GASTROENTEROLOGY 2008;135:1469–1492

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY

John P. Lynch and David C. Mertz, Section Editors

Gastrointestinal Neuroendocrine Tumors: Pancreatic Endocrine Tumors

DAVID C. METZ* and ROBERT T. JENSEN‡

**Division of Gastroenterology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; ‡Digestive Diseases Branch, National Institute for Diabetes and Digestive Kidney Diseases, National Institutes of Health, Bethesda, Maryland*

See Yamagami et al on page 1202 in *CGH*.

Pancreatic endocrine tumors (PETs) have long fascinated clinicians and investigators despite their relative rarity. Their clinical presentation varies depending on whether the tumor is functional or not, and also according to the specific hormonal syndrome produced. Tumors may be sporadic or inherited, but little is known about their molecular pathology, especially the sporadic forms. Chromogranin A appears to be the most useful serum marker for diagnosis, staging, and monitoring. Initially, therapy should be directed at the hormonal syndrome because this has the major initial impact on the patient's health. Most PETs are relatively indolent but ultimately malignant, except for insulinomas, which predominantly are benign. Surgery is the only modality that offers the possibility of cure, although it generally is noncurative in patients with Zollinger–Ellison syndrome or nonfunctional PETs with multiple endocrine neoplasia-type 1. Preoperative staging of disease extent is necessary to determine the likelihood of complete resection although debulking surgery often is believed to be useful in patients with unresectable tumors. Once metastatic, biotherapy is usually the first modality used because it generally is well tolerated. Systemic or regional therapies generally are reserved until symptoms occur or tumor growth is rapid. Recently, a number of newer agents, as well as receptor-directed radiotherapy, are being evaluated for patients with advanced disease. This review addresses a number of recent advances regarding the molecular pathology, diagnosis, localization, and management of PETs including discussion of peptide-receptor radionuclide therapy and other novel antitumor approaches. We conclude with a discussion of future directions and unsettled problems in the field.

Pancreatic endocrine tumors (PETs) have long fascinated clinicians and investigators because of their unusual and florid symptoms as well as the insights they provide into the actions of gastrointestinal (GI) hormones. PETs share many pathologic and biological features with GI carcinoids, but they have important differences that affect treatment, in addition to having a different pathogenesis,[1,2] and thus the 2 groups of GI neuroendocrine tumors (NETs) are best considered separately. There have been a number of recent advances in various aspects of PETs including diagnosis, management, insights into molecular changes, tumor localization, and the treatment of advanced disease. This article briefly reviews a number of these advances as well as their current management. This article does not cover all aspects of PETs because many features recently have been covered in reviews or consensus conferences.[3–7]

Epidemiology

PETs occur in 0.5%–1.5% of autopsies but are functional or symptomatic in less than 1 in 1000, resulting in a clinical detection rate of 1:100,000 population, which comprises 1%–2% of pancreatic neoplasms.[8] In older studies, nonfunctional PETs (NF-PETs), insulinomas, and gastrinomas had equal frequency;[9] however, in

Abbreviations used in this paper: CT, computed tomography; DOTA, 1,4,7,10-tetra-a2acyclododecane-1,4,7,10-tetra-acetate acid; EUS, endoscopic ultrasonography; FSG, fasting serum gastrin; GI, gastrointestinal; GRFoma, growth hormone-releasing factor secreting tumor; HACE, hepatic artery embolization with co-administration of chemotherapeutic agents; HAE, hepatic artery embolization; MEN1, multiple endocrine neoplasia-type 1; MRI, magnetic resonance imaging; NET, neuroendocrine tumors; NF-PET, nonfunctional pancreatic endocrine tumors; PET, pancreatic endocrine tumors; PPI, proton pump inhibitor; SRS, somatostatin receptor scanning; SS, somatostatin; US, ultrasonography; VIPomas, vasoactive intestinal polypeptide secreting tumor; ZES, Zollinger–Ellison syndrome.

0016-5085/08/$34.00
doi:10.1053/j.gastro.2008.05.047

Table 1. Pancreatic Endocrine Tumor Syndromes

Name of tumor (syndrome)	Hormone causing syndrome	Signs or symptoms	Primary location	Malignant (%)
Gastrinoma (Zollinger–Ellison syndrome)	Gastrin	Abdominal pain Diarrhea Esophageal symptoms	Pancreas: 60% Duodenum: 30% Other: 10%	60–90
Insulinoma	Insulin	Hypoglycemic symptoms	Pancreas: 99%–100%	5–15
Glucagonoma	Glucagon	Rash, anemia Diabetes/glucose intolerance Weight loss Thromboembolic disease	Pancreas: 99%–100%	60
VIPoma (Verner–Morrison, pancreatic cholera, WDHA)	VIP	Severe watery diarrhea Hypokalemia	Pancreas: 90% Other: 10% (neural, adrenal, peri-ganglionic tissue)	80
Somatostatinoma	Somatostatin	Diabetes mellitus Cholelithiases Diarrhea Steatorrhea	Pancreas: 56% Duodenum/jejunum: 44%	60
GRFoma	Growth hormone releasing factor	Acromegaly	Pancreas: 30% Lung: 54% Jejunum: 7% Other: 13% (adrenal foregut, retro-peritoneum)	30
ACTHoma (Cushing's syndrome)	ACTH	Cushing's syndrome	Pancreas: 4%–16% all ectopic Cushing's	>90
PET causing the carcinoid syndrome (carcinoid syndrome)	Serotonin tachykinins prostaglandins	Diarrhea Flushing	Pancreas: 100%	68–88
PET causing hypercalcemia	PTH-RP	Symptoms due to increased calcium	Pancreas: 100%	80–90
Nonfunctioning (PPoma, nonfunctional)	None (PP, CgA, NSE, and so forth[a])	Weight loss, hepatomegaly Abdominal mass Occasionally asymptomatic	Pancreas: 100%	60–90

[a]No symptoms were caused by product hypersecretion; other peptides not causing symptoms include ghrelin, neurotensin, calcitonin, subunits of human chorionic gonadotropin, and so forth.

ACTH, adrenocorticotropic hormone; CgA, chromogranin A; PTH-RP, parathormone-related peptide; NSE, neuron-specific enolase; PPoma, pancreatic polypeptide; WDHA, watery diarrhea, hypokalemia, achlorhydria.

recent studies NF-PETs were twice as frequent.[10,11] The relative frequency of PETs varies in surgical or medical series, but most studies suggest a relative order of: NF-PET > insulinoma > gastrinoma > glucagonoma > VIPomas somatostatinomas > others.[9,11] Four inherited disorders have an increased incidence of PETs: multiple endocrine neoplasia-type 1 (MEN1), von Hippel–Lindau disease, von Recklinghausen's disease (neurofibromatosis 1), and tuberous sclerosis.[12,13] The most important is MEN1 because 80%–100% of these patients develop NF-PETs, 50%–60% develop gastrinomas, 20% develop insulinomas, and 3%–5% develop vasoactive intestinal polypeptide secreting tumor (VIPomas) or glucagonomas with the result that 20%–25% of all gastrinomas and 4% of insulinomas are caused by this syndrome.[12,13] PETs (primarily NF-PETs) develop in 10%–17% of von Hippel–Lindau disease patients, in 0% to 10% of neurofibromatosis 1 patients (primarily duodenal somatostatinomas), and in less than 1% of tuberous sclerosis patients (primarily NF-PETs).[12,13]

Classification/Pathology

PETs are divided clinically into 2 groups: functional and NF-PETs. Functional PETs secrete biologically active peptides causing 1 of 9 well-established syndromes (Table 1). NF-PETs are not associated with a specific hormonal syndrome either because no peptide is secreted or the substance secreted does not cause specific symptoms. Most (>70%) NF-PETs are not truly nonfunctional because they secrete substances such as pancreatic polypeptide, other peptides (neurotensin, ghrelin, and so forth), neuron-specific enolase, chromogranins, or human chorionic-gonadotropin subunits, each of which does not cause specific symptoms[9,14] (Table 1). In addition to the well-established PET syndromes (Table 1), small numbers of patients are described with PETs producing other biologically active substances and new syndromes have been proposed, although in most cases too few patients have been described to clearly establish this point or its spectrum. GI tumors have been described secreting luteinizing-hormone causing masculinization,[15] secreting renin causing erythrocytosis,[16]

and secreting PYY causing constipation (primarily ovarian tumors).[17]

PETs share pathologic features with carcinoids: both are considered to arise from the diffuse neuroendocrine cell system; uncommonly show mitotic figures; commonly show electron-dense granules containing various peptides, chromogranins, neuron-specific enolase, and synaptophysin; and they have many similarities in biological behavior.[14,18] The latter properties, particularly the presence of chromogranin, are widely used to identify GI NETs.[14,18] Both functional and NF-PETs frequently (>50%) synthesize more than one peptide.[14,18] However, in most cases, these multiple peptides are not associated with specific syndromes. For this reason the diagnosis of a functional syndrome (Table 1) depends not on immunocytochemistry, but is diagnosed clinically.[9,14,18]

A recent standard World Health Organization classification has proposed GI NETs be assigned to 1 of 3 categories (well-differentiated tumor, well-differentiated carcinoma, and poorly differentiated carcinoma) based on histology, size, and proliferative indices.[14] In general, histologic classifications of PETs have failed to predict growth patterns for a given tumor. However, this classification will allow a more standardized comparison of results of different studies. A TNM classification for PETs also has been proposed[19] that is based on the World Health Organization classification of GI NETs and that may provide a more standardized assessment of patients and have important prognostic clinical value.

