Biology and Treatment of Metastatic Gastrointestinal Neuroendocrine Tumors

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ABSTRACT

Neuroendocrine malignancies of the gastroenteropancreatic axis include carcinoid and pancreatic endocrine tumors. These heterogeneous neoplasms arise from the enterochromaffin cells of the gastrointestinal tract and the islet cells of the pancreas. Histologically, most well-differentiated endocrine tumors consist of small, round, monomorphic cells, arranged in islands or trabeculae, with a distinct "salt-and-pepper" pattern of nuclear chromatin. Chromogranin and synaptophysin are useful as immunohistochemical markers of neuroendocrine differentiation. Other common features include the capacity to secrete peptide hormones and biogenic amines. A relatively indolent growth rate is characteristic of most gastrointestinal neuroendocrine tumors, with the exception of poorly differentiated tumors which are usually aggressive. Treatment strategies are designed to limit tumor progression and palliate hormonal syndromes. This article reviews the diverse biologic characteristics of gastrointestinal neuroendocrine tumors and current treatment options for metastatic disease.

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Neuroendocrine malignancies of the gastroenteropancreatic axis include carcinoid and pancreatic endocrine tumors (PETs). Metastatic gastroenteropancreatic neuroendocrine tumors are typically indolent malignancies characterized by a propensity to secrete hormones and vasoactive substances, resulting in characteristic clinical syndromes. Their clinical behavior varies based on site of tumor origin and histologic differentiation, which appear to be the most important prognostic factors in the natural history of metastatic carcinoid tumors. Although most gastrointestinal neuroendocrine tumors (NETs) are characterized by a relatively slow growth rate, poorly differentiated (PD) neuroendocrine carcinomas are highly aggressive malignancies.

Survival of patients with metastatic carcinoid and pancreatic endocrine tumors appears to have improved over the years. Treatment strategies largely aim to limit tumor progression and palliate hormonal syndromes. The distinct biologic characteristics of gastrointestinal neuroendocrine tumors and current treatment options for metastatic disease are reviewed herein.

CARCINOID TUMORS

Carcinoid tumors are thought to arise from enterochromaffin cells in the intestine and bronchial tree. They were first described in 1888 by Lubarsch who identified multifocal ileal tumors in two autopsy specimens.[1] In 1907, Oberndorfer coined the term "karzinoid tumoren" to describe ileal tumors that appeared to behave more indolently than typical intestinal adenocarcinomas.[2] The term "carcinoid" (meaning "cancer like") is somewhat of a misnomer, since even the smallest ileal neuroendocrine tumors can metastasize. Nevertheless, the terminology has persisted, despite efforts to revise the nomenclature. Approximately 70% of carcinoid tumors arise in the gastrointestinal (GI) tract and about 25% originate in the lungs.[3,4] Other rare primary sites include larynx, thymus, kidneys, and ovaries.

It was not until the 1950s that the carcinoid syndrome was described and serotonin was identified as the primary secretory product associated with symptoms such as flushing and diarrhea.[5,6] Serotonin is derived from the amino acid tryptophan, and is inactivated by the liver into 5-hydroxyindoleacetic acid (5-HIAA), a urinary metabolite. Consequently, the carcinoid syndrome occurs primarily in patients with metastatic tumors that secrete serotonin directly into the systemic (rather than portal) circulation. Other vasoactive substances elaborated by carcinoid tumors include biogenic amines (such as histamine, dopamine, and hydroxytryptophan), tachykinins (kallikrein, substance P), and prostaglandins.[7–10]

Carcinoid heart disease typically occurs in patients with high levels of circulating serotonin.[11,12] Characteristic thickening and fibrosis of right-sided cardiac valves produces tricuspid regurgitation and pulmonary stenosis.[13] The right heart is invariably affected due to its direct exposure to serotonin secreted by liver metastases. Left heart valves are clinically involved in only 10% of cases. The precise underlying mechanism of valvular fibroblast proliferation is uncertain.[14,15]

The annual clinical incidence of carcinoid tumors is estimated to be 2–4 per 100,000,[3,4] although studies that incorporate autopsy data indicate a higher subclinical incidence of 8 per 100,000.[16] The most common site of origin is the

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small intestine, followed by the rectum, appendix, colon, and stomach (Figure 1).[4] Median age at diagnosis is 60, with a slight female preponderance.[4]

Carcinoid Tumor Subtypes

Carcinoid tumors have distinct characteristics, depending on their site of origin. In the 1960s, Williams et al classified carcinoid tumors based on embryologic derivation, distinguishing between foregut (bronchial, stomach, duodenal), midgut (jejunal, ileal, cecal, appendiceal), and hindgut (distal colon and rectal) tumors.[17] As a rule of thumb, midgut carcinoid tumors, arising primarily from the ileocecal region, produce the typical carcinoid syndrome, hindgut tumors are hormonally inactive, and foregut tumors may be associated with atypical hormonal syndromes. While this classification has some utility, it is now evident that each specific site possesses its own unique clinical characteristics.

