Carcinoid and Neuroendocrine Tumors of the Colon and Rectum

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ABSTRACT

Carcinoid and neuroendocrine tumors of the colon and rectum arise from the amine precursor uptake and decarboxylation (APUD) cells of the intestine. Carcinoid tumors are most commonly found in the gastrointestinal tract and are located in decreasing order of frequency in appendix, ileum, rectum, stomach, and colon. The vast majority of lesions are asymptomatic and are found incidentally during endoscopy. The management of these lesions depends upon the size of the lesion, involvement of the muscularis, location, and presence of metastatic disease. Small lesions (1 cm) can often be treated locally, either endoscopically or transanally. However, larger lesions (> 2 cm) require a formal oncologic resection. Adjuvant therapy is indicated only for metastatic disease, and admirable advances have been made in the realm of chemotherapy for reduction of disease and palliation of the symptoms of carcinoid syndrome. In this article, we discuss the nature of these interesting and uncommon tumors, clinical presentation, treatment options, and prognosis.

KEYWORDS: Carcinoid, neuroendocrine tumor, colon, rectum

Objectives: Upon completion of this article, the reader should understand the basic evaluation and indications for surgical treatment of carcinoid and neuroendocrine tumors of the colon and rectum.

Historically, tumors that were clinically less aggressive and morphologically different from the more common gastrointestinal adenocarcinomas were given the name carcinoid tumors.[1] More recently, the World Health Organization (WHO) has proposed the term gastroenteropancreatic neuroendocrine tumors (GEP-NETs) as it is thought that the term carcinoid does not adequately cover this heterogeneous spectrum of neoplasms that secrete up to 40 different cytokines and hormones. Carcinoid and neuroendocrine tumors arise from the ubiquitous neuroendocrine cells, also referred to as clear cells or amine precursor uptake and decarboxylation (APUD) cells.[2] As a result, these tumors are capable of secreting many different cytokines and hormones, which may or may not be biologically active. The diversity of tumor subtypes is reflected in the complicated and often confusing nomenclature for their classification, for example, adenocarcinoid, goblet cell, crypt cell, mucous, and mixed carcinoid-adenocarcinoma. Each subtype of tumor appears to have different biological and clinical behavior. For example, pure carcinoid tumors tend to be slow growing and have a relatively indolent course, whereas adenocarcinoid tumors are very aggressive and fast growing.[3] Neuroendocrine tumors (NETs) arise from the neuroendocrine or APUD cells that are scattered throughout the mucosa of the

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gastrointestinal tract.[4] The term carcinoid is also used in this review because of its common usage in the literature to describe GEP-NETs, and we primarily deal with the well-differentiated, serotonin-producing NETs to which this term refers. Malignant carcinoid refers to the well-differentiated neuroendocrine carcinomas, that is, tumors that have invaded the muscularis propria or metastasized to regional lymph nodes or distant sites such as the liver or lungs.

NETs were originally classified according to the embryonic divisions of the digestive tract, that is, foregut/midgut/hindgut, by Williams and Sandler in 1963.[5] Midgut carcinoid usually refers to the relatively aggressive distal ileal tumors and ascending colon tumors as well as the more benign appendiceal tumors, with hindgut tumors represented by distal colic and rectal carcinoids.[6] Hindgut carcinoids are typically asymptomatic and rarely cause carcinoid syndrome.

The etiology of these tumors is still unknown, and the genetics underlying these tumors is just beginning to be understood. Most tumors appear to be sporadic, with familial syndromes such as multiple endocrine neoplasia type 1 leading predominantly to foregut tumors.[6,7] Genetic losses on chromosome 18q are believed to be an early event in the genesis of many midgut tumors, with the loss of 16q or gain of 4p, or both, representing late genetic mutations often found in metastatic tumors.[6] Inactivation of tumor suppressor genes on chromosome 11q has also been reported in midgut carcinoids.[6,8]

The incidence of NETs appears to have been increasing in recent decades, although this is more likely the result of improved detection with increasingly sophisticated modalities, such as endoscopy, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and scintigraphy.[9] Two thirds of all carcinoids occur in the gastrointestinal tract, with 27.4% occurring in the rectum based upon a survey of 13,175 carcinoids.[10]

