GASTROINTESTINAL (DIGESTIVE SYSTEM) CARCINOID TUMORS

What Is Cancer?

Cancer occurs when cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they all come about because of out-of-control growth of abnormal cells.

Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide more rapidly until the person becomes an adult. After that, cells in most parts of the body divide only to replace worn-out or dying cells and to repair injuries.

Because cancer cells continue to grow and divide, they are different from normal cells. Instead of dying, they outlive normal cells and continue to form new ones.

Cancer cells can travel to other parts of the body where they begin to grow and replace normal tissue. This process, called metastasis, occurs as the cancer cells build up and get into the blood stream or lymph channels of our body. When cells from a cancer like a gastrointestinal carcinoid tumor spread to another organ like the liver, the cancer is still called a gastrointestinal carcinoid tumor, not liver cancer.

Cancer cells develop because of damage to DNA. This substance is in every cell and directs all its activities. People can inherit damaged DNA, which accounts for inherited cancers. Many times though, a person's DNA becomes damaged from some environmental exposure, like smoking. In many cases, scientists still do not understand why a person's DNA becomes damaged and leads to cancer. Most of the time when DNA becomes damaged the body is able to repair it. In cancer cells, the damaged DNA has not been repaired.

Cancer usually forms as a tumor. Some cancers, like leukemia, do not form tumors. Instead, these cancer cells involve the blood and blood-forming organs (bone marrow, lymphatic system, and spleen) and circulate through other tissues where they accumulate. In addition, not all tumors are cancerous. Benign (noncancerous) tumors do not spread (metastasize) and, with very rare exceptions, are not life threatening.

Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates, respond to different drugs and often spread to different parts of the body. That is why people with cancer need treatment that is aimed at their kind of cancer.

Cancer is the second leading cause of death in the US. Half of all men and one third of all women in the US will develop cancer during their lifetimes. Today, millions of people are living with cancer or have been cured of the disease. The risk of developing most types of cancer can be reduced by changes in a person's lifestyle, for example, by quitting smoking and eating a better diet. The sooner a cancer is found and treatment begins, the better are the chances for cure.

What Is a Gastrointestinal Carcinoid Tumor?

The Gastrointestinal (Digestive) System

The digestive system processes food for energy and rids the body of solid waste. After food is chewed and swallowed, it enters the esophagus, a tube-shaped organ that carries food to the stomach through the neck and chest. The esophagus joins the stomach just beneath the diaphragm (the breathing muscle under the lungs). The stomach is a sac-like organ that holds food and begins the digestive process by secreting gastric juice. The food and gastric juices are mixed into a thick fluid called chyme, which is then emptied into the small intestine. The small intestine continues breaking down the food and absorbs most of the nutrients. It is the longest section of the gastrointestinal (GI) tract. The small intestine joins the colon, a muscular tube about 5 feet long. The colon continues to absorb water and mineral nutrients from the food matter and serves as a storage place for waste. The waste left after this process goes into the rectum. From there it passes out of the body through the anus.

The Diffuse Neuroendocrine System

The diffuse neuroendocrine system consists of cells that are in certain ways like nerve cells and in other ways like cells of endocrine (hormone-producing) glands. These cells do not form an actual organ like the parathyroid, adrenal, or thyroid glands. Instead, they are scattered throughout other organs like the esophagus, stomach, intestines, and lungs. Because of the size of the digestive system, it has the most endocrine cells of any organ. This may explain why carcinoid tumors most often start in the digestive system.

Neuroendocrine cells of the digestive system help regulate the release of digestive juices, help control the speed at which food moves along the gastrointestinal tract, and may help control the growth of other types of digestive system cells.

Carcinoid Tumors

Like most cells of the body, gastrointestinal system neuroendocrine cells sometimes undergo certain changes that cause them to grow too much and form tumors. The tumors that develop from neuroendocrine cells are known as neuroendocrine tumors (or neuroendocrine cancers). There are many varieties of neuroendocrine tumors, but the most common are the carcinoid tumors or carcinoids.

Like the neuroendocrine cells they develop from, cells of many carcinoid tumors continue to release certain hormones into the bloodstream. In about 10% of people, the carcinoid tumors release high amounts of those hormones and cause symptoms such as facial flushing, wheezing, diarrhea, and a fast heartbeat. These symptoms are often grouped together and called the

"carcinoid syndrome." Unlike most cancers, which cause symptoms only in the organs they start in or spread to, carcinoid tumors release substances into the blood that cause symptoms throughout the body.

Glandular cells of the inner lining of the digestive system can develop into adenomas (noncancerous gland cell tumors) or adenocarcinomas (cancers of gland cells). These tumors are quite different from carcinoid tumors in their symptoms, their prognosis (outlook for survival), and their treatment. For these reasons, it is important for doctors to find out whether a patient has a carcinoid tumor, an adenoma, an adenocarcinoma, some other type of tumor, or a noncancerous condition. And, it is important for patients to understand that carcinoids are not the same as other, more common types of tumors. By learning more about carcinoid tumors, patients can better participate in their health care and make informed decisions about treatment options.

What Are the Key Statistics about Gastrointestinal Carcinoid Tumors?

About 5000 carcinoid tumors are diagnosed each year in the US. About two thirds of these occur in the digestive system. Most of the remaining carcinoid tumors occur in the lungs.

Within the digestive system, the most common location of carcinoid tumors is the small intestine near the appendix (ileum). The next most common site is the rectum, followed by the colon (large intestine) and the rest of the small intestine. At one time, the appendix was a very common site, but that is not longer true. Only about 7% of all intestinal carcinoid tumors begin in the appendix.

