Current Status of Gastrointestinal Carcinoids

IRVIN M. MODLIN, MARK KIDD, IGOR LATICH, MICHELLE N. ZIKUSOKA, and MICHAEL D. SHAPIRO

Gastric Pathobiology Research Group, GI Surgical Division, Yale University School of Medicine, New Haven, Connecticut

Gastrointestinal (GI) carcinoids are ill-understood, enigmatic malignancies, which, although slow growing compared with adenocarcinomas, can behave aggressively. Carcinoids are classified based on organ site and cell of origin and occur most frequently in the GI (67%) where they are most common in small intestine (25%), appendix (12%), and rectum (14%). Local manifestations—mass, bleeding, obstruction, or perforation—reflect invasion or tumor-induced fibrosis and often result in incidental detection at emergency surgery. Symptoms are protean (flushing, sweating, diarrhea, bronchospasm), usually misdiagnosed, and reflect secretion of diverse amines and peptides. Biochemical diagnosis is established by elevation of plasma chromogranin A (CgA), serotonin, or urinary 5-hydroxyindoleacetic acid (5-HIAA), while topographic localization is by Octreoscan, computerized axial tomography (CAT) scan, or endoscopy/ultrasound. Histological identification is confirmed by CgA and synaptophysin immunohistochemistry. Primary therapy is surgical excision to avert local manifestations and decrease hormone secretion. Hepatic metastases may be amenable to cytoreduction, radiofrequency ablation, embolization alone, or with cytotoxics. Hepatic transplantation may rarely be beneficial. Chemotherapy and radiotherapy have minimal efficacy and substantially decrease quality of life. Intravenously administered receptor-targeted radiolabeled somatostatin analogs are of use in disseminated disease. Local endoscopic excision for gastric (type I and II) and rectal carcinoids may be adequate. Somatostatin analogues provide the most effective symptomatic therapy, although interferon has some utility. Overall 5-year survival for carcinoids of the appendix is 98%, gastric (types I/II) is 81%, rectum is 87%, small intestinal is 60%, colonic carcinoids is 62%, and gastric type III/IV is 33%.

This review provides a broad outline of progress that has been made in the elucidation of the biology and management of gastrointestinal (GI) carcinoid tumors. Because these lesions exhibit a high degree of morphologic and biologic heterogeneity, there is a lack of clarity regarding their individual characteristics. A more generic term, *neuroendocrine tumor* (NET) has been introduced to replace the term *carcinoid*, and such lesions are currently referred to as *gastroenteropancreatic (GEP) NETs* (GEP-NETs).[1] Although an improvement on the group colloquation "carcinoid," the classification still requires to be extended and further refined because a substantial group of NETs are of indefinable malignant potential and represent an indistinct biologic group whose behavior cannot be accurately predicted. This reflects the fact that traditional morphologic criteria of neoplasia have limited applicability. Molecular characterization (as yet lacking) is required to refine and further differentiate GEP-NETs. To date, the gene responsible for MEN-1 on chromosome 11q13, which is also mutated in up to 40% of sporadic GEP-NETs,[2] has been identified, and comparative genomic hybridization and allelic loss have detected a large number of genomic regions with loss or gain of genetic material.[3,4] Such

Abbreviations used in this paper: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptophan; ACTH, adrenocorticotropic hormone; AFP, α-fetoprotein; AP-1, activator protein-1 complex; CAG/A, chronic atrophic gastritis-type A; CBD, common bile duct; CCD, carcinoid cardiac disease; CEA, carcinoembryonic antigen; CgA, chromogranin A; CGH, comparative genomic hybridization; CTGF, connective tissue growth factor; DCC, deleted in colorectal carcinoma; EC, enterochromaffin; EM, electron microscope; FDG, fluoro-2-deoxy-Dglucose; FGF, fibroblast growth factor; G, gastrin; GC, gastric carcinoids; GCC, goblet cell carcinoma; GE, gastroesophageal; GEP, gastroenteropancreatic; hCG, human chorionic gonadotrophin; HLI, human leukocyte interferon; IGF-1, insulin-like growth factor; KNO, knockout; LI, labeling index; LOH, loss of heterozygosity; MEN-1, multiple endocrine neoplasia syndrome-type 1; MIBG, metaidobenzylguanidine; MRI, magnetic resonance imaging; MSI, microsatellite instability; NCAM, neural cell adhesion molecule; NETS, neuroendocrine tumors; NF1, neurofibromatosis-type 1; NSE, neuron-specific enolase; PA, pernicious anemia; PDCD4, programmed cell death protein 4; PDGF, platelet-derived growth factor; PET, pancreatic endocrine tumor; PLCB3, phospholipase CB3; PP, pancreatic peptide; PTC, percutaneous transhepatic cholangiography; SDHD, succinate ubiquinone oxidoreductase subunit D; SEER, surveillance epidemiology and end results; SI, small intestines; SPECT, single positron emission computed tomography; SRS, somatostatin receptor scintigraphy; SSTomas, somatostatinoma; SSTR, SST receptor; UGI, upper gastrointestinal; VEGF, vascular endothelial growth factor; VHL, von Hippel–Lindau syndrome; VIP, vasoactive intestinal polypeptide; ZE, Zollinger–Ellison.

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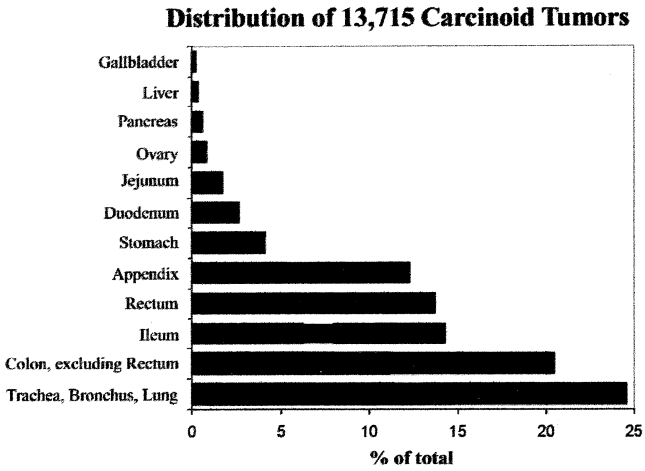

Figure 1. Distribution of 13,715 carcinoid tumors contained by the ERG, TNCS, and the SEER file (1950–1999) by organ site. Adapted from Modlin IM et al.[14]

studies have also confirmed that NETs in different localizations are genetically independent tumors. Hence, foregut NETs often show loss of 11q, which distinguishes them from NETs of the mid- and hindgut, which frequently show losses on chromosome 18q.[5,6] A major goal is to identify a series of molecular signatures that will identify genetic markers or constellations that will facilitate prediction of the biologic behavior of such lesions and enable the delineation of rational therapeutic strategies. This review provides a general outline of the background of GEP-NETs, their clinical diagnosis, and management with specific sections describing each tumor type and its characteristics in detail (Figure 1). The final section evaluates therapeutic strategy.

Concept Evolution

In 1888, Lubarsch described the microscopic features of a patient with multiple carcinoids of the ileum but regarded them as carcinomas.[7] Two years later, Ransom provided the first detailed descriptions of the classical symptomatology of carcinoid syndrome in a patient with an ileal carcinoid tumor and hepatic metastasis.[8] However, it was Oberndorfer in 1907, who coined the term *karzinoide* (carcinoma-like) to describe these tumors, which he believed to behave in a more benign fashion than adenocarcinomas (Figure 2).[9] The recognition of carcinoids as endocrine-related tumors was first outlined by Gosset and Masson in 1914.[10] In 1963, Williams and Sandler classified carcinoids according to their embryologic site of origin as foregut carcinoids (respiratory tract, stomach, duodenum, biliary system, and pancreas), midgut carcinoids (small intestine, appendix, cecum, and proximal colon), and hindgut carcinoids (distal colon and rectum).[11] This classification was the first to emphasize clinicopathologic differences between the tumor groups composing the gastroenteropancreatic neuroendocrine tumors (GEP-NETs) but never achieved general acceptance in routine diagnostic practice because it proved too imprecise to distinguish between the different biologically relevant GEP-NET entities.[12] This was particularly apparent in the foregut NETs, which differ so greatly in morphology, function, and biology that they cannot be classified as a single group.

However, with the introduction of immunohistochemistry, plasma immunoassays for peptides and amines and the development of novel diagnostic methodology (eg, computed tomographic [CT] scan, magnetic resonance imaging [MRI], SST receptor [SSTR] scintigraphy, and positron emission scanning), the management of NETs has advanced significantly in the last 2 decades. Furthermore, it has become apparent that the term "carcinoid" fails to convey the diverse spectrum of neoplasms with widely different secreting products that originate from different NE cell types. Although the precise identification of the specific cell type of each NE tumor of the GI tract is far from complete, the widespread use of

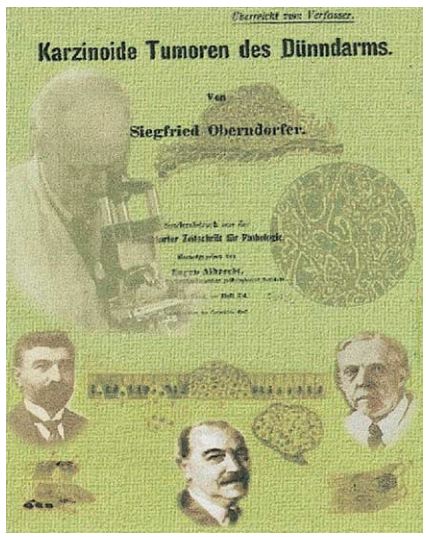

Figure 2. Siegfried Oberndorfer (1876-1944) (*top left*) presented his observations of multiple "benign carcinomas" (*Karzinoide*) of the small bowel at the German Pathological Society meeting of 1907 in Dresden (*top*). P. Masson and A. Gosset (*bottom left and right*, respectively) demonstrated the argentaffin staining properties of appendiceal carcinoid tumors in 1914 and suggested that gut enterochromaffin (EC) cells (*lower left*; *bottom right*) formed a diffuse endocrine organ. In 1928, they described these cells to be neural in origin and proposed them as progenitors of neuroendocrine tumors of the gut (carcinoids). The first description of the diffuse neuroendocrine system (DNES) was provided in 1938 by F. Feyrter (*bottom*), who described argentaffin or argyrophil "clear cells" ("*Helle Zellen*") in the gut and pancreas and proposed that such cells produced hormones that acted locally.

endoscopy, ultrasonography, computerized tomography, MRI, and SSTR scintigraphy have significantly enhanced the identification of previously undetectable lesions and allowed a more accurate delineation of metastases. As a consequence, carcinoid tumors of the gut "appear" to have increased in incidence over the last 20 years.[13,14]

Pathology

Terminology

The first WHO classification of endocrine tumors (1980) applied the term *carcinoid* to most NETs, exempting the endocrine tumors of the pancreas and thyroid, paragangliomas, small-cell lung carcinomas, and Merkel cell tumors of the skin. Carcinoids were divided into enterochromaffin (EC) cells, gastrin (G) cells, and an unspecified category, but this led to misunderstandings between pathologists and clinicians because the former applied the term *carcinoid* to all tumors with NE features, whereas the clinicians used the term *carcinoid* in reference to a serotonin-producing tumor with carcinoid syndrome. A further issue was the growing awareness of the heterogeneity of such tumors, and it was no longer possible to equate a gastric with an ileal or rectal carcinoid or to include among the carcinoids those in which atypical histology rendered inclusion in a carcinoid pathologic description problematic. Thus, the updated WHO classification of 2000 adopted the neutral and inclusive terms *NE tumor* and *NE carcinoma*.[15] In this classification, distinction was made between well-differentiated NE tumors (benign behavior or uncertain malignant potential), well-differentiated NE carcinomas (low-grade malignancy), and poorly differentiated (usually small cell) NE carcinomas of high-grade malignancy. Nevertheless, to obviate confusion, the term *carcinoid* was not utterly abandoned, and, for gastroenteric NETs, it is used synonymously with the term "well-differentiated NE tumor." The term "malignant carcinoid" is used synonymously with the term *well-differentiated NE carcinoma*, and, to refine further the classification, a further subdivision utilizing localization and biology of the tumors was included to achieve a prognostically relevant classification. Thus, the stomach, duodenum (and proximal jejunum), ileum (including the distal jejunum), appendix, colon-rectum, and pancreas were distinguished, and, in addition, morphologic/biologic criteria including tumor size, angio-invasion, proliferative activity, histologic differentiation, metastases, invasion, and hormonal activity (association with clinical syndromes or diseases) were included.

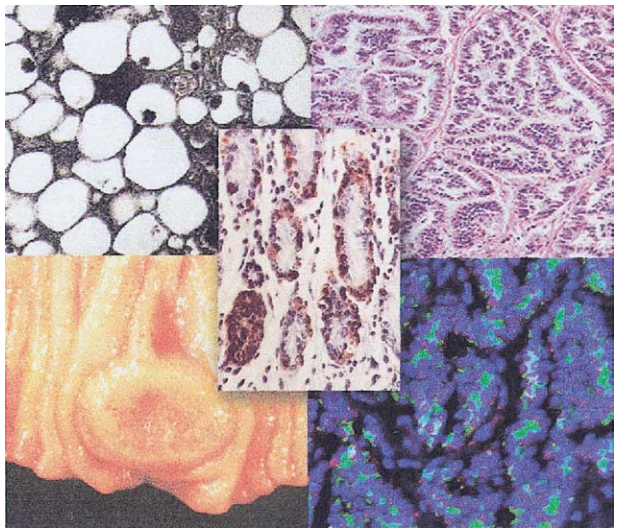

Figure 3. An electron micrographic view of ECL cell granules demonstrating the electron-dense and -lucent secretory vesicles (*top left*). A low-power view of a carcinoid demonstrating the typical ribbon-like pattern (*top right*). Pseudo 3-color image of a small bowel carcinoid showing significant overlap between cytokeratin and nuclear Ki-67 (MIB-1) staining in the tumor mucosa (*bottom right*). Dual nuclear staining (red Cy5, Ki-67 and blue, DAPI) results in purple. Green staining, tumor mask (cytokeratin, Alexa488). Gross specimen of an ulcerated small intestinal carcinoid (*bottom left*). Chromogranin A staining of a gastric carcinoid with linear hyperplasia and ECL cell tumor nests (*center*).

Pathology

Carcinoid tumors are *usually* classified by their embryonic gut origin, and the ubiquitous, yet inconsistently defined, classification of "typical" vs "atypical" carcinoids has become prevalent within the literature, usually in reference to their degree of differentiation. "Typical" carcinoids, by definition, are tumors with NE differentiation and classical histologic architecture of trabecular, insular, or ribbon-like cell clusters, with no or minimal cellular pleomorphism and sparse mitoses (Figure 3).[16] "Atypical" carcinoids, however, refer to aggressive forms of poorly differentiated carcinoid tumors with increased mitotic activity and the absence or limited extent of necrosis.[17] As mentioned earlier, the term *carcinoid* is no longer adequate to cover the entire morphologic and biologic spectrum of neoplasms of the disseminated NE cell system, and the current WHO classification prefers the general terms "NE tumor" and "NE carcinoma."[1] Although Oberndorfer,[9] in 1907, differentiated carcinoid tumors from carcinoma of the GI tract, these tumors were considered to represent a fairly homogeneous group, and it became customary to regard them as such in terms of classification, assessing prognosis, and defining therapy. In the last 2 decades, knowledge of the cellular origins and biologic behavior of GEP-NETs has increased greatly, due to advances in

clinical and morphologic diagnostics. As a result, a more refined view of the classification and treatment of GEP-NETs has developed. This supports the need to retire the archaic concept of "carcinoid."

