Carcinoid commonly refers to neuroendocrine tumors that originate in the gastrointestinal (GI) tract, lungs, appendix and thymus, although they can also occur in the lymph nodes, brain, bone, gonads (ovaries and testes) and skin. Carcinoid tumors are usually indolent (slow-growing) by nature and develop over the course of many years. However, aggressive, fast-growing forms of carcinoid cancer also exist.

Carcinoid tumors can secrete a variety of functional hormones and chemicals although not all carcinoid tumors do (Reidy, Tang, & Saltz, 2008). A few of the substances that are commonly secreted by carcinoid tumors are: serotonin, chromogranin A, histamine, pancreatic polypeptide and gastrin. Carcinoid tumors are referred to as functioning if they secrete hormones that cause a clinical syndrome (Reidy, Tang, & Saltz, 2008).

Functioning carcinoid tumors that occur in the digestive tract and pancreas release the substances they produce directly into the hepatic portal vein (a blood vessel in the abdominal cavity) which carries them directly to the liver where they are metabolized (broken down). Since the liver metabolizes these substances, their message is not sent to the rest of the body. Consequently, tumors of the digestive tract and pancreas are not usually detected until they have metastasized to the liver or cause obstructive symptoms (Kulke, 2007).

When carcinoid metastasizes to the liver, the liver is not always able to metabolize all of the hormones secreted. This excess of hormone called hypersecretion can cause an array of symptoms called carcinoid syndrome.

Carcinoids that occur in areas outside of the intestine and pancreas such as the lung and stomach do not release their hormones into the hepatic portal vein but release them directly into the bloodstream, bypassing the liver. Consequently, individuals with carcinoid in these locations can sometimes develop carcinoid syndrome without liver metastases as well as other symptoms and syndromes.

Common symptoms associated with Carcinoid Syndrome include diarrhea, flushing of the skin, abdominal cramping, asthma, arthritis, niacin deficiency, swelling of the feet, and wheezing. Carcinoid Syndrome occurs in approximately 10% of all individuals diagnosed with carcinoid (Vinik, Feliberti, Perry, & Nakave, 2008) and can lead to right-sided heart failure (Moller, Connolly, Rubin, Steward, Modesto, & Pellikka, 2003). Carcinoid Syndrome is most common in individuals with liver metastases from ileal carcinoids (Kulke, 2007).

Individuals with Carcinoid Syndrome can also experience carcinoid crisis which can occur spontaneously or be stress induced. A Carcinoid Crisis can be a life-threatening event that requires careful monitoring. Symptoms of a Carcinoid Crisis may include severe hypotension or hypertension, irregular and/or rapid heartbeat, wheezing, prolonged flushing, severe dyspnea (shortness of breath), and peripheral cyanosis (lack of oxygenated blood) (Oberg, Reubi, Kwekkeboom, & Krenning, 2010).
Carcinoid is classified as a rare cancer. Recent studies have determined that 4 to 5 out of every 100,000 people are diagnosed yearly with a neuroendocrine tumor and that there are over 100,000 people currently living with neuroendocrine tumors within the United States (Yao et al., 2009). For reasons not well understood, the incidence of carcinoid is rising. Since most individuals with carcinoid are asymptomatic until the tumors metastasize, the average time between tumor development and diagnosis is between 5 to 10 years (Vinik, 2008; Vinik et al., 2009). Survival rates for individuals with carcinoid vary and depend on tumor type, location, extent of metastases, and many other factors. Currently, surgery is the only cure for localized tumors (those which have not spread) and there is no cure for metastatic carcinoid (Yao, 2007).

What is a Tumor?
Cells are the building blocks of all life. All cells have highly specific functions, but not all cells have the same function. When cells that have similar functions are grouped together they form a tissue. Tissues when grouped together to perform a specific function are called organs. All cells of the human body have the same DNA (genetic language). Cell growth and replication is highly controlled and is encoded in each cell’s DNA. However if there are enough mutations (changes) within a cell’s DNA, a cell can grow and replicate uncontrollably.

A tumor is a mass formed by an abnormal growth of cells within the body. A tumor can be non-cancerous (benign) or cancerous (malignant). A tumor is considered cancerous when it has uncontrolled proliferation (abnormal growth) and can invade and destroy surrounding tissue. Malignant tumors can also have the ability to metastasize (spread to other organs of the body).

What is a Neuroendocrine Tumor?
The neuroendocrine system consists of highly specialized neuroendocrine cells which act as an interface or junction between the nervous system and the endocrine system. The endocrine system is made up of cells whose function is to produce and secrete hormones into the bloodstream. Hormones are biochemical messengers that help to regulate many different processes within the body. The nervous system is composed of specialized cells (neurons) that control the activities of all body parts. A neuroendocrine cell is a cell which receives neuronal input (a signal from a nerve cell) and releases hormones in response to this signal.

A neuroendocrine tumor can develop anywhere there are neuroendocrine cells. The most common sites from which neuroendocrine tumors arise are the lungs, appendix, small intestine, rectum and pancreas (Yao, Hassan, Phan, Dagohoy, Leary, Mares, Abdalla, Fleming, Vauthey, Rashid, & Evans, 2008). Neuroendocrine tumors that arise in the pancreas are called pancreatic neuroendocrine tumors or islet cell tumors. When neuroendocrine tumors originate in other areas, they are often classified as carcinoid tumors.

