Carcinoid Tumors

MATTHEW H. KULKE, M.D., AND ROBERT J. MAYER, M.D.

Carcinoid tumors were first described over 100 years ago by Lubarsch, who found multiple tumors in the distal ileum of two patients at autopsy.1 The term karzinoid was used by Oberndorfer in 1907 to describe similar tumors that appeared to behave in a more indolent fashion than typical adenocarcinomas.2 Carcinoid tumors have subsequently been reported in a wide range of organs but most commonly involve the lungs, bronchi, and gastrointestinal tract.

BIOLOGY

Carcinoid tumors are thought to arise from neuroendocrine cells. They are characterized histologically by positive reactions to silver stains and to markers of neuroendocrine tissue, including neuron-specific enolase, synaptophysin, and chromogranin. When viewed through an electron microscope, carcinoid tumors are typically found to contain numerous membrane-bound neurosecretory granules. These granules are composed of a variety of hormones and biogenic amines.

One of the best-characterized of these substances is serotonin. Serotonin is synthesized from its precursor, 5-hydroxytryptophan, by the enzyme aromatic acid decarboxylase. Serotonin is subsequently metabolized by monoamine oxidase to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine. In addition to serotonin, carcinoid tumors have been found to secrete corticotropin,3 histamine,4 dopamine,5 substance P,6 neurotensin,7 prostaglandins,8 and kallikrein.9 The release of serotonin and other vasoactive substances into the systemic circulation is thought to cause the carcinoid syndrome, the manifestations of which are episodic flushing, wheezing, diarrhea, and eventual right-sided valvular heart disease.10

In 1907, Oberndorfer in 1907 to describe similar tumors that appeared to behave in a more indolent fashion than typical adenocarcinomas.2 Carcinoid tumors have subsequently been reported in a wide range of organs but most commonly involve the lungs, bronchi, and gastrointestinal tract.

BIOLOGY

Carcinoid tumors are thought to arise from neuroendocrine cells. They are characterized histologically by positive reactions to silver stains and to markers of neuroendocrine tissue, including neuron-specific enolase, synaptophysin, and chromogranin. When viewed through an electron microscope, carcinoid tumors are typically found to contain numerous membrane-bound neurosecretory granules. These granules are composed of a variety of hormones and biogenic amines.

One of the best-characterized of these substances is serotonin. Serotonin is synthesized from its precursor, 5-hydroxytryptophan, by the enzyme aromatic acid decarboxylase. Serotonin is subsequently metabolized by monoamine oxidase to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine. In addition to serotonin, carcinoid tumors have been found to secrete corticotropin, histamine, dopamine, substance P, neurotensin, prostaglandins, and kallikrein. The release of serotonin and other vasoactive substances into the systemic circulation is thought to cause the carcinoid syndrome, the manifestations of which are episodic flushing, wheezing, diarrhea, and eventual right-sided valvular heart disease.

CLASSIFICATION

Carcinoid tumors have traditionally been classified according to their presumed derivation from different embryonic divisions of the gut.11 Foregut carcinoid tumors most commonly originate in the lungs, bronchi, or stomach; midgut carcinoid tumors in the small intestine, appendix, and proximal large bowel; and hindgut carcinoid tumors in the distal colon and rectum. Within these subgroups, the biologic and clinical characteristics of the tumors may vary considerably (Table 1). Many investigators have therefore adopted a classification system that takes into account not only the site of origin but also variations in the histologic characteristics of carcinoid tumors.12

Under this revised system, so-called typical tumors are classified as well-differentiated neuroendocrine tumors. These tumors are characterized by small cells containing regular, well-rounded nuclei and have five generally accepted growth patterns: insular, trabecular, glandular, undifferentiated, and mixed.13 Tumors with increased nuclear atypia, higher mitotic activity, or areas of necrosis have in the past been broadly termed “atypical” or “anaplastic” carcinoids. These tumors have more recently been classified as either well-differentiated or poorly differentiated neuroendocrine carcinomas (Fig. 1).