CLINICAL PRESENTATION AND DIAGNOSIS

The majority of NETs are asymptomatic at the time of discovery. In most patients with these tumors, the discovery is made incidentally at the time of surgery or other diagnostic evaluations.[11–14] In one series, carcinoid tumors were found in 1.22% of 16,294 autopsies in Malmö, Sweden, and 90% were incidental findings.[15] The classic carcinoid symptoms of cutaneous flushing and gut hypermotility occur in less than 10% of all patients, as the syndrome requires the presence of hepatic metastases. Symptoms that do occur tend to be vague and nonspecific, and more often these symptoms are related to the mass effects of the tumor. These can include vague abdominal pain, weight loss, bleeding, obstruction, and constipation, although the majority of patients have no symptoms. There may be nonspecific local effects of the tumor. For example, fibrosis from carcinoid tumors may cause obstruction from adhesions or stricturing of the intestinal lumen,[16] hydronephrosis and subsequent renal failure, or even mesenteric ischemia from constriction of the mesenteric vessels.[17] The pathogenesis of this fibrosis is poorly understood.

Patients with suspected NETs should undergo biochemical screening. The most commonly employed marker in patients suspected of having a carcinoid tumor is the urinary 5-hydroxyindole acetic acid (5-HIAA), although the specificity of this marker is only about 88%, and thus elevated 5-HIAA is not necessarily diagnostic.[18] However, 5-HIAA assays have the benefit of being widely available. Chromogranin A may be the best overall marker of NETs and is often elevated as much as 50 to 100% above normal in patients with these neoplasms.[19] The overall serum level may also be indicative of tumor burden and carry some prognostic significance in midgut tumors.[20]

Imaging techniques available in the evaluation of NETS include CT, MRI, Octreoscan, and ^{99m}Tc-labeled bone scintigraphy. CT and MRI remain the most common initial modes of evaluation for NETs. Typical findings include the triad of a calcified mass, spiculation, and stranding suggesting localized fibrosis.[21] Median detection rates of these two modalities are about 80%, with no significant difference between CT and MRI.[22]

Octreoscan scintigraphy using ^{111}In-labeled octreotide has an overall sensitivity of 80 to 90% and has the advantage of scanning the entire body. A review of several series suggests a median detection rate of 89% of carcinoid tumors using this modality. Positron emission tomography (PET) scans have limited utility in the evaluation of NETs because most NETs are well differentiated and have a low metabolic rate, resulting in detection rates between 25 and 73%. ^{99m}Tc bone scintigraphy is the main technique employed in the evaluation of bone metastases and has a detection rate above 90%.[23]

At present, treatment of carcinoid depends on the location and size of the tumor. Thus, we discuss the diagnosis and management of carcinoid on the basis of location. To date, the treatment of carcinoid tumors regardless of location relies heavily upon surgical resection.

Cecum and Ascending Colon

Up to 34.5 to 48% of all colorectal carcinoids occur in the cecum and ascending colon, although this may reflect in part tumors arising from the base of the appendix and extending into the cecum.[10,24] Midgut carcinoid tumors are more likely to be symptomatic at the time of diagnosis, by which time the tumor has typically grown

to greater than 5 cm in diameter; the late presentation of these tumor is due in large part to the greater capacitance of the right colon compared with the distal colon and rectum. As a result, up to two thirds of tumors are already metastatic at the time of discovery.[25,26] The carcinoid syndrome itself is not common. One series noted that up to 80% of patients with midgut tumors demonstrated significant mesenteric fibrosis at the time of surgery for obstruction.[27] Five percent of patients may have miliary seeding of tumor, further complicating surgical treatment.[27] In two series, the average size of tumors was about 5 cm at diagnosis.[24,28] Recent 5-year survival rates for localized, regional, and distant cecal tumors are 78.5%, 78%, and 43.6%, respectively.[10] In patients with early stage nonmetastatic disease, surgery may be effective in prolonging survival.