Molecular Pathogenesis

Little is known about the molecular pathogenesis of PETs.[1,2,8] This has occurred in part because alterations in common oncogenes (fos, jun, myc, k-ras, and so forth) or common tumor-suppressor genes (p53, retinoblastoma, and so forth) are not generally implicated in their pathogenesis.[1,2,8] Some of the most important insights have come from studies of inherited PET syndromes.[1,2,8,20] Altered genes causing these syndromes are important in some cases of sporadic PETs (ie, nonfamilial cases).[1,2,8,20] MEN1 is caused by mutations in the *MEN1* gene on chromosome 11q13, which encodes for a 610 amino acid protein, menin, a nuclear protein that binds to numerous transcription factors.[13,21,22] However, the exact mechanism leading to the development of PETs still remains unclear. Sporadic PETs show an acquired loss of heterozygosity at this locus in 20%–90%, and 27%–39% have a mutation.[1,2,8,23,24] In addition, recent studies have shown alterations in the p16/MTS1 tumor-suppressor gene, the DP64/SMAD4 gene, amplification of the HER-2/neu proto-oncogene, and loss of an unknown tumor-suppressor gene on chromosome 1 or 3p also could be important in the molecular pathogenesis of PETs.[1,2,8,20] Genome-wide allelotyping and comparative genomic hybridization show that chromosomal gains (especially 7q, 17q, 17p, and 20q) and losses (especially 1p, 3p, 3, 6p, 22q) frequently occur in PETs and carcinoids; however, their frequency varies markedly in these 2 GI NETs, providing evidence that they have a different pathogenesis.[1,2,8,20,25] Gene expression profiling using microarray analysis recently has identified in PETs numerous additional altered genes.[26–29] In comparison with normal islets in one study,[29] 66 genes were overexpressed (particularly genes for some growth factors [IFGFBP3], cell migration/adhesion molecules [fibronectin], and putative oncogenes [MLLT 10/AF10]), and 119 were underexpressed (particularly genes involved in cell-cycle regulation [$p21^{cip1}$], transcription factors [JunD], and a putative metastasis suppressor gene [NME3]). In a second study,[26] when gene expression patterns in NF-PETs were compared with normal islets and 3 neuroendocrine tumor cell lines, 667 genes were up-regulated (particularly SERPINA10, BIN1, LCK, and BST2) and 323 were down-regulated. At present, a clear concordance among studies is still lacking, but this approach is leading to the identification of numerous new candidate genes that may prove important in the pathogenesis of PETs or in determining growth behavior, which may have prognostic implications.

Tumor Biology, Prognosis, and Tumor Markers

PETs differ in their malignant potential and location (Table 1). Some PETs (insulinomas, glucagonomas, and VIPomas in adults) are found almost entirely within the pancreas, whereas others, although still referred to as PETs, actually occur in extrapancreatic locations (duodenal gastrinomas [60%–80%],[30–32] small intestinal somatostatinomas [40%–50%], and growth hormone-releasing factor secreting tumor (GRFomas) primarily in the lung [>70%]) (Table 1). Insulinomas are malignant in 5%–15%, whereas the other PETs are malignant in 50%–90%, with metastases usually developing initially in regional lymph nodes, later in the liver, and subsequently in distant sites such as bone.[6,8,14,30,33,34] PETs in different patients may show different growth patterns.[33,35–38] For example, in patients with gastrinomas, 75% show no growth/indolent growth whereas 25% show aggressive growth.[35,36] Furthermore, even in patients with liver metastases, aggressive growth occurred in less than one half of patients.[37] Therefore, identification of prognostic factors is particularly important in patients with PETs.[33] In almost every study, the presence or development of liver metastases, but not lymph node metastases, is a very important prognostic factor.[11,33,35,36,38–41] In one study[35] the 15-year survival rate in patients with liver metastases was 26%, whereas without liver metastases it was 96%. The extent or rate of growth of liver metastases, presence of bone metastases, primary tumor size or location (duodenal vs pancreatic gastrinomas), development of ectopic Cushing's syndrome, various histologic features, high tumor marker levels, various flow cytometric features, and high

Table 2. Presenting Features of ZES (Recent Series) and Causes of Hypergastrinemia

Presenting features of ZES (recent series)
Abdominal pain (75%–100%)
Diarrhea (35%–73%) (isolated in up to 35%)
Pain and diarrhea (55%–60%)
Heartburn (44%–64%)
Duodenal (and prepyloric) ulcers (71%–91%)
Ulcer complications (bleeding, 1%–17%; perforation, 0%–5%; or obstruction, 0%–5%)
With MEN1 (22%–24%)
Causes of hypergastrinemia
Appropriate
Antisecretory therapy (especially PPIs)
Atrophic gastritis (autoimmune pernicious anemia)
Helicobacter pylori pangastritis with atrophy
Vagotomy
Fundectomy
Chronic renal failure
Inappropriate
ZES
Retained antrum syndrome
Antral-predominant *H pylori* infection (antral G-cell hyperfunction)
Chronic renal failure
Gastric outlet obstruction
Massive intestinal resection

Data from Soga and Yakuwa,[60] Roy et al,[61] Jensen,[74] Miller et al,[177] Kaplan et al,[297] Farley et al,[298] and Mignon and Cadiot.[299]

proliferative indices (Ki_{67}, mitotic index) are important prognostic factors.[11,19,33,35–38,42–44] Survival is related to PET extent such that patients with primary tumors so small they are not found at surgery or with complete resections have survival rates of 90%–100%, those with incomplete resections have survival rates of 15%–75%, and those with diffuse unresectable liver metastases have survival rates of 25%–50%.[33,35,45–47] In some studies[48] but not others,[11,43,49] patients with functional PETs have better survival rates than those with NF-PETs. Recently, 2 studies[50,51] showed that complete resection of the primary PET decreases the rate of development of liver metastases and/or improves survival.[50]

In addition to the specific hormone released by a functional PET (Table 1), other putative tumor markers have been proposed that could be useful for diagnosis/prognosis. This is particularly the case for NF-PETs. The marker most widely used is plasma chromogranin A (increased in 88%–100%), although also proposed is plasma neuron-specific enolase (increased in 83%–100%), pancreatic polypeptide (PP), pancreastatin, and α or β subunits of human chorionic gonadotropin (increased in 25%–40%).[52–54] Chromogranins (A, B, and C) are acidic soluble proteins (molecular weight, 49 kilodaltons) found in large secretory granules of neuroendocrine cells and assessment of chromogranin A level is now being used increasingly to diagnoses and monitor changes in NF-PETs, carcinoids, and other PETs.[52,54–56] Chromogranin A has an overall diagnostic sensitivity of 60%–100% in patients with metastatic disease, but less than 50% in patients with localized/early disease.[56–58] Chromogranin A levels reflect tumor burden and it has been used to assess recurrences, tumor growth, and changes in tumor size.[52,55,58]

Clinical Features and Diagnosis of PETs

Gastrinoma: Clinical Features/Diagnosis

Gastrinomas secrete gastrin, which causes hyperchlorhydria, thereby producing the Zollinger–Ellison syndrome (ZES).[31,45,59,60] With a long mean delay (6.1 y) in presentation/diagnosis,[45,61,62] patients generally present with acid-peptic conditions including complicated and uncomplicated ulcers and/or gastroesophageal reflux disease (Table 2, *top*). Occasionally other manifestations such as diarrhea, malabsorption, or, in MEN1/ZES patients, various other endocrine features predominate (Table 2, *top*).[61,63,64]

In contrast to what occurs with normal physiological regulation,[65] with gastrinomas, the tumor secretion of gastrin is not physiologically regulated and sustained inappropriate hypergastrinemia occurs.

