed understanding of the various types of NETs, the methods of investigation, and the treatment options, as well as an overview of the challenges faced in living with NETs. As a result of reading this guide you will gain a deeper understanding of the needs of NET patients and ways in which you can help meet these needs. Recommendations for further reading are included at the end of each chapter should you wish to learn more about NETs.

Information in this booklet can be shared with patients and their families; however, it is important that you go through the booklet together with patients because—at first glance—the information can be overwhelming. By discussing the content together, the patient can gain a proper understanding of NETs and their treatments. This booklet is intended as a supplement to verbal information, not as a replacement.

For many people, cancer is a frightening term—synonymous with pain and death. The only person who can truly describe what it's like to have a serious, life-threatening disease is the patient. No verbal information or brochure can put the condition into words as well as someone suffering from the condition. So, it seems appropriate at the start of this guide that we include a poem written by a Norwegian NET patient, who describes her life with the condition.

LIFE CRISIS

In one day, my life changed.

My body harboured a life-threatening illness. Everything changed.

My world stopped. I cried bitter tears.

The world became joyless.

Why me? I asked. But that's just how life is.

So I picked myself up, stood tall, and told myself everything would be okay.

I so wanted to be healthy again and you've got to believe in yourself.

'Don't give up' – said my thoughts – 'otherwise it's curtains for you.'

At times the road seemed too tough.

But bit by bit things have gone better than I could have imagined.

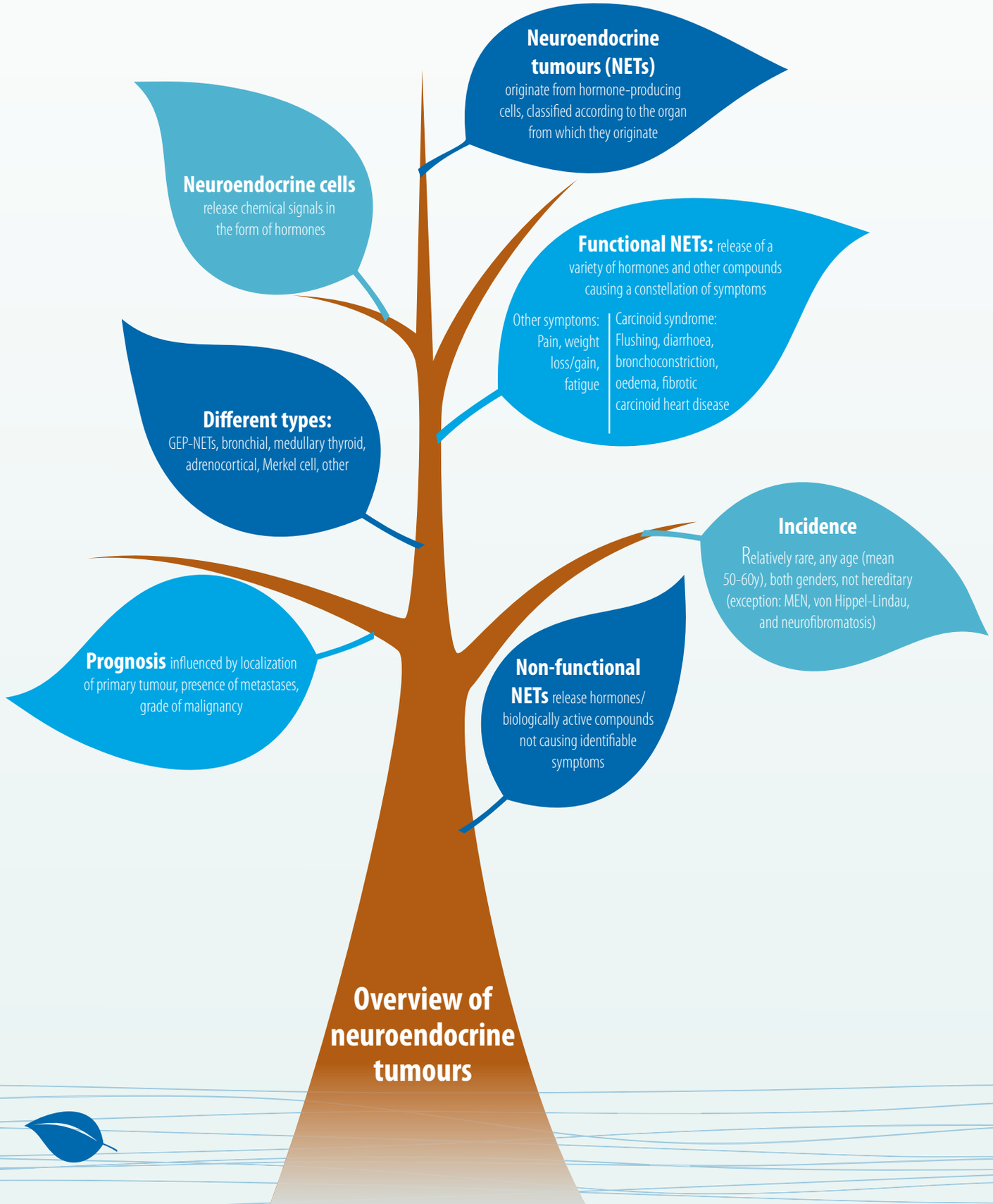
I've regained my zest for life; my wounded soul has healed.

Naturally, there are days when I feel down.

But never give up, and things, as they say, will turn out okay in the end.

Bjørg Elvira Røed

Chapter 1
Overview of neuroendocrine tumours



Introduction

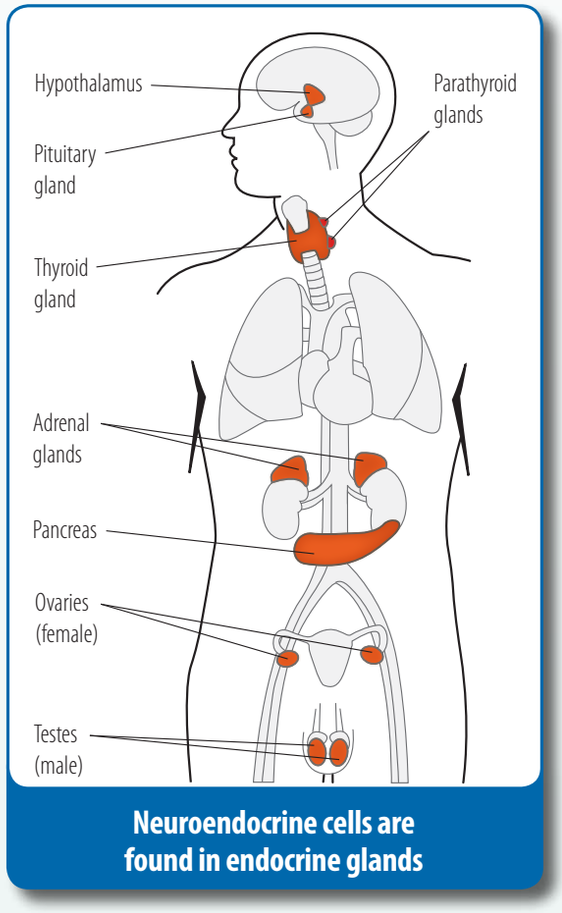
This chapter is intended to provide an insight into the function of neuroendocrine cells, and what happens when healthy cells develop into a tumour. After reading this chapter, you will have gained an overview into the characteristics of this type of cancer and how many people it affects. You will also gain an understanding of the various symptoms the disease causes and why these arise. This knowledge is important for you in your contact with patients. Being able to demonstrate a good theoretical and clinical understanding of them, in addition to your general nursing knowledge, will reassure your patients that they are going to be well looked after.

Neuroendocrine cells

Neuroendocrine cells, also known as neurosecretory cells, are specialised cells that respond to signals by releasing hormones into the blood. Upon receiving a signal, most neurons transmit information electrically along their axons to the nerve terminal where neurotransmitters are released that pass signals to other neurons or to other structures of the body, for example muscles. Neuroendocrine cells are different because they employ chemical, rather than electrical, signals in the form of hormones that are released into the bloodstream and send information throughout the body. That is, they act systemically, rather than locally. The nervous system is responsible for sensory perception and for motor control, as well as autonomic (unconscious) control of internal organs, while the endocrine system is composed of many glands that release hormones into the blood that regulate numerous bodily functions and the homeostasis (balance) of the internal environment.

Neuroendocrine cells are found in endocrine glands, such as the adrenal, pancreas, thyroid, and pituitary. They are also found in the ovary and testes, but it is predominantly the neuroendocrine cells in the mucosa of the lungs and gastrointestinal tract that give rise to neuroendocrine tumours (NETs).

The hormones released by neuroendocrine cells have a wide range of specific functions; those in the lungs are especially involved in processes that regulate the air and blood flow in the lungs and those in the gastrointestinal tract control the speed at which food is moved through the digestive system as well as other aspects of digestion.



Neuroendocrine cells are found in endocrine glands

Examples of hormones produced by neuroendocrine cells include:

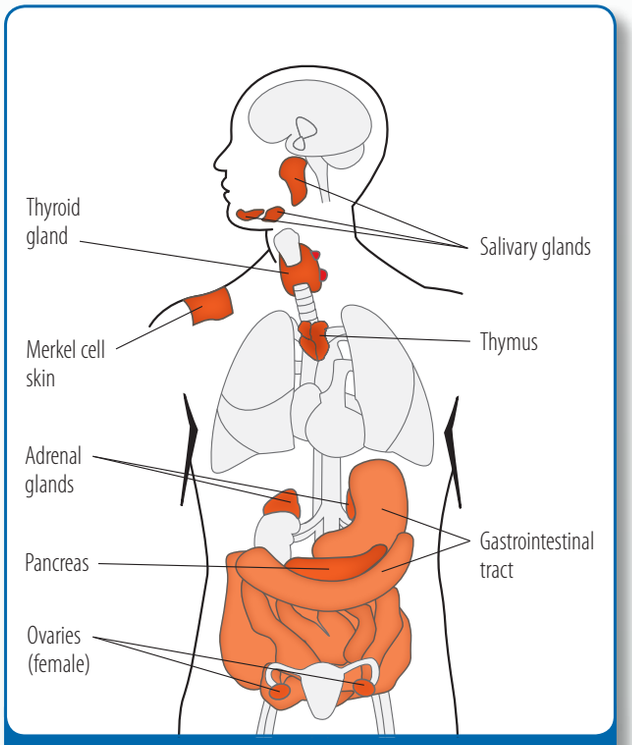
Hormone	Function
Serotonin (5-HT)	Regulating gastrointestinal activity
Gastrin	Regulating stomach acid production
Insulin	Regulating blood sugar

Neuroendocrine tumours

Like most cells in the body, hormone-producing cells can begin to divide and multiply without control or order, forming a growth of abnormal tissue: a tumour.

There are significant variations in tumour types, even when they originate from the same organ. Some can be benign, others malignant. A benign tumour is not cancerous, but may progress over time into a malignant tumour. A malignant tumour can invade and damage healthy tissues and organs, spreading to other parts of the body via the lymph or blood. These secondary tumours, resulting from spread of the original or primary tumour, are referred to as 'metastases'. By contrast, a benign tumour does not invade neighbouring organs and does not spread via lymph nodes or the circulation.

First identified in 1907, tumours originating in the neuroendocrine cells of the gastrointestinal tract or lung were called 'carcinoid', which means 'cancer-like' or 'carcinoma-like', since they seemed to grow slowly and therefore were not thought to be truly cancerous. This expression is rarely used these days; the preference/consensus is to use the expression 'endocrine' or 'neuroendocrine tumours' (NETs) as for any tumours originating from hormone-producing cells. There is still a lack of understanding of the biology, natural history, and clinical presentations of these tumours.



Tumours are classified according to the organ from which they orginate

The tumours are classified according to the organ from which they originate, and for endocrine pancreatic tumours according to the hormonal syndrome they produce. The vast majority of NETs are localized in the gastrointestinal (GI) tract (stomach, ileum, appendix, colon, rectum, and pancreas) and in the lungs, although they also occur in other (rare) sites - the thymus, adrenal glands, thyroid, skin, ovaries, and salivary glands. The tumours found in the GI-tract are referred to as gastro-entero-pancreatic neuroendocrine tumours (GEP NETs).

Symptoms

Neuroendocrine tumours are often very slow growing. The primary tumour is usually small and clinical symptoms are often absent until metastasis has occurred.

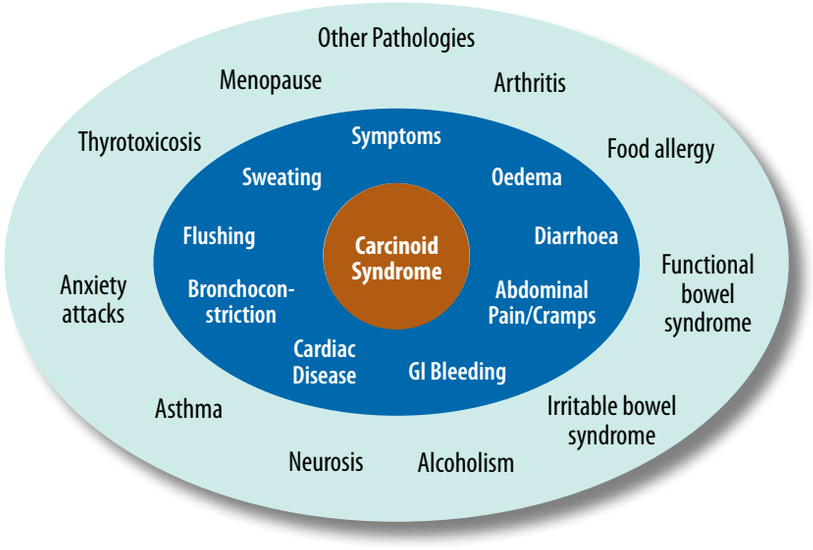
So for example, a patient could have a 'nagging' abdominal pain for many years, which was not seen as a sign of serious illness; suddenly, worsening symptoms occur caused by the presence of a bowel obstruction due to metastases from the previously unidentified GEP NET. Another scenario might be the equally sudden onset of symptoms that denote the presence of liver metastases.

Besides the symptoms indicative of metastases, NETs may produce a variety of different symptoms depending on the location of the tumour and from which cell type it originates.

NETs are defined as 'non-functional' or 'functional'. Non-functional NETs may release hormones or biologically active compounds, but in quantities that do not cause identifiable symptoms. Functional NETS, on the other hand, release a variety of hormones and other compounds that result in a constellation of systemic symptoms. Perhaps the most notable and well-recognised

collection of symptoms are those of the classic 'carcinoid syndrome' seen in patients with NETs. It is characterised by flushing, diarrhoea, bronchoconstriction, oedema, and fibrotic 'carcinoid' heart disease. This syndrome is believed to be caused by neurohormonal products, including serotonin, substance P, corticotrophin, histamine, dopamine, neurotensin, prostaglandins, kallikrein, and tachykinins, which can be released by an underlying tumour. It occurs in approximately 8%—35% of patients with NETs. So a number of pharmacological active agents are likely to contribute to carcinoid syndrome, but serotonin (5-HT) is probably most involved and contributes to many of the symptoms. This particular constellation of symptoms can be confused with other pathologies.

Together with symptoms caused by hormonal release a neuroendocrine tumour and its metastases can also cause:



Constellation of symptoms associated with carcinoid syndrome can be confused with other pathologies

- Pain
- Weight loss/gain
- Fatigue
- Disturbances in level of blood sugar (hypo- and hyperglycemia)
- Asthma-like symptoms
- Skin toxicity

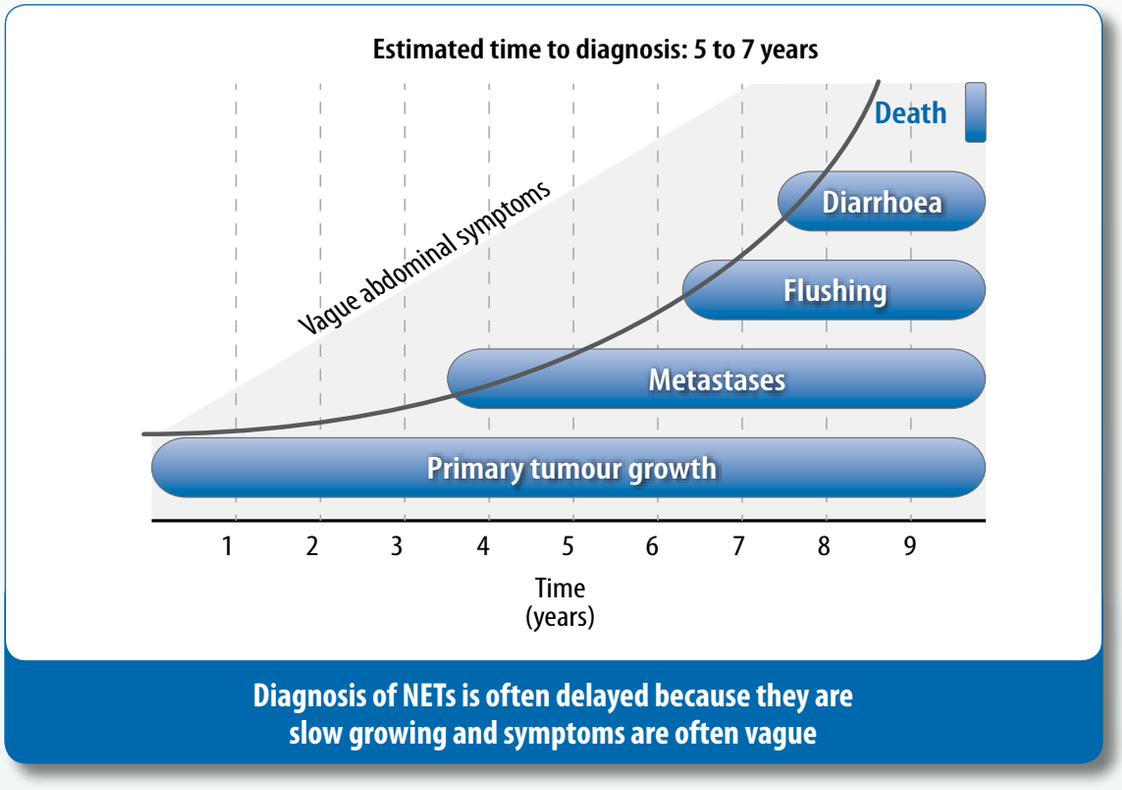
Incidence

Neuroendocrine tumours were originally thought to be relatively rare. However, probably due to the increased use of new diagnostic modalities (imaging, endoscopy) and an increased awareness, the incidence and prevalence have increased substantially over the past 30 years. Nevertheless, a definitive diagnosis is typically delayed by >3 years—even up to 7—because they are slow growing and the symptoms can be somewhat vague and easily confused with other conditions.

The mean age for onset of illness is 50-60 years, depending on the type of tumour. The disease may, however, occur in any age group from

childhood to people of advanced age. The distribution is relatively equally spread between the genders, but NETs of the lung and adrenal tumours are somewhat more common in women, whereas more men suffer from neuroendocrine rectal tumours.

Current understanding is that NETs are not hereditary, with the exception of multiple endocrine neoplasia (MEN), von Hippel-Lindau syndrome (where multiple haemangiomas/tumours develop in the central nervous system [CNS], adrenal, kidneys or pancreas) and neurofibromatosis. Any familial tendency to develop these tumour types should be revealed when a detailed family history is taken by a doctor.



Diagnosis of NETs is often delayed because they are slow growing and symptoms are often vague

Prognosis

The prognosis for patients with NETs is generally significantly better than for most other cancers. Experience shows that many patients live for a number of years, despite having numerous tumours and metastases. There is, however, a significant difference in how aggressive tumours in the same organ may be in different patients. Some tumours are so (close to) benign that there is scarcely any growth from year to year. However, albeit rarely, tumours can develop so rapidly and respond so badly to treatment that death may occur within months of the disease being diagnosed.

Prognosis also depends on the localization of the primary tumour, the presence of metastases (localization and number), grade of malignancy (as defined by the pathologist), the presence of biomarkers in the blood, and the presence of cardiac insufficiency. Survival, even with metastases, has improved due to the development and use of new treatments.

Further reading

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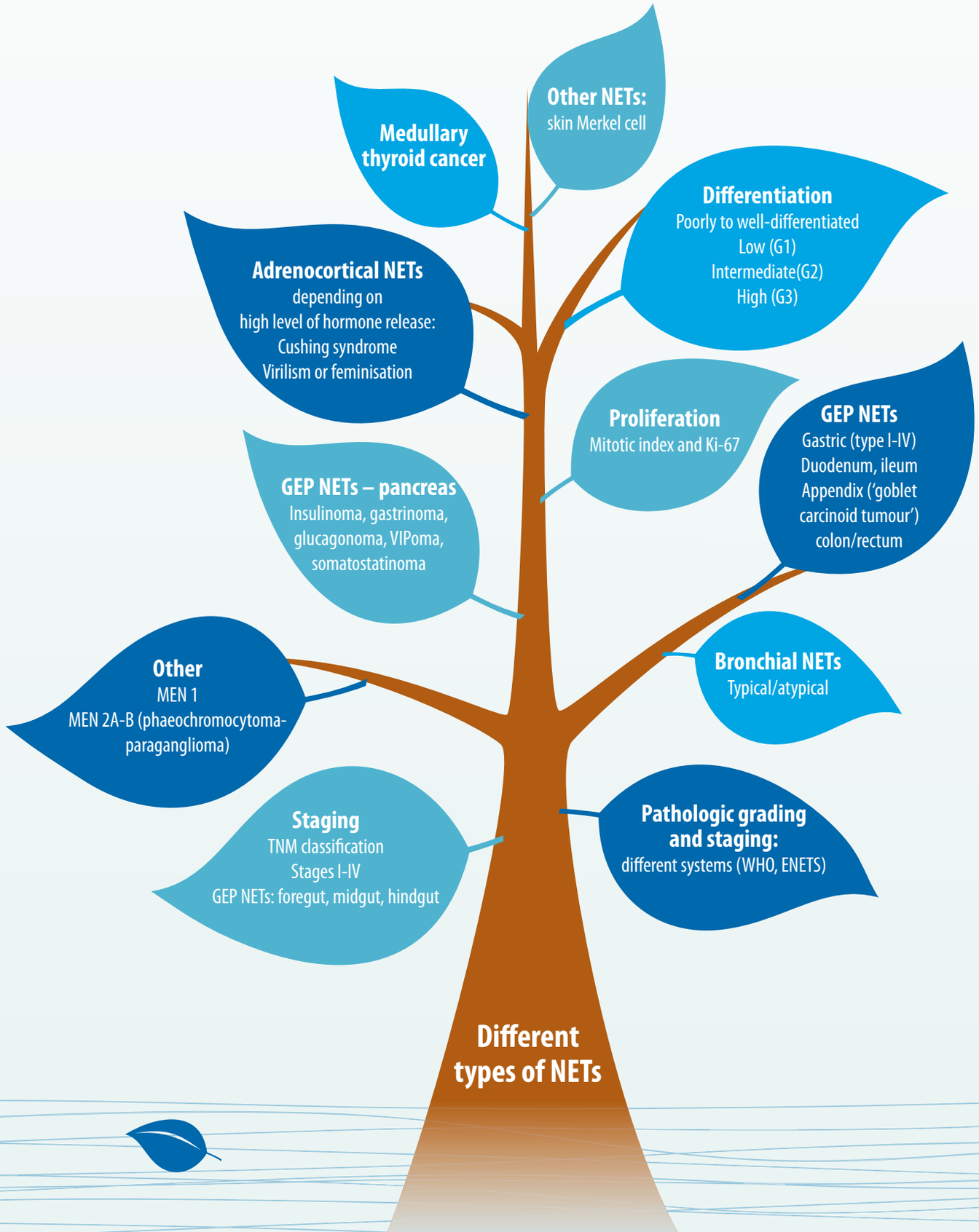
Chapter 2
Different types of neuroendocrine tumours



Introduction

After reading this chapter you will have gained insight into most types of NETs and understand how they are characterised.