Distal Colon

Colonic carcinoids have a peak incidence in the seventh decade of life and have a male/female ratio of 2:1.[28] These tumors are less common than cecal and rectal carcinoids, with one series reporting only 6% of all colonic carcinoids occurring in the transverse colon and 11% in the descending colon.[24] As with rectal carcinoids, lesions smaller than 2 cm are less likely to be metastatic at diagnosis, although up to 74% of larger tumors have metastasized by the time of presentation. These are most commonly diagnosed during evaluation for abdominal pain, anorexia, or weight loss. Only 16% of patients in one series had Hemoccult-positive stool.[28] Typical prognostic criteria such as size and invasiveness are less useful because most of these tumors already exceed 2 cm in size at presentation; pathologic criteria such as tumor grade, histology, and mitotic rate tend to be the most useful.[29] Survival tends to be worse than that with rectal carcinoids because of the later stage of diagnosis, with some authors reporting perioperative mortality as high as 22%.[29] Five-year survival ranges from only 33 to 42% because of the larger tumor sizes and presence of metastasis at the time of diagnosis, with local and regional disease associated with 76 and 72% survival, respectively.[23] Surgery remains the mainstay of treatment, employing standard wide resection techniques for colon cancer. Patients should be carefully evaluated for associated noncarcinoid tumors, which may occur in up to 13% of patients.[23] Patients with tumors less than 2 cm in size should have endoscopic or local resection. Those with tumors larger than 2 cm or with tumors that cannot be resected locally by endoscopic or transanal approaches should also undergo formal oncologic resection.

Rectum

Rectal carcinoids are typically diagnosed during routine lower gastrointestinal endoscopy as small, sessile masses or thickened areas.[30] African-American males had the highest incidence in one published series (2.12 per 100,000 population per year).[9] There is no evident gender predisposition, and they are diagnosed at a much earlier age than colonic carcinoids, with an average age between 48 and 52 years at diagnosis. Approximately half are asymptomatic; typical symptoms, when present, include discomfort, change in bowel habits or constipation, and bleeding.[30] The carcinoid syndrome is rare in these patients. Overall, less than 20% of rectal carcinoids are metastatic upon presentation, and the overall 5-year survival rate ranges from 88.3 to 98.3%.[10,31] The size of rectal carcinoids correlates closely with the likelihood of metastases. Tumors smaller than 1 cm are rarely metastatic, with only 3.7% of rectal carcinoids 0.5 cm or smaller being metastatic at the time of diagnosis; rates of metastatic disease increase to 13.2% in tumors 0.5 to 1.0 cm in size and 26 to 28% in tumors 1 to 2 cm in size.[31] Up to 70% of tumors larger than 2 cm may be metastatic.[10]

Patients with nonmetastatic small tumors (< 1 cm) can be treated with local excision, often transanally or endoscopically. In the past, radical excision (i.e., low anterior resection with total mesorectal excision or abdominoperineal resection) has been recommended by some authors for patients with larger tumors (> 2 cm) and those with intermediate tumors (1 to 2 cm) invading the muscularis propia.[32,33] Other authors have argued that radical surgery has little or no survival benefit in patients with tumors larger than 2 cm.[34,35] However, most of the data consist of relatively small series of patients studied in retrospective fashion. This issue remains one of significant controversy. At this time, the best recommendation is to tailor treatment on a case-by-case basis.

MEDICAL TREATMENTS AND THE ROLE OF DEBULKING

The primary medical treatments available for carcinoid syndrome are somatostatin analogues (e.g., octreotide) as up to 80% of carcinoid tumors have somatostatin receptors.[36] Octreotide can be particularly successful at alleviating the symptoms associated with carcinoid syndrome. Chemotherapy options remain limited, as chemotherapy regimens such as 5-fluorouracil plus streptozocin resulted in only a 33% response as measured by tumor burden and interferon-α resulted in only a 15% response as measured by urinary 5-HIAA.[26] Radiation therapy as it stands now also has extremely limited uses, mainly in the palliation of bone metastases. Debulking, particularly of limited liver metastases, if anatomically possible may alleviate symptoms and even prolong survival.[37] Other options include embolization of metastases, but as with all of these options, these must be carefully considered on a case-by-case basis.

SUMMARY

Great progress has been made in our understanding of this rare family of neoplasms, but our understanding remains poor and the clinical management is often difficult. Although surgery appears highly successful in the treatment of tumors smaller than 1 cm, guidelines for the treatment of larger tumors and metastatic disease remain unconsolidated. Standard surgical techniques may still provide a chance of cure but must be weighed carefully for each individual patient.

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