From: "[redacted]"
To: "jeevacation@gmail.com" <jeevacation@gmail.com>
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Treatment of carcinoid tumors and the carcinoid syndrome
Authors
Shanthi V Sitaraman, MD, PhD, FRCP
Stephen E Goldfinger, MD
Section Editors
Kenneth K Tanabe, MD
David C Whitcomb, MD, PhD
Deputy Editor
Carla H Ginsburg, MD, MPH, AGAF
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INTRODUCTION — Carcinoid syndrome is the term applied to a constellation of symptoms mediated by various humoral factors elaborated by some carcinoid tumors (table 1) [1]. Two of the most common manifestations are flushing and diarrhea (table 2). (See "Clinical features of the carcinoid syndrome".)
Management of patients with these tumors should include:

- Localization of the tumor and possible metastases by CT scan and somatostatin receptor scintigraphy [2,3]. (See "Diagnosis of the carcinoid syndrome and tumor localization".)

- Removal of the tumor if metastases have not occurred.
- Control of carcinoid symptoms if present.

More than 90 percent of patients with the carcinoid syndrome have metastatic disease, typically to the liver. Exceptions are bronchial and ovarian tumors that can produce symptoms without metastasis (table 3). (See "Bronchial carcinoid tumors".)
LOCALIZED CARCINOID TUMORS — The treatment of choice for a patient who has a localized carcinoid tumor is surgery. The extent of the surgical resection depends on the site of origin and size of the primary tumor. (See "Clinical characteristics of primary carcinoid tumors", for a detailed discussion on carcinoid tumors arising in specific organs).
Appendix — The prognosis of appendiceal carcinoids is best predicted by the size of the tumor. Tumors less than 2 cm in size (found in approximately 95 percent of patients) are unlikely to have metastasized when diagnosed (table 4). In contrast, up to 30 percent of larger tumors have already metastasized at diagnosis, mostly to regional nodes. (See "Clinical characteristics of primary carcinoid tumors".)
A TNM staging system is available for appendiceal carcinoids (table 5) that is distinct from the TNM staging system for carcinoids arising at other sites within the gastrointestinal tract, and primary lung carcinoids [4].
Because of the association of tumor size with prognosis, tumors less than 2 cm can usually be treated by simple appendectomy. In contrast, it is appropriate to perform right hemicolectomy to patients with larger appendiceal carcinoids or mesoappendiceal invasion because of the high local recurrence rate after appendectomy alone. Staging, treatment, and prognosis of appendiceal carcinoid tumors is addressed in detail elsewhere. (See "Cancer of the appendix and pseudomyxoma peritonei", section on 'Carcinoid tumors'.)
Small intestine — Small intestinal carcinoids have the potential to metastasize, irrespective of size (table 4).
Patients with small bowel carcinoid tumors should be treated with resection of the involved segment and small bowel mesentery. Resection may be required for palliation even in those with known metastatic disease. However, these are generally indolent tumors. The prognosis depends upon the stage of disease (table 6) [5]. However, even in patients with distant metastasis, five year survival is approximately 40 percent [5]. This subject is discussed in detail elsewhere. (See "Treatment of small bowel neoplasms", section on 'Carcinoid tumors'.)
The surgeon should also perform a complete inspection of the bowel since such patients may be at increased risk for synchronous neoplasms (see 'Synchronous or metachronous neoplasia' below).
Rectum — Prognosis is mainly dependent on tumor size. The TNM staging system that includes carcinoid tumors of the rectum is outlined in the table (table 7) [5].
Optimal treatment of rectal carcinoid tumors depends upon the size. Rectal carcinoids that are smaller than 1 cm can be treated by local excision [6]. Treatment of tumors that are larger than 1 cm but smaller than 2 cm has been controversial. Although local excision may suffice, some authorities recommend more extensive resection in patients who have muscular invasion or symptoms, which may be associated with a worse prognosis [7].
Tumors larger than 2 cm have usually been treated by low anterior or abdominoperineal resection, similar to treatment for rectal adenocarcinomas [8]. However, this aggressive approach has been questioned since improved survival has not been consistently demonstrated compared to local excision [9,10].
Thus, the treatment of carcinoid tumors larger than 1 cm should be considered on an individual basis, including comorbid illnesses and the patient's age in the decision.

