Neuroendocrine Tumours

A Guide for Patients

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**Introduction**

This booklet has been developed to provide some basic and easy to understand information about neuroendocrine tumours (NETs) for patients and their families. If there is any information in the guide that you do not understand please feel free to discuss it with your specialist nurse or doctor.

Further or more detailed information about your type of neuroendocrine cancer may also be available so please do not hesitate to ask for this as well. We encourage you to discuss any information you find on the internet with your healthcare team.

We hope this guide will be a helpful and informative resource throughout the coming weeks, months and years.

This is a general guide and all information provided can also be found on the following website:

[www.network.ac.nz](http://www.network.ac.nz) (Siobhan to check this still applies)

**What is Cancer?**

The body is made up of many different types of cells. Normally these cells divide and copy themselves in a controlled manner. In cancer one type of cell starts to divide and grow uncontrollably. These uncontrolled cells form into lumps (also called masses or tumours) that invade nearby parts of the body or can spread to more distant parts of the body through the lymphatic and blood systems. Not all tumours are cancerous, the non-cancerous or benign tumours do not spread throughout the body.

**Terminology**

Neuroendocrine Cancer has over the years been referred to by many different names.

In 1907, they were named ‘carcinoid’ (meaning ‘cancer-like’) as they seemed to grow slowly and were therefore not thought to be truly cancerous. This was recognized as incorrect a few years later. The term ‘carcinoid’ is being phased out in medical literature, as we know that all neuroendocrine cancers can be malignant. However the term carcinoid is still used when referring to Lung NETs.

Technically we should now call this family of cancers “Neuroendocrine Neoplasms “(NENs) according to experts at the WHO (2010). There are three groups of NENs:

* Slow growing Neuroendocrine Tumours (NETG1)
* Intermediate growing Neuroendocrine Tumours (NETG2)
* Faster growing Neuroendocrine Carcinomas (NECs; which some people call NETG3)

It can be quite confusing, however most people use the term “NET’s” to mean the whole family of neuroendocrine cancers, and this is how we use the term in this booklet.

Other names for NETs that you might hear include islet cell tumours, large cell carcinoma, small cell carcinoma, mixed adenocarcinoma and neuroendocrine carcinoma, (MANEC).

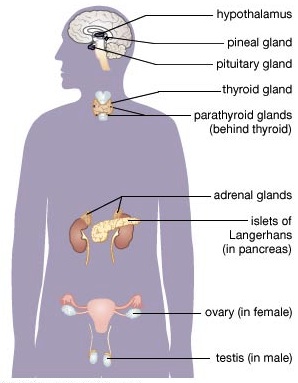
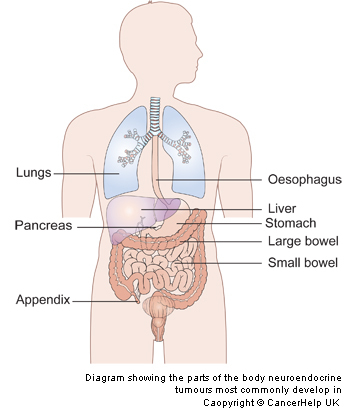
**What are neuroendocrine tumours?**

NETs arise from neuroendocrine cells. Neuroendocrine cells are highly specialized cells that normally release hormones and peptides into the bloodstream and control different organs in the body. They are often connected and controlled by very fine nerves.

In the same way that other cancers develop, NETs occur when a single neuroendocrine cell loses control of the way it grows, and forms a lump called a neuroendocrine tumour. Sometimes this tumour is malignant and invades the surrounding organ, and sometimes it spreads around the body. However sometimes it will not spread.

**Where do neuroendocrine tumours occur?**

Neuroendocrine cells can be found in many areas of the body, and therefore neuroendocrine tumours can also be found in many areas of the body.



Neuroendocrine cells are found in the lining cells of the lungs and the gastrointestinal tract (GI) and in endocrine glands such as the thyroid or adrenals. When neuroendocrine cells are working well, they release a number of hormones, which control different functions in the body. For example, in the lungs they control the air and blood flow, and in the GI tract they control things like the movement of food through the gut, stomach acid production and blood sugar levels. Each neuroendocrine cell releases one kind of hormone, for example pancreatic neuroendocrine cells release insulin or GI cells release serotonin. When a neuroendocrine cell becomes a neuroendocrine tumour, they might continue to release one or more hormones.