Since neuroendocrine tumor cells are derived from neuroendocrine cells, many of these tumor cells can behave like cells they originated from and can secrete a variety of hormones. A functioning neuroendocrine tumor is one that secretes biologically active hormones causing a clinical syndrome. Non-functioning neuroendocrine tumors do not cause clinical syndromes.

Carcinoid tumors and pancreatic neuroendocrine tumors share similarities including often indolent behavior, ability to secrete biologically active hormones, and well-differentiated histology (Reidy, Tang & Saltz, 2009).
INFORMATION REFERENCES


LOCATIONS & CLASSIFICATIONS

Carcinoid tumors can develop almost anywhere in the body. Carcinoid tumors can be classified by location, histology and biological activity in the following way:

**Embryonic Gut Derivation**

**Foregut Carcinoid Tumors**
Located in the lungs, thymus, stomach, first part of the duodenum (small intestine), or the pancreas.

**Gastric Carcinoids** (carcinoids of the stomach) are further classified as:
- **Type 1**: Associated with chronic atrophic gastritis (inflammation of the stomach lining) caused by hypergastrinemia (high levels of the hormone gastrin).
- **Type 2**: Implicated with Zollinger Ellison Syndrome and Multiple Endocrine Neoplasia Type 1 (MEN-1).
- **Type 3**: Sporadic, not associated with hypergastrinemia, can cause Atypical Carcinoid Syndrome and are frequently malignant.

**Pulmonary Carcinoids** (carcinoids in the lungs) are further classified as:
- **Typical Pulmonary Carcinoids** (benign or low-grade malignant): Considered to be well-differentiated, commonly located in the center of the lungs, and rarely metastasize (Fink, Krelbaum, Yellin, Bendayan, Saute, Glazer, & Kramer, 2001; Kulke 2007).
- **Atypical Pulmonary Carcinoids** (low-grade malignant): Poorly differentiated, commonly located in the periphery of lungs, characterized by frequent mitoses (cellular division), and frequently metastasize (Kulke, 2007; Fink et al., 2001).

**Midgut Carcinoid Tumors**
Located in the small intestine, appendix, or right colon (large intestine).

**Hindgut Carcinoid Tumors**
Located in the transverse colon, sigmoid colon, or rectum.

**Presence of Clinical Syndrome**

**Functioning**
A functioning carcinoid tumor secretes biochemically active substances such as hormones, which cause specific clinical syndromes such as Carcinoid Syndrome or Zollinger-Ellison syndrome.

**Non-functioning**
A non-functioning carcinoid tumor secretes specific substances but these substances are either inactive and/or do not cause any clinical syndrome.
Inherited Versus Sporadic

Sporadic
Cancer causing mutations arise randomly

Inherited
Cancer causing mutations are inherited due to MEN-1 or other familial factors

Carcinoid tumors can be familial or sporadic. Inherited carcinoid cancer refers to carcinoid cancer which is genetically inherited whereas sporadic carcinoid cancer has no hereditary basis. Carcinoid tumors are generally thought to be sporadic, except for a small proportion of which occur as a part of MEN (multiple endocrine neoplasia) syndromes (Babovic-Vuksanovic, Constantinou, Rubin, Rowland, Schaid, & Karnes, 1999). Other familial factors contribute to a small proportion of carcinoid tumors; these are less understood than MEN-1 causes.

Histological Features
Since neuroendocrine tumors, such as carcinoid cancer, represent a heterogeneous group of tumors, in 2000, the World Health Organization updated the classification system for them based upon their clinical pathological criteria (Kloppel, Perren, & Heitz, 2004). Each category includes both functioning and non-functioning tumors.

- Well-differentiated endocrine tumors, with benign or uncertain behavior.
- Well-differentiated endocrine carcinomas, with low-grade malignant behavior.
- Poorly differentiated endocrine carcinomas, with high-grade malignant behavior.
- Endocrine/exocrine carcinomas, with characteristics of both endocrine and exocrine tumors.

Carcinoid tumors and pancreatic neuroendocrine tumors generally fall within the classification of well-differentiated endocrine tumors.
LOCATIONS & CLASSIFICATIONS REFERENCES


SYMPTOMS & SIDE EFFECTS

Carcinoid Symptoms
Carcinoid tumors can cause life-threatening symptoms from both hormone hypersecretion (over production) as well as tumor growth and invasion. The majority of individuals with carcinoid tumors are asymptomatic until the tumors metastasize to the liver and cause symptoms of tumor secretion. However, as the tumors grow they can cause obstructive symptoms.

Obstructive Symptoms

Midgut and Hindgut
Individuals with midgut and (in rare cases) hindgut carcinoids may experience symptoms such as abdominal pain, nausea, and vomiting, even though diagnostic scanning shows nothing. Many individuals diagnosed with liver metastases have reported having undiagnosed abdominal pain for several years prior to their diagnosis of carcinoid.

Foregut
Individuals with bronchial (lung) carcinoids most commonly present with obstructive symptoms. These symptoms may include chronic lung infection such as bronchitis and pneumonia, breathing difficulties, chest pain, and chronic cough (Kulke, 2007; Fink, Krelbaum, Yellin, Bendayan, Saute, Glazer, & Kramer 2001). Less commonly, symptoms may include weakness, nausea, sweating, and Cushing’s Syndrome (Fink et al., 2001; Granberg, Winlander, Oberg, & Skogseid, 2000).

