

Enteroendocrine Tumors Other Than Carcinoid: A Review of Clinically Significant Advances

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Only relatively recently has there been an increased clinical recognition and characterization of the heterogeneous group of rare gastroenteropancreatic neuroendocrine neoplasms. Most have endocrine function and exhibit varying degrees of malignancy. This review summarizes the derivation of these tumors and the advances in their diagnosis and treatment over the past decade and a half. They are varied in their biological behavior and clinical courses and, depending on their cell type, can produce different hormones causing distinct clinical endocrine syndromes (insulinoma [hypoglycemia], gastrinoma [Zollinger–Ellison syndrome (ZES)], vasoactive intestinal peptideoma [VIPoma], watery diarrhea, hypokalemia-achlorhydria [WDHA], glucagonoma [glucagonoma syndrome], and so forth). In addition to surgery for cure or palliation (by excision and a variety of other cytoreductive techniques), they each are treated with antihormonal agents or drugs targeted to each tumor's specific product or its effects. The majority have benefited from the gut hormone-inhibiting action of somatostatin analogs. Because of their usual slow rate of growth it is recommended that, even when they are advanced and incurable, unlike in patients with common and more malignant cancers, patients with neuroendocrine tumors often can be palliated and appear to survive longer when managed with an active approach using sequential multimodality treatment. Advances in these various therapies are reviewed and the beneficial emergence of global self-help patient support groups is noted.

Neuroendocrine tumors (NETs) comprise approximately 2% of all malignant tumors of the gastrointestinal system and the incidence of all noncarcinoid NETs is approximately one half that of all carcinoids.¹ Noncarcinoid NETs have been reported to occur in .4–1.5/100,000 of the population.^{2–5}

This article provides a clinically relevant update of the biology, diagnosis, and management of these rare tumors and briefly summarizes their main features. The majority of noncarcinoid NETs arise from the pancreas. Many excellent comprehensive descriptions of the basic features of each of these tumors and their clinical syndromes are

available in a number of reviews and standard textbooks.^{6–12}

The most noteworthy recent advances in dealing with all gastroenteropancreatic (GEP) NETs have been: (1) increased recognition of their clinical features, which has led to greater awareness of these tumors and hence their increased diagnosis; (2) recognition of the wide spectrum of manifestations, clinical behavior, and response to treatment shown by these tumors; (3) wide acceptance and availability of reliable tests for chemical markers and imaging methods; (4) increasingly more aggressive application of effective surgical and medical treatments resulting in improved palliation and survival; and (5) development and growth of patient self-help support groups.

Basic Biology of GEP NETs

An understanding of the basic biology unique to NETs is necessary for optimum management of patients with these complex tumors. There are at least 14 endocrine cell types in the gut and these along with the endocrine cells of the pancreas produce at least 33 hormones and biogenic amines.^{13,14} These cells have many similarities to neural cells. They produce bioactive substances that serve transmitter functions, albeit via endocrine, autocrine, or paracrine modes, even in the absence of axons and synapses. In addition, they have many histologic similarities to neural cells such as secretory granules, similar cellular antigens, and the markers chromogranin-A, synaptophysin, and neurone-specific enolase. These features led to the designation *neuroendocrine cells*. They constitute the diffuse endocrine system.^{13,15,16} Pearse^{17,18} recognized that all of these cells have in

Abbreviations used in this paper: APUD, Amine precursor uptake and decarboxylation; CgA, chromogranin-A; GEP, gastroenteropancreatic; MEN-1, multiple endocrine neoplasia syndrome 1; NET, neuroendocrine tumor; PET, pancreatic endocrine tumor; SRS, somatostatin receptor scintigraphy; SST, somatostatin; SSTr, somatostatin receptor; ZES, Zollinger–Ellison syndrome.

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varying degrees a common biological function, the ability to take up amine precursor substances, and perform their decarboxylation. Hence, they can produce peptide hormones and biogenic amines (such as serotonin and catecholamines). The acronym Amine precursor uptake and decarboxylation (APUD) therefore has been applied to this cell system and tumors arising from neuroendocrine cells have been called apudomas. The APUD concept led to the belief that these cells arise from the embryologic neural crest. This hypothesis eventually was found to be incorrect by convincing evidence that now points to these cells arising mainly from multipotential stem cells of endodermal origin in the pancreas¹⁹ and scattered throughout the intestinal tracts.^{13,19} Collectively they are known as enteroendocrine cells. Because of their histologic staining affinity for chromium salts and silver salts they also are known as chromaffin or enterochromaffin cells, and in the gut they are known as Kulchitsky or argentaffin cells. If a reducing agent is required for staining with silver salts they then are called argyrophilic cells. Although sprinkled as individual cells in the gut mucosa, they are found in the pancreatic islets of Langerhans in microscopic glandular aggregates where, similar to the endocrine cells in the intestine, they differentiate into the various specific endocrine tissues and phenotypes.

Although the embryologic origin portion of the APUD concept has been disproved, the view of a common biochemical endocrine function of these cells has been useful and appears valid. The cell type-specific hormonal substance produced by the enteroendocrine cell defines the type of NETs originating from that cell (serotonin-carcinoid, gastrin-gastrinoma, vasoactive intestinal peptide-VIPoma, insulin-insulinoma, glucagon-glucagonoma, and so forth).²⁰ The clinical syndrome that may be associated with each of these tumors results from the excessive production of the tumor's resident hormone(s). Those NETs not producing an excess of clinically active hormones cause no clinical endocrine syndrome, and are called nonfunctioning NETs. However, there is considerable variation in the correlation of blood levels of pancreatic endocrine tumor (PET) hormonal products and clinical syndromes, some PETs produce several hormones but cause only one syndrome.²¹

Besides the NETs arising from the GEP system the diffuse endocrine system can be the source of NETs arising elsewhere such as the lung, bronchus, thymus and other tissues, small-cell carcinoma and medullary thyroid carcinoma, neuroblastoma, pheochromocytoma, Merkel cell carcinoma of the skin, and various NETs of the anterior pituitary.¹² Although our considerations in this article are directed to the noncarcinoid NETs of the GEP

system, much of the information presented has application to NETs of other organ systems.

