

# A Review of Carcinoid Cancer

July 2012 (updated)

*This document was prepared in order to further the Carcinoid Cancer Foundation's educational goals and inform you about the existence and characteristics of carcinoid cancer. While the information contained herein represents up-to-the-minute information about carcinoid cancer, it is not to be used as a substitute for a visit with your doctor if there is any question about your condition.*

## Introduction and Basic Concepts

In order for an answer to these questions to be meaningful to you, you must first understand some basic concepts about the body and how tumors develop and grow. Every part of the body from the skin to your heart, muscles, glands and all other organs, is composed of microscopic cells just like the bricks that make up the structure of a building, but unlike building bricks the body's cells are formed in classes specialized in appearance, structure and function for the purposes of the organ or the part they form. Furthermore, unlike the bricks of a building, which once formed and set in place are unchanging for the life of the building, the living cells of the body are constantly degenerating, wearing out, and being regenerated/replaced by identical cells. This replication process is going on continuously and is regulated by complex genetic and hormonal controls from both within the individual cells and also by influences from other parts of the body. When something goes wrong with this delicate, complex regulatory system, cell replication sometimes proceeds unrestrained and then a tumorous growth (neoplasm) is formed by that one type of cell overgrowing. If this overgrowth is somewhat limited and does not spread to other areas or threaten to squeeze out or replace adjacent structures, it is considered to be a benign tumor, that is, not life threatening. However, if the growth is more aggressive and threatens surrounding tissues or sends "seedlings" (metastases) to grow in distant areas then it has potential to be fatal and is considered malignant; that means it is a cancer

There are a few types of growths that are sort of midway between these two classifications of benign and malignant. Carcinoid tumors are the most often occurring of these rare types of "midway" growths. They have been called "cancers in slow motion" because even though they usually have the potential for ultimately being fatal, they mostly tend to grow so slowly that people afflicted with these tumors usually live for many years, indeed sometimes for a normal life time. The wide variety of treatment now available makes the outlook for most victims of the more aggressive carcinoids more hopeful than it used to be - but more on this later.

## Carcinoid Tumors - What Are They? Benign or Malignant?

Relative newcomers to medical recognition, carcinoid tumors were first identified as a specific, distinct type of growth in the mid 1800's, and the name "carcinoid" was first applied in 1907 by Oberndorfer in Europe in attempt to designate these tumors as midway between carcinomas (cancers) and adenomas (benign tumors).

They were found to arise from the cells of the Diffuse Neuroendocrine System, enterochromaffin cells (glandular endocrine-hormone producing cells) widely distributed in the body but found in greatest amounts in the small intestine and then in decreasing frequency in the appendix, rectum, lung, pancreas and very rarely in the ovaries, testes, liver, bile ducts and other locations. These cells have special peculiar features that make them identifiable under the microscope. They stain in a special way when put in contact with silver containing chemicals. Special stains for the particular hormones that enterochromaffin cells can make will identify the hormone substances in carcinoid tumor cells and thereby confirm the diagnosis of the microscopic exam on biopsied carcinoid tumors.

Only as recently as 1954 was the **Carcinoid Syndrome** first described and accepted as a specific disease entity. Thorsen, Biorck, Björkman and Waldenstrom, a group of doctors in the United States and Scandinavia, first recognized the nature of the various symptoms associated with some carcinoid tumors that have become known as Carcinoid Syndrome and they described it in a medical journal. This syndrome, which I will discuss in more detail later, consists of a group of symptoms and findings on physical and laboratory examination that are sometimes caused by the potent hormones produced by carcinoid tumors.

In the early 1990's the development and availability of [octreotide \(Sandostatin\)](#) by the Sandoz Pharmaceutical Company (now [Novartis](#)) provided a most important drug for the treatment of the Carcinoid Syndrome and for carcinoid tumor disease in general. This drug is derived from the naturally occurring hormone somatostatin. Along with this, Novartis aggressively educated doctors about the rare carcinoid tumor and syndrome and this has done much to increase awareness of the condition and to enhance its diagnosis and treatment. In Europe and some countries in other parts of the world one of two other somatostatin derivatives, [lanreotide \(Somatuline\)](#) (Ipsen) and [vapeotide \(Sanvar® IR\)](#), are also used.