Classification based on embryological origin (foregut, midgut, and hindgut) is an outdated but somewhat useful distinction because the features of carcinoid tumors derived from each respective location differ clinically, histologically, and immunochemically. Thus, foregut and hindgut carcinoids are typically argentaffin negative, contrary to midgut lesions that are argentaffin-positive.[18] More recently, sophisticated modern methods of analysis have fostered the development of precise classification systems that can discern the motley assortment of peptides and amines present in carcinoid tumors. Current estimates indicate the identification of as many as 40 different secretory products in the different varieties of carcinoid.[19] The diagnosis of carcinoid tumors is also supported by ultrastructural findings of intracytoplasmic electron-dense secretory granules and by immunoreactivity with antibodies to chromogranin A (CgA).[20]

Phenotypically, the cells of the GEP-NETs may be considered as part of the disseminated NE cell system, which Feyrter had first referred to as "Helle Zellen" (clear cells) and was subsequently defined by Pearse as "APUD cells."[21] These cells are scattered throughout the GI mucosa, or, in the pancreas, form the islets as described by Langerhans.[21] The term "NE" derives from the phenotypic relationship to neural cells in their expression of certain common proteins, including neuron-specific enolase (NSE), synaptophysin, and CgA. These proteins have utility as general markers in the morphologic diagnosis of GEP-NETs because, for the most part, they are independent of cell-specific hormone production. Immunocytochemical studies require some caution because CgA is rarely expressed by SST cells or in very poorly differentiated NET cells, whereas NSE identification can be marred by nonspecific reactions related to the presence of dimeric isoforms.

More specific markers of the normal and neoplastic NE cells are the bioactive products (hormones) of the GEP system. Although at least 12 different types of endocrine cells are currently recognized, less than half of the known hormones are expressed in GEP-NETs. In addition, it is of interest that the organ in which a particular hormone-producing tumor originates appears to be of biologic and clinical significance in determining outcome. Thus, duodenal gastrinomas exhibit a far less aggressive behavior pattern than pancreatic tumors derived from the same cell type (G cell).[22,23]

Molecular Genetics of GI Carcinoids

A number of genetic syndromes including multiple endocrine neoplasia syndrome-type 1 (MEN1), von Hippel–Lindau syndrome (VHL), and neurofibromatosis-type 1(NF1) may be associated with gut NE tumors. In the normal cell, these genes play a role in tumor suppression; aberrations in these regulatory genes can lead to the development of neoplasms, including carcinoids. The best defined of these symptoms is MEN1,[24] an autosomal dominant disorder associated with the gene locus *MEN1* located on 11q13. Its protein product (menin) is involved in transcriptional regulation and genome stability. GI carcinoids often (40%–75%) exhibit either somatic mutations or loss of heterozygosity (LOH) at 11q13,[24] and deletion of the wild-type allele leads to loss of tumor suppressor function of the MEN1 gene. One third of individuals with MEN1 develop gastric carcinoids, and loss of heterozygosity at the 11q13 location occurs in 75% of MEN1-Zollinger–Ellison (ZE) syndrome carcinoids and in 41% of MEN1 gastrinomas.[25] LOH at locations distal to 11q13, at the location of the succinate ubiquinone oxidoreductase subunit D (SDHD) gene (tumor suppressor gene), have also been implicated in the development of midgut (rather than foregut) carcinoids, MEN1, sporadic carcinoids of the lung,[26] and paragangliomas.[27] Using comparative genomic hybridization (CGH) 22% of ileal and duodenal carcinoids exhibit alterations in the distal part of 11q (location of SDHD).[26] Alterations on chromosome 11 therefore play a major role in the development of MEN1 and in foregut carcinoids. Alterations in other chromosomes have also been identified by CGH in GI carcinoids. Thus, in midgut carcinoid tumors, CGH identified 57% gains in chromosomes 17q and 19p and 50% in 19q and 4q (each) as well as in 4p (43%), 5 (36%), and 20q (36%). Losses were noted at 18q or 18p in 43% of midgut tumors, whereas 21% had full or partial loss of 9p.[5] Others have noted losses in 18q22-qter (terminal end of chromosome 18q) (67%) and 11q22-23 (33%) as the most common genetic defects in midgut carcinoids.[6] Of note, the 18q and 11q chromosomal losses occurred more frequently than the losses in 16q and gains in 4p, suggesting that losses on the long arm of chromosomes 11 and 18 are early events in midgut carcinoid tumorigenesis, whereas a loss on chromosome 16 and some gain-of-function on chromosome 4 are later events in carcinoid development (Figure 4).

NF1 or von Recklinghausen's Disease is an autosomal dominant genetic disorder (17q11) in which the *NF1* gene is a tumor suppressor whose mutation leads to premature truncation of the neurofibromin tumor-sup-

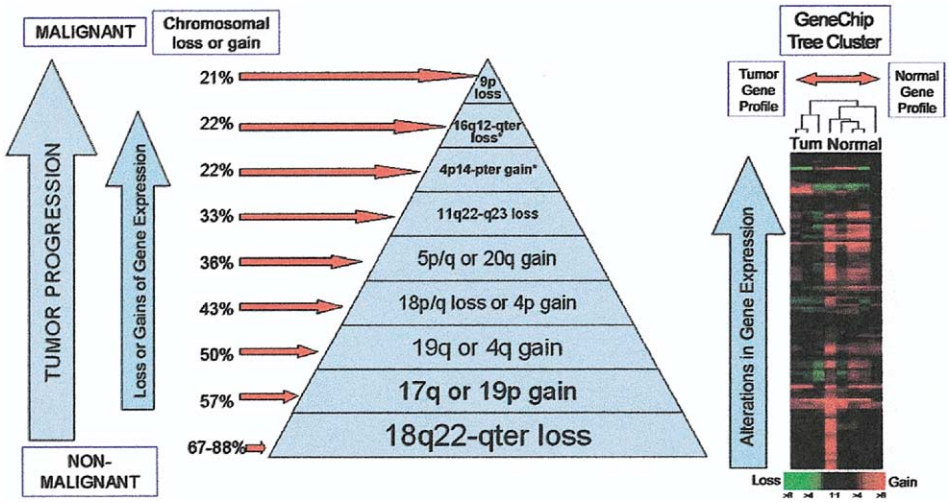

Figure 4. Chromosomal losses or gains from comparative genomic hybridization studies listed from most to least frequent (*bottom to top of pyramid*). This outlines the temporal relationship between chromosomal aberrations (and gene losses or gains) and malignancy of GI carcinoid tumors. The gene expression of GI carcinoid tumors compared with normal mucosa is represented by a tree cluster analysis (*right*). Alterations in chromosomal number result in differences in gene function that can be identified using a GeneChip strategy. *Identified in metastatic tissues. (Adapted from Tonnies et al[5] and Kytola et al[6]).

pressor gene product.[28] In a significant minority of patients, "carcinoid" of the duodenum (SSTomas) located in the region of the ampulla of Vater occur.[29–31]

A number of growth factors have been linked to NETs. These include the transforming growth factor (TGF) and platelet-derived growth factor (PDGF) family of peptides and receptors. These are discussed more fully in the fibrosis section.

Carcinoid Disease Models

A number of animal models exist to study carcinoid disease, including Mastomys, the cotton rat, transgenic mice models and knockout mice, and the Mongolian gerbil. In addition, the BON cell line, a pancreatic variant, has been evaluated, although it is probably a model of pancreatic endocrine tumor (PET) not GI carcinoid. Despite numerous attempts, there are no stable in vitro human gut carcinoid cell lines. The best-defined model of GI carcinoid disease is Mastomys (*Praomys natalensis*), a rodent related to the mouse that develops spontaneous gastric carcinoids whose development can be accelerated by pharmacologic acid suppression and the development of hypergastrinemia.[32] The development of tumors in this model is likely related to a gastrin receptor mutant that shows ligand-independent activity and is therefore constitutively activated.[33] The mechanism, as in humans, involves the Menin gene, and gastrin-mediated tumor induction in this model is via decrease in the negative regulators (JunD and Menin) of the AP-1 activator protein-1 (AP-1) complex, which regulates cell cycle progression via cyclin D1 expression.[34] A second, more recently defined model is the cotton rat (*Sigmodon hispidus*), which spontaneously develops a phenotypic admixture of neuroendocrine (enterochromaffin-like [ECL] cell) and gastric adenocarcinoma.[35] As in Mastomys, ECL cell-derived tumors can be rapidly generated by pharmacologic acid suppression,[36] but, unlike Mastomys, this model develops aggressive gastric adenocarcinomas rather than carcinoids.

Clinical Manifestations

Carcinoid lesions are the most common endocrine tumors and compose approximately 50% of all NETs of the GI tract.[37] In most instances, they are discovered incidentally at the time of surgery for other abdominal disorders, and their presence may be undetectable for years without obvious signs or symptoms. Evidence for this observation is supported by their relatively high incidence in large autopsy series.[38] When symptoms do occur, they are due either to local tumor mass effects, the effects of tumor-engendered fibrosis, or to the secreted bioactive products from the neoplasm. Symptoms caused by local tumor effects include vague abdominal pain (invasion, intussusception, fibrous adhesions, hypermotility), which is often undiagnosed or leads to erroneous diagnoses (Table 1). Carcinoids have protean clinical presentations, depending on what combination of bioactive substances (eg, serotonin [urinary 5-hydroxytryptamine], histamine, tachykinins, and prostaglandins among others) is secreted. The classical carcinoid syndrome occurs in fewer than 10% of patients, and its most typical clinical manifestations include cutaneous flushing and gut hypermotility with diarrhea, occurring in up to 75%.[38] Cutaneous flushing, most commonly of the face, neck, and upper chest, are hallmark features of the carcinoid syndrome and may persist for 10 to 30 minutes. It tends to resolve centrally first, producing gyrate and serpiginous patterns.[39] A rare cutaneous manifestation is a fibrotic scleroderma-like manifestation first noted in 1958 by Zarafonetis et al[40] with ileal carcinoid tumor

Table 1. Frequency of Symptoms in Gastrointestinal Carcinoids by Organ Site

	Stomach	Small bowel	Appendix	Colon	Rectum
Carcinoid syndrome	1+	2+	1+	1+	1+
Weight loss	1+	1+	1+	3+	2+
Vomiting	2+	1+	1+	1+	1+
UGI bleeding	1+	2+	1+	1+	1+
Rectal bleeding	1+	1+	1+	2+	2+
Obstruction	1+	3+	1+	1+	1+
Constipation	1+	1+	1+	1+	1+
Palpable mass	1+	2+	1+	2+	1+
Pain/discomfort	2+	2+	2+	3+	2+
Asymptomatic	2+	2+	3+	1+	2+

NOTE. Data from references.[87,175,195,210,216,221,230,239,244,251]
1+, rare (<10%); 2+, modest (11–50%); 3+, frequent (>50%).

and subsequently confirmed as carcinoid-related scleroderma, mostly affecting the lower extremities associated with ileal lesions.[41] Less frequent manifestations include cardiac valvular abnormalities, bronchospasm, myopathy, arthropathy, edema, and increased skin pigmentation.

Overall symptom interpretation is difficult because the symptoms can be both of variable intensity as well as paroxysmal, responding intermittently to a particular "trigger" agent, such as alcohol, cheese, coffee (these are serotonin-rich foods), or exercise. Many carcinoid tumors exhibit a significant association with other noncarcinoid tumors of various histologic types, and it is likely that this reflects the activity of a growth factor agent, which promotes phenotypic changes in susceptible cells and induces neoplastic transformation.[32] This is consistent with the role of NE cells in cell proliferation and differentiation in addition to the regulation of gut secretion, absorption, and motility. A relatively large percentage of carcinoids are multicentric, supporting the thesis that a common growth factor stimulus may influence similar progenitor cells in different locations.[32]

Fibrosis

Because of their inconspicuous size and submucosal location, primary carcinoid tumors are rarely diagnosed before metastasis. Tumors thus manifest clinically either with "carcinoid symptoms," or as the result of peritumoral fibrosis that leads to intestinal obstruction by adhesions of intestinal loops or luminal stricture.[42] Because carcinoid survival has increased because of the availability of supportive medication (SSTR2 targeted)[43] and an increasing variety of therapeutic interventions, it is evident that the clinical manifestations of fibrosis are emerging as a major issue in the morbidity and mortality of the disease. Fibrosis around mesenteric metastases causes fixation of the ileal mesentery to the retroperitoneum, with fibrous bands obstructing the small intestine and transverse colon.[44] Carcinoid-associated retroperitoneal fibrosis may lead to hydronephrosis and renal failure secondary to stenosis of the ureters.[45] Among patients who present with renal failure secondary to retroperitoneal fibrosis associated with midgut carcinoid tumors, all complain of flank pain at presentation.[46] Vascular occlusion may occur when mesenteric vessels become trapped in dense deposits of peritumoral fibrous tissue, and this may culminate in bowel (particularly small bowel) ischemia.[44]

Patients with mesenteric fibrosis often present with symptoms suggestive of intestinal obstruction, including feeding-related or crampy abdominal pain, cessation of diarrhea, a palpable abdominal mass, or weight loss.[47] Overall abdominal pain is the most commonly observed initial symptom, often described as episodic, colicky pain associated with distension and characteristic of intermittent intestinal obstruction.[48] Approximately 50% of patients with metastatic carcinoid initially present with and require surgery for intestinal obstruction or acute abdominal pain, often with an unknown diagnosis.[47] The incidence of intestinal obstruction secondary to mesenteric fibrosis associated with midgut carcinoid disease ranges from 42% to 66%.[47,49–52] In one surgical series, approximately 80% of patients with midgut carcinoid tumors who developed abdominal pain requiring laparotomy demonstrated marked mesenteric fibrosis at surgery.[52]

Approximately 5% of midgut carcinoid patients exhibit peritoneal miliary seeding, reflecting the facility with which these tumors can seed and grow locally. These individuals often develop a frozen abdomen and particularly pelvis, despite the absence of bulky liver metastases and present with small intestine (SI) obstruction.[52] Thus, although the "indolent" nature of the neoplasm accords an optimistic prognosis, the associated fibrosis may engender dramatic complications requiring emergency surgical intervention with significant morbidity and mortality.

Carcinoid cardiac disease. Fibrosis associated with carcinoid tumors is not limited to the peritoneum, and carcinoid cardiac disease (CCD) is a dangerous complication that occurs in two thirds of patients with the carcinoid syndrome and is responsible for one third of deaths in patients with carcinoid syndrome.[53] Cardiac lesions are characterized by plaque-like, fibrous endocardial thickening that principally involves the right side of the heart, causing retraction and fixation of the leaflets of the tricuspid and pulmonary valves as well as diminished right ventricular function. Tricuspid regurgitation is a

nearly universal finding; but tricuspid stenosis, pulmonary regurgitation, and pulmonary stenosis may also occur.[54] Left-sided heart disease occurs in less than 10% of patients.[55–57]

Pulmonary fibrosis. Pulmonary carcinoids compose approximately 2% of primary lung tumors,[58] and, of all carcinoid tumors, 25% are found in the lungs.[14] Pulmonary fibrosis has been reported in association with GI carcinoid tumors, commonly in the setting of advanced metastatic disease.[59] Furthermore, in one series of patients with carcinoid syndrome, 18% had "idiopathic" pleural thickening, although no underlying cause for pleural abnormality could be identified.[59] Individuals with bronchial carcinoid tumors can develop left-sided valvular lesions because the tumors secrete bioactive agents into pulmonary venous effluent, bypassing the liver and lungs, in which amines and peptides are usually metabolized.[60]

Pathogenesis of carcinoid-related fibrosis. Although the relationship between small intestinal carcinoid tumors and fibrosis has been well documented in the literature,[49,51,61,62] the mechanism of this relationship remains poorly understood. Currently, no techniques exist to determine the fibrotic potential of small intestinal EC cells, and there is no means by which the complication can be predicted or monitored.[44] The etiology is commonly attributed to the local and systemic effects of serotonin, which SI carcinoid tumors secrete in abundance.[49] The theory is controversial because antiserotonin agents do little to ameliorate both local and distant (eg, cardiac) fibrosis,[63] and serotonin alone does not promote fibroblast proliferation in culture.[64] In addition, serotonin antagonists used in migraine treatments (eg, cyproheptadine and pizotifen) that interact with the same receptor are not associated with fibroblastic responses,[65] and there has been no consistent relationship documented between carcinoid-induced mesenteric fibrosis and elevated blood or tumor levels of serotonin or bradykinin.[66]

More evidence, however, exists for serotonin as an etiologic agent in the development of carcinoid heart disease. Historically, the etiology of these lesions has been considered to be due to excess serotonin that was no longer degraded by monoamine oxidase in the lungs.[49] Several studies have demonstrated that, among patients with carcinoid tumors, those with cardiac involvement have higher levels of 5-HIAA, the serotonin metabolite, than do patients without cardiac involvement.[55,67] Heart valve disease associated with increased levels of serotonin has been observed in carcinoid tumors,[57,68] although treatment resulting in significant reductions of urinary levels of 5-HIAA is not associated with regression of the cardiac manifestations of carcinoid syndrome.[53] Whatever the mechanism, the finding that a serotonin antagonist (methysergide) causes fibrosis supports the contention that other factors are important in this process, and the relationship between serotonin and fibrosis may represent a correlatable epiphenomenon.