Gastric Carcinoid Tumors

Carcinoid tumors of the stomach originate from gastric neuroendocrine cells termed "enterochromaffin-like" (ECL) cells.[18] They can develop sporadically, or arise from the trophic effects of elevated serum gastrin. Three distinct types have been identified.[18–20]

Type I tumors occur in the setting of chronic atrophic gastritis and account for about 80% of gastric carcinoids.[18,19,21–23] In this condition, serum gastrin rises in response to gastric achlorhydria. Elevated serum gastrin, in turn, causes diffuse ECL hyperplasia and development of multifocal, polypoid carcinoid tumors. These tumors are generally benign, with no reported cases of tumor-related mortality.[18] The diagnosed incidence of type I gastric carcinoid tumors has been rising markedly with increasing use of upper GI endoscopy.[19] Usually, these tumors can be managed conservatively with endoscopic surveillance and snare polypectomy.[24] Rarely, antrectomy is recommended to eliminate the underlying gastrin stimulus.[25,26]

Type II gastric carcinoids likewise arise in the setting of hypergastrinemia. In these rare tumors, elevated gastrin is produced by pancreatic or duodenal gastrinomas typically in the setting of multiple endocrine neoplasia 1 (MEN1).[27] As is the case in type I gastric carcinoids, tumors tend to be small, multifocal, and clinically indolent.[18,27] Instances of tumor regression have been described among patients treated with somatostatin analogs.[28]

Sporadic gastric carcinoid tumors (type III) occur in about 15% of cases and are not associated with elevated gastrin levels.[27] These tumors have a much higher malignant potential than type I or type II gastric carcinoids, and are typically managed with radical gastrectomy when discovered at an early stage.

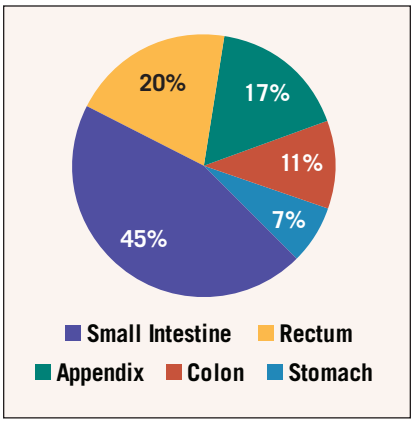

Figure 1. Distribution of gastrointestinal carcinoid tumors by primary tumor site.[4]

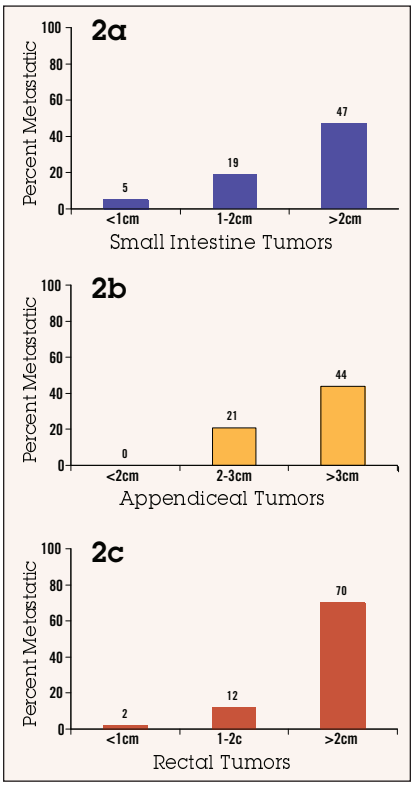

Figure 2. Relationship between tumor size and frequency of distant metastases in carcinoid tumors of the small intestine (2a),[29] appendix (2b),[40] and rectum (2c).[44]

Ileocecal Carcinoid Tumors

The majority of carcinoid tumors originate in the terminal ileum, where the concentration of enterochromaffin cells is highest. Up to 25% of ileal carcinoid tumors are multifocal on pathologic examination.[29] Malignant potential correlates closely with tumor size, however, even tumors smaller than 1 cm can metastasize (Figure 2a).[30,31] The most frequent sites of distant spread are the liver, bone, and peritoneal cavity.[31,32] Lymph node metastases at the root of the mesentery are common, and may be associated with dense desmoplastic fibrosis, rendering them unresectable (Figure 3).[29,31]

The carcinoid syndrome occurs primarily in patients with serotonin-secreting metastatic small intestinal carcinoid tumors. Common symptoms include flushing (a vasomotor phenomenon described as a sensation of warmth associated with erythema) and diarrhea.[5,31,33,34] Bronchospastic symptoms occur less frequently. The term "carcinoid crisis" describes circulatory collapse caused by an acute release of serotonin and other vasoactive substances into the circulation.[35,36] Triggers include general anesthesia[37] and epinephrine.[36]

Appendiceal Carcinoid Tumors

Appendiceal carcinoid tumors are found in approximately 1 in 300 appendectomy specimens, nearly always incidentally.[38] They typically arise from submucosal endocrine cells at the tip of the appendix.[39] Median age at presentation is approximately 40 with a female predominance of 2 to 1.[40] Large retrospective series confirm that metastatic disease occurs exclusively in tumors larger than 2 centimeters, regardless of local invasiveness (Figure 2b).[41] Thus, simple appendectomy is sufficient for the majority of appendiceal carcinoid tumors, whereas staging studies and right hemicolectomies are generally indicated for tumors larger than 2cm.[41,42]

Rectal Carcinoid Tumors

Carcinoid tumors originating in the rectum are often discovered incidentally during lower endoscopy or as a result of lower GI bleeding.[43] They are not associated with a hormonal syndrome.[44] Malignant potential closely correlates with size.[30] Tumors smaller than 1 cm rarely metastasize and can usually be resected endoscopically or

transanally, whereas tumors larger than 2 cm metastasize in over 50% of cases (Figure 2c).[43,45-48] The metastatic potential of intermediate size tumors appears to correlate with invasion of the muscularis propria.[45]

PANCREATIC ENDOCRINE TUMORS

Pancreatic endocrine tumors arise from the islet cells of the pancreas. These heterogeneous neoplasms can secrete a variety of peptide and amine hormones, including insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), ACTH, serotonin, somatostatin, and parathyroid hormone. Tumors that do not produce a hormonally active product are termed "nonfunctional." The annual incidence of pancreatic endocrine tumors is approximately 1 per 100,000.[49] Up to 20% are associated with MEN1, an autosomal dominant hereditary syndrome.

