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2022

# Neuroendocrine Tumors

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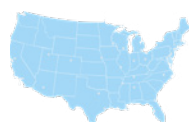


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## Neuroendocrine basics

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A neuroendocrine tumor (NET) is a rare type of tumor that can develop anywhere in the body. A NET may grow slowly or quickly and spread to other parts of the body. This chapter reviews the basics of how neuroendocrine tumors form and how they are diagnosed.

## Endocrine system

Your endocrine system is a complex network of glands and organs. It is often referred to as the body's messenger system because it uses hormones to regulate your metabolism, energy level, growth and development, and mood.

The endocrine system is made up of the following:

- **Hypothalamus** – located at the base of the brain. It secretes hormones to control water balance, sleep, temperature, appetite, and blood pressure.
- **Pineal gland** – located in the middle of the brain. The pineal gland produces melatonin. Melatonin is a hormone that helps the body know when it is time to sleep.
- **Pituitary** – located below the brain. Often referred to as the body's master gland, this pea-sized gland controls the activity of multiple hormone-secreting glands.
- **Thyroid and parathyroid** – located in the front of the neck. The thyroid maintains your metabolism. The parathyroid helps your body with calcium regulation.

- **Thymus** – located in the upper part of the chest. The thymus makes white blood cells (WBCs) that fight infections.
- **Adrenal gland** – located on top of each kidney. The adrenal glands help to regulate blood pressure, metabolism, and aspects of sexual development and function.
- **Pancreas** – located behind the stomach. The pancreas helps with hormone production and digestion.
- **Ovary** – located on both sides of the uterus, below the fallopian tubes. The ovaries produce hormones (estrogen and progesterone) and contain the egg cells necessary for reproduction.
- **Testis** – located in a pouch that hangs outside the body. The testes produce testosterone and sperm. Sperm is also necessary for reproduction.

## Neuroendocrine system

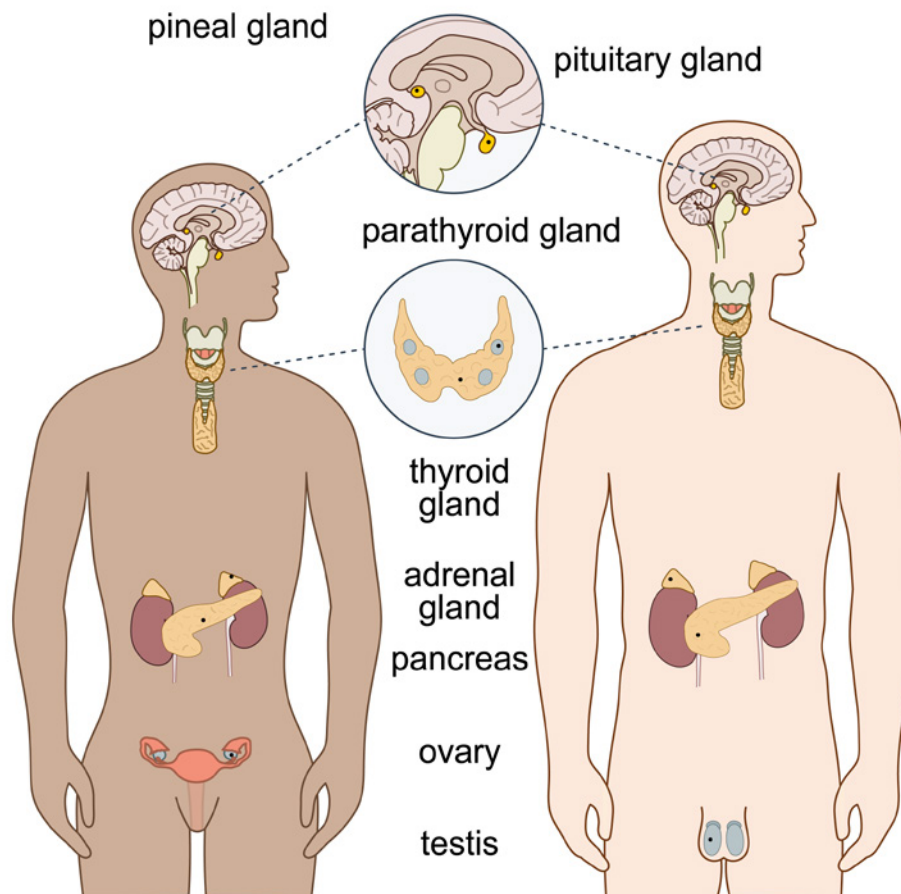
The neuroendocrine system refers to the internal working of the body. The glands of the endocrine system secrete hormones into the bloodstream to maintain homeostasis (stability) and regulate metabolism. Two glands (hypothalamus and the pituitary gland) are considered the control centers for much of the neuroendocrine system. Their roles are to direct hormones to specific locations throughout the body.

The neuroendocrine system produces neuroendocrine cells. Neuroendocrine cells have traits of both nerve cells and hormone-producing cells.

## The endocrine system

Pictured below is the endocrine system. The endocrine system is a complex network that helps to regulate the body's functions.

[https://commons.wikimedia.org/wiki/File:Endocrine\\_English.svg](https://commons.wikimedia.org/wiki/File:Endocrine_English.svg)



## Neuroendocrine tumor

A neuroendocrine tumor (NET) is a rare type of tumor that develops from neuroendocrine cells. NETs can develop anywhere in the body. Most often NETs are found in the lungs, pancreas, rectum, appendix, and small intestine. A NET may grow slowly or quickly and spread to other parts of the body.

Diagnosis and treatment of NETs depend on the type of tumor, its location, whether it produces excess hormones, how quickly it spreads, and whether it has spread to other parts of the body.

### Symptoms

Many people with NETs do not have symptoms. When symptoms do occur, they vary based on the location of the tumor.

NET signs and symptoms may include:

- Pain from a growing tumor
- Lump felt somewhere on your body
- Feeling unusually tired
- Weight loss (without trying)
- Nausea

If the tumor produces excess hormones, you may also have the following symptoms:

- Skin flushing
- Diarrhea
- Frequent urination
- Increased thirst
- Dizziness
- Shakiness
- Skin rash

## Stage

A cancer stage is a way to describe the extent of the cancer at the time you are first diagnosed. Stage focuses on a few factors such as the size of the tumor, where it is located, and whether cancerous cells have spread. A cancer stage is needed to plan and monitor treatment.

Because NETs can be found in different areas of your body, different staging systems are used depending on where they are found. Some specialists use a staging system for NETs similar to other cancer types. This staging system was created by the American Joint Committee on Cancer (AJCC).

### TNM scores

The tumor, node, metastasis (TNM) staging system is used for certain NETs. The TNM system is used to stage many soft tissue sarcomas. In this system, the letters T, N, and M describe different areas of cancer growth. Based on cancer test results, your doctor will assign a score or number to each letter. The higher the number, the larger the tumor or the more the cancer has spread. These scores will be combined to assign the cancer a stage. A TNM example might look like this: T2, N0, M0.

- **T (tumor)** - Size of the main (primary) tumor
- **N (node)** - If cancer has spread to nearby (regional) lymph nodes. Lymph node involvement is uncommon in most soft tissue sarcomas.
- **M (metastasis)** - If cancer has spread to distant parts of the body or metastasized

NETs of the GI tract and pancreas have their own staging systems based on location and characteristics of the tumor.

## NETs of the gastrointestinal tract

NETs of the gastrointestinal (GI) tract can start in the stomach, small intestine, appendix, colon, or rectum. While staging for each of these organs is slightly different, they all have stages 1 through 4. The higher the stage, the more advanced the cancer is, which may make it more difficult to treat.

### NETs of the stomach

- **Stage 1:** The tumor is less than or equal to 1 cm wide. It has not spread to any lymph nodes or distant parts of the body.
- **Stage 2:** The tumor is larger than 1 cm wide or has grown into other layers of tissue.
- **Stage 3:** The tumor has grown into the outermost layer of the stomach, or into nearby structures or organs. It may have spread to lymph nodes, but not distant parts of the body.
- **Stage 4:** Cancer has spread to distant parts of the body.

### NETs of the small intestine

- **Stage 1:** The tumor is less than or equal to 1 cm wide. It has not spread to any lymph nodes or outside the small intestine.
- **Stage 2:** The tumor is larger than 1 cm wide and has begun to grow into other layers of the small intestine. It has not spread to lymph nodes or distant body parts.
- **Stage 3:** The tumor is bigger and affecting nearby organs or the outermost covering of the small intestine. It may have spread to nearby lymph nodes but has not spread to other parts of the body.

- **Stage 4:** The cancer has spread to distant parts of the body.

### NETs of the appendix

- **Stage 1:** The tumor is less than or equal to 2 cm wide and has not spread to any lymph nodes.
- **Stage 2:** The tumor is wider than 2 cm. It may be growing into other tissue layers around the appendix. It has not spread to any lymph nodes or distant parts of the body.
- **Stage 3:** The tumor may have spread to nearby lymph nodes, or may be growing into the outermost layer of tissue of the appendix. The tumor has not yet metastasized to distant parts of the body, but it may have spread to nearby lymph nodes.
- **Stage 4:** The cancer has spread to distant parts of the body.

### NETs of the colon and rectum

- **Stage 1:** The tumor is less than or equal to 2 cm wide and has grown into deeper layers of cells (affecting the lamina propria or submucosa). The cancer has not spread to nearby lymph nodes or distant parts of the body.
- **Stage 2A:** The tumor is greater than 2 cm wide. The tumor has also grown into other tissue layers of the colon or rectum.
- **Stage 2B:** The tumor has grown into one of the outer layers of the colon or rectum. It has not yet spread to nearby lymph nodes.
- **Stage 3A:** The tumor has grown into the outer layer of the intestine or nearby

organs. It has not spread to nearby lymph nodes.

- **Stage 3B:** The tumor has spread to nearby lymph nodes. It has not yet spread (metastasized) to distant parts of the body.
- **Stage 4:** The tumor has spread to distant parts of the body.

### NETs of the pancreas

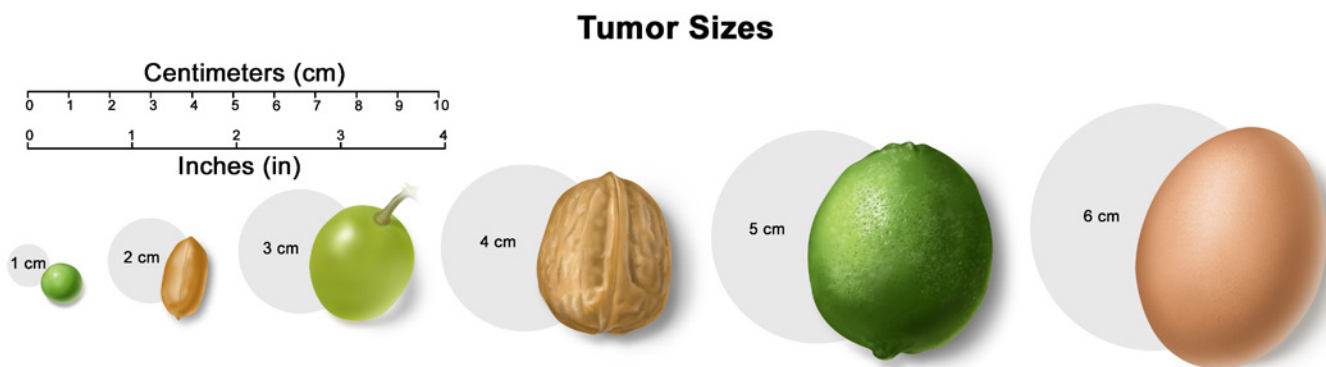
- **Stage 1:** The tumor is less than 2 cm across and only found in the pancreas.
- **Stage 2:** The tumor is between 2 and 4 cm and still only found in the pancreas.
- **Stage 3:** The tumor has grown into nearby organs.
- **Stage 4:** Cancer has spread to distant parts of the body.

### NETs of the lung

- **Stage 0:** The tumor has not spread to any nearby tissues. This stage is also referred to as “in situ.”
- **Stage 1:** The tumor is small and has not spread to nearby lymph nodes.
- **Stage 1A:** The tumor is less than or equal to 3 cm wide.
- **Stage 1B:** The tumor is between 3 cm and 4 cm wide.
- **Stage 2:** The tumor is larger than 4 cm. The tumor may or may not have spread to nearby lymph nodes.
- **Stage 2A:** The tumor is between 4 cm and 5 cm. It has not spread to lymph nodes.

## Tumor sizes

NETs of the gastrointestinal (GI) tract can start in the stomach, small intestine, appendix, colon, or rectum. Tumors are often measured in centimeters (cm).



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- **Stage 2B:** The tumor is less than or equal to 5 cm, and has spread to nearby lymph nodes. Or, the tumor is larger than 5 cm but has not spread to the lymph nodes.
- **Stage 3:** The tumor may have spread to the lymph nodes, but not to distant parts of the body. Stage 3 tumors are difficult to fully remove with surgery. This is especially true if they have grown into the heart or blood vessels.
- **Stage 4:** The tumor has now spread to the other lung or distant parts of the body, such as the brain or liver.
- **Stage 4A:** The tumor is both in the chest and in the heart or lungs.
- **Stage 4B:** The tumor has spread outside of the chest and lungs to one or more organs.

Neuroendocrine tumors develop from cells that produce hormones. This means the tumor can also produce hormones.

## Grade

Another factor used in staging is the tumor grade. Grade describes how abnormal the tumor cells look under a microscope and how quickly these cells are likely to grow and spread. The letter G stands for the grade. GX means the grade can't be determined, followed by G1, G2, and G3. G3 is the highest grade.

Grade also helps to describe how much cancer cells look like healthy cells when viewed under a microscope. This is referred to as degree of differentiation.

There are 2 degrees of differentiation:

- **Well differentiated:** Tumor cells are described as looking like healthy cells.
- **Poorly differentiated:** The tumor cells do not look like healthy cells. Poorly differentiated cells are also divided into large-cell and small-cell type. This refers to how the cells look under a microscope.

The tumor's grade and differentiation help your doctor predict how quickly the tumor will grow and spread. In general, the lower the tumor's grade and degree of differentiation, the better your outlook (prognosis).

## Key points

- ▶ Your endocrine system is a complex network of glands and organs. It is often referred to as the body's messenger system because it uses hormones to regulate your metabolism, energy level, growth and development, and mood.
- ▶ The neuroendocrine system refers to the internal working of the body.
- ▶ Two glands (hypothalamus and the pituitary gland) are considered the control centers for the body. Their roles are to direct hormones to specific locations throughout the body.
- ▶ The neuroendocrine system produces neuroendocrine cells.
- ▶ A neuroendocrine tumor (NET) is a rare type of tumor that develops from neuroendocrine cells.
- ▶ NETs can develop anywhere in the body. Most often NETs are found in the lungs, pancreas, rectum, appendix, and small intestine.
- ▶ A NET may grow slowly or quickly and spread to other parts of the body.
- ▶ Many people with NETs do not have symptoms. When symptoms do occur, they vary based on the location of the tumor.
- ▶ A cancer stage is a way to describe the extent of the cancer at the time you are first diagnosed. Stage focuses on a few factors such as the size of the tumor, where it is located, and whether cancerous cells have spread.
- ▶ Grade describes how abnormal the tumor cells look under a microscope and how quickly these cells are likely to grow and spread.
- ▶ The tumor's grade and differentiation help your doctor predict how quickly the tumor will grow and spread. In general, the lower the tumor's grade and degree of differentiation, the better your outlook (prognosis).

# 2

## Testing

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Treatment planning starts with testing. Testing is used to diagnose and plan treatment for neuroendocrine tumors. This chapter presents an overview of the tests you might receive and what to expect.

## Test results

Neuroendocrine tumors will be diagnosed based on a series of test results. Your diagnosis will determine your treatment plan. It is important you understand what these tests mean.

Keep these things in mind:

- Bring someone with you to doctor visits, if possible.
- Write down questions and take notes during appointments. Don't be afraid to ask your care team questions. Get to know your care team and help them get to know you.
- Get copies of blood tests, imaging results, and reports about your specific disease.
- Organize your papers. Create files for insurance forms, medical records, and test results. You can do the same on your computer.
- Keep a list of contact information for everyone on your care team. Add it to your phone. Hang the list on your refrigerator or keep it in a place where someone can access it in an emergency. Keep your primary care physician informed of changes to this list.



### Create a medical binder

A medical binder or notebook is a great way to organize all of your records in one place.

- Make copies of blood tests, imaging results, and reports about your specific type of cancer. It will be helpful when getting a second opinion.
- Choose a binder that meets your needs. Consider a zipper pocket to include a pen, small calendar, and insurance cards.
- Create folders for insurance forms, medical records, and tests results. You can do the same on your computer.
- Use online patient portals to view your test results and other records. Download or print the records to add to your binder.
- Organize your binder in a way that works for you. Add a section for questions and to take notes.
- Bring your medical binder to appointments. You never know when you might need it!

## General health tests

### Medical history

A medical history is a record of all health issues and treatments you have had in your life. Be prepared to list any illness or injury and when it happened. Bring a list of old and new medicines and any over-the-counter medicines, herbals, or supplements you take. Tell your doctor about any symptoms you have. A medical or health history will help determine which treatment is best for you.