Basal acid hypersecretion (present in >90% of patients) or after stimulation[59] is a consequence of the inappropriate hypergastrinemia. Because a fasting serum gastrin (FSG) level is often the initial determination performed in the United States in patients suspected of having ZES, it is important to remember that increased levels also can be caused by an appropriate physiologic response to hypochlorhydria/achlorhydria or an inappropriate response in other disease states (Table 2, *bottom*). With the dramatic increase in proton pump inhibitor (PPI) use in the population, a recent study raises concerns[66] about the

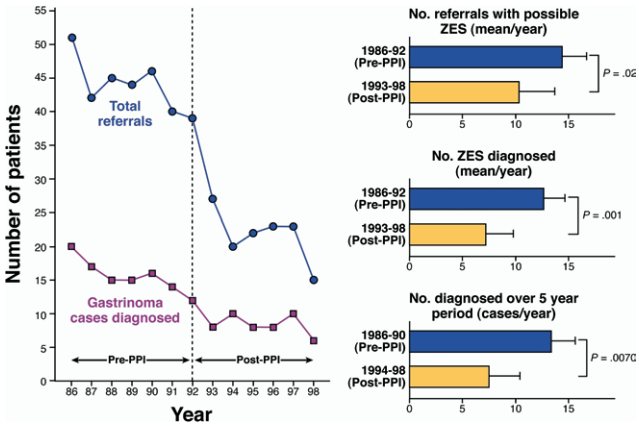

Figure 1. Effect of widespread use of PPIs on diagnosis and referral of ZES patients in 2 centers (Italian-La Sapienza University [Rome, Italy] and National Institutes of Health [Bethesda, Maryland]). The *left panel* shows the annual number of referrals of new cases before and after the widespread use of PPIs. The *right panel* shows the results for diagnosis of ZES at the National Institutes of Health center. Modified from Corleto et al.[66]

impact this is having on the diagnosis/presentation of ZES (Figure 1). This study[66] reported a 49% decrease in referrals of patients with possible ZES to 2 centers in the United States and Italy since the widespread use of PPIs, a 40% decrease in the number of patients with ZES diagnosed (Figure 1), and a 3-fold increase in the number of false-positive diagnoses of ZES. This occurred because PPIs can control the symptoms of acid hypersecretion in almost all ZES patients, in contrast to conventional doses of H_2 blockers, and thus mask the diagnosis. The increased false-positive rate occurred because treatment with PPIs in non-ZES patients can cause hypergastrinemia to a level seen in 60% of ZES patients.[31,53,67,68] This delay in diagnosis may lead to more patients with ZES presenting with advanced disease.[66]

Diagnosis of ZES requires a typical clinical syndrome together with the demonstration of inappropriate hypergastrinemia.[31,45,53,59,67,69] Fasting hypergastrinemia occurs in 97%–99% of patients so this is usually the initial study raising suspicion of the disease.[31,67] No absolute level of increase of FSG alone is diagnostic.[31,53,67,68] In the 40% of ZES patients with a FSG level greater than 10-fold increased, the diagnosis can be made with certainty (after excluding retained gastric-antrum syndrome by history) if the gastric pH is less than 2.[59,67,70] In the 60% of patients with an FSG that is increased less than 10-fold and a gastric pH of less than 2, assessment of basal acid output and a secretin test should be performed. A basal acid output of greater than 15 mEq/h with an increased FSG level in the absence of antisecretory therapy and a positive secretin test firmly establishes ZES. A recent study showed that the best criterion for a positive secretin test for ZES is an increase in FSG level after subcutaneous secretin injection (0.4 ug/kg) of greater than 120 pg/mL above baseline, producing a sensitivity of 94% and a specificity of 100% (a significantly improved accuracy over the older criterion of >200 pg/mL increase).[71,72] It is important to remember that hypochlorhydria/achlorhydria can cause a false-positive secretin test result. Because of this, PPIs need to be stopped to assess adequately for the presence of ZES and because of their long duration of action they generally need to be stopped for at least 1 week. PPI withdrawal should be performed with care by a group familiar with establishing the diagnosis of ZES because abrupt withdrawal in patients with ZES potentially can lead to serious consequences. The diagnosis of ZES in MEN1 can be complicated by the fact that successful treatment of the hyperparathyroidism, which is almost invariably present at the time of the presentation of ZES,[64] can decrease FSG level, acid secretion, and reverse a previously positive secretin test, thereby masking the disease.[73–75]

Insulinoma: Clinical Features/Diagnosis

Insulinomas ectopically secrete insulin, resulting in inappropriate hyperinsulinemia, which causes hypoglycemic episodes characterized by neuroglycopenic symptoms and sympathetic overdrive (Table 3, *top*). Symptoms classically develop during periods of relative substrate deficiency (fasting or exercise).[76,77]

Table 3. Features of the Insulinoma and Glucagonoma Syndromes

Features of the insulinoma syndrome
Neuroglycopenia (90%)
Amnesia or coma (47%)
Confusion (80%)
Visual changes (59%)
Convulsions (17%)
Altered consciousness (38%)
Sympathetic overdrive (60%–70%)
Weakness (56%)
Sweating (69%)
Tremors (24%)
Palpitations (12%)
Hyperphagia (14%)
Obesity (<50%)
Features of the glucagonoma syndrome
Migratory necrolytic erythema (70%–90%)
Weight loss (80%)
Glucose intolerance (40%–90%)
Normochromic, normocytic anemia (35%–90%)
Hypoaminoacidemia (80%)
Diarrhea (25%)
Thromoboembolism (15%–25%)
Glossitis, chelitis (15%–40%)
Psychiatric symptoms (0%–17%)

Data from Jensen,[9] Guillausseau and Guillausseau–Scholer,[47] Grant,[76] Soga and Yakuwa,[80] van Beek et al,[81] Kindmark et al,[82] Galbut and Markowitz,[300] Dizon et al,[301] Soga et al,[302] Fajans and Vinik.[303]

Similar to ZES, there is a delay in diagnosis (mean, 4 y).[76] Increased serum insulin levels may be appropriate (a consequence of increased blood glucose levels such as in type 2 diabetes mellitus) or inappropriate (with insulinomas, nesidioblastosis [MEN1-associated or after bariatric surgery], or exogenous insulin administration). A serum glucose level of less than 2.5 mmol/L (45 mg/dL) with an insulin level greater than 6 uU/mL (43 pmol/L by radioimmunoassay, ≥3 uU/mL by immunochemiluminescent assay) combined with an increased C-peptide level (≥200 pmol/L) and the absence of sulfonylurea in the plasma establishes the diagnosis.[76] The gold standard for establishing the diagnosis of insulinoma remains the 72-hour fast.[76] One third of patients will develop symptoms within 12 hours, 80% at 24 hours, 90% at 48 hours, and 100% at 72 hours.[76] Insulin levels are being determined increasingly by using immunochemiluminescent assays or insulin-specific immunoradiometric assays that have no cross-reactivity with proinsulin and give lower values, resulting in up to 60% of patients with insulinomas having plasma insulin levels less than 6 uU/mL.[78,79] In one recent study using these specific assays the most sensitive criterion for diagnosing insulinoma was the combination of an increased proinsulin level with a fasting glucose level of less than 45 mg/dL.[79]

Glucagonoma: Clinical Features/Diagnosis

Glucagonomas ectopically secrete glucagon, resulting in hyperglucagonemia. Glucagonomas cause glucose intolerance, weight loss, and a pathognomonic rash called *migratory necrolytic erythema*, characterized by erythematous macules that develop into papules, become necrotic, and heal with pigmented scarring[9,47,80–82] (Table 3, *bottom*). As with gastrinomas and insulinomas, glucagonomas present with a long history of symptoms (mean delay in diagnosis of 7 years, with reports of up to 18 years) and tumors are commonly large at presentation (mean, 6 cm).[9,47,80,81]

Despite controversy in the past regarding the specific cause of migratory necrolytic erythema, recent studies have shown that glucagon infusions can lead directly to migratory necrolytic erythema.[83–85] However, migratory necrolytic erythema is not specific for glucagonoma occurring also in celiac disease, cirrhosis, or pancreatitis.[81,85,86] Diagnosis of a glucagonoma requires demonstration of an inappropriately increased serum glucagon level (diagnostic at levels >500–1000 pg/mL). Lower increases may be associated with glucagonomas, but also can be caused by cirrhosis, pancreatitis, diabetes mellitus, prolonged fasting, sepsis, burns, renal failure, familial hyperglucagonemia, and acromegaly.[9,47,80,81]

VIPomas: Clinical Features/Diagnosis

VIPomas ectopically secrete vasoactive intestinal polypeptide (VIP), leading to large-volume diarrhea (90%–100%; 100% > 700 mL/day, 70%–80% > 3 L/day), electrolyte disturbances (notably hypokalemia, 70%–100%), dehydration (45%–95%), hyperglycemia (20%–50%), hypercalcemia (25%–50%), hypochlorhydria (35%–76%), and flushing (15%–30%).[9,39,87–89] The large-volume diarrhea often results in dehydration without an osmolar gap because it is secretory in nature.[9,39,87–90]

The diagnosis is confirmed by the presence of large-volume secretory diarrhea with an increased serum VIP level together with imaging evidence of a PET (in children the tumor commonly arises in extrapancreatic ganglioneuromas). However, even in the absence of a tumor able to be imaged, an increased serum VIP level (>500 pg/mL) in the presence of a documented secretory diarrhea is highly suggestive of VIPoma.[9,39,87–89]

Somatostatinoma: Clinical Features/Diagnosis

Somatostatinomas are somatostatin (SS)-secreting tumors primarily occurring in the duodenum or pancreas, which can produce the somatostatinoma syndrome, characterized by diabetes mellitus, gallbladder disease, weight loss, diarrhea, steatorrhea, and anemia.[9,40,91–93] In the literature there is no general agreement on the definition of a somatostatinoma, with most cases (55%–89%) described as a PET with somatostatin present by immunohistochemistry, but with no associated clinical syndrome. It has been proposed that the term *somatostatinoma syndrome* should be reserved for cases with the specific clinical syndrome only. Duodenal somatostatinomas uncommonly produce the somatostatinoma syndrome (<20%), whereas pancreatic tumors often do produce the somatostatinoma syndrome (>90%).[9,40,91–93] Because of the subtle nature of the syndrome these tumors have an even later presentation than other PETs. They can occur in association with MEN1 (0%–1% of all MEN1 patients) or in up to 10% of von Recklinghausen's disease patients.[13] The diagnosis is best confirmed by the presence of a pancreatic or duodenal mass together with an increased serum SS level in a patient with typical symptoms and a tumor staining for SS. However, serum levels should be interpreted with caution in individuals without concomitant masses. Unfortunately, there is no reliable provocative test to confirm the presence of a somatostatinoma in individuals with typical symptoms and no observable mass.

