56
Carcinoid Disease

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Introduction

Originally termed "Karzinoide" in reference to their indolent nature, carcinoid tumors are relatively slow-growing neuroendocrine neoplasms that secrete a diverse array of biologically active factors. The incidence in the United States is about 7–15 million a year and the overall 5-year survival is ~50 %.

Carcinoid tumors most commonly arise from enterochromaffin cells (Kulchitsky cells) in the gastrointestinal (GI) tract (75–87 %), specifically in the midgut (64 %), within 2–3 ft from the ileocecal valve. They can also be found in the respiratory tract (up to 28 %). Uncommon sites include the skin, retroperitoneum, ovary, prostate, or kidney (1–5 %). The bioactive factors they secrete vary with tumor location (Fig. 56.1). Foregut and respiratory tumors typically secrete serotonin and its precursor 5-hydroxytryptophan (5-HTP). Bronchial carcinoid tumors may also secrete ACTH or neuropeptides, while foregut GI tumors may secrete GI peptides and histamine. Midgut (jejunum to transverse colon) tumors produce serotonins and GI peptides but are less likely to produce 5-HTP. Hindgut tumors (left colon and rectum) may produce GI peptides but do not significantly produce any serotonin or 5-HTP.

Unfortunately, most carcinoid tumors are metastatic at presentation. Gastrointestinal carcinoids commonly present with bowel obstruction or vague abdominal pain that may be due to mucosal ulceration, intestinal obstruction, intussusception, adhesions, or hypermotility. Some intra-abdominal or retroperitoneal tumors may elicit a fibrotic desmoplastic reaction and may even cause a mass effect that impedes vascular flow resulting in mesenteric ischemia or venous congestion.

Pulmonary Carcinoids

Pulmonary carcinoid tumors comprise only 1–2 % of all lung tumors. Typical carcinoid pulmonary tumors have a low-grade malignant potential, whereas atypical carcinoids may act in a more aggressive fashion. These tumors tend to be centrally located in the main bronchi and may present with atelectasis, bronchial obstruction, hemoptysis, pneumonia, or pleural effusions. Many are asymptomatic and are discovered incidentally on a chest X-ray or computed tomography (CT) scan. Biopsy is required for diagnosis. Positron emission tomography (PET) scans and bronchoscopy are also utilized in the diagnosis.

Surgical resection with associated lymph node dissection remains the mainstay of treatment. Chemotherapy is of limited benefit but is still being studied in the form of molecular targeted therapy (i.e., angiogenesis inhibitors, tyrosine kinase inhibitors, and mTOR inhibitors). For patients with typical carcinoids that have undergone resection, the overall 5- and 10-year survival is 87–100 % and 87–93 %, respectively. Ten-year survival for atypical carcinoids is considerably lower at 30–50 %.

Gastric Carcinoids

Gastric carcinoids are amongst the rarest gastric malignancies (less than 0.5 %) but may comprise up to 10–30 % of all gastrointestinal carcinoids. They are broken into three types. **Type 1** gastric carcinoids are associated with chronic atrophic gastritis. **Type 2** gastric carcinoids are associated with Zollinger-Ellison syndrome/MEN type 1 syndrome. **Type 3** tumors are not associated with hypergastrinemia and have a higher malignant potential. Gastric carcinoids may present with abdominal pain, hematemesis, diarrhea, or gastric outlet obstruction but may also be incidentally discovered during endoscopy.

Treatment of gastric carcinoids is dictated by the size of the tumor. Smaller tumors (less than 1.5 cm) without evidence of local invasion are usually amenable to endoscopic excision with follow-up endoscopic surveillance. Intermediate lesions (1–2 cm) should be surgically excised while larger lesions (greater than 2 cm), which are usually type 3 lesions, warrant aggressive local resection, antrectomy, and local lymph node