### Family history

Some cancers and other diseases can run in families. Your doctor will ask about the health history of family members who are blood relatives. This information is called a family history. Ask family members about their health issues like heart disease, cancer, and diabetes, and at what age they were diagnosed.

### Physical exam

During a physical exam, a health care provider may:

- Check your temperature, blood pressure, pulse, and breathing rate
- Check your height and weight
- Listen to your lungs and heart
- Look in your eyes, ears, nose, and throat
- Feel and apply pressure to parts of your body to see if organs are of normal size, are soft or hard, or cause pain when touched. Tell your doctor if you feel pain.
- Feel for enlarged lymph nodes in your neck, underarm, and groin. Tell your doctor if you have felt any lumps or have any pain.

## What is your family health history?

Some cancers and other diseases run in families—those who are related to you through genes passed down from parent to child. This information is called a family health history. You can ask family members about their health issues like heart disease, cancer, and diabetes, and at what age they were diagnosed. For relatives who have died, ask about the cause and age of death.

Start by asking your parents, siblings, and children. Next, talk to half-siblings, aunts and uncles, nieces and nephews, grandparents, and grandchildren.

Write down what you learn about your family history and share the information with your health care provider.

Some of the questions to ask include:

- Do you have any chronic diseases, such as heart disease or diabetes, or health conditions such as high blood pressure or high cholesterol?
- Have you had any other diseases, such as cancer or stroke?
- How old were you when each of these diseases and health conditions was diagnosed?
- What is our family's ancestry—from what countries did our ancestors originate?

## Imaging tests

Imaging tests take pictures of the inside of your body. A radiologist, an expert in interpreting test images, will write a report and send this report to your doctor. Your test results will be discussed with you.

### CT scan

A computed tomography (CT or CAT) scan uses x-rays and computer technology to take pictures of the inside of the body. It takes many x-rays of the same body part from different angles. All the images are combined to make one detailed three-dimensional (3D) picture.

In most cases, contrast will be used. Contrast material is used to improve the pictures of the inside of the body. Contrast materials are not dyes, but substances that help enhance and improve the images of several organs and structures in the body. They are used to make the pictures clearer. Contrast might be taken

by mouth (oral) or given through a vein (IV). The contrast is not permanent and will leave the body in your urine immediately after the test.

Tell your doctors if you have had allergic reactions to contrast in the past. This is important. You might be given medicines, such as diphenhydramine (Benadryl) and prednisone (steroids), to avoid the effects of those allergies. Contrast might not be used if you have a serious allergy or if your kidneys are not working well.

### MRI scan

A magnetic resonance imaging (MRI) scan uses radio waves and powerful magnets to take pictures of the inside of the body. It does not use x-rays. Contrast might be used. An MRI may be used as an initial test, to check treatment results, and to see if the cancer has spread to other parts of the body.

### CT scan

**A CT scan uses x-rays to take pictures of the inside of the body. These pictures help to show where cancer activity is located.**

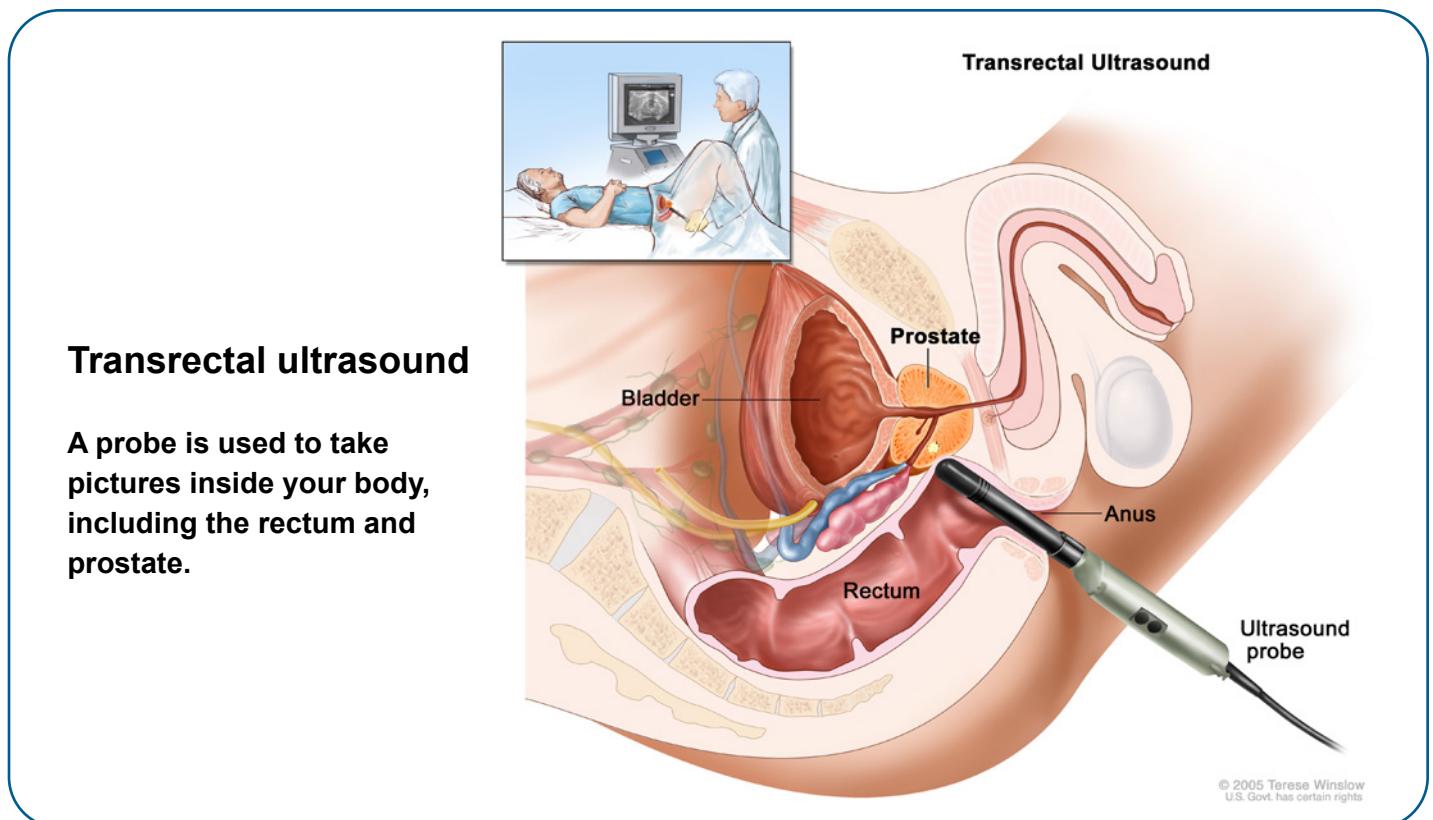


### PET scan

A positron emission tomography (PET) scan uses a radioactive drug called a tracer. A tracer is a substance injected into a vein to help see cancer cells in the body. PET scans are performed about an hour after the tracer is injected. PET scans are combined with CT or MRI scans (PET/CT or PET/MRI) to determine where the cancer cells are located. This combined test is considered to be more accurate than either scan alone. There are two types of PET scans that can be helpful for patients with neuroendocrine tumors (FDG-PET and SSTR-PET).

### FDG PET/CT scan

An FDG-PET scan uses 18-fluorodeoxyglucose as its tracer. This scan shows how fast your tumor cells use up a sugar called glucose. Active cancer cells use sugar faster than normal cells. This will make the cells look brighter in pictures. Many neuroendocrine tumors (NETs) are not fast-growing and not very bright on FDG-PET scans. FDG-PET scans can help determine if neuroendocrine tumors are becoming more aggressive.



### **SSTR-PET/CT scan**

A somatostatin receptor (SSTR) antagonist is a protein found on the surface of cells that bind to a hormone called somatostatin. Somatostatin helps to control other hormones in the body. SSTRs are found on many different types of cells, but especially cells in NETs. SSTR-PET uses a tracer that binds to these SSTRs, and causes even small NETs to be bright on PET images.

### **SSTR-PET/MRI scan**

An SSTR-PET/MRI scan is similar to SSTR-PET/CT, but uses MRI instead of CT to determine where the NETs are located. MRI can provide better imaging of soft tissues compared to CT.

### **Ultrasound**

An ultrasound (US) uses high-frequency sound waves to form pictures of the inside of the body. A probe will be pressed onto your abdomen. This is similar to the sonogram used for pregnancy. Ultrasound is painless and does not use x-rays, so it can be repeated as needed. It can show small areas of cancer that are near the surface of the body. Sometimes, an ultrasound or CT is used to guide a biopsy.

### **Endorectal ultrasound**

An endorectal ultrasound is used to look for anything out of the ordinary in the rectum and prostate. An endorectal ultrasound is also referred to as ERUS, transrectal ultrasound, and TRUS.



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## Blood and urine tests

Blood and urine tests check for signs of disease and how well the organs are working. These tests are also used to look for signs of hormone secretion or to see how well you are responding to certain treatments. Abnormal levels of certain chemicals found in the blood or urine may be a sign that the neuroendocrine tumor (NET) has spread to distant parts of the body.

### Comprehensive metabolic panel

A comprehensive metabolic panel (CMP) is a test that measures 14 different chemical substances in your blood. A CMP provides important information about how well your kidneys and liver are working, among other things. The test shows if the level of chemicals is too low or too high. Abnormal levels are an indication that there is an issue.

### Complete blood count

A complete blood count (CBC) measures the levels of red blood cells (RBCs), white blood cells (WBCs), and platelets (PLTs) in your blood. Your doctor will want to know if you have enough RBCs to carry oxygen throughout your body, WBCs to fight infection, and PLTs to control bleeding.

### Biochemical tests

Biochemical tests measure substances like hormones that may be present with a NET. Symptoms may be seen when your body makes too much of a hormone. Your doctor may consider these tests if you may have a NET or syndromes caused by a tumor. For a list of NETs, where they are located, symptoms, and tests needed, [see Guide 1](#).

### Urine tests

Urine tests look for signs of disease and assess your general health. Abnormal results may signal there's a problem with your kidneys or other organs. Abnormal results may be caused by kidney cancer or other health conditions. For a urine test, you will be asked to fill a small container with urine. The urine sample will be sent to a lab for testing.

### 5-HIAA test

5-HIAA (5-hydroxyindoleacetic acid) is a biomarker found in urine or blood that is used to confirm whether certain types of carcinoid tumor that secrete excess serotonin hormone are present. A carcinoid tumor is a type of NET that grows from neuroendocrine cells. A 5-HIAA urine test involves collecting a 24-hour urine sample. It can also be tested in a sample of blood. This test may also be used along with scans to check if you are responding to treatment.

## Guide 1

## Biochemical testing: Neuroendocrine tumors (NETs)

Tumor or syndrome	Symptoms	Test
<b>NETs of GI tract, lung, and thymus</b>	<ul style="list-style-type: none"> <li>• Flushing</li> <li>• Diarrhea</li> <li>• Cardiac valvular fibrosis</li> <li>• Bronchoconstriction</li> </ul>	<ul style="list-style-type: none"> <li>• 24-hour urine or plasma 5-HIAA</li> <li>• Test for Cushing syndrome</li> </ul>
<b>PPoma: Pancreas</b>	<ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• Serum pancreatic polypeptide</li> </ul>
<b>Insulinoma: Pancreas</b>	<ul style="list-style-type: none"> <li>• Hypoglycemia</li> </ul>	<ul style="list-style-type: none"> <li>• Serum insulin</li> <li>• Pro-insulin</li> <li>• C-peptide</li> </ul>
<b>VIPoma: Pancreas</b>	<ul style="list-style-type: none"> <li>• Diarrhea</li> <li>• Hypokalemia</li> </ul>	<ul style="list-style-type: none"> <li>• Serum VIP</li> </ul>
<b>Glucagonoma: Pancreas</b>	<ul style="list-style-type: none"> <li>• Flushing</li> <li>• Diarrhea</li> <li>• Hyperglycemia</li> <li>• Dermatitis</li> <li>• Hypercoagulable state</li> </ul>	<ul style="list-style-type: none"> <li>• Serum glucagon</li> </ul>
<b>Gastrinoma: Pancreas or duodenum</b>	<ul style="list-style-type: none"> <li>• Gastric ulcers</li> <li>• Duodenal ulcers</li> <li>• Diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>• Serum gastrin</li> </ul>

## Biopsy

A biopsy is the removal of a sample of tissue or group of cells for testing. It is an important part of an accurate diagnosis. Your sample should be reviewed by a pathologist who is an expert in the diagnosis of neuroendocrine tumors. This review is often referred to as histology, histopathology, or hematopathology review. The pathologist will note the overall appearance and the size, shape, and type of your cells. Tests will be done on the biopsied cells.

## Scopes

### Endoscopy

An endoscopy is a procedure where the inside of the body is studied, and is used to test for many diseases and conditions such as anemia, bleeding, inflammation, diarrhea, or cancers of the digestive system. It can also be used to locate and/or diagnose a NET. An endoscope (a flexible tube with a light and camera attached to it) is used to view pictures of your digestive tract on a color monitor.

### Colonoscopy

A colonoscopy is used to check for disease of the colon such as carcinoid tumor or colon cancer. A colonoscopy refers to a scope inserted through the anus into the large intestine. The large intestine is also known as the colon. A camera on the scope is used to view the colon and check for abnormal areas of concern.

### EGD

An EGD (esophagogastroduodenoscopy) is used to look for digestive disorders. An EGD refers to an endoscope inserted through your esophagus, stomach, and duodenum (part of your small intestine). It is an outpatient procedure. This means you can go home the same day. The procedure is estimated to take approximately 30 to 60 minutes.

### Endoscopic ultrasound

An endoscopic ultrasound (EUS) is a minimally invasive procedure to look for gastrointestinal (GI) and lung diseases. A special score uses sound waves to provide images of your digestive tract and chest.

### Gastric biopsy

A gastric biopsy refers to the removal of stomach tissue for examination. During the biopsy, a flexible tube is passed through the mouth and down the esophagus to the stomach. The tissue biopsy will be taken to a laboratory to be tested for bacteria and other organisms that can cause disease.

### Gastric pH test

A gastric pH test measures if acid is present in the stomach and can be helpful in workup of some gastric NETs. The test involves placing a thin tube into your esophagus. The tube device measures your stomach acid level (pH level).



## Genetic tests

Genetic testing is done using blood or saliva (spitting into a cup). The goal is to look for gene mutations inherited from your biological parents, called germline mutations. Some mutations can put you at risk for more than one type of cancer. You can pass these germline mutations on to your children. Also, other family members may have these mutations.

Tell your doctor if you have a family history of cancer or endocrine tumors. Depending on your family history or other features of your cancer, your health care provider might refer you for hereditary genetic testing to learn more about inherited risks for cancer. You may meet with a genetic counselor to discuss genetic testing options and/or to explain your test results.

### Hereditary conditions

Certain genetic (inherited) conditions may increase your risk for developing certain tumors. A genetic risk assessment by a genetic counselor or other health care provider can provide information about the likelihood you have a cancer risk factor and whether you may benefit from genetic testing, additional screening, or preventive interventions. Depending on the genetic risk assessment, you may choose to undergo genetic testing.

Genetic counseling can help you consider the risks, benefits, and limitations of genetic testing. It involves a review of your family history for cancer risk.

Hereditary syndromes closely related to neuroendocrine tumors include:

- Multiple endocrine neoplasia type 1 (MEN1)
- Multiple endocrine neoplasia type 4 (MEN4)
- Neurofibromatosis type 1 (NF1)
- Tuberous sclerosis complex (TSC1 and TSC2)
- Von Hippel-Lindau syndrome (VHL)

## Key points

- ▶ Neuroendocrine tumors (NETs) will be diagnosed and graded based on a series of test results. Your diagnosis will help guide your treatment plan.
- ▶ Some cancers and other diseases can run in families.
- ▶ Your doctor will ask about the health history of family members who are blood relatives. This information is called a family history.
- ▶ A computed tomography (CT or CAT) scan uses x-rays and computer technology to take pictures of the inside of the body.
- ▶ A magnetic resonance imaging (MRI) scan uses radio waves and powerful magnets to take pictures of the inside of the body. It does not use x-rays.
- ▶ Positron emission tomography (PET) scans provide information about NETs and are combined with CT or MRI. Somatostatin receptor (SSTR)-PET can be used to identify NETs by their SSTRs. FDG-PET can be used to determine if NETs are likely to be more aggressive.
- ▶ Blood and urine tests check for signs of disease and how well the organs are working. These tests are also used to look for signs of hormone secretion or to see how well you are responding to certain treatments.
- ▶ A biopsy is the removal of a sample of tissue or group of cells for testing.
- ▶ Genetic testing looks for gene mutations inherited from your biological parents called germline mutations.

# 3

## Treatment options

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This chapter presents an overview of the treatment types for neuroendocrine tumors (NETs). Not every person with a NET will receive every treatment listed in this chapter. Together, you and your doctor will choose a treatment plan that is best for you.

## Treatment team

Treatment decisions should involve a multidisciplinary team (MDT). An MDT is a team of doctors, health care workers, and social care professionals from different professional backgrounds who have knowledge (expertise) and experience with NETs. This team is united in the planning and implementing of your treatment.

Your MDT may include pathologists, endocrinologists, radiologists (including nuclear medicine specialists), and medical, radiation, and surgical oncologists.