### Statistics

Large studies of many individuals indicate that the occurrence of insignificant small carcinoids that seem to last a lifetime and cause no problems and do not spread is fairly common, occurring in approximately 1 out of every 100 individuals. The most common location in which carcinoids form is in the small intestine. Tumors of any kind in the small intestine are rare and comprise only 1% of all the cancers of the gastrointestinal tract. However, carcinoids of clinical importance (not the tiny coincidental tumors mentioned above) comprise about 50% of all small intestinal malignancies. Their size when first diagnosed is very important **since the likelihood of having already spread is in direct proportion to their size.** If the tumor is greater than 2 cm in diameter (almost 1 inch) chances of spread are greater than 50%. Initially the carcinoid tumor just grows into the wall of the intestine from the lining where it starts. However, eventually it may go through the wall and then extend into nearby lymph nodes, lymph channels, and blood vessels and can later spread to more distant locations such as the liver, lungs, bone, skin, brain and even the heart.

Approximately 20% (1/5) of the small intestine carcinoids will develop distant spread (metastases) and roughly 1/3 of those that have spread will develop symptoms of the Carcinoid Syndrome. From these numbers it is apparent that the Carcinoid Syndrome is very rare. Currently in the United States approximately 5 new clinically significant carcinoid cases are diagnosed each year per 100,000 individuals in the general population. In about 2/3 of these cases the carcinoid arises from the gastrointestinal tract. The occurrence of carcinoid tumors of clinical importance according to the location of origin breaks down as follows:

- 28.5% small intestine
- 5% appendix
- 14% rectum
- 28% bronchial system of the lungs
- 5-7% colon
- 4% stomach
- 1% pancreas
- >1% liver
- 8% other

There are also some very unusual and extremely rare locations from which carcinoids may arise or to which they have spread and they are: the gallbladder and bile ducts, the ovaries, the testicles, the urinary bladder, the prostate gland, the breast, the kidneys and the thymus gland and in some very rare cases of the eye and the ear.

Up to 25% of all GI tract carcinoids are associated at some time with another tumor of non-carcinoid type, such as the typical colon cancer, cancer of the lung, breast cancer and prostate cancer. Of all carcinoids, those arising in the appendix are the most benign, having only very rare distant spread

and 87% of people with carcinoid of the appendix diagnosed and removed by surgery remaining alive after 5 years. A carcinoid is found usually by accident in 1 of every 200-300 appendices removed at surgery.

The second most least malignant of these tumors are the rectal carcinoids with a 72% 5 year survival. If distant metastases are present when a carcinoid from any site of origin is found, the 5 year survival rate drops to 27% **if not treated**.

Gastric carcinoids; Carcinoid tumors originating in the stomach are sometimes very special. These gastric carcinoids occur as one of three types:

1. Those associated with pernicious anemia or other conditions causing degeneration of the stomach lining with loss of normal gastric acid production. These are usually multiple, small and even microscopic carcinoids which infrequently spread and rarely are fatal and sometimes can be made to shrink and even disappear by surgical removal of the gastrin hormone producing end portion of the stomach. In some cases sandostatin and other medical treatments can control and reverse these growths.
2. A very few gastric carcinoids can occur as part of the MEN syndrome. These are usually very slow growing and have low grade malignant potential. They are associated with other endocrine gland tumors in other organs.
3. Sporadic carcinoids, i.e. carcinoids that occur in the stomach as single or occasionally several tumors without a special predisposition, just like carcinoids elsewhere in the intestine. Those can slowly grow large and occasionally cause discomfort or bleeding or, in 50% of cases, spread in a malignant fashion. Carcinoids of the lung (bronchial carcinoid) are often associated with their own special peculiarities, diagnostic modalities and forms of treatment. An excellent summary of this subject can be found on the American Cancer Society's website: [Lung Carcinoid Tumor Information](#).