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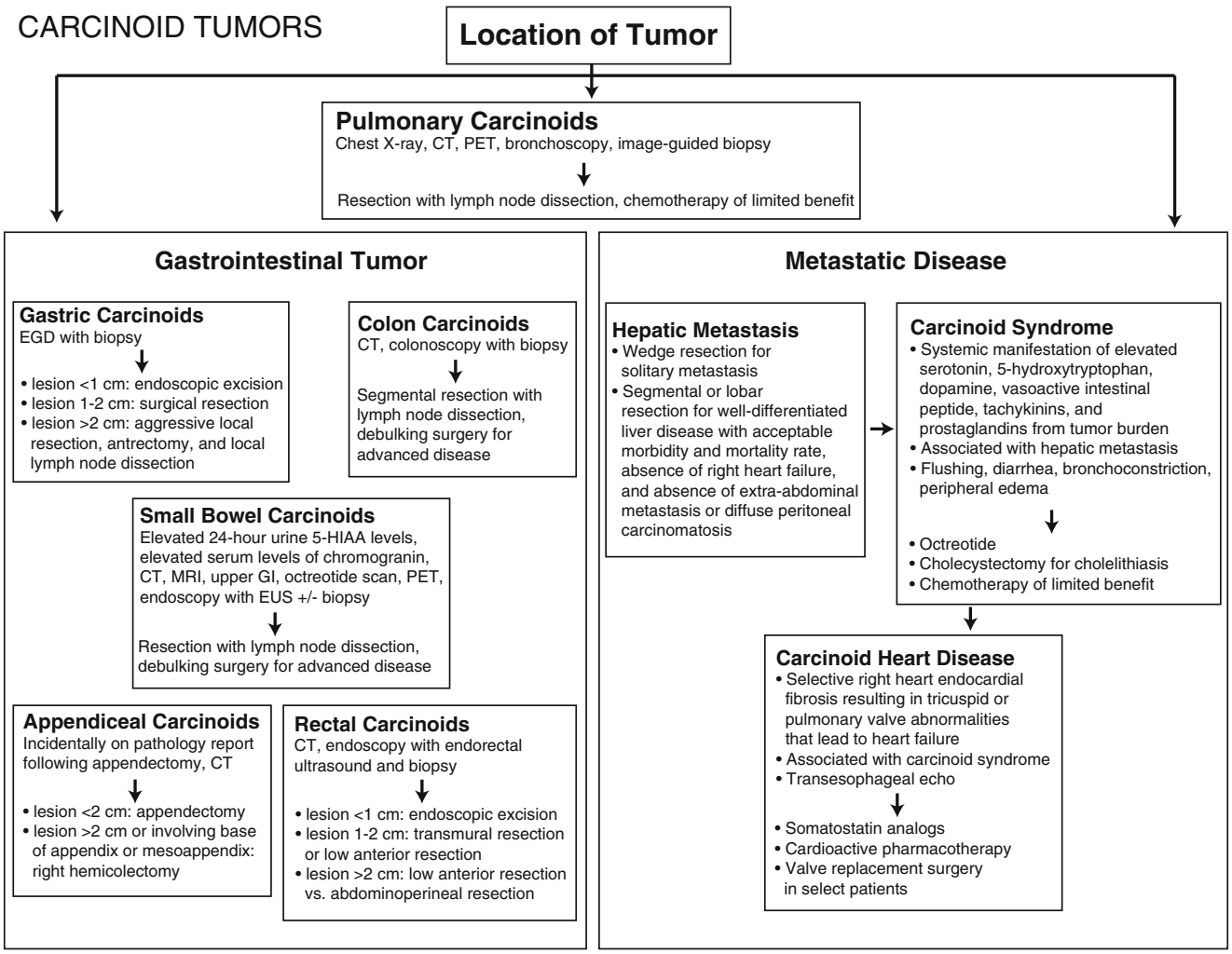

FIG. 56.1 Algorithm for diagnosis and treatment of carcinoid tumors. *CT* computed tomography, *PET* positron emission tomography, *MRI* magnetic resonance imaging, *GI* gastrointestinal, *EUS* endoscopic ultrasound

dissection. Occasionally, gastric carcinoids are associated with carcinoid syndrome, which can be treated with histamine antagonists. Proton pump inhibitors or H2 blockers are also utilized if the tumor is associated with hypergastrinemia.