Carcinoid Syndrome
Carcinoid tumors can secrete a variety of hormones which can cause many clinical symptoms such as flushing and diarrhea. Symptoms occurring together may be classified as a syndrome. Carcinoid Syndrome occurs in approximately 10% of individuals with carcinoid tumors and is most commonly found in individuals with midgut carcinoid tumors that have metastasized to the liver (Poncet, Faucheron, & Walter, 2010). In midgut carcinoid tumors, carcinoid syndrome does not normally develop until the tumors have metastasized since the liver is able to break down the excess hormones produced by these tumors (Kulke, 2007). However, once the tumors develop in the liver, the liver is no longer able to break down the excess hormones, and symptoms from them may occur. Carcinoid tumors that develop outside of the midgut can cause carcinoid syndrome without liver metastases, but rarely do.

Typical Carcinoid Syndrome
Typical Carcinoid Syndrome is the most common form of Carcinoid Syndrome and is most often caused by midgut carcinoids that have metastasized to the liver. Excess serotonin is the hormone most frequently related to Carcinoid Syndrome. The syndrome is characterized by brief episodes of flushing, diarrhea, cough, wheezing, shortness of breath, heart disease, and in rare cases, pellagra. Flushing and diarrhea are the two main symptoms that are associated with Carcinoid Syndrome. Diarrhea can be mild to severe which may lead to weight loss and
life style changes. The flushing may be light pink to a deep red and occurs in the face and in the nipple-line. It may be triggered by stress, alcohol, exercise and certain types of foods.

**Atypical Carcinoid Syndrome**

Atypical Carcinoid Syndrome is rare and is associated with foregut carcinoid tumors. It is characterized by extended episodes of flushing, headache, shortness of breath, and in rare cases, lacrimation (tears) (Tomassetti, Migliori, Lalli, Campana, Tomssetti, & Corinaldesi, 2001). The flushing can be deep purple and last for hours. It may be followed by increased blood flow to the limbs (arms and legs) and to the trunk (chest, stomach and back). This flush is not brought on by food (Tomassetti et al., 2001).

**Carcinoid Crisis**

Individuals with Carcinoid Syndrome can also experience Carcinoid Crisis which can occur spontaneously or be stress induced. A Carcinoid Crisis can be a life-threatening event that requires careful monitoring. Symptoms of a Carcinoid Crisis may include severe hypotension or hypertension, irregular and/or rapid heartbeat, wheezing, prolonged flushing, severe dyspnea (shortness of breath), and peripheral cyanosis (lack of oxygenated blood).

**Carcinoid Heart Disease**

Carcinoid tumors can secrete a variety of hormones and vasoactive substances such as serotonin. When these substances are released from liver metastases, the right side of the heart is exposed to them. As a result, patients may experience Carcinoid Heart Disease characterized by plaque lesions in the right side of the heart. Carcinoid Heart Disease can cause right-sided heart failure (Connolly, Modesto, Moller, Pellikka, Seward, & Rubin 2003). Carcinoid Heart Disease is most common on the right side of the heart but can also occur on the left side (Smith 1968). While serotonin production is related to development of Carcinoid Heart Disease, there is evidence of increased cardiac lesions during somatostatin analog therapy (Moller, Connolly, Rubin, Seward, Modesto, & Pelikka, 2003). All carcinoid cancer patients should be familiar with Carcinoid Heart Disease and discuss appropriate monitoring with their physician.

**Cushing’s Syndrome**

Bronchial (lung) carcinoid tumors can also secrete the adrenocorticotropic hormone (ACTH) which may cause Cushing’s Syndrome. Cushing’s Syndrome is characterized by excessive upper body weight gain, skin disorders (bruising and poor healing), baldness, and psychological disorders such as depression and anxiety.

**Zollinger-Ellison Syndrome**

Gastrinomas hypersecrete (over produce) gastrin causing Zollinger-Ellison Syndrome. Symptoms of Zollinger-Ellison Syndrome include diarrhea and peptic-ulcers. Patients with Zollinger-Ellison Syndrome may also develop gastric carcinoid as a result of prolonged gastrin hypersecretion.
DIAGNOSIS

How is a carcinoid tumor diagnosed?
Carcinoid tumors, like many neuroendocrine tumors, can be very difficult to diagnose. It is common for individuals with carcinoid cancer to remain asymptomatic until the tumors have metastasized or grow large enough to affect normal bodily functions. After an individual develops symptoms, diagnosis can be problematic since the symptoms of carcinoid cancer can mimic other diseases.

If your physician suspects you have a carcinoid tumor, there are specific biochemical tests which measure tumor markers and imaging tests that can help confirm a diagnosis and potentially determine the tumor type, location, load and prognosis. A tissue biopsy of a suspected tumor is, in most cases, the only definitive test.

If you have already been diagnosed with carcinoid cancer, biochemical and imaging tests are very important tools for disease staging and clinical management.

Biochemical Testing
Neuroendocrine tumors, such as carcinoid, produce a variety of substances which include hormones, proteins, and biogenic amines. Some tumors are termed functional since they are able to secrete an active form of these substances, which can cause a specific clinical syndrome such as Carcinoid Syndrome, Zollinger-Ellison Syndrome,
and Cushing’s Syndrome. However most carcinoid tumors are non-functioning and are not associated with a characteristic clinical syndrome either because the substances secreted are biologically inactive or because they do not cause any specific symptoms.