GRFoma: Clinical Features/Diagnosis

GRFomas ectopically secrete growth hormone–releasing factor, leading to uncontrolled pituitary release of growth hormone resulting in acromegaly.[9,94–96] Most cases of acromegaly are caused by pituitary tumors and only a small fraction (<2%) are caused by GRFomas. At least 50% of GRFomas arise in the lung (Table 1). Important clues to the presence of a GRFoma producing acromegaly are the absence of a pituitary tumor on imaging, the concomitant presence of MEN1, or the presence of an increased prolactin level.[9,94–96] GRFomas are diagnosed by the presence of an increased growth hormone–releasing factor level (>300 pg/mL).[9,94–96] There are no reliable provocative tests for GRFomas.

NF-PET: Clinical Features/Diagnosis

NF-PETs are not associated with a hormonal syndrome (Table 1). Because of this, they frequently are found by chance and patients generally present late in the disease course with large primaries (70% are >5 cm) and advanced disease (>60% have liver metastases).[9,97–101] NF-PETs produce symptoms caused by tumor growth/spread (ie, abdominal pain [40%–60%], weight loss [25%–50%], or jaundice [30%–40%]). In recent years, NF-PETs increasingly are being identified by chance (up to 35% of patients in one series[99]) because individuals undergo imaging studies for nonspecific symptoms. Asymptomatic detection results in lower rates of metastases, increased resectability, and improved survival.[102]

NF-PET is suggested by increased levels of serum chromogranin A (69%–100%) or PP (50%–100%) or positive SS-receptor scintigraphy (Octreoscan, In-pentetreotide scanning [Mallincrodt Medical, St. Louis, MO]) with a pancreatic mass. In the absence of a mass, other potential causes of increased serum PP levels (eg, old age, alcoholism, inflammatory conditions, renal failure, and bowel

resection) need to be considered. A confirmed diagnosis for NF-PET requires histologic confirmation.[9,97–101]

Tumor Localization/Staging

Imaging studies are essential for the management of patients with PETs. They are needed to localize the primary tumor as well as for staging to guide management, including surgical plans (curative resection, debulking, or medical management only), to monitor tumor growth, and for follow-up evaluation after therapy.[6,9,103–108]

Conventional Cross-Sectional Imaging Studies: Magnetic Resonance Imaging, Computed Tomography, Ultrasonography

Older studies evaluated various conventional imaging techniques (ultrasonography [US], computed tomographic [CT] scanning, or magnetic resonance imaging [MRI]) for localization/staging of PETs.[104,105,107,109–111] PET detection with these techniques (which may be suggestive of a PET specifically) is size-dependent with less than 20% of PETs less than 1 cm identified, 30%–40% of PETs 1–3 cm in diameter identified, and greater than 75% of PETs greater than 3 cm identified.[45,112] Most pancreatic VIPomas, glucagonomas, and somatostatinomas are large and therefore detectable with conventional studies. However, many gastrinomas, insulinomas, and duodenal somatostinomas are frequently less than 1 cm and will not be detected by these modalities.[104,105,109,110] For identifying patients with liver metastases, US is the least sensitive (identifies 40% of patients with metastases), whereas CT and MRI are positive in 70%–80%.[104,105,109,110] Figure 2 (*top*) shows liver metastases in a patient with gastrinoma by both CT and MRI scanning. As newer generations of scanners are being made available, these sensitivities may change.[105,107] At present, both high-resolution spiral CT and modern MRI are highly effective at identifying liver metastases (sensitivity, up to 94%) but somewhat less effective in identifying primary tumors (sensitivity, 55%–78%), because the more common functional tumors (insulinomas or gastrinomas) are often small.[113]

Endoscopic US

Although standard upper endoscopy is occasionally of value in identifying PETs that arise within the luminal GI tract (gastrinomas, somatostatinomas), endoscopic US (EUS) with fine-needle aspiration has become part of the standard armamentarium for evaluating pancreatic masses.[114–118] EUS/fine-needle aspiration is useful to distinguish PETs (especially NF-PETs) from adenocarcinomas and also to localize tumors not imaged with conventional studies.[117–120] EUS/fine-needle aspiration is reported to have a diagnostic accuracy of 80% for pancreatic adenocarcinoma and 46% for PETs.[117] Fine-needle aspiration rarely is needed with functional PETs (especially insulinomas/gastrinomas) because the diagnosis is made by biochemical/functional testing. EUS is more

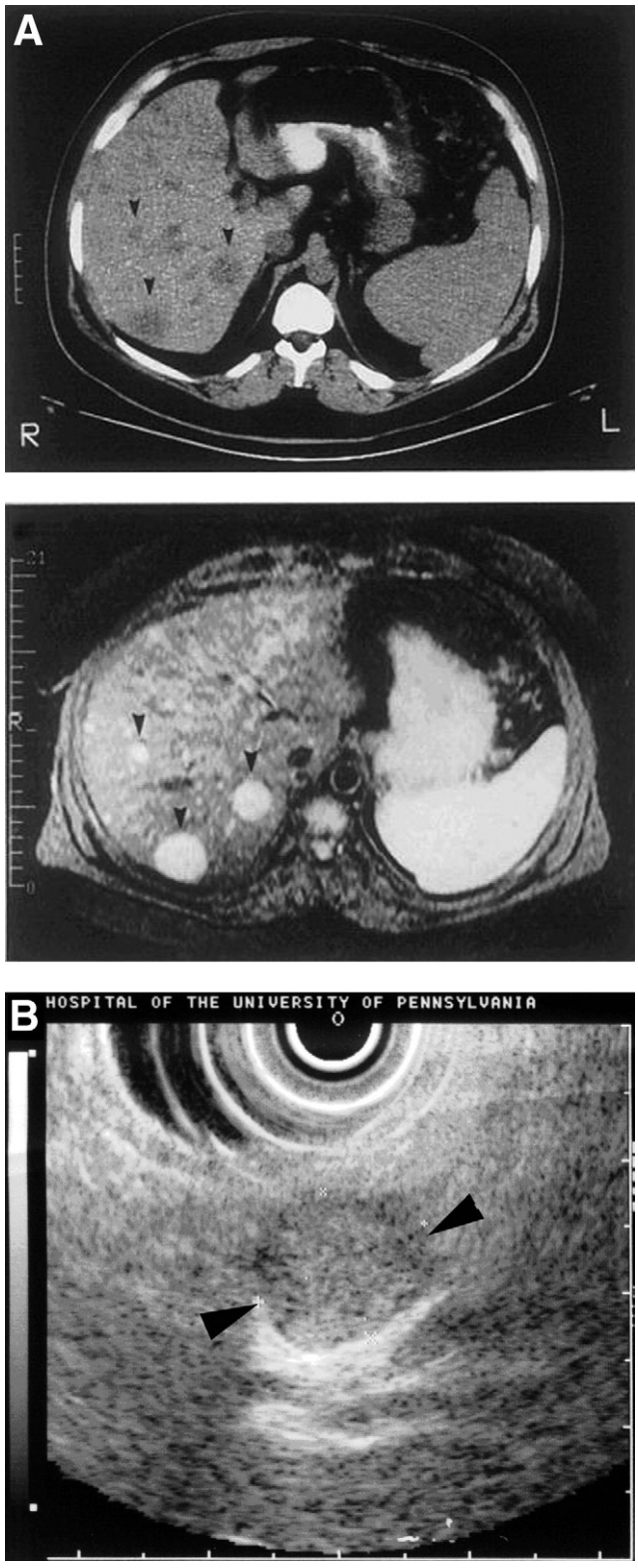

Figure 2. CT, MRI, and EUS in patients with PETs. (*A*) CT (*top*) and MRI (*bottom*) images of the abdomen in a patient with a metastatic gastrinoma. Liver metastases are indicated by *arrowheads*. (*B*) EUS image of a pancreatic body insulinoma confirmed at subsequent surgery. The tumor is indicated by the *black arrowheads*.

effective at localizing intrapancreatic PETs than extrapancreatic PETs such as duodenal gastrinomas.[117,121] EUS plays an especially important role in localizing primary insulinomas because they are pancreatic, commonly small (<1 cm), frequently missed by conventional studies, and frequently (>70%) are negative on somatostatin receptor scanning (SRS, see later) because of low density or lack of SS receptor subtypes that bind radiolabeled octreotide analogues with high affinity.[106,122–124] EUS is able to identify intrapancreatic primary PETs in approximately 90% of cases. Figure 2 (*bottom*) shows an EUS image of an insulinoma located in the body of the pancreas.