Ask who will coordinate your care.

Your physical, mental, and emotional wellbeing are important. You know your body better than anyone. Help other team members understand:

- How you feel
- What you need
- What is working and what is not



### Your treatment team

Treating neuroendocrine tumors takes a team of doctors and other experts. Your treatment team may include:

**Endocrinologist:** specializes in the diagnosis and treatment of disorders of the endocrine system

**Gastroenterologist:** specializes in diagnosing and treating diseases that occur in the gastrointestinal system

**Oncologist:** specializes in treating cancer

**Pathologist:** an expert in evaluating and testing tissue to diagnose and classify disease

Keep a list of names and contact information for each member of your team. This will make it easier for you and anyone involved in your care to know whom to contact with questions or concerns.

## Surgery

Surgery is the primary treatment for NETs with limited or no spread. Primary treatment refers to the main treatment used to get rid of cancer in the body. The method and extent of surgery depends on where the tumor is located and how far the disease has spread. Treatment will be based on whether the tumor can be removed by surgery (resectable) or not (unresectable).

Surgery may be considered even if the tumor cannot be completely removed (tumor in liver). Work with your treatment team to determine if surgery is right for you.

### Endoscopic resection

An endoscopic resection is where an endoscopic approach is used to remove abnormal tissues (lesions) from the gastrointestinal (GI) or lung tract. During the procedure, a flexible tube (endoscope) is passed down the esophagus, stomach, upper part of the small intestine (duodenum), or lung. The tube may be guided up through the anus to remove lesions from the colon. This procedure is used to remove tumors without surgery. It is also referred to as an endoscopic mucosal resection (EMR).

### Local excision

A local excision is a surgical procedure used to treat NETs from various sites of the hepatopancreatic duct (ampullary adenomas), small neuroendocrine tumors that develop in the ampulla of Vater (where your bile duct and pancreatic duct join and empty into your small intestine), and certain noncancerous conditions, such as inflammatory stenosis.

Get to know your care team and help them get to know you.

During this procedure, any visible tumors are removed, but the lymph nodes and surrounding tissues are typically left untouched.

### Bowel resection with regional lymphadenectomy

Bowel resection refers to a surgical procedure that removes diseased or damaged tissue or part of an organ. It is also referred to as a partial colectomy. A regional lymphadenectomy refers to surgery to remove lymph nodes near the tumor.

### Regional lymphadenectomy

A regional lymphadenectomy is a surgical procedure to remove one or more lymph nodes in the tumor area. After the lymph nodes are removed a sample of tissue is checked under a microscope for signs of cancer. It is also called a lymph node dissection.

### Whipple procedure

If the tumor is in the head of your pancreas, you will have a pancreaticoduodenectomy (Whipple procedure). A Whipple procedure is surgery that removes the head of the pancreas, the gallbladder, duodenum (first part of the small intestine), part of the bile duct, and often part of the stomach.

Lymph nodes near your pancreas will be removed and tested. Once the cancer has been removed, your surgeons will reconnect your organs so you can digest food. Possible life-threatening complications of this surgery are infection, bleeding, pancreatic leaks, and fistulas (an opening between organs).

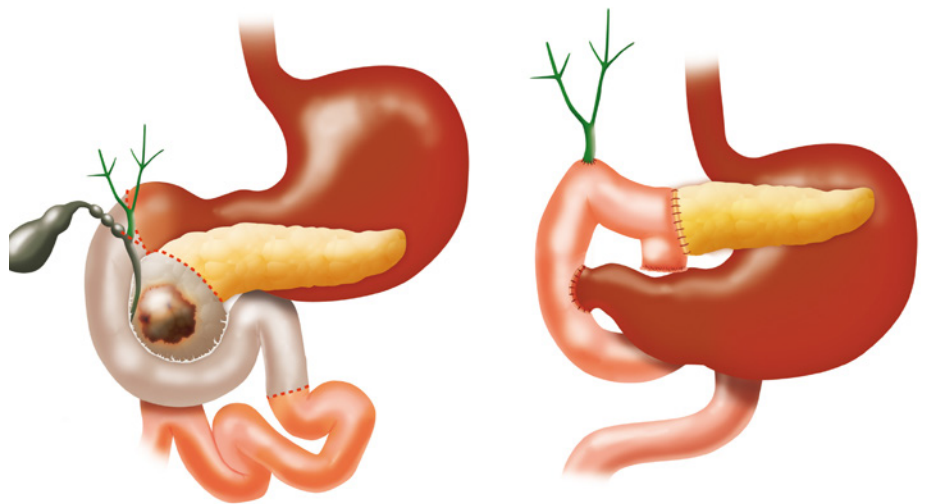
A Whipple procedure can be open or minimally invasive. It requires a great deal of skill. Blood vessels might have to be removed or pieces cut out and sewn back together. Parts of organs might have to be removed and sewn back together. All cancer must be removed to achieve a negative margin resection (R0). This might not be possible based on the type and stage of cancer.

### Simple appendectomy

An appendectomy is a surgical procedure to remove the appendix. The appendix is a small tube attached to the large intestine. An appendectomy is necessary when an infection has caused the appendix to become inflamed and swollen. This is often referred to as appendicitis. Most people recover quickly and without complications from this surgery.

### Whipple procedure

The image on the left shows cancer in the head of the pancreas. The image on the right shows how the organs might be reconnected during a Whipple procedure.



### Right hemicolectomy

A hemicolectomy refers to a surgical procedure that removes part of your large intestine called the colon. Once the colon is removed, the remaining parts of the intestine are joined together. The procedure has little to no impact on your digestion. That is, your colon can be partially removed without affecting the way your digestive system works.

Chemotherapy is given in cycles of treatment days followed by days of rest. This allows the body to recover before the next cycle of chemotherapy. The length of treatment and rest days vary based on the chemotherapy drugs used.

Chemotherapy is commonly used for high-grade NETs, poorly differentiated NETs, and NETs of certain tumors (pancreatic).

## Chemotherapy

Chemotherapy kills fast-growing cells throughout the body, including cancer cells and some normal cells. Chemotherapy drugs work in different ways to kill abnormal cells or to stop new ones from being made. Your doctor may use more than one chemotherapy drug. It is referred to as a combination regimen when two or more chemotherapy drugs are used.

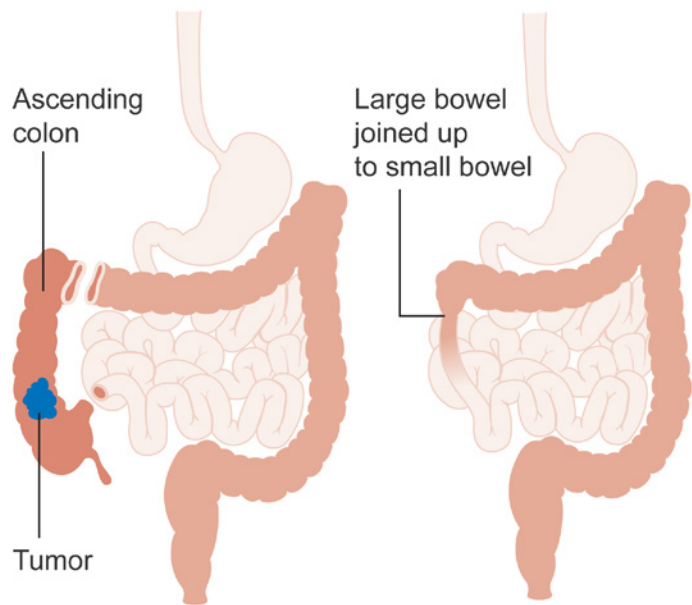
## Chemoradiation

Chemoradiation refers to a treatment that combines a lower-dose chemotherapy with radiation therapy (RT). These treatments can be given at the same time or be staggered.

### Right hemicolectomy procedure

The graphic shows how the colon is removed and the intestines are rejoined during the hemicolectomy procedure.

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## Immunotherapy

Immunotherapy increases the activity of your own immune system. The immune system is the body's natural defense against infection and disease. By targeting the immune system, immunotherapy improves your body's ability to find and destroy cancer cells. Immunotherapy can be given alone or with other types of treatment.

For more information, read the *NCCN Guidelines for Patients: Immunotherapy Side Effects*, available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines).



## Targeted therapy

Targeted therapy focuses on specific or unique features of cancer cells. Targeted therapies seek out how cancer cells grow, divide, and move in the body. These drugs stop the action of molecules that help cancer cells grow and/or survive.

## Somatostatin analogs

Somatostatin analogs are drugs used to slow down or stop hormone production from neuroendocrine tumors (NETs) to reduce symptoms such as diarrhea and flushing and to control tumor growth. Somatostatin analogs are made to have long-lasting activity in the body.

Somatostatin analogs used to treat NETs include:

- Lanreotide (Somatuline Depot)
- Octreotide acetate (Sandostatin, Bynfezia Pen)
- Octreotide acetate (LAR) (Sandostatin LAR Depot)

### Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) refers to a molecular targeted therapy. If your NETs progress on somatostatin analogs, a targeted treatment using a somatostatin analog attached to a therapeutic radioactive molecule (<sup>177</sup>Lu-dotatate, Lutathera) can be considered. The molecule attaches to the somatostatin receptors of the NET, which allows a high dose of radiation to be delivered directly to the tumor. Typically, this involves a series of 4 treatments given 8 weeks apart.



## Clinical trials

A clinical trial is a type of medical research study. After being developed and tested in a laboratory, potential new ways of fighting diseases need to be studied in people. If found to be safe and effective in a clinical trial, a drug, device, or treatment approach may be approved by the U.S. Food and Drug Administration (FDA).

Everyone with cancer should carefully consider all of the treatment options available for their cancer type, including standard treatments and clinical trials. Talk to your doctor about whether a clinical trial may make sense for you.

### Phases

Most cancer clinical trials focus on treatment. Treatment trials are done in phases.

- **Phase I trials** study the dose, safety, and side effects of an investigational drug or treatment approach. They also look for early signs that the drug or approach is helpful.
- **Phase II trials** study how well the drug or approach works against a specific type of cancer.
- **Phase III trials** test the drug or approach against a standard treatment. If the results are good, it may be approved by the FDA.
- **Phase IV trials** study the long-term safety and benefit of an FDA-approved treatment.

### Who can enroll?

Every clinical trial has rules for joining, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, or general health. These requirements ensure that participants are alike in specific ways and that the trial is as safe as possible for the participants.

### Informed consent

Clinical trials are managed by a group of experts called a research team. The research team will review the study with you in detail, including its purpose and the risks and benefits of joining. All of this information is also provided in an informed consent form. Read the form carefully and ask questions before signing it. Take time to discuss with family, friends, or others whom you trust. Keep in mind that you can leave and seek treatment outside of the clinical trial at any time.

### Start the conversation

Don't wait for your doctor to bring up clinical trials. Start the conversation and learn about all of your treatment options. If you find a study that you may be eligible for, ask your treatment team if you meet the requirements. If you have already started standard treatment you may not be eligible for certain clinical trials. Try not to be discouraged if you cannot join. New clinical trials are always becoming available.

### Frequently asked questions

There are many myths and misconceptions surrounding clinical trials. The possible benefits and risks are not well understood by many with cancer.

#### Will I get a placebo?

Placebos (inactive versions of real medicines) are almost never used alone in cancer clinical trials. It is common to receive either a placebo with a standard treatment, or a new drug with a standard treatment. You will be informed, verbally and in writing, if a placebo is part of a clinical trial before you enroll.

#### Are clinical trials free?

There is no fee to enroll in a clinical trial. The study sponsor pays for research-related costs, including the study drug. You may, however, have costs indirectly related to the trial, such as the cost of transportation or child care due to extra appointments. During the trial, you will continue to receive standard cancer care. This care is billed to—and often covered by—insurance. You are responsible for copays and any costs for this care that are not covered by your insurance.



## Finding a clinical trial

### In the United States

**NCCN Cancer Centers**  
[NCCN.org/cancercenters](https://www.nccn.org/cancercenters)

**The National Cancer Institute (NCI)**  
[cancer.gov/about-cancer/treatment/clinical-trials/search](https://www.cancer.gov/about-cancer/treatment/clinical-trials/search)

### Worldwide

**The U.S. National Library of Medicine (NLM)**  
[clinicaltrials.gov](https://clinicaltrials.gov)

**Need help finding a clinical trial?**  
**NCI's Cancer Information Service (CIS)**  
**1.800.4.CANCER (1.800.422.6237)**  
[cancer.gov/contact](https://www.cancer.gov/contact)

## General supportive care

Supportive care is health care that relieves symptoms and improves quality of life. It might include pain relief (palliative care), emotional or spiritual support, financial aid, or family counseling. Tell your care team how you are feeling and about any side effects. Best supportive care, supportive care, and palliative care are often used interchangeably.

### Blocked stomach

A tumor in the pancreas may also grow large enough to block food from passing out of your stomach through the first part of the small intestine (duodenum). This blockage can cause pain, vomiting, weight loss, and other problems. Treatments for a blocked stomach include removing the tumor (if possible), a stent, a PEG (percutaneous endoscopic gastrostomy) tube, or a stomach-duodenum bypass (gastrojejunostomy).

### Diabetes

Diabetes is a condition where the amount of glucose (a type of sugar) in your blood is too high. The amount of glucose in your blood is called your blood sugar level or blood glucose level. If you have diabetes or early-onset diabetes, a pancreatic tumor can change how the diabetes is managed. Diabetes can also happen when part or all of your pancreas is removed. Each type of diabetes is different and treated differently.

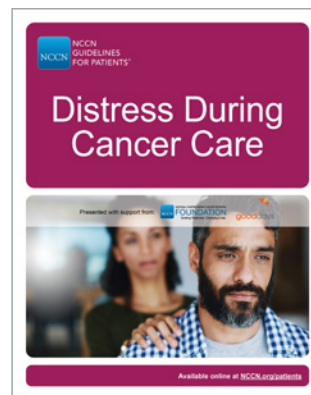
### Diarrhea

Diarrhea is frequent and watery bowel movements. Your care team will tell you how to manage diarrhea and may recommend medicines to stop the diarrhea. It is important to drink lots of fluids. Changes to your diet might help.

### Distress

Distress is an unpleasant experience of a mental, physical, social, or spiritual nature. It can affect how you feel, think, and act. Distress might include feelings of sadness, fear, helplessness, worry, anger, and guilt.

Depression, anxiety, and sleeping problems are common in cancer. Talk to your doctor and with those whom you feel most comfortable about how you are feeling. There are services and people who can help you. Support and counseling services are available.



For more information, see *NCCN Guidelines for Patients: Distress During Cancer Care*, available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines).

### Fatigue

Fatigue is extreme tiredness and inability to function due to lack of energy that cannot be easily explained. Let your care team know how you are feeling and if fatigue is getting in the way of doing the things you enjoy. Eating a balanced diet, exercise, yoga, and massage therapy can help. You might be referred to a nutritionist or dietitian to help with fatigue.

## Key points

- ▶ Treatment decisions should involve a multidisciplinary team (MDT). An MDT is a team of doctors, health care workers, and social care professionals from different professional backgrounds who have knowledge (expertise) and experience with neuroendocrine tumors (NETs).
  - ▶ Surgery is the primary treatment for NETs if they have limited or no spread. The method and extent of surgery depends on where the tumor is located and how far the disease has spread.
  - ▶ Chemotherapy kills fast-growing cells throughout the body, including cancer cells and some normal cells.
  - ▶ Chemoradiation refers to a treatment that combines a lower-dose chemotherapy with radiation therapy (RT).
  - ▶ Immunotherapy is a type of therapy that increases the activity of your own immune system.
  - ▶ Targeted therapy focuses on specific or unique features of cancer cells. Targeted therapies seek out how cancer cells grow, divide, and move in the body.
  - ▶ Somatostatin analogs are drugs used to slow down or stop hormone production and control the emptying of the stomach and bowel.
  - ▶ Peptide receptor radionuclide therapy (PRRT) is a treatment that targets somatostatin receptors and uses a radioactive molecule to deliver high doses of radiation to NETs.
- ▶ Everyone with cancer should carefully consider all of the treatment options available for their cancer type, including standard treatments and clinical trials.
  - ▶ Supportive care is health care that relieves symptoms and improves quality of life. It might include pain relief (palliative care), emotional or spiritual support, financial aid, or family counseling.

Possible side effects of somatostatin analogs include loss of appetite, weight loss, nausea, pain, and fatigue.

# 4

## NETs of the GI tract

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Neuroendocrine tumors of the gastrointestinal tract (GI NETs) are a rare type of cancer that starts in part of your digestive system. The digestive system includes the stomach, small intestine, colon, and rectum. This chapter reviews the different testing and treatment options.

## Diagnosis

A neuroendocrine tumor (NET) starts in the specialized cells of the neuroendocrine system. One of the most common places to find a NET is in the GI tract, also called the digestive system. The GI tract starts at the mouth/esophagus and ends at the anus. Main functions include digesting food and liquid,

and processing food waste. The most common place to find NETs in the GI tract is in the small intestine or rectum. However, they can also start in the stomach, appendix, colon, and other areas of the GI tract. A NET of the GI tract is also called a carcinoid tumor.