### What Is Carcinoid Syndrome?

Carcinoid cells can make hormones. Those carcinoid tumors which produce large amounts of hormones and other potent chemical substances and which are usually found to have spread to the liver, can cause hot red flushing of the face, diarrhea, and asthma like wheezing attacks. These episodes of "carcinoid crisis" may be very infrequent at first but gradually occur more often and are usually associated with abrupt low blood pressure and even fainting. However, in a few cases the attacks are accompanied by high blood pressure. Alcohol or stress (physical or emotional) sometimes provoke attacks but they often occur spontaneously. After a while the flush may become persistent in some individuals and may not be felt or noticed by them. The diarrhea may also be chronic and weight loss can occur. A specific type of heart valve damage can occur in some cases as well as other cardiac disturbances. All of these features constitute the [Carcinoid Syndrome](#).

The potent chemicals and hormones made by the "functioning" carcinoid tumors (as versus the more frequent "non-functioning" carcinoid tumors), through their effects on the cardiovascular, gastrointestinal, pulmonary and other systems of the body, cause the Carcinoid Syndrome. In many cases the symptoms of the Carcinoid Syndrome resulting from the hormones and chemicals produced are worse than the symptoms from the growth of the tumor itself.

Not all functioning carcinoid tumors produce the same large variety of chemicals and hormones and it is not yet entirely clear as to which of the substances are responsible for each of the symptoms of the Carcinoid Syndrome. However, almost all of these tumors make Serotonin, bradykinin, and chromogranin-A. Other substances whose names you may sometimes come across in connection with these tumors and which are often made in association with carcinoids are: [substance-P](#), [pancreastatin](#), [neurotensin](#), [pancreatic polypeptide](#), [neurokinin-A](#), [motilin](#) and [atrial natriuretic hormone](#) (ANH), as well as [other peptide hormones](#).

Carcinoids belong to a family of growths called neuroendocrine tumors. Each type of neuroendocrine tumor produces a different main hormone and hence a different syndrome - that is, it causes different symptoms. Why is this important for us to include in a discussion of carcinoid? First, and

most important, each of these syndromes, though having different features, can prominently include flushing and/or diarrhea and be confused with Carcinoid Syndrome. Secondly, a carcinoid can occasionally have "mixed" function causing one of these other syndromes along with Carcinoid Syndrome. This is the result of the carcinoid producing one or more of these other hormones along with production of its own specific hormones. Thirdly, an inherited familial (genetic) condition can cause the development in an individual of several different types of neuroendocrine tumors (and their respective syndromes). This can include carcinoid along with other types of neuroendocrine tumors. This is called [MEN \(multiple endocrine neoplasia\) syndrome](#).

### Diagnosis

Nonfunctioning carcinoid tumors are so slow growing that many years may pass between the onset of any symptoms and the diagnosis. They can cause intermittent abdominal pain and then a change in bowel habits that may lead to intestinal obstruction. In some cases they cause obscure intestinal bleeding or sometimes don't declare themselves until they cause painful enlargement of the liver due to large deposits of carcinoid metastases that have spread to that organ. The diagnosis is not usually suspected prior to surgery but is then established by biopsy.

The Carcinoid Syndrome, due to the presence of a functioning carcinoid tumor, is easily diagnosed when all the features of the syndrome are present or even when 1 or 2 of the main symptoms are present and the Carcinoid Syndrome is thought of. The biggest impediment to making the diagnosis is not thinking of the Carcinoid Syndrome, or even considering it because of its rarity. Once considered, the diagnosis usually can be confirmed quickly and painlessly by doing a [urine 5-HIAA test](#). This stands for 5-hydroxy indole acetic acid which is the main breakdown (waste) product of Serotonin. Its quantitative measurement in the urine which an individual excretes in a 24 hour period tells how much Serotonin is being made in the body during that time. In the presence of Carcinoid Syndrome the amount of 5-HIAA is almost always distinctly increased above normal. Certain foods and medicines must be avoided for a day or two before, and on the day of the urine collection, since they can cause false test results. These are: bananas, pineapple and its juice, red plums, avocado, walnuts and other nuts, kiwi fruit, tomatoes, various cough medicines muscle relaxing medicines, acetaminophen (Tylenol), caffeine, fluorouracil, iodine solutions (Lugol's solution), phenacetin, MOA inhibitors (certain antidepressant drugs), isoniazid, and phenothiazine drugs (Compazine, Thorazine). For more information how to prepare for a 24 hour urine test [click here](#). Sometimes urine 5-HIAA is not increased but other carcinoid "markers" in the blood can be measured and will be increased. These are chromogranin A (CgA) and serotonin. Blood tryptophan may be decreased below normal values. **The measurement of CgA is considered "the gold standard" of chemical tests** for confirming the diagnosis of carcinoid and neuroendocrine tumors and following their course.