INCIDENCE

The overall incidence of carcinoid tumors in the United States has been estimated to be 1 to 2 cases per 100,000 people.14,15 Because many carcinoid tumors are indolent, their true incidence may be higher. A Swedish study in which the frequency of carcinoid tumors was calculated on the basis of both surgical specimens and autopsies in a single geographic location reported the incidence to be 8.4 cases per 100,000 people.16

An analysis of 2837 cases in the United States, based on data from the End Results Group (1950–1969) and the Third National Cancer Survey (1969–1971), found that the appendix was the most common site of carcinoid tumors, followed by the rectum, ileum, lungs and bronchi, and stomach.14 A recent analysis of 5468 cases identified by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute between 1973 and 1991 found an increase in the proportion of pulmonary and gastric carcinoids and a decrease in the proportion of appendiceal carcinoids (Table 2).15 These changes in relative incidence may be due in part to variations in the detection and reporting of carcinoid tumors. Benign-appearing carcinoid tumors, for example, were not recorded in the SEER data base until 1986.
PULMONARY CARCINOID TUMORS

Pulmonary carcinoids make up approximately 2 percent of primary lung tumors.\textsuperscript{17,18} They are thought to arise from neuroendocrine Kulchitsky’s cells located in the bronchial mucosa.\textsuperscript{19,20} Pulmonary carcinoids can be classified along a spectrum of pulmonary neuroendocrine tumors, of which small-cell lung cancer is the most malignant.\textsuperscript{21}

Patients with typical pulmonary carcinoids (i.e., well-differentiated pulmonary neuroendocrine tumors) usually present in the fifth decade of life.\textsuperscript{18,22,23} The majority of the tumors are perihilar in location, and patients often present with recurrent pneumonia, cough, hemoptysis, or chest pain.\textsuperscript{23} These tumors may also have a variety of neuroendocrine manifestations. Ectopic secretion of corticotropin from pulmonary carcinoid tumors accounts for 1 percent of all cases of Cushing’s syndrome.\textsuperscript{3} Acromegaly due to ectopic secretion of growth hormone—releasing factor has also been reported.\textsuperscript{24} The carcinoid syndrome occurs in less than 5 percent of cases.\textsuperscript{23,25,27} Well-differentiated pulmonary neuroendocrine tumors are usually indolent, with metastases reported in less than 15 percent of cases.\textsuperscript{22,23,26,28} When they do occur, metastases usually develop in mediastinal lymph nodes, liver, bone, or skin. The presence of lymph-node metastases and the presence of symptoms at the time of diagnosis are adverse prognostic factors.\textsuperscript{27} Most studies have found five-year survival rates of more than 90 percent.\textsuperscript{17,18,22,23,25-29}

Approximately one third of pulmonary carcinoids have atypical histologic features and are more accurately classified as well-differentiated pulmonary neuroendocrine carcinomas.\textsuperscript{17,26} Atypical carcinoids occur in older patients, most commonly in the sixth decade of life.\textsuperscript{29,30} They tend to be larger than well-differentiated neuroendocrine tumors and occur more commonly in the peripheral lung fields.\textsuperscript{29,30} Atypical carcinoids have an aggressive clinical course, metastasizing to mediastinal lymph nodes in 30 to 50 percent of cases.\textsuperscript{25,29,30} The five-year survival rate is between 40 and 60 percent.\textsuperscript{17,25-27,30}

Conservative resection, consisting of wedge or segmental resection, is currently the preferred form of treatment for localized pulmonary carcinoid tumors.\textsuperscript{31} Such procedures have resulted in low rates of recurrence and excellent long-term survival.\textsuperscript{27,32,33} The adequacy of conservative resection in patients with atypical carcinoids has been questioned, and several authors have advocated more extensive surgical procedures for these patients.\textsuperscript{27,30} Endoscopic removal or laser photoablation may result in successful palliation of symptoms but is not recommended as definitive therapy.\textsuperscript{28}

GASTRIC CARCINOID TUMORS

Gastric carcinoid tumors make up less than 1 percent of gastric neoplasms.\textsuperscript{14,15} They can be separated into three distinct groups on the basis of both clinical and histologic characteristics: those associated