Genetics

The genetic studies indicating a difference between tumorigenesis of sporadic NETs of the pancreas and pancreatic adenocarcinomas have been well reviewed recently.⁶ Although at present no clearly identifiable common pattern of genetic aberration has emerged to form a molecular basis for the tumorigenesis of sporadic GEP NETs, recently a variety of genetic alterations has been found in some PET patients.²⁰ A loss of heterogeneity at chromosome 11q is common in functioning tumors and uncommon in nonfunctioning ones. Loss of heterogeneity at chromosome 6q was noted to be associated with nonfunctioning tumors.²² One third of PETs had allelic loss on chromosome 3p, which is adjacent to the small von Hippel-Lindau disease tumor-suppressor gene. Also, this allelic loss is associated with clinically malignant disease with extrapancreatic spread occurring with a 5-fold greater frequency.^{23,24} Patients with aneuploid tumors were found to have a shorter survival than those with diploid tumors.^{25,26}

In contrast to the limited knowledge of the molecular basis of tumorigenesis in sporadic GEP NETs, more certain important alterations have been identified for the familial syndromes²⁰: multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau disease, and neurofibromatosis type 1.^{27,28} They are inherited autosomal-dominant disorders. MEN-1 is associated with mutation and allelic loss in the *Menin* gene, a tumor suppressor on chromosome 11q 13.^{6,29} Allelic deletion of this gene also has been found in a number of well-differentiated sporadic PETs in various studies summarized by Rindi et al.³⁰ This suggests the likely importance for involvement of the MEN-1 gene in tumorigenesis of some sporadic NETs of the pancreas.

The 2-hit hypothesis of tumorigenesis of MEN-1 proposed by Knudson^{31,32} is based on the germline occurrence of MEN-1 gene mutation in all cells of the body, making the carrier of the inherited defective gene heterozygous and predisposed to tumor development in susceptible cells. The tumor develops when a second mutational event occurs (second hit), eliminating the remaining normal gene (ie, the second copy) or its function. This concept also explains tumor multiplicity and the earlier age of tumor onset in MEN-1 than occurs in sporadic NETs.

The MEN-1 syndrome usually consists of hyperparathyroidism and benign or malignant tumors of the pancreas and pituitary and, in a minority of cases, also may

include carcinoids and tumors of the adrenals, ovaries, and thyroid. Most common are parathyroid hyperplasia and concurrent pancreatic polypeptideoma (PPoma) and/or gastrinoma.^{11,33} Fifty-seven percent of MEN-1 patients have Zollinger–Ellison syndrome (ZES) and approximately 20% of ZES patients have MEN-1. Most of the latter are multiple and located in the duodenum. Thirty percent of all growth hormone releasing factoromas (GRFomas) are associated with MEN-1, as are 4%–5% of insulinomas. Eighty percent of patients with MEN-1 syndrome developed PETs, which often are multiple and may be benign or malignant.^{34,35} PETs are the most common cause of death in the MEN-1 syndrome.³⁶ However, only a small minority of all PETs are associated with the MEN-1 syndrome.

von Hippel–Lindau disease is even less common than MEN-1 syndrome. It consists of cerebelloretinal heman-gioblastomatosis and neoplasms of the pancreas, kidney, epididymis, and cysts or angiomas of the kidney or liver. PETs occur in 12%–17% of patients with von Hippel–Lindau disease.^{37,38}

Neurofibromatosis type 1, which is diagnosed on a clinical basis,³⁹ often is associated with duodenal somatostatinomas.^{39–42}

Incidence

A Medline search disclosed no long-term study addressing the changing incidence of noncarcinoid GEP NETs. However, because of increased awareness it is reasonable to presume that in recent years these tumors have had a significant increase in their reported incidence. Clinically significant PETs have been reported to occur in approximately 1 per 100,000 people per year and account for only 1%–2% of all pancreatic tumors.¹² Autopsy studies indicate that there is a much greater occurrence of unrecognized clinically insignificant PETs.⁴³ Kimura et al.,⁴³ in a meticulous study of the pancreas of patients dying from unrelated disease, discovered a remarkably high incidence of tiny asymptomatic NETs. A total of 1.6% were found on routine microscopic study of 3 random sections of the pancreas but 10% were found on histologic study of multiple sections taken from all portions of the pancreas. These observations are clinically relevant because the high diagnostic imaging sensitivity of currently available endoscopic ultrasonography may allow the discovery of very small clinically insignificant PETs that might be coincidental, unrelated to a patient's symptoms, and hence not require surgical excision.

Insulinomas are the most common functioning PETs with a 17% incidence, followed by gastrinoma (15%), PPoma (9%), VIPoma (2%), glucagonoma (1%), carci-

noid (<1%), somatostatinoma (1%), and the remainder are comprised of neurotensinomas, adrenocorticotrophic hormoneoma (ACTHoma), GRFomas, calcitonin-producing tumors, parathyroid hormone–related peptide tumors, and other exceedingly rare neoplasms. This whole group of very rare PETs accounts for no more than 1%–2%.^{43,44} It also must be borne in mind that almost all of the PETs can be multiple and also can arise outside of the pancreas, particularly gastrinomas ($\leq 77\%$), carcinoids (99%), and somatostatinomas (>40%).^{6,7,36,44}

Nonfunctioning PETs comprise the largest group of these tumors, 15%–30%.^{6,45} They formerly were thought to release no hormonal products. However, they are now known to produce the nonspecific substance chromogranin-A frequently, α and β subunits of human chorionic gonadotropin sometimes, and small amounts of neurotensin, various peptides, and in more than half the cases, pancreatic polypeptide. These are inert clinically.⁴⁵ Therefore, they cause no clinical syndrome and hence nonfunctioning PETs and PPomas often are classified together. Histologically, these tumors can not be distinguished readily from other PETs.^{9,46} Blood pancreatic polypeptide (PP) levels, however, also are increased in association with a large number of functioning GEP NETs, and in many other nonneoplastic diseases and conditions.⁹

Classification

Misunderstanding is perpetuated for the clinician by the different nomenclature, classifications, and terminology applied to the many varied types of NETs in efforts to either unify them based on shared characteristics or to separate them based on their type-specific differences, and also to indicate their levels of malignancy. In the past, pathologists called all GEP NETs *carcinoids* because their histology is quite similar without special staining. This practice still is continued sometimes. However, clinicians in general understand the designation *carcinoid* to mean a serotonin-producing tumor, functioning or nonfunctioning. A recently revised but not yet universally used classification of GEP and lung NETs appears to be an improvement and is the basis of a World Health Organization classification of these tumors.^{47–49} It relates their histopathology to their biological behavior. Five major categories of NETs are defined: (1) well-differentiated endocrine tumors (benign or low-grade malignancy), (2) well-differentiated endocrine carcinomas, (3) poorly differentiated endocrine carcinomas (small-cell carcinomas), (4) mixed exocrine and endocrine carcinomas (such as adenocarcinoids), and (5) several extremely rare neuroendocrine-like lesions.