In the last 2 decades, focus has shifted from serotonin to the mitogenic properties of growth factors as the etiologic agents of carcinoid-related fibrosis. This heterogeneous group of polypeptides has been recognized to play an increasingly significant role in development, wound healing, and carcinogenesis. They act locally and stimulate cell proliferation and differentiation by binding to specific high-affinity cell membrane receptors.[69] In particular, member of the TGF-β family are known to stimulate the growth of fibroblasts in cell cultures, and the presence of all subtypes of TGF-β in the fibroblasts of endocardial plaques in patients with midgut carcinoids has been described.[69] The TGF-β family stimulates fibroblasts to produce extracellular matrix and has been implicated in the proliferation of fibroblasts and matrix production in carcinoid heart lesions.[69]

Connective tissue growth factor (CTGF) is a novel cysteine-rich peptide involved in the coordination of complex biologic processes such as differentiation and tissue repair[70] and functions as a downstream mediator of TGF-β1 action in fibroblastic cells and is a mediator of some of the profibrotic activities of TGF-β. Thus TGF-β1 leads to the induction of CTGF, which acts in concert with TGF-β1 to drive the overproduction of collagen, a critical determinant in fibrosis.[71] The relationship of CTGF with TGF-β1 suggests that it is a cosecreted fibrotic factor, and, because the relationship of CTGF to fibrosis is well-defined, it may be intrinsically involved in the genesis of ileal carcinoid related fibrosis. Ileal carcinoid tumors overexpress and secrete CTGF in levels detectable in the serum of patients with ileal carcinoids and which correlate with fibrosis on a carcinoid tissue microarray.[72] Because serum CTGF can be measured, the detection of elevated levels may ultimately provide a diagnostic opportunity to predict fibrosis and preempt its local and systemic complications.

PDGF also plays a role in connective tissue cell proliferation during chronic inflammation, and the PDGF-β receptor, not normally expressed in normal tissues, is induced on connective tissue cells in chronic inflammatory conditions.[73] Carcinoid tumor fibroblasts express multiple PDGF receptors, suggesting that they respond to any of the 3 dimeric forms of PDGF, and the surrounding stromal component of these tumors synthesizes PDGF-α and -β chains stimulating the growth of carcinoid tumor cells in a paracrine manner. Furthermore,

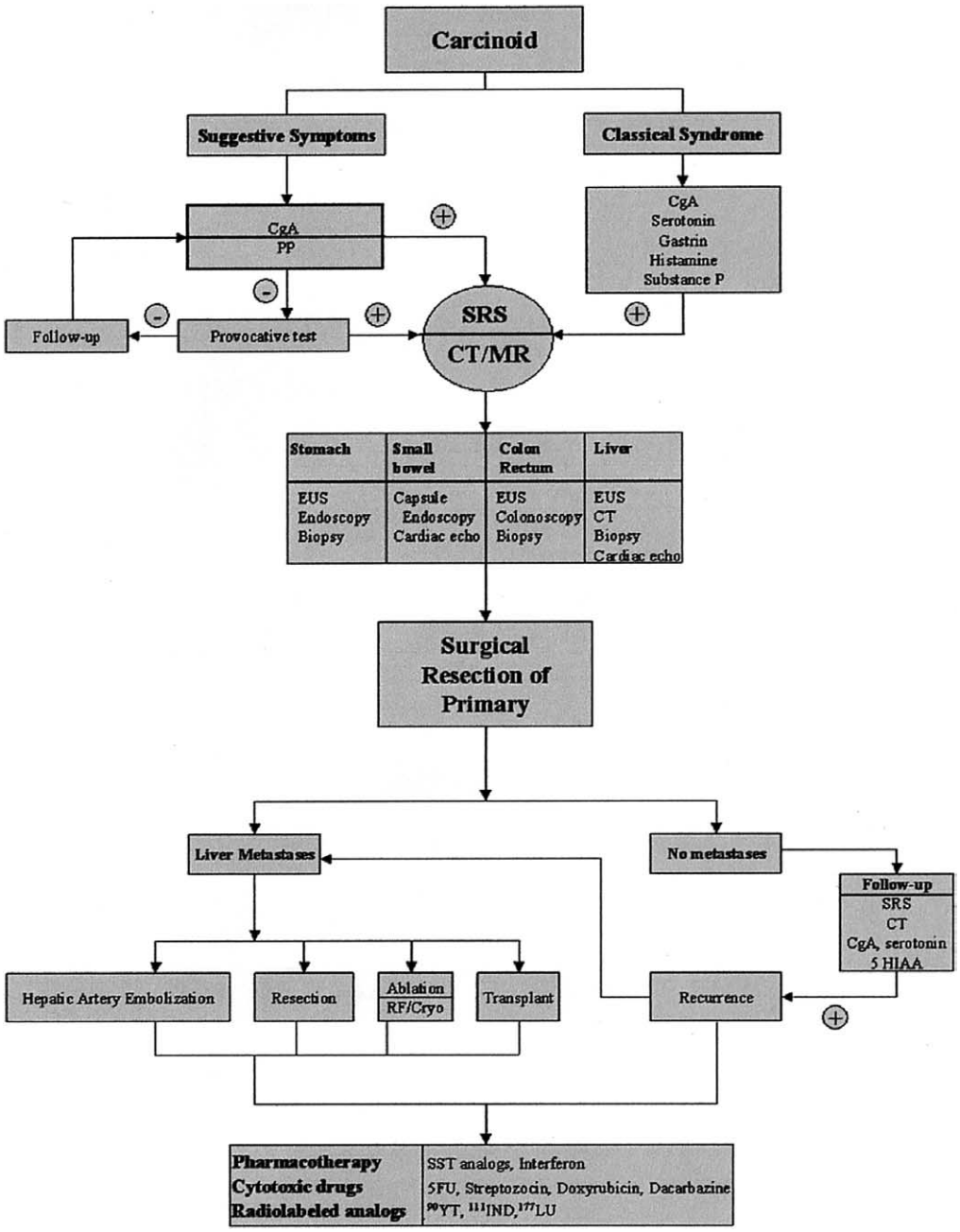

Figure 5. Diagnostic and management algorithm for gastrointestinal carcinoid tumors.

carcinoid tumor cells may directly or indirectly induce expression of the PDGF-β receptor on adjacent stromal cells in the tumor tissue. This may contribute to the stimulation of connective tissue cell proliferation in carcinoid tumors.[73]

Diagnosis

Strategy

A clinical constellation of symptoms should lead to confirmation of the diagnosis of carcinoid using biochemical tests (Figure 5). Thereafter, topographic localization of the primary lesion and metastases should be undertaken with a view to determination of therapeutic strategy. Care should be taken to consider issues special to carcinoids, namely: multicentricity, associated neoplasms (colon, lymphoma, breast), peritoneal and cardiac manifestations of fibrosis, and the association with MEN or a familial history.[74]

Because carcinoid tumors frequently present with obscure clinical manifestations, numerous investigatory procedures are often undertaken prior to establishing the correct diagnosis. Although clinical diagnosis is based on symptoms,[75] biochemical confirmation is necessary. The diagnostic strategies employed usually depend on the individual clinical presentation. If a "putative" classical

symptom complex can be identified, the relevant specific peptides and amines should be measured; however, the overall best "screening" plasma evaluation, irrespective of the primary site of the lesion is the measurement of CgA.[76] Gastric carcinoids exhibit elevated plasma histamine levels, whereas small intestinal lesions may variously exhibit increased levels of plasma substance P, serotonin, or increased urinary 5-HIAA. If biochemical results are equivocal, the tests should be repeated and plasma CgA measured because it is the most sensitive and reliable screening test.[77] The measurement of 24-hour urinary 5-HIAA is useful because it provides a summation of tumor secretory activity that may occasionally be missed by random plasma peptide sampling if secretion is paroxysmal.[78] It is, however, time-consuming and cumbersome, and numerous ingested drugs and agents may obfuscate the measurement. If CgA, urinary 5-HIAA, and plasma amines (substance P and serotonin) levels are equivocal, the use of a provocative study such as a pentagastrin test (injection) or alcohol ingestion may warrant careful consideration.[78] The risk of engendering a paroxysmal event, "carcinoid crisis," is not inconsequential, and provocation should not be undertaken except in a monitored area and with intravenous SST available. If the provocative study is positive or one of the peptides/amines is initially elevated, the precise localization of the primary lesion and its metastases should be undertaken, utilizing SSTR scintigraphy (Octreoscan, Mallinckrodt, MO). ^{111}In-labelled octreotide (6 mCi administered intravenously) can identify NETs expressing SSTRs, particularly of the subtypes 2 and 5 for which octreotide has a particularly high affinity.[79] The sensitivity of the study can be enhanced by the simultaneous use of single positron emission computed tomography (SPECT) imaging. Additional studies such as ultrasonography, triple-phase helical computerized tomography,[80] magnetic resonance imaging, and selective mesenteric angiography may identify an additional 10% to 15% of primaries but are probably only justified if surgery is contemplated and more precise topographic delineation considered necessary to define resection. Angiographic changes are distinctive, with narrowing or occlusion of the distal ileal arcade and stenosis of the intramesenteric arteries being a characteristic finding.[81] Patients with equivocal biochemistry, negative nonspecific markers, and negative Octreoscan should probably not be further investigated but instead followed up annually.[78]

Biochemical Markers

Urinary 5-HIAA. Urinary 5-HIAA (24-hour collection) is a useful laboratory marker that is widely available. The test is, however, cumbersome and time consuming and the specificity approximately 88%.[82] Certain serotonin-rich foods (bananas, avocados, plums, eggplant, tomatoes, plantain, pineapples, and walnuts) can increase urinary 5-HIAA levels and should be avoided during specimen collection.[83]

Chromogranin A. CgA is a member of the chromogranin family, which consists of at least 3 different water-soluble acidic glycoproteins (CgA, CgB, and CgC) stored in the secretory granules of NE cells. CgA is processed by proteases in the secretory granules,[84] and the type and amount of cleavage products such as pancreastatin, which are released with CgA and other peptides into the circulation, may differ in different NE tissues.[85] CgA exhibits the widest distribution and is a precursor for several peptides with a wide range of biologic activities. These include pancreastatin and vasostatin I and II, which inhibit vasoconstriction, (bovine) parathyroid hormone secretion, as well as stimulating cell adhesion via interaction with integrins.[86] Because CgA is a constitutive secretory product of most NETs, its detection in plasma can be utilized as a general tumor marker for carcinoids and even for "non-functioning" tumors. In carcinoid tumors, the highest concentrations of CgA were noted in metastatic midgut lesions with CgA elevation in 87% of lesions, whereas 5-HIAA increases was noted in 76%. CgA concentration correlated with tumor burden.[87] This relationship is attested by a postresection study in which the presence of ileal lymph node metastases was associated with CgA elevation in all 25 patients, whereas only 3 had elevated 5-HIAA.[88] CgA may be regarded as an early marker of carcinoids of the fore- and hindgut[77,89] and appears to be a better marker than 5-HIAA or platelet serotonin.[88]

Plasma CgA levels are sensitive but nonspecific markers of carcinoid tumors because they are also elevated in pancreatic NE tumors, as well as in other types of NE tumors.[90] Elevated CgA concentrations are not always specific for a NET because prostatic carcinoma can be associated with elevated CgA concentrations. However, current assessment of prostatic tumors suggests that some lesions may have a substantial NE component.[91] False-positive increased CgA concentrations can be seen in renal impairment, liver failure, atrophic gastritis, and inflammatory bowel disease.[92] Exercise, trauma-induced physical stress, or untreated hypertension can also produce higher concentrations of CgA than in the normal, resting state.[87]

In a study of 44 patients, specific radio-immunoassays identified elevated plasma CgA levels in 100% of patients, elevated CgB levels in 86% of patients, and elevated CgC levels in only 5%.[89] There appears to be no

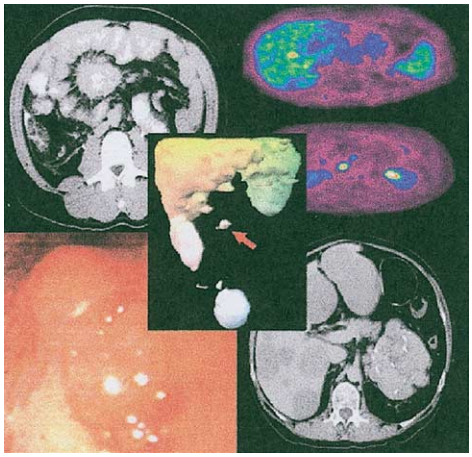

Figure 6. Diagnostic modalities. CT of a carcinoid tumor with central calcification and the characteristic desmoplastic response with spiculation of the adjacent mesentery (*top left*). ^{11}C-5-HTP positron emission tomography (*top right*). *Top image* is a hepatic metastasis, and *bottom image* an axial projection of mesenteric lymph nodes in a midgut carcinoid (*below*). CT of carcinoid hepatic metastases (*bottom right*), and a gastroscopic view of 2 carcinoid polyps in a pernicious anemia patient (*bottom left*). In the *center,* an Octreoscan demonstrating a peritoneal metastasis (*red arrow*) in a patient with fibrotic, disseminated small intestinal carcinoid disease.

correlation of chromogranin levels with survival, but definitive studies are lacking.

Other markers. Numerous other biochemical markers, including bradykinin, substance P, neurotensin, human chorionic gonadotropin (hCG), neuropeptide K, and neuropeptide PP have been described, but none have the specificity or predictive value of CgA or 5-HIAA, and their measurement is complex compared with the latter.[93]

Topographic Localization

In the past, barium studies and enteroclysis were widely used, but these have been supplanted by flexible endoscopy. Thus, upper GI endoscopy can identify lesions as far as the ligament of Treitz and lower and can detect some terminal ileal tumors as well as colon and rectal carcinoids. Luminal examination has been augmented by CAT scan and MRI. In the last decade, isotopic imaging has become the most widely used technique and is particularly useful in the identification of metastatic disease. Positron emission tomography scanning, although theoretically attractive, has as yet limited clinical applicability (Figure 6).

Octreoscan. ^{111}In-labeled SST analogue (DTPA-d-Phe10-[octreotide]) was developed for scintigraphy because it shares the receptor-binding profile of octreotide, rendering it an ideal radiopharmaceutic for imaging of SSTRs 2- and 5-positive tumors.[94] The overall sensitivity of Octreoscan is approximately 80% to 90%,[94] and it is effective in detecting primary and metastatic lesions not apparent by conventional radiologic-imaging techniques.[95–113] Octreoscan should be used as the initial imaging method in patients with carcinoid tumors (Table 2).

