Carcinoid Tumors

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Carcinoid tumors are rare, slow-growing neuroendocrine neoplasms that often are indolent and may not become clinically apparent until there has been metastatic spread or evidence of carcinoid syndrome. Recent evidence has revealed that the overall incidence of carcinoid tumors has been steadily increasing, and although the disease was thought to be relatively benign, it is now considered one of increasing malignancy. Carcinoid tumors derive from different embryonic divisions of the gut: foregut carcinoid tumors commonly originate in the lungs, bronchi, or stomach; midgut carcinoid tumors in the small intestine, appendix, or proximal large bowel; and hindgut carcinoid tumors in the distal colon or rectum. Carcinoid syndrome, although rare, is most associated with midgut carcinoid tumors. The diagnosis of a carcinoid tumor often is coincidental with surgery performed for another reason. Treatment and prognosis are dependent on the location of the primary tumor and the degree and extent of metastasis at the time of diagnosis. (Am Fam Physician 2006;74:429-34. Copyright © 2006 American Academy of Family Physicians.)

Carcinoid tumors are rare, slow-growing tumors that originate in the cells of the neuroendocrine system. The nerve cells rarely undergo hyperplasia or neoplastic transformation, whereas cells in the endocrine glands and in disseminated sites in the mucous membranes and skin may undergo a transformation commonly known as carcinoid tumors.[1] There are three main areas of origin for carcinoid tumors: foregut carcinoid tumors start in the lungs, bronchi, or stomach; midgut carcinoid tumors start in the small intestine, appendix, or proximal large bowel; and hindgut carcinoid tumors start in the distal colon or rectum.[2] The appendix is the most common site of carcinoid tumors, followed by the rectum, ileum, lungs, bronchi, and stomach.[3]

Historically, the classification and distribution of carcinoid tumors has been according to their derivation from different embryonic divisions of the gut. More recently, the World Health Organization presented new classifications of gastroenteropancreatic neuroendocrine neoplasms[1] based on their malignant potential: well-differentiated endocrine tumor (proliferation index [PI] less than 2 percent); well-differentiated endocrine carcinoma (PI greater than 2 percent but less than 15 percent); poorly differentiated endocrine carcinoma (PI greater than 15 percent); mixed exocrine-endocrine tumors; and tumor-like lesions. *Table 1*[2,4,5] provides an overview of the incidence rate, average age at onset, associated symptoms, likelihood of metastasis, and commonness of carcinoid syndrome for carcinoid tumors in different locations of the body.

There has been an overall increase in incidence of carcinoid tumors over the past 30 years, with 67.2 percent of patients having a five-year survival rate.

Carcinoid tumors pose a diagnostic challenge because they often are asymptomatic. The overall prevalence of carcinoid tumors in the United States is estimated to be one to two cases per 100,000 persons.[3,4] Because many carcinoid tumors are indolent, their true prevalence may be higher.[5] Data derived from a five-decade analysis of 13,715 carcinoid tumors revealed an overall increase in incidence over the past 30 years, with 67.2 percent of patients having a five-year survival rate regardless of the site of the tumor.[2] Prognosis varies widely depending on the location and stage of the tumor.[1,2] The disease is considered to be more aggressive and to have a worse prognosis than was thought previously.[2]

Clinical Presentation

Many carcinoid tumors are found during surgery for other reasons, usually at appendectomy or surgery for acute pancreatitis,

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
5-Hydroxyindoleacetic acid and serum chromogranin A are recommended as initial tests for patients with vasoactive symptoms and suspected carcinoid tumors.	C	13, 17
A multimodal approach is recommended for imaging and may include CT, MRI, somatostatin receptor scintography using indium-111 labeled octreotide, and endoscopic ultrasonography.	C	13
Patients with carcinoid tumors of the gastrointestinal tract should be evaluated for second primary malignancy.	C	21, 22

CT = computed tomography; MRI = magnetic resonance imaging.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 363 or http://www.aafp.org/afpsort.xml.

but also surgery for bowel obstruction or diseases of the female reproductive tract.[6,7] If there are symptoms, they usually are vague, nonspecific, and organ-related, causing relatively long delays in diagnosis. The average time from symptom onset to diagnosis is more than nine years.[8] Symptoms from the tumor can range from mild abdominal discomfort to intermittent intestinal obstruction.[9] Occasionally, a carcinoid tumor can be the lead point for an intermittent intestinal intussuception.[9] These tumors characteristically present at age 50 to 60.[8]

CARCINOID SYNDROME

A carcinoid tumor often is only considered after the onset of carcinoid syndrome, which typically does not occur until the tumor has metastasized to the lungs or liver.[9] The symptoms of carcinoid syndrome include flushing (pale, purplish, or red), diarrhea (watery and explosive), tachycardia or hypotension, bronchospasm, telangiectasia, and right-sided heart disease or failure.[1,9,10] Symptoms often are precipitated by exertion or by eating or drinking (especially items high in tyramine [e.g., blue cheeses, chocolate] or ethanol [e.g., red wine]).[1,9,10]