Gastro-entero-pancreatic-neuroendocrine tumours (GEP-NETS)

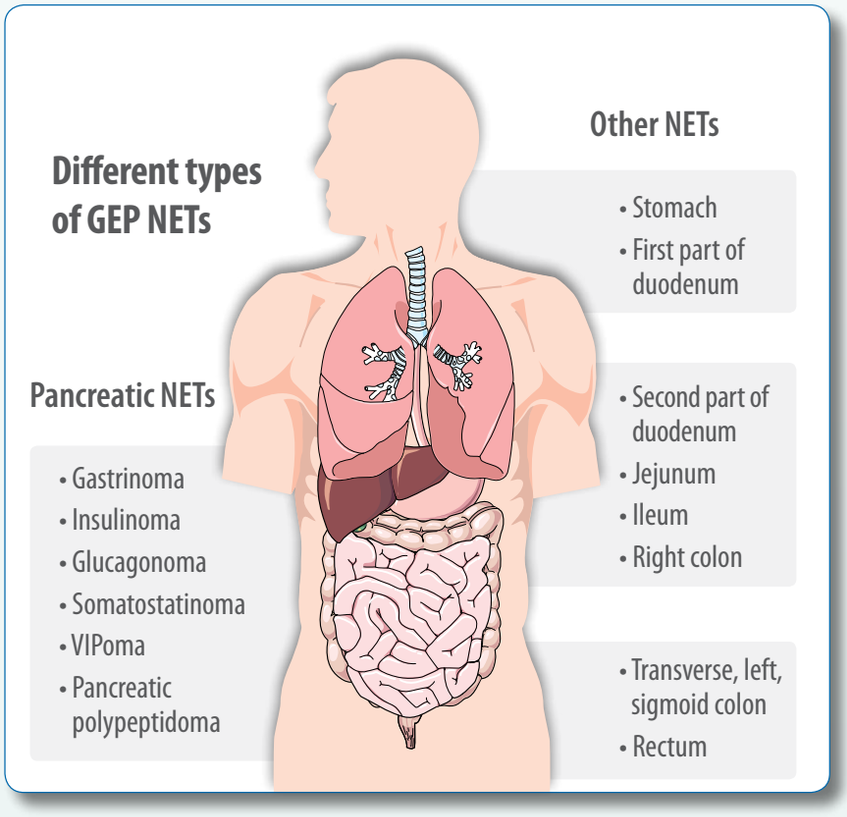
Gastric NETs

NETs of the stomach represent less than 1% of all gastric neoplasms. Small gastric NETs rarely cause symptoms and often tumours of this type are detected as a result of investigations for problems arising in connection with atrophic gastritis (e.g. pernicious anaemia, B12 deficiency). Larger tumours are more likely to give rise to symptoms since they can bleed, resulting in iron deficiency anaemia, or can cause epigastric pain.

> Atrophic gastritis is chronic inflammation of the gastric mucosa with loss of gastric glandular cells and replacement by intestinal-type epithelium, pyloric-type glands, and fibrous tissue.
> It has two main causes: *Helicobacter pylori* infection or is an autoimmune disease.

There are four types of gastric NETs.

Type I is the most common (70-80% of total gastric NETs), which often develops in association with atrophic gastritis and hyperplasia, and presents as polyps. The autoimmune activity in atrophic gastritis can result in increased production of gastrin, which may contribute to the formation of a neuroendocrine tumour. Type 1 has a relatively slow progression. The tumours are generally small, but numerous. Treatment is not immediately indicated, more 'wait-and-see', but if necessary, the lesions can usually be removed by polypectomy during a gastroscopy, or occasionally, by gastrectomy. They often reoccur, but the condition has a favourable prognosis.



Type II (5% of total gastric NETs) occur in the context of multiple endocrine neoplasia type 1 (MEN-1), with associated increased production of gastrin (which is known as the Zollinger-Ellison syndrome). The lesions are typically multifocal and generally less than 1.5 cm in diameter, in which case they can be managed conservatively, as for type 1.

Type III (15-20% of total gastric NETs) gastric NETs are often larger than 2 cm in diameter, and invade the surrounding tissue. The tumours often metastasise to lymph nodes and the liver. Treatment is surgical, usually a gastrectomy.

Type IV is a very rare variant of neuroendocrine gastric tumours. The primary tumour is often large (> 4 cm) and most often diagnosed at an advanced stage, when extensive metastases are usually already present.

NETs of the duodenum

There are several different types of duodenal and proximal jejunal neuroendocrine tumours. These NETs produce a variety of hormones such as somatostatin, polypeptides, serotonin, and calcitonin. They are often located in the papilla of Vater.

The majority of NETs in the duodenum are diagnosed when the patient presents with symptoms suggesting a gastric-duodenal ulcer. Pain is the most common symptom, and it is often dull, burning, aching, or nagging. The pain is frequently eased by eating, but also reoccurs some hours after the last meal. Pain at night is common. Some patients may develop anaemia due to bleeding from the lesion.

NETs of the ileum

NETs of the ileum and distal jejunum are often slow growing and are rarely symptomatic in the early phase of the disease. At the time of diagnosis, tumours of the ileum are often larger than 2 cm and have metastasised to regional lymph nodes and the liver.

Many patients visit their doctor complaining of abdominal pain, which may be caused by the tumour or fibrosis surrounding the tumour. Sometimes bowel obstruction can be the first sign of metastatic disease. Patients with liver metastasis may develop a 'classic carcinoid' syndrome.

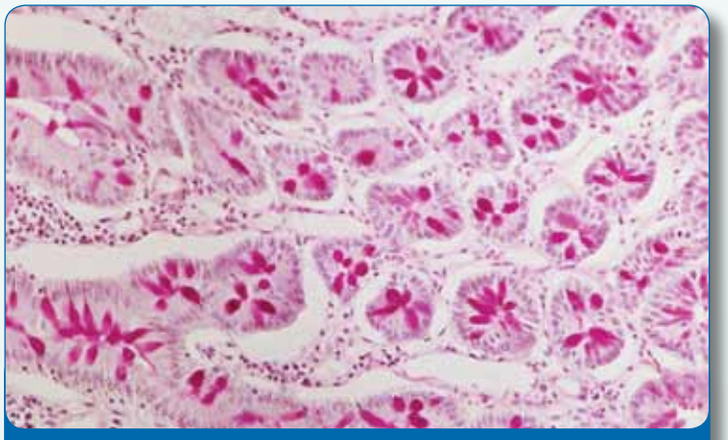
Approximately 20% of patients with NET of the ileum have carcinoid syndrome. Of these:

- Up to 80% have diarrhoea
- Flushing occurs in 15%
- Symptoms of reduced cardiac function occur in approximately 20-30%
- Asthma-like symptoms occur in approximately 15%

NETs of the appendix

NETs of the appendix are similar to ileal NETs but rarely metastasise to regional lymph nodes (unless they reach > 2.5 cm) and never to the liver. These tumours are usually discovered by chance during surgery for suspected appendicitis, or following removal of an abnormal-looking appendix.

Around 70-80% of neuroendocrine tumours of the appendix are less than 1 cm in size. A right hemicolectomy is normally performed, and surgery is often curative when the tumour is indeed less than 1 cm. NETs of the appendix do not cause carcinoid syndrome.



Goblet cells are shaped like miniature wine goblets

A unique and distinctive tumour type that occurs almost exclusively in the appendix is a *goblet cell tumour* (occasionally with rare cases encountered outside this location), also called 'goblet cell carcinoid' (GCC). Goblet cells are a type of epithelial cells whose sole function is to secrete mucin, which dissolves in water to form mucus, and is therefore also called mucin-producing NET. The name goblet cell tumour refers to the shape of the cells as they appear under a microscope—the epithelial cells in this case are shaped like miniature wine goblets. The most common clinical presentation is acute appendicitis, followed by abdominal pain and a mass. Fifty percent of the female patients present with ovarian metastases.

NETs of the colon and rectum

NETs of the rectum are quite common (27% all GEP-NETs and 16% of all NETs), whereas NETs of the colon are rare (e.g., annual incidence in the USA approximately 0.2 per 100,000). Colon NETs are large, highly malignant, and present in the same way as the more common colonic cancer (adenocarcinoma). The symptoms are the same as those in adenocarcinoma, with obstruction and bleeding. Flushing may also occur, because at the time of diagnosis, most patients have extensive metastases. Colon NETs have a poor prognosis.

In 50% of cases of rectal/colon NETs, the patient is asymptomatic and the tumour is discovered by chance (routine colonoscopy). The patient may develop local symptoms such as changed stool pattern, blood loss *per rectum* (PR), and/or pain. Metastases are often found in the liver and regional lymph nodes.

When the primary rectal tumour is less than 1 cm, the presence of metastases is rare but this is only seen in less than 5% of patients.

NETs of the pancreas (PNETs)

NETs of the pancreas arise from hormone-producing cells in the pancreas located in the islets of Langerhans. When the tumour develops there is usually an overproduction of one or more hormones. The tumours are functional or non-functional (see Chapter 1). This distinction is important for clinical presentation, diagnosis, and the treatment of these tumours. The type of hormone produced may also be an informative prognostic marker. Patients often develop symptoms caused by the tumour invading surrounding organs, e.g., pain and jaundice.

PNET can occur both sporadically and in patients with various inherited disorders, such as the MEN I (15-20% of PNET patients). Functional PNETs, in order of frequency, comprise insulinomas, gastrinomas, glucagonomas, VIPomas, somatostatinomas, and others. These tumours overproduce and release the following hormones (as their names suggest), which have a variety of metabolic consequences:

Insulin (insulinoma) High insulin levels result in hypoglycaemia (decreased blood sugar levels). Symptoms of hypoglycemia reflect a lack of glucose in the central nervous system (neuroglycopenia): confusion, altered consciousness and symptoms due to sympathetic overdrive (trembling, sweating (without exercising), palpitations, feelings of hunger and pallor). Lack of circulating glucose is worse in patients who have not eaten recently or have been fasting.

Gastrin (gastrinoma) High gastrin levels result in excess production of gastric acid in the stomach causing reflux oesophagitis, gastritis, gastric ulcers, and diarrhoea.

Glucagon (glucagonoma) High glucagon levels increase blood sugar levels above normal levels (hyperglycemia). Although glucagonomas are associated with glucose intolerance (causing fatigue, blurred vision, frequently urinating, dry mouth), clinically significant hyperglycemia occurs in only half of such patients. Patients with this type of PNET are often diagnosed by a dermatologist, after presenting with a rash (necrolytic migratory erythema), beginning in the perineum and involving the trunk and extremities.

VIP or vasoactive intestinal peptide (VIPoma, also called Verner-Morrison syndrome) VIP stimulates the secretion of water and electrolytes and acts on intestinal smooth muscle. Symptoms of VIPoma include frequent, watery diarrhoea, low blood potassium levels, achlorhydria (low gastric acid secretion), dehydration, weight loss, and flushing.

Somatostatin (somatostatinoma) Somatostatin has an inhibiting function on a number of other hormones. The symptoms of increased secretion include diabetes, diarrhoea, formation of gallstones, and weight loss.

MEN (Multiple endocrine neoplasia)

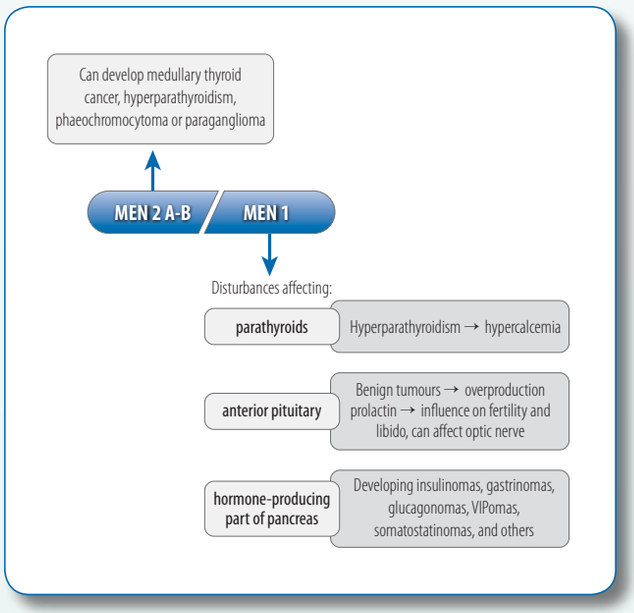
Multiple endocrine neoplasia (MEN) is a very rare hereditary illness where certain endocrine glands develop tumours. These are usually benign. NETs may be present in several organs, usually with several tumours in each organ. The glands affected vary from person to person, but to meet the diagnostic criteria, at least two of the glands must be overactive in the patient or any of their close relatives (since it is a hereditary condition).

It is normal to differentiate between MEN 1, MEN 2A, and MEN 2B (see below). There are no definitive treatments for the disease, but the various hormonal disturbances can be diagnosed and treated at an early stage to prevent progression to a more serious disease. The mutation, showing the type of MEN, can be detected by DNA analysis.

MEN 1

MEN 1 most commonly involves disturbances affecting the parathyroids, the anterior pituitary, and the hormone-producing part of the pancreas. The endocrine glands become overactive and secrete large quantities of hormones in various combinations, resulting in a variety of symptoms.

The most common disturbance in MEN 1 is a change in parathyroid function; approximately 90% of MEN 1 carriers have primary hyperparathyroidism. One or more parathyroid glands may become overactive and form small, benign tumours which release excess parathyroid hormone (PTH), resulting in increased calcium levels in the blood. The diagnosis is made by measuring the calcium level and the hormone PTH in the blood. Elevated calcium (hypercalcemia) can cause elevated calcium in the urine, which increases the risk of renal stones. High blood calcium levels also result in fatigue, muscle weakness and pain, constipation, digestive disturbances, and brittle bones.



Approximately 25% of MEN 1-carriers develop benign tumours of the pituitary, and this usually occurs before the age of 40. These tumours most commonly secrete an increased quantity of hormones. The most commonly overproduced pituitary hormone is prolactin. Fertility and libido can be affected by prolactin overproduction. The optic nerve, which passes immediately above the pituitary gland, can also be affected with consequent effects on the visual field.

Approximately 75% of MEN 1-carriers develop multiple hormone-producing tumours in the pancreas, as described above.

MEN 2A

In MEN 2A, patients often develop medullary thyroid cancer (cancer of the thyroid gland). The tumour produces the hormone calcitonin. Overproduction of this hormone can cause diarrhoea. The patient develops hoarseness and swallowing difficulties due to the presence of the tumour. In some cases the tumour will already have metastasised to regional lymph nodes, the liver, or bone at the time of diagnosis.

Approximately 25% of patients with MEN 2A have primary hyperparathyroidism due to overactivity of the gland, or tumours (see under MEN 1). Where a tumour of the throat is clinically diagnosed, lymph node metastases are normally present at the time of diagnosis.

Phaeochromocytomas develop from the adrenal medulla, and occur in almost half of patients with MEN 2A. Phaeochromocytomas are tumours that overproduce catecholamines (adrenaline and noradrenaline, seldom dopamine). The tumours are often numerous, and usually benign. However, in rare instances (10% of the phaeochromocytomas), they contain malignant cancer cells, which can cause spread to other parts of the body. The typical symptoms of excess catecholamines are headaches, profuse perspiration, and palpitation (trias), but also pallor, blood pressure abnormalities, thoracic pain, electrocardiographic alterations, visual blurring, weight loss, heat intolerance, hyperglycaemia, nausea and vomiting, psychiatric disorders (anxiety) and sweating.

Around 1 in 10 phaeochromocytomas occur elsewhere in the body than the adrenal medulla and are then called 'extra adrenal phaeochromocytomas' or *paragangliomas*, as they develop from paraganglia, cells that are part of the (extra adrenal) sympathetic and parasympathetic nervous system. About 85% of paragangliomas develop in the abdomen; only 12% develop in the chest and 3% in the head and neck region. Most of these rare tumours are asymptomatic, as only 20% of these produce catecholamines.

Although phaeochromocytomas (and paragangliomas) often occur in adults with MEN 2A syndrome, these tumours can also develop in children, causing the same symptoms.

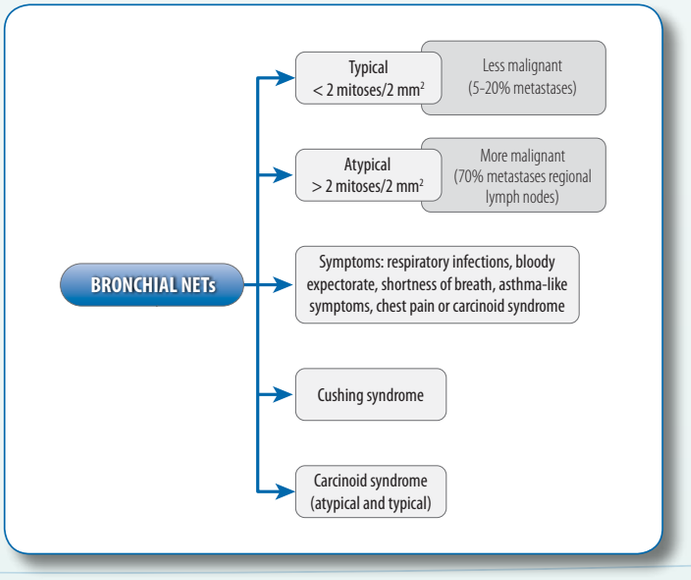
There is still discussion as to whether these type of tumours should be classified as NETs.

MEN 2B

MEN 2B is the rarest of the three MEN syndromes. The primary clinical problem in type 2B is medullary thyroid cancer (see MEN 2A); however, phaeochromocytomas (see MEN 2A) and multiple neurinomas of the mucosa also occur. Individuals with MEN 2B often have a characteristic appearance, including being very tall and thin with long, thin fingers (Marfanoid body type). Medullary thyroid cancer develops very early in patients with MEN 2B, and has a more aggressive course than in MEN 2A.

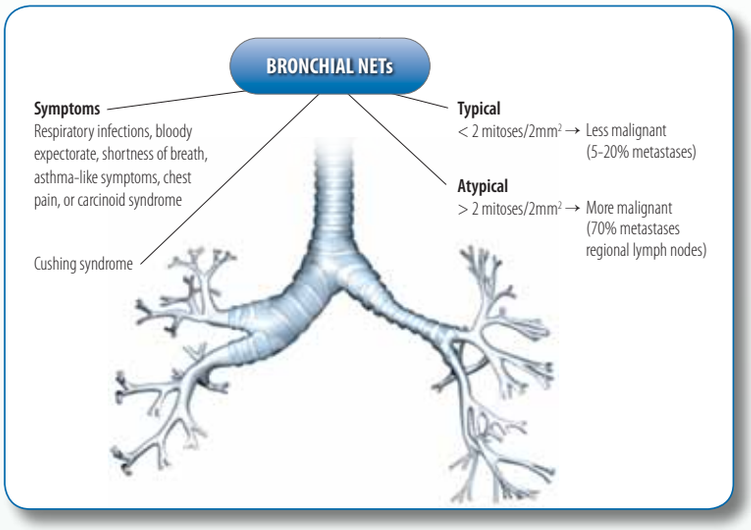
Bronchial NETs (Lung)

Bronchial NETs are rare tumours. Women are affected slightly more often than men. The disease may occur in all ages, even in children, but the mean age of onset is mostly between 50-60 years. The aetiology is not known, except that patients with the MEN1 syndrome have an increased risk. Bronchial NETs are subdivided into typical (<2 mitoses/2 mm^2 (10 HPF)) and atypical (2–10 mitoses/2 mm). Atypical bronchial NETs have a more malignant behaviour than typical ones. Metastases develop in 5–20% of patients with typical bronchial NETs and in up to 70% of patients with an atypical type, most frequently to regional lymph nodes, but also distantly to the liver, bones, brain, subcutaneous tissue, and mammary glands. Metastases may occur late, up to 30 years after diagnosis.



The degree to which neuroendocrine lung tumours develop varies between individuals. The majority of patients present with a cough, but in other cases, these NETs are diagnosed by chance, e.g., when undergoing chest X-ray during a routine health check-up. Other symptoms which may occur are respiratory infections, bloody expectorate, shortness of breath, asthma-like symptoms, and chest pain. NETs of the lungs also cause various hormone-related symptoms. Some tumours produce histamine, which causes the atypical carcinoid syndrome with flushing, swelling of the face, and increased tearing of the eyes. Other lung NETs can produce

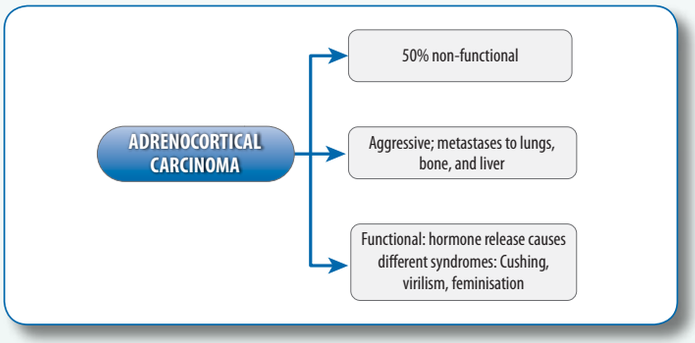
serotonin, which causes the classic carcinoid syndrome, with diarrhoea, flushing, reduced cardiac function, and asthma-like symptoms. Elevated levels of the hormone adrenocorticotrophic hormone (ACTH) can cause ectopic Cushing's syndrome, which may result in elevated blood pressure, abdominal obesity, 'moonface' appearance, and weight gain.