The substances secreted by a carcinoid tumor can be measured by biochemical tumor markers. Biochemical tumor markers can be divided into two categories: those which are specific to a particular carcinoid tumor location and those which are general. The most common tumor markers are:

**Chromogranin A (CgA)**

Chromogranin A is a secretory protein that is common to most neuroendocrine tumor cells, including carcinoid, and is a general tumor marker for neuroendocrine tumors. Since it is secreted into the blood stream it can be measured by a simple blood test. Blood plasma levels of CgA have been shown to relate to prognosis. (Janson, Holmberg, Stridsberg, Eriksson, Theodorsson, Wilander, & Oberg, 1997; Kulke, 2007a). In patients treated with somatostatin analogs CgA should be used with caution as somatostatin analogs can affect CgA levels (Oberg, Kvols, Caplin, Delle Fave, de Herder, Rindi, Rusniewski, Woltering, & Wiedenmann 2004). It has been recommended that CgA readings be taken at consistent time periods from somatostatin analog treatment (Vinik, Woltering, Warner, Caplin, O’Dorisio, Wiseman, Coppola, Go, 2010).

**5-hydroxyindoleacetic acid (5-HIAA)**

5-HIAA is a metabolite (a product from the breakdown) of serotonin. Serotonin is one of the most commonly secreted hormones by carcinoid tumors of the midgut and sometimes those of the foregut (Vinik, Silva, Woltering, Go, Warner, & Caplin, 2009). Consequently, 5-HIAA is usually elevated in midgut carcinoids but not in any others (Kulke, 2007a). A 24-hour urine collection is used to measure 5-HIAA levels. While 5-HIAA levels are commonly used to monitor patients with metastatic carcinoid tumors, studies have documented metastatic carcinoid tumors without elevated 5-HIAA levels (Feldman & O’Dorisio, 1986). 5-HIAA can also be elevated in patients with celiac, Whipple’s disease, and afterwards in those eating tryptophan-rich foods (Kulke, 2007a).

Certain foods such as bananas, walnuts, avocados and caffeine can also have an effect on 5-HIAA levels. Be sure to speak with your physician for a complete list before testing. More specifics can be found in the Inter Science Institute’s (ISI) handbook, *Neuroendocrine Tumors: A Comprehensive Guide to Diagnosis and Management*.

All neuroendocrine tumors, including carcinoid tumors, secrete hormones. However, what they secrete depends upon the type of tumor and the tumor location. Secretions of neuroendocrine tumors can sometimes change over time and so your physician may recommend evaluating a panel of markers over time. Generally speaking, all markers should be evaluated at a fasting state and at a consistent interval from long acting somatostatin analog treatment (Vinik et al., 2010). The following sections are divided by tumor location and the secreted substances associated with them.
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<td>Various (see above)</td>
<td>CgA</td>
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</table>

(Sundin, Garske, & Orlefors, 2007; Akerstrom, Hellman, & Osmak, 2005; Jensen et al, 2008)

**Imaging**

Along with biochemical testing, there are several imaging techniques which are useful to help determine a carcinoid tumor’s location, size, and extent of metastases. The imaging technique used and the combination thereof depend upon the primary tumor type, location, presence or absence of hormonal symptoms (functioning vs. non-functioning), and extent of the disease (Sundin et al., 2007). Imaging is especially important when liver metastases are suspected because liver function tests can be an unreliable predictor of liver metastases (Kulke, 2007a, Kulke, 2007b).
Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

Computed Tomography (CT) is an imaging technique that uses a highly specialized X-Ray machine and computers to create multiple cross sectional images of the body. CT can generate images of different body tissues as well as help detect tumors.

Magnetic Resonance Imaging (MRI) uses radio waves, a powerful magnetic field and a computer to generate detailed (2 or 3 dimensional) images of the body. These images are very useful in contrasting different types of tissue as well as detecting abnormal growths such as tumors within the body. MRI can create better images than CT, but is less commonly used.

CT/MRI are useful imaging techniques when used to visualize foregut carcinoids (those of the lungs, thymus, stomach and pancreas), to define the extent of metastasis (particularly liver and lymph-node metastasis), and to image secondary effects of midgut and hindgut carcinoids (such as scaring of the intestinal wall caused by tumor growth) (Dromain, de Baere, Caillet, Laplanche, Boige, Ducreux, Duvillard, Elias, Schlumberger, Sigal, & Baudin, 2005). CT/MRI can be used to detect midgut carcinoids although the detection of midgut carcinoids is often difficult due to the environment of the intestine and tumor size (Rockall & Rodney, 2007; Kulke, 2007a).

Somatostatin Receptor Scintigraphy (SRS) or Octreotide Scan

Somatostatin Receptor Scintigraphy (SRS) is a type of radionuclide scan that uses the radionuclide (radioactive substance) Octreotide (111-In-DTPA-octreotide) and a highly specialized machine to detect carcinoid tumors. When octreotide is injected into a patient’s vein, it can travel through the bloodstream and bind to carcinoid tumors.

Octreotide is a synthetic (man-made), radio-labeled analogue of the naturally occurring hormone somatostatin. Over 90% of all carcinoid tumor cells have receptors for somatostatin (Kvols, Brown, O’Connor, Hung, Hayostek, Reubi, & Lamberts, 1993; Reubi & Waser, 2003). Octreotide, like somatostatin, is able to bind to two of the five receptors (receptors two and five) on carcinoid tumors (Oberg, Reubi, Kwekkeboom, & Krenning, 2010).

SRS is used to find the tumors which bind octreotide. If the octreotide binds to the tumors, doctors can visualize them through the use of an imaging machine. Scans can be done at different intervals following an octreotide injection: 4 hours, 24 hours and 48 hours (Mamikunian, Vinik, O’Dorisio, Woltering, & Go, 2009). However a scan at 24 hours after octreotide injection is preferred (Sundin, et al., 2007). An octreotide scan is able to detect carcinoid tumors that bind octreotide and are larger than 1 - 1 1/2cm (Dromain et al., 2007).

