

## Update on Classic Gastrointestinal Carcinoid

### Overview

Carcinoid tumors are rare neoplasms arising from neuroendocrine cells scattered diffusely throughout the aerodigestive tract. The most common sites are small intestine (42%), rectum (25%), appendix (12%), and stomach (8.9%)<sup>8</sup>. Occasionally these tumors are found in bronchi (bronchial carcinoids). They are virtually always malignant, and have the potential to metastasize to nodes, liver, or less commonly bone, lung, brain and other organs. Despite this metastatic potential, carcinoids typically are slow-growing, insidious, and have a low mitotic index. The majority is sporadic, but hereditary syndromes have been described as well<sup>1</sup>. The range for median survival of advanced disease is unusually wide, months to many years (some have survived for decades), indicating that typical carcinoids may have long periods of inactivity<sup>2</sup>.

Carcinoid tumors may be non-functional or functional. Functional tumors secrete a variety of hormones, the most important of which are serotonin, histamine, and tachykinins. These hormones are cleared by first pass through the liver; therefore, systemic hormone excess and the resultant carcinoid syndrome (flushing, cramps, diarrhea, wheezing) mainly occurs when hepatic metastases are present, because direct access to the circulation occurs. An exception may occur with extragastrointestinal and bronchial carcinoids which occasionally may present with carcinoid syndrome because they have direct circulatory access. Additionally, as a result of stimulation of fibroblast proliferation by excess serotonin, 20-30% of patients with carcinoid syndrome develop fibrosis of the tricuspid valve and/or pulmonic stenosis<sup>1</sup>.

### Pathology and Staging

Carcinoids typically are well differentiated bland-appearing tumors characterized by the presence of neurosecretory granules demonstrated by special immunohistochemical stains for chromogranin, synaptophysin, Gremilium, and neuron-specific enolase (not as specific). A small percentage is graded as "atypical" and has an intermediately aggressive course<sup>2</sup>.

Frequently patients are asymptomatic or have vague symptoms and the diagnosis is made as an incidental finding at endoscopy or surgery. In other instances there is significant abdominal pain or even debilitating carcinoid syndrome. Extensive staging procedures probably are irrelevant when the tumor is tiny to small and strictly localized<sup>2</sup>. However, the majority of cases are discovered when metastatic disease is suspected; therefore, it is common to stage these cases for tumor size and location of possible metastases, and also to assess the amount of hormone secretion if the tumor is functional<sup>3</sup>.

The usual staging procedures are endoscopy, computerized tomography (using a liver protocol) or MRI, followed by octreotide scintigraphy. Octreotide is a synthetic analogue of the naturally occurring hormone somatostatin, which functions to inhibit secretion of many normal hormones, diminishes intestinal and pancreatic fluid secretion and intestinal motility, and causes vasoconstriction. Since carcinoids often possess high affinity receptors for somatostatin, tumors with the common type 2 receptors will attract radiolabeled octreotide to that site, identifying the location of the tumor. Also, patients with positive scans are more likely to respond to octreotide treatment, if that is required later<sup>2</sup>.

The preferred laboratory test is a 24-hour urinary 5-hydroxyindoleacetic acid, the breakdown product of serotonin, although this will not be elevated unless the tumor is functional and there are liver metastases. A serum serotonin test may be difficult to interpret due to diurnal variations<sup>2</sup>. Plasma chromogranin-A is elevated in 56-100% of carcinoids and the level correlates with tumor function and size. This test may be useful for following disease progression<sup>3</sup>, but false positives with gastritis, renal failure, and proton pump inhibitor therapy may make results difficult to interpret<sup>3</sup>.

### Local and Regional Disease

A common site of presentation is the appendix, where carcinoid tumor reportedly is found in 1 of every 300-500 appendectomies<sup>2,7</sup>. If the tumor is < 1cm, the chance of metastases is so low that simple resection suffices, and this probably holds as well, but is not as predictable, for tumors between 1- 2 cm. Carcinoid tumors > 2 cm frequently metastasize, so a formal right hemicolectomy is required in this situation to properly assess regional lymph nodes in the mesocolon<sup>2</sup>. The situation is entirely similar for the rectum where there is a high metastatic potential if > 2 cm<sup>2</sup>. Small bowel carcinoids have a high cure rate if node negative (93%), and still have an 80% 5 year survival rate if node positive. Since they tend to be small and deep in the wall of the small bowel, they rarely obstruct. Therefore, if metastases are found at surgery without an obvious primary, an extensive search for an asymptomatic tumor usually is not productive or indicated<sup>2</sup>.