Adrenocortical NETs

Adrenal NETs (adrenocortical carcinoma or ACC) affect the outer layer of the gland: the adrenal cortex. The adrenals produce a number of different hormones which govern various body functions. When cancer of the adrenal cortex develops there is an overproduction of some of these hormones or their precursors. Hormone precursors are larger forms of the hormonal molecule that are not active and require further processing to produce the active hormone, for example pro-insulin is converted to insulin. In NETs a large amount of prohormone may be released but as it is not processed further, it does not produce symptoms.

Approximately 50% of all ACC are non-functional tumours which produce inactive hormonal precursors. For adrenocortical NETs that produce active hormones, the symptoms will depend on what type of hormone the tumour releases. They are divided into various groups or 'syndromes':



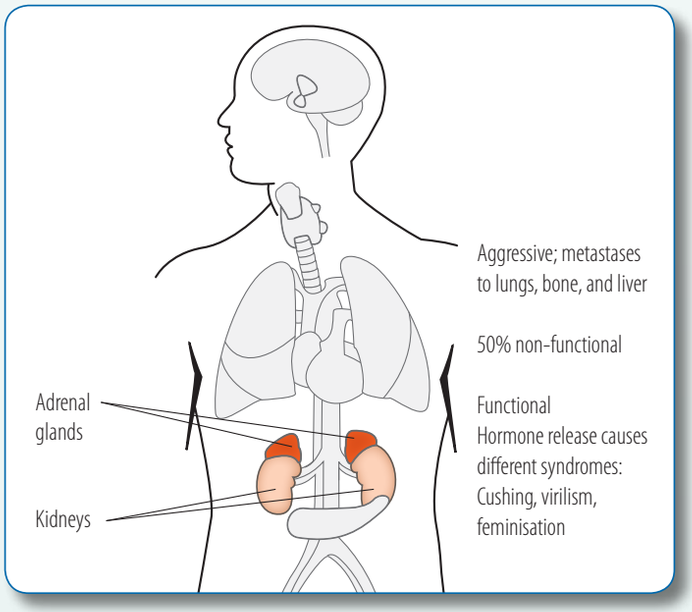
Cushing's syndrome is the result of high levels of the hormone cortisol that can lead to high blood pressure, abdominal obesity, moonface, weight gain, menstrual disturbances, reduced sexual function (libido), impotence, infertility, muscular atrophy/weakness, decreased bone density, and diabetes.

Virilism is caused by overproduction of the male sex hormones (such as androgen) in women, and this can result in increased hair growth (hirsutism), deep voice, spots, amenorrhoea, and infertility.

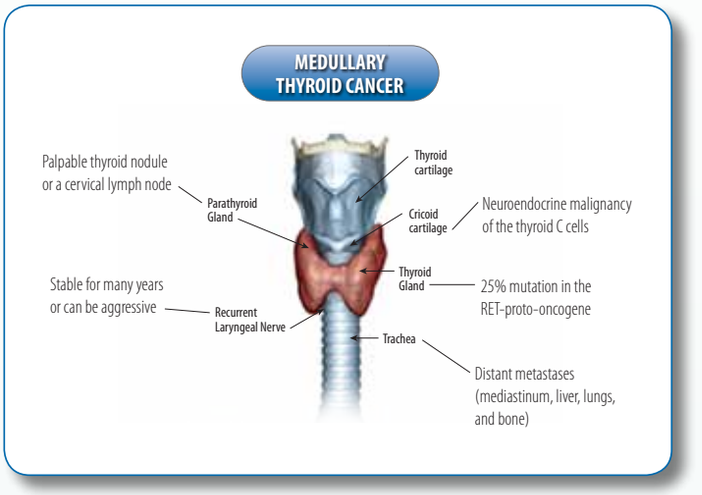
Feminisation is caused by an increased production of the female sex hormone in men, and this can result in gynaecomastia (breast enlargement), impotence, and decreased libido.

Patients with functional and non-functional tumours may additionally develop symptoms caused by the actual tumour, e.g., abdominal pain, weight loss and fatigue.

An ACC is a typically aggressive tumour and metastases to the lungs, bone, and liver are common; symptoms from these metastases may cause breathlessness and pain.



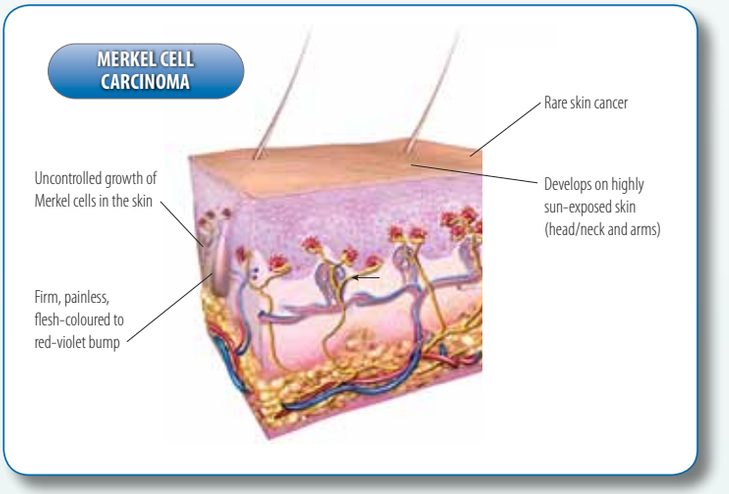
Medullary thyroid cancer



Medullary thyroid cancer (MTC) is a rare neuroendocrine malignancy of the thyroid C cells. These cells can make a number of peptides and hormones, such as calcitonin and carcinoembryonic antigen (CEA), which can be used to confirm the diagnosis as well as to follow up. Most MTCs are sporadic, but up to 25% of MTC cases result from a mutation in the RET-proto-oncogene and occur in the setting of the MEN syndrome type 2A, 2B or as familial MTC. MTC can appear as extremely indolent and can be stable for many years or can be aggressive and associated with a high mortality rate. Most thyroid NETs appear as a palpable thyroid nodule or a cervical lymph node, often asymptomatic. Elevated calcitonin levels can cause symptoms such as flushing, diarrhoea, and weight loss. Distant metastases are present in 10% to 15% of patients at the time of diagnosis (most common locations are the mediastinum, liver, lungs, and bone). The only curative treatment is complete surgical resection. Genetic testing for RET mutations has allowed identification of familial cases and prophylactic thyroidectomy for cure.

Merkel cell carcinoma

Merkel cell carcinoma (MCC) - also referred to as a NET of the skin - arises from uncontrolled growth of Merkel cells in the skin. Merkel cells are found in the epidermis and although the exact function of these cells is unknown, they are thought to be 'touch receptors.' They have both sensory and hormonal functions and are therefore sometimes referred to as neuroendocrine cells. This type of NET is a rare skin cancer with an incidence of about 1500 cases in the United States each year, and this number is increasing. The exact causes of MCC are not known. Factors strongly associated with the development of MCC include fair skin, a history of extensive sun exposure, chronic immune suppression (organ transplants or HIV), and over the age of 50. MCC usually develops on highly sun-exposed skin (head/neck and arms) and presents as a firm, painless, flesh-coloured to red-violet bump. The initial small bump tends to grow rapidly over weeks to months. The tumour can, however, occur anywhere on the body, including sun-protected areas such as the buttocks.



Example of normal Merkel cell within the skin. Images are courtesy of Paul Nghiem, MD, PhD & Quade Medical Group.

NETs may also occur in other organs such as the ovaries, cervix, testicles, spleen, and breasts. These, however, are very rare.

Classification systems: pathological grading and staging of NETs

NETs can arise in most organs of the body and many share common pathological features; however, the biological features of a NET vary between tumour types. The classification of these pathological features is essential to determine the clinical outcome and important for clinical decision making. Several different expert groups (e.g., NANETS, ENETS, etc.) have proposed NET classification systems to help standardise the information contained in pathology reports. The systems differ in the use of specific terminology and criteria for grading and staging, sometimes causing much confusion.

Grading

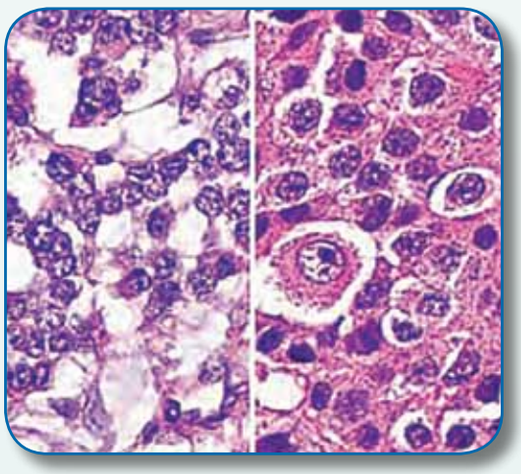
In general, most grading systems, such as that proposed by the World Health Organization (WHO), make a distinction between well-differentiated (low and intermediate grade) and poorly differentiated (high grade) NETs. Differentiation refers to the extent to which the neoplastic (abnormal) cells resemble the (normal) non-neoplastic ones.

The grade refers to the inherent biological aggressiveness of the tumour. Low-grade NETs (G1 in the ENETS grading system) are relatively indolent; intermediate tumours (G2) have a less predictable, moderately aggressive course; and high-grade NETs (G3) are extremely aggressive.

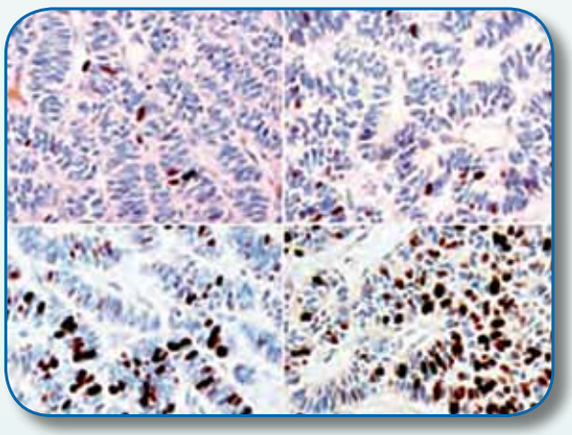
Differentiation	Grade
WHO - Well differentiated	Low grade – ENETS G1
	Intermediate grade – ENETS G2
WHO - Poorly differentiated	High grade – ENETS G3

The proliferative rate, which can be found on the pathology report, can provide more, significant, prognostic information. The proliferative rate can be assessed by using:

- The mitotic-index: The number of mitoses (process of cell dividing) per unit area of tumour (expressed as mitoses per 10 high-power microscopic fields or per mm^2)
- The Ki-67 labelling index: Ki-67 is a marker to determine the growth fraction of a given cell population and the percentage of Ki-67 positive cells often correlates with the clinical course of NET. For example; where Ki-67 is 5%, this means that 5% of the cells are undergoing proliferation; hence, the higher the Ki-67 percentage, the more aggressive the disease



Example of mitotic rate determination.
Images are courtesy of IM Modlin.



Immunostaining for Ki-67 antigen.
Images are courtesy of IM Modlin and D Klimstra.

In the ENETS grading system, the three tumour grades can also be defined by the mitotic index and/or the Ki-67 proliferation index.

Grade	Mitotic count (10 HPF)	Ki-67 index (%)
G1 low	<2	≤2
G2 intermediate	2-20	3-20
G3 high	>20	>20

Be aware that not all pathologists use the same methods and classification system; every report should identify the type of grading system that has been used.

Staging

To assure optimal treatment and maximise the chances of a good outcome, the multidisciplinary team (pathologists, radiologists, oncologists) can use the Tumour Node Metastasis staging system (TNM) to guide the decision making process. The TNM system indicates the degree of NET 'invasion' (localized, regional, or distant) and the presence of lymph nodes or distant metastases. There is a TNM and disease stage (0- IV) classification specifically for the staging of GEP-NETs.

The TNM system is based on the extent of the tumour **(T)**, the extent of spread to the lymph nodes **(N)**, and the presence of distant metastasis **(M)**. A number is added to each letter to indicate the size or extent of the primary tumour and the extent of cancer spread.

Primary Tumour (T)

TX	Primary tumour cannot be evaluated
T0	No evidence of primary tumour
Tis	Carcinoma *in situ* (CIS; abnormal cells are present but have not spread to neighbouring tissue; although not cancer, CIS may become cancer and is sometimes called preinvasive cancer)
T1, T2, T3, T4	Size and/or extent of the primary tumour

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be evaluated
N0	No regional lymph node involvement
N1, N2, N3	Involvement of regional lymph nodes (number of lymph nodes and/or extent of spread)

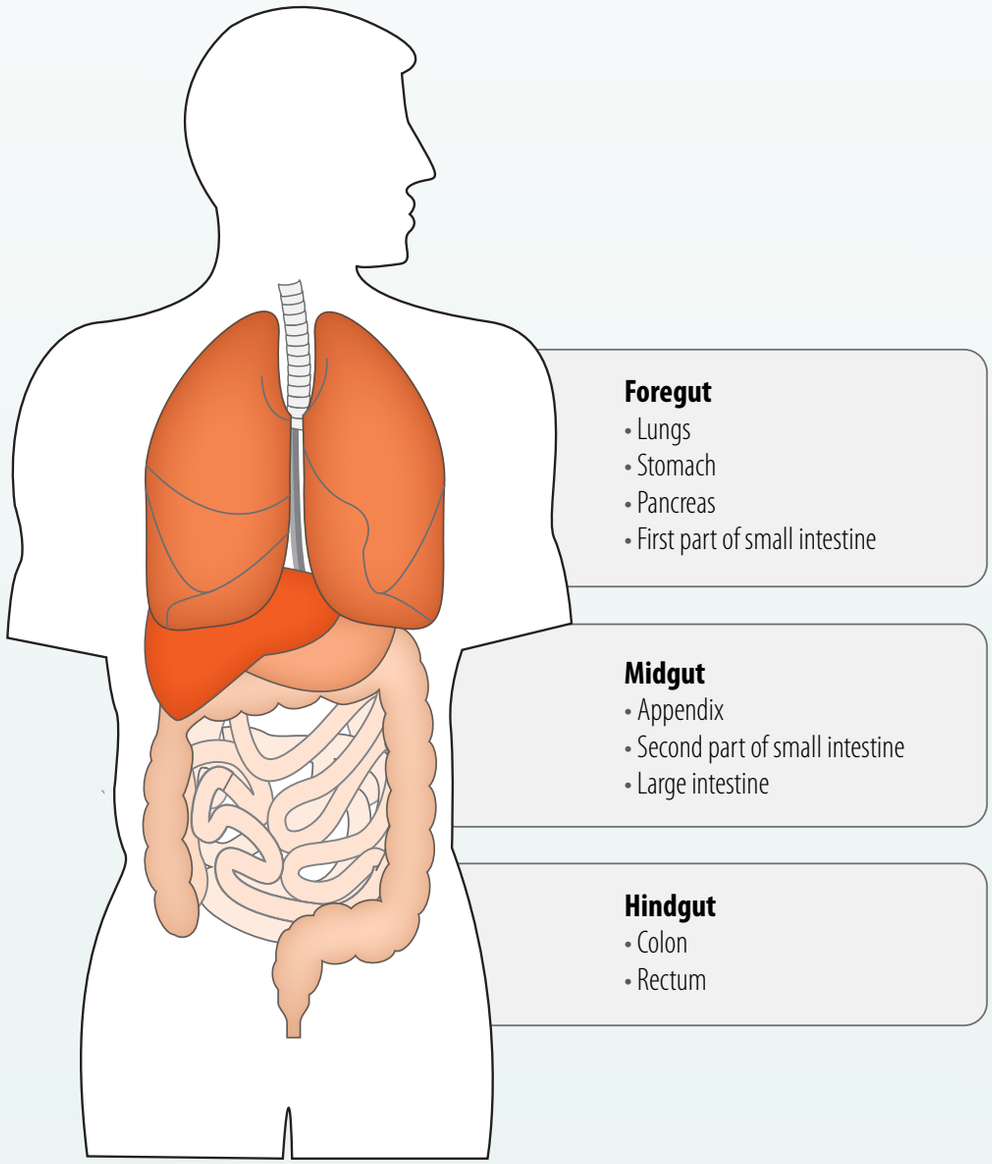
Distant Metastasis (M)

MX	Distant metastasis cannot be evaluated
M0	No distant metastasis
M1	Distant metastasis is present

Stage	Definition
Stage 0	Carcinoma *in situ*
*Stage I	T1; N0; M0 Local tumour, no lymph nodes involved, no metastases
*Stage II	T2-T3; N0; M0.Increased size of tumour, no lymph nodes involved, no metastases
*Stage III	Any T including T4;N1; M0 Larger tumours, lymph nodes involved, no metastases
Stage IV	Any T; Any N; M1. The cancer has spread to another organ(s). Also called advanced cancer

*Higher numbers indicate more extensive disease. Stages II and III may be subdivided into IIa and IIb and IIIa and IIIb

GEP-NETs are often separately categorized into 'regions', depending on the origin in the GI-tract:



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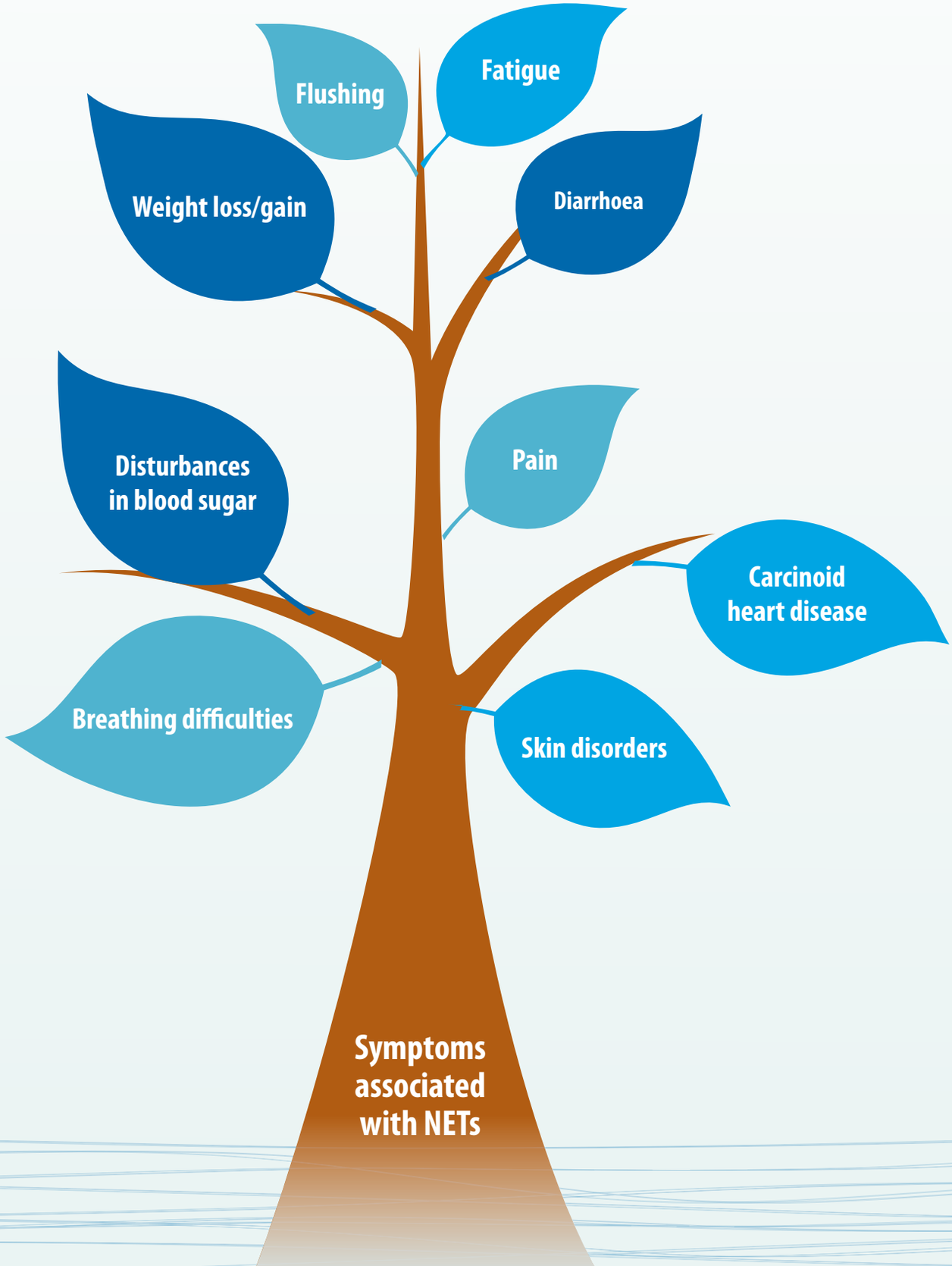
Chapter 3
Symptoms associated with neuroendocrine tumours



Introduction

After reading this chapter you should have a good understanding of the most common symptoms caused by neuroendocrine tumours. Finding good ways of managing these symptoms can be a crucial factor in influencing how well patients live with their disease. Since the symptoms vary depending on the site of the primary tumour, the presence of metastases and the hormones produced, the patient may experience a lot of the symptoms, only some of them, or none at all. They may also experience symptoms and problems not described here, such as headaches, profuse 'wet' perspiration, and palpitation (trias), but also pallor, blood pressure abnormalities, thoracic pain, electrocardiographic alterations, visual blurring, heat intolerance, nausea and vomiting and psychiatric disorders (anxiety). Patients must be encouraged to inform you if any new symptoms arise or current symptoms change.

Flushing

Flushing is when the patient becomes red and hot in their skin and face. It is important to always check the nature of the flushing and whether it can be ascribed to a NET, because:

- Intermittent flushing can be related to menopause, emotional distress, and possibly other causes
- Constant flushing can be seen in alcoholism and in cardiac disorders (mitral valve disease)
- Flushing can also be a symptom of a dermatological problem

Flushing is a common and frequently occurring symptom of carcinoid syndrome. Depending on the location of the tumour, the skin becomes deep pink to red in colour, typically affecting the face, neck, and upper trunk.

The type of flushing in carcinoid syndrome is characteristically 'dry' in women. This helps distinguish it from menopausal hot flushes, which are often accompanied by perspiration and not accompanied by a fall in blood pressure.

The specific cause of flushing in carcinoid syndrome is unknown, although patients may find that it is triggered by physical and psychological exertion and food. It varies in duration and intensity: from 2-5 minutes to several hours.

Transient hypotension, headache, and bronchoconstriction may coincide with flushing in patients with carcinoid syndrome, particularly in those with GEP NETs. These coinciding symptoms can be of help when diagnosing a patient; for instance, physicians could consider that menopausal hot flushes are not associated with a fall in blood pressure.