Recommended testing includes:

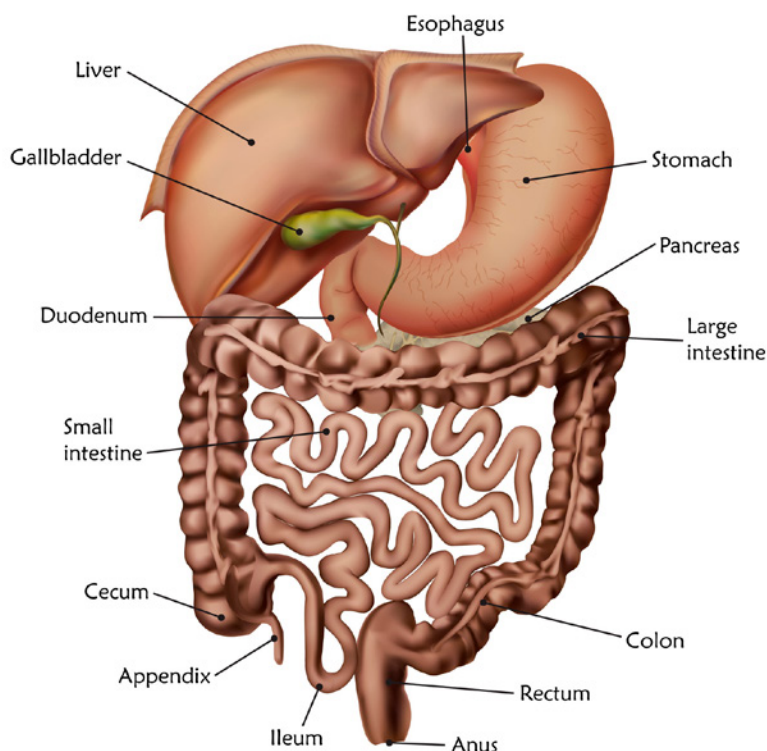
- CT or MRI of abdomen and pelvis

Additional testing may include:

- SSTR-PET/CT or SSTR-PET/MRI
- Colonoscopy or EGD/endoscopic ultrasound (EUS)
- Chest CT with or without contrast
- Biochemical tests

### Gastrointestinal tract

**The GI tract, also known as the digestive system, includes hollow organs joined in a long, twisting tube from the mouth to the anus. The digestive system provides energy to the body by breaking down the foods we eat.**



### Test results

Treatment options are based on the location of the NET and if it has spread to other areas near the tumor, such as the lymph nodes, or farther such as the liver.

The following terms are used to describe the location of NETs:

- **Locoregional disease** is the spread of cancer to places near the primary tumor. The disease has not spread far within the body.
- **Metastatic disease** is the spread of cancer from the primary tumor to a new (often distant) site in the body.

## Jejunum, ileum, and colon

If it is determined that you have locoregional disease, you will be treated with a bowel resection with removal of regional lymph nodes.

Your doctor may remove some lymph nodes and check the blood vessels in the area for cancer. Sometimes surgery is not an option for disease that has spread to other parts of the body. If your disease has spread, you may be offered a drug treatment instead of surgery or a combination of both. Work with your doctor and care team to develop the best course of treatment for your situation.

You will begin surveillance soon after surgery. Surveillance refers to being tested on a regular basis. Your doctors will watch for tumor growth, and may start treatment later if necessary. For more information on surveillance tests, [see Guide 3](#).

If you have metastatic disease, [see Guide 4](#).

## Duodenum

Treatment for NETs in the duodenum (first part of the small intestine) is broken up into 3 categories:

- Non-functioning NET
- Duodenal gastrinoma
- Metastatic disease

### Non-functioning NET

A non-functioning NET is a tumor that does not make hormones, or makes hormones that do not cause symptoms.

Primary treatment for a non-functioning NET includes one of the following:

- Endoscopic resection
- Local excision (transduodenal) and a regional lymphadenectomy
- Pancreatoduodenectomy

After primary treatment, your doctor will determine whether or not the tumor is invasive. An invasive tumor means the tumor has spread into muscle.

If the tumor is noninvasive, you will receive routine endoscopic surveillance.

If the tumor is invasive or you receive a pancreatoduodenectomy, you will be treated according to a specific surveillance schedule. [See Guide 3](#).

### Duodenal gastrinoma

A duodenal gastrinoma is a gastrin-secreting tumor. Gastrin is a hormone that helps your stomach produce acid. A gastrinoma secretes large amounts of gastrin, which causes your stomach to produce too much acid and may cause a burning sensation.

Primary treatment options for duodenal gastrinoma include:

- Local excision (transduodenal) and a regional lymphadenectomy
- Pancreatoduodenectomy

After primary treatment, your doctor will determine whether or not the tumor is invasive. An invasive tumor means the tumor has spread into muscle.

If the tumor is noninvasive, you will receive routine endoscopic surveillance.

If the tumor is invasive or you receive a pancreatoduodenectomy, you will be treated according to a specific surveillance schedule. [See Guide 3.](#)

### Metastatic disease

For treatment of metastatic disease, [see Guide 4.](#)

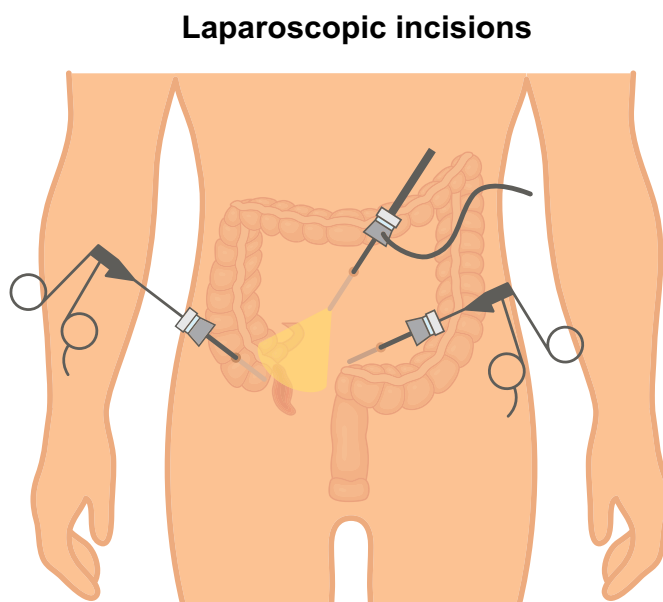
## Appendix

Neuroendocrine tumors (NETs) of the appendix are treated based on the size of the tumor as well as tumor penetration (how far it has spread).

If you have a tumor that is 2 centimeters (cm) or smaller, your appendix will be removed through a procedure called a simple appendectomy. No surveillance is needed.

### Appendectomy

An appendectomy is the surgical removal of the appendix. Pictured here are laparoscopes used to make small incisions.





If the tumor is larger than 2 cm, you had an incomplete resection, or there were positive nodes or margins found, your doctor will check for the extent of disease. A CT or MRI of the abdomen is recommended. An SSTR-PET/CT, or SSTR-PET/MR is possible. After this additional testing, your doctor may ask you to consider a right hemicolectomy. A hemicolectomy removes the right side of your colon.

For surveillance after treatment, [see Guide 3](#).

For treatment of metastatic disease, [see Guide 4](#).

## Rectum

Rectal NETs need different treatments than other more common types of bowel cancer. Rectal NETs are often small lesions that can be treated with an endoscopic resection. However, if there is lymph node metastasis, more invasive surgery may be needed.

Treatment for rectal NETs is broken up by size. You might have a rectal MRI or endorectal ultrasound to measure the tumor. Smaller tumors are removed by surgery. Next treatment options depend on if there is cancer remaining in the margins. A margin refers to no cancer cells found at the edge of the tissue. If cancer remains in the margin, you may require further treatment.

If there are no cancer cells found in the margin, no other treatment is needed.

If there are unknown margins, you will be treated based on the grade for your disease. For low grade (G1), will receive further testing by endoscope at 6 to 12 months to determine disease status. If the tests results are negative, no additional treatment is needed. If the test results are positive, you will be treated similar to other rectal tumors. [See Guide 2](#).

If your disease is an intermediate grade (G2), you will be treated similar to other rectal tumors. [See Guide 2](#).

### Guide 2

#### Other rectal tumors: T2 to T4

<p><b>Tumor is less than or equal to 2 cm</b></p>	<ul style="list-style-type: none"> <li>• Resection (transanal or endoscopic excision, if possible)</li> </ul>	<p>→</p> <ul style="list-style-type: none"> <li>• Less than 1 cm: No follow-up required</li> <li>• 1 cm through 2 cm: Endoscopy with rectal MRI or endorectal ultrasound at 6 and 12 months</li> </ul>
<p><b>Tumor is greater than 2 cm or node positive</b></p>	<ul style="list-style-type: none"> <li>• Low anterior resection</li> <li>• Abdominoperineal resection</li> </ul>	<p>→ See Guide 3</p>

For other rectal NETs, you will receive additional testing with either a rectal MRI or endorectal ultrasound. Test results will be used to define your tumor's size

**If your tumor is T1** (tumor has reached the lamina propria or submucosa and is less than or equal to 2 cm), primary treatment will be a resection.

Surveillance will be as follows:

- If your tumor was less than 1 cm, there will be no follow-up required.
- If your tumor is greater than 1 cm but less than 2 cm, you may receive an endoscopy with rectal MRI or an endorectal ultrasound at 6 months and 12 months after treatment.

**If your tumor is T2 through T4** (tumor has reached the muscularis propria or beyond, or is greater than 2 cm), you will receive additional testing before you begin treatment.

Recommended tests include:

- Colonoscopy
- Abdominal/pelvic multiphase CT or MRI
- SSTR-PET/CT or SSTR-PET/MRI (as needed)
- Chest CT with or without contrast (as needed)

Primary treatment for tumors less than 2 cm is a resection of the tumor. Surveillance activities are outlined in [Guide 2](#).

If your tumor is greater than 2 cm, you will be treated with one of the following:

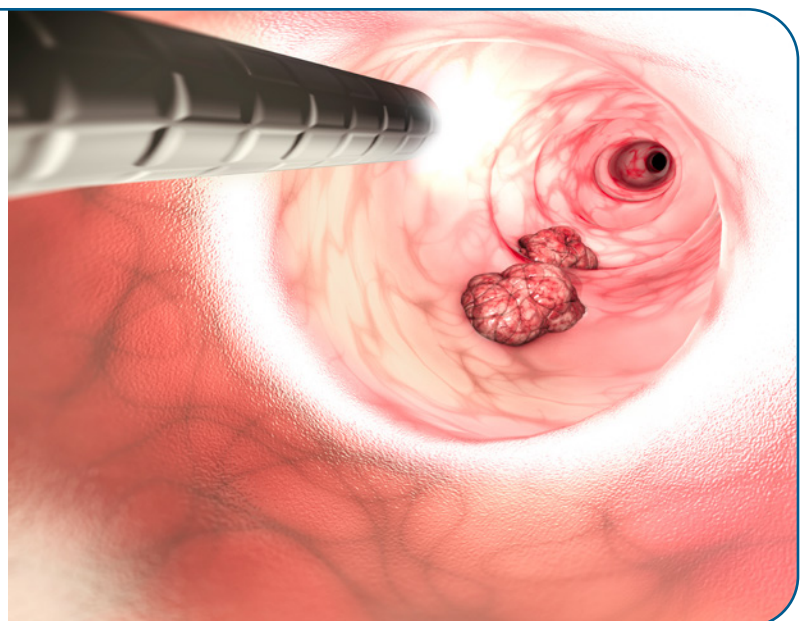
- Low anterior resection
- Abdominoperineal resection (APR)

For surveillance information, [see Guide 3](#).

For advanced or metastatic disease, [see Guide 4](#).

## Rectal tumors

Pictured is a 3-D image of tumors in the rectum.



## Stomach

NETs of the stomach are rare. Tumors start in the neuroendocrine cells of the stomach.

Additional testing will be used to determine your type of stomach (gastric) NET.

Testing may include:

- EGD
- Stomach biopsy
- Serum gastrin level
- Gastric pH (if appropriate)

Once your type has been identified, you may receive additional testing to determine treatment options.

### Type 1

If you are Type 1/hypergastrinemic, you may receive the following tests:

- Vitamin B12 level
- Baseline gastrin measurement
- Endoscopic ultrasound (EUS)

Primary treatment for Type 1 is endoscopic resection of large or bleeding/symptom-causing tumors.

After treatment, you should expect to receive endoscopic surveillance and endoscopic resection of prominent tumors every 2 to 3 years (or as needed).

If your disease has progressed (gotten worse), [see Guide 4](#).

### Type 2

If you are Type 2/hypergastrinemic, you may receive the following tests:

- Abdominal multiphasic CT or MRI
- SSTR-PET/CT or SSTR-PET/MRI
- EUS
- Other biochemical tests
- Consider genetic counseling and testing for inherited genetic conditions

Primary treatment for Type 2 depends on whether or not the primary gastrinoma can be resected.

If the primary gastrinoma can be resected, your doctor will determine whether or not the tumor is invasive. An invasive tumor means it has spread into muscle.

If the tumor is noninvasive, you will receive routine endoscopic surveillance.

If the tumor is invasive, you will be treated according to a specific surveillance schedule. [See Guide 3](#).

If the primary gastrinoma cannot be resected, you may be treated with the following:

- Endoscopic surveillance and endoscopic resection of prominent tumors
- Octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot), and manage gastric hypersecretion with high-dose proton pump inhibitors (PPIs)

If your disease has progressed (gotten worse), [see Guide 4](#).

**Type 3**

If you are Type 3/normal gastrin, you may receive the following tests:

- Endoscopic ultrasound (EUS)
- Abdominal multiphasic CT or MRI
- SSTR-PET/CT or SSTR-PET/MRI

Primary treatment for Type 3 may include the following:

- Partial or total gastrectomy (based on tumor location) with regional lymphadenectomy (preferred)
- Consider endoscopic or surgical wedge resection (if no evidence of regional lymphadenopathy on EUS or other imaging)

After treatment, you should expect follow-up tests to see how well the treatment worked. For a list of tests, [see Guide 3](#).

If your disease has progressed (gotten worse), [see Guide 4](#).

**Surveillance**

Surveillance tests are done at specific times after treatment to check if the cancer has returned. These tests can help find cancer early so you can start treatment again, if needed.

Surveillance tests may include general health tests such as a medical history and a physical exam, and imaging tests. One to 10 years after surgery, you can expect to have these tests every 1 to 2 years. If the first imaging tests are negative, you may receive scans less often. For a list of tests based on time since resection, [see Guide 3](#).

### Guide 3 NETs of GI tract: Surveillance tests

Time since resection	Tests, as needed
<b>12 weeks to 12 months</b>	<ul style="list-style-type: none"> <li>• General health tests</li> <li>• Biochemical tests</li> <li>• Abdominal with or without pelvic multiphasic CT or MRI</li> <li>• Chest CT with or without contrast</li> </ul>
<b>1 year to 10 years</b>	<ul style="list-style-type: none"> <li>• General health tests</li> <li>• Biochemical tests</li> <li>• Abdominal with or without pelvic multiphasic CT or MRI</li> <li>• Chest CT with or without contrast</li> </ul>
<b>Over 10 years</b>	<ul style="list-style-type: none"> <li>• Surveillance as needed</li> </ul>

## Advanced disease

Advanced disease can be locally or regionally advanced, or metastatic disease. Metastatic disease refers to cancer that has spread from the primary tumor site to a distant part of the body. If you are suspected of having advanced disease, you will receive more testing to confirm.

Testing may include:

- Multiphasic abdominal/pelvic CT or MRI
- Chest CT with or without contrast
- SSTR-PET/CT or SSTR-PET/MRI
- Biochemical tests

If the testing indicates that a complete resection is possible, the primary tumor and any areas of metastases will be removed.

After treatment, you should expect follow-up tests to see how well the treatment worked. For a list of tests, [see Guide 3](#).

### Asymptomatic, low tumor burden

If you have advanced disease but are not showing any symptoms, you may be

- Observed with imaging
- Treated with octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot)

You will receive additional tests every 12 weeks to 1 year that will include an abdominal/pelvic multiphasic CT or MRI and a chest CT (as needed) with or without contrast.

If your disease continues to spread, you will be treated with either octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot), if you have not already received it.

If your disease has not improved, you will receive one of the treatment options listed in [Guide 4](#).

## Guide 4

### NETs of GI tract: Advanced disease

Tumor type	Treatment
<b>Asymptomatic, low tumor burden</b>	<ul style="list-style-type: none"> <li>• Everolimus (Afinitor)</li> <li>• PRRT with 177Lu-dotatate (if SSTR-positive and progression on octreotide LAR or lanreotide)</li> <li>• Liver-directed therapy for liver-predominant disease</li> <li>• Palliative RT for symptomatic bone metastases</li> </ul>
<b>Locally symptomatic from primary tumor</b>	
<b>Significant tumor burden</b>	

### Locally symptomatic from primary tumor

Treatment for a locally symptomatic tumor is resection of the tumor.

You will receive additional tests every 12 weeks to 1 year that will include an abdominal/pelvic multiphase CT or MRI and a chest CT (as needed) with or without contrast. If your disease continues to spread, you will be treated with either octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot), if you have not already received it.

If your disease has not improved, you will receive one of the treatment options listed in [Guide 4](#).