<table>
<thead>
<tr>
<th>SITE AND SUBTYPE</th>
<th>PRESUMED CELL OF ORIGIN</th>
<th>HISTOLOGIC FEATURES</th>
<th>CLINICAL CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs and bronchi</td>
<td>Well-differentiated neuroendocrine tumor (typical carcinoid)</td>
<td>Epithelial endocrine cell</td>
<td>Minor cellular atypia, rare mitoses</td>
</tr>
<tr>
<td></td>
<td>Well-differentiated neuroendocrine carcinoma (atypical carcinoid)</td>
<td>Epithelial endocrine cell</td>
<td>Cellular atypia, increased mitoses, areas of necrosis</td>
</tr>
<tr>
<td>Stomach*</td>
<td>CAG-A–associated carcinoid tumor</td>
<td>Enterochromaffin-like cell</td>
<td>Well differentiated, noninvasive</td>
</tr>
<tr>
<td>Sporadic carcinoid tumor</td>
<td>Enterochromaffin-like cell</td>
<td>Well differentiated, but often invasive</td>
<td>May be aggressive, with high incidence of metastases; associated with atypical carcinoid syndrome</td>
</tr>
<tr>
<td>Small bowel</td>
<td>Epithelial endocrine cell</td>
<td>Usually well differentiated; contains serotonin and substance P</td>
<td>Often multiple, usually in ileum; associated with carcinoid syndrome</td>
</tr>
<tr>
<td>Appendix</td>
<td>Subepithelial endocrine cell</td>
<td>Usually well differentiated; contains serotonin and substance P</td>
<td>Usually indolent</td>
</tr>
<tr>
<td>Colon</td>
<td>Epithelial endocrine cell</td>
<td>Usually well differentiated; contains serotonin and substance P</td>
<td>Usually right-sided; often presents at late stage; Carcinoid syndrome rare</td>
</tr>
<tr>
<td>Rectum</td>
<td>Epithelial endocrine cell</td>
<td>Usually well differentiated; contains glicentin and glucagon</td>
<td></td>
</tr>
</tbody>
</table>

* CAG-A denotes chronic atrophic gastritis type A, and MEN-1 multiple endocrine neoplasia type 1.
with chronic atrophic gastritis type A (CAG-A), those associated with the Zollinger–Ellison syndrome, and sporadic gastric carcinoid tumors.

Up to 75 percent of gastric carcinoid tumors are associated with CAG-A (Fig. 2). More than half of patients with CAG-A–associated carcinoids also have pernicious anemia. Patients with CAG-A–associated carcinoids typically present in the sixth or seventh decade of life. The tumors are more common in women than in men. They are usually identified endoscopically during diagnostic evaluation for anemia or abdominal pain. They often measure less than 1 cm in diameter and are almost always located in the body or fundus of the stomach.

CAG-A–associated carcinoids are multifocal in over 50 percent of cases. Their multifocal nature is explained by their presumed origin from enterochromaffin-like cells in the gastric fundus. Patients with CAG-A usually have hypochlorhydria and hypergastrinemia. Gastrin hypersecretion has been postulated to result in hyperplasia of enterochromaffin-like cells. Indeed, CAG-A–associated carcinoids are almost invariably surrounded by areas of enterochromaffin-like cell hyperplasia. These hyperplastic lesions may develop into carcinoid tumors. However, proton-pump inhibitors have not yet been associated with the formation of carcinoid tumors in humans.

CAG-A–associated carcinoids are usually indolent, metastasizing in less than 10 percent of cases.

Figure 1. Classification of Neuroendocrine Tumors.
Panel A shows well-differentiated ileal carcinoid tumor (hematoxylin and eosin, ×400). Panel B shows gastric carcinoid tumor with staining for chromogranin (chromogranin immunoperoxidase, ×100). Panel C shows well-differentiated pulmonary neuroendocrine carcinoma (atypical carcinoid) with nuclear atypia and mitosis (arrow) (hematoxylin and eosin, ×200). Panel D shows poorly differentiated pulmonary neuroendocrine carcinoma with numerous mitoses (arrows) (hematoxylin and eosin, ×200). Photographs courtesy of Jonathan N. Glickman, M.D., Ph.D., Department of Pathology, Brigham and Women’s Hospital, Boston.
es.\textsuperscript{34,37} Although local recurrences have been reported, most recent series have reported no deaths from the disease in treated patients.\textsuperscript{34,35,39} Lesions less than 1 cm in diameter have been successfully treated with endoscopic resection followed by close endoscopic surveillance.\textsuperscript{37,39,46-48} Patients with larger, multiple, or recurrent tumors have generally undergone more extensive surgical resection. Antrectomy may result in the normalization of serum gastrin levels and has been reported to result in tumor regression in selected cases.\textsuperscript{37,46,49,50} The long-term benefits of antrectomy, however, are uncertain.