Symptom	NET type	Syndrome	Site
Flushing	Carcinoid Phaeochromocytoma Medullary thyroid carcinoma	Carcinoid	Foregut/midgut, adrenal, thyroid (medulla)

Diarrhoea

Diarrhoea, as defined by the World Health Organization, is 'the passage of 3 or more loose or liquid stools per day, or more frequently than is normal for the individual'.

Diseases and conditions (such as irritable bowel syndrome, Crohn's disease, or infections following surgery or due to intake of antibiotics) often present with diarrhoea. This type of diarrhoea is called 'malabsorptive' diarrhoea, often correlated with weight loss, pain, and sometimes fever.

NET patients may suffer from chronic diarrhoea; present in up to 80% of patients with carcinoid syndrome, it rarely causes electrolyte disturbances, but malnutrition may occur.

There are indeed many causes for chronic diarrhoea, however, certain characteristics may help identify whether this symptom is due to carcinoid syndrome.

In carcinoid syndrome diarrhoea is 'secretory' which means that large volumes of watery stool are passed because of intestinal hypermotility and hypersecretion. The increase in gut motility is most likely to be caused by serotonin, which is released as part of carcinoid syndrome and stimulates small bowel and colonic secretions and motility. Fasting does not reduce the diarrhoea, because the increased motility and increased secretion are independent of intake of fluid or food. This type of diarrhoea may be nocturnal, and a patient who has frequent diarrhoea may find it difficult to rest, resulting in increased fatigue. During treatment with somatostatin analogues (see Chapter 5), the diarrhoea can change from a 'secretory' to a 'malabsorptive' one. The stools will smell foul and have a pale colour. It may be difficult to flush the toilet, due to the presence of undigested food particles.

The frequent passage of stools can irritate the skin around the anus and it may be difficult to protect it against the liquid stools. The skin should be kept clean and dry. Patients should be advised to clean the skin around the anus of soiling (consider using oil) after passing stools, and to apply water-repellent cream. It may also help to warn them to have a change of clothing close at hand, and to be familiar with the location of toilets when not at home.

Physicians must consider other causes for chronic diarrhoea if this symptom is not controlled by therapy or if it's not assumed to be caused by the syndrome.

Symptom	NET type (most frequent)	Syndrome	Site
Diarrhoea	GEP NETs : Carcinoid, VIPoma, gastrinoma, or medullary carcinoma of thyroid	Carcinoid Zollinger Ellison Syndrome (ZES)	Foregut/midgut, thyroid (medulla)

Carcinoid heart disease (CHD)

Cardiac effects can occur in patients with NETs due to fibrosis, which primarily affects the tricuspid valve located between the right atrium and ventricle. CHD develops in 20% to 70% of patients with liver metastases and is a major cause of death in patients with carcinoid syndrome. The long-lasting exposure to overproduction of serotonin may play an important role in the pathogenesis of CHD. In patients with CHD, right atrial and/or right ventricular dilation is present in up to 90% of patients. The tricuspid valve leaflets are often thickened, caused by endocardial plaques of fibrous tissue leading to regurgitation. Patients may suffer tricuspid insufficiency (less commonly stenosis) and develop right-sided heart failure with ventricular hypertrophy, oedema, and ascites. In this instance they may experience shortness of breath even when at rest, due to the heart's reduced ability to pump, and with subsequent deleterious effects on the circulation. In late stages, the left ventricle may also be affected. Cardiac effects are associated with NETs releasing serotonin.

Symptom	NET type (most frequent)	Syndrome	Site
Cardiac effects	Serotonin-releasing NETs	Carcinoid heart disease	Heart valves

Breathing difficulties

Asthma-like symptoms may occur in individual NET patients due to bronchoconstriction caused by hormones released by the tumours. Bronchoconstriction may be accompanied by feelings of tightness in the chest and wheezing noises when breathing.

Symptom	NET type (most frequent)	Syndrome	Site
Wheezing	Serotonin-releasing NETs	Carcinoid	Foregut, lung

Pain

NETs can cause pain in and around the organ where the primary tumour or the metastases are located. Pain, however, is a very complex and highly subjective experience. Only the person experiencing the pain can know how it feels, how intense it is, and how long it lasts. The perception of pain is influenced by a number of factors such as emotions, the social and environmental context, socio-cultural background, beliefs, attitudes, and personal expectations and biological factors. These factors can either exacerbate or reduce the pain. A given pain stimulus can cause different pain perception in different patients and the grading of pain can also vary from one situation to another. In order to chart the patient's pain various pain scales and questionnaires can be used. The involvement of an expert pain team can be important.

Weight loss/gain

Weight loss or gain is often seen in patients with a NET and in cancer patients in general. The decrease or increase of the body weight is, however, unintentional; in other words, patients did not try to lose or gain weight for example by dieting or exercising.

Weight loss

Weight loss is common among people with cancer and is often the first sign of cancer that is noticeable. As many as 40% of people with cancer report unexplained weight loss at the time of diagnosis, and up to 80% of people with advanced cancer experience weight loss and general wasting, termed 'cachexia.'

In patients with NET, weight loss is a common symptom that is often related to diarrhoea and malabsorption of food caused by the overproduction of hormones.

Weight gain

Although more rare, NETs can also cause weight gain. The overproduction of hormones can lead to unintended increase of body weight. For example, high levels of insulin produced by an insulinoma will cause hypoglycaemia. As patients learn early in the disease process, eating resolves some of the symptoms of hypoglycaemia and this increased food consumption results in weight gain.

Patients with Cushing's syndrome have increased levels of ACTH and cortisol. This is often seen with bronchial, adrenal and pancreatic NETs and can lead to a specific type of obesity. Fluid retention will cause weight gain as well; peripheral oedema can be part of the carcinoid syndrome and can be a sign of heart failure. In the late stage (advanced disease) of the metastatic NETs, ascites can increase the body weight as well.

Fatigue

Many patients experience problems with fatigue and exhaustion through various stages of illness from NETs. While normal tiredness occurs following activity and resolves with sleep and rest, tiredness and exhaustion accompanying illness is caused by minor exertion and may persist even with rest. This state is called 'fatigue.'

Fatigue is also described as a feeling of loss of physical and/or mental energy, which causes more difficulties with – or even prevent – the performance of physical and/or mental activities. In other words, fatigued patients simply have no energy. Since fatigue is a subjective experience and intangible to others, sufferers may encounter a lack of understanding from other people who describe fatigue as just 'normal tiredness' and have the view that you just need to 'get over it.'

We normally distinguish between primary fatigue, which is largely due to the disease process, and secondary fatigue, which results from other conditions and illnesses (e.g., slow metabolism, pain, infection, anaemia, or depression). Fatigue may have a relatively acute onset associated, for example, with an ongoing phase of the disease, or with the start of a specific treatment. If tiredness and exhaustion persist beyond 3-6 months they are termed 'chronic.'

Medication, radiotherapy, and cancer treatments are known to exacerbate fatigue. Concern over one's family, undergoing investigations, and hospital-based treatment may also draw on energy reserves. There remains, however, little clear research-based knowledge on fatigue. Consequently, understanding of this condition is largely based on clinical experience.

Symptom	NET type (most frequent)	Site
Fatigue Weight loss/gain Pain	All NETs	All

Disturbances in level of blood sugar

Disturbances in the level of blood sugar may occur, with overproduction of glucagon or insulin. Overproduction of glucagon results in elevated blood sugar (hyperglycemia) and development of diabetes. Symptoms include increased micturition, increased thirst, weight loss, feelings of hunger, tiredness, and pruritus.

Overproduction of insulin results in lowering of blood sugar (hypoglycaemia). Symptoms of hypoglycaemia include confusion, palpitations, feelings of hunger, pallor, and increased sweating without exercising. Hypoglycemia is relieved with glucose or food containing easily assimilated glucose, sucrose, or other carbohydrate.

Symptom	NET type (most frequent)	Site
Hypoglycemia	Insulinoma	Foregut: pancreas, retroperitoneum, liver
Hyperglycemia (diabetes)	Glucagonoma Somatostatinoma Phaeochromocytoma ACTH-releasing NET	Foregut: pancreas, adrenocortical

Skin disorders

Patients with PNETs are frequently initially diagnosed by a dermatologist, presenting with rash (necrolytic migratory erythema/NME). This rash is red, blistering, and spreads across the skin, particularly the lower abdomen, buttocks, perineum, and groin. It is strongly associated with glucagonoma. The rash fluctuates in severity. Initially there is a ring-shaped red area that blisters, erodes, and crusts over. It can be quite itchy and painful. As it heals, it may leave behind a brown mark. It also results in a sore, smooth tongue, a sore mouth, cracked dry lips and ridging of the nails.

Patients with a Merkel cell carcinoma present with an asymptomatic shiny nodule that may be skin coloured or may appear in shades of red, blue, or purple. Most Merkel cell carcinomas appear on the face, head or neck, but they can develop anywhere on the body, even on areas not exposed to sunlight.

Serotonin releasing NETs can also cause 'pellagra dermatitis,' showing scaly and sore skin lesions. Pellagra, a disease of niacin-deficiency, may occur in association with the carcinoid syndrome. Niacin is also known as nicotinic acid, or vitamin B_3. Malabsorption and diarrhoea, frequently present in the carcinoid syndrome, reduce the availability of niacin by decreasing the amount ingested and absorbed.

Symptom	NET type (most frequent)	Site
Necrolytic migratory erythema	Glucagonoma	Foregut: pancreas
Shiny (or red, blue or purple) nodule	Merkel cell	Face, head or neck
Pellagra dermatitis	Serotonin-releasing NETs	Foregut: pancreas

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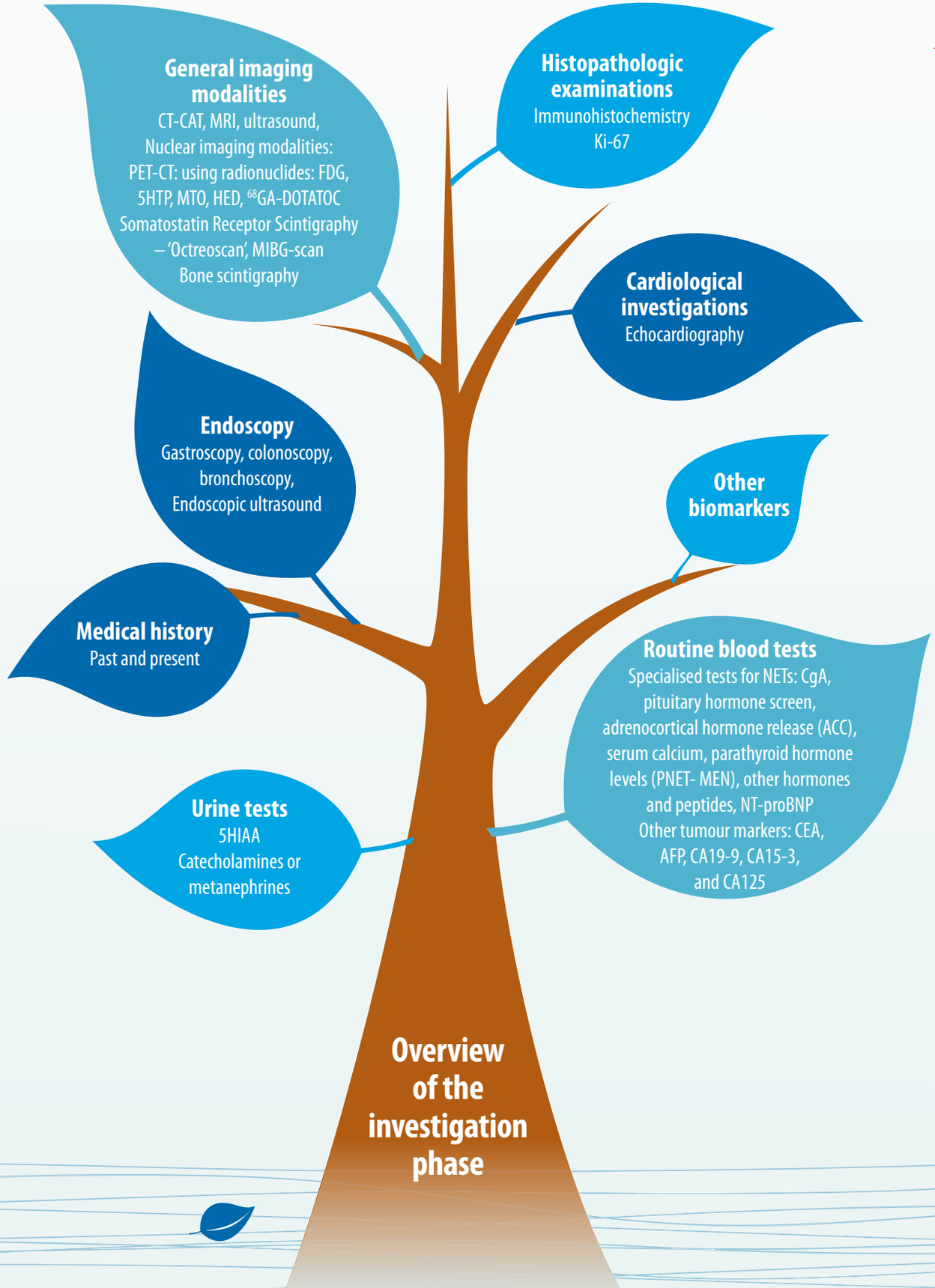
Chapter 4
Overview of the investigation phase



Introduction

After reading this chapter you will have gained insight into the most commonly used investigations in the diagnosis and staging of NETs. NETs represent a considerable diagnostic challenge because their presentation is frequently subtle and nonspecific, therefore the diagnosis has to be built on the results of a number of different examinations. It is important to understand that not all investigations are relevant for all patients, since the disease can present in many different forms. By using different investigative tools (biopsy, imaging, specific biochemical tests, etc), the origin of primary tumours and metastases can be located, the histopathology/grading of the tumour can be defined, and levels of specific hormones and biomarkers can be defined. All these pieces of information can be combined to obtain some indication of prognosis and to predict responses to treatment. Results of diagnostic procedures can also guide an optimal treatment of NETs.

The patient will not be given the results of all examinations at the time of the investigations. It is useful to remember that for your patient the waiting time between a diagnostic procedure and the result can be extremely stressful because it involves many uncertainties. These uncertainties may cause the patients enormous anxiety and, since access to information is limited, patients sometimes feel that the situation is out of their control.

Keep in mind that procedures before, during, and after investigations may differ between institutions, so please ask the relevant department to check what procedures are used.

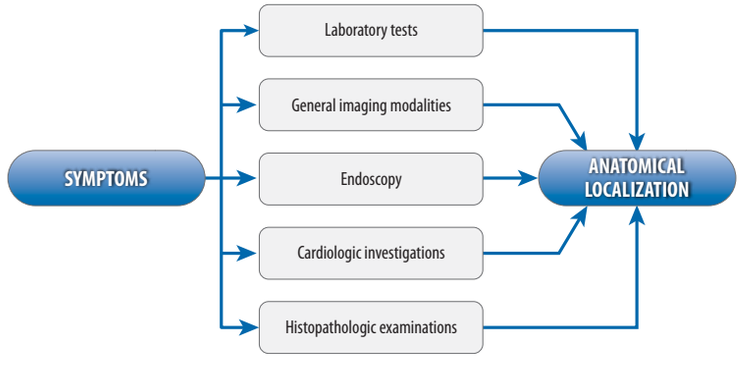
Medical history

The first phase of investigations usually takes place when the patient consults the general practitioner and is based on individual clinical presentation. It is not simple to recognise the symptoms associated with NETs, and therefore the condition is often overlooked or not suspected by the physician or the symptoms are attributed to other causes. For example, patients complaining of occasional loose stools and slight abdominal pain, are often misdiagnosed with conditions such as gastroenteritis or irritable bowel syndrome, and the real underlying disease may consequently be ignored for years.

Past medical history, familial diseases, and current symptoms need to be explored to identify the presence or absence of a NET. Increasing awareness and familiarity with the constellation of symptoms that are seen in NET can only help in addressing problems with late diagnosis.

In a small percentage of cases, NETs are discovered incidentally at the time of surgery for other abdominal or thoracic disorders. In the same way, post mortems often reveal NETs which were asymptomatic and unrelated to the cause of death. Thus, many people may have had a NET without ever suffering symptoms.

Patients should be referred to more specialised centres to confirm the diagnosis of a NET and to start treatment.



Useful diagnostic and imaging modalities for NETs

Laboratory tests

Blood tests

Routine blood tests (comprising the standard haematological testing and biochemistry) are usually normal in NET patients. Standard tests usually comprise:

- Full blood count
- Renal function tests (urea and electrolytes)
- Liver/pancreas function tests
- Thyroid function tests

A common feature of NETs is that they each secrete a variety of bioactive products. These biochemical products can be measured in the blood and plasma and elevated concentrations can give valuable information that identifies the biological nature and even the localization of the tumour (for example, increased gastrin levels indicate the presence of a gastric or duodenal NET). However, these tests are only performed when specifically requested by the investigating physician, so the index of suspicion needs to be raised by the presenting symptoms.

Depending on the suspected location of a NET several laboratory tests can be performed including:

Chromogranins (Cgs)

The best characterised circulating biomarkers that identify the presence of a NET are the glycoproteins chromogranin A (B and C). CgA can be measured in the serum or plasma and provide information regarding tumour burden (high levels are suggestive of a poor prognosis) and response to treatment. Care must be taken when measuring and evaluating CgA levels as evidence of a NET because a number of other conditions can also cause increased levels and influence the interpretation of the test values. Common conditions that can cause elevated plasma CgA include:

- Use of an acid suppressive agent - proton pump inhibitors or histamine 2 receptor antagonists. These are drugs used to prevent/treat pyrosis or gastric-duodenal ulcer (e.g., omeprazole, lansoprazole, pantoprazole). The administration of these drugs must be interrupted for at least 2 days prior to the test to avoid biasing the results.
- Chronic gastritis
- Renal failure
- Hepatic failure
- Disturbances in other hormone-producing organs
- Some other forms of cancer

Other commonly performed blood tests include:

- Pituitary hormone screen: adrenocorticotrophic hormone (ACTH), prolactin, growth hormones
- Adrenocortical hormone release (ACC): cortisol, testosterone, oestrogen, aldosterone
- Serum calcium, parathyroid hormone levels (in all pancreatic NET patients, as a simple screening test for MEN 1 syndrome)
- Other hormones and peptides :
  -Calcitonin (MTC)

-(nor)methanephrine, (nor)epinephrine (phaeochromocytoma and paraganglioma); special attention must be paid to the fact that stress and vigorous exercise may affect the test results. Therefore patients must be at rest 15 to 20 minutes prior to the blood sampling
- pancreatic polypeptide, gastrin, vasoactive intestinal peptide, neurotensin, somatostatin, neuron-specific enolase, and glucagon (GEP-NETs)

- NT-proBNP: An option to screen for cardiac dysfunction is the use of natriuretic peptide levels in blood. Atrial natriuretic peptide (ANP), as well as the second member B-type (brain) natriuretic peptide (BNP), are produced by myocardial cells and influence the electrolyte and fluid balance in an organism. Pro-BNP is secreted mainly by the ventricle and is cleaved into physiologically active BNP and the inactive degradation product N-terminal pro-brain natriuretic peptide (NT-proBNP). The stable peptide NT-proBNP is a useful marker for left ventricular dysfunction

- Other tumour markers: CEA, AFP, CA19-9, CA15-3, and CA125 (for a differential diagnosis)

Urine tests

5-HIAA

As discussed, NETs can, and often do, produce the hormone serotonin (5-hydroxytryptamine or 5-HT), responsible for the symptoms associated with many types of NET. Elevated plasma levels of serotonin or 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of 5-HT, are highly suggestive of the presence of an ileal NET, but can also be found in cases of a NET of the lung or pancreas. 5-HT also plays a key role in the development of peritoneal and cardiac fibrosis.

5-HIAA is eliminated in the urine in small quantities that can easily be measured in a 24-hour urine collection. Patients collect urine in an empty collection bottle. The 24-hour urine collection starts when the patient passes the first morning urine in the toilet (time is noted). Thereafter, all urine over the next 24 hours is collected in the bottle and the collection finishes after the patient passes the first morning urine of the next day. Of course, this procedure can vary somewhat from hospital to hospital.

Special attention must be paid to the fact that urinary 5-HIAA levels can be altered (increased or decreased) by certain drugs (e.g., paracetamol (acetaminophen), antihypertensive drugs, diazepam, nicotine, caffeine, etc) that affect renal function and by serotonin-rich foods such as pineapple, banana, kiwi fruit, plums, tomato, aubergine, walnuts, dates, and avocado. Therefore, the administration and intake of these drugs and food must be interrupted a couple of days before, and certainly during 24-hour urine collection, to exclude false-positive results.

24h urine test for catecholamines or metanephrines

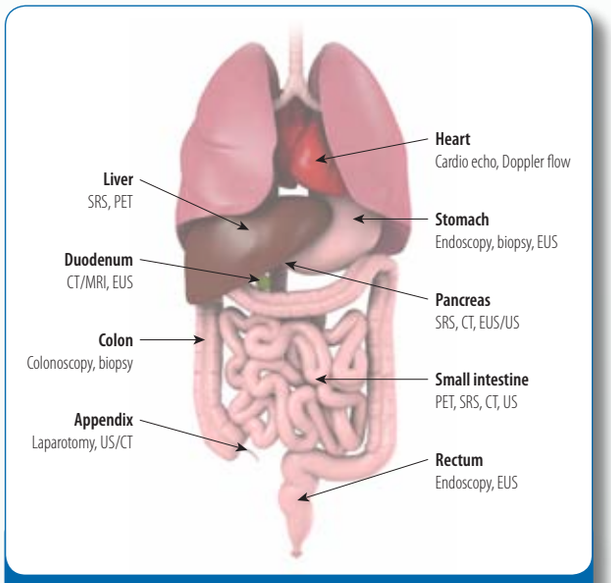
This test can be used for diagnosis of phaeochromocytomas. This type of NET produces large amounts of catecholamines.
Special attention must be paid prior to the testing (both blood and urine). Stress and vigorous exercise may affect the test results. Foods that can increase urinary catecholamines include coffee, tea, bananas, chocolate, cocoa, citrus fruits, and vanilla and should be avoided on the day before the start of the test. Some prescription medicines can interfere with metanephrine testing as well (e.g., acetaminophen, aminophylline, amphetamines, clonidine, dexamethasone, diuretics, epinephrine, insulin, lithium, methyldopa, monoamine oxidase (MAO) inhibitors, nitroglycerine, salicylates, theophylline, tetracycline, tricyclic antidepressants, vasodilators, etc). The effects of these drugs on metanephrine testing will be different from patient to patient and cannot be predicted. The physician will determine which of them can be safely interrupted and which must be continued. The urine collection bottle must contain an acid as a preservative and must not be refrigerated.