Patients who are being treated with a somatostatin analogue such as Sandostatin or Lanreotide are strongly encouraged to temporarily discontinue treatment before undergoing SRS because somatostatin analogues used for treatment and for the scan compete for the same receptors (Sundin, et al., 2007). Patients should speak with their physicians to determine when and for how long they should discontinue treatment to maximize SRS.

SRS is not only useful in imaging carcinoid tumors but is also commonly used to predict response to somatostatin analogue therapy as well as peptide receptor radionuclide therapy (PRRT) (Reidy, Tang, & Saltz, 2009; Modlin, Oberg, Chung, Jensen, de Herder, Thakker, Caplin, Delle Fave, Kaltsas, Krenning, Moss, Nilsson, Rindi, Salazar, Rusziniewska, & Sundin, 2008).
Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is another form of radionuclide scan that uses a radioactive material and a special scanning device to detect cancerous tumors. Most commonly, the radionuclide 18F-labelled deoxyglucose (FDG) is used to detect many forms of cancer. However FDG is not effective in detecting most carcinoid tumors with the exception of tumors with high proliferative activity and low differentiation (Adams, Baum, Rink, Schumm-Drager, Usadel, & Hor, 1998). Instead, 68Ga-DOTA-TOC is the radionuclide that is most commonly used with PET to detect carcinoid (Sundin, et al., 2007).

PET with 68Ga-DOTA-TOC works in a similar fashion to octreotide in that like octreotide, 68Ga-DOTA-TOC is able to bind to specific receptors on carcinoid tumors. Once bound, the tumors can be visualized with a PET scan. However, 68Ga can be accumulated much faster by carcinoid tumors and so the scan for the tumors can be done approximately one hour after the 68Ga has been administered (Sundin, et al., 2007). There is evidence that like SRS, 68Ga can be used to predict response to PRRT (Haug, Auernhammer, Wangler, Schmidt, Uebleis, Goke, Cumming, Bartenstein, Tiling, & Hacker, 2010). 68Ga-DOTA-TOC has been effective in detecting carcinoid tumors that are greater in size than 0.5 cm.

Other radionuclides that are used with PET are: 11C-labelled L-dihydroxyphenylalanine, 18F L-dihydroxyphenylalanine, and 5-Hydroxy-L-tryptophan.

Endoscopy

Endoscopy is a medical procedure that uses an endoscope to view the lining of multiple organs and tracts of the body. An endoscope is a flexible or rigid tube that has imaging capabilities and can enable small surgical procedures. Endoscopy can be used to visualize carcinoid tumors in the lungs and gastrointestinal tract (stomach, small and large intestine and rectum).

DIAGNOSIS REFERENCES


TREATMENT

Due to their varied nature and primary locations, carcinoid cancers can be very difficult to treat. Carcinoid tumors can be benign to highly malignant, indolent (slow growing) to very aggressive in development, and range from asymptomatic to causing debilitating syndromes. As a result, a multi-disciplinary team consisting of specialist physicians in NETs (gastroenterologists, oncologists, and endocrinologists), surgeons, radiologists, nuclear medicine specialists, histopathologists, and clinical nurse specialists is often recommended (Ramage, Ahmed, Ardill, Bax, Breen, Caplin, Corrie, Davar, Davies, Lewington, Meyer, Newell-Price, Poston, Reed, Rockall, Steward, Thakker, Toubanakis, Valle, Verbeke, Grossman, and UK and Ireland Neuroendocrine Tumor Society, 2012).

Treatment must be tailored to each patient’s tumor burden and symptoms. Treatments may be focused on inhibiting tumor growth or symptom relief. Often, this means that any given treatment plan may consist of a combination and/or series of several treatments. Be sure to discuss your treatment options thoroughly with your physician(s). Ultimately, all treatment decisions should be made by the patient. Please click here to visit the Neuroendocrine Tumor Research Foundation’s Doctor Database or call 617-948-2514 for help finding a physician well-versed in treating neuroendocrine tumor patients.

Surgery

The surgical treatment of carcinoid tumors depends on the tumor type, location, extent of metastases, as well as other factors. Surgery can often be curative for individuals whose tumors are localized (have not spread) and do not cause syndrome (Norton, 2005). For individuals who have metastases, surgery can often increase survival and provide palliative care depending on tumor size and location (Steinmuller, Kianmanesh, Falconi, Scarpa, Taal, Kwekkeboom, Lopes, Perren, Nikou, Yao, Dell Fave, O’Toole, & Frascati Consensus Conference participants, 2008). A multimodal approach combining surgery with embolization or other treatment methods may also be possible for patients with liver metastases. For all patients who undergo surgery, continued and extensive follow up is recommended.

Appendix

Carcinoid tumors are the most common appendiceal tumor and most frequently are benign (Akerstrom, Hellman, Hessman, & Osmak, 2007). These tumors are often incidentally discovered during surgery and are usually removed by an appendectomy (Kulke, 2007). An appendectomy is the complete removal of the appendix, which can be done either laparoscopically or as an open procedure. Low incidence of metastasis has been observed in patients undergoing appendectomy with tumors smaller than two cm (Kulke, 2007).