### Metastatic Disease

There is a full spectrum of presentations from asymptomatic to highly symptomatic overt carcinoid syndrome. Regardless, CT or MRI scanning, urine 5-HIAA measurement, and plasma chromogranin A are reasonable baseline tests; if the 5-HIAA is elevated, an echocardiogram should be included<sup>2</sup>. Radiolabeled somatostatin receptor (octreotide) SPECT imaging to document the primary and sites of metastases is an appropriate baseline study if octreotide therapy or surgery is contemplated. Depending on the type of symptoms, patients could require a more thorough evaluation which might also include a complete hormone work-up and possible endoscopy<sup>3</sup>.

If patients are asymptomatic, many experts believe that a no treatment, or a "watchful waiting" option is reasonable regardless of the presence of metastatic disease. The natural history of many metastatic carcinoids is so indolent that it is appropriate to establish tumor progression first by follow-up serial scans and/or hormone measurements before instituting therapy. Many cases may be static and require no therapy for years<sup>2</sup>. On the other hand, patients are candidates for treatment when there are symptoms due to tumor bulk, objective signs of progression, or uncontrollable symptoms due to hormone secretion.

### Systemic Therapy

The treatment of choice for patients symptomatic from functional carcinoid syndrome is octreotide (provided the scan is positive), which blocks serotonin secretion and is highly effective in improving symptoms related to its excess. An antiproliferative effect of octreotide had been postulated as well, but clinical evidence for this was considered equivocal until a recent placebo-controlled trial demonstrated a very significant eight month longer period of stability without tumor growth (but no evidence for regression) in the group treated with octreotide<sup>5</sup>.

Claims that interferon is effective for tumor regression have been overstated in the literature. Actual objective tumor regression occurs in about 10%, is quite minor, and intolerance to interferon is substantial<sup>2</sup>.

With respect to chemotherapy, the standard agent during the 1980-1990s was streptozocin, usually given as a two drug combination with 5-FU, doxorubicin, or cyclophosphamide. Overall survival was reported to be 11-36 months but objective review of these studies found the data to be highly unreliable, and streptozocin now is considered minimally active and fairly toxic<sup>2</sup>. Dacarbazine is an old drug with a reported 16% response rate, but also with considerable toxicity. Its oral equivalent, temozolomide has been administered with thalidomide with a 7% response rate<sup>2</sup>. Although many chemotherapy regimens have been tried, carcinoid tumors are still considered chemoresistant.

### Liver Metastases

Symptomatic liver metastases should be resected if a complete or near complete resection is possible. There is insufficient data in the literature, however, to assess whether resection actually prolongs overall, or progression free survival<sup>2</sup>. If unresectable, the options to control symptoms and tumor bulk are: local ablative therapy (RFA, cryotherapy, microwave), or hepatic regional therapy (arterial embolization, chemoembolization, radioembolization). Palliation by any of these procedures can be effective, but because of risks these should be reserved for symptomatic and overtly progressive patients.

### Targeted Therapy

These agents interfere with cell cycle signaling either by blocking an important surface receptor or a key intracellular pathway. The targeted agents still in clinical trials with reported activity in neuroendocrine tumors are: bevacizumab, sunitinib, everolimus, and temsirolimus. Objective response rates have been modest for islet cell tumors, but very minimal for carcinoids<sup>2</sup>.

### Radiolabeled Somatostatin Analogue Therapy

For tumors that take up octreotide, there has been an attempt to radiate them with an injectable radiolabeled somatostatin analog (177 Lu-octetate). A European study with this radiopharmaceutical reported 20% partial and another 20% minimal responses. This therapy has not yet been approved by the FDA, but the technique definitely holds promise for future treatment<sup>6</sup>.

### References

1. NCCN Pract. Guide., Neuroendocrine Tumors, v.1.2010
2. Saltz, L., medscape.com/2010/article 720580
3. Phan, A., medscape.com/2009/article 709466
4. Moertel, C., J Clin Oncol, 1987, 5:1502
5. Rinke A., J Clin Oncol, 2009, 27:4656
6. Kwekkeboom D., J Clin Oncol, 2005, 23:2754
7. Ramezani M., Am J Appl Sciences, 2006, 3:1640
8. Maggard M., Ann Surg, 2004, 240:117

*This publication is a review and not meant as a guideline for medical treatment.*