Pancreatic Endocrine Tumor Subtypes

Pancreatic endocrine tumors are classified according to the hormone they produce. Approximately 35% to 85% are considered nonfunctional.[50,51] Insulinomas and gastrinomas are the most common functional subtypes, with an annual incidence of 1–4 cases per million.[52] The incidence of rarer subtypes such as VIPomas and glucagonomas is estimated to be less than one per ten million.[53,54]

The majority of pancreatic endocrine tumors are malignant, with the exception of insulinomas, which are usually benign. Gastrinomas are most commonly associated with MEN1, where they tend to be multifocal.

Insulinomas

About 90% of insulinomas are smaller than 2 cm, and less than 10% are considered malignant.[52,55] Patients typically present with neuroglycopenic symptoms such as dizziness, lethargy, palpitations, and diaphoresis. Diagnosis is established during a monitored fast where serum glucose is measured along with insulin in order to demonstrate hypoglycemia (glucose <45 mg/dL) associated with inappropriate insulin elevation (> 6 μU/mL).[56] C-peptide can also be measured to exclude exogenous insulin administration.[57]

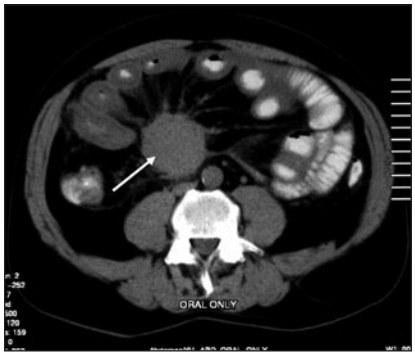

Figure 3. Metastatic carcinoid tumor to the root of the mesentery (arrow) causing typical circumferential desmoplastic fibrosis.

Computed tomography (CT) scans generally reveal small, round, hypervascular tumors. Other imaging techniques include magnetic resonance imaging (MRI) and ultrasonography (transabdominal, endoscopic, or intraoperative).[58] Somatostatin receptor scintigraphy using octreotide tagged with radiolabeled ^{111}Indium-pentetreotide (OctreoScan) is relatively insensitive, because up to 40% of insulinomas express insufficient somatostatin receptors.[59] In cases of occult tumor, arterial calcium stimulation with hepatic venous sampling can aid with tumor localization.[60]

Gastrinomas

Gastrinomas originate in the duodenum and the pancreas, typically in proximity to the pancreatic head. About 60%–80% are considered malignant and one third of patients present with distant metastases at diagnosis.[61,62] The MEN1 syndrome is implicated in about 20% of cases and is associated with tumor multicentricity.[63] The gastrinoma syndrome, also known as the Zollinger-Ellison syndrome,[64] is caused by hypersecretion of gastrin stimulating gastric acid release into the stomach. The most common manifestations are dyspepsia, heartburn, and diarrhea.[65] Peptic ulcerations can affect atypical locations such as the jejunum. Diarrhea results from the passage of excess gastric acid into the small intestine, neutralizing digestive pancreatic enzymes and causing malabsorption.

The diagnosis of gastrinoma can be established when serum gastrin levels exceed ten times the upper limit of normal (ie, > 1,000 pg/mL). It is important to note that acid blocking drugs, such as proton pump inhibitors, can elevate serum gastrin levels and lead to false-positive results.[66] In cases where the diagnosis is equivocal, a secretin stimulation test can help identify gastrinomas: a serum gastrin rise of > 200 pg/mL is considered diagnostic, with a sensitivity and specificity of 83% and 100%, respectively.[67] Useful imaging studies include CT scans, MRI, ^{111}In-pentetreotide scintigraphy,[68] and endoscopic ultrasonography.[69,70] Surgical duodenal transillumination can identify small duodenal gastrinomas.[71]

Prior to the advent of acid blocking medications, the Zollinger-Ellison syndrome was a highly morbid condition necessitating palliative gastrectomy or vagotomy.[72] Today, high-dose proton pump inhibitors effectively control symptoms in the majority of cases.[73,74] Some studies support titration of