**Different types of NETs**

There are many different types of NETs. They can start in different places, have different symptoms, and all look a little different under a microscope.

Doctors like to describe NETs according to the areas they are found, as this helps choose the right treatment. The place in the body where the NET appears first is called the “Primary Site”. If the NET spreads to other parts of the body these are often called “secondary” tumours or metastases. For example, the liver is a common place where metastases are found.

\*Gastrointestinal NETs can start in:

-stomach

-duodenum

-pancreas

-appendix

-small bowel

-large bowel

-rectum

\*NETs in the pancreas and duodenum have further subtypes that are named after the hormone that the tumour secretes:

-Gastrinoma

-VIPoma

-Insulinoma

-Glucagonoma

-Somatostatinoma

\* NETs can also start in Endocrine Organs such as

- Adrenal Glands (called a Phaeochromocytoma)

- Special nerves called sympathetic nerves (this NET is called a Paraganglioma)

- Thyroid Glands (one type of thyroid cancer called Medullary Thyroid Carcinoma is a type of neuroendocrine tumour)

\* Lung and the airways (called a bronchus)

\*Thymus

\*Skin (one type of skin cancer called Merkel Cell carcinoma is a neuroendocrine tumour)

Other rarer sites may include the ovaries and testes.

**What causes NETs?**

It is not fully understood what causes NETs. It is unclear what triggers the process of abnormal cell growth of neuroendocrine cells.

Some families have a higher than normal rate of certain type of cancer due to inheriting an abnormal gene. It is important to know the majority of NETs are NOT hereditary. The risk factors for NETs are poorly understood and most NETs occur without any known cause.

**What is known about NETs?**

NETs can range from being very slow growing cancers in some people, through to fast growing cancers in other people. Most NETs grow slowly, and some people can have one or more tumours for years, often without symptoms, before they are diagnosed. Slow growing NETs are sometimes discovered at the time of surgery or during investigation for other problems. At first it is can be hard for your doctor to know whether you have a slow or fast growing NET.

When you are diagnosed with any type of NET your specialist may review a biopsy sample (a small piece taken from the tumour) and give your tumour a 'proliferative index'. This is a measure of the number of cells in the tumour that are dividing (proliferating) at any one time. The most common proliferative index is called Ki-67. A Ki-67 of less than 2% means that the tumour is very slow growing. The higher the number, the faster the growth.

**Different NETs affect different people in different ways in terms of how the tumour grows, the symptoms produced, whether or not they spread and how they spread.**

**Diagnosing NETs**

NETs are difficult to diagnose. The onset of symptoms takes an average of 3 to 5 years, and even then symptoms are often non-specific and vague.

International experience shows that the average time from first symptoms to diagnosis is approximately 6 to 7 years.

Just like all cancers an early diagnosis can potentially mean a better outcome, which is called prognosis.

**Testing**

Like all cancer patients, if you have a NET you can expect to face numerous tests and scans that will provide your doctor with information about the disease, its spread and the rate of growth. Some of the tests you might undergo are the same as any cancer and some are specific for understanding NETs.

**Biopsy**

This involves taking a piece of tissue from the suspect tumour and having it analysed in the laboratory by a specialist called a pathologist.

**Blood tests**

Blood will also be collected for a range of tests.

You may be asked to have a fasting blood test called Chromogranin A which is often elevated in people with NETs.

Doctors may also look for other markers of NETs, depending on where your NET starts, and what symptoms you have. This is because ***some*** NETs keep making the normal hormones (for example gastrin, insulin, glucagon, adrenalin, noradrenaline or dopamine), but in vast amounts and this can cause specific problems.

Blood tests will also check how well your kidney and liver are functioning.

Some other tests may be requested if your doctor is concerned about whether your NET could run in your family, at which point you can ask to speak to a genetic counsellor.

**Urine tests**

When some hormones produced by NETs are broken down inside the body, the waste products are excreted in the urine as a substance called 5-hydroxyindoleacetic acid (5HIAA). Serotonin is produced by some NETs, and this is broken down to 5-HIAA, and so higher than normal levels of 5-HIAA can be a sign of a NET. You may be asked to do collect your urine over a 24 hour period so that your 5HIAA levels can be checked.