Other biomarkers

A wide variety of secreted products has been proposed as diagnostic biomarkers for NETs and/or as prognostic factors.
However, few of these have been accepted for routine use due to the technical difficulty with the measurement technique.
The majority of these markers can therefore only be measured in specialised centres or in clinical studies.

General imaging modalities

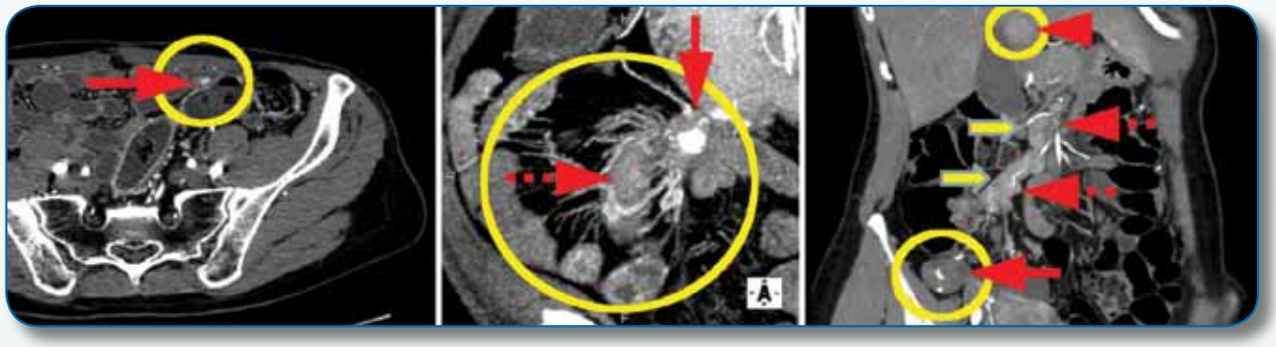
Imaging of the primary tumour location and the extent of the disease is needed in all phases of management of patients with NETs. It is also needed to determine whether a surgical resection is possible, to determine whether treatment for advanced metastatic disease is appropriate and during follow-up to assess the effects of any antitumor treatment or as surveillance of complete remission. A number of different imaging modalities have been widely used including conventional imaging studies (CT, MRI, and ultrasound); at least one of these modalities is generally available in most centres. Procedures before, during, and after investigations may differ between institutions, so the relevant department must be asked for advice.



Relevant imaging modalities depending on the anatomical location of the tumor

CT – CAT (Computed [Axial] Tomography)

The CT scan takes X-ray images of the body from various angles, and a computer assembles these images to produce either sectional images which divide the body into 'slices', or more sophisticated equipment can also create three-dimensional images. This is an accurate form of radiological investigation that is broadly effective for the localization of primary tumours in one or more organs and/or their metastases. CT is also an excellent tool for follow-up of NETs and for the assessment of response to treatment.



MRI (Magnetic Resonance Imaging)

An MRI is a radiological technique using nuclear magnetic resonance, defined as the absorption of electromagnetic energy by the nuclei of atoms placed in a strong magnetic field. Radio frequency fields are used to alter the alignment of the magnetic field. The nuclei of different atoms absorb unique frequencies of radiation depending on their environment, thus by observing which frequencies are absorbed when placed in a strong magnetic field (and later emitted again, when the magnetic field is removed), it is possible to learn about the structure of soft tissue. For NETs, the MRI is considered a sensitive modality for detection of bone and liver metastases.

Ultrasound (US)

Ultrasound waves can be converted into electrical signals, which are used to create an image. The returning signals are converted into an image, which is then displayed on a monitor. X-rays are not used in this investigation. Ultrasound investigation also determines the size and appearance of the organ being examined. It is possible to see whether blood vessels are normal and localise any tumours. This type of imaging is often combined with a fine-needle biopsy to distinguish a NET from other tumour types.

Nuclear imaging modalities

In nuclear imaging tests the patient is given – mostly intravenous – small quantities of a radioactive substance (radiotracers). After a period of time, which varies depending on the organ investigated, the distribution of the radioactive substance in the organ can be captured using a special camera (gamma camera). The distribution of radioactivity will be altered in the presence of benign or malignant processes in the organ. The radiation from these radioactive substances differs from the radiation of X-rays. During X-ray procedures, radiation is sent through the patient's body from an external radiation source, while in nuclear medicine tests, the radiation is emitted from the radioactive substance inside the patient's body. Since no contrast medium is used, patients with contrast allergy can safely undergo this procedure. Adverse events are remarkably infrequent – rarely a transient rash occurs. While radiology is useful in the initial localization of NETs, nuclear imaging techniques, using tumour-specific radiolabelled receptor analogues, are considerably more sensitive and specific for detecting NETs and their metastases.

PET—Positron Emission Tomography

PET is a nuclear medicine imaging technique that produces a three-dimensional image or picture, based on the metabolic activity of the tumour. Radionuclides used in PET scanning are typically isotopes with short half-lives such as carbon-11 (~20 min), nitrogen-13 (~10 min), oxygen-15 (~2 min), and fluorine-18 (~110 min). These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water, or ammonia, or into molecules that bind to receptors or other sites of drug action.

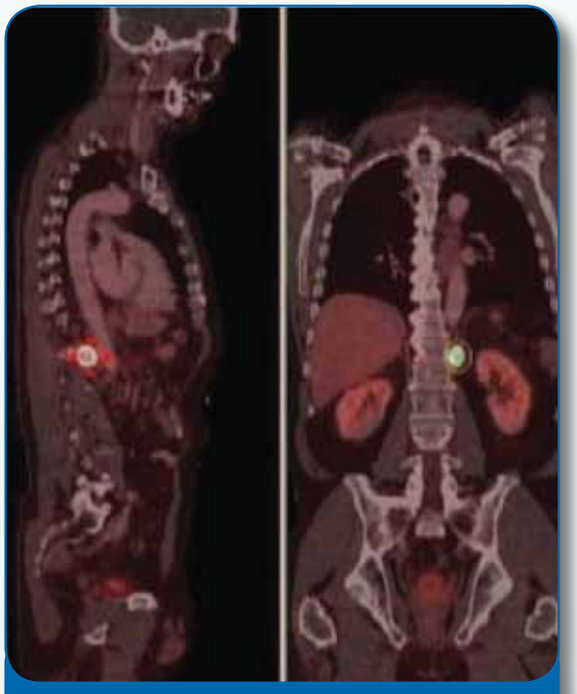
FDG-PET (^{18}F-fluorodeoxyglucose) can be used for the detection of undifferentiated and poorly differentiated tumours. When using ^{18}F-FDG, an analogue of glucose, the concentrations of tracer imaged, reflects the metabolic activity of the tissue in terms of regional glucose uptake. Many tumour cells are defined as 'active, fast growing' and will take high tracer concentrations, however, NET-cells are slowly growing cells, and consequently the uptake of glucose will be low. Therefore, the FDG-PET cannot be used to detect all different types of NETs and other tracer molecules, specifically metabolised by NETs, must be used in PET to have greater clinical utility.

5HTP-PET (^{11}C-5-HTP(5-hydroxytryptophan)) can be used for detection and/or visualization of well-differentiated NET; 5-hydroxytryptophan is a serotonin tracer, showing uptake in tumour tissue.

Metomidate PET (^{11}C-metomidate) can be used for detection of adrenocortical NETs, as ^{11}C-metomidate (MTO) is a potent inhibitor of the adrenocortical enzyme 11β-hydroxylase.

HED PET (^{11}C-hydroxyephedrine) can be used for detection of phaeochromocytoma. ^{11}C-hydroxyephedrine is a catecholamine analogue, showing uptake in tumour tissue.

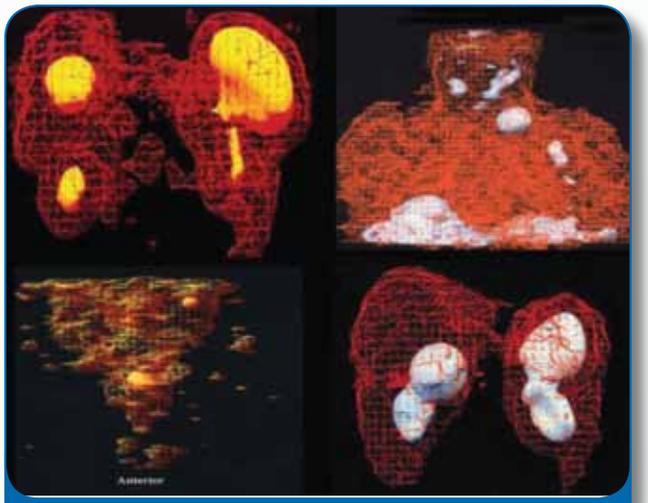
^{68}Ga-DOTATOC PET (^{68}Ga-DOTATOC or DOTATATE) can be used for detection of well-differentiated NET (glucagonomas, gastrinomas) as ^{68}Ga-DOTATOC or DOTATATE are able to visualize more lesions than ^{111}in-octreotide. This is extremely important when surgery will be planned as a curative treatment option (to be sure that all of the tumour lesions are removed). ^{68}Ga-DOTATOC is a radioactive labelled somatostatin analogue that can bind to (more) somatostatin receptors.



Pancreatic NET imaged with ^{68}Ga-DOTATOC

Somatostatin Receptor Scintigraphy (SRS – 'Octreoscan™')

SRS, also called an octreotide scan, is another type of scintigraphy used to detect NETs and other types of tumours. NETs express multiple somatostatin receptor subtypes (SSTR) and by using radiolabelled somatostatin receptor analogues, NETs (and the receptors) can be identified. Octreotide, a synthetic analogue of somatostatin, is radiolabelled with indium-111 (^{111}In-pentetreotide) and is injected into a vein. The radioactive octreotide attaches to tumour cells that have receptors for somatostatin, and the location of the tumour is revealed by the gamma camera.



Three-dimensional reconstruction of somatostatin receptor scintigraphy images.

In patients suspected of having insulinoma, an intravenous infusion of glucose should be available because of the potential for inducing severe hypoglycaemia.

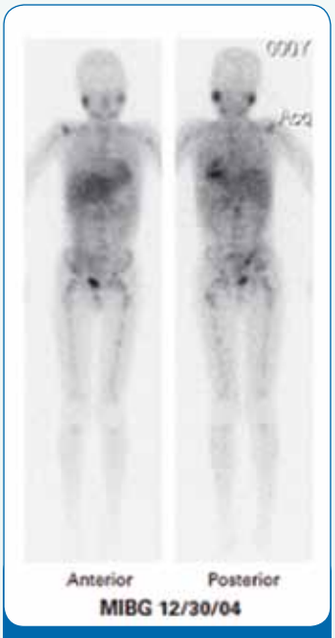
SRS may not always be successful or accurate. Inflammatory conditions (including Crohn's disease) are also associated with the expression of SSTR and may cause a false-positive result. However, octreotide scintigraphy is particularly relevant for patients with non-functioning neuroendocrine tumours and is important for identifying the best treatment option. (See chapter 5 – PRRT).

MIBG scan

An MIBG scan is a nuclear imaging scan which involves an injection of a liquid radioactive material called meta-iodobenzylguanidine (iodine-131-meta-iodobenzylguanidine). MIBG is a radiotracer similar to norepinephrine, which is made by sympathetic nerve cells. For patients with phaeochromocytoma, MIBG scintigraphy has a very high sensitivity of around 87%. The uptake of MIBG is not dependent on the presence of somatostatin analogues and this method can be used when other methods have failed.

Bone scintigraphy

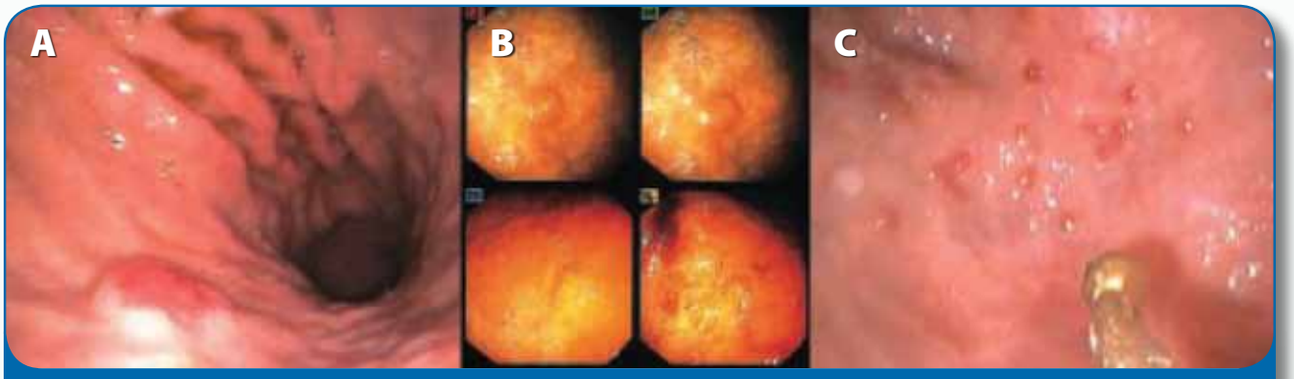
Bone scintigraphy is the principal imaging modality for identifying bone involvement with NETs. Bone scintigraphy images the distribution of a radioactive tracer in the skeletal system. The whole body scan is useful where there is uncertainty about the location or extent of bone lesions. The radiopharmaceutical is injected intravenously and, unless contraindicated, the patient should be well hydrated and instructed to drink one or more litres of water in the hour between the time of injection and the time of imaging. Patients should also void frequently during this time and immediately before the scan. Patients should also drink plenty of fluids in the 24 hours following the procedure. The images are recorded using a gamma camera that detects gamma radiation.



Bone metastases of the 4th rib - images of bone scintigraphy.

Endoscopy

Various parts of the gastrointestinal or bronchial tract can be investigated using a flexible endoscope. Mucosal biopsies can be taken and polyps can be removed (polypectomy). Complications are rare, but bleeding can occur. Very infrequently, perforation of the lung, oesophagus, stomach, or bowel may occur, which may require surgery.

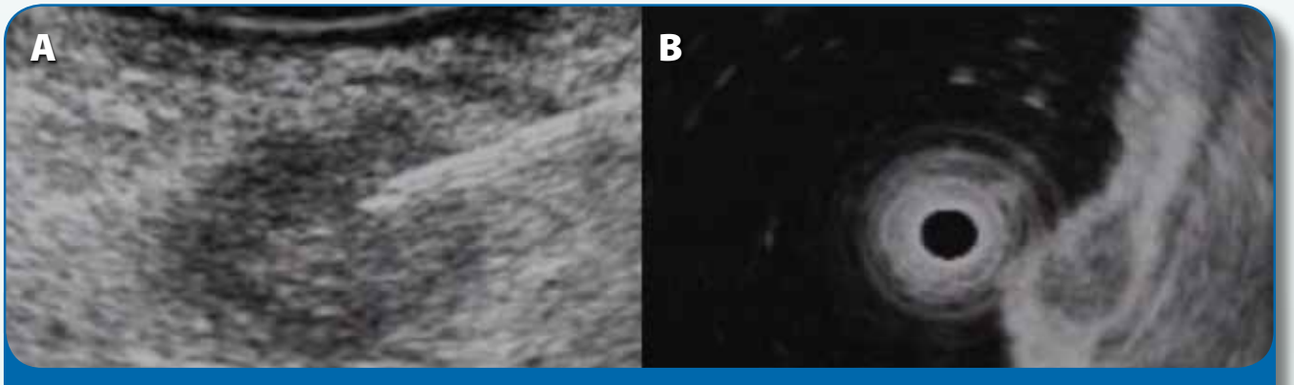


Panel A: Endoscopic images of a large solitary gastric neuroendocrine tumour (NET) arising in atrophic gastritis. Panel B: Small nodular gastric NETs. Panel C: Multiple punctate (micro-nodular) gastric NETs with an endoscopic biopsy.

Images are courtesy of IM Modlin.

Endoscopic ultrasound (EUS)

Endoscopic ultrasound is performed by inserting an ultrasound-fitting endoscope into the stomach, duodenum, or rectum; a balloon is inflated with saline solution and a transducer can be used to scan the pancreas, duodenal wall, or rectum. This is a particularly sensitive technique for the detection of gastric, duodenal, pancreatic, and rectal NETs, and superior to the 'standard' ultrasound technique described above. It is especially useful for the investigation of small tumours. This type of imaging is often combined with a fine-needle aspiration to distinguish a NET from other tumour types.



Panel A: Endoscopic ultrasound image of a small (7 mm) pancreatic neuroendocrine tumour with a fine needle for biopsy inserted. Panel B: Endoscopic ultrasound image of a subepithelial gastric neuroendocrine tumour.

Images are courtesy of IM Modlin.

Cardiologic investigations

Echocardiography is an ultrasound of the heart. A probe/transducer, placed on the skin of the patient's chest, is both a transmitter and receiver and sends out very high frequency radio waves. These radio waves hit the heart and its various structures. Some of these waves are absorbed, whereas others are transmitted to the probe and transformed into ultrasound images of the heart, which is displayed on a monitor. Echocardiography provides information about the heart's ability to pump and its valve function. Live film is produced of the appearance and movement of heart muscle and heart valves, including blood-flow measurements (doppler). In patients with NETs, particular attention should be paid to the valves on the right side of the heart (tricuspid and pulmonary), as these valves can be affected by the disease.

Histopathologic examinations

The final diagnosis of a NET is based on histopathologic findings (examination of a tissue sample under a microscope). These tissue samples are collected during a surgical procedure, via endoscopy, or under visually-guided biopsy using an ultrasound or CT scan. Neuroendocrine tumours have a special appearance which, is identified using immunohistochemical staining (IHC). Immunohistochemistry refers to the process of detecting antigens (e.g., proteins) in cells of a tissue slide by exploiting the principle of antibodies binding specifically to antigens in biological tissues. ICH staining in NETs is performed by using antibodies specific for chromogranin A, synaptophysin, and other biomarkers of NETs. These markers are useful for the diagnosis and staging of NETs, and some also provide prognostic information.

The Ki-67 protein (also known as MKI67) is a cellular marker for proliferation. Where Ki-67 is 5%, this means that 5% of the cells are undergoing proliferation; hence, the higher the Ki-67 percentage, the more aggressive the disease. The tumour's Ki-67 percentage is significant in terms of the choice of treatment method. (See also Chapter 2).

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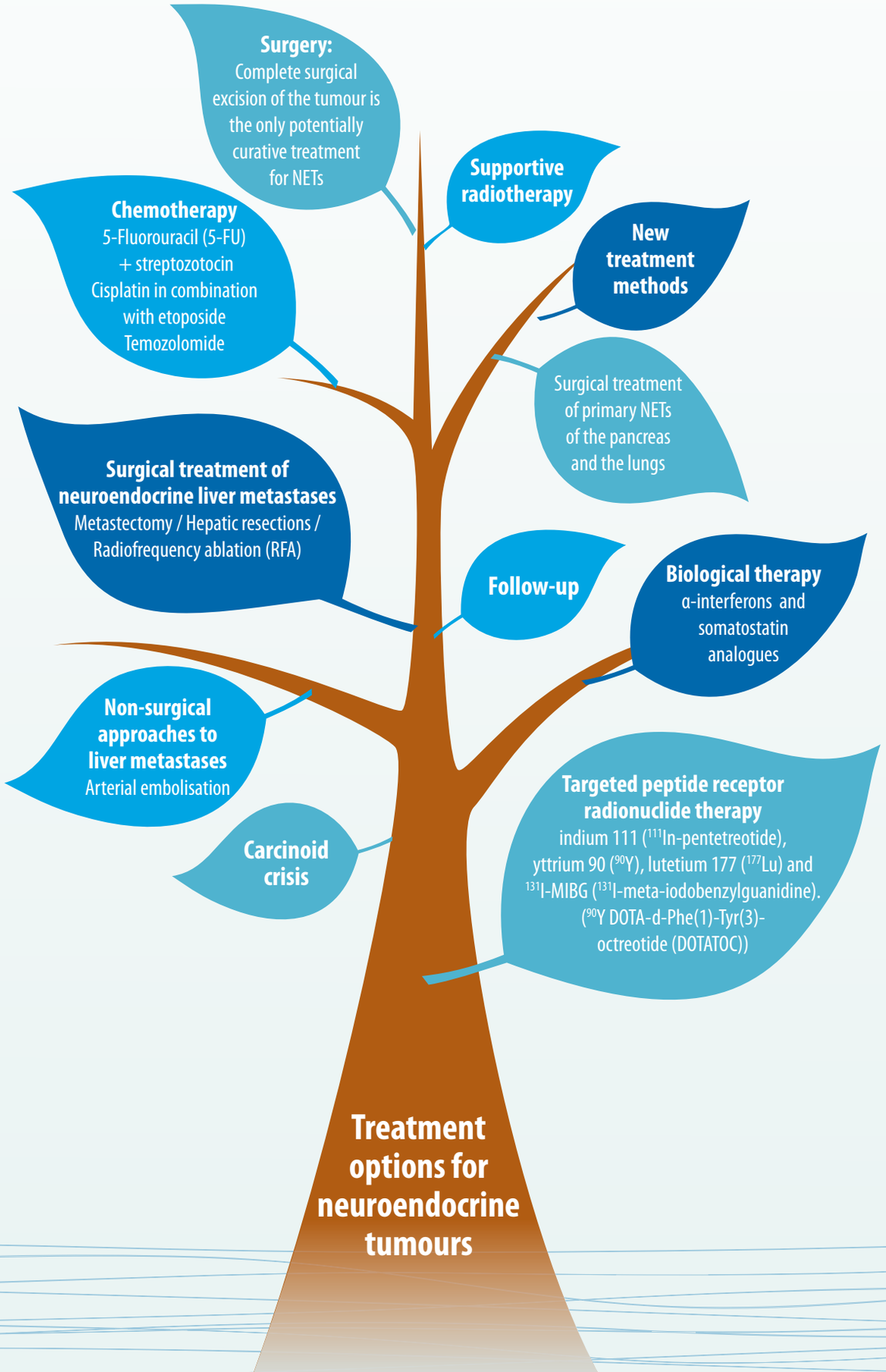
Chapter 5
Treatment options for neuroendocrine tumours



Introduction

After reading this chapter you will have gained an overview of the various treatments available for patients with neuroendocrine tumours.

A range of surgical and medical interventions are used in the management of NET patients. The choice of treatment depends on several factors:

- The location of the primary tumour
- Whether it has invaded surrounding areas or metastasised to other organs (number and location)
- The tumour type
- Hormone production
- Cardiac disease
- Patient's condition (performance status) and any co-morbidities

Carcinoid crisis

A carcinoid crisis is a severe complication of the carcinoid syndrome that can arise in patients with advanced metastatic neuroendocrine tumours. It can be triggered by hypercapnia, hypothermia, hypotension, hypertension, initiation of chemotherapy, or drugs that cause a release of histamine, but it can also be initiated by stress and tumour manipulation (surgery). It is the result of a massive release of serotonin and other products, such as histamine, kallikreins or catecholamines. In particular, levels of serotonin and its metabolites (5-HIAA) are elevated and remain so for several hours.