### Significant tumor burden

Tumor burden refers to the number of cancer cells, the size of the tumor, and the amount of cancer found in the body. If you have clinically significant tumor burden or progressive disease, you will be treated with octreotide LAR (Sandostatin LAR Depot) or lanreotide (Somatuline Depot). These drugs are used to control tumor growth.

If your disease has not improved, you will receive one of the treatment options listed in [Guide 4](#).

## Key points

- Neuroendocrine tumors of the gastrointestinal tract (GI NETs) are a rare type of cancer that start in part of your digestive system.
- The GI tract starts at the mouth/esophagus and ends at the anus. Main functions include digesting food and liquid, and processing food waste.
- Treatment options are based on the location of the NET and if it has spread to other areas near the tumor, such as the lymph nodes, or farther such as the liver.
- Treatment for NETs in the duodenum (first part of the small intestine) are broken up into 3 categories: non-functioning NET, duodenal gastrinoma, and metastatic disease.
- NETs of the appendix are treated based on the size of the tumor.
- Rectal NETs need different treatments than other more common types of bowel cancer.
- NETs of the stomach are rare. Tumors start in the neuroendocrine cells of the stomach.
- Surveillance tests are done at specific times after treatment to check if the cancer has returned.
- Advanced disease can be locally or regionally advanced, or metastatic disease. Metastatic disease refers to cancer that has spread from the primary tumor site to a distant part of the body.

# 5

## Pulmonary NETs

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Neuroendocrine tumors of the thymus and lungs can be aggressive types of cancer. This chapter reviews the different testing and treatment options for NETs of the thymus and lungs.

## Thymus

### Diagnosis

Neuroendocrine tumors of the thymus (NETT) are rare and can be difficult to treat. The thymus is a gland found in the chest between the lungs and above the heart.

Recommended testing includes:

- Chest CT and abdominal multiphasic CT or MRI

Additional testing may include:

- SSTR-PET/CT or SSTR-PET/MRI
- Biochemical tests for Cushing syndrome, if suspected
- Other biochemical tests
- Consider genetic counseling and testing for inherited genetic conditions

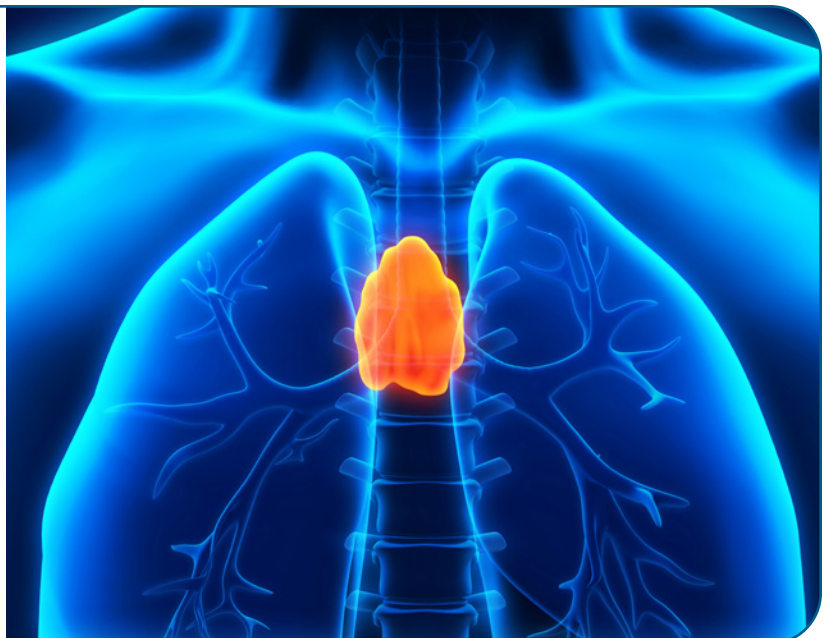
### Treatment

Treatment for NETs of the thymus is broken up by tumor stage:

- Localized disease (stage 1 and 2)
- Locoregional disease (stage 3A and 3B)
- Metastatic disease (stage 4)

### Thymus gland

The thymus gland is found behind the breastbone and between the lungs.





**Localized disease**

Surgery is the primary treatment option for stage 1 and 2 thymus tumors.

**Locoregional disease**

Treatment for stage 3A and 3B is broken up by whether the tumor can be surgically removed (resectable).

If your tumor can be surgically removed, and no other cancer cells are found around the tumor's margins, you should expect follow-up tests. For a list of surveillance tests, [see Guide 5](#).

If your tumor can be surgically removed, but the resection is incomplete or there are positive margins found after surgery, then you might have observation. If it the tumor is intermediate grade (atypical carcinoid), then radiation therapy might be given with or without chemotherapy.

A positive margin refers to cancer cells found at the edge of the tissue. This indicates that not all of the cancer has been removed.

If your tumor cannot be removed by surgery, [see Guide 6](#).

**Metastatic disease**

Metastatic disease refers to cancer that has spread from the primary tumor site to a distant part of the body. If you are suspected of having metastatic (advanced) disease, you will receive more testing to confirm.

For more information on testing and treatment of metastatic disease, [see Guide 7](#).

**Guide 5****NETs of the thymus or lungs: Surveillance tests**

Time since resection	Tests, as needed
<b>12 weeks to 12 months</b>	<ul style="list-style-type: none"> <li>• General health tests</li> <li>• Biochemical tests</li> <li>• Abdominal with or without pelvic multiphasic CT or MRI</li> <li>• Chest CT with or without contrast</li> </ul>
<b>1 year to 10 years</b>	<ul style="list-style-type: none"> <li>• General health tests</li> <li>• Biochemical tests</li> <li>• Abdominal with or without pelvic multiphasic CT or MRI</li> <li>• Chest CT with or without contrast</li> </ul>
<b>Over 10 years</b>	<ul style="list-style-type: none"> <li>• Surveillance as needed</li> </ul>

## Lungs

### Diagnosis

Neuroendocrine tumors (NETs) of the lungs are also referred to as lung carcinoid tumors. NET lung tumors often develop in the major bronchi (large tubes that lead air from the windpipe into the lungs).

There are 4 types of pulmonary (in the lungs) NETs:

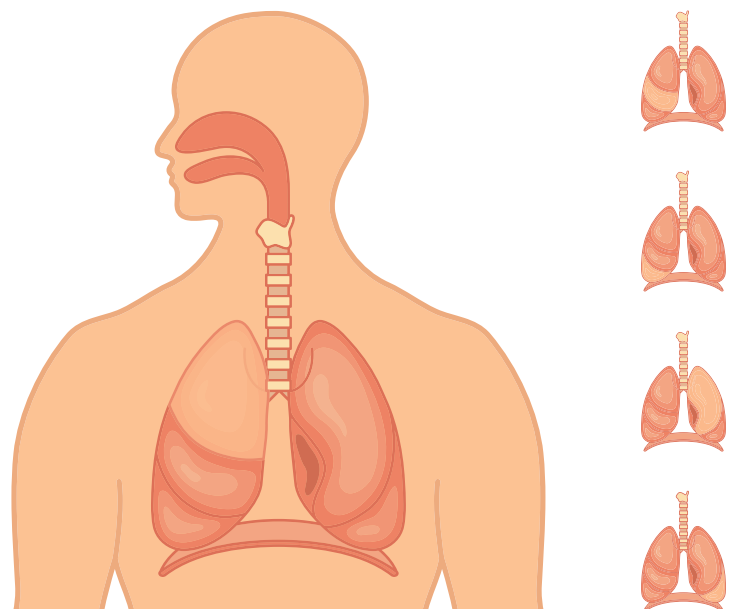
- Typical carcinoids (low grade) – slow growing and less likely to spread beyond the lungs
- Atypical carcinoids (intermediate grade) – rarer and grow more rapidly than typical tumors
- Small cell lung cancer (SCLC)
- Large cell neuroendocrine carcinoma

This chapter will cover typical and atypical carcinoids. For more information on SCLC, see *NCCN Guidelines for Patients: Small Cell Lung Cancer*, available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines).



### Lobectomy

**A lobectomy refers to a surgical procedure where an entire lobe of your lung is removed. The left lung has 2 lobes and the right lung has 3 lobes.**



Recommended testing for NETs of the lungs includes:

- Chest CT with contrast and abdominal multiphasic CT or MRI

Additional testing may include:

- SSTR-PET/CT or SSTR-PET/MRI
- Brain MRI
- Bronchoscopy
- Biochemical tests for Cushing syndrome and carcinoid syndrome
- Other biochemical tests
- Consider genetic counseling and testing for inherited genetic conditions

## Treatment

Treatment for lung NETs is broken up by stage.

### Stage 1 or 2

Primary treatment for stage 1 or 2 NET may include:

- Lobectomy or other resection and lymph node dissection (sampling)
- Thermal ablation or stereotactic body RT (SBRT)

### Stage 3A (resectable)

A tumor that can be removed with surgery is called resectable. Primary treatment for resectable stage 3A includes a lobectomy or other resection and lymph node dissection or sampling.

If you have a low grade (typical carcinoid) tumor, you will receive no further treatment. You will follow the surveillance schedule found in [Guide 7](#).

If you have an intermediate grade (atypical carcinoid) tumor, you may be asked to watch and wait (observe) or to consider treatment of cytotoxic chemotherapy.

Chemotherapy options include:

- Cisplatin with etoposide (Etopophos)
- Carboplatin with etoposide (Etopophos)
- Temozolomide (Temodar)

### Stages 3A, 3B, or 3C (unresectable)

If the tumor cannot be removed with surgery (unresectable), you will be treated based on tumor type as in [Guide 6](#).

### Stage 4 (metastatic)

For treatment of stage 4 (metastatic disease), multiple lung nodules or tumorlets and evidence of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), see [Guide 7](#).

## Guide 6

## NETs of the thymus or lungs: Unresectable locoregional disease

Type	Primary treatment	Follow-up therapy
<b>Low grade (typical carcinoid)</b>	<ul style="list-style-type: none"> <li>• Observation, if no symptoms</li> <li>• Octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot)</li> <li>• Everolimus (Afinitor)</li> <li>• Temozolomide (Temodar) with or without capecitabine (Xeloda)</li> <li>• Radiation therapy (RT)</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical trial (preferred)</li> <li>• Consider changing to alternate primary therapy</li> <li>• Consider peptide receptor radionuclide therapy (PRRT) with <sup>177</sup>Lu-dotatate (if SSTR-positive and disease worsens on octreotide LAR or lanreotide)</li> </ul>
<b>Intermediate grade (atypical carcinoid)</b>	<ul style="list-style-type: none"> <li>• Observation, if no symptoms and no disease progression</li> <li>• Radiation therapy. Cisplatin and etoposide (Etopophos) or carboplatin and etoposide might be given with RT</li> <li>• Cytotoxic chemotherapy with cisplatin and etoposide (Etopophos)</li> <li>• Cytotoxic chemotherapy with carboplatin and etoposide (Etopophos)</li> <li>• Cytotoxic chemotherapy and temozolomide (Temodar) with or without capecitabine (Xeloda)</li> <li>• Octreotide LAR or lanreotide (if SSTR-positive and/or hormonal symptoms)</li> <li>• Everolimus (Afinitor)</li> </ul>	

## Surveillance

Surveillance tests are done at specific times after treatment to check if the cancer has returned. These tests can help find cancer early so you can start treatment again, if needed. For a list of tests and time frames, see [Guide 5](#).

## Metastatic disease

Advanced disease, also called metastatic disease, refers to cancer that has spread from the primary tumor site to a distant part of the body. If you are suspected of having metastatic (advanced) disease, you will receive more testing to confirm. Treatment options for metastatic disease are based on grade and tumor burden.

### **Asymptomatic, low tumor burden and low grade (typical carcinoid)**

Primary treatment for a low tumor burden and low-grade tumor includes observation (watch and wait), or octreotide LAR (Sandostatin, Bynfezia Pen), or lanreotide (Somatuline Depot). These drugs are referred to as somatostatin analogs. Somatostatin analogs are drugs used to slow down or stop hormone production.

With observation, you should expect to have a chest CT with contrast and abdominal/pelvic multiphasic CT or MRI every 3 to 6 months to monitor the disease.

### **Significant tumor burden and low grade (typical carcinoid), or disease progression, or intermediate grade (atypical carcinoid), or symptomatic disease**

The preferred primary treatment for those that fall into this group is a clinical trial. If a clinical trial is not a possible treatment option, you will be treated with other options listed in [Guide 7](#).

### **Multiple lung nodules or tumorlets and evidence of DIPNECH**

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) refers to a rare disorder of the lungs that is caused by an abnormal overgrowth of pulmonary neuroendocrine cells in the lungs.

Treatment might include observation (watch and wait), octreotide LAR (Sandostatin, Bynfezia Pen), or lanreotide (Somatuline Depot).

With observation, you should expect to receive a chest CT (without contrast) every 12 to 24 months to monitor the disease.

Symptoms of DIPNECH include chronic cough, shortness of breath, and wheezing.

## Carcinoid syndrome

Carcinoid syndrome refers to a group of symptoms that may be a sign of neuroendocrine tumors (NETs). Carcinoid syndrome occurs when NETs (mostly of the GI tract) overwhelm your system with hormones (such as serotonin) as well as other substances. Flushed skin and watery diarrhea are the most common symptoms, but this syndrome can also thicken heart valves.

You may receive tests to determine if you have carcinoid syndrome. These tests include:

- Biochemical tests with 24-hour urine or plasma 5-HIAA
- Echocardiogram
- Imaging scans

After testing you will be treated with either octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot).

If you still have symptoms after primary treatment, you may be treated with any of the following:

- Hepatic arterial embolization or cytoreductive surgery for liver-predominant disease
- Telotristat (Xermelo) for diarrhea
- Other systemic therapy based on disease site

If there are no further symptoms after primary treatment, you should expect follow-up tests to see how well the treatment worked.

### Guide 7

#### NETs of the thymus or lungs: Metastatic disease

Type	Primary treatment	Follow-up therapy
<b>Significant tumor burden and low grade (typical carcinoid)</b>	<ul style="list-style-type: none"> <li>• Clinical trial (preferred)</li> <li>• Observation, in some cases</li> <li>• Octreotide LAR or lanreotide (if SSTR-positive and/or hormonal symptoms)</li> </ul>	<p>➔ Consider changing treatment option if disease progresses with primary treatment</p>
<b>Disease progression</b>	<ul style="list-style-type: none"> <li>• Everolimus (Afinitor) for lung NET</li> <li>• PRRT with 177Lu-dotatate (if SSTR-positive and progression on octreotide LAR or lanreotide)</li> </ul>	
<b>Intermediate grade (atypical carcinoid)</b>	<ul style="list-style-type: none"> <li>• Cisplatin and etoposide (Etopophos) or carboplatin and etoposide</li> <li>• Temozolomide (Temodar) with or without capecitabine (Xeloda)</li> </ul>	
<b>Symptomatic disease</b>	<ul style="list-style-type: none"> <li>• Liver-directed therapy for liver-predominant disease</li> </ul>	

### Follow-up testing

Testing during surveillance may include:

- Echocardiogram (every 1 to 3 years)
- Abdominal/pelvic multiphasic CT or MRI every 12 weeks to 12 months
- Chest CT with or without contrast

If testing shows that your disease has gotten worse, you will be treated based on if the advanced or metastatic disease is in the GI tract, lung, or thymus.

**Echocardiogram (echo) uses ultrasound to provide pictures of your heart's valves and chambers. It is used to see how well your heart is working.**

### Key points

- Neuroendocrine tumors of the thymus and lungs can be aggressive types of cancer.
- NETs of the thymus are rare and can be difficult to treat.
- The thymus is a gland found in the chest between the lungs and above the heart.
- Neuroendocrine tumors (NETs) of the lungs are also referred to as a lung carcinoid tumor.
- NET lung tumors often develop in the major bronchi (large tubes that lead air from the windpipe into the lungs).
- Surveillance tests are done at specific times after treatment to check if the cancer has returned. These tests can help find cancer early so you can start treatment again, if needed.
- Advanced disease, also called metastatic disease, refers to cancer that has spread from the primary tumor site to a distant part of the body.
- Carcinoid syndrome refers to a group of symptoms that may be a sign of NETs.
- Carcinoid syndrome occurs when NETs of the GI tract overwhelm your system with hormones (serotonin) as well as other substances.

# 6

## NETs of the pancreas

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A pancreatic neuroendocrine tumor (PNET) is a type of cancer that forms tumors in the pancreas. There is more than one type of PNET.

## Diagnosis

The pancreas is a large gland found in your abdomen. The pancreas lies behind the stomach and across the spine. The pancreas has 3 parts: the head, the body, and the tail.

The pancreas does 2 important things:

- It makes hormones (such as insulin and glucagon) that control the amount of sugar (glucose) in your blood. This helps your body use and store energy from food.

- It makes powerful substances called pancreatic enzymes that help digest food in your small intestine.