Small Bowel Carcinoids

About 64 % of carcinoid tumors arise from the small bowel. These tumors comprise 30–35 % of all malignant small bowel tumors, and their incidence increased fourfold from 1985 to 2005. They are most commonly located in the ileum (45 %), followed by the duodenum (18 %) and jejunum (6 %).

Because of their indolent nature and submucosal location, these tumors are typically small and found incidentally. Larger tumors may present with bleeding or obstruction and are typically metastatic at presentation. In up to 40 % of cases, there are multiple primary tumors, and in 20 % of cases, the tumors are associated with noncarcinoid synchronous or metachronous tumors – most commonly adenocarcinomas of the colon. Rarely, they can also be associated with multiple endocrine neoplasia type 1.

Diagnosis of midgut carcinoid is suggested by elevated 24-h urine 5-HIAA levels. Elevated 5-HIAA (a serotonin metabolite) has a 73 % sensitivity for localized disease and 100 % specificity in predicting the presence of midgut carcinoid. Carcinoids also have elevated serum levels of chromogranin A (a glycoprotein secreted by tumor cells), though elevated levels can also be seen with proton pump inhibitors, atrophic gastritis, renal impairment, or inflammatory bowel disease. Thus its lack of specificity precludes its use as a diagnostic tool.

Contrast studies such as an upper GI, CT scan, or magnetic resonance imaging (MRI) may identify larger lesions or the presence of metastatic disease. Functional imaging studies, such as an octreotide scan or a PET scan, can also

aid in localizing these tumors. An octreotide scan has greater than 90 % sensitivity for detecting metastases. Endoscopy with ultrasound (EUS) may be utilized to identify duodenal lesions. In cases where the above studies have not successfully localized a suspected tumor, capsule endoscopy, double-balloon enteroscopy, and ileocolonoscopy can also be utilized.

Treatment of primary small bowel carcinoid tumors without evidence of metastases is resection with regional mesenteric lymphadenectomy. At the time of surgery, there should be a careful examination for additional lesions. Smaller duodenal lesions (less than 1 cm) without evidence of local invasion may be amenable to endoscopic resection. Debulking is indicated for locally invasive disease, even in the presence of hepatic metastasis, as it decreases incidence of obstructive and ischemic complications. For functional tumors, preoperative prophylaxis with octreotide is prudent. Intraoperatively, a carcinoid crisis can be treated with an intravenous (IV) bolus of octreotide followed by an octreotide infusion. Antihistamines, hydrocortisone, and albuterol are also used as warranted.

Postoperatively, patients should be followed every 3 months to evaluate for symptoms of recurrence and to obtain urinary 5-HIAA measurements and surveillance CT scans. The 5-year survival for limited and metastatic small bowel carcinoid disease is 65 % and 35 %, respectively.

Appendiceal Carcinoids

Though rare, appendiceal carcinoids are the most common tumors of the appendix and generally have a more favorable prognosis than other carcinoid tumors. They are most commonly discovered incidentally on pathology following an appendectomy. Ten to fifteen percent of appendiceal carcinoids are associated with a synchronous adenocarcinoma at another site. Therefore, postoperative imaging and endoscopic evaluation for additional lesions is warranted.

Appendiceal carcinoids are most commonly located at the tip (70 %) and at the time of discovery are typically less than 1 cm without evidence of metastases. Appendectomy alone is adequate for tumors that are less than 2 cm, located at the tip, and lack evidence of local invasion or lymph node metastasis. A right hemicolectomy is indicated for tumors that are greater than 2 cm in size, involve the base, or have evidence of local mesenteric or lymphatic invasion. The 5-year survival for limited local or regional disease is 85–95 % versus 34 % for tumors with distant metastases.

Colon Carcinoids

Colon carcinoids are rare, comprising only 8 % of all carcinoid tumors. They are most commonly located in the cecum and right colon and are also commonly associated with synchronous neoplasms (25–40 % of cases). Compared to small bowel tumors that may present with obstruction or bleeding, these tumors present with vague abdominal pain and anorexia or as an incidental finding on routine colonoscopy. Unfortunately, more than 60 % of tumors are metastatic by the time they present.