For 3-7 days prior to the test you will be asked to avoid certain foods prior to and during the test including: chocolate, olives, bananas, pineapple and its juice, all tomato products, plums, aubergine/eggplant, avocado, kiwi fruit, grapefruit, walnuts, brazil nuts, cashew nuts, tea, coffee and alcohol. You will also be asked to avoid certain cough, cold and flu remedies.

This is because they contain substances that might artificially raise 5HIAA levels and give a false test result.

**SCANS**

There are a number of scans you may be asked to have. These will determine the exact size and position of the tumour or metastases.

Scans for ALL Cancers include:

**Endoscopy**

This is a way of examining your GI tract using a flexible fibre optic tube called an endoscope. The tube can be inserted down the back of the throat and down into the stomach, a procedure called a gastroscopy. Or it can be inserted into the colon via the anus (back passage), a procedure known as a colonoscopy. You will be offered sedation before either of the procedures, and the doctor may remove tiny biopsy samples of any suspicious areas for analysis.

**CT scan**

A computerised tomography (CT) scan provides a two dimensional picture of the inside of the body. It can be used to determine the position and size of NETs, and regular scans are useful to find out the rate of tumour growth.

**MRI scan**

This 'whole body' magnetic resonance imaging (MRI) scan can help reveal where the tumours are positioned. It uses magnetism rather than X-rays to take pictures of the inside of the body.

**FDG PET scan**

This type of scan picks up show spots of very high cell growth. This type of scan is therefore not very useful if your NET is slow growing, but might be useful in fast growing tumours.

**Bone scan**

A bone scan looks for abnormalities in bones that might be caused by cancer metastases. You will be given a small injection of radioactive tracer which over time will be absorbed into your skeleton. It takes about 3 hours for this to occur. Pictures of your skeleton are then taken using a special camera that detects the location of the tracer (called a gamma camera), and you will be asked to return for a second set of pictures 3 hours later. For this second set of pictures you will again be asked to lie or sit in front of the gamma camera. The scan will take approximately 30-45 minutes. These are not commonly used for NETs.

**Ultrasound scan**

Ultrasound imaging, also called ultrasound scanning or sonography, uses high-frequency sound waves to produce pictures of the inside of the body. Ultrasound exams do not use ionizing radiation (as used in x-rays). Because ultrasound images are captured in real-time, they can show the structure and movement of the body's internal organs, as well as blood flowing through blood vessels.

Specialised Scans for NETs include:

**Octreotide scan (or Tektrotyd Scan)**

This is a useful diagnostic test that can help reveal the site of NET tumours. Some NETs have special receptors on their cell surfaces called somatostatin receptors. Octreotide can stick to these receptors. When octreotide is combined with a mildly radioactive agent and then injected via a vein in the arm, it sticks to somatostatin receptors on the tumour surface and the tumours light up on the screen to show the location(s) of the NETs.

**Ga68 Octreotate PET Scan**

This type of scan is similar to an octreoscan, but uses a different kind of camera. The pictures can often give a more accurate picture of where the NET is located. At the moment this type of scan can only be found in Australia.

**MIBG scan**

This is a similar type of scan to the OctreoScan, except a different substance is connected to the radioactive tracer. An MIBG scan will show up those tumours which have receptors for meta iodo benzyl guanidine (MIBG) on the surface.

**Further testing**

There are further tests that you may need to have, for example:

-Endoscopic Ultrasound

-Barium Enema

-Wireless capsule

-Bronchoscopy for lung NETs

If required your specialist nurse or doctor can provide you with more information about these.

**Treatments you may be offered**

**Patients should ideally be treated within a specialist multidisciplinary team (MDT). Each patient will have an individualised treatment plan: there are a number of options available, depending on the type and location of your NET, and your general well-being.**

**Surgery**

Surgery is usually the first choice of treatment when it is possible to remove the tumour completely. This is the case when the tumour is contained in one area, (called localised). If the tumour has already spread to other parts of the body (called metastatic), the pros and cons of surgery have to be considered carefully.