EUS is playing an increasingly important role in patients with MEN1.[13,125–128] MEN1 patients have NF-PETs in 80%–100% of cases histologically, although often they are small (<0.5 cm).[13,125–128] EUS is able to detect PETS in MEN1 patients not seen on either SRS or conventional studies, especially in the size range from 0.4 to 1.1 cm, with the result that 55%–100% of asymptomatic patients had NF-PETs identified.[126,129] The management of these small asymptomatic NF-PETs is controversial because their natural history is largely unknown.[13] However, because EUS has been shown to have excellent specificity and reproducibility for small NF-PETs (<10 mm), it has been proposed that serial EUS studies could be used to monitor growth and determine when intervention should be considered.[125–127,130]

Similarly, in patients with von Hippel–Lindau disease, PETs develop in 10%–17% and they almost invariably are NF-PETs.[13,131–135] Their management also is controversial because these patients almost invariably are asymptomatic, especially if the PET is small (<2 cm). In various studies in which no patient with an NF-PET less than 3 cm had hepatic metastases, it has been recommended that PETs less than 3 cm not be resected routinely.[135–137] EUS is the most accurate method to assess PET size in these patients and could be used for serial studies similar to that proposed earlier in MEN1.

Angiography and Selective Hormone Sampling

Before the development of functional imaging studies (see later), angiography and sampling for hormone gradients were widely used and extremely helpful in patients with PETs.[138–141] Originally, selective sampling for hormonal gradients was performed by portal-venous sampling.[139,142] This method was largely replaced by selective-arterial injection of secretin (gastrinomas) or calcium (other functional PETs) with assessment of hepatic venous hormone concentrations because it can be performed at the time of angiography, has less complications, and requires less expertise, but is similarly sensitive to portal-venous sampling.[139,140,143,144] This approach also can be used to identify liver metastases after selective hepatic artery cannulation.[141] In recent years, with advancement in other functional tumor localization methods, the use of these invasive localization techniques has declined. The 3 remaining areas in which these studies still are used are as follows: (1) for localizing insulinomas after a negative Octreoscan/EUS, (2) for preoperative evaluation of the liver before debulking surgery, and (3) for localizing a functional PET in MEN1 patients with multiple lesions.[140,145] Numerous studies have shown that intra-arterial injection of calcium with hepatic venous insulin sampling is a sensitive method of localizing insulinomas, even in imaging-negative cases, being positive in 88%–100%.[139,140,145–149]

Functional Imaging (SRS and Positron-Emission Tomography)

Most PETs show high densities of sst2 or sst5 receptors, 2 of the 5 SS-receptor subtypes (designated *sst1–sst5*) that have high affinity for the SS analogues: octreotide and lanreotide.[150–153] Radiolabeled forms of these synthetic SS analogues with high affinity for sst2/sst5 receptors have proved sensitive and useful for localizing both the primary PET as well as metastases.[104,151,154,155] [^{111}In-diethylenetriaminepenetaacetic acid-DPhe^{1}]-octreotide is approved in the United States. SRS (or Octreoscan) identifies 50%–70% of primary PETs but less than 25% of insulinomas (which have absent or lower sst2/5 densities).[104,122–124,151,154,155] In one prospective study, SRS was as sensitive as all conventional studies and angiography combined.[155] SRS is particularly useful for showing liver metastases with the best sensitivity of any imaging modality (almost 90%).[104,155–157] The imaging results shown in Figure 3 in 2 patients with ZES show the greater sensitivity of SRS than conventional studies in localizing

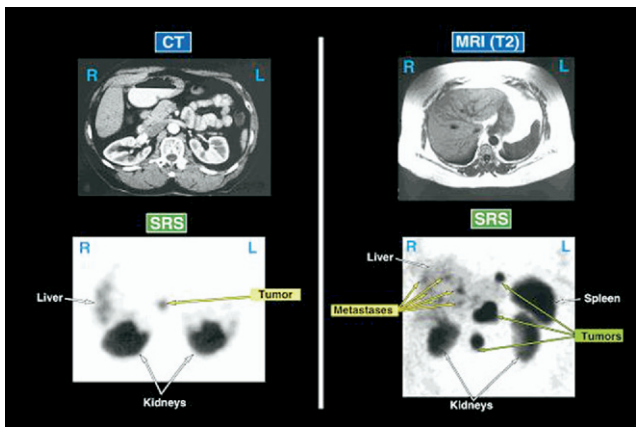

Figure 3. Comparison of conventional imaging (CT, MRI) and SRS to localize a primary gastrinoma (*left*) or metastatic disease (*right*) in 2 patients with ZES. In the left panel the patient had negative preoperative conventional imaging studies (CT, MRI) and angiography, but SRS showed a lesion in the pancreatic head area. At surgery, a 2-cm tumor was resected and the patient has remained disease-free. In the *right panel* neither the MRI nor CT showed recurrent disease in this patient's postresection of a gastrinoma; however, the fasting gastrin level was increased and the SRS showed extensive metastases in lymph nodes and the liver. Both of these results show the greater sensitivity of SRS for localizing primary PETs as well as metastatic disease.

both the primary as well as metastatic disease to the liver/lymph nodes. SRS allows whole-body scanning and therefore also is useful to identify tumors beyond the liver (eg, lungs/bone).[34,154,158] To achieve high sensitivity it is essential that single photon-emission tomography be used to isolate possible lesions from the renal background.[106,151,159] Studies have shown that SRS changes the management in 24%–47% of patients with PETs.[160–162] Although SRS has high specificity it is important to remember that a number of normal and abnormal tissues express increased densities of sst2/5 receptors that can result in false-positive scans. False-positive results can occur particularly with thyroid disease, breast disease, lymphoma, cholangiocarcinoma, hemangiomas, sites of inflammation, and granulomatous disease.[151,153,161] In one prospective study,[161] 12% of SRSs were false positive for a PET; however, when results were interpreted in the clinical context, the false-positive rate was only 3%. Detection of PETs by SRS is also size-dependent, with appropriately 50% of gastrinomas less than 1 cm in diameter not detected.[163] Therefore, there is a need for even more sensitive imaging methods.[154,163]

Positron-emission tomographic scanning is receiving increasing attention for PET localization.[106,164] Standard substrates such as ^{18}F-deoxyglucose are not useful for most PETs because of their slow glucose turnover and are only useful for the small subset with high proliferative rates and low differentiation.[106] ^{11}C-5-hydroxytryptophan (^{11}C-5-HTP) or ^{68}Ga-labeled SS analogues have greater sensitivity than SRS or conventional studies[106,164–166] and therefore may prove to be clinically useful in the future. Particularly important for the increased use of position-emission tomographic scanning in PET patients is the ability to make ^{68}Ga using a generator, similar to what is now used for technetium-99m in most nuclear medicine departments, rather than requiring a cyclotron as is the case for these other isotopes.[106] In a recent study[165] involving 84 patients with various GI NETs (carcinoids, 23 PETs), positron-emission tomographic scanning using ^{68}Ga-DOTA-Tyr^3-octreotide had a sensitivity of 97% compared with 55% for SRS and a greater accuracy (96% vs 58%; $P < .01$) with equal specificity for the 2 techniques. One particular benefit of this scanning is the potential for image fusing (ie, overlaying CT with PET images). It is likely that such scanning will play an increasingly important role in the future for imaging PETs. Figure 4 shows the increased sensitivity of positron-emission tomographic scanning with ^{11}C-5-HTP for detecting liver metastases compared with CT scanning in a patient with a malignant PET.