Of particular advantage is the fact that one scan images the entire body; thus covert metastases may be identified.[78] Intraoperative γ detection has been considered as theoretically superior to external SSTR scintig-

Table 2. Diagnostic Utility of ^{111}Indium-Octreotide in GI Carcinoid Patients

Investigator	Year	Number of patients	Detection rate (%)	Sensitivity (%)
Modlin et al[95]	2005	232	80	—
Belchocine et al[96]	2002	13	75	—
Lebtahi et al[97]	2002	16	91	—
Zuetenhorst et al[98]	2002	7	100	—
Banjegard et al[99]	2001	11	91	—
Hoegerle et al[100]	2001	17	—	57
Le Rest et al[101]	2001	11	91	—
Kaltsas et al[102]	2001	24	67	—
Virgolini et al[103]	2001	39	87	—
Gibril et al[104]	2000	16	75	75
Raderer et al[105]	2000	173	91	93
Shi et al[106]	1998	25	92	—
Frilling et al[107]	1998	24	100	—
Nocaudie-Calzada et al[108]	1996	31	—	85
Taal et al[109]	1996	20	82	84
Ahlman et al[110]	1994	27	70	84
Wiedemann et al[111]	1994	74	81	—
Pauwels et al[112]	1994	14	93	—
Hoefnagel[113]	1994[a]	451	—	86
Median (range)		24 (7–451)	89 (67–100)	84 (57–93)

NOTE. Pooled data from 35 centers that include over 1200 patients and span 2 decades reflect a median detection rate of 89% with sensitivities between 57% and 93%.

[a]Review summating 17 studies between 1992 and 1993.

raphy in the detection of small endocrine lesions, but high-background uptake (kidneys, liver, spleen) and inadequate collimators have considerably limited its general utility, and it remains a method under investigation.[114]

Bone scintigraphy with ^{99m}TcMDP is the mainstay for identifying bone metastases associated with NE tumors, with reported detection rates above 90%. Two studies that utilized ^{111}Indium-labeled octreotide demonstrated similar diagnostic rates, ranging between 60% and 100%.

CAT Scan and MRI. The radiographic findings associated with carcinoid tumors are defined by mass lesions and evidence of calcification and fibrosis. Radiating strands of fibrosis and spiculation are characteristic hallmarks, especially in conjunction with a mass lesion.[115] The degree of radiating strands detected by CT tends to increase with the degree of fibrosis seen histopathologically,[42] and mesenteric fibrosis may lead to traction or fixation of the bowel.[115] Mesenteric lymph node metastases are evident on CT scans in 91%.[52] MRI and CT provide important means of initial localization of carcinoid tumors or their metastases; however, their detection rates and sensitivities are lower than the more established approaches of hormone-based imaging with ^{111}Indium-labeled radio ligands. Median detection rate and sensitivity of CT and/or MRI are about 80%, in contrast to 89% detection rate and 84% sensitivity with ^{111}Indium-octreotide scanning.[78] The few trials that examine diagnostic efficacy of either CT or MR did not find substantial differences between the 2.[78] The reported detection rates of CT alone range between 76% and 100%, whereas MRI alone reported rates are between 67% and 81%.[78]

Positron emission tomography. This relatively novel, noninvasive radiologic technique facilitates biochemical and metabolic studies of human tumors. It is of as yet unproven clinical advantage in the detection of carcinoid tumors but may be of use in the quantification of the effects of medical treatment on metastatic disease.[116] Because neoplastic cells are characterized by a higher glycolytic rate than normal cells, the use of [^{18}F] fluoro-2-deoxy-Dglucose (FDG) was initially used in biochemical imaging for the diagnosis and staging of cancer.[117] There has been limited experience with positron emission tomography FDG and NE tumors,[118] and studies have produced both false-positive and false-negative results.[118] ^{18}F-labelled deoxyglucose was the first tracer used in positron emission tomography imaging of NETs. However, because NETs are mostly well differentiated and slow growing, they have a low metabolic rate and cannot be visualized efficiently with this tracer, as evidenced by detection rates ranging between 25% and 73%. Because carcinoid tumors characteristically synthesize serotonin, the administration of radioactive serotonin precursor ^{11}C-5 HT has been shown to provide excellent tumor visualization, with detection rates at 100%. More recently, ^{68}Ga and ^{64}Cu coupled to octreotide have been used as tracers for positron emission tomography imaging, achieving detection rates of 100%. However, these studies are limited by their small patient populations (a total of 11 carcinoids). Eriksson et al reported that ^{11}C-labeled 5-HT was particularly effective in patients with NETs and demonstrated excellent tumor visualization with detection rates of 100%.[119] Furthermore, positron emission tomography 5-HT was superior to CT images in 10 of 17 patients. A study of 5 patients with carcinoid tumors, comparing positron emission tomography FDG with Octreoscan, found that Octreoscan was positive in 3 patients, and positron emission tomography FDG was positive in 2 patients[120]; both identified tumors with high and moderate proliferative activity.[121] The sensitivity and specificity of positron emission tomography are not greatly superior to those of CT and MRI, and positron emission tomography is not superior to Octreoscan.[78] Positron emission tomography should be considered an investigational method for carcinoid imaging.

Radiolabeled metaidobenzylguanidine. Scanning with radiolabeled metaidobenzylguanidine (MIBG) (^{123}I-MIBG) alone or with CT have been studied[94,122] because MIBG is concentrated by carcinoid tumors. The overall sensitivity ranges from 55% to 70%, with a specificity of 95%. Although ^{123}I-MIBG may be more effective in visualizing metastases rather than primary tumors,[122] Octreoscan is more sensitive than ^{123}I-MIBG scintigraphy,[94] and the cumulative results of a dozen studies including more than 360 patients reflect a median detection rate of 50%, substantially lower than the 81% detection rate of ^{111}Indium octreotide scintigraphy. The sensitivities of the 2 techniques are similar at approximately 80%. MIBG imaging may, however, have a role in patients on long-acting octreotide in whom imaging may be compromised by analogue occupancy of tumor SST receptors.

Technetium-labeled isotopes. A number of investigational techniques using technetium-labeled isotopes have been tested, albeit on relatively small patient populations, with detection rates ranging between 50% and 100%. The combined SPECT/CT device that allows hybrid imaging using both SRS and low-dose CT has a reported 100% diagnostic sensitivity, in contrast to median sensitivities of 84% and 80% for either SRS or CT alone.[78] Three other protocols demonstrated sensitivities greater than 90%. Combination imaging with CT/MRI

and ^{18}F Dopa positron emission tomography, ^{131}MIBG and ^{111}In-octreotide, and SPECT imaging with ^{111}In-octreotide achieved sensitivities of 99%, 95%, and 90%, respectively.

Endoscopic ultrasound. Endoscopic ultrasound is a highly sensitive method for detecting carcinoid tumors of the stomach and duodenum[123] and is superior to conventional ultrasound, particularly in the detection of small lesions localized to the bowel wall because it can detect luminal lesions as small as 2 to 3 mm in size.[124]

Enteroscopy. Enteroscopy is an uncomfortable and time-consuming procedure that has been of some utility in identifying carcinoid lesions of the jejunum and ileum, particularly when an occult source of bleeding is investigated.[125] Despite the fact that it is not widely available and has a low diagnostic sensitivity between 21% and 52%, it has been useful in identifying carcinoid.[125] It is likely that its limited role will be superseded by capsule endoscopy.

Capsule endoscopy. This technique has obvious potential for surveillance of the SI for carcinoid tumors, and its utility in this respect has been noted.[126] A preliminary report comparing capsule endoscopy against conventional bowel-imaging techniques (CT and barium studies) demonstrated 2 SI carcinoids that were only visible using capsule endoscopy.[127]

Organ-Specific Carcinoids

Small Intestine

The SI (ileum) is the most common location for carcinoid tumors, composing 28% of all carcinoids (Figure 1), and is the most frequent neoplasm in the small intestine.[14,128] The actual incidence of small intestinal carcinoids is probably higher, given the relatively large number of asymptomatic lesions detected only at autopsy. Thus, in an autopsy series reported by Berge and Linell, carcinoids composed 95% of all small intestinal primary tumors, of which 88% were incidental findings.[38] The lesions occur 6.5–8.2 times more frequently in the ileum than in the duodenum and jejunum,[14,129] and their relative frequency increases aborally. In contradistinction, adenocarcinomas occur mostly in the duodenum and decrease distally.[128] The male-to-female (M/F) ratio shows a slight predominance for women (between 1.1 and 1.6), and the average age at diagnosis is 64.2 years.[14,130]

Duodenum and upper jejunum. Most lesions are discovered serendipitously at endoscopy for dyspepsia or during the investigation of an upper GI bleed. Pathologically, 5 types of duodenal NETs (carcinoids) can currently be distinguished: (1) duodenal gastrinomas ($\pm$65% of duodenal NETS); (2) somatostatinomas (SSTomas) (15%); (3) nonfunctioning (serotonin-, gastrin-, or calcitonin-producing tumors); (4) poorly differentiated, predominantly ampullary NE carcinomas; and (5) duodenal gangliocytic paragangliomas.[131] Burke et al,[132] in characterizing the histologic and immunohistochemical features of 65 duodenal carcinoids, reported that the majority (85%) exhibited a mixture of cribriform, insular, glandular, solid, and trabecular growth pattern. Over 80% had positive staining for CgA, Leu-7, and NSE, whereas 47% of the carcinoids were positive for SST, 56% for gastrin, 39% for serotonin, 19% for calcitonin, and 5% or less for insulin and PP. Xenin has been reported to be a marker of duodenal NETs because it is exclusively expressed in these tumors, regardless of their functional activity and hormone content.[133] An important feature of duodenal carcinoids is their association with von Recklinghausen's disease, ZE syndrome, and MEN.[134]

Duodenal gastrinomas are either sporadic or associated with MEN-1 and cause the ZE syndrome.[135] Such gastrinomas are located predominantly in part I or II of the duodenum, exhibit a trabecular/pseudoglandular pattern, are gastrin positive, and are usually $<$1 cm, although the MEN-1-associated lesions are usually multiple. Despite their small size and the fact that they are limited to the duodenal mucosa and submucosa at diagnosis, metastases are often evident in regional lymph nodes. Such metastases may be larger than the primary lesion and have erroneously been considered pancreatic endocrine tumors, especially if in close proximity to the pancreas.[22] This misconception previously resulted in the quixotic diagnosis of "primary lymph node gastrinomas" and the over-diagnosis of pancreatic gastrinomas. Inexplicably, metastasis to the regional lymph nodes occurs at an early stage, whereas liver metastases appear to be a relatively late occurrence. Pancreatic gastrinomas are usually sporadic (not associated with MEN-1) and liver metastases usually occur earlier than in duodenal gastrinomas.[22,23]

Duodenal SSTomas preferentially occur in the region of the papilla of Vater or periampullary area and, if the *muscularis propria* is invaded, it is likely that paraduodenal lymph node metastasis is present. Histologically, the tumors exhibit a glandular pattern with psammoma bodies and, immunocytochemically, SST is present. The SST syndrome (diabetes, cholelithiasis, and diarrhea) is rare compared with pancreatic SSTomas. Duodenal SSTomas are often associated with NF-1 and bilateral pheochromocytoma.

Nonfunctioning duodenal NETs usually consist of serotonin-producing cells but may occasionally exhibit gastrin- or calcitonin-positive cells. Their prognosis is

much more favorable than ZE syndrome-associated gastrinomas or ampullary SSTomas, with metastases only evident once the tumor has extended beyond the submucosa.

Poorly differentiated duodenal carcinomas occur primarily in the region of the papilla of Vater, are usually hormonally inactive, and exhibit advanced metastasis into the regional lymph node and the liver. Usually, they are undifferentiated, often small cell carcinomas with strong synaptophysin positivity and slight or no CgA positivity.

Duodenal gangliocytic paragangliomas occur in the peri ampullary area, and, although often >2 cm with invasion of the *muscularis propria*, they generally exhibit a benign course. Lesions are characterized by a gangliocytic component and well-differentiated NE cells and express SST, PP, and S-100.

Negative prognostic features associated with metastases in duodenal NETs include tumor size greater than 2 cm, involvement of the *muscularis propria,* and the presence of mitotic figures.[136] Small duodenal lesions may be resected endoscopically with a good outcome, although bleeding is a hazard.[137] Local resection is technically difficult if the ampulla is in proximity to the lesion, and pancreatico-duodenectomy may be advisable to ensure complete resection of the lesion or if local spread or lymph node disease is evident.[138] No rigorous studies are available to provide definitive assessment of the various technical strategies for resection.

Ileum and distal jejunum. The clinical presentation of jejuno-ileal carcinoids differs from those occurring in other sites of the gut in that they are usually at an advanced stage at the time of presentation. In many instances, they are only detected at surgery for unexplained bowel obstruction, perforation, or bleeding (Table 1). Previously, they were often identified at exploration of the SI in search of a primary tumor once distant metastases had been detected, but this circumstance is diminishing with greater awareness of the disease. "Carcinoid syndrome" is reported to occur in up to 18% of patients with jejuno-ileal carcinoids[44] but is rarely evident in carcinoids of the duodenum. In general, the carcinoid syndrome is clinically only apparent once hepatic metastases are present, although direct extension into the retroperitoneum and its systemic venous drainage or ovarian lesions may also be responsible. In some tumors, extensive liver metastases without a carcinoid syndrome may occur, reflecting the "non-secretory" nature of certain lesions. SI carcinoids are nonlocalized in 64.1% of patients, the second highest percentage after the colon of carcinoids of the GI tract (Table 3).[14] An association with other noncarcinoid neoplasms is evident in 29% of patients and constitutes the largest percentage among all GI carcinoids. This observation supports the hypothesis that the cell type responsible for SI carcinoids has the highest propensity for the production of growth factors.[48]

Table 3. The Distribution of GI Carcinoid Lesions and Overall 5-Year Survival rates

Gastrointestinal distribution		Overall 5-year survival (%)
Stomach	Type I/I	81
	Type III/IV	33
Duodenum		60
Jejunum		60
Ileum		60
Appendix	Benign	98
	Malignant	27
Colon		62
Rectum		87

NOTE. Adapted from references 13 and 14.

On barium studies, carcinoid tumors of the SI can present as smooth, solitary, intraluminal defects[139] but may also exhibit cicatrisation, narrowing, and obstruction. Multiple nodularity or ulceration may be associated with bleeding. Additional studies (previously detailed), including enteroscopy, capsule endoscopy, ultrasonography, computerized tomography, magnetic resonance imaging, SSTR scintigraphy, and positron emission tomography, may provide useful information to determine multicentricity and metastatic spread.

Typical jejunal and ileal carcinoids display an insular growth pattern (type I), which consists of solid nests or cords of cells with clearly defined boundaries.[129,140] The trabecular pattern (type II) consists of narrow cell bands forming ribbons, regularly anastomosing along a highly differentiated vascular network. Type III has a glandular pattern, consisting of cells arranged in alveolar, acinar, or rosette patterns with glandular cavities or pseudocavities. Type IV and V carcinoids consist of undifferentiated and mixed cells, respectively. The frequency of multicentricity lies between 26% and 30%.[129,141] Endocrine cell hyperplasia and small proliferating endocrine cell aggregates within the mucosal crypts are often seen in association with the small intestinal carcinoids, suggesting that such lesions originate from an intraepithelially located endocrine cell and subsequently infiltrate through the basement membrane into the lamina propria.[140] Transmural invasion and extensive fibrosis are common features contributing to the aggressive local behavior of the neoplasm,[129] and local and distant metastases are common.[129] The tumor cells are characteristically argyrophil and argentaffin positive,[129,140] and over 85% of the tumors exhibit positive reactions for CgA, Leu-7, NSE, and serotonin.[129] The vast majority of small intes-

tinal carcinoids are "classical" ileal carcinoids with production of serotonin and substance P but rare tumors producing enteroglucagon, PP, or peptide YY occur. In addition, carcinoembryonic antigen (CEA) is present in approximately two thirds of ileal and jejunal carcinoids, prostatic acid phosphatase in approximately 20%, and S-100 protein in 7%. In most instances, surgery is required to provide definitive diagnosis and treatment.