What Are the Risk Factors for Gastrointestinal Carcinoid Tumors?

A risk factor is anything that increases a person's chance of getting a disease such as a type of cancer. For example, unprotected exposure to strong sunlight is a risk factor for skin cancer and smoking is a risk factor for lung, mouth, throat, kidney, bladder, colorectal, and several other cancers. However, cancer can develop without any risk factors present. Risk factors for gastrointestinal carcinoid tumors include:

Family history of multiple endocrine neoplasia, type 1: Multiple endocrine neoplasia, type I (MEN1) is a hereditary condition that has a very high risk of developing tumors of 3 glands: the pituitary, parathyroid, and pancreas. Carcinoid tumors are a less common component of this condition. Some studies estimate that MEN1 is responsible for about 10% of carcinoid tumors. Most of these are gastric (stomach) carcinoids. MEN1 is inherited by about half of the children of each affected parent. If your family is affected by the MEN1 syndrome, you should speak with your doctor about the advantages and disadvantages of biochemical or genetic testing for this condition. The DNA mutations that cause tumors in people with multiple endocrine neoplasia, type I (MEN1) have been identified. Testing for these gene mutations currently is only available in research settings.

Smoking: Smoking may double the risk of developing a carcinoid tumor of the small intestine, according to a recent European study.

Race and gender: Carcinoid tumors are slightly more common among African Americans than

whites. Researchers do not yet know why. In general, there is not much difference in carcinoid tumor risk between men and women.

Age: The average age of people diagnosed with carcinoid tumors is 55 to 65 years.

Other stomach conditions: People with certain diseases that damage the stomach and reduce acid production by the stomach have a greater risk of developing stomach carcinoid tumors, but their risk for carcinoid tumors of other organs is not affected.

Diet: Risk of developing gastrointestinal carcinoid tumors does not appear to be increased or decreased by any specific foods.

Do We Know What Causes Gastrointestinal Carcinoid Tumors?

Very little is known about the causes of gastrointestinal carcinoid tumors.

As with other cancers, scientists have recognized some changes in the DNA of carcinoid tumor cells that are probably responsible for their increased growth and abnormal spread. But, the causes of these changes are not yet known.

Doctors do know that carcinoid tumors start out very small and grow slowly. When patients have parts of their stomach or small intestine removed to treat other diseases, close examination under the microscope often shows small groups of neuroendocrine cells that look like tiny carcinoids. Most of these miniature tumors, sometimes called "tumorlets," never develop into an actual carcinoid tumor. Researchers still do not know why some remain so small and others begin to grow and become large enough to cause symptoms.

Can Gastrointestinal Carcinoid Tumors Be Prevented?

At this time, there is no known way to prevent gastrointestinal carcinoid tumors. Since smoking may increase the risk of carcinoid tumors of the small intestine, not starting or quitting smoking may reduce the risk for this disease.

Can Gastrointestinal Carcinoid Tumors Be Found Early?

Because carcinoid tumors usually grow and spread slowly, about half of all gastroinestinal carcinoid tumors are found at an early or localized stage.

Incidental Diagnosis of Carcinoid Tumors

In many cases, carcinoid tumors are found incidentally. This means that the tumors did not cause any symptoms but were discovered during tests done for other diseases or because parts of the gastrointestinal system were removed to treat other diseases. For example, a person with symptoms due to inflammation of the stomach may have a test called endoscopy. During this test, the doctor viewing the stomach lining through a flexible lighted tube may incidentally notice a small bump in the stomach wall that turns out to be a carcinoid tumor.

Sometimes a routine sigmoidoscopy or colonoscopy (viewing the large bowel through a flexible lighted tube) for colorectal cancer screening will incidentally find a small carcinoid tumor.

Occasionally, when a person's appendix is removed to treat acute appendicitis (infection and inflammation of the appendix that causes abdominal pain), doctors may incidentally find a small carcinoid, in addition to the expected finding of inflammation. Some studies found that about 1 of every 300 people who have appendix surgery done for other diseases turn out to have a tiny carcinoid near the tip of their appendix. In most of these cases, the carcinoid was still too small to have caused any problems. The number of these appendix carcinoids is dropping. Some people think that is because these days, surgeons are less likely to remove the appendix in the course of an abdominal operation for another problem.

How Are Gastrointestinal Carcinoid Tumors Diagnosed?

If there is a reason to suspect you may have a gastrointestinal carcinoid tumor, the doctor will use one or more methods to find out if the disease is really present.

Signs and Symptoms of Gastrointestinal Carcinoid Tumors

About half of all carcinoid tumors are discovered because they cause symptoms. The most common symptom of localized carcinoid tumors (those which have not spread beyond the organ it developed in) is abdominal pain caused by "kinking" or blockage of the intestines. This pain can be mild and last for a couple of years or more before the carcinoid tumor is found. Sometimes, carcinoid tumors may cause intestinal bleeding. Many are found in the course of a routine examination of the intestinal tract.

About 10% of the time, carcinoid tumors produce hormone-like substances that are released into the bloodstream. The carcinoid syndrome results from the effect of these substances. Symptoms include facial flushing (redness and warm feeling), severe diarrhea, wheezing, and fast heartbeat. Many patients find that stress, strenuous exercise, and drinking alcohol may make these symptoms worse. Over a long time, these hormone-like substances can damage heart valves, causing shortness of breath, weakness, and a heart murmur (abnormal heart sounds a doctor can hear through a stethoscope). Some carcinoid tumors may produce adrenocorticotrophic hormone (ACTH), a substance that stimulates the adrenal gland to produce excessive amounts of cortisol and related adrenal hormones. Symptoms of excessive amounts of adrenal hormones include weight gain, weakness, secondary diabetes, and increased body and facial hair.