Between 5 and 10 percent of gastric carcinoids are associated with the Zollinger–Ellison syndrome.\textsuperscript{34} Like carcinoids associated with CAG-A, carcinoids associated with the Zollinger–Ellison syndrome are thought to arise from enterochromaffin-like cells in patients with hypergastrinemia and are associated with hyperplasia of surrounding enterochromaffin-like cells.\textsuperscript{34} Carcinoids associated with the Zollinger–Ellison syndrome occur almost exclusively in patients with multiple endocrine neoplasia type 1, an autosomal dominant genetic disorder associated with the loss of \textit{MEN1}, a putative tumor-suppressor gene located on chromosome 11q13. The disease is characterized by tumors of the pituitary gland, pancreatic islet cells, and parathyroid glands.\textsuperscript{51,52} Allelic loss on chromosome 11q13 has been reported in carcinoid tumors associated with the Zollinger–Ellison syndrome, suggesting that loss of function of the \textit{MEN1} gene is required for progression to true neoplasia.\textsuperscript{53} The treatment and long-term prognosis of carcinoids associated with the Zollinger–Ellison syndrome are similar to those of CAG-A–associated carcinoids.\textsuperscript{34}

\begin{table}[h]
\centering
\caption{Anatomical Location of Carcinoid Tumors Reported in the United States between 1950 and 1991.\textsuperscript{*}}
\begin{tabular}{|c|c|c|c|}
\hline
\hline
Lungs, bronchi, and trachea & 10.2 & 14.1 & 32.7 \\
Stomach & 2.2 & 2.0 & 3.8 \\
Duodenum & 1.8 & 2.3 & 2.1 \\
Jejunum & 1.0 & 2.0 & 2.3 \\
Ileum & 10.8 & 13.8 & 17.6 \\
Appendix & 43.9 & 35.5 & 7.6 \\
Cecum & 2.7 & 3.0 & 5.0 \\
Colon & 4.7 & 3.9 & 6.3 \\
Rectum & 15.4 & 12.3 & 10.1 \\
Other & 7.3 & 11.1 & 12.5 \\
\hline
\end{tabular}
\end{table}

\footnotesize*Data are adapted from Modlin and Sandor.\textsuperscript{15} ERG denotes the End Results Group, TNCS the Third National Cancer Survey, and SEER the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.

Between 15 and 25 percent of gastric carcinoids are sporadic.\textsuperscript{34} In contrast to CAG-A–associated carcinoids, these lesions are more frequent in men than in women, are usually solitary, and arise in normal-appearing mucosa.\textsuperscript{34} They are usually more than 1 cm in diameter, and although they appear histologically to be enterochromaffin-like cell tumors, they may also contain other cell types.\textsuperscript{34,37} Sporadic carcinoid tumors have been associated with an atypical carcinoid syndrome that is manifested primarily by flushing and is thought to be mediated by histamine.\textsuperscript{37} The majority of sporadic carcinoid tumors are metastatic at the time of presentation, and the disease is often fatal.\textsuperscript{34} Because of the aggressive nature of these lesions, most are treated with radical gastrectomy.

**CARCINOID TUMORS OF THE SMALL INTESTINE**

Small-bowel carcinoid tumors make up approximately one third of small-bowel tumors in surgical
series.\textsuperscript{54} They are most frequently located in the distal ileum and are often multicentric, occasionally appearing as dozens of lesions lining the small bowel.\textsuperscript{59} Small-bowel carcinoids are thought to arise from serotonin-producing intraepithelial endocrine cells. Foci of hyperplastic intraepithelial endocrine cells have been reported in association with ileal carcinoid tumors; however, the cause of this hyperplasia remains unknown.\textsuperscript{56,57}

Patients with small-bowel carcinoids generally present in the sixth or seventh decade of life, most commonly with abdominal pain or small-bowel obstruction. Because standard imaging techniques, such as computed tomography (CT) and small-bowel barium contrast studies, rarely identify the primary tumor, the preoperative diagnosis of small-bowel carcinoid is difficult.\textsuperscript{58} Patients frequently have vague abdominal symptoms for several years before diagnosis.\textsuperscript{55,58}