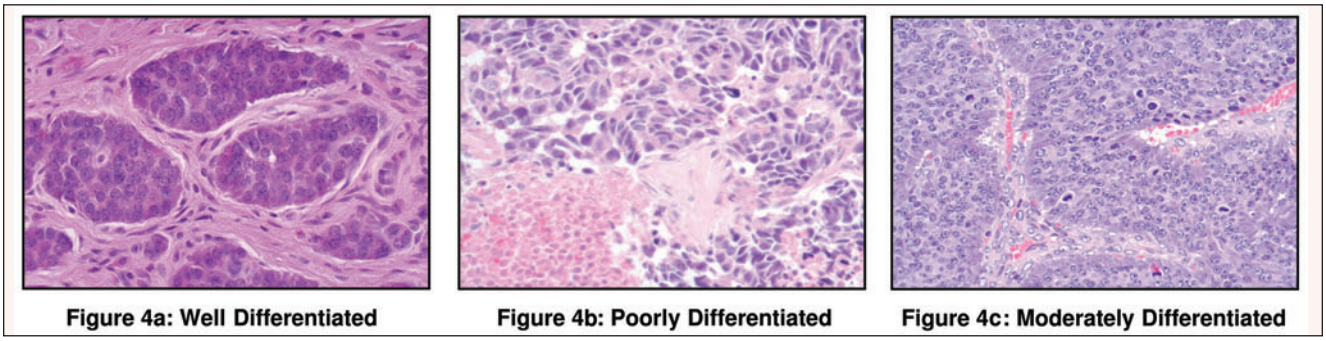

Figure 4: Examples of well differentiated (4a), poorly differentiated (4b), and moderately differentiated (4c) gastrointestinal neuroendocrine tumors. Photographs courtesy of Nasir Aejaz, MD, Department of Pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa.

acid-blocking agents to achieve an optimal gastric acid secretion rate of < 10 mEq/h.[75]

Rare Subtypes

VIPomas secrete vasoactive intestinal peptide.[76] The resulting syndome (also known as the Verner-Morrison syndrome) is characterized by profuse watery diarrhea, often exceeding 3 liters a day.[54,77,78] Due to the severity of the diarrhea, the syndrome is sometimes described as "pancreatic cholera."[79] Other complications include flushing, dehydration, hypochlorhydria, and hypokalemia.[80] VIPomas are typically large at presentation (> 3 cm) and usually originate in the tail of the pancreas. The majority are malignant.[54]

Glucagonomas arise from the alpha cells of the pancreas.[81] The clinical manifestations are protean, and may include hyperglycemia, anorexia, weight loss, venous thromboses, cheilitis, and an unusual rash called necrolytic migratory erythema (NME).[53] NME characteristically manifests as painful, weeping, erythematous papules or plaques involving the face, perineum, and flexural regions.[82] The underlying mechanism of NME is uncertain.

HISTOLOGIC CLASSIFICATION

The majority of gastrointestinal neuroendocrine tumors are described histologically as well-differentiated (Figure 4a). This term identifies tumors with a relatively monomorphic population of small, round cells, a low mitotic rate of < 2 mitoses/10 high powered fields (HPF), a low Ki-67 proliferative index (< 2%), and absence of necrosis.[83-88] Well-differentiated neuroendocrine tumors (WD-NETs) are clinically indolent and associated with prolonged survivals, even in the metastatic setting. Poorly differentiated (PD) neuroendocrine carcinomas (Figure 4b) are associated with cellular pleomorphism, a mitotic rate > 10 mitoses/10 HPF, a Ki-67 proliferative index >10%, and tumor necrosis. These are highly aggressive malignancies that closely resemble small-cell carcinoma of the lung, both in morphologic appearance and clinical behavior.[87–89] Intermediate grade or "moderately differentiated" (Figure 4c) tumors of the gastroenteropancreatic axis are not well defined in the medical literature, but appear to have an intermediate prognosis.[84,86,90]

In recent years, the World Health Organization (WHO) developed a classification system for endocrine tumors of the gastrointestinal tract. Using the WHO (2000) nomenclature,[91] the term "carcinoid" is applied to serotonin-producing WD endocrine neoplasms of the small intestine, appendix, and colon. A clinicopathologic classification has also been proposed by WHO (2004)[92] for pancreatic endocrine neoplasms that distinguishes between WD endocrine tumors (benign or uncertain behavior), WD endocrine carcinomas, and PD endocrine carcinomas, based on tumor size, local invasion of adjacent organs, angioinvasion, perineural invasion, Ki-67 proliferation index, and the presence of metastases.[87,91,92]

GENETICS AND HEREDITARY PREDISPOSITION

Although the majority of gastroenteropancreatic tumors are sporadic, several autosomal dominant hereditary syndromes have been identified. The underlying genetic abnormalities yield insight into oncogenic pathways of familial and sporadic tumors. Multiple endocrine neoplasia 1 (MEN1) is an autosomal dominant hereditary syndrome characterized by a predisposition to tumors of the parathyroid glands, anterior pituitary, and pancreatic islet cells.[93] The underlying tumor suppressor gene mutation has been identified in the long arm of chromosome 11 (11q13).[94] Its protein product "menin" has been recently cloned and appears to be a regulator of gene expression.[95] Germline MEN1 genetic testing appears to have a 70%–90% sensitivity in familial MEN1 cases and a somewhat lower sensitivity in sporadic cases.[96]

The most frequent manifestation of MEN1 is parathyroid hyperplasia, which typically develops in the second to fourth decade.[97] Pituitary adenomas form in about 15%–20% of patients. Pancreatic endocrine tumors become clinically apparent in about one third of patients, with a higher rate of subclinical disease. Gastrinomas occur most often, followed by insulinomas. Tumors are almost invariably multifocal;[98] consequently, the role of curative surgical therapy is controversial.[99,100] An exceptionally indolent growth pattern is characteristic of these tumors; consequently life expectancy appears to be only modestly diminished in MEN1 patients.[101,102]

Von-Hippel Lindau (VHL) syndrome is caused by an autosomal dominant mutation in the VHL gene located on chromosome 3p25.[103] This gene is involved in the regulation of a hypoxia-inducible gene (HIF-1alpha) expression. Induction of hypoxia-associated cytokines, including erythropoietin, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF), is thought to stimulate tumor growth, but the precise mechanism of tumorigenesis is unknown. A variety of tumors can develop in VHL syndrome, including renal cell carcinomas, hemangioblastomas, pheochromocytomas, pancreatic cysts, and pancreatic endocrine tumors. The latter occur in only 10% of cases,[104] and tend to progress in an indolent fashion.