Intestine

The majority of carcinoid tumors originate in the gastrointestinal tract. Of these, intestinal carcinoids are the most common (Modlin, Lye, & Kidd, 2003). After diagnosis of an intestinal carcinoid, a small bowel resection may be performed. A small bowel resection is the surgical removal of one or more parts of the small intestine. The extent of the resection depends on a variety of factors, including tumor size, number, and extent of metastasis. If the tumor has metastasized to the surrounding tissues and liver, a more invasive surgery may be conducted. In certain cases, the removal of these tumors can help to decrease Carcinoid Syndrome, alleviate abdominal pain, prevent further metastases and increase survival. (Norton, Kivlen, Li, Schneider, Chuter & Jensen, 2003).
Liver
The liver is the most common site for carcinoid tumors to metastasize but it is rare for the liver to be the primary site of carcinoid development. (Norton, Warren, Kelly, Zuraek, & Jensen, 2003; Steinmuller et al., 2008). The type and extent of surgery for liver metastasis is contingent upon tumor type, size, location, disease progression, site of origin and other factors. Liver resection, the surgical removal of part of the liver, is a common treatment protocol for individuals for whom a complete resection is possible (Reidy, Tang, & Saltz, 2009). For individuals for whom a complete resection is not possible, surgery, in combination with other treatment modalities, may be used to debulk (decrease) tumor burden. Resection and debulking (for individuals for whom the majority of tumor burden is removed) have resulted in increased survival and a decrease in disease symptoms. Presence of liver metastasis is a major prognostic factor with presence of liver metastasis indicating worse outcome (Norton, 2005).

In certain cases, a two-stage surgical resection can be done for patients with extensive liver metastases. The first phase of a two-stage resection involves the radical resection of a portion of the left side of the liver with right portal vein ligation to encourage the left side of the liver to regenerate. After the liver is allowed to regenerate, the right side of the liver is then removed. (Kianmanesh, Sauvanet, Hentic, Couvelard, Levy, Vilgrain, Rusziewski, & Belghiti, 2008).

In a very small group of individuals with carcinoid liver metastases, orthotopic liver transplantation (OLT) has been used. OLT is the process in which the diseased liver is completely removed and replaced with a healthy, donor liver.

Currently, there is little clinical evidence on the results of radical, two-part liver resections and orthotopic liver transplantation. Due to the lack of clinical evidence, the benefit of these procedures, in particular OLT, has yet to be determined (van Vilsteren, Baskin-Bey, Nagorney, Sanderson, Kremers, Rosen, Gores, Hobday, 2006; Blonski, Reddy, Shaked, Siegelman, & Metz, 2005).

Lung
Bronchial carcinoid tumors can develop almost anywhere in the lungs. Surgical management is the recommended treatment for most bronchial carcinoids. The type and extent of the surgery depends on the nature, location and size of the tumor(s) (Fiala, Petras, Cernohorsky, Kinkor, Krepela, & Zatloukal, 2003). A lobectomy, which is the surgical removal of one lung lobe, is the most common surgical method used to treat bronchial carcinoids. If more than one lobe is affected and surgery is possible, an individual may undergo a bilobectomy, which is the surgical removal of two lung lobes or a pneumonectomy, which is the surgical removal of a lung. A sleeve resection, which is the surgical removal of a section of bronchus or trachea along with the infected lobe, may also be used to remove bronchial carcinoids. A wedge resection, which is the surgical removal of the affected lung tissue and the surrounding margins, may be used to remove the tumor and leave the lung lobe. A wedge resection is less invasive than a lobectomy and is the preferred treatment method when clinically possible (Chughtai, Morin, Sheiner, Wilson, & Mulder, 1997).
Lymph Nodes
Lymph nodes are often the site of carcinoid metastases. When an individual is diagnosed with carcinoid and is a surgical candidate, the lymph nodes surrounding the affected area should be examined for metastases and removed if affected. A lymphadenectomy is the surgical removal of one or more groups of lymph nodes.

Rectal Carcinoids
Rectal carcinoids represent just over 10% of all carcinoids and are most commonly incidentally found during routine endoscopic cancer screenings. Treatment of rectal carcinoids depends on the size and invasiveness of the tumor. Tumors that are < 1 cm can usually be treated by an endoscopic excision, a minimally invasive surgical procedure which involves the removal of the tumor and the surrounding tissues. However the histological features of these tumors should still be examined to make sure they have not invaded the surrounding tissue (Kulke, 2007). Tumors that are ≥1 cm will need further investigation and depending on size and invasiveness may require a rectal resection, the surgical removal of a portion of the rectum (Kulke, 2007).

Stomach
The surgical removal of gastric carcinoids will depend on their type, size, quantity, extent of invasiveness and response to somatostatin analogues. Endoscopic excision, a minimally invasive surgical procedure, can be used for smaller type I and II gastric carcinoids. A gastric resection (gastrectomy), the partial or complete surgical removal of the stomach, may be done for individuals who have large and multiple type I or II gastric carcinoids as well as for nearly all type III gastric carcinoids (Borch, Ahren, Ahlman, Falkmer, Granerus, & Grimelius, 2005).

Non-Surgical Therapies
If curative surgery is not possible, other treatment options are available to individuals with carcinoid cancer. Currently, there is no non-surgical curative treatment, but there are several non-surgical treatment options which can result in decreasing tumor bulk, halting tumor progression, and/or managing tumor symptoms. The type of treatment used is determined by tumor type, size, location, disease progression, as well as many other factors.