The majority of patients with small-bowel carcinoids present with metastases to the lymph nodes or the liver, and 5 to 7 percent present with the carcinoid syndrome.\textsuperscript{55,59} Tumor size is an unreliable predictor of metastatic disease, and metastases have been reported even from tumors measuring less than 0.5 cm in diameter.\textsuperscript{58} Long-term survival correlates closely with the stage of the disease at presentation. The five-year survival rate is 65 percent among patients with localized or regional disease and 36 percent among those with distant metastases.\textsuperscript{15}

Small-bowel resection, together with resection of the associated mesentery, is the treatment of choice for small-bowel carcinoids.\textsuperscript{60} These tumors are frequently associated with “buckling” of the intestine as a result of extensive mesenteric fibrosis.\textsuperscript{52} Occasionally, mesenteric ischemia due to either fibrosis or an associated mesenteric angiopathy may occur.\textsuperscript{61} Resection is therefore undertaken for palliative purposes, even in patients with known metastatic disease.

**APPENDICEAL CARCINOID TUMORS**

Carcinoid tumors are the most common cancers of the appendix.\textsuperscript{62} In contrast to carcinoids of the small intestine, appendiceal carcinoids are thought to arise from subepithelial endocrine cells present in the lamina propria and submucosa of the appendix wall.\textsuperscript{63,64} They are most often diagnosed in the fourth or fifth decade of life.\textsuperscript{15} The relatively young age at which appendiceal carcinoids are detected may in part be due to the fact that appendectomies are performed most often in young adults, and the true median age for the development of these often asymptomatic tumors may therefore be greater. Some authors have postulated, however, that appendiceal carcinoids may regress with age.\textsuperscript{62,64} Such regression would parallel the behavior of appendiceal subepithelial endocrine cells, which are most numerous in young people.\textsuperscript{65}

Appendiceal carcinoids are more common in women than in men.\textsuperscript{15} Their greater frequency in women has been attributed to an increased rate of incidental appendectomy in women undergoing cholecystectomy or such operations as hysterectomy, oophorectomy, and cesarean section.\textsuperscript{62} Recently, however, incidental appendectomy has become less common, and most appendiceal carcinoids are found during surgery for acute appendicitis.\textsuperscript{66} In the SEER data base, the frequency of noncarcinoid appendiceal tumors among men and women is similar, further suggesting that the higher rate of appendiceal carcinoids in women may not be due solely to higher rates of appendectomy.\textsuperscript{15} In addition, the preponderance of girls among children with appendiceal carcinoids cannot be explained by differences in appendectomy rates.\textsuperscript{67,69}

Less than 10 percent of appendiceal carcinoids cause symptoms,\textsuperscript{70} because approximately 75 percent are located in the distal third of the appendix, where they are unlikely to cause obstruction. Most of the remainder are located in the middle third, and less than 10 percent at the base.\textsuperscript{62}

The size of the tumor is the best predictor of prognosis in patients with appendiceal carcinoid tumors. Over 95 percent of appendiceal carcinoids are less than 2 cm in diameter.\textsuperscript{62,71} Although metastases from tumors of this size have been reported, they are rare and are usually diagnosed at the time of presentation.\textsuperscript{71,76} In contrast, approximately one third of patients with tumors more than 2 cm in diameter have either nodal or distant metastases.\textsuperscript{70} As with small-bowel carcinoids, there can be distant metastases to the liver, and the carcinoid syndrome has been reported in patients with liver metastases.\textsuperscript{62} The five-year survival rate is 94 percent for patients with local disease, 85 percent for patients with regional metastases, and 34 percent for patients with distant metastases.\textsuperscript{15}

The optimal surgical approach to appendiceal carcinoid tumors has been inferred retrospectively from surgical series.\textsuperscript{70} Patients with tumors less than 2 cm in diameter are usually treated by simple appendectomy if there is no gross evidence of local spread. Although some authors consider the presence of mesoappendiceal invasion to be a poor prognostic factor and an indication for hemicolectomy, there have been no reported recurrences in these patients after simple appendectomy.\textsuperscript{75,77} Most tumors more than 2 cm in diameter are treated with right colectomy, since local recurrence following simple appendectomy, though uncommon, has been observed.\textsuperscript{70} Whether right colectomy decreases the probability of distant recurrence is unclear. In older patients with other illnesses, simple appendectomy may sometimes be appropriate, even for large tumors.