Tuberous sclerosis is an autosomal dominant syndrome characterized by low-grade neoplasms and hamartomas in multiple organs, including skin, brain, and kidney. Pancreatic endocrine tumors occur in 1%–5% of cases.[105] Two variants have been described: TSC1 caused by a mutation on chromosome 9q34[106] encoding hamartin and TSC2 on chromosome 16p13 encoding tuberin.[107] A complex of hamartin and tuberin is thought to regulate cell-cycle progression, possibly through upregulation of the mTOR cell-signaling pathway.[108,109]

Hereditary syndromes have not been identified in carcinoid tumors, and a family history is reported in less than 1% of patients.[110] The relative risk of a carcinoid tumor diagnosis in a patient with a first degree affected relative is estimated to be 3.6,[111,112] thus the absolute risk remains low and does not warrant screening.

The genetic aberrations in sporadic gastrointestinal neuroendocrine tumors are poorly understood. Oncogenes and tumor suppressor genes that are mutated in common human malignancies (p53, APC, Rb, K-ras) do not appear to be implicated in neuroendocrine tumor development.[113–116] Mutations of the MEN1 gene (chromosome 11q13) occur in about 20% of sporadic, solitary pancreatic endocrine tumors,[117,118] whereas chromosome 18 deletions are common in midgut carcinoid tumors.[119–121] Techniques such as compar-

ative genomic hybridization have identified gains and losses in numerous chromosomes.[120–123] These genetic abnormalities appear to increase in pancreatic endocrine tumor metastases compared to matched primary tumors.[124] Nonfunctional pancreatic endocrine tumors also appear to contain an increased frequency of chromosomal aberrations compared to functional tumors.[125]

Cell-signaling pathways influence tumor growth and hormonal activity. Neuroendocrine cells can express the insulin-like growth factor (IGF) as well as its receptor (IGFR).[126] Cell line studies indicate that IGF-1 can act in an autocrine and paracrine fashion to inhibit apoptosis and stimulate secretion of chromogranins, possibly by activating the PI3K-AKT pathway.[127] Vascular endothelial growth factor is also expressed by neuroendocrine tumors,[128,129] and elevated levels of circulating VEGF have been associated with tumor progression.[130] Cyclin D1, an important component of cell cycle regulation, has been found to be overexpressed in pancreatic endocrine tumors.[131]

IMMUNOHISTOCHEMICAL AND SERUM MARKERS

General immunohistochemical markers of neuroendocrine differentiation include chromogranin, synaptophysin, CD56, protein gene product (PGP) 9.5, and neuron-specific enolase (NSE). Chromogranins are a family of glycoproteins associated with dense-core secretory vesicles found ubiquitously in neuronal and endocrine tissues.[132] Chromogranin A (CgA) was first isolated from chromaffin cells of the adrenal medulla.[133] Synaptophysin is a synaptic vesicle membrane protein also found commonly in neuronal tissues and in endocrine tumors.[134] Neuron-specific enolase is a cytoplasmic enzyme detected in tumors of neuroendocrine differentiation, but lacks specificity compared to CgA and synaptophysin.[135] Chromogranin positivity generally correlates with the extent of granularity on electron microscopy. WD-NETs tend to exhibit diffuse and intense expression of CgA and synaptophysin, whereas PD neuroendocrine carcinomas show significantly reduced CgA expression while maintaining intense staining for synaptophysin.[83]

Immunostaining for specific hormones can aid in the diagnosis of neuroendocrine tumors. The various hormone-specific markers used in immunophenotyping of pancreatic endocrine tumors include insulin, glucagon, somatostatin, gastrin, VIP, calcitonin, serotonin, ACTH, and neurotensin. This immunoreactivity, however, does not necessarily correlate with serum hormone levels or clinical syndrome. For example, a study of nonfunctional pancreatic endocrine tumors demonstrated that 87% were immunoreactive to at least one peptide hormone, such as insulin or glucagon.[136]

Serum and urine tumor markers include hormones and their metabolites (eg, serotonin, 5-HIAA, insulin, glucagon, gastrin) and nonspecific tumor markers such as chromogranin, pancreatic polypeptide (PP), NSE, and substance P. Hormone levels should be assessed in accordance with the patient's clinical syndrome. The specificity of a 24-hour 5-HIAA urine collection approaches 100% in metastatic carcinoid tumors, and sensitivity is high for detection of the carcinoid syndrome.[133,137] Strict avoidance of serotonin-rich foods during urine collection is necessary to prevent false-positive test results.[138]

The most sensitive general serum marker of neuroendocrine tumors is chromogranin A.[133] It is released into the circulation in approximately 90% of pancreatic endocrine tumors and 70%–100% in metastatic gastrointestinal carcinoid tumors.[139,140] False positive tests, however, can occur with renal or hepatic impairment or with atrophic gastritis and proton pump inhibitor use (due to ECL hyperplasia). Serum levels of CgA tend to be highest in metastatic midgut carcinoid tumors and correlate with tumor burden,[141,142] as well as response to treatment.[143]