In a SEER database series, the five-year survival rates for localized, regional, or distant disease involving the rectum or rectosigmoid junction over the last decade were 90, 49, and 26 percent, respectively [8].

Stomach — Management depends on the type of gastric carcinoid (type 1, 2, or 3). (See "Clinical characteristics of primary carcinoid tumors", for definition and characteristics of the different types of gastric carcinoids).

Sporadic (type 3) gastric carcinoids are treated by partial or total gastrectomy with local lymph node resection [11].

For type 1 and 2 gastric carcinoids smaller than 1 cm, endoscopic resection is the treatment of choice [12,13]. Close endoscopic follow-up every 6 to 12 months is needed since these patients continue to exhibit mucosal changes and ECL hyperplasia due to sustained hypergastrinemia. However, progression to a malignant phenotype or disease-related death is rare [14].

Antrectomy is recommended if there are more than five tumors or any that are larger than 1 cm in diameter [13]. More aggressive surgical therapy is rarely needed, unless there is extensive tumor involvement of the gastric wall (which increases the risk for adenocarcinoma [15]) or for emergent bleeding [16].

Antrectomy reduces hypergastrinemia by reducing the gastrin-producing cell mass in the stomach; in most cases, this leads to regression of tumors [13,17-19]. The success of this approach was shown in a series of 51 patients with type I carcinoids, 10 of whom underwent antrectomy (eight in conjunction with endoscopic removal of the largest tumor). Seven of the eight with residual disease became endoscopically tumor-free, and one progressed and died of metastatic disease. In all, 9 of the 10 patients treated with antrectomy remained tumor-free for an average of 65 months.

The role of medical rather than surgical therapy (anti-gastrin maneuvers such as acidification by diet or dilute oral hydrochloric acid, or somatostatin analog therapy) for type 1 tumors is debated [11,20-22]. Gastrin levels may or may not decrease, and continued endoscopic surveillance is necessary. Such therapy is best restricted to patients who are not suitable for surgical treatment.

The TNM staging system that includes carcinoid tumors of the stomach is outlined in the table (table 8) [5].

Colon — Patients with colonic carcinoids should be treated with radical colectomy, although local resection has been reported to be effective for early stage disease. Small localized tumors are most likely to be cured by resection. [8,23].

The TNM staging system that includes carcinoid tumors of the colon is outlined in the table (table 7) [5].

Bronchial — The preferred treatment for bronchial carcinoids is surgical resection. The clinical features, diagnosis, and treatment of bronchial carcinoid tumors are discussed separately. (See "Bronchial carcinoid tumors".)

POSTTREATMENT FOLLOW-UP — There is limited evidence from which to make recommendations for follow-up after resection of a carcinoid tumor. Guidelines from the National Comprehensive Cancer Network based upon expert consensus include the following recommendations for follow-up after treatment of an islet cell tumor [24]:

- Three months postresection — History and physical examination, tumor markers, and CT/MRI.
- Long-term — History and physical examination with tumor markers every six months for years 1 to 3, and annually thereafter; imaging studies only as clinically indicated.

TREATMENT OF THE CARCINOID SYNDROME — As noted previously, 90 percent of patients with the carcinoid syndrome have metastatic disease, typically to the liver. Exceptions are bronchial and ovarian tumors that can produce symptoms without metastasis. Patients with the carcinoid syndrome may benefit from therapies for the different components of the syndrome.

Control of symptoms — Patients should be advised to avoid factors that induce flushing episodes, such as alcohol ingestion or specific forms of physical activity that involve pressure or trauma to the right upper quadrant.