Somatostatin Analogues
The excess of hormones produced and secreted into the body by carcinoid tumors can cause several symptoms, which when grouped together may be classified as a syndrome, such as Carcinoid Syndrome or Cushing’s Syndrome. Most neuroendocrine tumors, including carcinoid, have five highly specialized receptors for the naturally occurring hormone somatostatin (Reubi, Kvolz, Waser, Nagorney, Heitz, Chaboneau, Reading, & Moertel, 1990). When somatostatin is bound to these receptors, especially receptors two and five, it inhibits the release of the various hormones that cause many of the symptoms associated with carcinoid tumors (Oberg, Reubi, Kwekkeboom, & Krenning, 2010). Synthetic analogues (man-made versions) of somatostatin can mimic somatostatin by binding to receptors two and five and inhibiting hormone secretion. Currently, there are two synthetic somatostatin analogue products available: octreotide (Sandostatin) and lanreotide (Somatuline Depot). These somatostatin analogues have been proven to control, decrease and prevent symptoms associated with carcinoid. In a recent study, octreotide also demonstrated possible antitumor effects when compared to a placebo in patients with well-differentiated carcinoid tumors of midgut origin, limited hepatic tumor mass and a resected primary tumor (Rinke, Muller, Schade-Brittinger, Lose, Barth, Weid, Mayer, Aminossadati, Pape, Blacker, Harder, Arnold, Gress, Arnold, & PROMID Study Group, 2009).
Novel somatostatin analogs such as pasireotide are currently in clinical trials to determine their role in treating characteristic syndromes from neuroendocrine tumors and/or for antitumor effects. Pasireotide is one somatostatin analog in clinical development which binds to somatostatin receptors one, two, three and five.

Interferon-α
Interferons are naturally occurring proteins that are secreted by specialized cells in the body to activate the body’s natural protective response to harmful substances including some tumors. There are many types of interferon produced by the body. A synthetic version of one type, interferon-α, can be used in combination with somatostatin analogue for symptom management in individuals whose symptoms are not controlled by somatostatin analogues (Janson, Holmberg, Stridsberg, Eriksson, Theodorsson, Wilander, & Oberg, 1997). However, interferon-α can have severe side-effects, such as myelosuppression (the decrease in bone marrow activity resulting in lower blood cell levels), fatigue, depression and changes in thyroid function.

Cytotoxic Chemotherapy
Cytotoxic chemotherapy is the use of anticancer drugs that target and kill rapidly proliferating (dividing) cells. Thus far, there has been little clinical evidence for the use of chemotherapeutic drugs in the treatment of well-differentiated (typical) carcinoid tumors (Kulke 2007). However, studies have demonstrated that poorly-differentiated (atypical) carcinoid tumors are more responsive to chemotherapeutic drugs, especially the combination of cisplatin and etoposide (Toumpanakis, Meyer, & Caplin, 2007).

Ablative Therapies
Hepatic Artery Embolization
All cells require an adequate blood supply to survive. The human liver has two main sources of blood: the portal vein and hepatic artery. The portal vein supplies blood to most liver cells while tumor cells mostly depend on the hepatic artery for their blood supply. A hepatic embolization is a non-surgical procedure which involves the blockage of selective branches of the hepatic artery that supply tumor cells with blood. This blockage is made possible by the injection of embolic particles (specialized particles that cause a blockage) which travel to and cut off tumor blood supply. There are two types of embolization of the hepatic arteries: 1) bland embolization – the injection of just embolic particles, and 2) chemoembolization – the injection of embolic particles and chemotherapeutic agent (drug).

Individuals with liver metastases may be considered candidates for hepatic embolization or hepatic chemoembolization if they have non-resectable liver metastases, uncontrolled growth of liver metastases and/or uncontrolled symptoms (Reidy, Tang, & Saltz, 2009). However, other factors such as physical health and the extent of tumor growth must also be taken into consideration. These procedures can have very positive but short-term results of: a decrease in tumor size, a decrease in tumor symptoms, and a halt in tumor progression. Duration of response is highly variable (Reidy, Tang, & Saltz, 2009). Individuals who are candidates may undergo more than one embolization.
Common side-effects of either procedure can include fever, fatigue, abdominal pain, nausea and vomiting. The severity of these varies for each individual.

**Radioembolization**

Radioembolization is a form of selective internal radiation therapy (SIRT). It is a minimally invasive procedure that combines embolization and radiation therapy to target liver metastases. Radioembolization involves the injection of millions of radioactive microspheres (microscopic beads) into a branch of the hepatic artery which supplies blood to the tumor. From there, the microspheres travel to the tumor site where they inhibit the blood supply to the tumor and emit radiation effectively killing tumor cells.

Currently, there are two radioactive microsphere products available for patients with metastatic tumors to the liver, one made of glass and the other resin. Both products use Yttrium-90 (90Y), a beta emitting radionuclide. Individuals with liver metastases may be considered candidates for hepatic embolization or hepatic chemoembolization if they have non-resectable liver metastases, uncontrolled growth of liver metastases and/or uncontrolled symptoms (Saxena, Chua, Bester, Kokandi, & Morris, 2010). Other factors such as physical health, extent of tumor burden and prior treatment therapies must also be taken into consideration. These procedures can have very positive but short-term results of: a decrease in tumor size, a decrease in tumor symptoms, and a halt in tumor progression. Currently, the role of radioembolization in combination with other therapies is not well understood (Reidy, Tang, & Saltz, 2009).

Common side-effects of radioembolization can include fever, abdominal pain, fatigue, nausea and vomiting. The severity of these varies for each individual.