TREATMENT OF METASTATIC DISEASE

Metastatic neuroendocrine tumors vary widely in their clinical manifestations and rate of growth. Many patients remain asymptomatic and can be managed conservatively with close observation. Others progress rapidly and develop symptoms related to hormonal secretion and/or tumor burden. Standard treatment options include somatostatin analogs, surgical cytoreduction, cytotoxic chemotherapy, interferon, and hepatic artery embolization. Novel therapies under investigation include angiogenesis inhibitors, mTOR inhibitors, and radiolabeled somatostatin analogs. The choice of treatment depends on several factors, including location of primary tumor, pattern of metastatic spread, levels of somatostatin receptor expression, and hormonal activity.

Somatostatin Analogs

The human hormone somatostatin is released by neuroendocrine cells of the gastrointestinal tract and has an inhibitory effect on bowel motility, gastrointestinal secretion, and absorption of nutrients. The actions of somatostatin are mediated through 5 receptors (SSTR 1–5).[144] Several of these receptors, including SSTR subtypes 2 and 5, are important in the inhibition of gastrointestinal and pancreatic hormone secretion, whereas SSTR subtype 1 is thought to mediate cell-cycle arrest and apoptosis.[145,146] The antisecretory effects of somatostatin have made it an important tool in the management of hormonally active neuroendocrine tumors, the majority of which express somatostatin receptors. However, clinical use of native human somatostatin is impeded by its short half-life of approximately 2 minutes.

The first clinically useful analog of somatostatin was octreotide, a synthetic octapeptide with a half life of 2 hours and avid binding affinity to SSTR 2. The initial clinical study of octreotide in patients with the carcinoid syndrome reported amelioration of flushing and diarrhea in 88% of patients and major reductions in urinary 5-HIAA in 72%.[147] Numerous additional studies have confirmed the powerful antisecretory effects of octreotide at dose ranges of 100 μg to 500 μg administered subcutaneously 2 to 3 times daily.[148,149] A long-acting depot formulation of octreotide (Sandostatin LAR®) has become available more recently, enabling monthly dosing.[150] Doses of 10 mg to 60 mg administered every 4 weeks have been found to be well tolerated with no dose-related increase in adverse events. Side effects include nausea and steatorrhea. Due to the inhibitory effects of octreotide on gallbladder contractility, an increased rate of biliary stone formation is observed, but it is rarely of clinical significance. Another somatostatin

analog, lanreotide, has similar somatostatin-binding properties, clinical activity and side-effect profile.[151]

Studies of octreotide in pancreatic endocrine tumors have also demonstrated an antisecretory effect.[152] Octreotide is especially active in management of the glucagonoma and VIPoma syndromes.[153,154] Its efficacy in insulinomas is limited by the relative paucity of somatostatin receptors in these tumors. Several studies have described palliation of hypoglycemia with octreotide therapy,[155–157] however, others have reported exacerbation of symptoms, probably due to suppression of glucagon.[158]

The effects of somatostatin analogs on tumor growth are controversial. While objective response rates are observed in fewer than 5% of patients treated with octreotide,[159,160] there is laboratory and clinical evidence of an inhibitory effect on cell proliferation and tumor growth.[161] Studies have demonstrated growth inhibition in a variety of cell lines and xenograft models treated with somatostatin analogs.[145,161–165] Proposed mechanisms include a direct inhibitory effect via somatostatin receptors on tumor cells vs. an indirect effect mediated by inhibition of growth factors such as IGF or VEGF.[163,166,167] Clinical evidence of an antitumor effect comes from single-arm phase II studies demonstrating a relatively high rate of disease stabilization among patients with progressive metastatic tumors.[168–169]

Table 1. Trials of cytotoxic chemotherapy in metastatic carcinoid tumors.

Regimen	Year	Response rate
Streptozocin + 5-FU vs. streptozocin + cyclophosphamide[184]	1979	33% vs. 26%
Streptozocin + 5-FU vs. doxorubicin[188]	1984	22% vs. 21%
5-FU + doxorubicin + cyclophosphamide + streptozocin[189]	1987	30%
Dacarbazine[190]	1994	16%
Doxorubicin + 5-FU vs. streptozocin + 5-FU[186]	2005	15%
Temozolomide + thalidomide[191]	2006	7%

Abbreviations: 5-FU = 5-fluorouracil

Table 2. Trials of cytotoxic chemotherapy in metastatic pancreatic endocrine tumors.

Regimen	Year	Response rate
Streptozocin + 5-FU vs. streptozocin[192]	1980	63% vs. 36%
Streptozocin + doxorubicin vs. streptozocin + 5-FU[193]	1992	69% vs. 45%
Dacarbazine[195]	2001	31%
Streptozocin + doxorubicin + 5-FU[194]	2006	39%
Temozolomide + thalidomide[191]	2006	7%

Abbreviations: 5-FU = 5-fluorouracil

Radiolabeled Somatostatin Analogs

Approximately 80% of gastroenteropancreatic neuroendocrine tumors express somatostatin receptors and can be visualized with the radiolabeled somatostatin analog ^{111}In-pentetreotide.[170,171] After somatostatin binds with its receptor, a fraction of the ligand-receptor complex internalizes.[172,173] Thus, delivering targeted radiotherapy to neuroendocrine tumor cells using the somatostatin receptor represents a logical therapeutic approach. The first clinical trials of somatostatin-labeled radiotherapy assessed the use of high, cytotoxic doses of ^{111}In-pentetreotide.[174,175] Objective responses with this compound were rare, probably due to the small particle range and short tissue penetration of Auger electrons emitted by the ^{111}In isotope.