A number of drugs are effective for patients with flushing or diarrhea (table 9). Mild diarrhea may respond to codeine phosphate, and cholestyramine may ameliorate the diarrhea if the patient has had a distal ileal resection to remove the primary tumor. More severe symptoms usually require treatment with a somatostatin analog. (See 'Octreotide and lanreotide' below.)

Asthma can be treated with theophylline or the beta-2 adrenergic agonist albuterol (which does not precipitate flushing attacks).

Octreotide and lanreotide — For patients with severe flushing and/or diarrhea, the mainstay of treatment is the somatostatin analog octreotide. Flushing and diarrhea are initially relieved in 75 to 80 percent of patients treated with octreotide (initial dose 50 microg three times daily subcutaneously). The dose is generally titrated to symptom control; higher doses (up to 500 microgram three times daily) are often required over time. Besides improving symptoms associated with hormonal hypersecretion, octreotide may also slow tumor growth. However, radiographic regression of disease during treatment with somatostatin analogs is rare. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'Octreotide and lanreotide'.)

A depot form of octreotide (Sandostatin LAR®), which can be administered on a monthly basis, has largely eliminated the need for patients to inject themselves with octreotide daily.

Octreotide is usually well tolerated, but about one-third of patients have nausea, abdominal discomfort, bloating, and/or loose stools during the first several weeks of therapy, after which the symptoms subside. Although symptoms are usually mild, some patients do not tolerate them. More importantly, octreotide reduces postprandial gallbladder contractility and delays gallbladder emptying, and up to 25 percent of patients develop asymptomatic cholesterol gallstones or sludge during the first 18 months of therapy. Prophylactic treatment with ursodeoxycholic acid may be beneficial [25]. (See "Nonsurgical treatment of gallstone disease".)

Management of refractory symptoms — For patients who do not respond to or cannot tolerate octreotide or lanreotide, therapy varies with the primary symptom and site of the tumor. Patients with diarrhea can be treated with cyproheptadine, a serotonin

antagonist, while gastric carcinoids that elaborate histamine can often respond to a histamine blocker. Cyproheptadine also may be of benefit in patients with malignant carcinoid syndrome who develop anorexia or cachexia [26].
Interferon-alfa (IFNa) has been reported to result in biochemical responses in 40 to 50 percent of gastrointestinal neuroendocrine tumors, including carcinoids. The addition of IFNa to octreotide has also been effective in controlling symptoms in patients who are resistant or refractory to octreotide alone. However, it is not clear that combined therapy is superior to either agent alone for initial therapy in terms of symptom control, objective antitumor response, or survival. Furthermore, the widespread use of IFNa in these patients has been limited by side effects, which may include flu-like symptoms, fatigue, and depression. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'IFNa with and without octreotide'.)
Surgery — In general, surgery has a limited role in the treatment of patients with the carcinoid syndrome because almost all have extensive metastatic disease. Nevertheless, potentially curative surgery can be offered to the rare patient with resectable nodal, hepatic, or isolated brain metastasis. (See 'Hepatic resection' below and "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'Surgical options for metastatic disease'.)
Surgery is also an appropriate option for patients with extraintestinal primary tumors such as bronchial and ovarian carcinoids that rarely cause the carcinoid syndrome without hepatic metastasis. (See "Clinical characteristics of primary carcinoid tumors", section on 'Ovary' and "Bronchial carcinoid tumors".)
Resection is also recommended for small intestinal carcinoids, even in the presence of metastases, to prevent the development of fibrosing mesenteritis. (See "Diagnosis and staging of small bowel neoplasms", section on 'Diagnostic testing for carcinoid'.)
Valve surgery can be performed in those with symptomatic carcinoid heart disease [27]. (See "Carcinoid heart disease".)
Surgical procedures in patients with carcinoid syndrome are potentially hazardous due to the precipitation of carcinoid crisis during induction of anesthesia or surgical manipulation of tumors. This complication can be prevented by pretreatment with octreotide, which should be used prophylactically. (See 'Carcinoid crisis' below.)
Hepatic resection — The liver is the predominant site of metastatic disease. Hepatic resection is indicated for the treatment of metastatic liver disease in the absence of diffuse bilobar involvement, compromised liver function, or extensive extrahepatic metastases (eg, pulmonary, peritoneal). Although the majority of cases will not be cured by surgery, symptoms of hormone hypersecretion are effectively palliated, and prolonged survival is often possible, given the slow-growing nature of these tumors.
As a general rule, resection should be undertaken only in patients with a limited number of hepatic metastases and is most successful when undertaken with curative intent. Concomitant resection of the primary is indicated if the primary site is causing symptoms, or if both the primary site and liver metastases are amenable to potentially curative resection. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Hepatic resection.)
Other liver-directed therapies for hepatic predominant disease