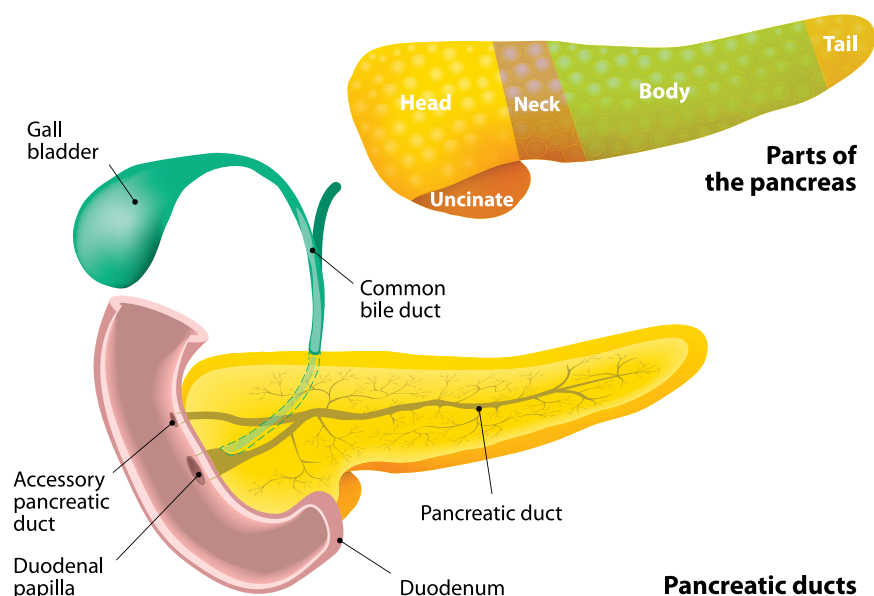
A pancreatic neuroendocrine tumor (PNET) is a type of cancer that forms tumors in the pancreas. Endocrine cells of the pancreas make hormones. These are released directly into the bloodstream. PNETs are either functional (produce hormones) or, more commonly, nonfunctional (do not produce hormones).

There are 4 types of functional pancreas NETs:

- **Gastrinoma** – This type of tumor makes too much gastrin. Gastrin is a hormone that causes acid production in the stomach. Too much stomach acid can cause severe ulcers (referred to as Zollinger-Ellison syndrome).

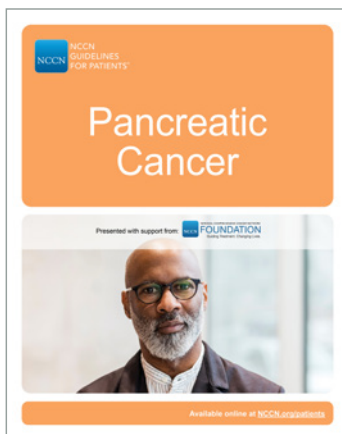
### Parts of the Pancreas

The pancreas consists of a wide end called the head (includes neck and uncinete process), a middle part called the body, and a narrow end called the tail.



- **Glucagonoma** – This type of tumor makes too much glucagon. Glucagon is a hormone that increases glucose (sugar) levels in the blood. Too much blood glucose is called hyperglycemia.
- **Insulinoma** - This type of tumor makes too much insulin, which can rapidly lower blood sugar (referred to as hypoglycemia or low blood sugar). Insulinomas are typically noncancerous.
- **VIPoma** – This type of tumor starts in the cells of the pancreas that make vasoactive intestinal peptide (VIP). VIP is a hormone that helps move water into the intestines. Too much VIP can cause chronic, watery diarrhea. This is referred to as Verner-Morrison syndrome.

PNETs need different treatment than the more common type of pancreatic cancer. For more information on pancreatic cancer and pancreatic adenocarcinoma, see *NCCN Guidelines for Patients: Pancreatic Cancer*, available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines).



## Treatment

Treatment for PNETs is based on the following:

**Location** - whether the cancer is found in one or multiple areas of the pancreas, and whether it is in the tail or head of the pancreas (more complicated surgery to remove).

**Metastases** – whether the cancer has spread to lymph nodes or other parts of the body such as the liver, lung, peritoneum, or bone.

Standard treatment for PNETs includes:

- Surgery
- Chemotherapy
- Hormone therapy
- Targeted therapy
- Supportive care

Specific treatments for PNETs are described next.

### Duodenotomy

A duodenotomy refers to an incision of the duodenum.

### Pancreatoduodenectomy

Pancreatoduodenectomy refers to surgery that removes the head of the pancreas, gallbladder, duodenum (first part of the small intestine), part of the bile duct, nearby lymph nodes, and often part of the stomach. This is known as a Whipple procedure. This surgery can be open or minimally invasive.

## Pancreatectomy

There are 2 types of pancreatectomy:

- **Distal pancreatectomy** – refers to surgery that removes the body and tail of the pancreas, and sometimes the entire spleen (splenectomy). The left adrenal gland might also be removed. This surgery can be open or minimally invasive.
- **Total pancreatectomy** – refers to surgery that removes the whole pancreas, part of the small intestine, part of the stomach, the common bile duct, the gallbladder, the spleen, and nearby lymph nodes. It is usually done as open surgery.

## Peripancreatic lymphadenectomy

A peripancreatic lymphadenectomy refers to a surgical procedure that removes lymph nodes and obtains a tissue sample to look for cancer.

## Splenectomy

A splenectomy refers to a surgical procedure that partially or completely removes the spleen.

## Nonfunctioning pancreatic tumors

Non-functioning pancreatic neuroendocrine tumors (PNETs) are caused by abnormal growth and reproduction of neuroendocrine cells in the pancreas. Nonfunctioning PNETs often do not show any symptoms related to hormones.

Symptoms of a nonfunctioning PNET may include:

- Abdominal pain
- Nausea
- Weight loss
- Jaundice (yellowing of the skin)

Recommended testing for nonfunctioning PNETs:

- Abdominal with or without pelvis multiphasic CT or MRI

Additional testing may include:

- SSTR-PET/CT or SSTR-PET/MRI
- Chest CT with or without contrast
- Endoscopic ultrasound (EUS)
- Biochemical tests
- Consider genetic counseling and testing for inherited genetic conditions

Treatment for nonfunctioning PNETs is broken up by locoregional disease and metastatic disease.

### Locoregional disease

Locoregional disease is the spread of cancer to places near the primary tumor. The cancer has not spread to distant parts of the body.

If the tumor is equal to or smaller than 2 centimeters (cm), you will receive one of the following treatment options:

- Observation (in select cases)
- Removal of the tumor (enucleation) or without regional lymphadenectomy
- Resection with or without regional lymphadenectomy

If the tumor is larger than 2 cm, invasive, or node positive (cancer cells in lymph nodes), you will be treated based on the part of the pancreas affected:

- For tumors in the pancreas head, you will be treated with a pancreatoduodenectomy and a regional lymphadenectomy.
- For tumors in the distal part of the pancreas (body or tail), you will be treated with a distal pancreatectomy, splenectomy, and a regional lymphadenectomy.

### Metastatic disease

For treatment of metastatic disease, [see Guide 10](#).

## Gastrinoma

Gastrinoma refers to a rare tumor that is found in neuroendocrine cells (usually in the duodenum or head of pancreas). Gastrinomas make too much gastrin. Gastrin helps your body control the amount of acid in your stomach and helps to digest food. Too much acid can cause ulcers in your stomach or duodenum.

Symptoms of gastrinoma may include:

- Abdominal pain
- Heartburn
- Nausea
- Diarrhea
- Blood in vomit or feces

Recommended testing to diagnosis gastrinoma includes:

- Serum gastrin level
- Abdominal with or without pelvis multiphasic CT or MRI
- Genetic counseling and testing for inherited genetic conditions

Additional testing may include:

- SSTR-PET/CT or SSTR-PET/MRI
- Chest CT with or without contrast
- EUS
- Other biochemical tests

Treatment for gastrinoma is broken up by locoregional disease and metastatic disease.

### Locoregional disease

Primary treatment for gastrinoma includes:

- Manage gastric hypersecretion with high-dose proton pump inhibitors (PPIs)
- Octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot)

Further treatment is described in [Guide 8](#).

Locoregional disease refers to cancer cells that have spread to organs and/or lymph nodes near the primary tumor site.

## Guide 8

### Gastrinoma: Treatment by location

Location	Treatment
<b>Occult (no primary tumor or metastases found on imaging)</b>	<ul style="list-style-type: none"> <li>• Observe (wait and watch)</li> <li>• Duodenotomy and intraoperative ultrasound</li> <li>• Local resection/enucleation of tumors and node dissection</li> </ul>
<b>Duodenum</b>	<ul style="list-style-type: none"> <li>• Duodenotomy and intraoperative ultrasound</li> <li>• Local resection/removal (enucleation) of tumor(s) and periduodenal lymph node dissection</li> </ul>
<b>Head of pancreas (exophytic or peripheral tumors)</b>	<ul style="list-style-type: none"> <li>• Enucleation of tumor and periduodenal lymph node dissection</li> </ul>
<b>Head of pancreas (deeper or invasive tumors and those close to the main pancreatic duct)</b>	<ul style="list-style-type: none"> <li>• Pancreatoduodenectomy</li> </ul>
<b>Body and/or tail of pancreas (distal)</b>	<ul style="list-style-type: none"> <li>• Distal pancreatectomy with splenectomy, and removal of regional nodes</li> </ul>

## Glucagonoma

A glucagonoma is a rare tumor found usually in the tail of the pancreas. It occurs when your body makes too much of the hormone glucagon. Glucagon is a hormone that helps the body control glucose (sugar) levels in the blood.

Symptoms of glucagonoma may include:

- Skin rash
- Weight loss
- Diabetes
- Mouth ulcers
- Diarrhea
- Blood clots
- Mood changes

Recommended testing includes:

- Glucagon and blood glucose
- Abdominal with or without pelvis multiphasic CT or MRI

Additional testing may include:

- SSTR-PET/CT or SSTR-PET/MRI
- Chest CT with or without contrast
- Endoscopic ultrasound (EUS)
- Biochemical tests
- Consider genetic counseling and testing for inherited genetic conditions

Treatment is broken up by locoregional disease and metastatic disease.

### Locoregional disease

Primary treatment for glucagonoma includes:

- Octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot)
- Treatment for hyperglycemia and diabetes, as appropriate

Further treatment will be based on tumor location in the pancreas:

- Head (rare) – pancreatoduodenectomy and peripancreatic lymphadenectomy
- Distal – distal pancreatectomy with peripancreatic lymphadenectomy dissection and a splenectomy

### Metastatic disease

For treatment of metastatic disease, [see Guide 10](#).

## Insulinoma

Insulinoma refers to a tumor in your pancreas. This type of tumor makes too much insulin (more than your body can use). Insulinomas are known to cause hypoglycemia (low blood sugar).

Symptoms of insulinoma may include:

- Confusion
- Sweating
- Weakness
- Rapid heartbeat

Recommended testing for insulinoma includes:

- Abdominal with or without pelvis multiphasic CT or MRI
- Serum insulin, pro-insulin, and C-peptide levels during very low blood sugar (hypoglycemia)

Additional testing may include:

- Endoscopic ultrasound (EUS)
- Other biochemical tests
- SSTR-PET/CT or SSTR-PET/MRI
- Chest CT with or without contrast
- Consider genetic counseling and testing for inherited genetic conditions

Treatment for gastrinoma is broken up by locoregional disease and metastatic disease.

### Locoregional disease

Primary treatment for locoregional insulinoma starts by getting your glucose (sugar) levels stable with a change in diet and/or diazoxide (Proglycem) and/or everolimus (Afinitor).

Further treatment is determined by the tumor type and location:

- For surface tumors or those growing outward (exophytic), you will receive a tumor enucleation. A tumor enucleation is a procedure where tumor cells are removed, but the pancreas is left intact.
- For deeper or invasive tumors close to the main pancreatic duct in the head of the pancreas, you will receive a pancreatoduodenectomy.
- For deeper or invasive tumors close to the main pancreatic duct in the distal part of the pancreas, you will receive a distal pancreatectomy. The entire spleen will not be removed. Minimally invasive surgery will be considered.

### Metastatic disease

For treatment of metastatic disease, [see Guide 10](#).

## VIPoma

A VIPoma is a rare tumor found in the pancreas. A VIPoma secretes vasoactive intestinal peptide (VIP). VIP is a hormone that helps the body to release sodium, chloride, potassium, and water in the small intestine.

Symptoms may include:

- Abdominal pain and cramping
- Severe diarrhea
- Dehydration
- Flushing of the face
- Muscle cramps
- Weight loss

Recommended testing includes:

- Electrolytes (as potassium level may be low)
- VIP levels
- Abdominal with or without pelvis multiphasic CT or MRI

Additional testing may include:

- SSTR-PET/CT or SSTR-PET/MRI
- Chest CT with or without contrast
- Endoscopic ultrasound (EUS)
- Biochemical tests
- Consider genetic counseling and testing for inherited genetic conditions

Treatment is broken up by locoregional disease and metastatic disease.

### Locoregional disease

Primary treatment for VIPoma includes:

- Octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot)
- Correct any electrolyte imbalance and dehydration

Further treatment will be based on tumor location in the pancreas:

- Head (rare) – pancreatoduodenectomy and peripancreatic lymphadenectomy
- Distal – distal pancreatectomy and peripancreatic lymphadenectomy with or without a splenectomy

### Metastatic disease

For treatment of metastatic disease, [see Guide 10](#).

## Surveillance

Surveillance tests are done at specific times after treatment to check if the cancer has returned. These tests can help find cancer early so you can start treatment again, if needed.

Surveillance tests may include general health tests such as a medical history and a physical exam, and imaging tests. For a list of tests and time frames, [see Guide 9](#).



## Advanced disease

Advanced disease, also called metastatic disease, refers to cancer that has spread from the primary tumor site to a distant part of the body. If you are suspected of having metastatic (advanced) disease you will receive more testing to confirm. Treatment options for metastatic disease are based on tumor burden and whether the tumor could be removed by surgery.

Testing may include:

- Abdominal with or without pelvic multiphasic CT or MRI and chest CT with or without contrast
- SSTR-PET/CT or SSTR-PET/MRI
- Biochemical tests
- Tumor classification and grade

### Complete resection is possible

If the testing indicates that a complete resection is possible, the primary tumor and any areas of metastases will be removed. After treatment, you should expect follow-up tests to see how well the treatment worked. For a list of surveillance tests, [see Guide 9](#).

Surveillance tests help to ensure quality cancer care. They are used to find early signs of disease recurrence or increased risk for disease.

### Guide 9

#### PNETs: Surveillance tests

Time since resection	Tests, as needed
<b>12 weeks to 12 months</b>	<ul style="list-style-type: none"> <li>• General health tests</li> <li>• Biochemical tests</li> <li>• Abdominal multiphasic CT or MRI</li> <li>• Chest CT with or without contrast</li> </ul>
<b>1 year to 10 years (every 6 to 12 months)</b>	<ul style="list-style-type: none"> <li>• General health tests</li> <li>• Biochemical tests</li> <li>• Abdominal multiphasic CT or MRI</li> <li>• Chest CT with or without contrast</li> </ul>
<b>Over 10 years</b>	<ul style="list-style-type: none"> <li>• Surveillance as needed</li> </ul>

**Asymptomatic, low tumor burden, and stable disease**

Primary treatment for asymptomatic tumors, lower tumor burden, and stable disease includes:

- Observe with biochemical tests and abdominal/pelvic multiphasic CT or MRI every 12 weeks to 12 months and chest CT with or without contrast (as needed)
- Consider octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot)

**Symptomatic or significant tumor burden or significant progressive disease**

Symptoms will be managed. An alternative front-line therapy may be given. For disease progression, you may be treated with octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot).

For treatment options for disease progression, metastatic disease, or alternate front-line options, [see Guide 10](#).

**Guide 10****PNETs: Disease progression and alternate front-line treatments**

Clinical trial

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Everolimus (Afinitor)

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Sunitinib (Sutent)

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Temozolomide (Temodar) and capecitabine (Xeloda)

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PRRT with <sup>177</sup>Lu-dotatate, if SSTR-positive and progression on octreotide LAR or lanreotide

---

Other cytotoxic chemotherapy

---

Belzutifan (Welireg) in the setting of germline *VHL* (von Hippel-Lindau) alteration

---

Liver-directed therapy for liver-predominant disease

---

Palliative RT for symptomatic bone metastases

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## Key points

- The pancreas is a large gland found in your abdomen. The pancreas lies behind the stomach and across the spine. The pancreas has 3 parts: the head, the body, and the tail.
- A pancreatic neuroendocrine tumor (PNET) is a type of cancer that forms tumors in the pancreas. PNETs are either functional (produce hormones) or, more commonly, nonfunctional (do not produce hormones).
- Non-functioning PNETs are caused by abnormal growth and reproduction of neuroendocrine cells in the pancreas.
- Gastrinoma refers to a rare tumor that is found in neuroendocrine cells. Gastrinomas make too much gastrin. Gastrin helps your body control the amount of acid in your stomach and helps to digest food.
- A glucagonoma is a rare tumor found in the pancreas. It occurs when your body makes too much of the hormone glucagon.
- Insulinoma refers to a tumor in your pancreas. The tumor makes too much insulin (more than your body can use).
- A VIPoma is a rare tumor found in the pancreas. A VIPoma secretes vasoactive intestinal peptide (VIP). VIP is a hormone that helps the body to release sodium, chloride, potassium, and water in the small intestine.



### **Let us know what you think!**

Please take a moment to complete an online survey about the NCCN Guidelines for Patients.

[NCCN.org/patients/response](https://www.nccn.org/patients/response)

# 7

## Other NETs

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- 67 Well-differentiated grade 3 NET
- 70 Poorly differentiated neuroendocrine carcinoma
- 71 Key points



This chapter reviews diagnosis and treatment for NETs that do not have a known original tumor site.

advanced or metastatic disease in the NETs of the GI tract, lung, or thymus sections of this book.