In jejuno-ileal carcinoids, several factors are determinants of their relatively malignant nature, including lesion size, local spread, and extent of metastases at the time of diagnosis, mitotic rate, multiplicity, female sex, depth of invasion, and presence of carcinoid syndrome.[129] Although tumor size is currently accepted as the most predictive correlate of spread and prognosis, it is not always accurate as might be expected, given that it is unlikely that all SI carcinoids arise from the same NE cell type.[129] Metastatic spread to the regional lymph node is a prominent feature of small intestinal carcinoids; en bloc resection is advisable. Because multicentric lesions, liver metastases, and other noncarcinoid malignancies may occur, even in the presence of small primaries, surgery should involve diligent assessment of the abdomen. If liver metastases are present at diagnosis, the primary tumor should nevertheless be resected to avoid later complications, which may include obstruction, bleeding, and perforation. The prognosis of small intestinal carcinoids reflects the malignant nature of the tumor with "early" dissemination to both lymph nodes and liver. Jejuno-ileal carcinoids, in particular, have a poor 5-year survival rate (60.5%) compared with other GI carcinoids.[14] A possible explanation may be the fact that carcinoids of the rectum, the duodenum, and the stomach are detected at an earlier time point in their timeline by routine endoscopy. Conversely, the symptoms of jejuno-ileal carcinoids are either overlooked (irritable bowel, allergy, menopause) or are only evident when transmural invasion or metastases result in surgical intervention for perforation, bleeding, or obstruction. The 5-year survival rate of patients with hepatic tumor spread is 18%–32%.[14,142,143] An increased median survival (4.4 years) is evident in patients with jejuno-ileal carcinoids, which exhibit a mixed insular/glandular pattern.[144] In contrast, patients with an undifferentiated pattern have a median survival of only 6 months. In those lesions with a pure insular and trabecular pattern, an intermediate prognosis is evident, with a median survival time of 2.9 years and 2.5 years, respectively.

Meckel's diverticulum. Meckel's diverticulum, a vestigial remnant of the omphalo-mesenteric or vitelline duct is the most common developmental abnormality of the GI tract, popularly characterized by Thorek as a diverticulum occurring in 2% of the population, 2 feet from the ileo-cecal valve, 2 inches in length, twice as common in males than females, containing 2 ectopic tissues (gastric and pancreatic), and responsible for 2 typical complications (hemorrhage and inflammation).[145] It is a rare location for primary carcinoid tumors and, after sarcoma, is the second most common tumor arising from Meckel's diverticulum, with 174 reported cases. The tumors demonstrate a propensity for males (75%), with age ranging from 14 months to 82 years. Almost half of the patients are symptomatic, with abdominal pain, diarrhea, hematochezia, weight loss, nausea, and vomiting as the most common complaints. Such lesions are typically found incidentally, and patients remain asymptomatic; however, at the time of onset of symptoms, 77% of these tumors have already metastasized,[146] and at least 24% demonstrate metastases at the time of presentation.[146] It is likely that these lesions are analogous to type I gastric carcinoids in that they develop in a diverticulum in gastric mucosa containing ECL cells. This is similar to older persons with gastric atrophy and elevated gastric pH who develop gastric carcinoid tumors. Simple excision of the diverticulum and a mesenteric wedge provide a cure in most reports,[147] but, even in more advanced cases, aggressive surgical intervention is associated with an 83% 5-year survival rate.[148]

Appendix

In 1928, Masson identified the sub epithelial "Kultschitzky" cells as the origin of appendiceal carcinoid tumors and demonstrated that these cells exhibit both endocrine and neural characteristics.[149] A subsequent study by Shaw confirmed the neuroectodermal origin of appendiceal carcinoids and noted that subepithelial NE cells were more numerous toward the tip, consistent with the observation that 70%–80% of appendiceal carcinoids occur at the tip, 5%–20% in the body, and only 7%–8% at the base of the organ.[150] Carcinoid tumors of the appendix are usually small, clinically apparently benign lesions and are often discovered as an incidental finding during surgery performed for other reasons (usually appendicitis or gynecological procedures). The diagnosis is often made at laparotomy or laparoscopy, undertaken to evaluate nonspecific symptoms, although abdominal ultrasound may occasionally establish a preoperative diagnosis. A minority present with signs and symptoms of acute appendicitis, and the "carcinoid syndrome" or symptoms are exquisitely rare (Table 1). In such circumstances, widespread metastases predominantly to the liver or retroperitoneum are usually evident.[151] Patients are generally young, and it is noteworthy that those with larger tumors and metastases are

usually younger (29 years of age) than those with smaller and clinically "benign" lesions (42 years of age).[152] Associated noncarcinoid tumors are evident in 18.2% of lesions, the second highest percentage in the GI tract after SI carcinoids.[14]

Appendiceal epithelium is composed of colonic type mucin-secreting cells, diffuse neuroendocrine cells of the crypts, and Paneth cells. In addition, a population of subepithelial neuroendocrine cells located in the lamina propria has also been described. Epithelial tumors of the appendix are essentially composed of the same counterpart cell types with more or less differentiated proportions. Appendiceal adenocarcinomas possess an identical phenotype to that of colonic tumors, whereas the "conventional" carcinoid tumors of the appendix exhibit an exclusively neuroendocrine phenotype. The majority of these carcinoids are EC-cell tumors producing serotonin and substance P and exhibiting a typical insular pattern. The nonargentaffin L-cell tumors are much less common. Appendiceal tumors exhibiting both neuroendocrine differentiation and mucin production and/or glandular differentiation are rare and are regarded as "variants" of the "true" appendiceal carcinoid.[153] Such lesions have previously been variously designated as adenocarcinoid, goblet cell carcinomas (GBC), and mixed adenocarcinoma-carcinoid. It remains controversial whether GBCs should be considered adenocarcinomas or as part of the carcinoid tumor spectrum. They appear to arise from subepithelial lamina propria without association with intraepithelial neuroendocrine cell hyperplasia or dysplasia of the appendiceal crypt epithelium. Because both the clinical and the pathologic features of the goblet cell carcinoid are sufficiently distinctive, they are probably best recognized as a separate entity.

Although previously recognized as the most frequently occurring of carcinoid tumors, the relative frequency of appendiceal tumors appears to have decreased over time (4.7% of all carcinoid tumors and 7.4% of all GI carcinoids; Figure 1).[14] A possible explanation may be the decreased surgical commitment to incidental appendectomy in the past 2 decades.[154] In addition, the relative frequency of appendiceal carcinoids compared with all tumors of the appendix has decreased in the past 20 years, from 40% to 25.3%.[14] Identification of the lesion occurs in 5 or 6 per 1000 appendectomies,[155] but an exact incidence is unknown because many lesions remain asymptomatic. Berge and Linell identified appendiceal carcinoids in 0.04% of individuals in an autopsy series of 16,294 cases between 1958 and 1969.[38] The true number is assumed to be much higher because immunocytochemistry to detect NE tumors is a relatively recent development. Although a marked female predominance (over 80%) has been reported,[156] the female predominance of appendiceal carcinoids has decreased from 77% to 57% in the latest SEER data analysis.[14] Appendiceal carcinoids present in a younger patient population than other GI carcinoid tumors, with a median age of 49.3 years, probably reflecting the role of appendectomy in the identification of such lesions.[14]

Appendiceal carcinoids have the best prognosis among all types of carcinoids (Table 3), and this essentially benign course reflects the anatomic site, its early detection and removal, or the biology of the tumor itself. The most predictive determinants of survival are the factors that influence metastatic development. In this respect, the size of the primary tumor is clinically the most reliable determinant of the risk of metastases. Thus, appendiceal carcinoids <2 cm rarely metastasize ($<3\%$), whereas the risk of metastatic spread is considerably higher in lesions >2 cm (30%–60%).[152,157] Furthermore, the metastatic potential depends greatly on the depth of penetration and the site of origin.[158] Thus, mesoappendiceal invasion occurs more frequently in patients with distant and lymph node metastases and should be used as a determinant in indicating the need for right hemicolectomy.[159] However, some reports have suggested that the invasion of the mesoappendix is not a reliable predictor of metastatic potential.[157,160] Five-year survival rates for localized lesions, regional spread, and distant metastases are 80.8%, 88.1%, and 9.6%, respectively, with an overall survival rate of 71%.[14] These data do not, however, differentiate tumors into specific subtypes such as high- or low-grade goblet cell. In the future, it is likely that the definition of specific molecular signatures will enable prediction of behavior, irrespective of size.[161]

Rectum

Approximately 50% of the patients with rectal carcinoids are asymptomatic, and the diagnosis is made during routine proctoscopic, sigmoidoscopic, or colonoscopic examination (Table 1). Generally, they present as small, mobile, submucosal nodules or focal areas of submucosal thickening identified after a bleeding episode. Symptoms include discomfort in the anorectal area, constipation, bleeding, or change in bowel habit.[162] Rarely, rectal pain (late presentation) and *pruritus ani* may occur. Occasionally, a tumor mass may be detected during routine digital examination, but most lesions are small nodules, usually identified in the rectal vault on the anterior and lateral portion of the lower one third and best identified by endoscopy. Although metastatic spread is a common feature in colonic carcinoids (the second-highest percentage of nonlocalized lesions at the time of

diagnosis of all carcinoids), rectal carcinoids present with metastasis in only 4%–18% of cases.[14]

Rectal carcinoids comprise 12.6% of all carcinoid tumors, represent the third largest group of the gut carcinoids, and are associated with noncarcinoid tumors in 13.1% (Figure 1). There is no specific sex predominance, and the average age at diagnosis is markedly lower than for colonic carcinoids (48–52 years).[14] The age-adjusted incidence rates are 3- to 4-fold higher in the African-American than the American white population. Macroscopically, the lesions are usually nodular, polypoid, or sessile.[163] Overall, rectal tumors fall into 2 groups: small solitary tumors measuring <1 cm and larger lesions with the possibility of metastases. Histologically, the ribbon histologic type is the most common pattern, followed by mixed and acinar patterns, respectively.[164] On light microscopy, the cells are small to intermediate in size, arranged in clusters, with extensive necrosis. At the ultrastructural level, neurosecretory granules 80–200 nm in diameter can occasionally be observed.[165] Rarely, mucus-secreting cells may be found, and, as in the appendix, an adenocarcinoid variety with a propensity for metastasis is evident.[166] Some rectal carcinoids are classified as goblet cell carcinoids, and adenocarcinoids and even NE carcinomas have been reported.[167] Although most carcinoids of the rectum immunohistochemically exhibit numerous amines and peptides in parallel to that of normal mucosa of the rectum, presentation with clinical symptoms or the "carcinoid syndrome" is very rare.[168] The majority of the tumors are argyrophil positive by the Grimelius method, and only a few are argentaffin positive. They display moderate neurofilament staining, and stain positive for CgA (>70%) and NSE (>50%), but the pattern is variable.[165] Immunohistochemical identification of SST, glicentin, PP, peptide YY, enkephalin, endorphin, and serotonin has been described.[169] Prostate-specific acid phosphatase is expressed by 80%–100%, and occasionally tumors may exhibit elevated serum acid phosphatase levels as well as high levels of serotonin or glucagons.[170] Classic tumor markers, such as CA 19-9, CA-50, CEA, and α-fetoprotein (AFP) are consistently absent.[171]

Because of their low propensity to metastasize, classic rectal carcinoids have a generally favorable prognosis with an overall 5-year survival rate of 88.3% (Table 3).[14] Several parameters have been suggested as predictive criteria in the assessment of the malignant nature of these neoplasms, including tumor size, histologic growth pattern,[172] histologic microinvasion,[173] presenting symptoms,[173] and DNA ploidy.[174] Tumor size and microinvasiveness are probably the 2 most important prognostic factors. At diagnosis, approximately 80% of the lesions are <1 cm in size and submucosal and have no metastatic spread. Thus, most lesions can be managed by a minor procedure (endoscopic or transanal resection).[175] For tumors between 1 and 2 cm in size (10% of cases) without evidence of lymph node metastasis, a wide excision with a meticulous evaluation to exclude muscular invasion is recommended.[176] If the neoplasm is 2 cm or greater (10% of cases) or muscular invasion or lymph node metastases are present, radical surgery (low anterior resection with total mesorectal excision or abdomino perineal resection) should be performed.[177] The management of patients with rectal carcinoids >2 cm with hepatic and lymph node metastases should be similar to that for adenocarcinoma with similar metastasis. Local excision to prevent bleeding, tenesmus, and obstruction is reasonable, with surgical therapy regarded as palliative. If the lesion exhibits an adenocarcinoid or NE carcinoma phenotype, it should be treated as an adenocarcinoma.[178] The role of various chemotherapeutic agents is limited, but streptozotocin, 5-fluorouracil (5-FU), doxorubicin, β-interferon, and cyclophosphamide have all been utilized, with modest if any benefit.[168]

Colon

Carcinoid tumors of the colon compose 7.8% of all carcinoids and occur most frequently (39%–48%) in the cecum.[14,179] It is probable that some of the cecal lesions in earlier series represented appendiceal carcinoids that had extended.[14] Most present in a fashion indistinguishable from a mass lesion of the colon with the usual manifestations, including abdominal pain, alteration in bowel habit, and bleeding. The presence of classical carcinoid symptomatology is extremely rare (<5%). Over half of the patients exhibit nonspecific symptoms such as weight loss and weakness, but occasionally diarrhea or bright red rectal bleeding may occur, suggesting a tumor location distal to the hepatic flexure.[162,179] Occasionally, asymptomatic lesions are identified at colonoscopy, and diagnosis is confirmed by biopsy. The tumors exhibit equal sex distribution, and the average age at the time of diagnosis is 70 years.[14] Of note is that a marked white population predominance is evident (African American/white ratio of 0.13:0.6).[14,179]

In general, carcinoids of the colon resemble the rectal lesions and will therefore not be described in detail. However, they generally exhibit a more undifferentiated pattern with clinically more aggressive features, whereas well-differentiated histologic patterns, such as insular, trabecular, and glandular patterns are less common.[179] Although tumor size and microinvasiveness are the main prognostic factors in GI carcinoids, these criteria are of little use in the assessment of the prognosis of colonic

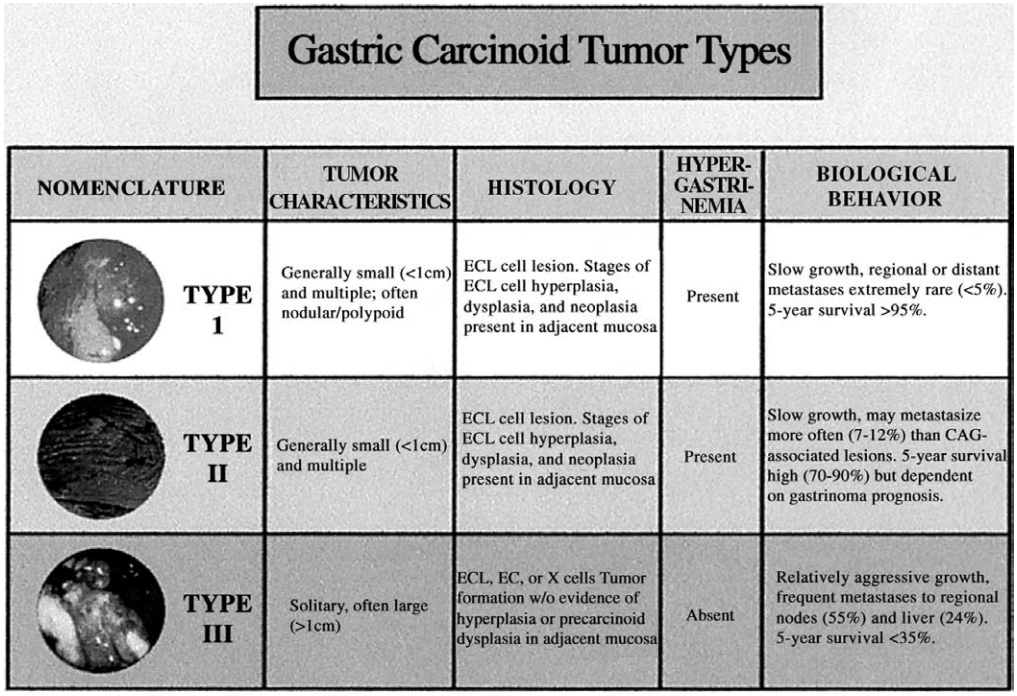

Figure 7. The characteristic features of the different types of gastric carcinoid tumors. Adapted with permission from Modlin IM, Sachs GS. Acid-related diseases: biology and treatment. Philadelphia, PA: Lippincott Williams & Wilkins, 2004.

carcinoid tumors because the majority of these lesions exceed a size of 2 cm and involve the muscularis propria at presentation.[179] Nuclear mitotic rate, overall tumor grade, and the histologic pattern of the neoplasm significantly influence survival.[179,180] Associated noncarcinoid tumors occur in 13.1%.[14] Unexpectedly, colonic carcinoids exhibit the worst prognosis among all GI carcinoid tumors, with an overall 5-year survival of 33%–42% (Table 3).[14,142] One explanation of this is the large tumor size at the time of diagnosis, with a high percentage of metastatic spread.[14,179] Local excision is only recommended in the minority of patients who present with a tumor size of less than 2 cm. Analysis of the Connecticut Tumor Registry data noted that only 1 out of 6 tumors with a size of less than 2 cm was nonlocalized, whereas metastases were evident in more than two thirds of patients with a tumor of more than 2 cm in diameter. Thus, a wide resection, including lymph node dissection, is advocated, particularly in lesions >2 cm in size. For practical purposes, colon carcinoids should be managed as if they were adenocarcinomas of the colon.