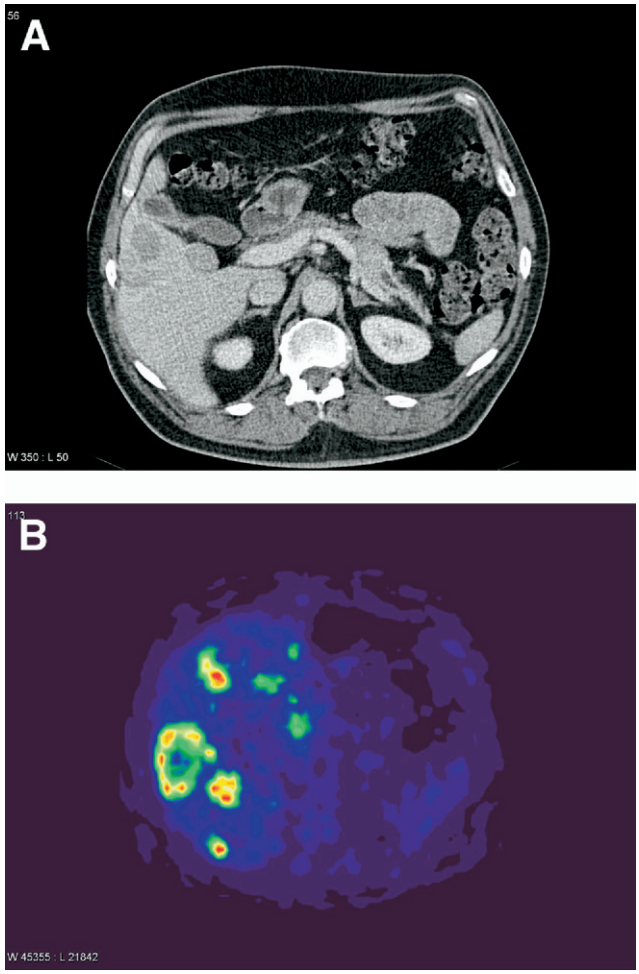

Figure 4. Comparison of the extent of liver metastases in a patient with a malignant PET on CT scanning (*top panel*) and positron emission tomographic scanning (*bottom panel*). This patient with a malignant PET had a few liver metastases seen on CT scanning (*top*) and SRS (not shown), but much more extensive disease on positron emission tomographic scanning with ^{11}C-5-HTP showing its greater sensitivity. (Images kindly provided by Professor Anders Sundin, Department of Radiology, Uppsala University Hospital, Uppsala, Sweden).

Medical Management of the Hormonal Excess State

Gastrinoma: Medical Management

In ZES acid hypersecretion is the most important clinical effect.[45,62,167,168] Because of their potency and long duration of action, PPIs are the agents of choice for management.[31,45,53,167,169,170] Histamine H_2-receptor antagonists or SS analogues are effective, but the former drug class is limited by the need for frequent, high-dose administration,[167,169] whereas the latter class is limited by the need for parenteral therapy.

Once- or twice-daily oral PPIs (ie, omeprazole [40 mg], lansoprazole [30 mg], rabeprazole [20 mg], pantoprazole [40 mg], or esomeprazole [40 mg]) are effective in virtually all ZES patients.[167,169,171–175] It is important to document control of acid output (ie, <10 mEq/h in the last hour before the next dose of drug [intact stomachs] or <5 mEq/h [prior gastric resections]) in patients with uncomplicated disease (ie, no MEN1, mild GERD, and no prior Billroth 2 resection) rather than to titrate drug dosages to symptoms because asymptomatic individuals may still have uncontrolled acid hypersecretion.[45,167,176]

Patients with complicated disease (ie, MEN1, moderate-severe gastroesophageal reflux disease, Billroth 2 resection) often need higher doses and usually are best treated with at least twice-daily dosing.[177–179] It is recommended that patients with uncomplicated disease be started initially on 40–60 mg of omeprazole (or equivalent) to adequately control acid output acutely[180]; however, with time the dosage can be decreased in up to 60% of patients.[179] Long-term follow-up evaluation of patients receiving PPIs showed no tachyphylaxis and an excellent safety profile,[170–172,181] although drug-induced achlorhydria may lead to substrate deficiencies (vitamin B_{12} is more of a concern than iron).[181,182] Even though in animal studies long-term high-dose PPI treatment can lead to the development of gastric carcinoids, there is no evidence of an increased rate of their development with chronic PPI treatment in ZES patients.[167,183–185] Almost every ZES patient shows some degree of enterochromaffin-like cell hyperplasia,[183,185–187] which is more severe in MEN1 patients.[7,183,186] Patients with MEN1/ZES develop gastric carcinoids in 23%–33% of cases[183,185,186]; however, the rate in patients with sporadic ZES is less than 1%[183,185–187] and there is no evidence that PPIs alter this rate in either group.

Intermittent intravenous PPI treatment (with pantoprazole [80 mg], lansoprazole [60 mg], or esomeprazole [80 mg]) given 2 or 3 times daily effectively substitutes for oral therapy for brief periods in patients who cannot take oral drug.[188,189] Three times daily therapy is generally recommended because this more frequent administration precludes the requirement to document effective control of acid in situations when the patients may be quite ill. There is no longer a role for gastric surgery to reduce acid output in ZES patients.

Insulinoma: Medical Management

Most patients (>85%) have a single small benign insulinoma,[76,77,190] except for those with MEN1 in which multiple tumors frequently occur[13] and therefore they are treated surgically soon after diagnosis with an excellent cure rate.[76,77,190] However, before surgery and for the 5%–15% (Table 1) with malignant disease, treatment for the hypoglycemia is needed. In addition to frequent small feedings the initial drug generally used is diazoxide (200–600 mg/day in divided doses), a benzothiadiazide that directly inhibits insulin release and causes adrenergic stimulation promoting glycogenolysis.[9,76] Diazoxide controls hypoglycemia in 50%–60% of patients and has been used effectively for more than 20 years.[76,77,190,191] Diazoxide frequently results in sodium/fluid retention requiring diuretics, as well as nausea and occasional hirsutism.[76,77,190,191] Long-acting SS analogues (octreotide, lanreotide) are effective in 35%–50% of patients with insulinomas; however, they need to be used with care because in some cases they worsen the hypoglycemia, presumably by inhibiting counter-regulatory mechanisms.[123,153,190] Therapy with other agents such as verapamil, propranolol, or phenytoin also has been described, although these agents are generally not first-line choices.

Other Functional PET Tumor Syndromes: Medical Management

Until the availability of octreotide (see later), specific therapy for PETs included blood transfusions; insulin, zinc, and amino acid transfusions for glucagonomas; replacement of volume losses and correction of acid-base disturbances for VIPomas; nutritional repletion and insulin administration for the somatostatinoma syndrome; and administration of adrenolytic agents (such as ketoconazole, aminoglutethimide, metyrapone, or dichlorodiphenyldichlorethane) or adrenalectomy for ectopic adrenocorticotrophin-producing hormone–producing tumors. However, octreotide availability has largely supplanted the need for many of these approaches.

SS is a widely distributed 14–amino acid cyclic paracrine peptide that exerts multiple inhibitory effects on secretory and motor functions.[150,153] Its effects are mediated by binding to 1 of 5 receptor subtypes, designated *sst1–sst5*, which are all G protein–coupled receptors.[150] SS has a short serum half-life of about 2 minutes, precluding its use clinically, but its synthetic analog, octreotide, with a serum half-life of at least 1 hour, has been used successfully to inhibit secretion from a variety of cell types including PETs, which usually show high sst2-receptor densities.[153,192,193]

Octreotide is approved for use in patients with acromegaly, VIPomas, and the carcinoid syndrome, but it also is useful off label to lower portal pressure in patients with bleeding from esophageal varices caused by portal hypertension, to control diarrhea in patients with acquired immune deficiency syndrome enteropathy and short-bowel syndrome, and to control hormonal syndromes in patients with other NETs.[153] Octreotide usually is prescribed at doses ranging from 100 to 500 ug 3 times daily by subcutaneous injection initially, but this form of administration then can be overlapped with once-monthly depot injections of an even longer-acting formulation, octreotide long-acting release at doses of up to 30 mg/mo.[7,8,194] Lanreotide sustained release or autogel is another depot SS analog available in Europe.[195]

In VIPomas, octreotide reduces serum VIP levels in greater than 80% of patients and improves diarrhea in greater than 75%, but the response is often short-lived (<1 y) without dose increases. In glucagonomas, octreotide decreases plasma glucagon levels in greater than 80% and improves migratory necrolytic erythema in 90% (with complete resolution in 30%). There are anecdotal reports of efficacy of octreotide in somatostatinoma syndrome as well as therapy for GRFomas.[7–9,153] Octreotide therapy is not recommended for hormonal control of

gastrinoma. Octreotide should be used with care in patients with insulinomas (as discussed earlier). The mean duration of octreotide treatment in studies is 1 year and frequently tachyphylaxis develops, which may be overcome with higher doses.[8]

Adverse effects of SS analogues generally are mild and include diarrhea/steatorrhea, flatulence, fluid retention, nausea, gallstones, and glucose intolerance. Such side effects are reported in 50% of patients treated with octreotide, but rarely have been serious enough to stop treatment.[153] In long-term treatment of patients with acromegaly only 5% developed side effects severe enough to stop treatment.[194,196] During long-term treatment concern has been raised about the possibility of an increased rate of gallstone development. This has been particularly well studied in patients with acromegaly with a mean incidence of 29%, however, only 1% develop symptomatic gallbladder disease.[194]