Differentiating a carcinoid crisis from a severe episode of the carcinoid syndrome can be difficult. A crisis is characterized by a sudden (violent) onset of different symptoms at once; these symptoms can consist of prolonged cutaneous flushing, severe dyspnoea, peripheral cyanosis, tachycardia, and sometimes hemodynamic instability, which can be life-threatening and fatal. Given the severity of, and risk associated with, a carcinoid crisis, the multidisciplinary team should consider implementing preventative measures before surgery or drug therapy.

Treatment of a carcinoid crisis consists of blocking the release of the mediators from tumour tissue by administering somatostatin analogues, such as octreotide. Ketanserin has been used successfully in patients with a carcinoid crisis to block the actions of mediators. It is a selective antagonist of the 5-hydroxytryptamine receptor 2, the α1-adrenoreceptor, and the H1-histamine receptor and decreases the central sympathetic outflow. Catecholamines should never be used for the treatment of hypotension, as they may stimulate tumour cells to release even more serotonin.

Surgery

Complete surgical excision, or *curative resection*, of the tumour, with complete removal of all cancerous tissue is the only potentially curative treatment for NETs. When this cannot be achieved, a number of patients will still benefit from palliative resection (also known as debulking surgery), where the greatest possible amount of tumour tissue is removed. In this instance some tumour may remain in situ for technical reasons (e.g. lack of access or tumour infiltration into blood vessels). A further distinction is made between surgical resection of the primary tumour and removal of metastases, in practice these are mostly liver metastases.

Surgical treatment of primary neuroendocrine tumours

Intestinal neuroendocrine tumours

- *Duodenum*: Neuroendocrine tumours of the duodenum constitute a heterogeneous group, which can be difficult to locate during surgery. Depending on the size and location of the tumour, various surgical approaches may be indicated: from simple resection of part of the bowel wall, to major procedures, potentially involving both the stomach and pancreas

- *Ileum:* In neuroendocrine tumours of the ileum the primary treatment is small-bowel resection, normally with resection of a larger or smaller part of the associated small-bowel mesentery, since these tumours usually cause significant amounts of fibrosis, and frequently metastasise to lymph nodes along the blood vessels in the mesentery. The objective is radical removal, and it may be necessary to remove more small bowel than the actual primary tumour would indicate, because removal of the affected mesentery may extend to the blood supply of the remaining part of the small bowel. Where a significant proportion of small bowel is removed, the patient may suffer 'short bowel syndrome', with loose stools and reduced absorption in the gut
- *Appendix:* It is estimated that NETs are found in around 1 in 300 removed appendixes, usually as a chance finding. Where the tumours are large, it is always recommended that the right hemicolon is removed (right hemicolectomy) to minimize the risk of recurrence
- *Rectum:* The surgical treatment is, in principle, as for other malignant tumours of the rectum. Size and location will determine whether this can be done via resection with primary bowel anastamosis, or whether ano-peritoneal resection must be performed with formation of a permanent fistula (sigmoidostomy)

Neuroendocrine tumours of the pancreas

Surgical treatment of a NET of the pancreas depends on the type of tumour, the size, and localisation in the pancreas. For tumours in the body or caudal (tail) part of the pancreas, distal resection of the pancreas (laparoscopically) is performed. For tumours of the pancreatic head, a Whipple's resection (pancreaticoduodenectomy) is the usual surgical technique used.

The various tumour types have a different natural development and prognosis. The previous considerations, together with the fact that the pancreas is an extremely difficult organ on which to operate—with significant risk of complications—means that each case must be assessed individually before deciding which approach to recommend.

Neuroendocrine tumours of the lungs

In the same way as for a gastrointestinal NET, complete surgical resection of lung NETs is the only curative treatment. Surgical methods vary in terms of size and localisation. Most commonly this will involve wedge resections, segment resection or resection of an entire lobe of a lung. Preservation of as much normal lung tissue as possible is always a goal.

Surgery

Location of NET	Surgical techniques used
Intestinal neuroendocrine tumours	
Duodenum	Various procedures from simple resection of part of the bowel to major resection including stomach and pancreas
Ileum	Small-bowel resection. May include part of mesentery. May cause 'short bowel syndrome'
Appendix	Resection. For large tumours right hemicolectomy may be necessary
Rectum	Resection with primary bowel anastamosis. Ano-peritoneal resection (sigmoidostomy)
Pancreas	
Body or caudal pancreas	Distal resection
Head of pancreas	Whipple's resection (pancreaticoduodenectomy)
Lungs	Wedge resection, segment resection, or lobe resection

Surgical treatment of neuroendocrine liver metastases

When neuroendocrine tumours spread, it is normally to the liver. These metastases can be much larger than the primary tumour and can cause pain and hormonal symptoms. The symptoms from these metastases can be worse than the symptoms due to the primary tumour.

No standard treatment plan exists for patients with asymptomatic liver metastases. The surgical approach will depend on where the tumours are located and how many are present. In the case of small tumours, proper management involves observing the condition for a time before deciding on surgery, since such tumours can progress in very different ways—from very slow growth in some cases, making surgery less urgent or even not needed, to extremely rapid progression of massive, diffuse tumour spread in others. Despite the technique used, where surgical removal of the metastases is possible, there is evidence that this can prolong survival and achieve cure in some cases.

Metastectomy

Isolated liver metastases are resected, but this is only feasible where the metastases are few in number. Often the metastases are too numerous and impossible to remove surgically due to their location. The option then is to perform arterial liver embolisation or radiofrequency ablation. This can reduce the quantity of tumour tissue in the liver significantly. These treatments can also be repeated where new tumours develop.

Hepatic resections

Where the number of metastases is too great to perform resection of each individual metastases, but the metastases are located in one area of the liver, then some degree of partial liver resection may be appropriate. In the case of large tumours which technically cannot be removed by surgery, liver resection will be recommended in a number of cases.

Radiofrequency ablation (RFA)

Radiofrequency ablation is a minimally invasive treatment to treat liver metastasis. In RFA, high-frequency electrical currents are passed through an electrode inserted into the metastases, creating heat that destroys the abnormal cells. RFA is an image-guided technique that can be used during open surgery, laparoscopy, or by percutaneous procedure where the electrode is inserted into the liver through the skin. It can be used:

- When the tumours are small in diameter
- When metastases are present in both lobes of the liver
- In combination with surgery, when tumours are surgically removed in one half of the liver, and can be used to treat a small number of tumours in the other half of the liver
- To treat individual small tumours centrally in the liver, where surgery may be technically difficult

Non-surgical approaches to managing liver metastases

Arterial embolisation

Embolisation is a non-surgical, minor-invasive procedure performed by an interventional radiologist. It involves the selective occlusion of blood vessels by purposely introducing emboli (blockages). The normal liver cells receive blood from the hepatic artery and portal vein. The cancer cells receive blood from the hepatic artery only. By blocking the arteries to the tumour with small particles, it can prevent blood supply to the tumour tissue, and the entire tumour—or part of it—will die. The normal cells in the area survive because they also receive blood from the portal vein. This treatment can be used when:

- There are numerous large metastases in the liver
- The tumour is producing a lot of hormones
- Drug treatments have not controlled the NET symptoms
- Chemotherapy needs to be administered during the embolisation

Although not as invasive as surgery, this is still a serious procedure and patients often feel unwell following the intervention. Commonly, they experience fever, nausea, and pain, and require monitoring for the first few hours (up to a few days) with frequent measurement of vital signs. Because the tumour cells die, are degraded, and the resultant chemicals are passed out of the body, it is important to increase urine output in order to increase elimination of these waste products. Consequently, intravenous fluids are given over the first few days, all urine output is measured, and fluid balance is carefully monitored.

There is some risk of carcinoid crisis due to the significant release of hormones into the bloodstream; therefore patients are normally given somatostatin analogues for the first few days following embolisation. Hospitalisation is required after embolisation.

Liver metastases

Type of metastases	Surgical interventions	Other interventions
Small number	Resection of individual metastases (metastectomy)	Radiofrequency ablation (RFA)
Large number, closely positioned	Partial hepatectomy (possibly in conjunction with RFA)	Arterial embolisation
Extensive or very large	Partial hepatectomy	Arterial embolisation

Biological therapy

Biological therapies use substances that occur naturally in the body to destroy cancer cells. Biotherapy for NETs essentially includes treatment with α-interferons and somatostatin analogues.

Interferon

Interferon (IFN-α) is a protein that occurs naturally in the body in very small amounts. It has also been produced in the laboratory for therapeutic use. Interferon has a number of functions; it can have a growth-inhibiting effect on both normal and malignant cells. When given therapeutically, in doses far above those found in the body, it acts as an immunomodulator (immunotherapy) and stimulates the body's own immune system to inhibit growth of several tumour types, including NETs.

Interferon is given as an injection just under the skin (subcutaneously), usually in the thigh or abdomen. There are several forms in clinical use:

- IntronA® (Interferon alfa-2b) is supplied in a ready-to-use pen, in various concentrations (expressed in international units (IU)), and is given by subcutaneous injection either daily or at 1-3 day intervals, preferably in the evening. IntronA should be refrigerated, and the temperature kept between +2 and +8°C
- PegIntron® (Peginterferon alfa-2b) is supplied in a ready-to-use pen, in various concentrations (expressed in international units (IU)), given by subcutaneous injection once a week, preferably in the evening

The patient is taught to self-administer the injections. In individual cases where the patient is unable to manage this independently, relatives can be trained, or the primary health service contacted to assist in injecting.

Side effects of interferon vary significantly compared to those from chemotherapy; almost all adverse effects resolve after cessation of treatment. Common/transient side effects:

- Influenza-like symptoms such as fever, chills, headache, joint pain, muscle pain, and lassitude
- These reactions can be reduced by giving the patient the injection before bedtime, or symptoms may be treated with paracetamol or an NSAID (ibuprofen)

Common/late side effects (commonly after some months of treatment):

- Fatigue, low blood values (haemoglobin, WBC, and platelets), elevated hepatic enzymes (ASAT and ALAT), diarrhoea, anorexia, depression, anxiety, dizziness, confusion, dry mouth, taste alterations, hair loss, and itching

Less common side effects:

- Mild hypotension, depression, sleep disturbances, difficulty concentrating, diabetes, hypothyroidism, hyperthyroidism, allergic reactions, pulmonary infiltrates, reduced libido and reduced fertility

The treatment will probably be long-term over several months. Those patients who have benefited from the treatment may suffer relapse when the treatment is discontinued. Short interruptions (drug holidays) in treatment, however, do not appear to affect outcome.

Several pharmaceutical companies provide special information leaflets for patients and health care providers; experience shows that patients who undergo immunotherapy tolerate it better if they receive explanations and education about the treatment, adverse reactions, and the disease for which they are being treated.

Somatostatin analogues

Somatostatin is a hormone that inhibits the release of growth hormone and secretion of a number of hormones within the gastrointestinal tract. Somatostatin also inhibits contraction of the gall bladder and secretion of pancreas enzymes.

Somatostatin analogues are drugs used to treat functioning NETs that are causing hormone-related clinical syndromes due to excessive somatostatin production. They work by blocking the release of somatostatin and thereby reduce the symptoms (flushing and diarrhoea) and improve the quality of life. Two commonly used somatostatin analogues are octreotide and lanreotide. Octreotide has been studied in a placebo-controlled, double-blind, prospective, randomized study in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours. This study showed that octreotide LAR significantly lengthened time to progression compared with placebo in this patient setting.

Most cells in neuroendocrine tumours have receptors to which the drug binds. This binding may mean that the tumour stops growing and, in the best case scenario, wil shrink in size. If the tumour has no receptors somatostatin analogues cannot be expected to be effective. The potential efficacy of somatostatin analogues can be determined using octreotide-scintigraphy (see chapter 4 - Somatostatin Receptor Scintigraphy).

There are 2 different types of somatostatin analogues:

- Short-acting octreotide: this is given as a short-acting injection subcutaneously up to three times a day. Patients can be taught to self-inject
- Long-acting octreotide: These injections are given deep into the gluteal area once every 4 weeks, depending upon the drug used and the situation

Long-acting octreotide is not given until the patient has tried the short-acting form, and the treatment is tolerated and effective. Patients on short-acting octreotide, who are switched to the long-acting form, will need to continue the short-acting injections until the sustained-release preparation has reached full effect. This transitional period will vary from patient to patient.

Short-acting octreotide ampoules and vials, as well as the pre-filled, single-use syringes (long acting), are stored in a refrigerator, but are brought to room temperature prior to injection.

Common side effects of octreotide are:

- Reactions at the injection site (transient pain and local redness)
- Gastrointestinal side effects: diarrhoea, soft stools, abdominal pain, flatulence, nausea, and vomiting occur at the start of treatment then decrease in frequency and intensity with continued treatment

  -Treatment: oral digestive enzymes

Less common side effects include:

- Gallstone formation, usually asymptomatic
- Altered blood sugar regulation in diabetics can be expected, but is rarely a problem

Several pharmaceutical companies provide special information leaflets for patients and health care providers. Experience shows that patients who undergo somatostatin analogue therapy better tolerate this treament if they receive explanations and education about the treatment, adverse reactions, and the disease for which they are being treated.

Biological therapy

Drug	Brand names	Mode of action	How given	Side effects
Interferon alfa-2b Peginterferon alfa-2b	IntronA® PegIntron®	Stimulates the body's own immune system	Subcutaneously Supplied in ready-to-use pens	• Early/transient effects: influenza-like symptoms (fever, chills, headache, joint pain, muscle pain, lassitude) • Late effects: fatigue, low blood count, elevated liver enzymes, diarrhoea, anorexia, depression, anxiety, dizziness, confusion, dry mouth • Less commonly: mild hypotension, depression, sleep disturbances, difficulty concentrating, diabetes, hypothyroidism, hyperthyroidism, allergic reactions, pulmonary infiltrates, reduced libido, reduced fertility
Somatostatin analogues Octreotide Lanreotide	Sandostatin®, Somatuline Long-acting formulations: Sandostatin LAR®, Somatuline LA®, Somatuline Autogel®	Acts like natural somatostatin to decrease the production of some hormones	Short acting formulations are given as a short-acting injection under the skin (subcutaneously) up to three times a day. Patients can be taught to self-inject. Long-acting formulation given deeper under the skin once every 4 weeks	• Common side effects of somatostatin analogues are: reactions at the injection site (transient pain and local redness) • Gastrointestinal side effects: diarrhoea, soft stools, abdominal pain, flatulence, nausea, and vomiting occur at the start of treatment, then decrease in frequency and intensity with continued treatment • Less common side effects: gallstone formation, usually asymptomatic. Altered blood sugar regulation in diabetics can be expected, but is rarely a problem

Chemotherapy

Cytotoxic drugs act by inhibiting cell proliferation, and can act at different points in the cell cycle. Cytotoxic drugs are normally used in combination to treat different cancers—this approach results in different side effect profiles depending on the combination of drugs used. Individuals' response to chemotherapy can vary significantly, as can the patient's tolerance. Some patients feel very sick, while others tolerate the drugs relatively well.

The cytotoxic drugs used most commonly to treat NETs are:

- 5-Fluorouracil (5-FU) in combination with streptozotocin
- Cisplatin in combination with etoposide
- Temozolomide

Usually this type of treatment is given in cycles, and depending on hospital practices, patients will be hospitalized or treated in an outpatient setting. The efficacy of treatment with cytotoxic drugs is usually assessed every 3-5 months by CT scan. Patients may receive chemotherapy for several years.

The cytotoxic drugs used in the management of neuroendocrine tumours usually have relatively few side effects compared with many other chemotherapy treatments. The following adverse reactions have been reported:

- 5-FU: Bone marrow depression and gastrointestinal symptoms including anorexia, nausea, vomiting, diarrhoea, and mucositis. Alopecia (mild), hyperpigmentation, skin atrophy, and neuropathy can also be seen
- Streptozotocin: Nausea and vomiting. Anorexia, stomatitis, oesophagitis, and diarrhoea. Bone marrow depression (3-5 weeks after administration), such as leukopenia and thrombocytopenia. Renal impairment is the most important dose-limiting adverse reaction to streptozotocin. Lung injury in the form of fibrosing alveolitis and interstitial pneumonia may occur
- Cisplatin: Nausea and vomiting. Dose-dependent toxic renal effects, necessitating close monitoring of renal function. Ototoxicity, electrolyte disturbances such as hypomagnesaemia, peripheral and central neurotoxicity can also occur. Some patients develop an allergic reaction with risk of hypovolaemic shock
- Etoposide: Transient nausea and vomiting, anorexia, diarrhoea, stomatitis are common. Leukopenia and/or thrombocytopenia and a transient alopecia can also occur. Uncommonly: abdominal pain, mucositis/oesophagitis, and stomatitis occur and sometimes there is peripheral neuropathy, which is normally limited in nature
- Temozolomide: Nausea, vomiting, constipation, diarrhoea, anorexia, alopecia, headache, fatigue, lymphopenia, thrombocytopenia, and convulsions

Patients need to know what side effects can be expected. It is important to bear in mind that an information provision must be adapted to the individual's learning needs and literacy level. Although the general view is that the most well-informed patient is the one who best tolerates the treatment, it is also possible that nausea and vomiting may develop because the patient expects it (anticipatory nausea and vomiting). The aim of patient education is to help the patient develop mastery in managing treatment side effects, many of which occur at home. This will help reduce treatment-related morbidities, ameliorate side effects, and motivate the patient to stick with treatment in the long term.

Chemotherapy

Drug	Mode of action	How given	Side effects
5-fluorouracil (5-FU)	5-fluorouracil (5-FU)	Intravenous injection or infusion. (Sometimes as a cream for skin cancers)	Bone marrow depression and gastrointestinal symptoms including anorexia, nausea, vomiting, diarrhoea, and mucositis. Alopecia (mild), hyperpigmentation, skin atrophy, and neuropathy can also be seen.
Streptozotocin	Alkylating agent	Intravenous infusion	Nausea and vomiting. Anorexia, stomatitis, oesophagitis, and diarrhoea. Bone marrow depression (3-5 weeks after administration), such as leukopenia and thrombocytopenia. Renal impairment is the most important dose-limiting adverse reaction to streptozotocin. Lung injury in the form of fibrosing alveolitis and interstitial pneumonia may occur.
Cisplatin	Platinum derivative	Intravenous infusion (prehydration required)	Nausea and vomiting. Dose-dependent toxic renal effects, necessitating close monitoring of renal function. Ototoxicity, electrolyte disturbances such as hypomagnesaemia, peripheral and central neurotoxicity can also occur. Some patients develop an allergic reaction with risk of hypovolaemic shock.
Etoposide	Synthetic alkaloid	Intravenous infusion or capsules	Transient nausea and vomiting, anorexia, diarrhoea, stomatitis are common. Leukopenia and/or thrombocytopenia and a transient alopecia can also occur. Uncommonly: abdominal pain, mucositis/ oesophagitis, and stomatitis, occur and sometimes there is peripheral neuropathy, which is normally limited in nature.
Temozolomide	Imidazotetrazine derivative	Intravenous infusion or capsules	Nausea, vomiting, constipation, diarrhoea, anorexia, alopecia, headache, fatigue, lymphopenia, thrombocytopenia, and convulsions

Targeted peptide receptor radionuclide therapy (PRRT)

Most neuroendocrine tumours have 5 highly specialized receptors that bind to the naturally occurring hormone somatostatin. Octreotide is able to attach to two of these five somatostatin receptors. Peptide receptor radionuclide therapy (PRRT) combines octreotide with a radionuclide (a radioactive substance) to form highly specialized molecules called radiolabelled somatostatin analogues or radiopeptides. These radiopeptides can be injected in the bloodstream and go directly to the tumour cells that have receptors for them. Once bound, these radiopeptides emit radiation and kill the tumour cells they are bound to. So, almost all of the radiation is absorbed by the tumour and very little goes to normal healthy tissues. That is why it is called 'targeted therapy'.

There are different radionuclides that are attached to octreotide to create radiopeptides including

- yttrium 90 (^{90}Y) - DOTATOC
- lutetium 177 (^{177}Lu) - DOTATATE
- ^{131}I-MIBG (^{131}I-meta-iodobenzylguanidine)

These radiopeptides differ in the type of radiation they emit, as well as the depth of tissue into which they penetrate. Tissue penetration is an important factor since a certain range of radiation is necessary to kill tumour cells but not damage surrounding, healthy tissues. In radionuclide therapy the dose of radiation that is being used is higher than the one needed for imaging purposes (see chapter 4 - Histopathologic examinations).

Individuals whose tumours can be visualized by somatostatin receptor scintigraphy (SRS) and have inoperable NETs that are growing, or individuals whose symptoms are not well managed by somatostatin analogues, may be candidates for PRRT. However, the extent of tumour growth, kidney function, liver function, prior treatments, and many other factors must also be considered.

All side effects associated with radionuclide therapy are mild and transient. They comprise nausea, vomiting, abdominal pain, hypotension, fatigue, leucopenia, and thrombocytopenia. Other less-common side effects are bone, liver, and kidney toxicity, and mild hair loss.

New treatment approaches

New treatment methods are being investigated for NETs. In the future, there will probably be a number of biological drugs available that will be capable of inhibiting tumour growth in different ways. Called targeted therapies, these are a type of drug that blocks the growth of cancer cells by interfering with specific molecules needed for carcinogenesis and tumour growth, rather than by simply interfering with any rapidly dividing cells (the action of traditional chemotherapy). Targeted cancer therapies may be more effective than current treatments and less harmful to normal cells. Examples of such biological drugs include

Afinitor ® (Everolimus) – for the treatment of pancreatic NETs

Everolimus is a once-daily oral inhibitor of mTOR (mammalian target of rapamycin), a protein that acts as a central regulator of tumour cell division, cell metabolism, and blood vessel growth.

Sutent® (Sunitinib) - for the treatment of pancreatic NETs

Sunitinib is an oral therapy administered once daily that inhibits cellular signalling by targeting multiple receptor tyrosine kinases (RTKs), involved in the development of blood vessels, such as platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGF).

Pasireotide (SOM230)

Pasireotide is a multi-receptor targeted somatostatin analogue which blocks more somatostatin receptors than octreotide.

Pasireotide is being evaluated in phase III clinical trials in patients with neuroendocrine and metastatic carcinoid tumours, acromegaly, and Cushing's disease. The long-acting form of this drug is administered once-monthly, intramuscularly.

Isotopes

New and more effective isotopes are continually being added to the field of radioactive isotope treatment.

Clinical trials

Some of these drugs are still under investigation, in clinical trials or are not yet available in all countries. Clinical trials (in centres of excellence) can offer more treatment opportunities, patients sometimes need to travel to have access to these trials.