**Curative surgery**

This is when the cancer has not spread outside the organ or area where it first started. If the tumour can be removed whole and intact with a surrounding margin of normal healthy tissue, then the surgery might be curative and no other treatment may be necessary. A follow-up plan will need to be put into place after surgery.

**Palliative surgery**

If a NET has already spread, or become too large to remove completely, then surgery may be considered in specific situations. Surgery may be performed if the NET is causing symptoms by pressing on other organs, or by releasing hormones. In this instance surgery aims to reduce the symptoms by removing a large chunk of the tumour (called ‘debulking’), or bypassing the part of the disease that is causing the problems.

**Pre-emptive surgery**

This occurs when we can see that an area of tumour is critically placed close to an important structure that might become blocked as the tumour grows, such as a blood vessel or the main bile duct, or the bowel. Even though this will not cure the disease, we can prevent immediate problems by removing tumours from key areas, before the vital structure has been damaged or blocked.

**Cardiac surgery**

This involves valve replacement and may be required for patients with

carcinoid heart disease.

**Most planned surgery for NETs should be done after the surgeon has been able to talk to a team including oncologists, gastroenterologists, nurses, radiologists and doctors all of whom have particular expertise in managing NET cancers. These are rare and complex tumours so it is best to have a dedicated team of experts jointly involved in helping to decide which treatment is best for each patient.**

**TREATMENTS THAT TARGET NETs THROUGHOUT THE BODY**

**Somatostatin Analogues**

Somatostatin analogues are synthetic versions of somatostatin, a naturally occurring hormone produced in the brain and digestive tract that acts like an ‘off’ switch for some of the normal processes in the gut.

Injections of these analogues can stop the overproduction of hormones that cause symptoms such as flushing and diarrhoea.

Injections are also used to help slow tumour growth in some slower growing NETs.

**Chemotherapy**

Many chemotherapy regimens involve intravenous drugs (this means given through a drip), however there are now also oral chemotherapy drugs and your oncologist will discuss the most appropriate option with you.

The proliferative index of the tumour (the Ki-67 mentioned earlier) may help the oncologist decide the type of treatment you receive.

Chemotherapy is not useful for slow growing NETs. Intermediate growing NETs are usually treated with a combination of drugs called Streptozocin and doxorubicin (or 5FU), or another combination called Temozolomide and Capecitabine. Fast growing NETs are often treated with Carboplatin and Etoposide.

You may be asked to be involved with clinical trials that look into different combinations of chemotherapy agents that are most appropriate for different types of NETs.

Chemotherapy is most commonly used as a palliative option for patients with metastatic NETs. The term palliative is used when a cancer cannot be cured, but the aim of the treatment is to slow the cancer down as much as possible.

**Molecular Targeted Therapies**

Drugs such as Sunitinib and Everolimus are used for Pancreatic NETs.

We do not have funding for these in New Zealand.

**Interferon**

This is a naturally occurring substance that is produced by the body’s immune system. Taking extra injections of interferon activates the body’s immune system and is used to treat some patients with NETs. In some patients it is given on its own, but more often it is given as a combination therapy with a somatostatin analogue. This is only used in specific situations because of the side effects that some people experience.

**Peptide Receptor Radionuclide Therapy PRRT**

These treatments work in a similar way to an octreoscan, except that a higher dose of radioactive tracer is attached to the octreotide. This high dose is enough to kill the tumour cell that the octreotide binds to. To decide whether this therapy is suitable, you will be asked to take an Octreoscan (or a Ga68-Octreotate PET scan in Australia) as described in the diagnosis section. The results of these scans will indicate whether or not your NET has enough receptors present on tumour cells, and whether this sort of therapy would be an option. This treatment is not available in NZ and if you are a suitable candidate you will be referred to a centre in Australia by your Oncologist. At the moment funding is not available for this treatment.

**TREATMENTS THAT TARGET LIVER METASTASES**

For people with NETs that are mostly sitting in the liver, it makes sense to target the liver directly. The two main ways of doing this are embolization (blocking the blood supply to parts of the liver) or ablation (directly targeting individual tumour spots in the liver).

**Embolisation**

1) Hepatic artery embolisation (HAE). In this procedure, a catheter is placed in a blood vessel in the groin, and then threaded up to the hepatic artery that supplies blood to the tumours in the liver. Tiny particles (or microspheres) are injected through the catheter into the artery. These particles block the blood supply to the tumour, which can cause the tumour to shrink or even die. This procedure would be done by a specialist called an interventional radiologist. The patient would be sedated for the treatment.