Standard X-ray and imaging techniques can be helpful in finding a carcinoid tumor and identifying its spread. This could include routine chest X-ray, CT scans, MRI, barium enema and upper GI and small bowel X-ray studies. Sometimes upper and lower GI tract endoscopy (looking inside the body with a flexible fiber optic tube through which biopsies can be taken) is also helpful. A universally approved (though costly) way of finding carcinoid tumors, as well as other neuroendocrine tumors, is the [OctreoScan](#). It is successful in 85% of carcinoids and consists of a harmless injection of a minute dose of a short duration radioactive isotope which is specifically attracted to, and concentrated in, carcinoid tumor tissue (and any other neuroendocrine tumor) where it lights up when a radiation scan is taken over the entire body. It is dissipated in a few days, and again I emphasize it is harmless. OctreoScan should be done in almost all cases even when the diagnosis is known. This is especially important in those cases where standard imaging (i.e. CT-scans, MRI) and chemical markers have failed to reveal the diagnosis and location of tumors. There are occasional cases in which all the symptoms and chemical findings of Carcinoid Syndrome are present but standard tests fail to reveal a tumor. In these cases octreoscan can be a great help in confirming the diagnosis and locating the tumor(s). A positive octreoscan usually predicts a good response to treatment with octreotide.(Sandostatin)

### Outlook (Prognosis)

Typical carcinoids are slow growers. Data on survival of patients with small tumors not causing Carcinoid Syndrome and without spread, treated by surgical removal alone, indicates that a

complete cure is usually possible in these cases.

In those tumors that are somewhat larger and have spread to local tissues and local lymph nodes but which, along with these locally invaded tissues, are still totally removable surgically, the average survival has been 8 years with a range up to 23 years.

Even when the tumor from the small intestine has spread in a manner that has made complete surgical removal impossible, the older statistics show that approximately one half of the patients survive an average of 5 years. Since various types of treatment have been introduced in the past decade patients appear to have an even longer survival and improved quality of life.

Atypical carcinoids, which is a group whose microscopic appearance looks different and more aggressively malignant than the typical carcinoid, follow a more rapid course with a more uncertain outlook. An even worse forecast can be made for the very more malignant rare group called "neuroendocrine carcinoma". Atypical carcinoids can cause the Carcinoid Syndrome, but neuroendocrine carcinoma rarely do.

The tempo of the course of the illness in patients with Carcinoid Syndrome is different than that of carcinoid patients without the functioning syndrome. However, this has been remarkably improved and the outlook is much more hopeful with the advent of octreotide and similar somatostatin analogues and other new modes of treatment. In the early decades before effective treatment was available the average survival from the onset of flushing for a Carcinoid Syndrome patient was 3 years, and from the time of diagnosis was 2 years, though the range extended to over 10 years. Seventy five percent of the patients would die as a consequence of the harmful effects on the body from the excessive amounts of potent hormones released into their circulation by the tumors. Tumor growth and spread itself was fatal in only 25% of cases. In the last 10 years, since we have used effective combinations of treatment with octreotide (and similar somatostatin analogues), various types of surgery, chemotherapy, hepatic artery injections and biological response mediators, the average survival time from the start of treatment (which unfortunately is often quite delayed after the diagnosis is made) has increased to almost 12 years - with a wide range often being observed.

### **Is there a cure? What treatments are available?**

Carcinoid tumors vary greatly in their size, location, symptoms and growth. Therefore the treatment in each case should be individualized to what is best for each particular patient.