- Embolization and chemoembolization — Liver metastases derive most of their blood supply from the hepatic artery, whereas healthy hepatocytes derive most of their blood supply from the portal vein. This provides the rationale for therapeutic embolization of the hepatic artery, with the goal of inducing necrosis of the metastases with minimal damage to normal liver parenchyma.

Hepatic arterial embolization with or without selective hepatic artery infusion of chemotherapy is frequently applied as a palliative technique in patients with symptomatic hepatic metastases who are not candidates for surgical resection. In uncontrolled trials, up to 75 percent of patients with carcinoid hepatic metastases have marked symptomatic improvement in flushing and diarrhea. The duration of response ranges from 4 to 24 months; eventually, all patients progress. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'Hepatic artery embolization'.)
Early studies noted a significant incidence of severe postembolization complications, including renal failure, hepatic necrosis, and sepsis. More recently, improvements in technique have reduced the incidence of such complications, making embolization an important and generally safe treatment option for patients with metastatic neuroendocrine tumors. Nevertheless, careful patient selection is mandatory because of treatment and disease-related adverse effects, which can range from transient symptoms (pain, nausea, fever, fatigue) and biochemical abnormalities (elevated liver enzymes) to florid carcinoid crisis, which may be fatal. Prophylactic octreotide is indicated prior to embolization. (See 'Carcinoid crisis' below.)

- Radioembolization — Experience with radioembolization using 90 Y-labeled resin microspheres is limited but growing. In the largest series of 148 patients with unresectable liver metastases, 64 percent had an objective response [28]. Fatigue (7 percent) was the most common side effect. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'Radioembolization'.)

In the absence of randomized trials, it is difficult to know when to choose this technique over any other nonsurgical liver-directed therapy. It cannot be recommended as a first-line approach, particularly in view of its extraordinary expense.

- RFA and cryoablation — Other approaches to the treatment of hepatic-predominant disease include radiofrequency ablation (RFA) and cryoablation, either alone or in conjunction with surgical debulking. These procedures, which can be performed using percutaneous or laparoscopic approaches, appear to be less morbid than either hepatic resection or hepatic artery embolization. However, both techniques are applicable only to smaller lesions, and their long-term efficacy is uncertain. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'RFA and cryoablation'.)

- Liver transplantation — The number of patients with liver-isolated metastatic disease in whom orthotopic liver transplantation (OLT) has been attempted is small, and follow-up data are insufficient to judge whether complete cure has truly been achieved. The limited availability of donor organs in many regions has restricted investigation of this procedure. Until more data become available, most clinicians consider that liver transplantation is an investigational approach for metastatic carcinoid. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'Liver transplantation'.)

Chemotherapy and novel treatment approaches — The best systemic therapy option for patients with progressive metastatic carcinoid tumors is not established. Although many cytotoxic drugs have been tried in various combinations, randomized trials have revealed only minor activity (even for streptozocin plus 5-FU). As a result, there is no standard regimen, and the role of chemotherapy continues to be debated. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'Combination chemotherapy for carcinoid tumors'.)