**CARCINOID TUMORS OF THE COLON**

Carcinoids make up less than 1 percent of colonic tumors.\textsuperscript{15} Like carcinoid tumors of the small intes-
tine, they are thought to arise from serotonin-producing epithelial endocrine cells. Patients with colonic carcinoids most commonly present in the seventh decade of life with symptoms of pain, anorexia, or weight loss. Less than 5 percent of patients present with the carcinoid syndrome. Approximately two thirds of these tumors are found in the right side of the colon, most of them in the cecum. Most patients do not become symptomatic until they have advanced disease. The average tumor diameter at presentation is 5 cm, and over two thirds of patients have either nodal or distant disease at the time of presentation. The five-year survival rates are 70 percent for patients with local disease, 44 percent for those with regional metastases, and 20 percent for those with distant metastases. In rare cases when patients present with early-stage disease, local excision has been reported to be effective. The majority of patients, however, are treated with radical colectomy.

RECTAL CARCINOID TUMORS

Rectal carcinoid tumors make up 1 to 2 percent of all rectal tumors and are more common in the sixth decade of life. In contrast to carcinoids of the small intestine and colon, rectal carcinoids usually contain glucagon and glicentin-related peptides, rather than serotonin. Approximately 50 percent of tumors are asymptomatic and are found on routine endoscopy. Patients who have symptoms usually present with rectal bleeding, pain, or constipation. The carcinoid syndrome is rare.

Rectal carcinoids most commonly metastasize to local lymph nodes and the liver; metastases to lung and bone are unusual. The size of the primary lesion correlates closely with the probability of metastases, which occur in less than 5 percent of patients with tumors measuring less than 1 cm in diameter but in the majority of cases in which lesions are more than 2 cm in diameter. The five-year survival rates are 81 percent for patients with local disease, 47 percent for patients with regional metastases, and 18 percent for patients with distant metastases.

Tumors less than 1 cm in diameter account for two thirds of rectal carcinoid tumors and are successfully treated with local excision. The management of tumors measuring 1 to 2 cm is controversial. Although most tumors of this size can be treated by local excision, several authors have suggested that muscular invasion, symptoms at diagnosis, and ulceration are poor prognostic factors that warrant more extensive surgical procedures. Tumors more than 2 cm in diameter have traditionally been treated by low anterior resection or abdominoperineal resection. The value of these procedures in the treatment of rectal carcinoids has recently been questioned, however, because they do not appear to extend survival beyond that observed with local excision in retrospective series. An individualized approach, taking into account the patient’s age and coexisting conditions, may therefore be appropriate in deciding on a surgical approach to large rectal carcinoids.

METASTATIC CARCINOID TUMORS

Patients in whom metastatic disease is suspected should be evaluated with abdominal CT to rule out liver metastases. Liver-function tests are an unreliable indicator of tumor involvement of the liver, and the serum alkaline phosphatase level is frequently normal despite extensive involvement of the liver by carcinoid tumor. Carcinoid liver metastases are often hypervascular and may appear isodense relative to the liver after the administration of intravenous contrast material. CT should therefore be performed both before and after the administration of intravenous contrast agents.

Measurement of the serotonin metabolite 5-HIAA in a 24-hour urine collection may be useful in confirming the diagnosis and in the subsequent monitoring of patients with metastatic carcinoid tumors. In one study involving primarily patients with metastatic disease, elevated urinary 5-HIAA excretion predicted the presence of carcinoid tumor with a sensitivity of 73 percent and a specificity of 100 percent. The measurement of serum chromogranin has also been reported to be useful in detecting carcinoid tumors.

The clinical course of patients with metastatic carcinoid tumors is highly variable, and some patients remain free of symptoms for years. In a retrospective analysis of 71 patients, most of whom had metastatic carcinoid tumors of the midgut, an elevated level of plasma chromogranin A was an independent predictor of an adverse prognosis. Although the primary tumor site, the level of urinary 5-HIAA, and specific histologic growth patterns have all been suggested as potential prognostic factors, they have not reliably predicted survival in large studies. Positive antibody staining of tumor cells for carcinobrmic antigen is a poor prognostic factor and arouses concern that the tumor in question may contain features of adenocarcinoma. Such mixed tumors have been classified as adenocarcinoids and are usually treated as adenocarcinomas rather than as carcinoid tumors.