Surgery, with complete removal of all of the tumor tissue, is the first and best treatment when it is possible, and **if detected early can result in a complete and permanent cure**. However, even when all tumor tissue cannot be removed, surgery may be necessary for various purposes such as relief of intestinal obstruction or control of intestinal bleeding. When the Carcinoid Syndrome is present, removing or destroying large portions of the tumor (debulking) can effectively diminish the amount of harmful hormones being produced and flooding the circulation. Because of the slow growth of most carcinoids, this can relieve symptoms for a long time. Technique of using a freezing probe (cryoablation) or radiofrequency ablation (RFA) are used at major medical centers to destroy carcinoid tumor metastases in the liver when it has not been possible to excise them surgically. Another way to debulk unresectable carcinoid tumors that have spread to the liver is to inject the liver artery supplying blood to the metastases with a combination of embolic material and chemotherapy drugs or with radioactive microscopic emboli which give intensive localized radiotherapy to the liver tumors. Chemoembolization shuts off the blood flow with its oxygen supply to the tumors and also loads them with tumor destroying and growth inhibiting chemotherapy. Thus this chemotherapy is concentrated in the tumors where it can have a much greater effect than in the rest of the body. However, opinion is divided regarding whether chemotherapy injection with embolus is of greater benefit than embolus (bland embolization) alone.

Chemotherapy for carcinoid given by intravenous injection or by mouth has been in use for over 20 years. There are many drugs available. Individual drugs used alone have been disappointing but a number of combinations of these drugs have been beneficial. Some of these combinations are: leucovorin-fluorouracil and streptozotocin, cytoxan- Doxorubicin and cisplatin, dacarbazine-fluorouracil, etoposide-cisplatin. One or another of these combination has produced

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good response in only 20-30% of the cases. Fortunately however, those patients in whom one chemotherapy routine is ineffectual may respond well to one of the other drug combinations. In other words, failure to respond to one combination does not necessarily mean another combination of chemotherapy will also be ineffectual. The site of the origin has considerable influence on likelihood of the tumor(s) responding to chemotherapy. For instance pancreatic and lung carcinoids respond to some forms of chemotherapy better than intestinal carcinoid. A number of newer drug combinations are currently approved or under investigation, including: [everolimus \(Afinitor\)](#), [sorafenib \(Nexavar\)](#), [sunitinib \(Sutent\)](#), [atiprimod](#), [SOM230](#), [bevacizumab \(Avastin\)](#), [temozolomide \(Temodar\)](#), [capecitabine \(Xeloda®\)](#), and others.

Somatostatin analogue (octreotide/lanreotide and vapreotide) injections not only usually squelch the symptoms of Carcinoid Syndrome but are now believed to sometimes inhibit or even reverse growth of the tumors. This has become the mainstay of treatment for most carcinoid tumors, with or without the Carcinoid Syndrome. Somatostatin analogues (octreotide/lanreotide/vapreotide) are now available in the US and other countries in three forms: octreotide- trade name - Sandostatin s.c.®, and Sandostatin LAR® (given every 3-4 weeks) manufactured by [Novartis](#), lanreotide - trade name - [Somatuline®](#), manufactured by [Ipsen](#) (In the US contact [Tercica](#)). In a few patients needing large amounts of octreotide continuous injection of Sandostatin s.c. is given by a special tiny injection pump as is used for insulin in some diabetics. (see paper by Dr. Eugene Woltering, [click here](#))

### [Patient Assistant Program \(PAP\) by Novartis Pharmaceuticals](#)

Novartis Pharmaceuticals Corporation's Patient Assistance Program (PAP) provides assistance to patients experiencing financial hardship who have no third party insurance coverage for their medicines.

For more information, about this program and insurance reimbursement issues, call their Hotline 1-800-282-7630. For information about Sandostatin LAR® Depot reimbursement, visit their [website](#).