Surgical Therapy for Cure

Surgery is the only treatment modality with the potential to cure patients with PETs. However, surgery is only likely to be effective in patients without diffuse metastatic disease who are able to tolerate the intervention and, in the case of ZES specifically, only in those with sporadic disease.[13,113,197–199] Negative preoperative localization should not be considered a contraindication to surgery in patients with proven functional PETs because an experienced PET surgeon will very frequently localize the tumor (>95% of insulinomas or gastrinomas).[76,113,198,200] On the other hand, preoperative identification of diffuse disease beyond regional lymph nodes precludes attempts at curative surgery, although many authorities favor debulking surgery in cases in which 90% or more of identifiable disease is thought resectable (see later). In the 5%–15% of patients with limited hepatic metastases, many authorities attempt resection because this approach may result in extended disease-free survival in selected patients.[46,201–204] Patients with MEN1 develop potentially curable PETs of various types (insulinomas, VIPomas, somatostatinomas, glucagonomas, and GRFomas);[13,205–210] however, both the NF-PETs and gastrinomas are invariably multiple, arising throughout the pancreas or the proximal duodenum.[30,127,211,212] At present, most authorities do not recommend subjecting patients with MEN1/ZES to a Whipple resection or patients with multiple NF-PETs with MEN1 to total pancreatectomy because these surgeries are extensive, the long-term consequences are unclear, postoperative morbidity can be significant, and the long-term prognosis of these patients without such treatment remains excellent.[121,127,198,206,209,213] In MEN1 patients the surgical treatment of NF-PETs (80%–100% of patients) and gastrinomas (40%–60% of patients) remains controversial because of multiplicity of primary tumors and failure of enucleation to result in cure.[121,127,198,206,209,213] Potential approaches in these patients include not performing routine surgery, performing surgery with aggressive removal of all larger PETs, or only operating in patients with tumors greater than 2 cm able to be imaged.[121,127,198,206,209,213,214] This latter approach stems from a number of studies that showed that patients with MEN1 and NF-PETs or gastrinomas less than 2 cm in diameter have an excellent prognosis (survival equal to patients without PETs or 100% at 15 years) and they rarely develop advanced disease.[127,197,198,206,215]

In advance of surgery patients should be vaccinated against encapsulated microorganisms (pneumococcus, *H influenza*, meningococcus) in anticipation of a possible splenectomy and they should receive a bowel preparation in anticipation of an expected enterotomy (mandatory in the case of gastrinomas and other hormonal syndromes with a predilection for duodenal primaries).[198,216–219] In general, all PETs (except imaged insulinomas) should be approached by laparotomy to permit an extensive exploration of the entire abdomen.[113,203,219–221] An exception to this rule is surgery for insulinoma in non-MEN1 individuals because at least 85% of these tumors are benign, there usually is a single primary, and, if they can be localized preoperatively, laparoscopic resection is successful in 70%–100% of cases and its use hastens postoperative recovery.[121,222–224] It is also important to examine the entire pancreas, which requires complete mobilization of the duodenum and exposure of the pancreatic tail.[32,198,216–219] Surgical exploration is assisted by intraoperative ultrasonography using appropriate transducers for evaluation of the liver (5 MHz) and pancreas (7.5–10 MHz). Intraoperative endoscopic transillumination plus duodenotomy is required for tumors with a predilection for the duodenum (GRFomas, somatostatinomas, and especially gastrinomas) because they frequently are small (<0.5 cm), are not detected by ultrasound or palpation, and primarily are localized in the first and second part of the duodenum.[113,198,216–220,225–227] Some authorities favor intraoperative hormonal localization as well.[228]

The aims of surgical resection for cure are to remove the primary tumor and regional lymph nodes (if affected) with minimal disruption to the underlying anatomy. Enucleation is advised for insulinomas because they generally are benign, as well as for localized tumors of the pancreatic head. Duodenal tumors generally are resected unless small and then may be removed endoscopically in some cases, conversely if they are large they may require a duodenectomy.[30,229] Tumors in the pancreatic tail generally are resected (with splenic preservation if possible) as opposed to enucleated unless they are insulinomas.[113,198,216–220] MEN1 patients who come to surgery should have a careful exploration of the entire pancreas with enucleation or resection of all dominant masses, realizing that the largest lesion identified may not necessarily be the lesion causing the functional syndrome. In general, blind pancreatectomy in the rare case of no identifiable tumor after

a careful exploration of the entire abdomen is not believed to be an acceptable approach.

In appropriate hands, cure rates for insulinomas approach 100%.[76,230] For sporadic gastrinomas the figure is 60% immediately postoperatively and 30%–40% at 5 years.[198,216] In general, cure rates for other PETs are lower because they generally are larger at presentation, often with metastases. Surgical resection of the primary PET should be attempted whenever possible if the patient does not have another medical problem limiting life expectancy, substantially increasing surgical risk, or diffuse metastatic disease because studies in patients with ZES show resection of the primary tumor both decreases the rate of development of liver metastases and extends survival by preventing the development of progressive disease.[50,51]

Treatment of Metastatic Disease

General Treatment of Metastatic Disease

In recent studies the long-term outcome in patients with PETs is increasingly dependent on tumor growth. However, even with widespread liver metastases many patients remain relatively well with slow progression, especially early on in the disease process, such that many authorities advocate delaying the introduction of disease-modifying agents until there is clear development of enlarging tumor burden, or symptoms develop. Furthermore, standard antitumor therapies are not curative and frequently have limited efficacies.

Biotherapy

Octreotide/interferon. Biotherapy with long-acting SS analogues (octreotide long-acting release or lanreotide sustained release or lanreotide autogel) frequently is instituted first in patients with enlarging tumor burdens, especially patients with slow-growing tumors without extensive (<50%) liver involvement.[8,231] This approach is used commonly even though the results are controversial and there are no studies that clearly have shown it prolongs survival owing to inhibition of tumor-related growth.[103,232] SS analogues frequently are used first because these agents are well tolerated and numerous studies suggest they have a tumoristatic effect, causing a decrease or cessation of growth in 30%–80% of cases, without tumor regression in most cases (<15%) that showed growth before treatment.[103,206,232–235] It is presumed that this tumoristatic effect will result in improved survival, but at present this remains unproven. The tumoristatic effect can be prolonged (>2 y) and is seen more frequently in slow-growing tumors with a low proliferative index; therefore, some recommend that rapidly growing tumors or tumors with high proliferative indices be treated with other modalities.[8,206,231,233,236] The exact mechanism of SS analogue action in PETs is not completely clear; however, they induce apoptosis and in various cells activate phosphatases, suppress release of growth factors, inhibit insulin-like growth factor-1 signaling, have immunomodulatory effects, and inhibit angiogenesis.[150]

Interferon therapy (human leukocyte/interferon-alfa) also is used frequently for the treatment of metastatic disease but, as with octreotide, its major effect is tumor growth stabilization rather than inducing regression (<20% of cases).[8,103,232,234] Similar to SS analogues it is hoped that this tumoristatic effect will result in improved survival, but at present this is also unproven.[232] The mechanism of interferon's antiproliferative effect in PETs is not completely known; however, it increases tumor expression of bcl-2, resulting in decreased cell proliferation and in other cells inhibits protein and hormone synthesis angiogenesis and stimulates the immune system.[8] Unfortunately, interferon therapy causes frequent side effects including flu-like symptoms (which may improve with prolonged therapy); fatigue; weight loss; lipid, thyroid, and liver enzyme abnormalities; and cytopenias including leukopenia, which may persist and interfere with the acceptability of long-term treatment.[232,233]

Because both interferon and octreotide therapy are tumoristatic by different mechanisms, combination therapy was believed to have promise. Nonrandomized studies were suggestive of additive effects,[232,237] but a recent prospective study[238] showed no additivity; however, a number of reservations have been raised about this study, primarily methodologic issues.[239]

Peptide-receptor radionuclide therapy. Peptide-receptor radionuclide therapy uses the fact that PETs almost uniformly overexpress SS receptors and internalize radiolabeled SS agonist analogues, thereby facilitating the delivery of cytotoxic doses of localized radiation to the PET.[153,233,240–244] Three different radiolabeled SS analogues have been developed and investigated in patients with malignant NETs including analogues labeled with ^{111}In (emits conversion and auger electrons, γ-rays), ^{90}Y (strongly emits β-particles), and ^{177}Lu (emits β-particles and γ-rays).[240–244] The effect of ^{111}In-DPTA-octreotide was examined in 2 studies[240,245] including 52 patients with malignant progressive NETs and complete tumor regression was seen in 0%, partial regression was seen in 0%–8%, and tumor stabilization was seen in 42%–81%. [^{90}Y-DOTA,Tyr^3]-octreotide, [^{90}Y-DOTA]lanreotide or [^{90}Y-DOTA-,Tyr^3]octreotate were examined in 7 studies involving more than 280 patients with malignant NETs and complete tumor responses occurred in 0%–3%, partial responses in 6%–37%, and stabilization in 44%–88%.[240,245] In one study a longer survival was reported in patients treated with [^{90}Y-DOTA-,Tyr^3] octreotate than those previously treated with ^{111}In-DPTA-octreotide (mean, 37 vs 12.5 mo).[240,246] One study reported results with 129 patients with malignant NETs treated with [^{177}Lu-DOTA,Tyr^3]octreotate and found a complete tumor response in 2%, a partial response in 32%, and stabilization in 34%.[240,247] To date, no controlled studies have shown that peptide-receptor radionuclide therapy extends sur-

vival. In general, peptide-receptor radionuclide therapy with the different isotopes has been safe with severe side effects uncommon.[240,244–246] Approximately 30% of the patients develop acute side effects (nausea, pain, vomiting) that usually are mild, can be controlled with symptomatic therapy, and do not interfere with continued treatment.[240] More severe side effects include hematologic toxicity (15% usually transient, 0.3% develop myelodysplastic syndrome) and renal toxicity (which occurs almost entirely in patients given ^{90}Y-labeled SS analogues and can be limited by co-administration with amino acids).[240,244,245] Although not yet approved for use in any country, the promising results described earlier have led to peptide-receptor radionuclide therapy undergoing evaluation in a number of centers in the world to clearly establish its exact utility.