Not all gastrointestinal carcinoid tumors can cause the carcinoid syndrome. Rectal carcinoids usually do not produce the hormone-like substances that cause these symptoms. Also, normal liver cells break down these substances. Because blood from the gastrointestinal tract flows through the liver, substances produced by gastrointestinal carcinoid tumors are broken down in the liver and do not cause symptoms. But spread of gastrointestinal carcinoids to the liver interferes with the breakdown of substances produced by the tumor cells. When spread to the liver occurs, carcinoid syndrome may result if the tumor cells produce large amounts of symptom-causing hormones.

Medical history and physical exam: A medical history is an interview in which the doctor asks questions about symptoms and risk factors you may have. If you have one or more symptoms that suggest this type of tumor, the doctor will specifically ask about other symptoms of the carcinoid syndrome, as well as symptoms caused by the presence of a mass in the stomach, intestines, or rectum.

Some patients with carcinoid tumors also have cancers or benign tumors of other organs, so doctors will ask about symptoms that might suggest other tumors are present. A thorough physical exam will provide information about signs of carcinoid tumor and other health problems. The doctor will pay special attention to the abdomen, looking for a tumor mass or enlarged liver.

Imaging Tests

Barium x-rays: These x-ray studies use a barium-containing solution that coats the lining of the esophagus, stomach, and intestines. These are often useful for the diagnosis of some gastrointestinal carcinoid tumors. They are least effective in finding small intestine carcinoid tumors. The coating of barium helps find abnormalities of the lining of these organs. Barium studies can be used to examine the upper or lower parts of the digestive system.

A barium swallow or upper gastrointestinal (GI) x-ray study is used to examine the lining of the esophagus, stomach, and the first part of the small intestine. Patients undergoing this test drink a barium solution before the x-ray pictures are taken.

A barium enema with air contrast is used to examine the inner surface of the large intestine. Strong laxatives and enemas are used to cleanse the bowel the night before and the morning of the examination. For this test, the barium solution is given in the anus. When the colon is about half full of barium, the patient is turned on the x-ray table so the barium spreads throughout the colon. In addition to barium, air can be blown into the large intestine to help push the barium towards the wall of this organ and better coat its inner surface. When air is added to a barium x-ray study, it is a called a double-contrast study.

Computed tomography (CT): The CT scan is an x-ray procedure that produces detailed cross-sectional images of your body. Instead of taking one picture, as does a conventional x-ray, a CT scanner takes many pictures as it rotates around you. A computer then combines these pictures into an image of a slice of your body. The machine takes pictures of multiple slices of the part of your body that is being studied. This test can help tell if your carcinoid tumor has spread into lymph nodes or other organs such as your liver. Often after the first set of pictures is taken you will receive an intravenous (IV) injection of a contrast agent, or dye, which helps better outline structures in your body. A second set of pictures is then taken.

CT scans can also be used to guide a biopsy needle precisely into a suspected metastasis. For this procedure, called a CT-guided needle biopsy, the patient remains on the CT scanning table, while a radiologist moves a biopsy needle toward the location of the mass. CT scans are repeated until the doctors are confident that the needle is within the mass. A fine needle biopsy sample (tiny fragment of tissue) or a core needle biopsy sample (a thin cylinder of tissue about ½-inch long and less than 1/8-inch in diameter) is removed and examined under a microscope.

CT scans are more tedious than regular x-rays because they take longer and you need to lie still on a table while they are being done. But just like other computerized devices, they are getting faster and your stay might be pleasantly short. Also, you might feel a bit confined by the ring you lay within when the pictures are being taken.

You will need an IV line through which the contrast dye is injected. The injection can cause some flushing. Some people are allergic and get hives, or rarely, more serious reactions like trouble breathing and low blood pressure can occur. Please be sure to tell the doctor if you have ever had a reaction to any contrast material used for x-rays.

Radioactive scans: Two procedures have been used. The older one is called I^{131}-MIBG scan. This procedure uses a chemical called MIBG to which radioactive iodine (I^{131}) is attached. This is injected into your vein and then your body is scanned to look for areas that picked up the radioactivity. These would most likely be carcinoid tumors, although other kinds of neuroendocrine tumors will also pick up this chemical.

A second kind of scan is indium^{111}-labeled DTPA-octreotide scintigraphy or octreoscan. Octreotide is a hormone-like substance that attaches to carcinoid cells. A small amount of this radioactive octreotide is injected into a vein. This material is attracted to carcinoid tumors. A special camera scans your body to show where the radioactivity collects. This procedure and the I^{131}-MIBG scan are useful in detecting spread of gastrointestinal carcinoid tumors to other areas of the body.

Positron emission tomography (PET): This is a special kind of radioactive scan. PET scanning for carcinoid tumors uses a radioactive form of 5-hydroxytryptophan, a chemical the is taken up and used by carcinoid cells. A special camera can detect the radioactivity. PET scans are useful when your doctor thinks the cancer has spread but doesn't know where. PET scans can be used instead of several different x-rays because it scans your whole body. Some doctors have found it to be more accurate than a CT scan for detecting spread of disease.

Other Tests

Endoscopy: This test uses a flexible lighted tube with a video camera on the end. The camera is connected to a television set, allowing the doctor to clearly see any masses in the lining of the digestive organs. If abnormalities are noted, small pieces of tissue can be removed through the endoscope (biopsy). The tissue can be examined under the microscope to find out if cancer is present and what kind of cancer it is.