2) Hepatic Artery Chemoembolisation (HACE).

This treatment is the same as HAE, but the microspheres are coated with chemotherapy.

3) Selective Internal Radiation Therapy (SIRT)

This treatment is the same as HAE, but the microspheres are coated with radiation.

**Ablation**

This is used when a patient has relatively few secondary tumours (metastases). A needle is inserted into the centre of each spot of tumour, and either radiowaves, microwaves or freezing cold are conducted into the tumour so that it dies.

**Multidisciplinary Care**

The care of NET cancers can be complex, and for the patient the journey can encompass a whole host of emotions, as well as a wide range of investigations, treatments and healthcare professionals.

The very fact that there is often not just one treatment option at diagnosis and throughout the patient journey, means that there has to be a collaboration among all key healthcare professional groups, who are making clinical decisions for individual patients.

This collaboration has been termed an MDT (multidisciplinary team), and the place they meet is called a multidisciplinary meeting (MDM). This is a formula that is now being used across the world in the care of cancer patients.

An MDT will usually be formed by a particular specialist with expertise and interest in NETs. This specialist is commonly an endocrinologist, oncologist or surgeon.

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

\* Medical Oncologist

\* Surgeon

\* Endocrinologist

\* Radiology staff

\* Radiation Oncologist

\* Nuclear medicine physician

\* Dietitian

\* Nurse Specialist

\* Palliative Care Team

\* Pain Team

\* General Practitioner/Practice Nurse

\* Counselling Staff

\* Various Technicians

\* Clinic Staff

\* Hospital Staff

\* Hospice Team

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

**Communicating with the Health Care Team**

Being diagnosed with cancer can be a confusing and frightening time for you and your loved ones. Although your healthcare team will do their best to support you, medical appointments can be stressful and it is worthwhile to be reminded of ways to get the most out of each appointment.

A few things to keep in mind:

• The most important part of your healthcare team is YOU

• YOU know more about YOU than anyone else does

• Your doctor can help you more if you are an active partner in your treatment

Tips:

- Bring a trusted friend or family member with you to the appointment if you can. If you are feeling anxious, you may not hear everything that’s said, or ask all the questions you wanted to. It helps to have additional ears there to listen, and your guest may help to make sure your concerns are brought up.

- Try taking notes on how you are feeling, and take these notes into your appointments.

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

- Deciding on a treatment strategy can be difficult so encouraging your doctor to seek opinions from other specialists can be valuable. Physicians are usually very open to this because they appreciate the fact that making an effective treatment choice can be very challenging.

- If getting a second opinion through your specialist is not possible, you can get a referral from any of your physicians, including your general practitioner. Another option is to request that your case be discussed at an MDT.

-You have the right to know as much about your own prognosis as you wish and you have the right to know the overall treatment strategy, including what options are available to you if initial treatments do not work to stabilise your disease.

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

**Living with a NET:- Diet, Exercise and Psychological Support**

**Diet**

Dietary advice will vary from patient to patient since patients with NETs have different symptoms. One general piece of advice is that all patients are encouraged to eat a varied and proper diet so that energy and nutritional requirements are met and weight is kept stable. When problems such as loss of appetite or diarrhoea occur this can be difficult. Sometimes talking with a dietician can be very helpful, which your specialist doctor or nurse can arrange for you.

**Exercise**

Regular physical activity improves well-being, functional ability, muscular strength, and may counteract side effects of treatment. These factors in combination improve a patients’ quality of life.

**Psychosocial Support**

Being diagnosed with a cancer can change your view of life. Being diagnosed with a cancer can be a challenging life situation. For people with NETs that produce extra hormones, this can provide additional challenges as these can affect normal bodily functions. Having an understanding of your disease and its effects on your body can be helpful in developing coping strategies.

There are support people around to help you understand your disease. Sometimes it is helpful to talk with a counselor or psychologist to help you develop strategies for coping with your particular concerns. **USEFUL CONTACT NUMBERS**

Hospital:...................................................................................

GP:..........................................................................................