Newer treatments

Drug	Indication	Mode of action	How given
Everolimus (Afinitor®)	Pancreatic NETs	Inhibitor of mTOR (mammalian target of rapamycin)	Once-daily oral
Sunitinib (Sutent®)	Pancreatic NETs	Targets multiple receptor tyrosine kinases (RTKs), involved in the development of blood vessels, such as PDGFR and VEGF.	Once-daily oral
Pasireotide	On clinical development program	A multi-receptor targeted somatostatin analogue, that blocks more somatostatin receptors than octreotide	Long acting form: once-monthly intramuscularly

Supportive radiotherapy

Radiotherapy may have an effect on bone metastases which can cause pain or impinge on nerves.

Follow-up

All patients should see their physician for follow-up on a regular basis. This follow-up period is not restricted to a short period as even when the patient has undergone radical surgery, any remaining tumour tissue can continue to grow, but so slowly that it can take years before a relapse occurs. Frequent check-ups can lead to early diagnosis and better prognosis.

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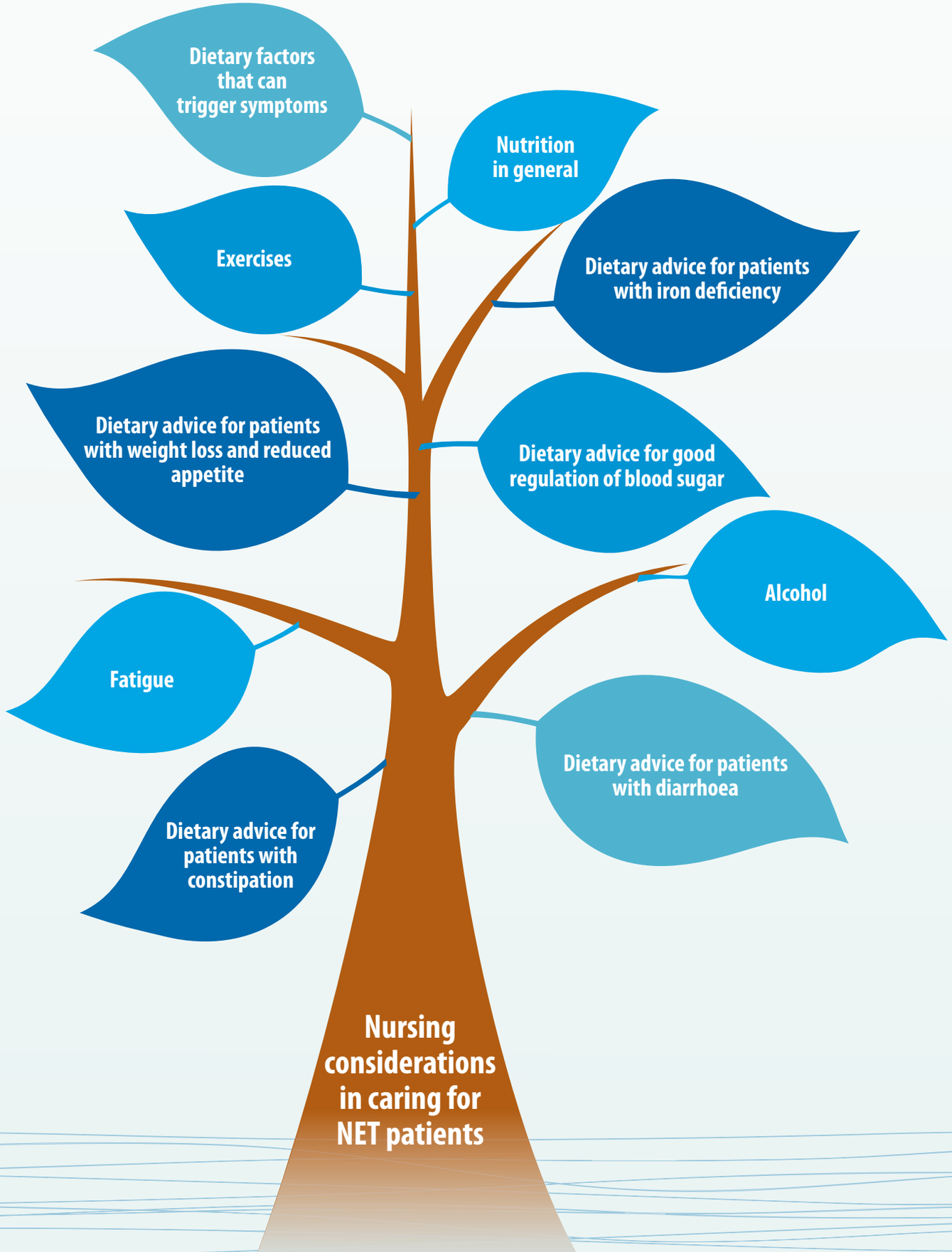
Chapter 6
Nursing considerations in caring for NET patients



Introduction

After reading this chapter you should understand different aspects of the care of patients with NETs, especially symptom management. This chapter will also give you an introduction on how to approach the everyday concerns of patients with NETs and how you can best help them cope with their illness. Much of the information in this chapter is based on clinical experience rather than research evidence. There is a huge need for more clinical research on many aspects of the care of patients with NET, especially in regard to nutritional issues.

Many NET patients will have suffered with a distressing and frustrating road to diagnosis. They may have seen many doctors, visited various institutions and gone through a whole gamut of scans and investigations before being diagnosed with a NET. Once diagnosed, the NET patient may still have to overcome a variety of hurdles including ignorance, access to treatments, lack of collaborative care, differing perceptions, and a long journey experiencing disease progression, disease stabilisation, cure or death.

For many patients, being diagnosed with a NET, will lead to changes in their daily life. Most cancer sufferers want to live as normally as possible, but they may well have to redefine what—for them—is 'normal'. One of the roles of nurses caring for patients with neuroendocrine cancer is to make sure that they provide useful, accurate, and supportive information, to help patients make the necessary adjustments in relation to lifestyle that will increase their comfort and strengthen their coping strategies.

Nutrition

The importance of nutrition in NETs

NET is a disease which affects diet, digestion, and the body's ability – to a lesser or greater extent, depending on the type of tumour —to extract nourishment from food. There are significant differences between individuals in terms of the type and degree of nutritional problems that can arise. This section deals with the most common nutritional problems, but it is important to remember this advice does not apply to all patients; there are different dietary recommendations dependent on the type of NET a patient has and treatments that they have received.

Dietary interventions cannot alleviate all symptoms, but a properly adapted diet can significantly reduce symptoms. It is important to consult a dietician, who will assess and adapt the diet based on individual needs. When the patient is asymptomatic, a normal diet is recommended.

The aim of dietary advice is to:

- Reduce symptoms
- Ensure adequate intake of different essential nutrients
- Avoid unnecessary dietary restrictions
- Improve general health and quality of life
- Maintain stable weight and avoid inappropriate weight loss or weight gain

The various types of neuroendocrine cancer can cause different nutritionally-related problems. The most serious problems are weight loss caused by reduced appetite or chronic 'secretory' or 'malabsorptive' diarrhoea. It is important that patients are adequately nourished in order to obtain the best possible response to treatment.

General nutritional advice for patients with NETs

Dietary advice will vary from patient to patient, since patients with NETs have different symptoms, there is one piece of general advice, which can be applied to all patients: the diet should be based on regular meals, with moderate portions of food at each meal.

Patients should be advised to eat a varied and proper diet so that energy and nutritional requirements are met and weight kept stable. When problems such as loss of appetite or diarrhoea occur, it may be difficult to achieve this.

Proteins and carbohydrates

The diet should largely comprise a combination of starch and complex carbohydrates with good sources of protein. In other words, a diet rich in food such as bread, potatoes, fruit and vegetables, alongside proteins and low-fat dairy products should be consumed. Patients with NETs often have low levels of some important amino acids (eg tryptophan). To avoid deficiency, it is important that good sources of protein are offered at all meals. Each meal should contain a portion of cheese, milk, yoghurt, eggs, poultry, meat, fish, or shellfish, in addition to the carbohydrate.

Fat

The general rule for the whole population is that up to a third of total daily energy should be derived from fat. This is acceptable for many NET patients; however, some patients will benefit from a more moderate intake of dietary fat. Diarrhoea is a frequent symptom in many patients with different types of NET, and fatty foods will exacerbate diarrhoea. Fatty meals require more bile salts to digest than lower-fat meals. In the presence of increased gut motility, the bile salts will more readily enter the large bowel and increase the diarrhoea.

In patients with (partial) bowel resection, transport time through the gut is often shorter, resulting in mild diarrhoea. In such cases the diet should be relatively low in fat. It is particularly important that patients with diarrhoea use caution in respect of eating fatty foods.

In case of mild to moderate diarrhoea, patients should be advised to try the following:

- Using weak gravy or gravy thickened with flour or cornstarch (corn flour). When making sauces, they can be thickened with flour or cornstarch and then some fat (low-fat sour cream, butter) may be added if the sauce requires it, and thus the sauce has a lower fat content
- Baking food rather than frying, since baked foods require less fat in their preparation
- Choosing low-fat versions of cheeses and dairy products
- Using only 2 tablespoonsful of oil or plant margarine in food per day
- Removing visible fat from meat
- Moderating the quantities of fat per meal and avoiding large, fatty meals
- Choosing the right types of fat sources from fatty fish, plant oils, soft margarine, mayonnaise, nuts, avocado, olives – but remembering, moderate quantities – they are still fats!

Fruit and vegetables

Raw vegetables, salads, or fruits are foods that many people find problematic to digest. However, they are important components of the diet and provide soluble fibre, vitamins, minerals, and antioxidants. Baked and boiled then mashed vegetables are better tolerated than their raw equivalents. Mashed and pureed fruit are better tolerated than whole fruit. Fruit and vegetables are better tolerated with a meal than when eaten on their own.

Vitamins and minerals

It is recommended that all patients with NETs take standard multi-vitamin and mineral supplements. The best way of meeting the need for vitamins and minerals is still to eat a varied diet and it is important that major food groups are not excluded from the diet. However, in the case of chronic diarrhoea, general reduced dietary intake, or in the presence of weight loss, patients may be experiencing general vitamin and mineral deficiency.

In patients with neuroendocrine tumours that overproduce the hormone serotonin, there may be a deficiency of the vitamin B_3. In such cases it may be beneficial to add B-vitamins to the diet. This should be assessed in consultation with a doctor or clinical nutritionist. Good sources of vitamin B_3 can be found in protein-rich foods such as meat, poultry, and fish, as well as corn products and vegetables.

Fibre

Soluble fibre forms a gelatinous mass in contact with liquid; when ingested it increases transport time in the gut. Soluble fibre also has a good effect on regulation of blood sugar and may help reduce blood cholesterol. This type of fibre is especially abundant in oats, beans, peas, lentils, vegetables (excluding broccoli), root vegetables (such as potato, sweet potato, carrots and onion), fruit pulp, berries, and dried fruit.

Insoluble fibre passes unchanged through the gut, provides more volume, and increases transport time, even more so than soluble fibre. This type of fibre is beneficial in preventing constipation, but not when the bowel is already obstructed. Insoluble fibre can be found in wholemeal bread, bran, vegetables (green beans, celery, cauliflower, and squash) edible skins of fruits and potatoes, nuts, and seeds.

Summary of nutritional advice

Topic	Recommendations
General dietary advice	The aim of dietary advice is to: • Reduce symptoms • Ensure adequate intake of different essential nutrients • Avoid unnecessary dietary restrictions • Improve general health and quality of life • Maintain stable weight and avoid inappropriate weight loss or weight gain • Regular meals with moderate portions!
Protein/carbohydrates	• Meals should include combination of starch and complex proteins
Fat	• Caution in eating fatty foods
Fruit and vegetables	• Mashed and pureed
Vitamins and minerals	• Eat varied diet • Add standard multi-vitamin and mineral supplements
Fibre Soluble Insoluble	• Good effect on regulation of blood sugar • Beneficial to prevent constipation

Dietary advice for patients with weight loss and reduced appetite

In the presence of weight loss due to reduced appetite, diarrhoea, or for other reasons, it is important that the amount of carbohydrates and nutrients in the diet is increased. This is achieved most effectively by eating small meals, up to 5-6 meals per day, including snacks. Because fat tolerance is often low, it is difficult to increase energy in the diet using increased fat intake. In such cases it is important that the amount of fat a patient can tolerate is apportioned equally between all meals.

Snacks

Dried fruit, tinned fruit, jelly, yoghurt, ice cream, and dessert puddings with a little vanilla sauce are examples of small snacks which can increase energy intake during periods of poor food intake. It is important to protect dental health by drinking a little water after a sweet meal.

Energy supplements

Taste-neutral carbohydrate powder can be obtained from the pharmacist and used as a supplement, where it can be added to any meal. The powder can be used in cold and hot drinks, soups, porridges and desserts and in the preparation of food. A drink may be made by putting 2-4 level tablespoonsful of the powder in a drinking glass of water (1.5 dL) and stirring well. If the drink is cold, leave it to stand for five minutes to ensure that the powder is properly dissolved. In order for the powder to give a significant energy supplement. 1.5-2 dL should be given per day (equivalent to 12-16 level tablespoonfuls). This provides 285-380 kcal.

Dietary advice for patient with diarrhoea

Diarrhoea is a symptom occurring frequently in several types of NETs. Chronic diarrhoea is one of the reasons for weight loss since it can lead to dehydration and reduced uptake of nutrients.

It may be useful to suggest the following guidelines to patients:

- Drinks such as apple juice with mineral water, light tea with a little sugar, clear soup, or blueberry juice contribute to maintaining fluid and electrolyte balance
- Sour milk contains lactobacillus, which has a beneficial effect on the gut's bacterial flora
- Soluble fibre in the form of oatmeal (or barley) porridge can reduce transit time in the gut
- Some foods can be beneficial in help producing more solid stools, these include:
  - -Blueberry juice
  - -Purified or grated apple
  - -Boiled and mashed carrot
  - -Bread
- Foods to be avoided include:
  - -Prunes, figs, dried fruit, fresh fruit containing substantial quantities of acid (boiled/tinned fruit is better tolerated)
  - -Insoluble fibre (linseed, sesame seeds)
  - -Coffee, alcohol
  - -Foods containing a lot of sugar
  - -Sugar alcohols such as sorbitol, mannitol, xylitol (found in 'sugar-free' versions of some foods and drinks)
  - -Fatty foods in fat-intolerant patients
  - -In the presence of secondary lactose intolerance: milk, dairy products, and goats' milk cheese

Beside these nutritional guidelines, anti-diarrhoeal drugs, somatostatin analogues or pancreatic enzymes are used to decrease diarrhoea. All drugs used for diarrhoea reduction must only be given under the guidance of the treating physician. This is especially important for somatostatin analogues as these drugs are used in the treatment of the NET.

Dietary advice for patients with constipation

Constipation, bleeding, and pain are symptoms that can occur with neuroendocrine tumours of the rectum. Consequently, it is important to ensure that patients with these tumours consume a diet containing plenty of fibre and fluid. Dietary fibre prevents and treats constipation by binding water, increasing stool bulk, stimulating bacterial growth in the gut, and increasing transit time in the gut.

Fluids

Increased intake of fibre results in increased need for fluid. Patients should drink a minimum 2 litres of fluid per day – ideally even more. It is important to drink with meals. This dilutes the content of the bowel and speeds passage through the gut. Fluid intake between meals is necessary to meet fluid requirements. Intake of full-cream milk should be restricted since this can have a constipating effect; a maximum of 1/2 a litre per day is recommended. Cultured milks are good alternatives because they contain lactobacillus, which promotes healthy gut flora.

Constipating foods

In the presence of constipation the intake of constipating foods such as rice, pasta, white bread, cornstarch (corn flour), pancakes, certain types of oatmeal (made of fine flour, rice or sour cream) large quantities of cheese and dairy products, as well as ripe bananas should be limited.

Exercise

Regular physical activity is important for healthy digestion. All forms of exercise, e.g., walking, will increase gut motility and result in a shorter transit time in the gut. Exercise directly after meals is particularly effective and daily exercise is crucial.

Dietary advice for patients with iron deficiency

Sometimes NETs can cause (minor) bleeding (e.g. in the presence of peptic ulcer due to a NET of the duodenum). Such bleeding can result in iron deficiency. In these cases it is important to ensure good dietary intake of iron.

A number of dietary factors influence iron absorption. Ascorbate (vitamin C) and citrate (in citrus fruits) increase iron absorption. Conversely, iron absorption is inhibited by plant phytates and tannins. Phytates are prominent in wheat and some other cereals, while tannins are prevalent in (non-herbal) teas.

The following information may help patients to find ways in which to increase their iron intake:

- The combination of orange juice and wholemeal bread increases uptake of inorganic iron and red meat in particular, but also poultry and fish are rich in iron as well
- Coffee and tea inhibit iron uptake and should be avoided in combination with meals containing iron

Dietary advice for good regulation of blood sugar

In the presence of NETs of the pancreas there may be overproduction of insulin, which again results in low blood sugar (hypoglycaemia). In the presence of overproduction of glucagon, blood sugar will be elevated (hyperglycaemia). These hormone disturbances can result in diabetes. Good regulation of glucose in the blood is important and can be achieved with proper diet, but it may be difficult for patients to manage. In this case the help of a nutritionist is recommended. Patients should be advised to pay attention to their meals and the spacing of meals. Guidelines include:

- Eating regularly-spaced meals at intervals of 3.5-4 hours
- Remembering the 'plate model' and eating 1/3 of each: Vegetables/salad + potato/rice/pasta + meat/fish/chicken
- Each meal should contain a good amount of soluble fibre
- Each meal should leave the patient feeling full
- Snacks should be eaten as necessary

If needed, anti-diabetic drugs must be used to maintain a normal glucose level in the blood. These drugs must be used under the guidance of the treating physician.

Dietary factors that can trigger symptoms

Specific dietary factors can trigger reactions that exacerbate symptoms. Reactions are dose-dependent and vary from person to person. 'Vasoactive amines' is a general term for amines found in foods that affect blood vessels. The amines can cause tumours to release substances that cause symptoms such as flushing or diarrhoea. Examples of foods with a high natural content of amines are matured cheese, alcohol, and smoked or salted fish or meat. Foods with a moderate content of amines are drinks containing caffeine, chocolate, and peanuts. In general the foods which most commonly exacerbate symptoms include:

- Large meals, irrespective of content
- Alcohol
- Fatty meals
- Coffee, and drinks containing caffeine
- Spicy foods
- Raw vegetables
- Foods rich in amines

It is only prior to and during collection of 24h urine testing 5-HIAA (5-hydroxyindoleacetic acid) that patients should avoid foods rich in serotonin (pineapple, banana, kiwi fruit, plums, tomatoes, walnuts, dates, and avocado). Serotonin in foods does not exacerbate symptoms, and does not increase tumour growth.

For 24h urine test for catecholamines or metanephrines, special attention must be paid to the fact that stress and vigorous exercise may affect the test results. Foods that can increase urinary catecholamines include coffee, tea, bananas, chocolate, cocoa, citrus fruits and vanilla, should be avoided on the day before the start of the test.

Alcohol

There are no general restrictions or requirements for abstinence from alcohol following the diagnosis of neuroendocrine cancer. However, flushing triggered by alcohol is a known problem. Sensible drinking has to be encouraged within healthy limits.

Summary of nutritional advice

Topic	Recommendations
Special nutritional problems	
Weight loss/reduced appetite	Snacks, energy supplements
Diarrhoea	• Drink to maintain fluid and electrolyte balance. Sour milk has a beneficial effect on the gut's bacterial flora • Soluble fibre can reduce transit time in the gut **Constipating food** • Foods to be avoided: prunes, figs, dried fruit, fresh fruit containing strong acids, fibre, coffee, alcohol, foods containing a lot of sugar, sugar alcohols, fatty foods in fat-intolerant patients, in the presence of secondary lactose intolerance: milk, dairy products, and goat's milk cheese • Add anti-diarrhoeal drugs, somatostatin analogues or pancreatic enzymes to decrease diarrhoea. Remember to obtain guidance from the treating physician before giving any drugs to the patient
Constipation	• Increase fluid intake • Limit intake of constipating food (rice, pasta, . . .) • Exercise: regular physical activity • Remember to obtain guidance from the treating physician before giving any drugs to the patient
Iron deficiency	Good dietary intake of iron
Good regulation of blood sugar	• Spacing of meals • Intake of food with high satiety index
Dietary factors possibly triggering symptoms (e.g. flushing)	**Try to avoid:** • Large meals, irrespective of content • Alcohol • Fatty meals • Coffee, and drinks containing caffeine • Spicy foods • Raw vegetables • Foods rich in amines
Alcohol	• No general restrictions • Sensible!

Fatigue

When fatigue occurs concomitantly with active development of an illness, or a specific treatment or medication, the focus will usually be on easing the symptoms by encouraging the patient to rest and save their energy. Such measures can be initiated by the patient, family/friends or healthcare providers. The most important measure is to save energy. Available energy should be directed towards activities that are important and meaningful. Less important activities can either be put aside, or be performed by others recruited to help. In this way, the patient's energy can be channeled towards the most important activities. Many individuals also find that they have more energy when they do something fun and interesting. By charting fluctuations in energy levels over the course of the day, implementation of important activities can be planned for times when the patient has the most energy.

In patients who have little mental energy, it is important to prioritise which information should be given and find a time to share this information while the patient is not fatigued. It is also important that healthcare professionals consider how routines and activities can be adapted to the individual's fluctuating energy levels. Some patients find that routine tasks require less energy than new tasks. Since the illness may mean changing established routines, patients may find new activities and routines disproportionately tiring. So, for example, fatigued patients may find it less tiring to go shopping in a familiar store than an unfamiliar one.

It is worth pointing out to a fatigued patient that careful planning can save energy, e.g. by planning activities so that you only need to make one trip to the same place to get the things you need. A common feature of such measures, however, is that by reducing the patient's level of activity in order to master living with fatigue, one also reduces their physical activity and capacity.

Some individuals also experience severe tiredness and fatigue after completing treatment for the disease. Research suggests that adapted and regular physical activity in this phase contributes to building up capacity and reducing symptoms associated with fatigue. Some use the 'rest-exercise-principle' in the training phase, where one consciously chooses between periods of exercise and controlled rest through the day. It is important that the level of activity is not increased too quickly beyond the capacity the patient has at the time. A key challenge to healthcare workers, therefore, is helping fatigue sufferers find a good balance between activity and rest.