Stomach

Gastric carcinoid (GC) tumors were previously thought to be extremely rare lesions. In the pre-endoscopic era, they composed only 0.3% of all gastric tumors and 1.9% of all GI carcinoids.[142,181] More recent studies have reported that as many as 10%–30% of all carcinoids may occur in the stomach.[182] Gastric carcinoids exhibit an increased incidence in individuals with atrophic gastritis, pernicious anemia (PA), auto immune diseases, and MEN-1–associated gastrinoma.[183] This apparent increase represents increased awareness, increased endoscopy, and, possibly, a real change in incidence. A 40-year analysis of 265 GCs from the National Cancer Institute (NCI) database revealed an increase in GCs among all gastric malignancies from 0.3% to 0.54%.[184] A 50-year analysis of 562 GCs from the same database noted a further increase to 1.77%[14,185] and that the percentage of gastric carcinoids among all GI carcinoids had increased from 2.4% to 5.6% to 7.1%.[14,185] The average age at diagnosis remained stable (62.4 vs 63.8 years, respectively). Based on the distinct pathobiologic behavior of the lesion, 3 distinct tumor types have been proposed: type I, associated with type A chronic atrophic gastritis (CAG/A); type II, associated with a ZES-MEN-1; and type III, associated with sporadic gastric carcinoids.[186] Type I and II lesions are associated with hypergastrinemia, and the tumors consist mainly of ECL cells. Type I is most frequent and composes approximately 65% of all gastric carcinoids.[187] The lesion is localized in atrophic oxyntic mucosa (body fundus) in individuals with CAG/A with or without PA. Characteristically, the lesions are multicentric, small, and polypoid and exhibit little propensity to metastasize (Figure 7). Type II lesions consist mainly of ECL cells, as do type I carcinoids,[188] and exhibit argyrophil cell hyperplasia/dysplasia throughout the oxyntic mucosa, which, in contrast to CAG/A patients, is usually massively rugose. Type II is

intermediate between the type I and type III tumors in terms of malignancy. Type III (sporadic carcinoids) are less frequent (21%) and display a moderately aggressive behavior with invasive growth and a high incidence (24%–55%) of metastasis.[186,187] They are usually solitary large lesions that evolve in a normal gastric mucosa with normal plasma gastrin levels. Histopathologically, they comprise a variety of cell types including ECL, EC, and X cells and exhibit growth patterns (trabecular, gyriform, medullary or solid, glandular or rosette-like growth, or a mixture of these types) similar to those observed in carcinoids from other locations.[186] Some classifications include a type IV lesion, although this is in actuality an NE carcinoma whose appearance and behavior is indistinguishable from an adenocarcinoma, except that varying percentages of NE cells (CgA positive) can be identified within the tumor matrix. Over 80% of gastric carcinoids are argyrophilic, but a minority (14%) stain positively for argentaffin.[189] Immunohistochemically, CgA, synaptophysin, and Leu-7 are present in over 90% of cases, whereas NSE and serotonin are detectable in only 60% and 34%, respectively.[189]

Clinically, gastric carcinoids present with nonspecific symptoms and signs, including pain, vomiting, upper GI bleeding, dyspepsia, anemia, heme-positive stools, and gastric polyps at endoscopy. It is unusual (<5%) to exhibit symptoms of either a typical or atypical carcinoid syndrome.[182,186] The latter symptoms (especially gyrate [spiral/whorl-like] flushing, sweating) are usually associated with the "sporadic" gastric carcinoid tumors, which often behave as NE carcinomas. In earlier series, approximately half of the gastric carcinoid tumors were not localized to the stomach at diagnosis.[184] Data derived from the recent SEER database (1992–1999) noted the following: 67.5% of the gastric carcinoids were localized, 3.1% regionalized, 6.5% had distant metastases, and 22.9% were unstaged.[14,185] An association with other malignant neoplasms was evident in 7.8% of cases. UGI endoscopy with biopsy is the most useful diagnostic tool, but endoscopic ultrasound is of value in identifying submucosal lesions and determining the degree of transmural spread. The lesions are typically fundic, multiple, small, rounded, submucosal erythematous nodules that may often also have a yellow color.[190] Larger lesions are sometimes solitary and often ulcerated. Biopsy of surrounding mucosa reveals varying degrees of ECL cell hyperplasia, dysplasia, and even invasive spread, attesting to the ECL cell field defect throughout the oxyntic (fundic) mucosa.[186] Barium contrast studies are of limited use in diagnosing polypoid tumors and have been supplanted by endoscopy and ES ultrasound.

Hypergastrinemia-associated GCs (type I and II) have a good prognosis, are generally noninvasive, and result in metastasis in only a small percentage (7.6%–12%) of individuals.[185] Type III lesions often display markedly aggressive local behavior and metastasize. The 5-year survival rate is significantly higher for localized disease (64.3%) and for lesions with regional metastases (29.9%) than for lesions with distant metastases (10%).[184] Although the tendency to metastasize correlates with tumor size, minute tumors have been reported with spread.[191] Factors that predict aggressive behavior include cellular atypia, 2 or more mitoses per 10 high-powered fields, angioinvasion, and transmural invasion.[186,192] NE carcinomas, previously known as "atypical carcinoids," represent an aggressive NE neoplasm that bears greater resemblance to "sporadic carcinoids" than to hypergastrinemia-associated tumors. These lesions display invasive growth, metastasize with great frequency, and progress rapidly with a prognosis indistinguishable from gastric adenocarcinoma.[186]

Hypergastrinemia-associated lesions of less than 1 cm in size and fewer than 3–5 in number should initially be managed by endoscopic excision of polypoid lesions if possible.[193] If the lesion is >1 cm, >5 lesions are present, or a recurrence of endoscopic polypectomy is present, a local excision of the lesion should be undertaken. There is controversy as to whether fundic resection or antrectomy should be undertaken at this time. Antrectomy eliminates the trophic stimulus (gastrin) that promotes tumor growth, but it is not possible to predict when tumors have become gastrin autonomous. Regression, however, of lesions has been reported after antrectomy alone.[194] This is not always the case, and the criteria for predicting whether regression will occur are unknown. Fundic resection removes all ECL cells and carcinoids; hence, no recurrence is possible. In some circumstances in which tumors are multicentric and large and the patient young, a total gastrectomy may be considered to avoid lifetime endoscopic surveillance. The use of long-acting SST analogues (decrease plasma gastrin, inhibit ECL cell proliferation) has been reported to be efficacious.[185] Such therapy avoids surgery but requires repeated depot injections, continuous endoscopic surveillance, and is associated with adverse effects including hypertension. Both endoscopic polypectomy or surgical excision and antrectomy/fundic resection should be followed by surveillance endoscopy with biopsy at 6-month intervals. Sporadic lesions and NE carcinomas require an aggressive surgical management (as for adenocarcinoma) on diagnosis, and complete or partial gastrectomy with regional lymph node dissection is mandatory.[195] The 5-year survival rate in gastric carcinoid

tumors of all types (types I, II, and III) is 64.3% when the lesion is localized, 29.9% with regional, and 10% with distant metastases.[184] There is, however, a far higher survival rate (>95%) for type I lesions.

Rare GI Carcinoids

Esophagus. Esophageal carcinoids are extremely rare, and, after the first description in 1969,[196] only 31 cases have been reported.[197] They usually occur in the lower esophagus of males (male-to-female ratio of 6:1) who present with dysphagia and may represent neoplasia in metaplastic epithelium, supporting the observation of an increased number of endocrine cells in the setting of Barrett's metaplasia.[198] Most occur in the lower one third or at the GE junction, paralleling the increasingly distal distribution of endocrine cells. Lesions are typically large, polypoid, and confined to the submucosa or lamina propria, and most have invaded the esophageal wall at presentation, with lymph node metastases present in approximately 50%.[199] The age at diagnosis ranges from 30–82 years, and the most common symptoms include dysphagia, weight loss, pain, reflux esophagitis, fatigue, and melanotic stools. The carcinoid syndrome has occurred in only 1 case.[200] Diagnosis is as for any esophageal mass, (barium, endoscopy with biopsy, and CT scan).[201]

The lesions demonstrate marked cellular atypia with large, pleiomorphic nuclei; and immunohistochemical studies are positive for NSE, vasoactive intestinal peptide (VIP), and serotonin; but many tumors lack argentaffin and argyrophilic staining. Patients with tumor stages I and II are usually disease free after resection; those with stage III and IV grade tumors typically succumb to the disease, as a result of local spread. The small patient sample size limits any well-founded treatment recommendations, but esophagogastrectomy or subtotal esophagectomy with gastroesophageal anastomosis are the preferred interventions.[201] Overall, there is an approximate 70% survival rate of at least 6 months with stages I and II lesions and less than a 25% 6-month survival rate observed in stage III or IV tumors.[201]

Pancreas. Since their first description in 1959 by Pataky et al,[202] 138 cases of primary pancreatic carcinoids have been reported.[197] They compose 0.6% of all carcinoid tumors,[14] and the age of onset ranges from 22 to 78 years, with a mean age of 49.3 years in a series of 30 patients.[203] Females are more affected (1.5:1 [F:M]), compared with the 1:1.5 F:M ratio observed with pancreatic cancer.[203] Abdominal pain, diarrhea, flushing, and nausea are among the most frequently encountered symptoms.

Diagnosis includes abdominal and EUS, CT scan, and ERCP as well as Octreoscan. Ultrasound typically demonstrates round or oval masses with hyperechoic capsules, occasionally containing calcifications. CT scanning, however, remains the most useful method for detecting and staging pancreatic lesions, although MRI with dynamic gadolinium enhancement and fat suppression may be superior in the detection of smaller pancreatic lesions.[204] Intraoperative US can visualize small impalpable masses, with a 96% predictive value,[205] and can provide information concerning the malignant potential of carcinoid tumors because benign lesions may be more distinctly demarcated than malignant tumors.[205] Angiography may be useful to demonstrate increased vascularity of these lesions and delineate vascular invasion.[203]

The classification of such carcinoids remains controversial because much of the literature preceded the development of immunohistochemical staining. Common characteristic histologic findings in pancreatic carcinoids include trabecules of small- to medium-size cells with argyrophilic, granular eosinophilic cytoplasm, and monomorphic round nuclei.[203] On immunohistochemical analysis, most lesions demonstrate a positive reaction for serotonin, CgA, synaptophysin, and, in some cases, NSE.[203]

Pancreatic carcinoids are most frequently managed by pancreatectomy, with a prognosis that depends mostly on the extent of local or distant spread. Although rare, these tumors constitute a particularly malignant form of carcinoid with an ostensibly pernicious prognosis because the majority of patients (approximately 72%–81%) exhibit advanced, nonlocalized disease at the time of diagnosis. Although patients with no evidence of metastatic tumor may expect a normal survival, those with metastatic disease demonstrated a median survival of only 7 months in 1 series.[203] The overall 5-year survival rate was only 37.5% in the SEER database of the National Cancer Institute.[14] However, unlike pancreatic adenocarcinoma, carcinoids have an indolent clinical course more amenable to therapy and therefore potentially likely to have a more auspicious clinical outcome.

Liver. Although the liver is the second most common location for carcinoid metastases (lymph node being first), it is rarely the site of primary carcinoid tumors.[197] It is thus mandatory to exclude the presence of a distant primary tumor before concluding that the liver is the site of origin of the tumor. Primary hepatic carcinoids were first described in 1958,[206] and, to date, 95 such cases have been reported,[197] accounting for 0.3% of all carcinoids.[14] Although no sex predominance is evident, these carcinoids present in a relatively young patient popula-

tion, with an average age of approximately 45 years, ranging from 8 to 83 years of age.[14]

The clinical onset is often nonspecific and related either to the destruction of viable hepatic parenchyma by tumor or pain, weight loss, a palpable mass, and even gastric outlet obstruction because of mass effect. The classical carcinoid syndrome, often a pathognomonic feature of metastatic hepatic carcinoid, occurs in only 5% of primary hepatic carcinoids.[207] This almost certainly reflects the fact that the liver NE cells of tumor origin are different from that of the more ubiquitous ileal EC cell. Diagnosis and determination of resectability can be established by Octreoscan, abdominal and chest CT scan, MRI, bronchoscopy, hepatic venous sampling, and laparoscopy. PET scan using the serotonin precursor 5-HT labeled with ^{11}C has proved to be of value.[119] Conventional ultrasonography typically reveals a hyperechoic mass containing multiple cystic lesions, whereas low-density, moderately enhanced areas that confirm a cystic pattern are evident on CT scan. Angiography may demonstrate multiple hypervascular and centrally located radio-lucent areas. Diagnosis can be ascertained by percutaneous fine-needle aspiration (FNA) or biopsy followed by immunologic and electron microscopic assessment. Caution should be exercised with liver puncture, given the hypervascular nature of the lesion. Immunohistochemical identification of CgA, NSE, chromostatin, CEA, and synaptophysin are confirmatory.[16] Given that the incidence of secondary hepatic carcinoids far outnumbers that of primary lesions, a thorough search for covert carcinoid lesions at a distant site should be pursued, preoperatively. Long-term follow-up should include measurement of plasma CgA levels and SSTR scintigraphy.[208]

Diverse therapeutic interventions have been used in curative or palliative approaches to primary carcinoid tumors including hepatic lobectomy, systemic chemotherapy, hepatic artery chemoembolization, and octreotide alone or in conjunction with surgery in attempts to manage hepatic lesions. In the past, cyproheptadine and methylsergide were therapeutic mainstays, but, currently, the SST analogue class of drugs and interferon-α are the most efficacious.[209] Chemotherapeutic agents, such as 5-FU and streptozocin, are of some utility, but their adverse effects far outweigh any realistic benefit.[207] Contrary to the poor prognosis of hepatocellular carcinoma or hepatic carcinoid metastases, primary hepatic lesions appear to exhibit a better prognosis, with survival ranging from several months to 18 years.[207] Nevertheless, based on the SEER database, the prognosis of primary hepatic carcinoids is poor; the 5-year survival rate of such patients from 1973 to 1991 and 1992 to 1999 were 14.3% ± 13.2% and 18.4% ± 8.9%, respectively.[14] However, these data are old and based on small numbers. Recent case reports documenting aggressive treatment with liver resection or orthotopic liver transplants demonstrate more favorable 5-year outcomes (>75% disease free after 3 years).[210]