Criteria on which categorization of the tumor is based are as follows: size, presence or absence of necrosis and/or metastases, and histology (tumor architecture, presence and extent of cellular atypia, and proliferation index). The proliferation index is determined by the percent of cells staining positively with a monoclonal antibody directed against a nuclear antigen in proliferating cells (KI-67/MIB-1) (>2% indicating increasing degrees of malignancy). Also included, particularly for lung carcinoids, are the designations *typical* and *atypical*,⁵⁰ largely determined by a mitosis count of 1 or less/10 high-power fields and the absence of necrosis for the former and 2–10/10 high-power fields plus necrosis for the latter. Greater than 10/10 high-power fields indicates the lesion is a small- or large-cell neuroendocrine carcinoma.⁵¹ Occasionally, the descriptions typical or atypical are applied to nonpulmonary carcinoids or other NETs.

Presentation and Natural Course

Similar to enteric carcinoids, all other GEP NETs present with symptoms or manifestations caused by the mechanical effects of their presence, growth, and metastases, or caused by the effect of their particular endocrine products. Sometimes they may be tiny (gastrinoma, insulinoma, VIPoma) and in other instances they may be very large and bulky (nonfunctioning NETs). They usually are very slow growing and therefore their diagnosis almost always is delayed for a long time, averaging 4–6 years.^{7,36} Their presenting symptoms are varied and usually nonspecific: heartburn, dyspepsia, abdominal pain, diarrhea, weak spells, change in weight (loss or gain), facial flush, skin rash, jaundice, or a self-discovered mass. Sometimes these tumors are found coincidentally at surgery. Because these symptoms are related mainly to the gastrointestinal tract or abdomen, gastroenterologists commonly become involved. However, the best care for these patients usually is achieved by a multidisciplinary team, which also may include a surgeon, endocrinologist, oncologist, interventional radiologist, and other specialists.⁵²

Even though the rate of growth of these NETs usually is slow in comparison with the more common carcinomas and their aggressiveness and pattern of growth vary widely, spanning the spectrum from nearly benign to very malignant, nevertheless it generally is recognized that with the exception of 90% of insulinomas they almost all have long-term malignant potential. Most are overtly malignant at the time of diagnosis, with 60% or more presenting with metastases to the liver.^{6,36,52–57} Indeed, the most common cause of death from PETs is hepatic failure.⁵⁸

With the advent of this recognition there has been increased development and use of effective antihormonal treatment (such as somatostatin analogs and proton-pump inhibitor drugs) for most of the functioning enteroendocrine tumors. This has led to an increase in the duration of survival of these patients to equal that of the nonfunctioning NETs. Consequently, at present, the main cause of death in both groups of NETs is their malignant proliferation. Recognition of the underlying malignant potential of these tumors in the setting of a slow rate of growth has led to much greater aggressiveness in their treatment with both surgical and medical modalities. This aggressive approach considerably exceeds that applied to the faster-growing common cancers. The outcomes emerging from this more active approach to treatment are improved quality of life and further prolongation of survival. In 1988, a 40% chance of 5-year survival was reported for patients with unresectable PETs with liver metastases.⁵⁹ In 2002, Que et al.⁶⁰ reported an 82% chance of 5-year survival for patients with metastatic PETs of all types who underwent surgery with an aggressive approach including partial hepatectomy, prophylactic cholecystectomy, and excision of gross nodal disease and the primary tumor. Adjunctive intraoperative cytoablative modalities (radiofrequency ablation, cryoablation) also sometimes were used and the need for their availability at surgery was emphasized. The intent of this surgery was to reduce hepatic metastases by 90%. These investigators also pointed out that although the 5-year survival rate for partial hepatectomy in their 63 metastatic islet cell tumor patients was 82%, only 51% of their 92 NET patients undergoing orthotopic liver transplantation survived 5 years. Over the past decade many others have reported on the increased benefits of aggressive surgery in treating these patients.^{61–69}

Although complete surgical excision is the only cure for any of the GEP NETs, various adjunctive surgical and nonsurgical cytoreductive and biological modalities have been developed and used with and without palliative surgery. The sequential use of these treatments often further enhances palliation and survival and must be considered in the management of incurable NETs. Choice and timing of each modality must be customized for each specific tumor and patient. These therapies include the following: cryoablation, radiofrequency ablation, hepatic artery embolus injection (with or without chemotherapy), biotherapy (somatostatin analogs octreotide and lanreotide, and interferon alfa), chemotherapy, and radiotherapy (external beam and radioisotope via systemic or organ-targeted injection).^{70,71} These treatments are discussed in more detail later.