Throughout the world, dozens of patients with carcinoid metastases to the liver and no discernible tumors outside the liver have undergone liver transplant. Their survival has been about equal to those patients with equivalent disease treated by the more conventional means outlined above. At this time I do not see a role for this extremely expensive and debilitating treatment in any but the most extraordinary carcinoid case. Interferon is a natural substance originally derived from white blood cells that inhibits growth of carcinoid and certain other tumors as well as certain viruses. There are several varieties of interferon (Intron A and Roferon A) of which the alpha form has seen the most use for treating carcinoid and is commercially available. Drugs of this class are considered "biologic response mediators" or "immunomodulators" rather than tumor cell poisons (cytotoxins) such as chemotherapy drugs. Though beneficial in suppressing tumor growth in at least half the carcinoid patients treated, interferon often causes unpleasant side effects of extreme fatigue and flu like symptoms. Side effects are often avoided or reduced by using low doses of this medicine which even then can often be effective.

Radiotherapy in carcinoid is useful only in pain relief and regressing tumors when they have spread to the skeletal system and when causing severe pain. Radiation treatment to the specific painful spot will usually provide relief. It has not been useful in treating metastases in the liver or in other non skeletal tissues. Experimental studies are underway, using internally injected radioactive isotopes in selected carcinoid patients, in a number of research centers abroad. The current favored isotopes are Yttrium 90 (Y90), Lutetium 177 and Gallium 68. Increasing evidence of the effectiveness of these very expensive treatments is emerging and efforts to start their use in the US are under way. An additional new treatment for liver metastases emerged during the past decade and consists of injecting the hepatic artery with radioactive isotope Yttrium 90 impregnated microsphere emboli ([Therasphere](#), [SirSpheres](#)). Results are very promising. This is meeting with considerable success when the sole or dominant site of metastases is located in the liver. Narrow beam radiotherapy such as [CyberKnife](#) is being tried in a few places and appears promising.

### Supportive Treatment

Besides the various anti-tumor treatments reviewed above, there are many benefits resulting from a nutritious high protein diet, vitamin supplements - particularly niacin, mineral supplements (such as potassium, magnesium, calcium, iron and even salt) when these are deficient due to diarrhea. In



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addition to the use of octreotide or lanreotide to control diarrhea, conventional anti-diarrheal medications such as Lomotil and Imodium may be helpful. Cyproheptadine (Periactin) may also help the diarrhea as well as flushing. Large portions of freshly grated nutmeg (1 teaspoon eaten 3 times a day) will sometimes control the diarrhea remarkably well. Antihistamines and alpha adrenergic blocking drugs such as Dibenzylamine are sometimes used to prevent Carcinoid Syndrome attacks. All carcinoid patients should avoid alcoholic beverages and physical and emotional stress since these can precipitate carcinoid crisis attacks. Similarly, adrenaline like drugs should be avoided. These include various asthma inhalers, nasal decongestants and adrenaline itself. Certain very severe and prolonged carcinoid crises associated with bronchial (lung) carcinoids or some carcinoids of the stomach are responsive to treatment with corticosteroids (prednisone, Decadron) and Thorazine or Compazine. There is recent emphasis for carcinoid inhibiting properties of black raspberry extract.

### Conclusion

As you can see there is good reason to be hopeful. There are abundant treatments for carcinoid tumors and syndrome though choice of treatment and their applications can be quite complex. Even though this is a rare disease there are experts available who are interested and willing to help and a great deal of research is in progress which promises additional effective therapy in the foreseeable future. See [list of experts and other physicians](#) diagnosing and treating carcinoid patients.

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Medical References by Dr. Warner 1958-Present time  
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General questions can be answered by calling The Foundation at 888-722-3132.

It must be emphasized to our visitors that the Foundation can only answer general questions. THE MISSION OF THE FOUNDATION IS TO EDUCATE REGARDING CARCINOID AND RELATED NEUROENDOCRINE CANCERS AND TO PROMOTE CARCINOID/NET RESEARCH, not render authoritative medical consultations. If such an opinion were sought it would require review of all the specific technical details in a patients medical records including review of CT-scans, X-ray films, blood tests etc. A person's health is too important to have decisions based on casual suggestions and general impressions. A physician experienced and expert in carcinoid cancer should be consulted for case specific questions.

NOTE: Since all inquiries are given personal attention, due to an exceptionally large volume of requests for information, responses by either e-mail or telephone may be somewhat delayed from time to time.

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