Extrahepatic biliary tracts. The clinical presentation of carcinoid tumors of the extrahepatic biliary system parallels that of any other pathology involving biliary obstruction, with pain, jaundice, and pruritus ranking among the most common symptoms. The common bile duct (CBD) is the most common anatomical site, accounting for approximately 60%, but tumors can occur in the perihilar region, cystic duct, ampulla of Vater, and common hepatic duct.[211,212] These lesions account for 0.2%–2% of all GI carcinoids,[14] and are one of the rarest primary sites with only 111 cases reported since Davies[213] first described a carcinoid tumor of the distal common bile in 1959.[197] The incidence of biliary carcinoids peaks in the fifth decade of life[211] (range, 19–79 years of age), with women more affected than men (ratio, 2.2:1.05 [F:M]).[14,211] Neurofibromatosis patients are at a high risk for periampullary tumors, particularly SST-rich carcinoids, and, in 2 separate series, 25% of ampullary carcinoids occurred in such individuals.[212] Elucidation of the bile duct obstruction includes abdominal ultrasound, CT, ERCP with biopsy, or percutaneous transhepatic cholangiography (PTC) in cases of complete obstruction. Microscopically, these carcinoids exhibit a trabecular or nesting pattern with occasional tubule formation,[214] and 92%–100% express CgA with SST, serotonin, cytokeratin, and synaptophysin less commonly evident.[212,214]

Surgical excision of the neoplasm remains the therapy of choice when feasible, but approximately one third of patients have metastases, mostly to the liver and regional lymph node, at diagnosis.[211,212] The former can be managed by either wedge or major lobar resection concurrently performed to attempt cure, but the paucity of adequate data makes it difficult to ascertain accurately whether it is indeed curative or merely palliative. In most instances, a complete surgical resection is commonly associated with a more favorable prognosis.[211] Among those who presented with localized tumors without evidence of metastases, 5-year survival ranges from 60% to 100%.[14]

Gallbladder. Joel first described a case of carcinoid tumor of the gallbladder in 1929,[215] and, to date, 42 cases of gallbladder carcinoids have been reported,[197] composing 0.2% of all carcinoids. The sex distribution of these lesions parallels that of gallbladder carcinomas, with a marked female predominance that accounts for

75%.[14] Most present (38–81 years of age) with jaundice and right upper quadrant pain indistinguishable from cholecystitis or are diagnosed after cholecystectomy for cholecystitis, incidentally at autopsy, or after surgical treatment for suspected biliary malignancy. Routine studies rarely suggest a NET, and angiographic findings are similar to those in other gallbladder cancers, including encasement, dilatation, and obstruction of the cystic and superficial arteries of the gallbladder.[216] As in other carcinoids, size and metastases predict prognosis[217]; however, approximately 50% of gallbladder carcinoids are histologically definable as endocrine cell carcinomas, with a far worse prognosis than "classical" carcinoids. Kaiho et al described "hallmark" pathologic findings that distinguish the "classical" carcinoid tumors from their "carcinomatous" counterparts.[218] In general, classical carcinoids of the gallbladder have neither a metastatic nor invasive character nor exhibit a more propitious prognosis. The "atypical" variants, however, are associated with marked cell atypia and mitosis, as well as a poor prognosis. Histologically, most analyzed tumors are positive using Grimelius and CgA.[219] Two case reports describe clear cell carcinoid tumors of the gallbladder as another distinctive manifestation of von Hippel–Lindau disease because of its diffuse immunoreactivity for inhibin.[220]

Most patients require surgical excision, with the extent dependent on size and stage of the lesion, particularly whether or not liver metastases were present. Reservations have been expressed regarding laparoscopic excision because it carries a high risk of port metastases and dissemination.[219] The SEER database (1992–1999) indicates that 82.4% of gallbladder carcinoids remain localized, 11.8% exhibit distant metastases, and an overall 5-year survival of 60.8% ± 14.8%.[14]

Therapy

Overview

Surgery is generally regarded as the most effective treatment for both local tumor effects (obstruction, bleeding, perforation) and symptoms caused by the secretory agents because it removes the primary lesion and decreases levels of bioactive agents. In essence, surgery may be categorized as (1) adequate resection with curative or palliative intent for primary and regional lesions; (2) surgical resection of regional or distant metastatic disease with cytoreductive intent, and (3) resection of disease for symptom palliation without cytoreductive intent. If residual tumor is present after surgery (liver, lymph nodes, peritoneal), long-acting SST analogues have proven efficacious in the management of carcinoid syndrome symptomatology.[221]

Table 4. Five-Year Survival Rates and Disease Extent by Site and Stage 1973–1999

	Localized		Regional		Distant	
Carcinoid site	Extent (%)	5-year (%)	Extent (%)	5-year (%)	Extent (%)	5-year (%)
Stomach	61	68	6	35	12	10
Small bowel	30	57	37	67	27	40
Appendix	60	91	27	81	9	28
Colon	26	74	30	51	35	25
Rectum	78	87	4	41	4	25

NOTE. Data for this Table are derived from the SEER (1973–1999) (NCI) registry. Localized: lesion described as in situ or confined to organ of origin. Regional: local invasion or lymph node metastasis. Distant: evidence of metastatic invasion of other organs. Adapted from references 13 and 14.

The precise surgical management depends on the location and extent of the lesion. Carcinoid tumors of the appendix and rectum have the best prognosis (Tables 3 and 4), and local excision is usually the most appropriate treatment if lesions are <1 cm. Tumors of the colon and SI exhibit the worst prognosis, and a wide resection is appropriate. In the stomach, the surgical management depends on the lesion type. Whereas sporadic (aggressive) carcinoids (type III) require a gastrectomy, GCs associated with hypergastrinemia (types I and II) may be managed by endoscopic or local excision if limited in size and extent (Figure 7).

Hepatic metastases can be resected because debulking (cytoreductive surgery) may reduce the symptoms, facilitate pharmacologic management, and improve survival.[222] Similarly, hepatic artery occlusion, either by ligation, embolization, or chemoembolization, is beneficial and decreases symptoms of carcinoid syndrome, with tumor regression in 65% of patients.[223] However, the duration of palliation may be limited because of either recurrence or rearterialization of lesions.[224] Hepatic artery embolization combined with sequential chemotherapy has been more encouraging, resulting in a reduction of tumor size in 78% of patients.[225] Similarly, embolization with Yttrium-labeled microspheres has been useful in some circumstances.[226] Cryosurgical debulking or radiofrequency ablation of hepatic carcinoid metastases have been described as of some benefit for palliation of carcinoid syndrome, but their efficacy remains to be rigorously evaluated.[227]

Conventional chemotherapeutic agents such as streptozotocin, 5-FU, doxorubicin, and cyclophosphamide alone have been disappointing, with an overall 20%–40% response rate.[228] Etoposide may be marginally more effective either alone or in combination with cisplatin.[229]

The introduction of long-acting SST analogues and depot administration has facilitated the control of most

carcinoid syndrome symptoms[221,230,231] and greatly improved quality of life with only modest adverse effects (nausea, cramps, loose stools, mild steatorrhea, flatus; biliary sludge, or cholelithiasis in up to 50% of patients but only 1% with acute symptoms warranting cholecystectomy; impaired glucose metabolism with hyper- or hypoglycemia or rarely overt DM; local pain and erythema at injection site; very rarely gastric atony).[221,232] It has been reported that such agents induce arrest of tumor growth, but the rigorous data are lacking.[233] Intravenous SST analogues are particularly effective in the management of a "carcinoid crisis," which is usually engendered by anesthesia, surgical, or radiologic intervention. This dramatic clinical scenario is characterized by profound hypotension and tachycardia often associated with mortality without rapid preemptive pharmacologic intervention.[234] Recombinant leucocyte interferon-α may be of some use in the treatment of disseminated carcinoid tumors and carcinoid syndrome alone or in combination with SST,[230,235] but its use can be associated with significant toxic adverse effects. It has, however, been reported to ameliorate flushing and diarrhea and even induce a degree of tumor regression in some patients.[236]

Supportive care of carcinoid tumors or carcinoid syndrome includes avoiding stress and conditions or substances that precipitate symptoms; dietary supplementation with nicotinamide is also recommended.[237] Mild diarrhea responds to antidiarrheal agents, such as loperamide or diphenoxylate, and bronchospasm to bronchodilators that interact with β-adrenergic receptors and do not exacerbate flushing. Cyproheptadine decreases diarrhea in 50%,[238] but adverse effects (20%) can be prohibitive. Cardiac failure may require diuretics and even valve replacement.[239] Some brief relief with prednisone has been reported, but its adverse effects warrant caution.[240] Overall SSTR analogue therapy has supplanted most other medication, and its efficacy is such that a retrospective case series has suggested survival duration has increased since its introduction.[241]

Specific Modalities

Palliative surgery. Unless carcinoids are identified serendipitously at operation (appendix) or by endoscopy (gastric, rectal), most exhibit local or regional spread and even hepatic metastasis at diagnosis. Debulking of tumors to obviate mechanical bowel obstruction and amelioration of symptomatology provides palliation and may even prolong survival in some patients.[238,242] In patients with carcinoid syndrome, the excision of mesenteric tumors may result in substantial symptomatic relief[148]; however, more often than not this is not feasible and leads to either multiple enterotomies or mesenteric devascularization and subsequent ischemic bowel infarction. In patients with metastatic spread, resection of mesenteric lymph node and/or liver metastases may result in alleviation of symptoms and increased survival.[222,243] Surgical debulking of hepatic disease has been shown to improve survival,[244] although curative treatment of NE tumor disease can only reliably be achieved in patients with small primary NE tumors or tumors with limited local disease. Current assessments indicate that removal of 90% of the disease is required to achieve palliation.[245] Nevertheless, whereas tumor debulking and resection controls symptoms in most patients with carcinoid syndrome, symptoms recur in approximately 60% of patients, and the 5-year survival is approximately 35%.[222] Surgery should therefore be carefully evaluated because symptom relief can be achieved at far less risk with SST analogue therapy, although cytoreductive surgery may decrease bioactive product release such that pharmacotherapy is more effective.

SSTR-targeted therapy. Somatostatin was identified in 1973 in ovine hypothalami[246] and has since been recognized as a major neurotransmitter with a mostly inhibitory capacity in that it regulates exocrine secretions,[247] glandular secretions, neurotransmission, smooth muscle contractility, and absorption of nutrients.[248] Of particular interest is its experimental ability to act as a cytostatic agent to tumor cells.[249] These effects are modulated via inhibition of autocrine, paracrine, neuracrine or endocrine growth factors, direct binding of SSTRs, and antiangiogenesis properties.[250,251]

Chemically constructed analogues (congeners) based on the structure of natural somatostatin act on 5 specific high-affinity membrane subtypes of SSTRs in target tissues, including the brain, pancreas, pituitary, and GI tract and neoplastic tissue.[252] Fifty percent of the amino acids are identical among the 5 SSTRs subtypes, and labeling studies demonstrate that all 5 SSTR subtypes bind SST analogues with high, but varying, degrees of affinity.[247] Short, synthetic analogues such as SMS201-995, MK678, RC-160, or BIM 23014 display different binding profiles; high-affinity binding is observed for type 2 and type 5 receptors, low affinity for type 1 and type 4, and medium affinity for type 3.[247] A more recent analogue (SOM230) exhibits nanomolar or subnanomolar potency at types 1, 2, 3, and 5 with no agonist activity at the type 4 receptor. This analogue has particular potency at SST 5 compared with octreotide, which is currently in phase II clinical trials.[254–255]

SST and its analogues (octreotide and lanreotide) inhibit flushing, diarrhea, and other symptoms of carcinoid syndrome, but the short half-life (2–4 minutes) of the natural agent (SST) limited its clinical applications and

Table 5. Effects of Octreotide on Patients With GI Carcinoids

Year and reference number	Patients No.	Biochemical response (%)	Tumor response (%)	No disease progression (%)		Symptomatic response (%)	
				Biochemical	Tumor	Diarrhea	Flush
1986[250]	25	72	0	28	62	88	92
1987[266]	19	63	0	—	—	—	—
1989[267]	14	75	0	25	50	75	100
1991[263]	23	27	9	36	—	50	
1993[264]	20	—	0		50	71	
1992[265]	24	45	0	17	62	—	—
1993[268]	55	37	2	49	—	69	70
1994[269]	28	50	—	—	—	79	48
1996[233]	64	33	0	—	55	64	75
1996[261]	31	77	3	23	—	40	50
1998[79]	10	33	—	77	—	—	—
2003[258]	27	25	0	25	48	81	
2003[230]	35	0	0	46		—	—
2004[231]	12	17	0	75	75	—	—
Median (range)	24 (10–64)	37 (0–77)	0 (0–9)	28 (17–77)	55 (48–75)	71 (40–88)	71 (48–100)

NOTE. Pooled data from 14 centers and 400 patients reflect median biochemical and tumor response rates of 37% and 0% in patients treated with Octreotide. The agent resulted in a median decrease in diarrhea and flushing of 71%. In addition, no disease progression was noted in biochemical parameters (28%), and 55% exhibited no tumor progression.

led to the development of clinically effective analogues with a half-life of 90–120 minutes.[256,257] Such agents can be administered subcutaneously every 6 to 12 hours and decrease release of bioactive secreted products with effective resolution of flushing and diarrhea in between 70% and 80% of patients.[231,258] The dosage of octreotide (Sandostatin; Novartis, East Hanover, NJ) varies from 50 μg to 500 μg subcutaneously 3 times a day and can adjusted in accordance with clinical needs. In the event of symptom breakthrough (which may represent tachyphylaxis or increased tumor growth) dosage can be increased.[231] The introduction of a depot formulation of octreotide (Sandostatin LAR) that has a longer half-life, reaches a steady state in 8 to 12 weeks, and requires monthly replacement has the advantage of abrogating the need for multiple daily injections. Although, in some instances, this formulation may not provide as effective control and may exhibit some local adverse effects, the utility of decreasing daily multiple injections is advantageous.[221] Lanreotide, a long-acting SST analogue administered every 10 to 14 days, does not differ significantly in treatment of carcinoid symptoms.[221] Breakthrough or escape can occur in the last week of the cycle and may require "rescue" with a short-acting agent or by increasing either the dose or the frequency of the depot injection. Intermediate-acting SST analogues such as Sandostatin should be used to supplement long-acting agents until a steady state is reached.[221] A new slow-release depot preparation of lanreotide Autogel is administered by deep subcutaneous injection once every 4 weeks. In a 6-month, open, noncontrolled, dose-titration study, Ruszniewski et al evaluated the efficacy and safety of 28-day aqueous PR formulation of lanreotide in 75 patients.[259] The outcomes were comparable with those of other lanreotide preparations, with 30% of patients exhibiting a biochemical response and 75% and 80% of patients experiencing resolution of diarrhea and flushing, respectively. The cumulative response to the 28-day PR formulation was better in patients naïve to somatostatin analogs (46% vs 34%, respectively). Although previous studies have demonstrated that, once steady-state levels are achieved, the immediate-release octreotide is as efficacious as the 28-day prolonged release formulation of octreotide[260] or the lanreotide 30-mg microparticle formulation,[261] there have been no studies to date to compare directly the 28-day PR formulations of lanreotide and octreotide. Other drugs with affinities to other SSTR subtypes have been developed recently and are currently undergoing phase I and II testing.

In addition to demonstrating improvement in symptoms, some studies of SST analogues have reported objective tumor volume shrinkage, and a number of trials have investigated their "antitumor" effects. Although biochemical response rates ranged from 0% to 77%, tumor response rates were very low (0%–9%) (Tables 5 and 6).[79,209,230,231,233,250,258,259,262–277] A recent overview of 182 patients noted only 3 partial responses (2%) and generously suggested that SST analogues may be more effective in stabilizing tumours than in causing tumor shrinkage.[237] There are little data to support the notion that SST analogue therapy has a predictable or significant inhibitory effect on tumor progression, although some nonrandomized and corporation-supported trials have claimed disease stabilization.[233,264,278] Nevertheless,

Table 6. Effects of Lanreotide on Patients With GI Carcinoids

Year	Patient no.	Biochemical response (%)	Tumor response (%)	No Disease progression (%)		Symptomatic response (%)	
				Biochemical	Tumor	Diarrhea	Flushing
1994[275]	8	62	0	38	90	100	87
1994[270]	12	—	0	—	58	42	86
1996[271]	19	54	0	—	90	—	—
1996[272]	33	42	—	46	—	38	53
1999[273]	48	27	8	52	81	38	
1999[276a]	19	—	9	—	52	—	
2000[262]	10	—	0	—	90	90	80
1994[269]	28	50	—	—	—	89	41
2000[274]	12	42	8	—	—	36	100
2000[277b]	38	40	5	24	54	—	40
2002[278]	10	0	0	83	—	90	
2004[259]	55	30	—	—	—	75	81
Median (range)	19 (10–55)	42 (0–62)	0 (0–9)	46 (46–83)	81 (58–90)	75 (36–90)	80 (38–100)

NOTE. Pooled data from 11 groups of close to 300 patients reflect median biochemical and tumor response rates of 42% and 0% respectively, in patients treated with Lanreotide (Ispen, France). Disease stability was maintained in 46% and 81% respectively, of patients, with a median decrease in diarrhea and flushing of 75% and 80%, respectively.