Histologic Predictors

The 2 most important indicators to differentiate between low-grade and intermediate-grade malignancy for PETs are the mitotic rate and the presence of necrosis.⁷² The absence of necrosis and less than 2 mitoses/50 high-power field indicate a low-grade classification and the presence of microscopic necrosis, and more than 2 mitoses/50 high-power field indicate an intermediate grade of malignancy. The 5-year survival rate in the intermediate group has been reported as almost half that of the patients with low-grade tumors. Additional investigators have made similar observations, reporting mitoses in terms of less than 2/10 high-power fields.^{73,74} The third prognostic predictor, angioinvasion, also has been emphasized recently.⁷⁵

The proliferation index inversely correlates well with the length of survival.^{76–81} The criteria for a shorter survival and increased level of malignancy as predicted by these indicators vary somewhat among clinical investigators with some classifying a tumor as intermediate grade when its size on diagnosis is more than 2 cm, angioinvasion is present, and a proliferation index is greater than 2%.⁴⁸ Others consider a proliferation index greater than 5% necessary to predict a shorter survival for a PET patient.⁷⁹

Clinical Predictors

Tumor size correlates with outcome, the larger the tumor at diagnosis the worse the prognosis. A size greater than 2 to 3 cm is considered the boundary between indolent and moderately malignant. However, size alone is not a good independent predictor.⁷² The presence of liver metastases at the time of diagnosis is also a predictor of shorter survival.⁷⁹ Nonfunctioning PETs tend to be more advanced when first diagnosed because their lack of a clinical hormone-produced syndrome leads to a greater delay in diagnosis.⁸¹

Clinical Markers

All GEP NETs have the potential to produce almost any of the 2–3 dozen APUD system endocrine products. The most common are chromogranin-A (CgA), PP, gastrin, vasoactive intestinal peptide, serotonin, pancreastatin, α and β subunits of human chorionic gonadotropin, calcitonin, neurone-specific enolase, neurotensin, motilin, somatostatin (SST), substance P, neurokinin-A, histamine, adrenocorticotrophic hormone, growth hormone releasing factor, growth hormone, glucagon, insulin, catecholamines, dopa, various rarer peptide hormones, and urine 5-hydroxyindoleacetic acid.

Many of these substances are associated with a specific clinical syndrome when in excess (see Table 1).

Any PET can express more than one hormone or biogenic amine during its lifetime and hence cause a mixture of several clinical syndromes or a change in syndrome with the passage of time as the dominant hormone changes.^{82,83} Also, patients may develop meta-chronous NET syndromes as part of the MEN-1 syndrome.⁸⁴

Many of these tumor products are inert clinically and are secreted regardless of the presence or absence of a clinical syndrome. Some are very useful nonspecific markers for the presence of a neuroendocrine tumor. Blood CgA level is by far the best of the nonspecific markers.^{46,85–88} Its assay now is available commercially almost universally and its blood levels are increased in 60%–100% of almost all GEP NETs with the exception of insulinoma, in which it is expressed by only a small percentage of cases.^{36,46,86,89,90} A better marker for these tumors is chromogranin-B^{91,92}; however, there is no commercial availability for testing this marker.⁹³ CgA correlates somewhat with tumor burden except perhaps in gastrinoma, in which it has been shown to be produced by enterochromaffin-like cells in response to hypergastrinemia.⁹⁴ It may help predict prognosis and is useful in following-up tumor progression or regression.^{46,95,96} Its changes may precede radiographic changes. It can be reduced in response to somatostatin analog treatment even without concomitant tumor regression. In interpretation of the clinical significance of CgA levels one must consider a number of non-NET conditions, which can increase its blood levels significantly (see Table 2).

Although CgA is the best nonspecific marker for NETs, interpretation of the blood levels in any given case should be correlated with the values found for the marker specifically associated with any clinical syndrome present such as gastrin in ZES, vasoactive intestinal peptide in VIPoma syndrome, 5-hydroxyindoleacetic acid/serotonin in carcinoid syndrome, and so forth.

Additional nonspecific markers are helpful along with CgA for diagnosing and following-up nonfunctioning tumors, and also most functioning NETs.^{46,97} Those most commonly used are PP and the α and β subunits of human chorionic gonadotropin.^{46,97–100} Some clinicians also measure neurone-specific enolase.^{46,101–103}

Pancreastatin, a split product of the CgA molecule, first was isolated in 1986 and although its assay is available commercially, it is not used widely clinically, having been superseded by the assay of CgA.¹⁰⁴ Occasionally, however, it may be the only abnormal marker expressed by a PET.

Table 1. Enteroendocrine Tumor Syndromes Other Than Carcinoid

Tumor	Syndrome	Hormone	Clinical features	Site	Percent malignant	Treatment
Insulinoma	Insulinoma	Insulin Proinsulin	Hypoglycemia Weight gain	>95% Pancreas	>10	Surgery, diet intravenous dextrose, chemotherapy, diazoxide, SSTA
Gastrinoma	ZES	Gastrin	Abdominal pain, peptic ulceration, diarrhea, gastric hypersecretion	Duodenum 70%, pancreas 25%	60–90	Proton pump inhibit, surgery, SSTA, chemotherapy
VIPoma	Verner-Morrison pancreatic cholera WDHA	Vasoactive intestinal peptide	Secretory diarrhea hypokalemia, achlorhydria, metabolic acidosis, flushing, weight loss	90% Pancreas	>50	Intravenous fluids, surgery, SSTA, chemotherapy
Glucagonoma	Glucagonoma syndrome	Glucagon	Diabetes, necrolytic migratory erythema, deep vein thrombosis, depression	Pancreas	>50	Surgery, diet, SSTA, insulin, anticoagulant, chemotherapy
Somatostatinoma	Somatostatinoma syndrome	Somatostatin	Diabetes, gallstones, weight loss, steatorrhea	Pancreas 56%, upper intestine 44%	70–80	Surgery, insulin, pancreatic enzymes
Extremely rare tumors						
ACTHoma	Ectopic Cushing's syndrome	Adrenocorticotrophic hormone	Hypertension, diabetes, weakness	Pancreas 30%, lung 50%	>99	Surgery, chemotherapy, SSTA
PTHrPoma	Hyperparathyroidism	Parathyroid hormone-related peptide	Hypercalcemia, nephrolithiasis	Pancreas	>99	Surgery, chemotherapy
Neurotensinoma	?	Neurotensin	Diabetes, diarrhea, flushing, hypertension, weight loss, edema	Pancreas	?	Surgery, chemotherapy
Calcitoninoma	?	Calcitonin	?	Pancreas, lung	>80	Surgery, chemotherapy
GRFoma	Acromegaly	Growth hormone– releasing factor	Acromegaly	Pancreas, lung, thymus	30	Surgery, SSTA

SSTA, somatostatin analog; WDHA, watery diarrhea-hypokalemia-achlorhydria.