The questionable efficacy of conventional cytotoxic chemotherapy has prompted investigation of novel therapeutic approaches for patients with advanced carcinoid. These include the use of targeted radiotherapy, as well as regimens incorporating inhibitors of angiogenesis (eg, bevacizumab) and small molecule tyrosine kinase inhibitors (eg, sunitinib). These topics are discussed in detail elsewhere. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'Molecularly targeted therapy' and "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'Targeted radiotherapy'.)

CARCINOID CRISIS — Profound flushing, extreme changes in blood pressure, bronchoconstriction, arrhythmias, and confusion or stupor lasting many hours or even days can occur in patients with carcinoid tumors. This syndrome, called carcinoid crisis, can occur spontaneously, after palpation of tumor masses (at the bedside or during surgery), during induction of anesthesia, after administration of chemotherapy, or after hepatic arterial embolization, particularly in patients with extensive disease [29,30]. The crisis may be fatal. Octreotide should be given before general anesthesia and before hepatic artery embolization to prevent carcinoid crisis.

When it does occur, treatment for carcinoid crisis differs from other causes of acute hypotension, because calcium and catecholamines provoke release of mediators from the carcinoid tumor and may worsen the syndrome. The blood pressure should be supported by infusion of plasma and octreotide (300 micrograms intravenously; a continuous intravenous drip of octreotide at a rate of 50 to 150 micrograms/hour may also be used) [31]. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on 'Prevention and management of carcinoid crisis'.)

SYNCHRONOUS OR METACHRONOUS NEOPLASIA — Several series have described a higher than expected rate of synchronous or metachronous noncarcinoid cancers in patients diagnosed with carcinoid tumors [8,32-34]. Many of these tumors are adenocarcinomas involving the gastrointestinal tract while others arise in the lung, prostate, cervix, and other diverse sites. One of the largest series to evaluate this issue included 13,715 carcinoid tumors that were studied in surveillance programs from the National Cancer Institute [8]. Overall, 22 percent of carcinoid tumors were associated with other noncarcinoid neoplasms. The highest percentage occurred in association with small intestinal carcinoids (29 percent) compared with carcinoids found in the rectum, gallbladder, appendix, or pancreas (range 13 to 19 percent).

The biologic basis for these observations is unclear. Some authors have hypothesized that the tumors may result from prolonged exposure to growth factors secreted by the carcinoid tumors [8]. However, direct evidence for such an association has not been demonstrated.

Whether patients diagnosed with a carcinoid tumor should undergo screening and then regular surveillance for these noncarcinoid tumors is unclear. Some authors suggest that surveillance of the colon, rectum, small intestine, lung, cervix, and ovaries is appropriate for patients with carcinoid tumors, particularly those involving the small intestine, appendix, or colon [8]. However, such a program has several implications, including the exposure of patients to unnecessary invasive testing and its associated morbidity, costs, and effects on quality of life. Furthermore, the yield and benefits of such a surveillance program have yet to be defined.

PROGNOSIS — The observed survival rates for almost 3000 cases of gastrointestinal (GI) neuroendocrine tumors diagnosed between 1990 and 2000 in the NCI SEER (Surveillance, Epidemiology and End Results) database and stratified according to stage at diagnosis are outlined in the table (graph 1) [5].

Prognosis can be further refined by considering the following factors in addition to tumor size and the presence or absence of metastatic disease at diagnosis:

- Site of origin
- Histology
- The presence or absence of the carcinoid syndrome

A review of eight reports evaluating prognosis of carcinoid tumors indicated that patients with tumors arising in the appendix had a five-year survival of 71 to 100 percent; the rectum 75 to 100 percent, the stomach 51 to 91 percent; small intestine 52 to 77 percent; and colon 33 to 75 percent [35].

The wide range in the prognostic estimates may be due to a focus on selected subgroups of patients. As an example, the lowest survival rate for appendiceal carcinoid was reported by investigators who reviewed only specimens resected with curative intent because of concern for malignancy, thus excluding incidental carcinoids found at simple appendectomy. The variation in reported survival among patients with gastric carcinoids is undoubtedly due to the distribution of patient cohorts with type 1 or type 2 gastric carcinoids (which have an excellent prognosis) as compared to type 3 tumors.