Physical activity

A small number of studies have been performed studying the effect of physical activity in patients with NET. These studies show that cancer patients in general, and patients with NET, reduce their level of physical activity after being diagnosed with cancer. In the past patients treated for chronic illnesses (such as NET) were often advised to rest and reduce physical activity. However, excessive rest can result in the patient losing physical function, strength and mobility. There is evidence to show that regular physical activity improves well-being, functional ability, muscular strength, and may counteract side effects of treatments. These factors in combination, can help improve patients' quality of life. Even patients undergoing intensive treatment with chemotherapy can benefit from physical activity. However, in some clinical situations – for example when the patient has advanced disease – patients should avoid heavy physical exercise.

Possible benefits from regular physical activity

Possible benefits from physical activity include:

- Maintenance and improvement in physical function
- Improved balance; reduced risk of falls and fractures
- Reduced risk of developing heart disease
- Prevention of loss of bone density
- Improved circulation to legs and prevention of thrombus formation
- Improved ability to manage without assistance from others
- Improved self-esteem and coping
- Reduced anxiety and depression
- Reduced nausea
- Increased ability to maintain social network
- Reduced fatigue
- Improved ability to maintain stable weight
- Improved quality of life
- Stimulation of appetite to help intake of a good and varied diet

What factors should be taken into consideration?

The level of physical activity that a patient can undertake is affected by on-going treatment, time since previous treatment, medication, the patient's physical condition and factors such as low haemoglobin. It is known that physical activity increases muscular strength, improves general functional ability and the ability to tolerate drugs and reduces fatigue. Physical activity may also provide an improved feeling of self-control.

When deciding how much physical activity to recommend it is important to consult with the physician responsible for the treatment and a physiotherapist who can help tailor the exercise programme to the patient's individual needs. Where the patient has no special physical symptoms, 30-60 minutes of physical activity daily is recommended. Such activity should be consistent with the activity the patient undertook before his/her disease was diagnosed.

During treatment some special considerations should be adhered to:

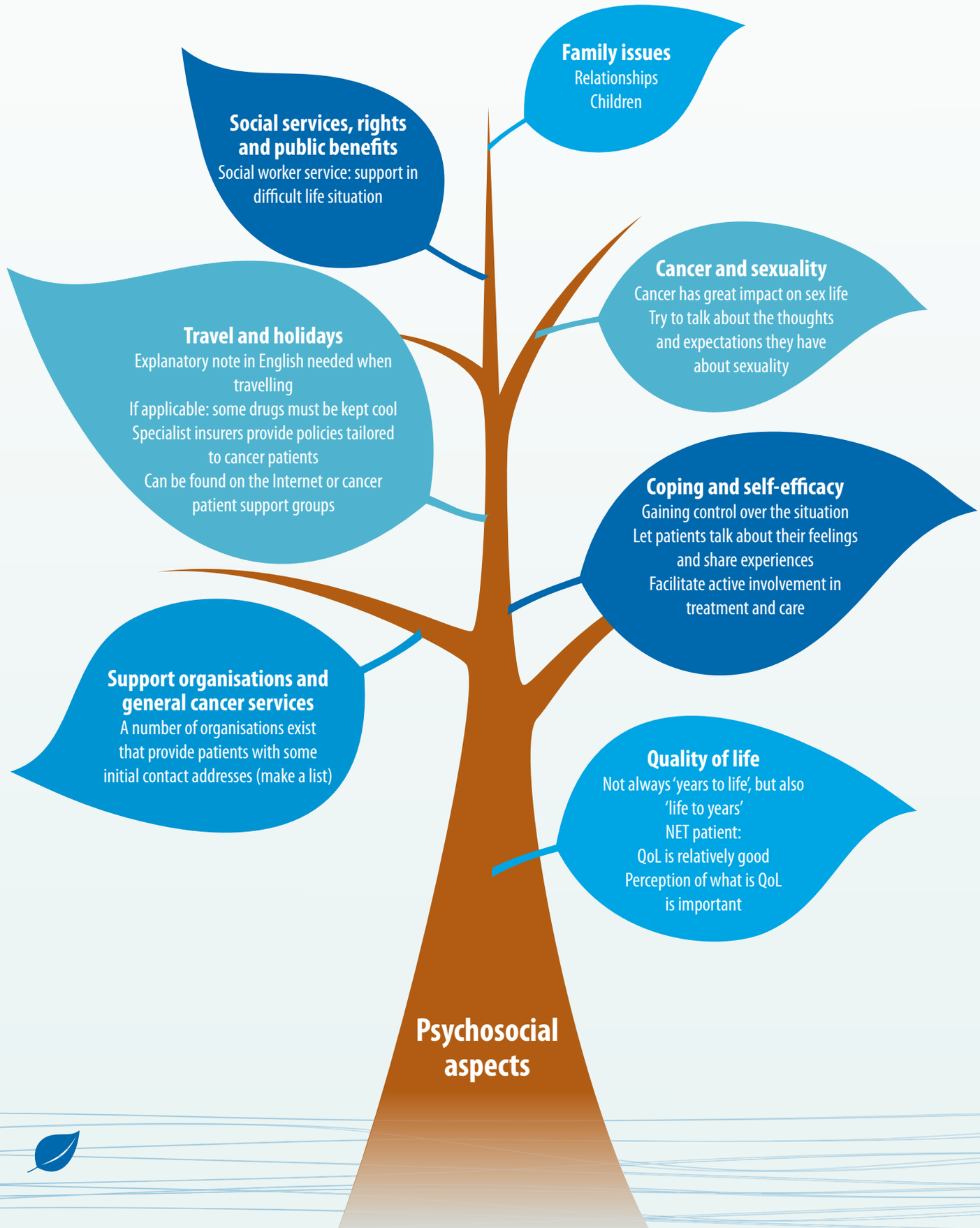
- Patients should undergo a general check-up before performing any new physical activity
- Patients should be advised to avoid:
  -High intensity activity if they have a low haemoglobin level (< 8.0 g/dl)
  -Activities involving increased risk of bacterial infection in cases of neutropenia (neutrophils $< 0.5 \times 10^9$/L)
  -Activities which may cause increased risk of bleeding, where platelets are $< 50 \times 10^9$/L (e.g. contact sports etc.)

If the patient has shortness of breath, the cause should be established and physical activity adjusted to a tolerable level. If the patient has bone pain from metastases, activities that can cause increased risk of fracture should be avoided (e.g. contact sports etc.).

Further Reading

Further Reading can be found at the end of Chapter 7

Chapter 7
Psychosocial aspects



Introduction

After reading this chapter you should have an understanding of the psychosocial aspects that you should take into consideration when caring for a patient with neuroendocrine tumours. It will give you an insight into how the disease impacts on the patient's quality of life and coping ability, and how deeper understanding can help patients exert some control over these aspects of life. Dealing with family or carers can be difficult in a situation when a patient has been newly diagnosed with cancer, and in this chapter we will give an overview of the role of the relative, and of how cancer can affect the relationships between patients, their relatives, and friends.

Quality of life

The term 'quality of life' (QoL) can have many different meanings, but most people associate it with positive experiences and well-being, including how a person views their existence. We know that when someone has a serious illness their view of life changes in terms of what they perceive as being important for a good quality of life. It is important in the treatment of various illnesses that the individual patient experiences of the situation are taken into consideration, so that it is not a matter of adding 'years to the life', but 'life to the years' in other words, life should be worth living.

When patients with a NET describe their quality of life, they normally describe it as relatively good. However, they do experience a number of physical problems that can be related to the illness (e.g. diarrhoea, flushing, breathing difficulties, and abdominal pain). Problems such as anxiety (e.g. anxiety about the diagnosis; that the illness will get worse, and anxiety about their family), depression, and irritation can also occur. Social restrictions due their illness and its treatment are also factors that have an impact on life quality. Although the initial diagnosis can be quite a shock, patients usually perceive their quality of life as improving sometime later, showing that, despite symptoms and problems related to their illness and its treatment, people with NETs can still experience a relatively good quality of life.

When patients discussed what they felt was important in terms of good quality of life, it was not primarily the physical aspects (e.g. being healthy or symptom free) that they talked about, but social aspects, such as being with their family and having the opportunity to do the things in life they wanted to do was what mattered. This shows that it is not always those areas that present the most problems to us that we perceive as being most important in terms of our quality of life; consequently, we can say that good quality of life can be achieved despite illness and treatment. This makes it important for the patient to talk with healthcare providers about their perceptions of their quality of life. Only then can they be given the help and support they need. Although nurses and physicians the patient encounters will have significant experience in caring for patients with a similar illness to their own, they cannot know how the illness and treatment will affect an individual patient's quality of life unless the person concerned talks about it.

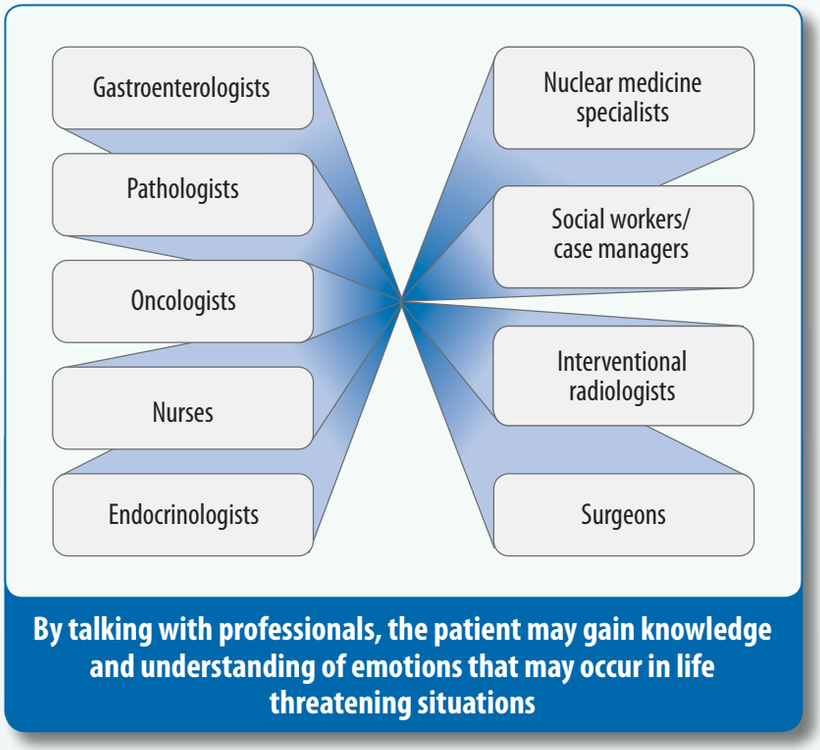
Coping and self-efficacy

Developing self-efficacy may be a useful coping strategy when confronted with a challenging life situation such as getting a diagnosis of a life-threatening disease. Self-efficacy is the individual's beliefs in his or her ability to succeed in a particular situation. Mastery experiences (previously successful performance of different tasks) provide the main basis in developing self-efficacy for one's coping strategies. People who are diagnosed with NETs develop self-efficacy differently. A number of factors influence how individuals respond to the various physical and psychological challenges faced during an illness trajectory. How the individual utilizes these experiences is related to age, knowledge, abilities, and attitudes.

Often patients with NETs manage to deal with problems such as diarrhoea or abdominal pain by utilizing mastering experience transferred to the situation they are currently in (i.e. what they did previously to successfully managing this problem). If patients are unable to create associations with mastery experiences they may learn by modelling other patients (i.e. observing other patients), or they may talk with a contact person at their hospital to ask for assistance.

Drawing on mastery experiences to deal with emotional challenges caused by the diagnosis of NET may be difficult since many patients find it difficult to talk about their own emotions. However, it is important that patients talk honestly with healthcare professionals about personal (with regard to this situation, personal is more specific than their own) emotions. By talking with professionals, the patient may gain knowledge and understanding of emotions that may occur in life threatening situations. In addition, they can understand why they react specifically to their illness. By understanding their own emotions and reactions, it may be easier to understand and deal with how people react to their illness.

Most people diagnosed with NET have limited knowledge about their illness. Consequently, they seek knowledge from different sources including patient associations. Contact with a patient association may provide them with the opportunity to meet other people in the same situation with whom they can share experiences. Sharing experiences is a useful way to disseminate knowledge and enable patients to understand the limits of their own knowledge base. Talking with others can also help patients deal with their emotions. Moreover, sharing similar stories and experiences may help patients feel less isolated and help the person feel that 'my situation is normal'. Continuing with social activities may be important for their overall satisfaction and well-being. Consequently, the individual is taking responsibility for his or her own life.



By talking with professionals, the patient may gain knowledge and understanding of emotions that may occur in life threatening situations

Taking responsibility for one's life is important at a time where everything may feel so uncertain and threatening. Giving patients the opportunity to participate actively in medical treatment may help patients take control over their lives. It is important to encourage patients to take their therapy as prescribed; therefore, they are playing an active part in preventing progression of their disease. In addition, offering the patients options to call the hospital to clarify uncertainties may be very reassuring.

Developing self-efficacy when confronted with a challenging life situation may help patients to cope through the difficult trajectory. Believing in oneself reflects the beliefs in one's own competence and skills, and increases the possibility of achieving one's goals. There are many ways in which patients can be helped to develop self-efficacy; therefore, health professionals need to employ different strategies (e.g. providing clear explanations and encouragement) to facilitate patients to develop these important skills.

Social services

Social workers work with people who need help and support in a difficult life situation. The title and role of a 'social worker' can differ amongst institutions across Europe and social services can be organized in a different way in different countries. When sickness occurs, life can change - both for the affected person and their family. Social workers can help by increasing the individual patient's skills and ability in mastering the changed life situation.

The social worker can help the patient and his/her relatives:

- By discussing the emotional responses the illness can trigger
- By providing information, advice, and guidance in relation to changes that may occur in work, school, and home situation
- By providing information, advice, and guidance about social security entitlements, financial matters, and various welfare schemes
- By establishing contact with (palliative) support services outside the hospital

The most common issues that concern patients and are likely to be raised with social workers include:

- How will the disease impact my family situation and on individual family members?
- What, and how, shall I tell my children about the situation?
- How will I manage to pay my mortgage while I am sick?
- Who will look after my children and clean the house while I'm sick?
- What about my job?
- How long will I be off sick?
- Will I be able to work again after the treatment?

If the patient wants to talk with the hospital social worker, you, as a nurse, or the doctor, can make such a referral. Hospital social workers are bound by patient confidentiality in the same way as are other healthcare workers.

Family issues

Relationships

Cancer is an illness which does not just affect the patient. The sufferers' families and the family's internal dynamic will also be affected. In difficult situations and crises, people go to their loved ones for help and support. Relatives and carers can preserve the patient's identity, and stimulate hope and a zest for life, in a way that is quite different to what the healthcare personnel can achieve.

Carers or supporters are not always family. Carers and supporters are those who have a close relationship with each other, and who have a mutual dependency and contact relationship. Patients must define who they consider their closest support, and the person whom they wish to receive information and to be included in discussions about their situation.

It is important to remember that relatives/carers also need help and support in the challenges they face. The health service may have expectations of relatives/carers as helpers, but may have little understanding of the challenges relatives face in this role.

Relationships between relatives and patients, which have previously been unproblematic, may face new challenges when serious, life-threatening illness ensues. The relative may also experience a crisis due to their own anxiety and concern for their sick loved one. This may be expressed as irritation about the hospital system, the patient, or other family members. In order for people to have the strength to support their relative, it is crucial that they feel 'visible' to healthcare personnel. Support and help for relatives/carers should be seen as an integral part of nursing care of the patient.

Patients with NETs can live for a long time with the disease, but it can be a roller coaster of a cancer journey, with various hurdles to overcome along the way. The relatives have no personal knowledge of how the disease actually feels on a physical level, and need help to understand the sufferer's reactions to the disease's symptoms, treatment, and what it is like to live with a serious diagnosis. In order to plan support for the cancer patient in the best possible way, the relatives must have an understanding of the disease and its potential course. They want to know what form of cancer the patient has, what investigations are required, what medical treatment is planned and what symptoms and problems the patient may have as a result of the disease and its treatment.

It is important that healthcare personnel include the relatives when providing information about the progression of the disease, important investigations or new treatment. Relatives should also be included in multi-disciplinary case conferences involving the patient and the medical and nursing staff. However, it is important to understand that information about the patient, pursuant to the Act on Patient Rights, may only be given with the patient's consent. It is also important to understand that not all patients have close relatives. These people may be in a difficult and lonely situation, and need extra support and attention from healthcare personnel.

Children

Many children experience situations where their mother, father, a sibling or grandparent, or other person they are close to, has cancer. The parents are the most important persons in a child's life, and children and parents share a mutually deep relationship.

It is important that healthcare personnel include children and young people in conversations about illness affecting a parent or other close family member. Despite their youth, children and young people still need to feel that they are important in the situation and children's needs for information are often underestimated. Children are good observers of their surroundings; they make their own interpretations of change. When children do not receive information, fantasy takes over and this can be more frightening than the reality. Therefore, it is important to be open and to give information – but the information must be adapted to the child's developmental stage. It is important to understand that the child often has episodes of rapidly changing emotions; one moment the child may be angry and sad, only to play happily the next. This is a completely normal reaction.

As a starting point, the parents are probably the best people to give the child information. As a nurse, you can talk with the parents about the importance of informing the child, and that the child should be allowed to participate in discussions about the mother or father's illness. In this way the child will have the opportunity to understand events, and to have an outlet for fears and unpleasant thoughts. Children should be encouraged to visit the hospital, and the hospital should make the child feel welcome. Through play, drawing, and stories, the child can express his/her thoughts and feelings, and the nurse can participate through active listening, or by providing the child with everything from information on day-to-day experiences to the situation the family are experiencing. Although it is recommended that children and young people visit, they must not feel forced to do something they do not want to. Many children need time to adjust to changes in their lives, and they should be given it.

Adolescents and young adults are particularly vulnerable when one of their parents, or another family member, is diagnosed with cancer. They are in the process of breaking free from the parents, and their focus is outside the home. When one of the parents becomes sick, changes occur in the family dynamic, and the young person is drawn back into the home. The young person may be given practical tasks such as housecleaning and care of younger siblings. Here it is important that the adults make sure that the young person is not overloaded.

Nurses can help the parents see the importance of informing the school, kindergarten, health centre, students and friends of the child – or teenager's home situation. This is important in terms of the child and the young person's mastering, i.e. that those around them know about their home situation.

There are organisations that aim specifically to aid children and young people in this situation. Patient groups may be able to provide contact information and there are some mentioned in the list at the end of this booklet.

Cancer and sexuality

Living with cancer can impact on a patient's sex life. There can be several causes: the disease itself; the challenges of learning to live with cancer; the consequences of treatment; and treatment-related symptoms, such as fatigue.

During a period of sickness and treatment, sex is often something that the individual is neither interested in, nor has energy for. This is completely normal. However, intimacy is still important during this period. Those who live with a partner should know how to care for their relationship in other ways. Many patients find it difficult to discuss their concerns about sex with the doctors and nurses, so it might be worth saying to patients something along the lines: 'If you want to have sex, there is of course nothing to stop you. It's not dangerous for your partner if you have sex when you are sick; your partner cannot catch cancer from you. Don't be embarrassed - just ask your doctor if there are any special precautions applicable to you, your disease or your treatment.'

It may also be helpful to tell patients that they and their partners should try to talk about the thoughts and expectations they have about sexuality. Point out that it is easy to misunderstand and misinterpret each other's comments and actions and that many problems can be avoided by talking with each other about thoughts relating to sexuality and intimacy. A known problem is that the partner is afraid of getting close to the sick person for fear of 'forcing themselves' on them, while the sick person goes round feeling hurt because the partner is keeping his/her distance. Encourage couples to talk to each other about their wants and needs, and about things they find difficult. Although your patient has had treatment which affects his or her body generally, and may – thereby – also affect his or her sexual function, it is important to remember that sexuality is in the head, not in a part of the body.

Travel/holidays

If the patient is planning a trip abroad, it is important that the physician writes an explanatory note in English detailing the patient's disease and any medication being used. This information is important if the patient should become sick while travelling. It will also prevent the patient from having any problems with Customs if they have syringes and/or other equipment with them.

The patient must be made aware that some drugs must be kept cool, i.e. they will require a refrigerator or similar. Interferon, however, may be stored for a total of 48 hours (2 days) at up to 25°C over a 4-week period. Short-acting somatostatin analogues may be stored for up to 2 weeks at room temperature (not above 30 °C). The long-acting form may be stored at room temperature on the day of injection.

Travel insurance

People with cancer may find that some travel insurers are reluctant to insure them or will only do so if they charge a very high premium. However, there are now specialist insurers who take a more balanced and realistic view of the likelihood of a cancer patient being ill while on holiday and so provide policies tailored to cancer patients and charge more sensible premiums. You might like to suggest to your patients who plan to have a holiday that they should do a little research to locate a suitable insurance provider. Many can be found on the Internet or cancer patient support groups can be helpful.

Support organisations and general cancer services

A number of organisations exist to help with every aspect of living with cancer. Individuals will vary in the extent to which they embrace external help and support. Nevertheless it is worth mentioning to patients that these organisations exist and, if possible, providing them with some initial contact addresses to start. If appropriate you could prepare a list of patient organisations and other support groups in your local area.

There are a number of NET patient groups in different European countries including:

Bulgaria	APOZ – Association of Cancer Patients and Friends (http://oncobg.info/)
France	Association des Patients porteurs de Tumeurs Endocrines Diverses (http://apted.fr)
Germany	Bundesorganisation Selbsthilfe NeuroEndokrine Tumoren (www.netzwerk-net.de)
The Netherlands	Stichting NET-groep (www.net-kanker.nl)
Norway	CarciNor (www.carcinor.no)
Poland	Stowarzyszenie Pacjentow I Osob Wspierajacych Chroych na Guzy Neuroendokrynne (www.rakowiak.pl)
Sweden	CARPA (www.carpapatient.se)
United Kingdom	NET Patient Foundation (www.netpatientfoundation.com)

Further information on NETs

More information on NETs can be found at the following sites:

European Neuroendocrine Tumor Society (www.enets.org)

Worldwide NET Cancer Awareness Day (http://netcancerday.org/)

Further reading

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Chapter 8
Conclusion

It is hoped that this guide has been helpful to you, and that you have gained new knowledge about NETs and what it is like to live with this condition. The guide provides a comprehensive reference where you will easily be able to find information about investigations, treatments and follow up of NETs, as well as different aspects of nursing care. It is hoped that this information will help you in your encounters with NET patients and their relatives so that they feel safe and cared for in this difficult life situation. Good luck with your future work!

In closing, we would like to include a poem written by Bjørg Elvira Røed.

LIFE

I went so bravely out in the world,
with both joy and reason.
But I met resistance on my journey,
as I knew I might.

Often I stumbled,
in holes and tussocks along the way:
But my legs took me there,
and I thought everything was fine again.

I so want to be old,
with children and grandchildren and Kjell.
But it won't be me that decides
when my final curtain will fall.

For life can end
suddenly and without warning.
But a ripe old age,
is what I'm hoping for.

Bjørg Elvira Røed