For upper endoscopy, the tube is passed down through the mouth to view the esophagus, stomach, and first part of the small bowel. In a colonoscopy, a colonoscope (type of endoscope) is inserted through the anus up into the colon. The colonoscope allows the doctor to see the lining of the entire rectum and colon. If you have a colonoscopy, you will need to take a bowel preparation (laxative agent) beforehand to clean your colon so that there will not be any stool to block the view. A colonoscopy usually does not cause pain because you will be given medication through a vein to make you feel relaxed and sleepy during the procedure. A colonoscopy may be done in a hospital outpatient department, in a clinic, or in a doctor's office. It usually takes 15 to 30 minutes, although it may take longer if a tumor is seen and a biopsy taken.

Endoscopic ultrasound: This is a new technique in which a special instrument is used in patients having endoscopy. For this test, the endoscope has a small ultrasound probe on the end. This probe releases high frequency sound waves and then detects the sound wave echoes that bounce off tissues of the stomach wall. A computer then translates the pattern of echoes into an image of the wall of the esophagus, stomach, intestine, or rectum.

Endoscopic ultrasound is sometimes useful in determining how far a tumor has spread through the wall of the esophagus, stomach, intestine, or rectum. The test can also help predict whether the tumor has spread beyond the wall of these organs to nearby tissues or lymph nodes.

Biopsy: Even if a barium x-ray and/or CT scan finds a mass, these imaging tests cannot tell if the mass is a carcinoid tumor, some other type of tumor (benign or cancerous), or a localized infection. The only way to know for sure is to remove cells from the abnormal area and examine them under a microscope. This procedure is called a biopsy.

There are several ways to take a sample from a gastrointestinal tumor. One way is through the endoscope. When a tumor is found, the doctor can use a biopsy forceps (pincers or tongs) through the tube to take a small sample of the tumor. Even though the specimen the doctor takes will be very small, doctors can usually make an accurate diagnosis. Bleeding after a biopsy from a carcinoid tumor is a rare but potentially serious problem. If bleeding becomes a problem, doctors can sometimes inject drugs that constrict blood vessels through the endoscope into the tumor to stop the bleeding.

In rare cases, neither an endoscopic biopsy nor a CT scan-guided needle biopsy (refer to section on CT scan above) will be able to provide tissue to identify the type of tumor. A laparotomy (surgically opening the abdomen) to remove a tissue sample will be needed. For example, an endoscope cannot be passed into the small intestine and surgery may be needed to diagnose small intestinal carcinoids.

Blood and urine tests: Blood tests may be done to detect some of the hormone-like substances produced by carcinoid tumors, particularly if the patient has symptoms of the carcinoid syndrome, caused by excessive levels of such substances in the blood. The most commonly used blood tests measure levels of chromogranin A or neuron-specific enolase. Depending on the patient's symptoms, doctors may recommend additional blood tests.

Serotonin is one of the substances produced by some carcinoid tumors, especially those developing in the small intestine. Serotonin in the blood is broken down to 5-hydroxyindoleactic acid (abbreviated 5-HIAA), which is released into the urine. Urine tests to measure 5-HIAA levels are very useful in diagnosing carcinoid tumors that produce serotonin and have spread to the liver. However, localized gastrointestinal carcinoid tumors often do not have positive urine 5-HIAA results.

How Are Gastrointestinal Carcinoid Tumors Staged?

Staging is the process of finding out how localized or widespread the carcinoid tumor is. It will show if the tumor has spread and how far. The treatment and prognosis (the outlook for chances of survival) for a patient with a gastrointestinal carcinoid tumor depends, to a large extent, on the tumor's stage.

There is no standard system for describing the spread of gastrointestinal carcinoid tumors. Some doctors use the same systems that are used for other cancers of the same organs. Many doctors simply divide all gastrointestinal carcinoid tumors into 3 general stages: localized, regional spread, and distant spread. This approach is easy for patients to understand and is useful in considering treatment options.

Localized: The carcinoid tumor has not spread beyond the wall of the organ it developed in (for example, the stomach, intestine, or rectum).

Regional spread: The carcinoid tumor has spread through the wall of the organ it started in to involve nearby tissues such as fat, ligaments, muscle, or lymph nodes.

Distant spread: The carcinoid tumor has spread to tissues or organs that are not near the organ where the cancer started. Spread of a gastrointestinal carcinoid tumor to the liver, bones, or lungs, for example, is considered distant spread.

5-year survival rates by stage and primary site: Five-year survival rates are calculated based on how many patients live at least 5 years. Many may indeed live much longer than 5 years, but it is the 5-year mark that is used as a standard measurement for statistics and research.

Five-year survival rates for people with gastrointestinal carcinoid tumors are:

Localized 78%
Regional spread 72%
Distant spread 39%
All stages 68%

Of course, these survival rates were calculated from patients who were diagnosed 5 to 10 years ago. The outlook for patients diagnosed recently may be better, due to better advances in diagnosis and treatment.

How Are Gastrointestinal Carcinoid Tumors Treated?

After the carcinoid tumor is found and staged, the cancer care team will suggest one or more treatment plans. This is an important decision. It is also important for you to take time and think about all of the choices.

The main factors in selecting treatment options for gastrointestinal carcinoid tumors are the size and location of the tumor, whether it has spread to lymph nodes, liver, bones or other organs, whether there are any other serious medical conditions, and whether the tumor is causing bothersome symptoms. It is often a good idea to seek a second opinion. A second opinion may provide more information and help the patient feel more confident about the treatment plan that is chosen.