In a survey of published literature in which tumor size was reported and a distinction made between metastases to the nodes and to distant sites, carcinoids of the small bowel less than 1.0 cm at discovery had an excellent prognosis, with nodal and

distant metastases present in 12 and 5 percent, respectively [35]. For tumors between 1.1 and 1.9 cm, nodal or distant metastases were present in to 70 and 19 percent of patients, respectively. A lower frequency of metastases for intermediate size carcinoids was reported for tumors arising in the appendix (7.5 percent) and the rectum (5 percent). Carcinoids exceeding 2.0 cm were associated with distant metastases in 47 percent when arising from the small bowel, 2 percent from the appendix, 39 percent from the colon and 40 percent from the rectum. Prognosis for appendiceal carcinoids is discussed in more detail elsewhere. (See "Cancer of the appendix and pseudomyxoma peritonei", section on 'Carcinoid tumors'.)

Histologic features of carcinoids that predict reduced survival include depth of tumor invasion, vascular and lymphatic invasion, cellular atypia, areas of focal necrosis, and an increased mitotic index (number of mitoses per 10 high power fields). One report described a five-year survival of 61 percent for patients with ordinary histology as compared with 18 percent of those with atypical histologic appearance despite the fact that both groups had metastatic disease [36]. Other studies have described an association with the Ki-67 proliferation marker, which correlates with histological atypia, with decreased survival [37].

Carcinoid syndrome and metastatic disease — The percentage of patients who have carcinoid syndrome has declined since the syndrome was described in the 1950s, almost certainly due to earlier detection and treatment as well as the increased identification of type 1 gastric and rectal carcinoids that are almost never associated with the syndrome. It is estimated that carcinoid syndrome occurs in only 7.7 percent of all carcinoids, with small intestinal carcinoids accounting for the highest number of cases, 35 percent.

Patients with the carcinoid syndrome have a worse prognosis than those who have metastatic disease without carcinoid syndrome [35]; however, median survival is still five to eight years. Individuals with severe carcinoid heart disease have a lower five-year survival, in the range of 30 percent. (See "Carcinoid heart disease".)

Serum markers — Preliminary data suggest that serum levels of chromogranin A (CGA) and N-terminal pro-brain natriuretic peptide (NT-proBNP) might represent important biomarkers for both survival and the presence and severity of tricuspid regurgitation (TR) as a manifestation of carcinoid heart disease among patients with neuroendocrine tumors [38]. However, the utility of CGA as a marker of prognosis has been limited by wide variability in CGA ranges in the setting of metastatic disease, as well as variability in CGA assays in the United States and Europe. (See "Management of metastatic gastroenteropancreatic neuroendocrine tumors", section on Biomarkers.)

Furthermore, most clinicians consider that echocardiography remains the standard for detection and quantitation of TR in patients with carcinoid disease. Baseline echocardiogram is generally recommended in all patients with carcinoid syndrome, and in those who develop clinical features of right heart failure. (See "Carcinoid heart disease", section on 'Biomarkers'.)

SUMMARY AND RECOMMENDATIONS

- Management of patients with carcinoid tumors includes localization of the tumor and possible metastases by CT scan and somatostatin receptor scintigraphy, removal of the tumor if metastases have not occurred, control of carcinoid symptoms if present.
- For patients with a localized carcinoid tumor, we recommend surgery, the extent of which depends upon the site of origin and size of the primary tumor (Grade 1B). (See 'Localized carcinoid tumors' above.)
- Guidelines for follow-up after resection are described above. (See 'Posttreatment follow-up' above.)
- An approach to patients with metastatic carcinoid tumors and carcinoid syndrome depends upon the location of the tumors, severity of symptoms and response to therapy. (See 'Carcinoid syndrome and metastatic disease' above.)

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