The next generation radiolabeled somatostatin analog was [^{90}Y-DOTA^0,Tyr^3]-octreotide.[176–178] The radionuclide ^{90}Y is a β-particle emitter with a maximum tissue range of 12 mm. Objective response rates in several phase I and II trials were in the range of 10%–30%.[179] Dose-limiting side effects included hematologic and renal toxicity.[180]

The most recent research studies involve the compound [^{177}Lu-DOTA^0,Tyr^3]-octreotate, a compound with increased affinity for SSTR subtype 2.[181] Whereas ^{90}Y is a β-particle emitter, ^{177}Lu is both a β- and γ-emitting radionuclide with a shorter range of tissue penetration (2 mm) than ^{90}Y.[182] A trial evaluating 131 patients treated with [^{170}Lu-DOTA^0,Tyr^3]-octreotate at cumulative doses of 600–800 mCi demonstrated an objective response rate of 28%, with relatively mild nephrotoxicity and bone marrow suppression. Among patients who had stable disease or tumor regression, median duration of disease control was in excess of 3 years.[183]

Chemotherapy

Evidence is accumulating that well-differentiated carcinoid tumors are relatively resistant to cytotoxic chemotherapy. Early trials showing high response rates to streptozocin-based combinations did not employ strict radiographic criteria.[184] Contemporary trials have demonstrated low response rates and short progression-free intervals (Table 1).[185–191] Thus, it appears that cytotoxic chemotherapy adds little value to the treatment of metastatic well-differentiated carcinoid tumors.

In contrast, trials of cytotoxic chemotherapy in pancreatic endocrine tumors have established the activity of several drugs including streptozocin, doxorubicin, 5-fluorouracil (5-FU), and dacarbazine (Table 2). Early trials at the Mayo Clinic reported response rates of 63% using streptozocin with 5-FU[192] and 69% using streptozocin with doxorubicin.[193] Contemporary chemotherapy trials employing stricter response criteria have documented response rates of 39% using the combination of 5-FU/streptozocin/doxorubicin[194] and 33% using single-agent dacarbazine.[195] Several studies have substantiated the theory that response rates to chemotherapy differ based on primary

tumor site. For example a recent trial of temozolomide combined with thalidomide demonstrated an objective response rate of 45% in pancreatic endocrine tumors vs. only 7% in metastatic carcinoid tumors.[191]

Poorly differentiated neuroendocrine tumors appear to be highly sensitive to platinum-based cytotoxic chemotherapy. This was demonstrated in a trial of cisplatin and etoposide, documenting a response rate of 67% in poorly differentiated neuroendocrine tumors vs. only 7% in well differentiated tumors.[89] Unfortunately, response durations tend to be relatively short.

Interferon

Interferon-α appears to exert an antiproliferative and antisecretory effect on neuroendocrine tumors. Mechanisms include stimulation of T-cells as well as direct inhibition of tumor cell-cycle progression.[196] An early trial of human leukocyte interferon in patients with the carcinoid syndrome demonstrated an objective tumor response rate of 11%, a significant tumor marker reduction in one half, and symptomatic improvement in two thirds of patients.[197] Subsequent trials with recombinant interferon-α have confirmed objective response rates of approximately 5%–10% with disease stabilization occurring in about 50% of cases.

Several studies have examined the combination of interferon with somatostatin analogs. A trial of patients taking octreotide for progressive carcinoid syndrome reported symptomatic improvement in 49% of patients after the addition of interferon-α.[159] Another study reported a 67% rate of disease stability in patients with progressive neuroendocrine tumors treated with the same combination.[198] However, larger randomized trials have not confirmed that adding interferon to octreotide improves outcomes compared with monotherapy.[198,199]

The optimal dose of interferon-α is unclear. Clinical trials have studied doses ranging from 3×10^6 units to 24×10^6 units administered daily or every other day. Side effects are often dose related and include fevers, chills, myalgias, headaches, and depression. Myelosuppression is common with higher doses. It is uncertain whether responses are dose dependent.

Angiogenesis Inhibitors

Neuroendocrine tumors are highly vascular and express both the VEGF ligand and receptor. Moreover, elevated levels of circulating VEGF (among other angiogenic cytokines) have been associated with tumor progression in neuroendocrine tumors. Thus, it is likely that VEGF-mediated angiogenesis plays an integral role in the metastatic progression of neuroendocrine tumors.

Several studies have evaluated angiogenesis inhibitors in neuroendocrine tumors. A single-arm trial of endostatin in patients with metastatic neuroendocrine tumors demonstrated no objective radiographic responses.[200] Results were somewhat more favorable in a trial of sunitinib malate, a small molecule tyrosine kinase inhibitor of VEGFR-1, -2, and -3, as well as PDGF, KIT, and Flt3. In this study, partial responses were observed in 13% of pancreatic endocrine tumors and 5% of carcinoid tumors.[201]

A randomized phase-II trial comparing the VEGF antibody bevacizumab to pegylated interferon-α demonstrated prolonged progression free survival in the bevacizumab arm.[202] Larger trials are planned to confirm this benefit.