TREATMENT WITH SOMATOSTATIN ANALOGUES

Somatostatin analogues have a central role in both the diagnosis and the treatment of metastatic carcinoid tumors. Somatostatin is a 14-amino-acid peptide that inhibits the secretion of a broad range of hormones, including growth hormone, insulin, glucagon, and gastrin. It acts by binding to somatostatin receptors, which are expressed on more than 80 percent of carcinoid tumors. Somatostatin receptors belong to the superfamily of G protein-
Coupled receptors; activation of these receptors results in inhibition of adenylyl cyclase, decreased conductance of voltage-sensitive calcium channels, activation of potassium channels, and stimulation of tyrosine phosphatase activity. To date, five subtypes of somatostatin receptors have been cloned and characterized. Octreotide, an eight-amino-acid, long-acting somatostatin analogue that has been widely used for both detection and treatment of carcinoid tumors, binds primarily to receptor subtypes 2, 3, and 5. Its clinical efficacy appears to be related primarily to its ability to bind to receptor subtype 2.

Scintigraphy with radiolabeled octreotide has been successfully used to localize previously undetected primary or metastatic lesions. In two large European studies, somatostatin scintigraphy detected carcinoid lesions with a sensitivity of 89 percent. Such information is particularly helpful in confirming the presence of limited disease before one undertakes a potentially curative resection. In patients with the carcinoid syndrome, the detection of metastatic lesions with somatostatin scintigraphy predicts a response to therapy with somatostatin analogues.

Somatostatin analogues are highly effective in relieving the symptoms of the carcinoid syndrome. In an initial study, subcutaneous administration of octreotide at a dosage of 150 µg three times a day improved symptoms in 88 percent of patients and decreased urinary 5-HIAA excretion in 72 percent of patients. Subsequent studies with octreotide and a related peptide, lanreotide, have confirmed their efficacy in treating the carcinoid syndrome. Radiographically demonstrated tumor regression, however, is rare.

CARCINOID HEART DISEASE

Carcinoid heart disease occurs in two thirds of patients with the carcinoid syndrome. Carcinoid heart lesions are characterized by plaque-like, fibrous endocardial thickening that classically involves the right side of the heart and often causes retraction and fixation of the leaflets of the tricuspid and pulmonary valves (Fig. 3). Tricuspid regurgitation is a nearly universal finding; tricuspid stenosis, pulmonary regurgitation, and pulmonary stenosis may also occur. Left-sided heart disease occurs in less than 10 percent of patients.

The preponderance of lesions in the right side of the heart suggests that carcinoid heart disease is related to factors secreted into the hepatic vein by liver metastases. Among patients with the carcinoid syndrome, patients with heart disease have higher levels of serotonin in serum and 5-HIAA in urine. Whether serotonin is directly responsible for the cardiac lesions, however, is unclear. Treatment resulting in decreased urinary 5-HIAA excretion does not result in regression of cardiac lesions. The anorectic drugs fenfluramine and dexfenfluramine appear to interfere with normal serotonin metabolism and have been associated with valvular lesions identical to those seen in carcinoid heart disease. Further elucidation of the mechanism underlying the heart disease associated with the administration of these agents may shed more light on the pathogenesis of carcinoid heart disease.

The effective use of somatostatin analogues to ameliorate the symptoms of the carcinoid syndrome has led to increased interest in the management of the associated valvular disease. Right-sided heart failure may lead to substantial morbidity and mortality. Valvular replacement in patients with symptomatic carcinoid heart disease has been associated with high perioperative morbidity and mortality, particularly in older patients. Surviving patients, however, appear to have substantial improvement of symptoms.