TABLE 1
Characteristics of Carcinoid Tumors by Location

Location	*Percent*	*Approximate age at presentation*	*Symptoms*	*Metastasis at diagnosis*	*Carcinoid syndrome (%)*
Rectum	26	60	Rectal bleeding, pain, constipation	Tumor size < 1 cm: 5 percent Tumor size > 2 cm: majority	< 5
Small intestine	25	60 to 70	Abdominal pain, small bowel obstruction	Majority present with metastasis, usually to lymph nodes or liver	5 to 7
Lungs, bronchi, and trachea	23	50	Recurrent pneumonia, cough, hemoptysis, chest pain	< 15 percent	< 5
Appendix	12	40 to 50	Appendicitis caused by tumor presence; incidental discovery during other pelvic procedures	< 5 percent	< 5
Stomach	7	60 to 70	Anemia, abdominal pain	< 10 percent	5 to 10; also Zollinger-Ellison syndrome
Colon	7	70	Pain, anorexia, weight loss	> 66 percent	< 5

Information from references 2, 4, and 5.

Carcinoid tumors contain many neurosecretory granules that are capable of the synthesis, storage, and release of substances, including serotonin, histamine, prostaglandins, kallikrein, bradykinins, substance P, gastrin, corticotrophin, and neuron-specific enolase.[9,11] The most prominent of these substances is serotonin (i.e., 5-hydroxytryptamine). Degradation of 5-hydroxytryptamine results in 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine. When released in the systemic circulation, 5-hydroxytryptamine can result in the symptoms of carcinoid syndrome; the excitation of smooth muscle leads to increased gastrointestinal motility, bronchoconstriction, platelet aggregation, or vascular constriction and dilatation.[12]

The lungs and liver metabolize many of the substances secreted by carcinoid tumors, thus preventing their release into the systemic circulation until metastases develop.[9] The syndrome is variable: patients may not have all symptoms, and the symptoms may vary in intensity and timing.[9] Carcinoid syndrome occurs in only 10 percent of all patients with carcinoid tumors,[8] and it is most often associated with midgut tumors.[5] *Table 2*[10] is a differential diagnosis of carcinoid syndrome symptoms.

Although the exact secreted substance responsible for the flushing is uncertain and controversial, the diarrhea seems to be largely caused by excessive serotonin in the system.[8,9] Bronchospasm may be mediated by serotonin and bradykinin, although this has not been definitively delineated.[8] Right-sided valvular heart disease is thought to be caused by prolonged high serum levels of serotonin and is therefore a later complication. Patients with carcinoid heart disease demonstrate higher levels of serum serotonin and urine 5-HIAA than other patients with carcinoid syndrome.[6] Endocardial fibrosis is the underlying pathology that results in thickened and contracted heart valves, producing the most common lesions of pulmonic stenosis and tricuspid insufficiency. Left-side heart valves usually are less affected because of the metabolism of serotonin in the lungs.[9,11]

Diagnosis

Although a significant percentage of carcinoid tumors are innocuous at the time of presentation, there are useful diagnostic techniques that facilitate identification and localization. Because the presentation varies with the embryologic origin of the tumor, there are differing approaches to the diagnosis. The indolent nature of carcinoid tumors makes test selection complex. For patients with vasoactive symptoms, measuring the urinary excretion of 5-HIAA and serum chromogranin A level is recommended.[13] For those with symptoms of bowel dysmotility syndromes, computed tomography (CT) and magnetic resonance imaging (MRI) may be helpful and often will note the coincidental presence of hepatic metastases that may be the first clue as to the presence of the primary tumor.[9,11]

URINALYSIS

The biochemical properties of carcinoid tumors reflect the presence of neurosecretory granules that these tumors share with other similarly classified tumors referred to as APUDomas (Amine Precursor Uptake and Decarboxylation).[14] Carcinoid tumors are classified as biochemically typical or atypical based on the presence of high levels of serotonin in so-called typical tumors.[15] The best

TABLE 2
Differential Diagnosis of Carcinoid Syndrome

Flushing
Menopausal syndrome; pheochromocytoma; mastocytosis; benign cutaneous flushing; medullary carcinomas of the thyroid; ingestants (e.g., food, drugs)
Wheezing
Asthma; anaphylaxis; pulmonary edema; bronchial foreign body
Diarrhea
Gastroenteritis; inflammatory bowel disease; infectious colitis; laxative abuse
Heart valve symptoms
Rheumatic heart disease; subacute bacterial endocarditis; dilated cardiomyopathy; ischemic heart disease with papillary muscle dysfunction

Information from reference 10.

known metabolite of serotonin in carcinoid tumors is 5-HIAA. In a 24-hour sample, the urinary level of 5-HIAA is the test most commonly used in the endocrine work-up of carcinoid tumors. Despite its popularity, it lacks the sensitivity and specificity for the diagnosis of carcinoid tumors because 5-HIAA may not be elevated in atypical carcinoids and can be elevated in other conditions such as tropical sprue, celiac disease, Whipple's disease, and small bowel obstruction, and can be caused by ingestion of foods high in serotonin, or certain medications.[16]

Carcinoid syndrome occurs in only 10 percent of patients with neuroendocrine tumors.