**Radiofrequency Ablation (RFA)**

Radiofrequency ablation (RFA) is a minimally invasive procedure that uses a high frequency electrical current to destroy tumor cells. RFA involves placing a small probe into a tumor. Electrical currents (which are at the same range of radiofrequency) are sent through the probe. This effectively raises the temperature of the tumor tissue and destroys it. RFA can be done laparoscopically but is more commonly done in combination with liver resection.

Individuals with inoperable carcinoid tumors may be candidates for RFA. RFA has been shown to temporarily decrease tumor burden, stall tumor progression and temporarily relieve tumor symptoms. There are many limitations to RFA, including tumor size and tumor location. Tumors that are greater in diameter than 3 cm are difficult to eradicate and RFA cannot be used in tumors that are greater in diameter than 5 cm (Poncet, Faucheron, & Walter, 2010).

**Peptide Receptor Radionuclide Therapy (PRRT)**

Most neuroendocrine tumors, including carcinoid, have five highly specialized receptors that bind to the naturally occurring hormone somatostatin. Octreotide is a synthetic analogue (a man-made version) of somatostatin that is able to attach to two of these five somatostatin receptors.
Peptide receptor radionuclide therapy (PRRT) combines octreotide with a radionuclide (a radioactive substance) to form highly specialized molecules called radiolabeled somatostatin analogues or radiopeptides. These radiopeptides can be injected into a patient and will travel throughout the body binding to carcinoid tumor cells that have receptors for them. Once bound, these radiopeptides emit radiation and kill the tumor cells they are bound to.

There are three radionuclides that are attached to octreotide to create radiopeptides: indium 111 (111In), yttrium 90 (90Y) and lutetium 177 (177Lu). These radiopeptides differ in the type of radiation they emit as well as the depth of tissue into which they penetrate. Tissue penetration is an important factor since a certain range of radiation is necessary to kill tumor cells but not damage surrounding, healthy tissues. 111In emits both Auger electrons and γ-radiation and has the shortest range of tissue penetration (10 µm), 90Y emits β-radiation and has a range of 12 mm, and 177Lu emits both β-radiation and γ-radiation and has a range of 2 mm (Kwekkeboom, de Herder, van Eijck, Kam, van Essen, Teunissen, Krenning, 2010).

Studies have shown that in certain individuals, the short-term results of PRRT with 177Lu and 90Y (and 111In to a much lesser degree) are: a decrease in tumor size, a decrease in symptoms, and a halt in tumor progression (Bushnell, O’Dorisio, O’Dorisio, Menda, Hicks, Van Cutsem, Baulieu, Borson-Chazot, Anthony, Benson, Oberg, Grossman, Connolly, Bouterfa, Li, Kacena, LaFrance, & Pauwels, 2010).

Common side-effects of radiopeptide therapy are nausea, vomiting and abdominal pain. Other less common side-effects are bone, liver and kidney toxicity, and mild hair loss. (Bushnell et al., 2010).

Individuals whose tumors can be visualized by somatostatin receptor scintigraphy (SRS) or 68 GA –DOTATE PET/CT (Haug, Auernhammer, Wangler, Schmidt, Uebleis, Goke, Cumming, Bartenstein, Tiling, & Hacker, 2010) and have inoperable carcinoid tumors that are growing or individuals whose symptoms are not well managed by somatostatin analogues may be candidates for PRRT. However, the extent of tumor growth, kidney function, liver function, prior treatments, and many other factors must also be considered. (Bushnell et al., 2010; Haug et al, 2010).

**Molecular Targeted Therapies**

Carcinoid tumors are formed by an abnormal growth of cells within the body. Normally, the growth and replication of all cells within the body is strictly regulated at a molecular and genetic level. However, tumors are made up of cells that have undergone multiple mutations in their genetic code, which allow them to grow and replicate without the normal controls. By understanding what molecular and genetic mutations have occurred, scientists can develop drug therapies that target these mutations (targeted therapies) effectively stopping tumor cell growth and even promoting tumor cell death. At this time, there are two molecular pathways for which novel targeted therapies are being developed.

**Vascular Endothelia Growth Factor (VEGF) Inhibitors**

All cells require an adequate blood supply to survive. Cancer cells, since they tend to replicate faster than normal cells, require an even greater blood supply. In order to achieve this, many tumors, including carcinoid, undergo
angiogenesis, the development of new blood vessels. Vascular endothelial growth factor (VEGF) is a highly specialized chemical signal that cells produce in order to stimulate new blood vessel growth. In carcinoid tumors, this signal is over expressed. Targeted therapies called angiogenic inhibitors are currently being investigated to see if they can effectively suppress VEGF in carcinoid or inhibit pathways that would disrupt its production or effects. Bevacizumab and sunitinib malate are two drug therapies that interrupt VEGF and their effects on carcinoid are being investigated.

**Mammalian Target of Rapamycin (mTOR) Inhibitors**

Normally, cells that have unfixable mutations in the genetic code will undergo apoptosis (programmed cell death). Carcinoid tumors cells, like other cancer cells, do not do this. Instead, their growth and death is unregulated (Chan & Kulke, 2009). The mammalian target of rapamycin (mTOR) is a protein that is involved in many cellular pathways including cell growth and death (Reidy, Tang, & Saltz, 2009; Vignot, Feliberti, Perry & Nakave, 2008). In carcinoid, mTOR is not regulated and consequently promotes tumor cell growth. Targeted therapies called mTOR inhibitors deactivate mTOR and prevent cellular growth and replication. Everolimus (RAD001) is drug therapy that inhibits mTOR. Its effects on carcinoid are being investigated.

**TREATMENT REFERENCES**