Surgery

Most gastrointestinal carcinoid tumors are cured by surgery alone. The type of operation will depend on a number of factors, including the size and location of the tumor, and whether the patient has any serious diseases of other organs, and whether the carcinoid tumor is causing the carcinoid syndrome.

In general, surgeons try to cure localized carcinoid tumors by removing them completely. This strategy is usually successful. The surgical treatment options for gastrointestinal carcinoid tumors with local or distant spread are more complex. Because most carcinoid tumors grow very slowly and some do not cause any symptoms, attempts at complete surgical removal of metastatic

carcinoid tumors may not always be necessary. In some patients, surgery to remove all visible cancer is the best option. This is particularly true if removing most of the cancer will reduce the hormone-like substances responsible for symptoms.

There are several operations that may be used to treat gastrointestinal carcinoid tumors. Some of these operations remove the primary tumor (in the organ the cancer started). Other operations are intended to remove or destroy metastases in other organs.

Local excision: This operation removes the primary tumor and a zone of surrounding normal tissue. The edges of the defect are then sewn together. There is usually no permanent effect on the digestive system. This operation is usually done for small carcinoid tumors (no larger than 2 centimeters, or about 3/4 inch). The most common example of this is when an appendectomy is done and the carcinoid tumor is discovered after the surgery. Most doctors feel that if the carcinoid tumor was small, less than 1 centimeter (1/2 inch), the appendectomy is curative. Local excision (surgical removal of the area around the tumor) of rectal carcinoid tumors may be done through the anus, without cutting the skin. Local excision of other gastrointestinal system carcinoid tumors can sometimes be done through an endoscope but usually is done through a skin incision.

Electrofulguration: This treatment destroys a tumor by heating it with electric current. It is sometimes used for small rectal carcinoid tumors.

More extensive excision: When the carcinoid tumor is larger than 2 centimeters, then most surgeons prefer to do a larger operation to make sure they remove the entire tumor. This also gives them the opportunity to see if the cancer has invaded other tissues so they can get to these areas and remove the invading tumor.

- **Segmental colon resection or hemicolectomy:** This operation removes between 1/3 and 1/2 of the colon, as well as nearby blood vessels and lymph nodes.
- **Low anterior resection:** This operation is used for some tumors of the upper part of the rectum. It removes some of the rectum and the remaining ends are sewn together, without much impact on digestive function.
- **Abdominoperineal resection:** This surgery is for large or very invasive cancers of the lower part of the rectum. After this operation, the end of the colon is connected to the surface of the front of the abdomen and waste is eliminated from the body through this opening called a colostomy.
- **Liver resection:** This is an operation to remove one or a few metastases from the liver. It is not usually expected to cure the cancer but is often helpful in reducing symptoms of carcinoid syndrome.

Procedures to destroy liver metastases: These methods are often useful in destroying carcinoid metastases that have spread to the liver, especially if the number or location of the liver metastases make surgical removal difficult or impossible. CT scan images are used to guide a needle precisely into the tumor deposits. The cells are then destroyed by injecting concentrated alcohol through the needle, or liquid nitrogen can be used to cool the needle and kill the carcinoid cells by freezing. One new approach, called radiofrequency ablation, uses high-energy radio waves for treatment. A thin, needle-like probe temporarily placed into the tumor releases these radio waves. Placement of the probe is accurately guided by CT scans. The probe releases high frequency alternating current that destroys the cancer cells.

Liver transplantation: This is a rarely used treatment that may be effective for young patients

with carcinoid tumors that have only spread to the liver. Although this is very difficult treatment for patients to go through, it can be curative and should be considered in young patients.

Medical Treatments

Chemotherapy: Chemotherapy uses anticancer drugs that are injected into a vein or a muscle or taken by mouth to kill cancer cells. These drugs enter the bloodstream and reach all areas of the body (called systemic treatment), making this treatment useful for some types of cancers that have spread or metastasized to organs other than the one where they started growing. Unfortunately, carcinoid tumors are often not very sensitive to chemotherapy. Because of this, chemotherapy is generally used only for carcinoid tumors that have spread to other organs, are causing severe symptoms, and have not responded to other medications. Some of the chemotherapy drugs used in this situation include 5-fluorouracil (5-FU), doxorubicin (Adriamycin), etoposide, dacarbazine, streptozocin, cisplatin, and cyclophosphamide. Several chemotherapeutic drugs are sometimes used together to treat metastatic carcinoid tumors, often in combination with other types of medications.

Chemotherapy drugs kill cancer cells but also damage some normal cells. Therefore, your doctors will pay careful attention to avoiding or minimizing side effects. These depend on the type of drugs, amount taken, and length of treatment. Temporary side effects might include nausea and vomiting, loss of appetite, loss of hair, and mouth sores. Because chemotherapy can damage the blood-producing cells of the bone marrow, you may have low blood cell counts. This can result in an increased risk of infection (due to a shortage of white blood cells), bleeding or bruising after minor cuts or injuries (due to a shortage of blood platelets), and fatigue or shortness of breath (due to low red blood cell counts).

Some side effects disappear within a few days after treatment. In addition, there are medicines that can help prevent or minimize treatment side effects. For example, your doctor can prescribe drugs to help prevent or reduce nausea and vomiting.

Chemoembolization and intra-arterial therapy: Metastasis of a carcinoid tumor to the liver is sometimes treated by intra-arterial chemotherapy, directly injecting the chemotherapy drug into the artery that supplies blood to the liver. This approach exposes the liver metastases to high doses of the drug and limits exposure of the rest of the body to avoid many of the side effects described above. Sometimes the chemotherapy drug is injected together with a material that embolizes (plugs up) the artery. When the arteries leading to them are blocked, the tumors become starved for nutrients and oxygen and many die off. This can be more effective when combined with chemotherapy. This combined approach is called chemoembolization.