Imaging

In diagnosing NETs there continues to be a role for conventional abdominal ultrasound, endoscopic ultrasound, ingested (barium) contrast studies, computed

tomography and magnetic resonance imaging scans, and, rarely, diagnostic angiography (sometimes with appropriate venous blood sampling for hormone assay). Endoscopic ultrasound is the most sensitive technique for imaging small PETs and often allows for fine-needle aspiration biopsy examination of such lesions.¹⁰⁵

Table 2. Nonneoplastic Causes of Increased Blood CgA Levels

Decreased renal function
Decreased liver function
Hypergastrinemia caused by achlorhydria
Proton pump inhibitor
Atrophic gastritis
Retained gastric antrum
Inflammatory bowel disease
Physical stress and trauma

Somatostatin receptor scintigraphy (SRS), (Indium In-III pentetreotide [Octreoscan], MallinKrodt, Inc, St. Louis, MO) currently is recognized as the gold standard, the best and most sensitive modality for imaging almost all NETs (80%–90%) and their metastases, except for insulinoma.^{36,97,106,107} SRS can differentiate PETs from pancreatic adenocarcinomas.¹⁰⁸ Imaging by SRS is not dependent on endocrine function of a NET (a nonfunctioning tumor can image as well as a functioning one)

Table 3. Conditions Other Than GEP NETs That May Exhibit a Positive Response on SRS

Non-GEP NETs
Some pituitary tumors
Pheochromocytomas, neuroblastomas, paragangliomas
Merkel cell tumors of the skin
Ectopic Cushing's syndrome tumors
Other tumors
Benign cavernous hemangiomas
Small-cell lung cancers
Carcinomas of breast, prostate, lung, kidney, ovary, thyroid
Medullary thyroid carcinomas
Hepatocellular carcinomas
Melanoma and Hodgkin and non-Hodgkin lymphomas
Meningioma and well-differentiated astrocytomas
Normal structures
Gall bladder
Female breast (diffuse uptake)
Accessory spleen
Inflammatory reactions and granulomatous/autoimmune diseases
Recent surgical incision
Postradiation therapy
Recent cerebrovascular accident
Sarcoidosis, tuberculosis, rheumatoid arthritis, systemic lupus erythematosus
Hashimoto's thyroiditis, Grave's disease
Weggener's granulomatosis, Crohn's disease
Aspergillosis <i>Mycobacterium avium</i> granuloma
Henoch-Schönlein purpura

but is determined by the tumor's endowment of type 2 somatostatin receptors (SSTr2) and, to a lesser degree, by type 5 (SSTr5). The density of appropriate receptors rather than the tumor size determines the intensity of the scintigraphy.¹⁰⁶ It has been proposed that SRS should be the initial imaging study in all NETs except insulinoma.¹⁰⁹ Activated lymphocytes in a number of inflammatory granulomatous and autoimmune conditions and various nonneuroendocrine tumors express SSTrs to varying degrees and can image on SRS and be mistaken for NETs. Similarly, SSTrs can be diminished or blocked in some situations and hence the scan will register negatively. These conditions have been identified and summarized and should be borne in mind by the clinician when evaluating the Octreoscan in an equivocal case (see Table 3).^{106,109-112} SRS is the best initial test for localizing and indicating the extent of metastasis of gastrinoma. When combined with endoscopic ultrasound, more than 90% of pancreatic gastrinomas will be imaged.¹⁰⁹ It largely has replaced secretin and calcium infusion tests in diagnosing gastrinoma. Besides confirming the diagnosis and localizing a NET, SRS has proved useful in imaging metastases or staging,¹¹³ monitoring progression or regression of tumors, predicting response to cold somatostatin analog treatment (the more strongly positive SRS, the greater the likelihood of a favorable response to this treatment), and predicting the

likelihood of a favorable response to a therapeutic dose of radiolabeled somatostatin analog (peptide-receptor radio-nuclide therapy).^{114,115} A negative SRS in the presence of a progressing tumor could indicate more strongly the need for aggressive surgery and/or chemotherapy.

A hand-held γ -detecting probe has been developed and is being used increasingly intraoperatively for detecting and localizing small occult NETs.¹¹⁶⁻¹¹⁸

There are 5 somatostatin receptor subtypes (SSTr1-5).¹¹⁹ They all are expressed by PETs^{120,121} and all 5 subtypes avidly bind native somatostatin but the clinically used analogs, octreotide and lanreotide, bind with high affinity only with SSTr2 and SSTr5.¹²² In more than 80% of the GEP NETs, subtype 2 predominates.^{119,123,124} Hence, a majority of NETs will image on SRS examination in current clinical use. Clinical trials are in progress for a new somatostatin analog, SOM230, which has a prolonged half-life, is more potent, and has a much greater binding affinity for SSTr1, 2, 3, and 5 than do the current clinically available somatostatin analogues.^{86,125,126} This new compound therefore promises more effective imaging and therapy, including the minority of tumors not visualized with the current SRS.

¹²³I- (¹²³iodine) and ¹³¹I-labeled (¹³¹iodine) metaiodobenzylguanidine has been in use for more than a decade in imaging and treating neuroendocrine tumors, particularly those of neural crest origin arising outside of the GEP system, such as pheochromocytoma, paraganglioma, and medullary carcinoma of the thyroid. These latter 3 image fairly well with this catecholamine analog. The tumors' uptake of this amine substance is dependent on the APUD mechanism and these 3 types of tumors also exhibit some degree of objective response to both cold and labeled metaiodobenzylguanidine. However, few PETs (9%) image with labeled metaiodobenzylguanidine. SRS clearly is superior for imaging GEP NETs.¹²⁷⁻¹³¹

18-fluorodeoxyglucose, the standard positron-emission tomography PET scan, is useful for imaging some GEP NETs—those more aggressive tumors with high proliferative and metabolic activity and low cellular differentiation.¹³² This method may be used to distinguish more-malignant from less-malignant NETs.¹³³ Most GEP NETs do not image with fluorodeoxyglucose PET.