SERUM ANALYSIS

Although a number of other tumor markers have been investigated for carcinoid tumor overproduction, serum analysis of chromogranin A, a glycoprotein that is secreted with other hormones by neuroendocrine tumors, appears to be the most promising, with specificity approaching 95 percent and sensitivity for carcinoid tumors approaching 80 percent. A 40 percent false-positive rate has been seen in patients with multiple myeloma.[17]

DIAGNOSTIC IMAGING

Diagnostic imaging techniques may be relative to the origin and the degree of dissemination at the time of diagnosis. A multimodal approach is recommended, using combinations of imaging studies depending on the suspected site of the tumor.[13] Barium contrast studies or CT may detect mucosal thickening, a submucosal mass, or luminal narrowing.[8,18] CT is an excellent technique to show the mesenteric extension of tumors and liver metastases. Carcinoids that have infiltrated have a characteristic CT appearance that is spiculated with a stellate pattern.[8] The appearance of carcinoids with MRI seems to resemble that seen with CT.[8] Endoscopic ultrasonography is also an imaging option.[13]

NUCLEAR MEDICINE

Meta-iodobenzylguanidine (MIBG) is a structural analogue to norepinephrine, and I-labeled MIBG can be used for the detection of neuroendocrine tumors.[8] There is some new evidence that indicates that positron emission tomography (PET) may be useful in the diagnosis of neuroendocrine tumors as well.[19] Somatostatin receptor scintigraphy with indium-111 labeled octreotide is superior to CT scans for localizing the primary tumor site and to MIBG scans in the diagnosis of carcinoid tumors, with a 60 percent sensitivity and a greater than 90 percent sensitivity in patients with symptoms of carcinoid syndrome.[13,20]

Second Primary Malignancy

In a patient with a known carcinoid tumor of the gastrointestinal tract, there is an additional concern about a second primary malignancy. The rate of second primary malignancy with carcinoid tumors ranges from 12 to 46 percent, with an average of 17 percent, which is significant when compared with rates of second primary malignancy in other cancers, where 2.3 percent of patients undergoing surgery and 8.1 percent of autopsied patients have a second primary malignancy.[20,21] Most second primary malignancies present concurrently and are more aggressive, resulting in cancer-mediated death.[22] The most common sites for second primary malignancies are the gastrointestinal tract, genitourinary tract, and lung or bronchial system.[21]

Treatment

Treatment decisions for patients with carcinoid tumors are complex and related to the location of the primary tumor and whether or not metastasis has occurred. The main treatment options and approaches are outlined in *Table 3*.[1,23] Options include surgery, chemotherapy, and radiation with somatostatin analogues such as octreotide (Sandostatin) or alpha-interferon.[15,24,25] Further discussion of treatment options for carcinoid tumors is available in a recent British guideline,[13] the series by Oberg and colleagues,[26] and the National Comprehensive Cancer Network Guidelines (http://www.nccn.org).[27] Patients with carcinoid tumors should be referred to subspecialists who have expertise in its diagnosis, staging, and treatment.

TABLE 3
General Treatment Options for Malignant Carcinoid Tumors

Carcinoid tumor
Surgical resection if possible:
Hepatic metastases dominant: long-acting somatostatin analogues; hepatic artery embolization or ligation with or without interferon, with or without chemotherapy
Systemic spread: chemotherapy or interferon or long-acting somatostatin analogues
Carcinoid syndrome
Systematic progression through treatment options:
Heart disease: diuretics, long-acting somatostatin analogues, occasional valvular replacement
Flushing: avoid precipitating food and alcohol; 5-HT3-receptor antagonist; long-acting somatostatin analogues; interferon; hepatic artery embolization or ligation with or without interferon, with or without chemotherapy
Diarrhea: antidiarrheal agents; 5-HT3-receptor antagonist; long-acting somatostatin analogues; interferon; hepatic artery embolization or ligation with or without interferon, with or without chemotherapy
Wheezing: selective bronchodilators; long-acting somatostatin analogues; interferon; hepatic artery embolization or ligation with or without interferon, with or without chemotherapy

5-HT3 = serotonin receptor subtype 5-hydroxytryptamine-3.
Information from references 1 and 23.

Prognosis

Most patients with carcinoid tumors seek treatment for metastatic disease.[24] The prognosis for patients with these tumors is variable and related to the site of the primary tumor, the presence of metastatic disease, and time of diagnosis. Importantly, the most common cause of carcinoid syndrome is metastatic liver disease arising from a small bowel carcinoid tumor. For these patients, the prognosis is uniformly poor.[3]

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