[a]data include other types of GEP tumors.

[b]Overlapping patient population with Ruszniewski et al.[271] Response defined as >30% decrease in biochemical markers.

treatment with SST analogues is generally well tolerated, and their efficacy in symptom relief is unparalleled. Several adverse events including gallbladder stones and sludge effects, steatorrhea, sinus bradycardia, cardiac conduction abnormalities, and arrhythmias as well as endocrine abnormalities (hypothyroidism, hypoglycemia, hyperglycemia [more commonly]) may occur and warrant monitoring.[221,237]

Interferon. Interferon usage including human leukocyte interferon (HLI), interferon-α, and interferon-β have all been used in the treatment of carcinoids.[235,279] The precise mechanism of action is not well understood but may include direct inhibition of cell proliferation, immune cell-mediated cytotoxicity, inhibition of angiogenesis, and induction of differentiation via cell cycle block in the G0/G1 phase by dephosphorylation of the retinoblastoma gene.[280] Although these agents are more toxic than SST analogues, they may exhibit greater antitumor activity, but substantial adverse effects include fever, fatigue, anorexia, and weight loss as well as alopecia and myelosuppression.[221,237] In human studies, biochemical response rates ranged from 7% to 53%, and objective tumor response rates ranged from 7% to 20%,[281] and a pooled study (60 patients) noted 40% with reductions in biochemical markers (>50%) and 12% objective tumor responses.[237] Interferon-α studies[282] reported biochemical response rates of 7%–66%, and objective tumor response rates range from 0% to 25%.[235,283,284] In a pooled carcinoid data analysis (290 patients), 40% had evidence of biochemical response, and 12% had objective tumor responses. The combination of interferon-α and interferon-γ is ineffective.[285] Similarly, there was little advantage in the use of a combination of octreotide and interferon-α in patients in whom octreotide alone or interferon-α produced no benefit.[209,265] Although biochemical responses were reported in 77%, 72%, and 75% of patients, no objective tumor regression was observed. It is debatable whether SST analogues and interferon-α exhibit a synergistic effect in carcinoid syndrome symptom management.

Tamoxifen. Tamoxifen was initially reported to improve symptoms in 2 patients with carcinoid syndrome,[286,287] but no studies have validated this observation.[288]

Chemotherapy. The majority of studies utilizing single-agent chemotherapy (5-FU, doxorubicin, actinomycin D, dacarbazine, and streptozocin) demonstrated no beneficial effect.[289] As a result, multiple phase II combination chemotherapy trials have been conducted, but these studies have not resulted in corresponding increases in response rates. Of the innumerable permutations, 5-FU and streptozocin with or without cyclophosphamide is the most extensively studied.[290] Biochemical and tumor responses were evident in approximately 8%–25% of patiens.[291] A study of doxorubicin revealed 21% response rate.[292] In a separate study in which 20 patients randomly received either 5-FU and streptozocin or human leukocyte interferon,[281] none of the former responded, whereas the interferon group exhibited 50% (5 patients) biochemical responses and 20% (2 patients) tumor responses. There is no basis as determined by objective criteria to advocate the use of 5-FU

and streptozocin in the treatment of carcinoids. Furthermore, there is no evidence that any existing multiagent chemotherapy regimens are effective in this essentially chemoresistant disease. No regimen has demonstrated a response rate greater than 15% using the criterion of a 50% reduction of bidimensionally measurable disease.[221] The combination of existing chemotherapy agents (streptozocin, doxorubicin, or 5-FU alone) and immunotherapy with interferon-α has been studied in 2 small trials, but the results indicated no benefit.[293,294]

Management of Hepatic Metastases

Surgery. Carcinoids are indolent tumors that may take years to reach a significant size, and the liver is often the only site of this disease. The detection of lesions not evident by topographic study is critical to ensure complete clearance because hepatic resection that leaves residual disease is inadvisable. Nevertheless, excisional surgical resection of liver metastases may be of benefit in patients with limited hepatic metastatic disease but depends on the overall patient status and the extent of the disease. Such surgery has resulted in long-term relief of symptoms and prolonged survival in selected patients, and resection of solitary or localized liver metastasis should be encouraged.[244,245,295] Alternative strategies such as radio-frequency ablation or cryoprobe ablation have been utilized. In one study, ~90% of patients experienced complete relief of symptoms for a median interval of 11 months, and approximately 60% showed decreased 5-HIAA secretion.[296] However, during the follow-up period of 26 months, approximately 90% of patients experienced recurrence, and approximately 50% of hepatic recurrences were observed in previously cytoreduced sites. Hepatic recurrence in the short-term (<35 months) occurs in ~20% of patients,[297] whereas the local hepatic tumor recurrence-free survival for cryoablation alone or combined with resection was 20%.[298] The results for curative intent thus may be as low as 25%.[223] Although they can be deployed laparoscopically (advantageous in terms of avoiding laparotomy), they are not without major adverse effects, including bleeding, sepsis, and intrahepatic biliary ductal damage. This approach has resulted in a partial or significant decrease in tumor markers during 5-year follow-up in 65% of patients.[299] In the same study, new liver lesions developed in 28% of patients, new extrahepatic disease in 25%, and local liver recurrence in 13%, whereas existing liver lesions progressed in 13%. Likewise, 3 patients with unresectable bilobar hepatic metastases treated with radio-frequency ablation demonstrated decreased symptoms in the first 3 months following treatment.[300] One patient was able to discontinue octreotide treatment, and the other 2 patients required decreased octreotide dosages. These data demonstrate that, although feasible and effective, these approaches are supported by little rigorous data by which efficacy can be gauged.

The role of orthotopic 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. The results of a recent series, however, are more encouraging.[301] A multicenter French study recently reported a 5-year survival rate of 69% among highly selected patients who underwent liver transplantation for metastatic carcinoid tumors.[302] Of 74 patients undergoing hepatic resection for NE tumors (50 of the 74 patients had carcinoid tumors), the overall 4-year survival rate was 73%.[244] However, even when resection with curative intent was possible, relapses were common. In this group, 2 perioperative deaths (2.7%) occurred, and major complications were evident in 18 patients (24%). Although early tumor recurrences are common after hepatic transplantation for most metastatic malignancies, this approach to NE tumors has resulted in several reports of long-term survival.[303,304] In a 1997 series of 31 (15 carcinoids) orthotopic liver transplants, 8 patients experienced major transplant-related complications, and 1 died perioperatively. The 5-year survival rate for carcinoids was 69%, and 7 patients were disease free at the time of the report.[302] Bone was the most common site of relapse following transplantation. Further investigation is needed to evaluate the benefits of major hepatic resection and liver transplantation for multifocal hepatic metastases. More recently, 5-year actuarial and disease-free survivals of 24%–73% have been observed after orthotopic liver transplantation for metastatic neuroendocrine tumors, with symptomatic relief occurring in ~90% of patients.[305] Although disease-free survival has been disappointing, this may be a reflection of poor patient selection, with some studies reporting up to 40% of patients presenting with extrahepatic disease prior to transplantation. The examination of histologic and cytologic features of the tumor and the reduction of perioperative mortality by performing staged resection, rather than resecting complex primary tumors at the time of transplantation, may lessen the risk of the transplantation procedure.

Hepatic artery occlusion therapy. Given that current biologic and chemotherapies have minimal potential for hepatic tumor cytoreduction and surgical excision may be either too risky or technically unfeasible, alternative strategies have evolved. Hepatic-artery occlusion or embolization is an alternative for patients who are not

candidates for hepatic resection. It is based on the principle that tumors receive most of their blood from the hepatic artery, whereas hepatocytes are also perfused by the portal venous circulation. Vascular occlusion therapy is thus a relatively safe mode of addressing the dominant site of carcinoid metastasis.[306] Initially, surgical ligation of the common hepatic artery was utilized to effect selective tumor necrosis, but early successes were short-lived because of rapid development of collateral vessel circulation.[306] The subsequent advances of invasive radiologic techniques of transient ischemia[307] and more selective embolization of tumor vasculature[308] were far less morbid and reduced reactive angiogenesis and collateral formation and surgical ligation of hepatic arteries is rarely indicated.[223,237] Nevertheless, vascular occlusion therapy requires careful patient selection and hospitalization and should be undertaken with caution because treatment- and disease-related adverse effects are common and serious.[237,309] These may range from transient symptoms (pain, nausea, fever, fatigue) and biochemical abnormalities (liver enzymes, postembolization syndrome) to florid "carcinoid crisis" (massive bioactive peptide release) with death. The latter can be obviated by the use of SST analogues prior to embolization.[309] Other adverse effects include GI bleeding, gastric and duodenal ulceration, hepatic abscesses, ischemic necrosis of the gallbladder and small bowel, pancreatitis, sepsis, renal failure, hepatorenal syndrome, portal vein thrombosis, sclerosing cholangitis, arterial thrombosis, and arrhythmias.[310]

The use of occlusive agents alone yields biochemical responses from 7% to 75% and tumor responses from 8% to 60%.[307,311] Combinations including chemoembolization or intraarterial chemotherapy in addition to embolization produce biochemical response rates of 12%–75% and tumor response rates of 11%–60%.[225,310,312–314] The duration of the response after hepatic-artery occlusion or embolization is often short, and, in 1 uncontrolled study (n = 65), 23 patients treated with hepatic-artery occlusion alone achieved a response rate (tumor regression or urinary 5-HIAA) of 65%, lasting a median of less than 7 months.[315] Forty-two patients treated with hepatic-artery occlusion followed by systemic chemotherapy had a response rate of 81%, for a median duration of 20 months.[316] Whether such a combined approach results in a survival benefit is unclear. Few rigorous or randomized trials have been undertaken, and there appears to be no definitive data to support the addition of chemotherapeutic agents to vascular occlusive material such as gelfoam, Ivalon, starch particles, lipiodol, or radio isotope-loaded spheres.[237]

Peptide receptor radionuclide therapy. In general, carcinoids are resistant to radiotherapy, although external beam therapy has been used for palliation of bone metastases and the management of spinal cord compression and brain metastases.[317] More recently, systemic receptor-targeted or metabolically directed radiotherapy has been introduced for inoperable or metastasized GEP tumors using ^{131}I-MIBG or a variety of radiolabeled SST analogues. These therapies involve complex dosimetry and require patient isolation during treatment but have modest adverse effects and effect some degree of disease stabilization. Reports of responses to ^{131}I-MIBG, [^{111}In-DTPA-D-Phe]octreotide, ^{90}yttrium, and ^{177}lutetium-labeled SST analogues have been published.[113,318–324] Taal et al[325] treated 30 and 20 carcinoid patients, respectively, with ^{131}I-MIBG and unlabeled MIBG; biochemical response rates were <10% in both groups.

Initial studies with high dosages of [^{111}In-DTPA^0]octreotide in patients with metastasized NETs were encouraging but partial remissions exceptional. On average, response rates were between 13% and 20%.[319–322] The subsequent use of [^{90}Y-DOTA^0, Tyr^3]octreotide (^{90}Y-DOTATOC; OctreoTher) have suggested increased efficacy with some partial remissions (10% and 30%), better than those obtained with [^{111}In-DTPA^0]octreotide, but a number of these studies could not demonstrate objective tumor regression.[326,327] The effects of radionuclide therapy are better at maintaining the status quo, with 53% and 79% of patients achieving biochemical or tumor size stability, respectively. The newest radiolabeled somatostatin analogue [^{177}Lu-DOTA^0,Tyr^3]octreotate, which has a higher affinity for the somatostatin receptor subtype 2 and is labeled with the β and γ-emitting radionuclide ^{177}Lu, has resulted in complete or partial responses in 30% of 76 patients and tumor responses in 48% of patients, respectively.[328,329] In these studies, tumor regression was positively correlated with a high uptake on the Octreoscan, limited hepatic tumor mass, and high Karnofsky performance score. Overall symptomatic improvement may occur with either ^{111}In, ^{90}Y, or ^{177}Lu-labeled somatostatin analogues that have been used for peptide receptor radionuclide therapy (PRRT), but the results obtained with [^{90}Y-DOTA^0,Tyr^3]octreotide and [^{177}Lu-DOTA^0, Tyr^3]octreotate are more encouraging in terms of tumor regression. An issue of concern is renal damage, but this can be decreased by a pretherapy amino acid infusion, which produces an added degree of kidney protection. Because the adverse effects of this type of therapy are few and mild and the duration of the therapy response for

radiopharmaceuticals more than 2 years, this modality of therapy is a promising new therapeutic tool.

Management of Carcinoid-Related Fibrosis

There is no effective pharmacotherapy to obviate the development of fibrosis.[47] Abdominal surgery is necessary if obstructive symptomatology or ischemia is evident, but such intervention is often difficult given the "cocoon effect" of fibrosis and has a high morbidity because of the fibrosis and sclerosis of the mesenteric vessels with associated poor anastomotic vascularization. Nevertheless, palliative intervention provides durable, long-term symptom relief and substantial periods of survival.[47] Although the most widely accepted therapy for carcinoid heart disease is valvular replacement surgery, this approach is associated with high perioperative morbidity and mortality, particularly in older patients, but survivors have substantial improvement of symptoms and increased quality of life.[56,330] Patients with symptomatic carcinoid heart disease may also benefit from palliative balloon pulmonary valvuloplasty in conjunction with cardiac catheterization.[331]

Conclusion

Carcinoid tumors of the GI tract are relatively rare compared with their adenocarcinomatous counterparts. Nevertheless, they may display a similar aggressive biology, in particular when they are located in the colon, stomach, and SI. An early and accurate diagnosis is often absent because symptoms and signs may be vague and nonspecific and misconstrued as irritable bowel syndrome, asthma, or perimenopausal symptoms or part of an anxiety or food allergy response. In fact, the "classical" carcinoid syndrome is expressed in relatively few instances. Because each lesion is composed of its own distinct NE cell(s), depending on the organ of origin, each tumor behaves as a different biological entity that requires a site-specific therapeutic approach. However, common to all carcinoid tumors is the high percentage of coexisting noncarcinoid tumors and multicentricity, warranting a meticulous evaluation during diagnosis and treatment. To assure progress, it is necessary to elucidate the different NE cell types, define their growth regulation, characterize their secretory products, and establish the molecular basis of the individual tumors. The need to define a plasma or genetic marker to predict or identify early lesions is paramount. NE cell lineage, phenotype regulation, and transformation stimuli need to be delineated to either predict tumor initiation or facilitate the development of effective therapeutic strategies. Although surgery has some application in decreasing tumor bulk, molecular techniques to identify micrometastasis are needed, and targeted therapeutic probes must be identified to enable ablation of metastases not amenable to excision. Although SSTR therapy is useful in ameliorating symptoms, alternative strategies (drug delivery, receptor affinity) to improve efficacy are needed. There are currently no methods to predict or detect fibrosis and no therapeutic agent to obviate the consequences of cardiac or peritoneal fibrosis. Radiolabeled therapy appears of some utility in stabilizing some carcinoids, but the technique needs refinement and further rigorous evaluation to improve delivery, dosing, and safety. Overall, the elucidation of the fundamental biologic parameters of NETs is necessary to facilitate diagnosis, improve the delineation of principal prognostic factors, and refine future therapeutic modalities.[253]

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Address requests for reprints to: I. M. Modlin, M.D., Ph.D., F.R.C.S. (Ed,Eng), FACS, Yale University School of Medicine, 333 Cedar Street, P.O. Box 208062, New Haven, Connecticut 06520-8062. e-mail: imodlin@optonline.net; fax: (203) 737-4067.

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