For bony metastases the standard ^{99m}Tc (⁹⁹technetium) bone scan remains the most sensitive imaging technique.¹³⁴

New promising but still investigative isotope imaging PET scans not dependent on SSTrs take advantage of the APUD metabolic function of these tumors by using ¹¹C-labeled 5-hydroxy-L-tryptophan, ¹⁸F-labeled L-DOPA ([¹⁸fluorine] labeled L-3,4-dihydroxyphenylalanine), or the uptake of ¹¹C-labeled mono-

amine oxidase inhibitors, clorgyline or harmine by monoamine oxidase receptors.^{133,135-138}

Selected Observations in Specific Enteroendocrine Tumors

Insulinomas

Neuroglycopenic symptoms are present in almost all insulinoma patients.¹³⁹ Cardiovascular symptoms are the main presenting features in 17%.^{139,140} Almost all (97%) are located in the pancreas and mostly are small.^{140,141} One-half or more are undetected before surgery but more than 90% can be localized by palpation alone or aided by intraoperative ultrasound.^{142,143} It has been noted that octreotide treatment may make hypoglycemia worse in insulinoma patients lacking SSTR2 and 5, and therefore can fail to suppress insulin production and may blunt compensatory glucagon response. Hence, this treatment should be reserved for only the minority of insulinoma patients with positive imaging on SRS.⁷

Gastrinoma

As noted earlier, diagnosis usually is delayed (4–6 y) and more than 50% of gastrinomas have liver metastases at the time of diagnosis.¹⁴⁴ Up to one half of the patients present with diarrhea as their primary symptom rather than ulcer.¹⁴⁵ Up to 70% of gastrinomas occur in the duodenum, tend to be small, may be multiple, and are less often malignant than those arising in the pancreas. Sporadic and MEN-1 gastrinomas each can occur in the duodenum or the pancreas. Sporadic gastrinomas usually are solitary and more malignant and do tend to originate more often in the pancreas. Sixty-eighty percent of these are malignant.^{146,147} Nonetheless, MEN-1-associated gastrinomas causing ZES, although usually smaller, are multiple and rarely curable by surgical resection. Five percent of gastrinomas arise in other locations such as lymph nodes adjacent to the pancreas, stomach, and more distant sites.⁹ Although a significant percentage of these tumors, particularly when small, fail to localize preoperatively by SRS sonography or endoscopy, they usually can be found at surgery by palpation, intraoperative sonography, or a hand-held γ detector.¹⁴⁸ The most important predictor of survival is the presence and extent of liver metastases at diagnosis.^{149,150} In 2 studies the gastrinoma was indolent in 75% of patients and aggressive in 25%.^{149,150} The 10-year survival of patients with indolent tumors was 96% and only 30% in those with aggressive tumors.¹⁵⁰ The factors predicting a poor prognosis in addition to liver metastases and their diffuse extent were bone metastases, the size of the primary tumor (>3 cm), development of Cushing's syn-

drome, female sex, absence of MEN-1, a short clinical course before diagnosis, markedly increased serum gastrin levels (>5157 pg/mL), lymph node metastases, and aneuploidy on flow cytometry.³⁶ Twenty percent to 25% or more of gastrinomas are associated with MEN-1.³⁶

The role of surgery in the ZES patient with MEN-1 is controversial with no general consensus on management because the likelihood of cure with surgery is poor.¹⁵¹

If the patient has no hepatic metastases and is a limited surgical risk, several groups have advocated a very aggressive early surgical approach incorporating distal pancreatectomy, topical lymph node dissection, and duodenotomy with thorough duodenal exploration.^{6,152} The failure rate in effecting a surgical cure in ZES MEN-1 patients with a pancreatic tumor greater than 3 cm is nearly 100%.^{152,153}

The role of surgery in management of ZES patients with sporadic gastrinoma also is controversial because medical therapy with proton-pump inhibitor drugs can control gastric acid hypersecretion in all cases. It has been proposed as sufficient treatment without surgery in many instances.¹⁵⁴ However, because 60%–90% of these tumors are malignant, progression of the tumor ultimately is the main determinant of survival. Surgery is reported to cure one third of sporadic cases and to alter the natural course of the disease favorably, improving survival even when not curing. Postoperative evaluation is recommended to include a secretin test as the most sensitive assessment of cure vs tumor recurrence.¹⁵⁵ Because medical treatment controls the endocrine function of nearly all gastrinomas, in some cases there still may be a beneficial role for surgery because resection of the primary tumor and debulking metastases have been shown to decrease the rate of development of metastases and benefit the natural course of the disease.⁶⁴ This very aggressive approach possibly combined with newer, more effective, chemotherapy protocols may enhance palliation and survival.⁶³

A recent study of long-term octreotide treatment of progressive metastatic gastrinoma showed 53% responders with a mean duration of response of 25 months. In a 4- to 8-year follow-up evaluation, 25% of responders died whereas 71% of the nonresponders died. It was suggested that this biotherapy was effective antitumor treatment for approximately 50% of progressing gastrinomas and should be considered as replacement for standard chemotherapy, particularly for the slow-growing tumors.¹⁵⁶ Although of course it might augment chemotherapy even better, further evaluation is required.

Concern over long-term treatment with proton-pump inhibitor drugs possibly causing enterochromaffin-like cell hyperplasia and gastric carcinoid in humans appears

to be unnecessary, even though patients with ZES with MEN-1 are prone to gastric carcinoids, unlike those with sporadic ZES.^{157,158}

The diagnosis of ZES requires clinical suspicion and demonstration of increased serum gastrin and basal acid output. Increased serum CgA levels and other nonspecific markers are helpful. Many conditions other than gastrinoma can be associated with markedly increased serum gastrin and basal acid output, and still other conditions can be associated with high gastrin and decreased basal acid output. These are reviewed by Alexander and Jensen.⁹ It has been reported that when measurements of basal acid output are not available, a pH level greater than 2 of the unmedicated fasting patient's gastric content virtually excludes the diagnosis of ZES.¹⁵⁹ Of the various provocative tests developed to clarify a persistent uncertain diagnosis of ZES, the secretin test is the best.¹⁵⁹