For more information on chemotherapy, see the American Cancer Society document, "Understanding Chemotherapy: A Guide for Patients and Families."

Other drugs for treating carcinoid tumors: Several medications are available for controlling the symptoms of carcinoid syndrome (problems arising from the release of substances produced by some of these tumors and found through blood and urine tests) in patients with metastatic carcinoid tumors. Octreotide and lanreotide are drugs chemically related to a natural hormone, somatostatin. They are very helpful in treating the flushing (skin redness and feeling hot), diarrhea, and wheezing from carcinoid syndrome. Although these drugs rarely shrink carcinoid tumors, they often slow or stop their growth. Although this is not curative, it can prolong life. The main side effects of these medications are pain at the site of the injection, and rarely, stomach cramps, nausea, vomiting, headaches, dizziness, and fatigue. These drugs have become available

in long-acting injections that need to be given only once a month.

Interferons are naturally occurring substances that normally activate the body's immune system. They also slow the growth of tumor cells. Alpha-interferon is helpful in occasionally shrinking some metastatic carcinoid tumors, slowing the growth of many others, and improving symptoms of carcinoid syndrome. Its usefulness is sometimes limited by its flu-like side effects, which may be severe. The drug is given by injection.

Other medications are also available to control specific symptoms. Please ask your doctor about these, or describe your symptoms to your doctor and ask about medications to control them.

Radiation Therapy

Radiation therapy uses high-energy radiation to kill cancer cells. Although most cases of carcinoid tumor are cured by surgery alone, radiation therapy may be an option for those who cannot undergo surgery.

External-beam radiation therapy is the type of radiation used most often for most types of gastrointestinal cancer. It is like having a regular x-ray except it takes longer and involves much higher amounts of radiation. Patients typically have treatments for 5 days a week for several weeks. Unfortunately, radiation therapy often is not very effective against most gastrointestinal carcinoid tumors. It is used primarily to treat pain from carcinoid tumors that have spread to the bones.

The main side effects of gastrointestinal radiation therapy are fatigue (tiredness), nausea, vomiting, diarrhea, and mild temporary, sunburn-like skin changes.

For more information on radiation therapy, see the American Cancer Society document, "Understanding Radiation Therapy: A Guide for Patients and Families."

Clinical Trials

The purpose of clinical trials: Studies of promising new or experimental treatments in patients are known as clinical trials. A clinical trial is only done when there is some reason to believe that the treatment being studied may be valuable to the patient. Treatments used in clinical trials are often found to have real benefits. Researchers conduct studies of new treatments to answer the following questions:

- Is the treatment helpful?
- How does this new type of treatment work?
- Does it work better than other treatments already available?
- What side effects does the treatment cause?
- Are the side effects greater or less than the standard treatment?
- Do the benefits outweigh the side effects?
- In which patients is the treatment most likely to be helpful?

Types of clinical trials: There are 3 phases of clinical trials in which a treatment is studied before it is eligible for approval by the US Food and Drug Administration (FDA).

Phase I clinical trials: The purpose of a phase I study is to find the best way to give a new treatment and how much of it can be given safely. Doctors watch patients carefully for any harmful side effects. The treatment has been well tested in laboratory and animal studies, but the

side effects in patients are not completely known. Doctors conducting the clinical trial start by giving very low doses of the drug to the first patients and increasing the dose for later groups of patients until side effects appear. Although doctors are hoping to help patients, the main purpose of a phase I study is to test the safety of the drug.

Phase II clinical trials: These studies are designed to see if the drug works. Patients are given the highest dose that doesn't cause severe side effects (determined from the previous phase I study) and are closely observed for an effect on the cancer. The doctors will also look for side effects.

Phase III clinical trials: Phase III studies involve large numbers of patients. Some clinical trials may enroll thousands of patients. One group (the control group) receives the standard (most accepted) treatment. The other groups receive the new treatment. Usually doctors study only 1 new treatment to see if it works better than the standard treatment, but sometimes they test 2 or 3. All patients in phase III studies are closely watched. The study will be stopped if the side effects of the new treatment are too severe or if one group has had much better result than the others.

If you are in a clinical trial, you will receive excellent care. You will have a team of experts looking after you and monitoring your progress very carefully. The study is especially designed to pay close attention to you.

However, there are some risks. No one involved in the study knows in advance whether the treatment will work or exactly what side effects will occur. That is what the study is designed to discover. While most side effects disappear in time, some can be permanent or even life threatening. Keep in mind, though, that even standard treatments have side effects. Depending on many factors, you may decide to enroll in a clinical trial.

Deciding to enter a clinical trial: Enrollment in any clinical trial is completely up to you. Your doctors and nurses will explain the study to you in detail and will give you a form to read and sign indicating your desire to take part. This process is known as giving your informed consent. Even after signing the form and after the clinical trial begins, you are free to leave the study at any time, for any reason. Taking part in the study will not prevent you from getting other medical care you may need.

To find out more about clinical trials, talk to your cancer care team. Among the questions you should ask are:

- Is there a clinical trial for which I would be eligible?
- What is the purpose of the study?
- What kinds of tests and treatments does the study involve?
- What does this treatment do?
- What is likely to happen in my case with, or without, this new research treatment?
- What are my other choices and their advantages and disadvantages?
- Will I know which treatment I receive?
- How could the study affect my daily life?
- What side effects can I expect from the study? Can the side effects be controlled?
- Will I have to be hospitalized? If so, how often and for how long?
- Will the study cost me anything? Will any of the treatment be free?
- If I am harmed as a result of the research, what treatment would I be entitled to?
- What type of long-term follow-up care is part of the study?
- Has the treatment been used to treat other types of cancers?