MANAGEMENT OF HEPATIC METASTASES

Surgical resection of liver metastases may be of benefit in patients with limited hepatic disease. Such surgery has resulted in long-term relief of symptoms and prolonged survival in selected patients. Hepatic-artery occlusion or embolization is an alternative for patients who are not candidates for hepatic resection. Hepatic-artery occlusion or embolization in the treatment of liver metastases is based on the principle that tumors receive most of their blood from the hepatic artery, whereas hepatocytes are able to receive blood from the portal venous circulation. A commonly used technique is the infusion of gel foam powder into the hepatic artery through an angiography catheter. Drugs such as doxorubicin may be given in the same way. This approach has resulted in effective palliation of symptoms in selected patients, although it can be associated with substantial
side effects, including fever, nausea, pain, and occasionally, the hepatorenal syndrome.118-123

Unfortunately, the duration of the response after hepatic-artery occlusion or embolization is often short. In one uncontrolled study of 65 patients with metastatic carcinoid tumors, 23 patients treated with hepatic-artery occlusion alone achieved a response rate, measured by either tumor regression or a decrease in urinary 5-HIAA, of 65 percent lasting a median of less than seven months. Forty-two patients treated with hepatic-artery occlusion followed by systemic chemotherapy had a response rate of 81 percent for a median duration of 20 months.124 Whether such a combined approach results in a survival benefit is unclear.

The role of liver transplantation in the treatment of metastatic carcinoid tumors is still unclear, and the number of patients in whom liver transplantation has been attempted is small. In early series there were high rates of both perioperative mortality and tumor recurrence.125 The results of a recent series, however, are more encouraging.126 A multicenter French study recently reported a five-year survival rate of 69 percent among highly selected patients who underwent liver transplantation for metastatic carcinoid tumors.127

**MEDICAL MANAGEMENT OF METASTATIC DISEASE**

The ability of leukocyte interferon to stimulate T-lymphocyte function and to control the secretion of tumor products led to its initial use in patients with the carcinoid syndrome.128 A trial using interferon alfa in 111 patients with the carcinoid syndrome found decreases in urinary 5-HIAA in 42 percent of patients and tumor regression in 15 percent.129 The addition of interferon alfa to therapy with somatostatin analogues has also been effective in controlling the symptoms of patients whose disease is resistant to therapy with somatostatin analogues alone.130 However, the low rate of tumor regression and the high incidence of side effects, which may include fever, fatigue, anorexia, and weight loss, have limited the routine use of interferon in the treatment of metastatic carcinoid tumors.

Cytotoxic chemotherapy has had only limited success in the treatment of metastatic carcinoid tumors. In a trial by the Eastern Cooperative Oncology Group, 118 patients with metastatic carcinoid tumors were randomly assigned to receive either streptozocin and cyclophosphamide or streptozocin and fluorouracil.131 The response rates, measured by either tumor regression or a decrease in urinary 5-HIAA, were 33 percent for streptozocin plus fluorouracil and 26 percent for streptozocin plus cyclophosphamide. There was no difference in survival between the two treatment groups, and both regimens were associated with substantial toxicity. A subsequent Eastern Cooperative Oncology Group trial increased the interval between cycles of streptozocin plus fluorouracil from 6 to 10 weeks and compared this regimen with doxorubicin alone.91 Although the longer interval between cycles resulted in less toxicity, the response rates for streptozocin plus fluorouracil decreased to 22 percent, as compared with only 21 percent for doxorubicin alone. A combination of fluorouracil, doxorubicin, cyclophosphamide, and streptozocin was evaluated by the Southwest Oncology Group in 56 patients.92 This regimen produced a response rate of 31 percent and was therefore not thought to be superior to the previously tested regimen of streptozocin plus fluorouracil.

Systemic chemotherapy may be of more benefit in patients with aggressive variants of carcinoid tumor. A combination of cisplatin and etoposide, a regimen commonly used in the treatment of small-cell lung cancer, produced a 67 percent response rate in patients with neuroendocrine carcinomas.132 In contrast, patients with typical carcinoid tumors did not respond to this form of therapy.

The use of radiation therapy in the treatment of carcinoid tumors has not been extensively studied. External-beam radiation can result in effective palliation of bone or central nervous system metastases.133 Recently, the therapeutic use of radiolabeled somatostatin analogues has been reported to result in tumor shrinkage and clinical improvement in a small number of patients with metastatic carcinoid tumors.134,135 Further trials are necessary to establish the long-term benefits of this therapy.

**REFERENCES**


Supported by a grant from the National Institutes of Health (ST32CA09172) and by the Irving Janock Fund.