Nonfunctioning PETs and PPoma

PETs without increased hormonal secretion are not associated with any clinical syndrome and also those that secrete detectable quantities of PP and other hormonal substances of types that do not cause clinical syndromes all are considered nonfunctioning and are lumped together for clinical considerations. This group constitutes 15%–30%, the largest component of all PETs.⁴⁵ One half to three quarters of nonfunctioning PETs secrete PP.⁹ Very few secrete only PP and perhaps only these should be designated as pure PPomas.⁹ There is no difference in the biologic behavior of those producing PP and those that do not. These tumors usually cause symptoms by their size and are diagnosed late when local invasion occurs.⁹ PP also is produced by a large percentage of functioning PETs and extrapancreatic carcinoids.¹⁶⁰ Not only is PP a nonspecific indicator, but its plasma level can be increased by a wide variety of non-neoplastic conditions.⁹ These tumors usually are solitary but when multiple often are associated with MEN-1.⁹

VIPoma

VIPomas are rare NETs that arise from the pancreas 90% of the time, but 10% can develop in neurogenic tumors of the sympathetic ganglia or other sites (colon, bronchus, adrenals, liver), particularly in children.^{141,161} More than 60% will have metastasized by the time they are diagnosed.^{141,161,162} Besides the severe secretory diarrhea, hypokalemia, hypochlorhydria or achlorhydria, bicarbonate wasting, and other electrolyte imbalances they produce (hypercalcemia and hyperglycemia), they can cause facial flushing. Hence, they can be confused with carcinoid syndrome or other endocrine diarrhea-pro-

ducing diseases accompanied by flushing. Markedly increased vasoactive intestinal peptide levels in the blood occur in most vasoactive intestinal peptide patients and will help in diagnosing this condition.¹⁶³ Intravenous fluid and electrolyte replacement is essential in these patients, accompanied by octreotide, which will control symptoms promptly in more than 90% of patients.¹⁶⁴

Glucagonoma

Glucagonomas are functioning NETs that usually are large, originate almost entirely in the pancreas, and have metastasized to the liver or lymph nodes when diagnosed in more than 50% of cases.^{6,165} Although small glucagonomas tend to be benign, the larger they are the greater the incidence of malignancy: 60%–80% that are larger than 5 cm are malignant.¹⁶⁶ They are characterized by the 4 Ds: dermatitis (necrolytic migrating erythema), diabetes, deep venous thrombosis, and depression. Also prominent are diarrhea, weight loss, anemia, and hypoaminoacidemia. Deficiency in zinc also is noted. Somatostatin analog treatment usually, and sometimes dramatically, will improve most of the manifestations of this disease.^{9,160,167,168} Surgery, oral hypoglycemic drugs, diet, insulin, and chemotherapy usually are essential in treating these patients, in addition to fluid and electrolyte replacement.

Carcinoid of the Pancreas

Less than 1% of carcinoids arise in the pancreas. Another article in this issue of *GASTROENTEROLOGY* discusses this in further detail (see Modlin et al on page 1717).

Somatostatinoma

Most somatostatinomas are large and have metastasized when first diagnosed. Approximately two-thirds arise in the pancreas and one-third in the duodenum or upper jejunum.¹⁶⁹ The extrapancreatic tumors often are associated with von Recklinghausen's disease and MEN-1, are smaller, and less often have metastasized or cause the clinical somatostatin syndrome.^{12,169} Duodenal somatostatinomas may present with obstructing symptoms.^{170,171} More often the pancreatic somatostatinoma produces an excess of somatostatin that inhibits the secretion of insulin, glucagon, gastrin, growth hormone, cholecystokinin-mediated secretion of pancreatic enzymes, intestinal absorption, and gastric secretion.¹⁷² This leads to the tumor syndrome characterized by diabetes, gallstones, and diarrhea-steatorrhea.^{170,171}

Other Extremely Rare PETs

GRFoma. Somatotropinoma secretes growth hormone-releasing factor and can cause acromegaly. Only

30% arise in the pancreas. Most arise in the lung and a few stem from the jejunum and adrenal gland. Some unresectable tumors can be palliated by octreotide treatment.⁹

ACTHoma. Almost all of these Cushing's syndrome-producing tumors are malignant, respond poorly to chemotherapy, and have a poor prognosis. Only 4%–16% of all established Cushing's syndrome cases are caused by PETs.^{9,36}

PPHRPoma. Hypercalcemia caused by secretion of a parathyroid hormone-related protein by a PET resulting in hyperparathyroidism has been reported.¹⁷³ The tumor usually is large and has metastasized when diagnosed. Surgery and chemotherapy may be of benefit.

Calcitoninoma. A few cases have been reported of calcitoninoma in which PETs secreted calcitonin and in some of these patients their main symptom of diarrhea disappeared on treatment of the tumor.¹⁷⁴ The possibility of this being a specific syndrome is suggested but more observations are required for confirmation.³⁶ Increased blood levels of calcitonin associated with watery diarrhea and facial flushing often is seen in medullary thyroid carcinoma, a NET that can be part of the MEN-2 syndrome.

Neurotensinoma. Neurotensinoma is exceedingly rare, arising from the pancreas or lung, and features a syndrome that appears to consist of diarrhea, diabetes, weight loss, hypotension, edema, and flushing. This is very similar to watery diarrhea-hypokalemia-achlorhydria syndrome. Surgery and chemotherapy with streptozotocin have been effective in most of the small numbers of reported cases.¹⁷⁵

Treatment

There are 3 general types of treatments for NET patients: (1) medical supportive, (2) surgery (curative intent, palliation, cytoreductive intent including radiofrequency ablation, cryoablation, and hepatic artery chemoembolus or bland embolus injection), and (3) nonsurgical cytoreduction (biotherapy, chemotherapy, and radiotherapy).

Most often, modalities of all 3 categories are used concurrently or sequentially, varying with the features of each patient. Significant advances have been made in each category. The single most important advance in the medical treatment of all GEP NETs has been the recognition of the effectiveness and use of somatostatin analogs in improving the symptoms of most of the functioning tumors, and in gastrinoma the introduction of proton pump inhibitors.^{97,176–179} A significant step forward has been the development and introduction into clinical use of the long-acting, slow-release form of octreotide and

the sustained-release form of lanreotide.^{180–186} These agents are effective in ameliorating the endocrine symptoms associated with functioning PETs in most patients with gastrinoma (in conjunction with proton pump inhibitors), VIPoma, glucagonoma, GRFoma, and some insulinomas.^{187–189} The demonstrated presence of appropriate SSTrs in the tumor predicts response to such treatment.^{190,191} This is determined best clinically by SRS.