The American Cancer Society offers a clinical trials matching service for patients, their family, and friends. You can gain access to this service through the ACS cancer information center (1-800-ACS-2345) or Web site (www.cancer.org). Based on the information you provide about your cancer type, stage, and previous treatments, this service compiles a list of clinical trials that match your medical needs. In finding a center most convenient for you, the service can also take into account where you live and whether you are willing to travel.

You can also get a list of current clinical trials by calling the National Cancer Institute's Cancer Information Service toll free at 1-800-4-CANCER or by visiting the NCI clinical trials Web site at www.cancer.gov/clinical_trials/.

Complementary and Alternative Therapies

There is a great deal of interest today in complementary and alternative treatments for cancer. Before changing your treatment or adding any methods of your own, please be sure to talk to your doctor or nurse. Some methods can be safely used along with standard medical treatment for cancer. Others, however, can interfere with standard treatment or cause serious side effects. That is why it's important to talk openly with your doctor or nurse. For more information, please see the American Cancer Society document, "Complementary and Alternative Methods of Cancer Treatment."

Treatment of Gastrointestinal Carcinoid Tumor by Stage

Localized

Treatment of localized carcinoid tumors is based mostly on their size. Experts in this field occasionally disagree on the exact size cutoffs for making treatment decisions, and there are some "gray zones" of size where many admit that it has not been determined exactly what treatment is best.

Stomach: Small carcinoid tumors of the stomach can often be completely removed through an endoscope. For larger tumors, particularly those larger than 1 centimeter (slightly less than 1/2 inch), removal of the tumor and some surrounding stomach tissue through an incision in the abdomen may be needed. In some patients, formation growth of stomach carcinoid tumors may be stimulated by gastrin, a hormone released by cells of the antrum of the stomach (the part next to the small intestine). In these patients, doctors may recommend removing the antrum of the stomach.

Small intestine: Local excision (surgical removal of the tumor and some surrounding normal tissue) is the usual treatment for carcinoid tumors occurring in the small intestine that are smaller than 1 centimeter (slightly over 3/8 inch). Surgery for larger tumors involves taking more surrounding normal-appearing intestine tissue, as well as some surrounding blood vessels and lymph nodes.

Large intestine (other than appendix and rectum): The usual treatment is local excision. If the carcinoid tumor is smaller than 1 centimeter, this procedure can often be done through a colonoscope. If the tumor is larger, surgery usually involves an incision through the skin.

Appendix: Nearly all cancer specialists agree that an appendectomy (surgical removal of the

appendix) is the only treatment needed for carcinoid tumors of the appendix that are smaller than 1.5 centimeters (slightly larger than 1/2 inch).

For carcinoid tumors in the appendix that are between 1.5 and 2 centimeters, most doctors believe that removing the appendix is all that is needed. But they also consider other factors, such as the patient's age, general health, and the patient's degree of worry about the possibility of the cancer coming back-to determine whether additional treatment is needed.

Most specialists agree that more extensive surgery should be considered for tumors larger than 2 centimeters (slightly over 3/4 inch). For these tumors over 2 centimeters, removal of about a third of the colon next to the appendix, along with nearby blood vessels and lymph nodes is a consideration for patients younger than 60 years of age who are otherwise in good health. Because carcinoid tumors grow and spread slowly, people older than age 60 or people with other serious health problems (especially if these problems make surgery more risky) are not likely to benefit from more extensive surgery.

Rectum: Rectal carcinoid tumors that are smaller than 1 centimeter (about 3/8 inch) are usually treated by fulguration (destroying the cancer by burning it with an electrical current). Carcinoid tumors larger than 2 centimeters (slightly over 3/4 inch) have a high risk of aggressive growth and spread, so they are removed by the same operations used for adenocarcinomas (the usual type of rectal cancer). This treatment involves low anterior resection if the carcinoid is in the upper area of the rectum. If the lower part is involved, abdominoperineal resection and colostomy are used. But this is a very complex area. Because many of these tumors will have already spread, it is not certain that such an extensive operation is worthwhile.

For rectal carcinoid tumors between 1 and 2 centimeters, the best approach is often determined by how deeply the carcinoid tumor invades the wall of the rectum, as well as other details of each patient's medical situation.

Deeply invasive tumors measuring 1 to 2 centimeters are often treated the same as larger tumors. Less invasive tumors measuring 1 to 2 centimeters often are treated the same as smaller tumors, by local excision (removing the cancer and a margin of normal rectal tissue). If local excision is used, careful follow-up to check for recurrence is needed.

Regional Spread

If possible, the primary tumor and areas of spread to adjacent tissues and lymph nodes should all be removed by surgery. If this is not possible, surgery should remove as much cancer as possible without causing severe side effects. Surgery should also relieve symptoms such as intestinal blockage caused by the local growth of cancer. For example, surgery to redirect the flow of feces around a blocked area of intestine can be done by connecting adjacent areas of the intestine.