## NETs of unknown primary

Neuroendocrine tumors (NETs) of unknown primary refer to tumors that do not have a known original tumor site. If the original tumor site cannot be identified, the tumor will be treated as a tumor of unknown primary.

Testing will include:

- Chest CT with or without contrast and multiphasic abdominal/pelvic CT or MRI
- SSTR-PET/CT or SSTR-PET/MRI

You may also have the following additional tests:

- FDG-PET/CT and brain imaging (CT or MRI) with contrast in poorly differentiated carcinomas only
- EGD or EUS and/or colonoscopy

After testing, your doctor will let you know whether or not the primary site has been found.

- If the primary site has been found, you will be treated based on the tumor type and its location.
- If the primary site has not been found, you will be treated based on the tumor grade: poorly differentiated, well-differentiated grades 1 and 2, or well-differentiated grade 3. For well-differentiated grades 1 and 2, treatment can be found under

## Well-differentiated grade 3 NET

A grade 3, well-differentiated NET is considered high grade. This means the cells of the tumor are fast growing. High-grade tumors are more likely to spread to other areas of the body.

Testing will include:

- Multiphasic abdominal/pelvic CT or MRI with contrast with or without a chest CT as needed
- Pathology review
- SSTR-PET/CT or SSTR-PET/MRI

You may receive the following tests:

- FDG-PET/CT
- Biochemical tests
- Tumor mutational burden (TMB) testing
- Assessment of p53, Rb, p16 by histopathologic analysis, or molecular profiling if uncertain about differentiation
- Genetic counseling and testing for inherited genetic conditions, especially for duodenal or pancreatic NET (PNET)

Treatment for Grade 3 tumors is broken up by whether the tumors are locoregional (resectable), locally advanced, or metastatic.

### Locoregional disease

If surgery is possible based on the tumor features, you will receive a resection and regional lymphadenectomy.

If surgery may not be the best option based on the tumor features, then you will be treated with one of the following:

- Clinical trial (preferred)
- Resection with regional lymphadenectomy
- Neoadjuvant chemotherapy on a case-by-case basis; options include:
  - Temozolomide (Temodar) with or without capecitabine (Xeloda)
  - Oxaliplatin (Eloxatin)-based therapy (FOLFOX or CAPEOX)
  - Cisplatin with etoposide (Etopophos) or carboplatin with etoposide

Neoadjuvant chemotherapy is given to shrink the tumor before surgery. Then if surgery is possible, you may receive a resection with regional lymphadenectomy.

After treatment you will be monitored to see if the disease returns. You should expect tests every 12 to 24 weeks for the first 2 years and then every 6 to 12 months for up to 10 years.

Follow-up testing may include:

- Physical exam
- Abdominal/pelvic MRI with contrast or abdominal/pelvic multiphasic CT
- Chest CT

### Locally advanced or metastatic disease

Treatment for a locally advanced or metastatic neuroendocrine tumor is broken up by whether or not you can receive surgery based on tumor features. Tumor features can be favorable or unfavorable. Ask your doctor what this might mean.

#### Resectable

If you are able to have surgery you will receive a resection of the primary tumor and any metastatic sites.

After treatment you will be monitored to see if the disease returns. You should expect tests every 12 to 24 weeks for the first 2 years and then every 6 to 12 months for up to 10 years.

Follow-up testing may include a physical exam Abdominal/pelvic MRI with contrast or abdominal/pelvic multiphasic CT, and chest CT

#### Unresectable

Unresectable options are divided into:

- Significant tumor burden or evidence of disease progression
- Asymptomatic, tumor burden
- Unfavorable tumor features (biology)

**If you have significant tumor burden or evidence that your disease has spread,** you will receive one of the following treatment options:

- Octreotide LAR or lanreotide (if SSTR-positive and/or hormonal symptoms)
- Clinical trial (preferred)

- PRRT with <sup>177</sup>Lu-dotatate
- Everolimus (Afinitor)
- Sunitinib (pancreas only)
- Pembrolizumab (for specific tumor types)
- Chemotherapy
- Liver-directed therapy for liver-dominant disease

**If you have asymptomatic, low tumor burden** that is also asymptomatic (no symptoms), you will be treated with one of the following:

- Observation (in some cases)
- Octreotide LAR or lanreotide (if somatostatin receptor-positive and/or hormonal symptoms)

After treatment you will be monitored to see if the disease returns. You should expect tests every 12 to 24 weeks (depending on tumor biology).

Testing may include:

- Physical exam
- Chest CT with or without contrast
- Abdominal/pelvic MRI with contrast or abdominal/pelvic multiphasic CT
- SSTR-PET/CT or SSTR-PET/MRI or FDG PET/CT
- Biochemical tests

**If you have locally advanced or metastatic disease with unfavorable tumor features,** you will be treated with one or more of the following:

- Clinical trial (preferred)
- Cisplatin with etoposide (Etopophos) or carboplatin with etoposide
- Temozolomide (Temodar) with or without capecitabine
- Oxaliplatin-based therapy
- Pembrolizumab (for specific tumor types)
- Irinotecan-based therapy
- Nivolumab (Opdivo) with ipilimumab (Yervoy)
- Liver-directed therapy such as embolization, selective internal radiation therapy (RT), ablation, or SBRT
- Palliative RT for symptomatic bone metastases

After treatment you will be monitored to see if the disease returns. You should expect tests every 8 to 12 weeks (depending on tumor biology).

Testing may include:

- Physical exam
- Chest CT with or without contrast
- Abdominal/pelvic MRI with contrast
- FDG PET/CT
- Biochemical tests

## Poorly differentiated neuroendocrine carcinoma

Poorly differentiated neuroendocrine carcinomas (NECs) are rare tumors that can develop anywhere in the gastrointestinal tract, as well as other locations. This neuroendocrine tumor (NET) type may also include large or small cell carcinoma or mixed neuroendocrine-non-neuroendocrine neoplasm.

There are 3 different tumor types:

- Poorly differentiated NEC
- Large or small cell carcinoma (other than lung)
- Mixed neuroendocrine-non-neuroendocrine neoplasm

Recommended testing includes:

- Chest/abdominal/pelvic CT or
- Chest CT and abdominal/pelvic MRI

You may receive the following tests:

- Brain MRI or CT with contrast
- FDG-PET/CT
- Biochemical tests
- Microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) tumor testing

Once testing is complete, your tumor will be defined as resectable, unresectable (locoregional), or metastatic.

### Resectable

Treatment options depend on where your tumor cells are found.

Treatment may include:

- Resection followed by chemotherapy with or without RT
- Chemotherapy with or without RT, followed by resection
- Chemotherapy alone
- Chemoradiation with cisplatin and etoposide (Etopophos) or chemoradiation with carboplatin and etoposide (Etopophos)

After treatment you will be monitored to see if the disease returns. You should expect tests every 12 weeks to 1 year, then every 6 months.

Follow-up testing may include:

- Physical exam
- Chest CT with or without contrast and abdominal/pelvic MRI with contrast
- Chest/abdominal/pelvic multiphase CT



**Locoregional, unresectable**

Treatment options for locoregional, unresectable disease include:

- Radiation therapy (RT) and chemotherapy
- Chemotherapy

After treatment you will be monitored to see if the disease returns. You should expect tests every 6 to 16 weeks.

Follow-up testing may include:

- Physical exam
- Chest CT with or without contrast and abdominal/pelvic MRI with contrast
- Chest/abdominal/pelvic multiphase CT

**Metastatic**

Metastatic disease is treated with chemotherapy. If disease progresses after treatment on chemotherapy, you will be asked to consider nivolumab (Opdivo) and ipilimumab (Yervoy).

After treatment you will be monitored to see if the disease returns. You should expect tests every 6 to 16 weeks.

Testing may include:

- Physical exam
- Chest CT with or without contrast and abdominal/pelvic MRI with contrast
- Chest/abdominal/pelvic multiphase CT

**Key points**

- Neuroendocrine tumors (NETs) of unknown primary refer to tumors that do not have a known original tumor site.
- If the original tumor site cannot be identified, the tumor will be treated as a tumor of unknown primary.
- A Grade 3 well-differentiated NET is considered high grade. This means the cells of the tumor are fast growing.
- High-grade tumors are more likely to spread to other areas of the body.
- Poorly differentiated NECs are rare tumors that can develop anywhere in the gastrointestinal tract.

# 8

## Multiple endocrine neoplasia type 1

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Multiple endocrine neoplasia type 1 (MEN1) is a rare, inherited condition that can put one at increased risk for developing tumors in the endocrine glands. Anyone with suspected MEN1 should receive genetic counseling and testing for inherited genetic conditions.

## Overview

Multiple endocrine neoplasia type 1 (MEN1) is a rare, inherited condition that can put one at increased risk for developing tumors in the endocrine glands and parts of the small intestine and stomach. Endocrine glands include the parathyroid glands, pancreas, and pituitary gland. In MEN1, endocrine glands grow tumors that create excessive amounts of

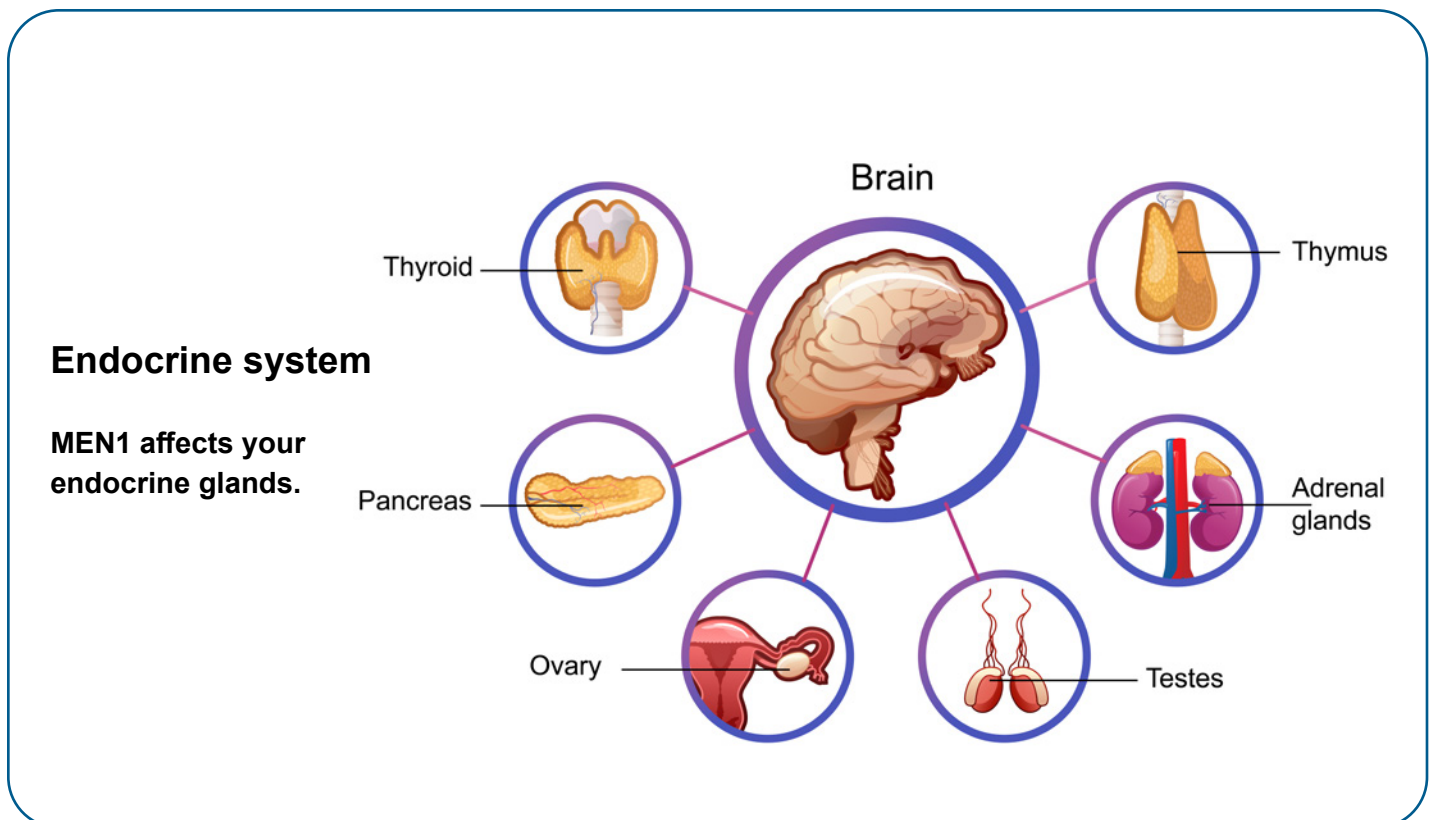
hormones. However, the tumors are usually benign (not cancer). MEN1 is also referred to as Wermer syndrome.

## Symptoms

MEN1 symptoms are caused by the release of too many hormones in the body.

Symptoms may include:

- Tiredness
- Bone pain
- Broken bones
- Kidney stones
- Ulcers in the stomach or intestines



## Testing

Testing for MEN1 is specific to where the tumor is found, such as the parathyroid glands, pancreas, pituitary gland, lungs, or thymus gland. However, anyone with suspected MEN1 should receive genetic counseling and testing for inherited genetic conditions.

### Parathyroid glands

The parathyroid glands are 4 pea-sized organs found in the neck. For a tumor in the parathyroid glands, you might have the following tests:

- Serum calcium
- Parathyroid hormone (PTH) and 25-OH vitamin D
- Imaging (neck ultrasound, parathyroid sestamibi with SPECT scan, or 4D-CT)

### Pancreas

For a tumor in the pancreas, also referred to as PanNET, you might have the following tests:

- Biochemical tests (recommended)
- Abdominal with or without pelvic multiphasic CT or MRI (recommended)
- Endoscopic ultrasound (EUS)
- Somatostatin receptor (SSTR)-PET/CT or SSTR-PET/MRI

### Pituitary

For a tumor in the pituitary gland, you might have the following tests:

- Pituitary or sella MRI with contrast
- Biochemical tests

### Bronchial/thymic

For a tumor in the thymus or lungs, you might have the following tests:

- Chest CT with contrast and abdominal/pelvic multiphasic CT or MRI
- Biochemical tests

## Treatment

Treatment for MEN1 is based on tumor location.

### Parathyroid glands

If a tumor is found in the parathyroid glands, you will be treated with one of the following:

- Subtotal parathyroidectomy. Cryopreservation of parathyroids and thymectomy might also be done.
- Total parathyroidectomy with autotransplantation. Cryopreservation of parathyroids and thymectomy might also be done with the total parathyroidectomy.

## Pancreas

If a tumor is found in your pancreas, you will be treated with one or more of the following:

- Observation
- Enucleation with or without regional lymphadenectomy
- Resection pancreatectomy with or without regional lymphadenectomy
- Pancreatoduodenectomy with regional lymphadenectomy (if the tumor is in the head of the pancreas)
- Distal pancreatectomy with splenectomy and regional lymphadenectomy (if the tumor is in the distal part of the pancreas)

## Pituitary gland

Treatment for an adrenal tumor located in the pituitary gland will begin with a referral to an endocrinologist for more testing.

## Bronchial/thymic

Treatment for tumors of the lungs and thymus can be found in Chapter 5: Pulmonary NETs.

## Surveillance

Surveillance tests are done at specific times after treatment to check if the cancer has returned. These tests can help find cancer early so you can start treatment again, if needed. Surveillance tests will likely include blood and imaging tests.

## Key points

- Multiple endocrine neoplasia type 1 (MEN1), is a rare, inherited condition that causes tumors in the endocrine glands and parts of the small intestine and stomach.
- In MEN1, your endocrine glands (parathyroids, pancreas, and pituitary) grow tumors that create excessive amounts of hormones.
- Testing and treatment for MEN1 is based on where the tumor is located, such as the parathyroid glands, pancreas, pituitary gland, lungs, or thymus.
- Anyone with suspected MEN1 should receive genetic counseling and testing for inherited genetic conditions.
- Surveillance tests are done at specific times after treatment to check if the cancer has returned. These tests can help find cancer early so you can start treatment again, if needed.

# 9

## Making treatment decisions

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It's important to be comfortable with the cancer treatment you choose. This choice starts with having an open and honest conversation with your doctor.

## It's your choice

In shared decision-making, you and your doctors share information, discuss the options, and agree on a treatment plan. It starts with an open and honest conversation between you and your doctor.

Treatment decisions are very personal. What is important to you may not be important to someone else.

Some things that may play a role in your decision-making:

- What you want and how that might differ from what others want
- Your religious and spiritual beliefs
- Your feelings about certain treatments like surgery or chemotherapy
- Your feelings about pain or side effects such as nausea and vomiting
- Cost of treatment, travel to treatment centers, and time away from school or work
- Quality of life and length of life
- How active you are and the activities that are important to you

Think about what you want from treatment. Discuss openly the risks and benefits of specific treatments and procedures. Weigh options and share concerns with your doctor. If you take the time to build a relationship with

your doctor, it will help you feel supported when considering options and making treatment decisions.