Improved palliation and survival has resulted from more aggressive surgery for GEP NETs, particularly those with a clinical endocrine syndrome. The beneficial response has been noted especially when surgery has been combined sequentially with other medical and cytoreductive modalities.^{68–71,155,187,192} Better appreciation of this more aggressive approach for these slow-growing malignant tumors is needed. Because they are more indolent than the commonly encountered cancers, acceptance of this concept is not universal.

During the past decade the introduction of cryoablation and radiofrequency ablation for unresectable tumors in the liver has enhanced excisional surgery and substituted for it when tumor resection is not feasible.^{193–196}

Orthotopic liver transplant has been performed in a relatively small number of NET patients worldwide with approximately one-half surviving 5 years. This roughly is equal to the survival for similar patients treated actively by standard sequential multiple medical and surgical modalities.^{197,198} Therefore, at present it appears that although orthotopic liver transplantation can offer relief of hormonal symptoms and fairly long survival, its benefits exist in very selective cases unresponsive to standard medical and surgical treatment.

Bland embolus injection or hepatic artery chemoembolus injection treatment is the interventional radiologic technique for devascularizing NETs with or without co-administered chemotherapy. These techniques have been in use since the early 1980s.^{199–201} The use of these methods has increased slowly and they now are available at most large medical centers. Most patients have symptomatic and chemical responses and approximately half of those with pretreatment tumor progression exhibit tumor shrinkage after the treatment.²⁰² There is no universally practiced common technique for performing these treatments and the type, size, and amount of particles and the cytotoxic drugs, their doses injected, and the extent of liver injected at any single treatment varies considerably from one medical center to another.²⁰² A number of reviews of this subject are available.^{12,71,202–204} Although there are no randomized studies of hepatic artery chemoembolus vs bland embolus injection, the impression of longer and improved response rates to

hepatic artery chemoembolus held by many observers has been strengthened by the finding of a recent study evaluating this question.²⁰⁵

Biotherapy for antitumor effect uses somatostatin analogs or interferon alfa, alone or in combination. These drugs have been found to have tumoristatic effectiveness, particularly when combined, resulting in tumor stabilization of both functioning and non-functioning NETs.^{81,156,206–213} Their tumoricidal effects, however, are weak. A few patients who fail to respond or cease responding to standard somatostatin analog treatment will have a symptomatic and biochemical response to a very high dose of the analog (>3 mg/day of octreotide).²

Chemotherapy has a definite role in the treatment of faster-growing advanced and metastatic PETs with a 40%–70% response rate, in contrast to that of less than 30% for most midgut carcinoids.^{6,213–216} Combinations of drugs rather than single-agent therapy are more effective.^{6,9} For high-grade neoplastic neuroendocrine malignancies with high-proliferation treatment with etoposide and cisplatin is the accepted standard.²¹⁷ For all other advanced metastatic progressive PETs, streptozotocin-based combinations are used as first-line chemotherapy with the current favored regimen consisting of fluorouracil, doxorubicin, and streptozotocin.²¹⁸ A number of other cytotoxic drugs have been in use in treating PETs with varying degrees of response.^{9,12,160,216} Many newer agents in combinations have shown activity against more common cancers and are currently in various phases of clinical trials for GEP NETs.

External beam radiotherapy traditionally has been considered ineffective for NETs except for bone and brain metastases. There have been exceptions to this viewpoint.²¹⁹ However, great progress has been made in treatment with internal radiation using injection of peptide-receptor radionuclide agents that are targeted to those NETs having an abundance of receptors with an affinity for the injected isotope-bearing ligand. These isotopes are I¹¹¹, Y⁹⁰ (⁹⁰yttrium), and LU¹⁷⁷ (¹⁷⁷lutetium) bound to somatostatin analogs. Initial results are very promising, particularly for Y⁹⁰ and LU¹⁷⁷, but these still are experimental and not generally available.²²⁰ Y⁹⁰-impregnated microspheres injected via catheter into the hepatic artery has been approved for the treatment of colorectal metastases in the liver and a good response to this treatment also has been reported in hepatocellular carcinoma.^{221,222} Our own preliminary experience with this modality for NETs has been favorable as have been the unreported observations of others who also have evaluated this treatment.

Patient Self-Help Support Groups

Because of their rare occurrence and only recent recognition as medical entities, widespread knowledge and experience in the management of GEP NETs has been limited. Simple, accurate, and understandable information for the patient has been sparse. Hence, patients with NETs have gathered together to form self-support groups varying from small, casual, informal enclaves to large, well-structured, and even incorporated organizations. Some have issued periodic publications and newsletters, scheduled meetings with expert lecturers, and have telephone hotlines. They aid the NET novice caller seeking emotional support or guidance in finding a medical expert consultant in their area. There are now more than 40 organized carcinoid and NET self-help groups recorded in the United States and at least 6 in Europe including the United Kingdom (see the Carcinoid Cancer Foundation web site: <http://www.carcinoid.org>). They not only have served patient educational and emotional needs well but also have provided stimulus for patients' physicians and pharmaceutical companies and have prompted and supported research. All NET patients are included in most of the carcinoid support groups. Some of the support groups are as follows: NAAPNET (North American Alliance for Patients With Neuroendocrine Tumors), Metro New York Carcinoid Support Group, NCF (Neuroendocrine Cancer Fighters-Northern California), Pacific Northwest Support Group (Washington). These and all other similar support groups can be found at the Carcinoid Cancer Foundation web site (<http://www.carcinoid.org>).

Conclusion

Significant advances in our knowledge of the biology of enteroendocrine tumors and their diagnosis and treatment made over the past 1–2 decades have been reviewed. It has been noted that there is a need for enhanced awareness of the heterogenous features of these tumors as well as the multiplicity of modalities available for their treatment. There is increasing acceptance of the more aggressive and customized treatment with recognition that favorable responses in these patients result from sequential use of multiple modalities.

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