Nurse Specialist:.....................................................................

Cancer Society: …..................................................................

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**FURTHER SUPPORT AND SOURCES FOR INFORMATION**

It is important to understand as much as possible about your NET cancer. Below is a list of websites or contacts that you may find useful.

**Unicorn Foundation NZ**

<http://unicornfoundation.org.nz/>

This is a New Zealand based organisation that aims to provide support and accurate information to patients, families and medical professionals involved in NET cancer. Unicorn Foundation NZ (UFNZ) brings patients together either in person or online to provide an opportunity for support from people who are facing similar challenges.

**NETwork!**

[www.network.ac.nz](http://www.network.ac.nz)

This is a website run by the research team in Auckland who are trying to understand NETs and improve treatment. Some parts of the website are for patients, some parts for doctors, and some parts for members of the research team.

**NET Patient Foundation UK**

[www.netpatientfoundation.org](http://www.netpatientfoundation.org)

This is a UK based website with extensive information and multiple in depth information leaflets on specific NET types.

**The NET Alliance**

<http://www.thenetalliance.com/>

This is an American website with extensive information for patients and their caregivers. This is from Novartis Oncology pharmaceutical company

**Glossary**

Benign- non-cancerous (doesn’t invade or spread); only dangerous if it presses on important parts of the body, or blocks important tubes.

Biochemical markers- any hormone, enzyme, antibody, or other substance can be found in the urine, blood, or other body fluids or tissues that may serve as a sign of a disease.

Blood System- Blood vessels that are interconnected to provide the body with oxygen breathed in by the lungs, and to remove waste such as carbon dioxide.

Carcinoid- “cancer-Like”; from the German word “Karzinoide”. Carcinoid is the original name for NETs. Used less and less because of confusion in it’s meaning. Some people use it to mean the family of NETs, others only for slow growing NETs, and others still only for small intestinal NETs.

Cells- the basic structural and functional unit of living organisms; building blocks of our organs and all other tissue in the body.

Diagnosis- finding the nature or cause of a disease. Accurate diagnosis allows treatment to be chosen correctly

Fibrosis- development of white, hard fibrous tissue (often equivalent to ‘scar tissue’).

Functional NET- NETs that secrete enough hormones to cause a person to have symptoms directly related to the hormone. These are the minority of NETs. A common type of functioning NET produces a hormone called “serotonin” which causes ‘carcinoid syndrome’. Too much serotonin can cause diarrhoea, flushing, wheezing and damage to the valves in the heart.

Gastrointestinal- often used as a synonym of the digestive tract. Includes the oesohagus, stomach, small intestine, large intestine and rectum. Some people also include the pancreas in this term.

Glucagon- A hormone secreted by special neuroendocrine cells in the pancreas called alpha cells, that cause a rise in blood sugar levels by stimulating the breakdown of glycogen (a storage sugar) in the liver.

Hormone- a chemical substance produced in the body which controls the activity of certain cells or a certain organ or organs. Bigger than a peptide.

Insulin- a hormone formed in the pancreas. It helps in controlling sugar levels in the body.

Intravenous- inside a vein.

Localised- confined or restricted to a particular location.

Lymphatic system- an extensive network of capillary vessels that transport the interstitial fluid of the body (the watery part of blood) back to the blood circulation.

Malignant- invading or spreading.

Metastatic- Travel by cancer cells from an original site to one or more sites elsewhere in the body, usually by way of the blood vessels or lymphatics.

Non functional NET- has no symptoms caused by hormone production by a NET. NETs can still cause symptoms like pain or weight loss, but this is still a non-functioning NET if the symptom is not directly resulting from hormone production by the tumour cells.

Palliative- non curative.

Peptide- a chemical substance produced in the body which controls the activity of certain cells or a certain organ or organs . Smaller than a hormone.

Primary- Site of Origin. Where the cancer started.

Prognosis- A prediction about the future course and outcome of a disease.

Secondary- A spot or growth which has been derived from a primary tumour.

Serotonin- a hormone (actually a very small molecule called an amine) and neurotransmitter found in many tissues which has many physiologic properties including slowing of secretion in the stomach, stimulation of smooth muscles, and control of the size of blood vessels that feed the gut.

Tissue- a collection of cells which together perform certain special functions.