Management of Liver Metastases

The liver is the predominant site of metastatic disease in gastrointestinal neuroendocrine tumors. Patients with hepatic metastases may experience symptoms resulting from tumor burden as well as from uncontrolled hormonal syndromes. Liver-directed treatment options include cytoreductive hepatic surgery, hepatic artery embolization (with or without chemotherapy), or liver transplant.

Surgery is often advocated in patients with limited liver metastases.[203,204] Various ablation techniques have also been described, including cryoablation, alcohol ablation, and radiofrequency ablation (RFA).[205–208] Proponents of cytoreductive surgery cite numerous retrospective studies describing palliation of symptoms and prolonged survival durations among patients undergoing cytoreductive surgery with curative or near-curative intent.[209–212] Nonrandomized studies comparing surgical to nonsurgical therapies also suggest improved survivals associated with aggressive surgical management.[213,214] However, patients managed surgically often present with relatively limited disease; thus comparisons with patients treated medically are inherently biased.

Hepatic artery embolization is typically performed in patients with diffuse, symptomatic and unresectable liver metastases. The rationale is that liver metastases derive their vascular supply primarily from the hepatic artery, whereas normal hepatocytes are fed primarily by the portal vein. To limit morbidity, individual hepatic artery branches are embolized selectively in two to three stages. A variety of embolic materials have been tested, including Gelfoam (Pharmacia & Upjohn Company, Kalamazoo, MI), polyvinyl alcohol (PVA) particles, and trisacryl gelatin microspheres (Embospheres; BioSphere Medical Inc, Rockland, MA) with or without the addition of antineoplastic agents, such as cisplatin, doxorubicin, streptozocin, and 5-FU (Table 3).[215–224] Radioembolization

Table 3. Reviews of hepatic artery embolization in neuroendocrine tumors.

Technique	Year	Response rate
Surgical occlusion or Gelfoam embolization[222]	1994	72%
Intraarterial doxorubicin followed by Gelfoam embolization[219]	1993	33%
Gelfoam embolization[217]	1998	52%
Intraarterial multiagent chemotherapy followed by Gelfoam or PVA embolization[216]	2003	67%
PVA or microsphere embolization[215]	2006	48%

Abbreviations: PVA = polyvinyl alcohol.

using yttrium 90 microspheres has also been reported in very limited numbers of patients.[225] Radiographic response rates are approximately 50%, with higher rates of symptomatic improvement and decline in tumor markers.[215] In the absence of randomized comparative studies, it is unclear whether addition of chemotherapeutic agents to the embolic material (chemoembolization) improves outcomes.

Short-term, predictable toxicities associated with embolization include abdominal pain, nausea, fever, and transaminase elevation, all caused by ischemic hepatitis. Serious adverse effects can include hepatorenal failure, bowel or gallbladder perforation, and hepatic abscess. With prophylactic hydration and antibiotics, treatment-related mortality is exceptionally rare.

The benefit of liver transplantation for patients with metastatic neuroendocrine tumors is uncertain.[226–230] Although data from institutional series vary, most centers document relatively high rates of postoperative morbidity and disease recurrence. In the largest meta-analysis of liver transplants, 5-year survival was 47%, with only 24% of patients free of disease recurrence.[231]

DISCUSSION

The survival of patients with metastatic neuroendocrine tumors appears to have improved over the years. One of the first large epidemiologic studies examining data from 1950–1969 reported a 5-year survival rate of 19% for metastatic small bowel carcinoid tumors, 0% for metastatic tumors of the stomach, and 7% for tumors originating in the rectum.[232] A more recent review of SEER (Surveillance Epidemiology and End Results) data compared survival data from the 1970s and 1980s to contemporaneous survival data.[3] In this analysis, the 5-year survival rate for metastatic small bowel carcinoid tumors improved from 36% to 50%, with corresponding improvements in prognosis for metastatic tumors of gastric, rectosigmoid, and appendiceal origin. Other institutional reviews point to a substantial increase in median survival from approximately 2 years historically[29,184] to over 5 years at the present time.[32,141] A large retrospective study of patients with carcinoid heart disease likewise demonstrated an improvement in median survival from 1.5 years to 4.4 over the past 3 decades.[233]

The most important prognostic factor in the natural history of metastatic carcinoid tumors appears to be the primary tumor site, confirming the diverse biology of carcinoid tumors. Small intestine carcinoid tumors are associated with the longest survival durations, followed by metastatic rectal and stomach tumors.[3,4] Other prognostic variables include gender (survival in women exceeds men), age, and extent of hepatic metastases.[234]

Survival of patients with pancreatic endocrine tumors has also improved over time. An analysis of SEER data indicates an increase in median survival from 13 months (1973–1980) to 39 months (1995–2000) for tumors of all stages.[51] A recent retrospective institutional study of 90 patients with metastatic pancreatic endocrine tumors demonstrated a median survival of 70 months from time of diagnosis for metastases.[235] Hormonally functioning tumors appear to have an improved prognosis compared to nonsecretory tumors, probably due to earlier diagnosis. Due to the scarcity of large, prospective trials, it is difficult to assess the factors contributing most strongly to improved prognosis. Randomized studies are needed to identify new biologic agents that will benefit patients with metastatic neuroendocrine tumors.

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Disclosures of Potential Conflicts of Interest

Dr. Strosberg has received honoraria from Novartis.