## Second opinion

It is normal to want to start treatment as soon as possible. While cancer can't be ignored, there is time to have another doctor review your test results and suggest a treatment plan. This is called getting a second opinion, and it's a normal part of cancer care. Even doctors get second opinions!

Things you can do to prepare:

- Check with your insurance company about its rules on second opinions. There may be out-of-pocket costs to see doctors who are not part of your insurance plan.
- Make plans to have copies of all your records sent to the doctor you will see for your second opinion.

## Support groups

Many people diagnosed with cancer find support groups to be helpful. Support groups often include people at different stages of treatment. Some people may be newly diagnosed, while others may be finished with treatment. If your hospital or community doesn't have support groups for people with cancer, check out the websites listed in this book.

## Questions to ask your doctors

Possible questions to ask your doctors are listed on the following pages. Feel free to use these questions or come up with your own. Be clear about your goals for treatment and find out what to expect from treatment.

## Questions to ask about diagnosis and testing

1. What type of neuroendocrine tumor do I have?
2. Is there a cancer center or hospital nearby that specializes in neuroendocrine tumors?
3. What tests are needed? What other tests do you recommend?
4. How do I prepare for testing?
5. How and where will the test be done?
6. How soon will I know the results and who will explain them to me?
7. Would you give me a copy of the pathology report and other test results?
8. Will you explain my pathology report to me?
9. Who will talk with me about the next steps? When?

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## Questions to ask your doctors about their experience

1. Who will be part of my health care team, and what does each member do?
2. Who will be leading my overall treatment?
3. What is your experience in treating people with neuroendocrine tumors?
4. Who else will be on my treatment team?
5. What other diagnostic tests or procedures will I need?
6. I would like to get a second opinion. Is there someone you recommend?
7. How many patients like me (of the same age, gender, race) have you treated?
8. Will you be consulting with experts to discuss my care? Whom will you consult?
9. How many procedures like the one you're suggesting have you done?
10. Is this treatment a major part of your practice?
11. How many of your patients have had complications? What were the complications?
12. Who will manage my day-to-day care?

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## Resources

### American Cancer Society

[cancer.org/cancer/pancreatic-neuroendocrine-tumor.html](https://cancer.org/cancer/pancreatic-neuroendocrine-tumor.html)

### Carcinoid Cancer Foundation, Inc.

[carcinoid.org/for-patients](https://carcinoid.org/for-patients)

### Chemocare

[chemocare.com](https://chemocare.com)

### The Healing NET Foundation

[thehealingnet.org](https://thehealingnet.org)

### Los Angeles Carcinoid Neuroendocrine Tumor Society

[lacnets.org](https://lacnets.org)

### National Cancer Institute

[cancer.gov/search/results?swKeyword=neuroendocrine+tumors](https://cancer.gov/search/results?swKeyword=neuroendocrine+tumors)

### National Coalition for Cancer Survivorship

<https://canceradvocacy.org>

### National Financial Resource Directory

- Patient Advocate Foundation

[patientadvocate.org/explore-our-resources/national-financial-resource-directory/](https://patientadvocate.org/explore-our-resources/national-financial-resource-directory/)

### National Hospice and Palliative Care Organization

[nhpco.org](https://nhpco.org)

### Neuroendocrine Cancer Awareness Network (NCAN)

[Netcancerawareness.org](https://netcancerawareness.org)

### Neuroendocrine Tumor Research Foundation (NETRF)

[Netrf.org](https://netrf.org)

### OncoLink

[oncolink.org](https://oncolink.org)

### Patient Access Network Foundation

[panfoundation.org](https://panfoundation.org)

### Radiological Society of North America

[radiologyinfo.org](https://radiologyinfo.org)

### Testing.com

[testing.com](https://testing.com)



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And help make the  
NCCN Guidelines for Patients  
better for everyone!

[NCCN.org/patients/comments](https://NCCN.org/patients/comments)



## Words to know

**adjuvant therapy**

Treatment that is given after surgery to lower the chances of the cancer returning.

**adrenal gland**

A small organ on top of each kidney that makes hormones.

**aggressive cancer**

A cancer that grows or spreads fast.

**allergic reaction**

An abnormal response by the body to a foreign substance that is harmless.

**anus**

The opening of the intestinal tract between the legs through which stool passes out of the body.

**appendix**

A small tube-like organ attached to the first section of the large intestine.

**biochemical test**

A test to measure the level of chemicals in the body.

**biopsy**

A procedure that removes fluid or tissue samples to be tested for disease.

**bronchopulmonary**

A term used for the airways that lead to the lungs (bronchi and pulmonary).

**bronchoscopy**

A procedure to work inside the airways with a device that is guided down the throat.

**bronchus**

One of the airways that extends into the lungs. The plural form is bronchi.

**cancer grade**

A rating of how much cancer cells look like normal cells.

**cancer stage**

A rating of the outlook for people with cancer based on the cancer's growth and spread.

**carcinoid syndrome**

A group of symptoms that happen when carcinoid tumors release serotonin and other chemicals into the blood.

**carcinoid tumor**

A neuroendocrine tumor found most commonly in the gastrointestinal tract, lungs, bronchi, thymus, and other areas in the body. It may secrete the hormone serotonin and other chemicals.

**carcinoma**

A cancer of cells that line the inner or outer surfaces of the body.

**chemoradiation**

Treatment with a combination of chemotherapy and radiation therapy.

**chemotherapy**

Drugs that kill cancer cells by damaging or disrupting the making of the genetic code.

**clinical trial**

A type of research that assesses health tests or treatments.

**colon**

The hollow organ in which eaten food turns from a liquid into a solid form.

**computed tomography (CT)**

A test that uses x-rays from many angles to make a picture of the insides of the body.

**contrast**

A dye put into your body to make clearer pictures during imaging tests.



**cortisol**

A hormone that controls blood sugar, metabolism, and other functions in the body.

**Cushing syndrome**

A condition caused by the release of excess cortisol in the body.

**deoxyribonucleic acid (DNA)**

A chain of chemicals in cells that contains coded instructions for making and controlling cells. Also called the “blueprint of life.”

**duodenum**

A part of the digestive tract that receives food from the stomach and mixes it with digestive juices.

**endoscope**

A device that is passed through a natural opening to do work inside the body.

**enucleation**

Removal of an organ or tumor in such a way that it comes out clean and whole, like a nut from its shell.

**first-line or front-line therapy**

The first drug or set of drugs given to treat cancer.

**gastrin**

A hormone made and released by the stomach.

**gastrointestinal (GI) tract**

The group of organs through which food passes after being eaten. Also called digestive tract.

**gene**

Coded instructions in cells for making new cells and controlling how cells behave.

**genetic testing**

A lab test (usually performed on blood or saliva) to identify abnormal genes (coded

instructions in cells that are passed down within a family) that impact your risk of developing cancer.

**glucagon**

A hormone made by the pancreas that works with insulin to control blood sugar levels. It raises the blood sugar levels.

**hereditary**

Passed down from parent to child through coded information in cells.

**hives**

A skin rash caused by the body trying to rid itself of a foreign substance.

**hormone**

A chemical in the body that triggers a response from cells or organs.

**hypothalamus**

A part of the brain that works with the nervous system and glands that make hormones in the body.

**ileum**

The last section of the small intestine.

**imaging**

A test that makes pictures (images) of the insides of the body.

**immune system**

The body’s natural defense against infection and disease.

**immunotherapy**

A treatment with drugs that help the body find and destroy cancer cells.

**insulin**

A chemical that controls the amount of sugar in the blood. It lowers the blood sugar levels.

**jejunum**

The middle section of the small intestine.

**liver**

The largest organ and gland in the body with many vital functions.

**lung**

One of a pair of organs that consists of airways and air sacs.

**lymph node**

A small, bean-shaped disease-fighting structure.

**magnetic resonance imaging (MRI)**

A test that uses radio waves and powerful magnets to make pictures of the insides of the body.

**medical history**

A report of all your health events and medications.

**metastasis**

The spread of cancer cells from the first (primary) tumor to a new site.

**multiple endocrine neoplasia (MEN)**

An inherited syndrome that causes tumors to grow in the glands of the endocrine system. The two main types are MEN1 and MEN2.

**mutation**

An abnormal change in cells.

**neoadjuvant treatment**

A treatment given before the main treatment to reduce the amount of cancer. Also called preoperative treatment if given before an operation.

**neuroendocrine cells**

A cell that receives signals from the nervous system to make and release hormones into the blood.

**neuroendocrine tumor (NET)**

A tumor that starts in neuroendocrine cells.

**observation**

A period of testing for changes in cancer status while not receiving treatment.

**ovary**

One of a pair of organs in women that produce eggs and hormones.

**palliative care**

Health care that includes symptom relief but not cancer treatment. Also sometimes called supportive care.

**pancreas**

An organ that makes fluids that help digest food and hormones that control blood sugar.

**pelvis**

The body area between the hipbones.

**peptide receptor radionuclide therapy (PRRT)**

A procedure that uses a radiopharmaceutical drug to target and treat certain neuroendocrine tumors.

**physical exam**

A study of the body by a health expert for signs of disease.

**pineal gland**

A small gland in the cerebrum of the brain.

**pituitary gland**

An organ in the brain that controls certain body functions and other hormone glands. Also called the “master gland.”

**positron emission tomography (PET)**

A test that uses radioactive material to see the shape and function of body parts.

**primary treatment**

The main treatment used to rid the body of cancer.

**primary tumor**

The first mass of cancer cells.

**progression**

The growth or spread of cancer after being tested or treated.

**prostate**

A male gland that makes fluid that protects sperm from the acid in the vagina.

**radiation therapy (RT)**

A treatment that uses high-energy rays or related approaches to kill cancer cells.

**radiopharmaceutical**

A drug that carries a certain amount of radioactive material.

**rectum**

An organ that holds stool until expelled from the body.

**serotonin**

A hormone that sends signals between nerve cells and controls things like mood, sleep, and memory.

**somatostatin**

A peptide hormone that attaches to receptors and controls the endocrine system and nervous system.

**somatostatin receptor (SSTR) scintigraphy**

A type of imaging scan used to assess carcinoid tumors that have somatostatin receptors.

**stomach**

An organ of the digestive system that turns solid food into a more liquid form.

**supportive care**

Health care that includes symptom relief but not cancer treatment. Also called palliative care.

**surgery**

An operation to remove or repair a part of the body.

**surgical margin**

The normal-looking tissue around the edge of a tumor that is removed during surgery.

**targeted therapy**

A drug treatment that impedes the growth process specific to cancer cells.

**testicle**

One of a pair of egg-shaped glands found inside the sac between the legs of a man.

**thymus**

A gland that is behind the breastbone.

**tumor marker**

A substance found in body tissue or fluid that may be a sign of cancer.

**ulcer**

A sore on the skin or mucous membrane in the body.

**ultrasound**

A test that uses sound waves to take pictures of the insides of the body.

**vasoactive intestinal polypeptide (VIP)**

A hormone that controls the amount of water and minerals absorbed into the small intestine during digestion.

**x-ray**

A test that uses small amounts of radiation to make pictures of the insides of the body. Also called a plain radiograph.

# NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Neuroendocrine and Adrenal Tumors, Version 1.2022. It was adapted, reviewed, and published with help from the following people:

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# NCCN Cancer Centers

Abramson Cancer Center  
at the University of Pennsylvania  
Philadelphia, Pennsylvania  
800.789.7366 • [penmedicine.org/cancer](http://penmedicine.org/cancer)

Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer  
Center and Cleveland Clinic Taussig  
Cancer Institute  
Cleveland, Ohio  
800.641.2422 • UH Seidman Cancer Center  
[uhhospitals.org/services/cancer-services](http://uhhospitals.org/services/cancer-services)  
866.223.8100 • CC Taussig Cancer Institute  
[my.clevelandclinic.org/departments/cancer](http://my.clevelandclinic.org/departments/cancer)  
216.844.8797 • Case CCC  
[case.edu/cancer](http://case.edu/cancer)

City of Hope National Medical Center  
Los Angeles, California  
800.826.4673 • [cityofhope.org](http://cityofhope.org)

Dana-Farber/Brigham and Women's  
Cancer Center | Massachusetts General  
Hospital Cancer Center  
Boston, Massachusetts  
617.732.5500 • [youhaveus.org](http://youhaveus.org)  
617.726.5130  
[massgeneral.org/cancer-center](http://massgeneral.org/cancer-center)

Duke Cancer Institute  
Durham, North Carolina  
888.275.3853 • [dukecancerinstitute.org](http://dukecancerinstitute.org)

Fox Chase Cancer Center  
Philadelphia, Pennsylvania  
888.369.2427 • [foxchase.org](http://foxchase.org)

Fred & Pamela Buffett Cancer Center  
Omaha, Nebraska  
402.559.5600 • [unmc.edu/cancercenter](http://unmc.edu/cancercenter)

Fred Hutchinson Cancer  
Research Center/Seattle  
Cancer Care Alliance  
Seattle, Washington  
206.606.7222 • [seattlecca.org](http://seattlecca.org)  
206.667.5000 • [fredhutch.org](http://fredhutch.org)

Huntsman Cancer Institute  
at the University of Utah  
Salt Lake City, Utah  
800.824.2073 • [huntsmancancer.org](http://huntsmancancer.org)

Indiana University  
Melvin and Bren Simon  
Comprehensive Cancer Center  
Indianapolis, Indiana  
888.600.4822 • [www.cancer.iu.edu](http://www.cancer.iu.edu)

Mayo Clinic Cancer Center  
Phoenix/Scottsdale, Arizona  
Jacksonville, Florida  
Rochester, Minnesota  
480.301.8000 • Arizona  
904.953.0853 • Florida  
507.538.3270 • Minnesota  
[mayoclinic.org/cancercenter](http://mayoclinic.org/cancercenter)

Memorial Sloan Kettering  
Cancer Center  
New York, New York  
800.525.2225 • [mskcc.org](http://mskcc.org)

Moffitt Cancer Center  
Tampa, Florida  
888.663.3488 • [moffitt.org](http://moffitt.org)

O'Neal Comprehensive  
Cancer Center at UAB  
Birmingham, Alabama  
800.822.0933 • [uab.edu/onealcancercenter](http://uab.edu/onealcancercenter)

Robert H. Lurie Comprehensive Cancer  
Center of Northwestern University  
Chicago, Illinois  
866.587.4322 • [cancer.northwestern.edu](http://cancer.northwestern.edu)

Roswell Park Comprehensive  
Cancer Center  
Buffalo, New York  
877.275.7724 • [roswellpark.org](http://roswellpark.org)

Siteman Cancer Center at Barnes-  
Jewish Hospital and Washington  
University School of Medicine  
St. Louis, Missouri  
800.600.3606 • [siteman.wustl.edu](http://siteman.wustl.edu)

St. Jude Children's  
Research Hospital/  
The University of Tennessee  
Health Science Center  
Memphis, Tennessee  
866.278.5833 • [stjude.org](http://stjude.org)  
901.448.5500 • [uthsc.edu](http://uthsc.edu)

Stanford Cancer Institute  
Stanford, California  
877.668.7535 • [cancer.stanford.edu](http://cancer.stanford.edu)

The Ohio State University  
Comprehensive Cancer Center -  
James Cancer Hospital and  
Solove Research Institute  
Columbus, Ohio  
800.293.5066 • [cancer.osu.edu](http://cancer.osu.edu)

The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins  
Baltimore, Maryland  
410.955.8964  
[www.hopkinskimmelcancercenter.org](http://www.hopkinskimmelcancercenter.org)

The University of Texas  
MD Anderson Cancer Center  
Houston, Texas  
844.269.5922 • [mdanderson.org](http://mdanderson.org)

UC Davis  
Comprehensive Cancer Center  
Sacramento, California  
916.734.5959 • 800.770.9261  
[health.ucdavis.edu/cancer](http://health.ucdavis.edu/cancer)

UC San Diego Moores Cancer Center  
La Jolla, California  
858.822.6100 • [cancer.ucsd.edu](http://cancer.ucsd.edu)

UCLA Jonsson  
Comprehensive Cancer Center  
Los Angeles, California  
310.825.5268 • [cancer.ucla.edu](http://cancer.ucla.edu)

UCSF Helen Diller Family  
Comprehensive Cancer Center  
San Francisco, California  
800.689.8273 • [cancer.ucsf.edu](http://cancer.ucsf.edu)

University of Colorado Cancer Center  
Aurora, Colorado  
720.848.0300 • [coloradocancercenter.org](http://coloradocancercenter.org)

University of Michigan  
Rogel Cancer Center  
Ann Arbor, Michigan  
800.865.1125 • [rogelcancercenter.org](http://rogelcancercenter.org)

University of Wisconsin  
Carbone Cancer Center  
Madison, Wisconsin  
608.265.1700 • [uwhealth.org/cancer](http://uwhealth.org/cancer)

UT Southwestern Simmons  
Comprehensive Cancer Center  
Dallas, Texas  
214.648.3111 • [utsouthwestern.edu/simmons](http://utsouthwestern.edu/simmons)

Vanderbilt-Ingram Cancer Center  
Nashville, Tennessee  
877.936.8422 • [vicc.org](http://vicc.org)

Yale Cancer Center/  
Smilow Cancer Hospital  
New Haven, Connecticut  
855.4.SMILOW • [yalecancercenter.org](http://yalecancercenter.org)

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# Neuroendocrine Tumors

2022

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