Regardless of the size of the lesion, segmental colon resection with regional lymphadenectomy and en bloc resection of additional involved tissues is the standard treatment for carcinoids of the colon. Debulking is indicated for unresectable tumors, as it significantly reduces symptoms and complications of advanced disease. The 5-year survival for localized and metastatic colonic carcinoids is 42 % and 71 %, respectively.

Rectal Carcinoids

Rectal carcinoids are more common than colon carcinoids. Fortunately they usually present early, have a lower malignant potential, and are rarely associated with carcinoid syndrome. They may present on digital rectal exam as firm, discrete, mobile submucosal lesions. Endoscopic biopsy usually establishes the diagnosis. Colonoscopy, endorectal ultrasound, and CT scans are utilized to evaluate extent of disease.

Similar to gastric carcinoids, treatment of rectal carcinoids is dictated by size. Smaller lesions that are less than 1 cm can be treated with endoscopic excision followed by endoscopic surveillance. Intermediate-size tumors that are 1–2 cm can be treated with transmural resection with adequate margins. Intraoperative pathology may be required to ensure disease-free margins. Larger lesions that are greater than 2 cm are usually associated with metastases and warrant aggressive surgical resection with a low anterior resection or abdominoperineal resection.

Metastatic Disease

Hepatic Involvement

More than 60 % of carcinoid tumors are metastatic at the time of diagnosis, and in most cases the liver is the involved organ. Wedge resection is indicated for solitary hepatic metastasis. Contraindications for liver resection include the presence of extra-abdominal metastases, diffuse peritoneal carcinomatosis, and significant comorbid illnesses. Those that undergo a curative resection have a 60–80 % 5-year survival rate. If surgical resection is not an option, other interventions such as ablative procedures, embolization, and liver transplantation may be considered. Functional liver metastases may also be palliated with debulking surgery.

Carcinoid Syndrome

Carcinoid syndrome is used to describe the clinical picture caused by the systemic release of a variety of humoral factors, including serotonin, 5-hydroxytryptophan, dopamine, vasoactive intestinal peptide, tachykinins, and prostaglandins. The syndrome occurs typically with GI carcinoid tumors that have metastasized to the liver or with tumors whose bioactive products do **not** undergo metabolism by the liver via the porta hepatis (e.g., retroperitoneal, ovarian, or pulmonary carcinoids). The syndrome can be seen in about 20 % of patients with midgut carcinoid tumors. It can be diagnosed by elevated levels of 5-hydroxyindoleacetic acid (5-HIAA) in the urine (>10 mg/24 h).

Classic symptoms of the syndrome include flushing (94 %), diarrhea (78 %), bronchoconstriction (19 %), and peripheral edema (19 %). Flushing is usually seen in the face, neck, and upper chest and can be transient or of longer duration. The diarrhea is usually episodic, explosive, and watery.

The symptoms of carcinoid syndrome, particularly the diarrhea and flushing, can be temporized with medical therapy, namely, long-acting somatostatin analogs such as octreotide and lanreotide. Long-term treatment with somatostatin analogs is associated with gallstone formation; accordingly, a cholecystectomy should be considered at the time of primary tumor resection. Chemotherapy has proven to be of limited benefit, though certain agents such as 5-fluorouracil, streptozocin, and interferon-alpha have been shown to decrease tumor burden.

Carcinoid Heart Disease

Cardiac involvement can be seen in up to 60 % of patients with carcinoid syndrome and is associated with an unfavorable clinical outcome. Specifically the syndrome is associated with selective right heart endocardial fibrosis that is initiated by the release of systemic serotonin, resulting in tricuspid or pulmonary valve abnormalities that lead to heart failure. The left heart is involved in 10 % of cases. Treatment includes medical management with somatostatin analogs and cardioactive pharmacotherapy. More recently, valve replacement surgery has increasingly been shown to improve clinical outcome and lengthen survival. Cytoreductive surgery and hepatic metastatic ablative therapies in the presence of carcinoid heart disease may also improve overall clinical outcome. Cardiac abnormalities should be screened for with an echocardiogram when carcinoid disease is diagnosed.