Distant Spread

Surgery in this situation does not attempt to cure the cancer, since this is not possible. Rather, the goal is to relieve symptoms and slow the course of the disease. For example, removing or bypassing areas blocked by cancer growth can relieve some symptoms. If distant metastases are not causing symptoms, treatment may not be needed, although chemotherapy or immunotherapy (with interferon) may help delay the onset of symptoms in some patients. If carcinoid syndrome is causing bothersome symptoms, treatment options include chemotherapy, immunotherapy, or removing the metastatic tumors by surgery. If metastatic tumors cannot be removed without

causing severe side effects from removing essential organs and tissues, ablative methods (removal with surgery) are used to destroy as much of the tumor tissue as possible. These ablative methods, used mostly for liver metastases, include chemoembolization, radiofrequency ablation, cryosurgery, and alcohol injection. Patients should also be advised to avoid alcoholic drinks, stress, strenuous exercise, spicy foods, and certain medications that can make the symptoms of carcinoid syndrome worse.

What Should You Ask Your Doctor about Gastrointestinal Carcinoid Tumors?

It is important to have honest, open discussions with your cancer care team. They want to answer all of your questions, no matter how trivial you might think they are. For instance, consider these questions:

- What kind of carcinoid tumor do I have?
- What is the stage of my carcinoid tumor and what does that mean to me?
- What treatment choices do I have?
- What do you recommend and why?
- Based on what you've learned about my carcinoid tumor, what is my prognosis?
- What risks or side effects are there to the treatments you suggest?
- What are the chances of recurrence of my carcinoid tumor with these treatment plans?
- What should I do to be ready for treatment?

In addition to these sample questions, you may wish to write down some of your own. For instance, you might want more information about recovery times so you can plan your work schedule. Or, you may want to ask about second opinions or clinical trials for which you may qualify.

What Happens After Treatment for Gastrointestinal Carcinoid Tumors?

Depending on the size and extent of spread of your carcinoid tumor, you may be asked to return to the doctor for regular physical examinations and, in some cases, x-rays, blood tests, and urine tests. These exams and tests will help find any recurrences of the tumor as early as possible. Because some carcinoid tumors recur (come back) many years after treatment, patients at high risk for recurrence should not stop having regular examinations, even after they have been well for many years following treatment.

It is important for the patient to report any new symptoms to the doctor right away. They might be signs of the tumor's recurrence or of side effects from treatment.

What's New in Gastrointestinal Carcinoid Tumor Research and Treatment?

There is always research going on in the field of gastrointestinal cancer. Scientists are looking for the causes of, ways to prevent, and novel new approaches to the diagnosis and treatment of gastrointestinal carcinoid tumors.

Diagnosis: Because the outlook and treatment of gastrointestinal carcinoid tumors and gastrointestinal carcinomas are very different, accurate diagnosis is important. Researchers have

made great progress in developing tests that can detect specific substances found in the cells of carcinoid tumors but not gastrointestinal cancers. Other substances may be found in both carcinoid tumors and carcinomas but higher levels are found in one type. Most of these tests involve treating tissue samples with special antibodies produced in the laboratory. The antibodies are designed to recognize specific substances in certain types of tumors.

Imaging: Researchers are testing ^{111}In-DTPA-octreotide scintigraphy (octreoscan) and other nuclear medicine methods for the early detection of carcinoid tumors.

Treatment: New chemotherapy drugs are being tested to find drugs that are active against carcinoid tumors. Other drugs are being developed to prevent the release of substances that are responsible for the symptoms of carcinoid syndrome. Also, there is work being done using highly radioactive MIBG to kill carcinoid tumors.

Additional Resources

National Organizations and Web Sites

The following organizations can also provide additional information and resources.*

National Cancer Institute
Telephone: 1-800-4-CANCER
Internet Addresses: www.cancer.gov

The Carcinoid Cancer Foundation, Inc.
Telephone: 1-888-722-3132 or 1-914-683-1001
Internet Address: www.carcinoid.org

**Inclusion on this list does not imply endorsement by the American Cancer Society.*

Additional American Cancer Society Information

Books
American Cancer Society's Guide to Pain Control (Book; Code #9438)

Cancer in the Family: Helping Children Cope with a Parent's Illness (Book; Code #9435)

Caregiving: A Step-By-Step Resource for Caring for the Person with Cancer at Home (Book; Code #9422)

Coming to Terms with Cancer: A Glossary of Cancer-Related Terms (Book: Code #9505)

Consumers Guide to Cancer Drugs (Book; Code #9436)

Informed Decisions, Second Edition: The Complete Book of Cancer Diagnosis, Treatment, and Recovery (Book; Code #9449.02)

Brochures
After Diagnosis: A Guide for Patients and Families (Booklet; Code #9440)

Caring for the Patient with Cancer at Home (Booklet; Code #4656)

Questions and Answers About Pain Control (Booklet; Code #4518.00)

Other Publications*

Capossela C, Warnock S. *Share the Care: How to Organize a Group for Someone Who Is Seriously Ill*. New York: Simon and Schuster, 1995.

Dollinger M, Rosenbaum EH, Cable G. *Everyone's Guide to Cancer Therapy: How Cancer Is Diagnosed, Treated, and Managed Day to Day,* 4th Edition. Kansas City, Mo: Andrews McMeel Publishers, 2002.

Hoffman B, ed. *A Cancer Survivor's Almanac: Charting Your Journey*. National Coalition for Cancer Survivorship. Minneapolis, Mn: Chronimed Publishing, 1996.

Holland JC, Lewis S. *The Human Side of Cancer: Living with Hope, Coping with Uncertainty.* New York: HarperCollins Publishers, 2000.

Morra M, Potts E. *Choices,* 4th Edition. New York: HarperCollins Publishers, 2003.

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For additional assistance please contact your American Cancer Society
1 · 800 · ACS·2345 or www.cancer.org