Liver-Directed Therapy (Embolization, Chemoembolization)

Most malignant PETs metastasize to the liver where they derive their blood supply from hepatic artery branches (75%–80%), in contrast to native liver tissue, which derives the majority of its blood supply from the portal vein.[9,248,249] Recent studies have shown that liver metastases show rapid growth in less than 50% of patients and up to 30% show no growth on follow-up evaluation.[33,37,250] Consequently, the usual approach to palliative therapy for liver metastases is to delay therapy until symptoms supervene owing to the metastases per se, the tumor shows rapid growth, or the patient develops refractory symptoms from a functional PET.

Selective deprivation of blood supply to metastases for the palliative management of metastatic disease can be achieved by surgical ligation, but interventional radiologic approaches via intra-arterial catheterization of the iliac/brachial arteries without (hepatic artery embolization [HAE]) or with co-administration of chemotherapeutic agents (HACE) permits a similar result.[9,248,249,251] Absolute contraindications to HAE/HACE are portal venous thrombosis, liver failure, and biliary reconstruction (Whipple resection), whereas relative contraindications are hepatic tumor loads greater than 50%, contrast allergy, extensive extrahepatic disease, and poor performance status.[249,252] There are no randomized studies comparing embolization alone (HAE) with those with embolization combined with chemotherapeutic agents (HACE) such as 5-fluorouracil, cisplatin, mitomycin C, or streptozotocin.

The usual approach to HAE/HACE is sequential catheterization of peripheral radicals of the hepatic artery in one liver lobe followed by repeated administration of therapy on the other side about 6–8 weeks later.[248,249,253] In various studies 55%–100% of patients with malignant NETs treated by HAE/HACE have symptomatic improvement and 20%–80% have an objective response with tumor shrinkage.[9,248,249,251,253–256] The mean duration of response is 6–42 months.[248,254–256] A lower response rate has been reported in patients with greater than 75% of the liver involved and in patients with an intact primary tumor or extrahepatic metastases.[254]

HAE/HACE is not without side effects, with an overall mortality rate of less than 3%, but pain develops in 50%–100%, nausea and vomiting in 50%–90%, and fever/leukocytosis in 30%–60%. In 5%–15% of patients serious side effects can occur including hepatic failure, bleeding, gallbladder necrosis, hepatic abscess formation, and renal failure.[9,248,253]

At present there is no uniform agreement on when HAE/HACE should be used in patients with malignant PETs. In patients with functional PETs not responding to other therapies, or malignant PETs with diffuse hepatic metastases only that are increasing in size or causing local symptoms caused by tumor bulk, this procedure may be considered and may be quite helpful in controlling symptoms.[248,251,254]

Surgical Debulking (Cytoreductive Surgery)/ Radiofrequency Ablation of Hepatic Metastases

The role of cytoreductive surgery in patients with malignant PETs with incompletely resectable metastatic disease is controversial. Although numerous studies have shown that surgery may help control symptoms in patients with advance metastatic functional PETs and likely prolong life expectancy in patients with malignant PETs, in most studies the patient groups are not strictly comparable and no randomized studies have examined this approach.[9,46,201,257–261] In an analysis of 63 patients with malignant PETs from 5 different surgical series who underwent surgical resection, the surgical mortality rate averaged 6%, symptom control was achieved in 85%, and the 5-year survival rate was 60%–80%.[257] We, as well as those in a number of other surgical series, concluded that surgical resection should be attempted in patients with malignant PETs whenever it is determined that at least 90% of the visible tumor likely could be removed.[201,202,255,257,259–262] In one recent[255] retrospective comparison of results with cytoreduction or embolization in 120 patients with malignant NETs (33 PETs, 87 carcinoids), patients undergoing cytoreductive surgery had longer survival times and a greater reduction in symptoms.

Radiofrequency ablation is being used increasingly in patients with PETs with hepatic metastases, either alone or in combination with other treatments.[248,263–266] Radiofrequency ablation can be performed at the time of surgery for isolated hepatic metastases or laparoscopically.[248,264,265] Factors limiting its application include tumor size (usually used in tumors $<$3.5 cm) and number (usually used in cases with $<$5 lesions).[248,264,265] Radiofrequency ablation morbidity is low ($<$15%), although

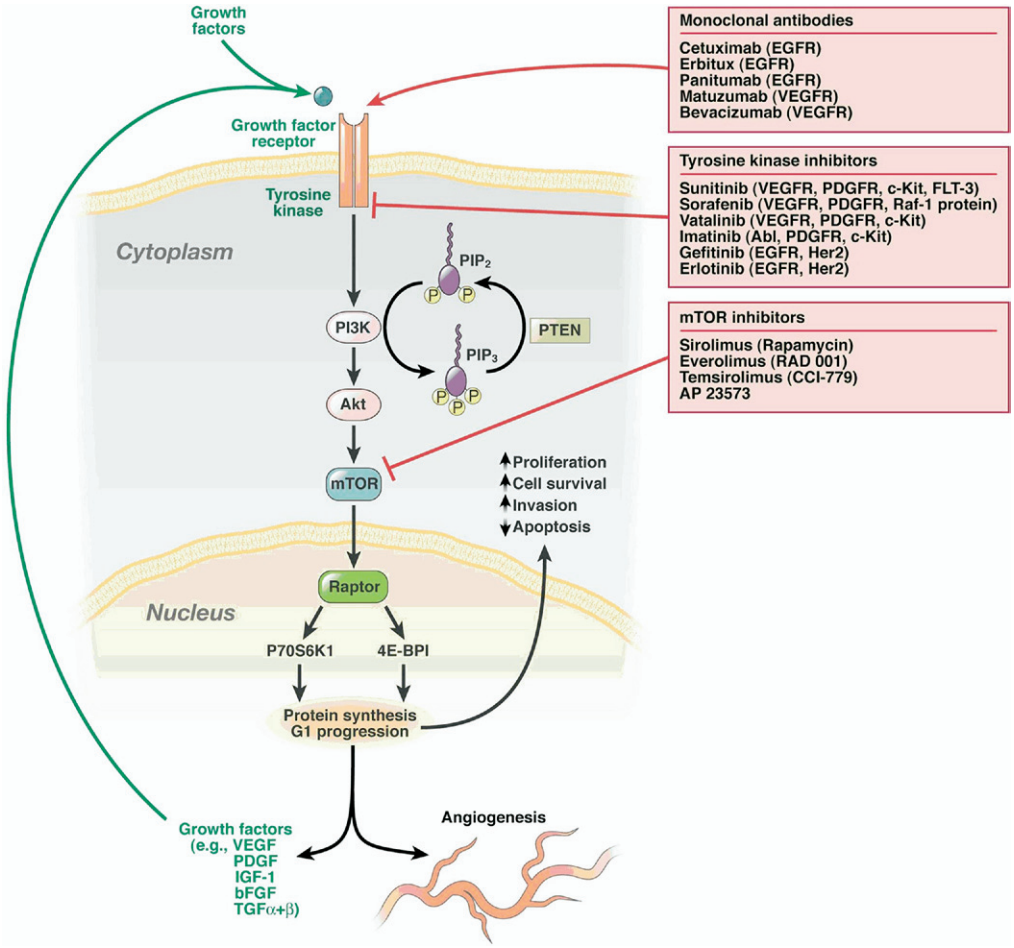

Figure 5. Theoretical pancreatic endocrine tumor cell, smooth muscle cell (pericyte), or endothelial cell showing the sites and mechanism of action of novel agents for the management of metastatic PETs. These cellular components of PETs all show surface growth factor receptors (eg, vascular endothelial growth factor receptor [VEGFR], platelet-derived growth factor receptor [PDGFR], insulin-like growth factor-1 receptor [IGF-1R], c-KITR, and so forth), which when occupied by their respective growth factors (in an autocrine or paracrine manner) lead to autophosphorylation of the intracellular tyrosine kinase component of the receptor. Tyrosine kinase phosphorylation activates the PI3K-AKT-mammalian target of rapamycin (mTOR) pathway (among others), ultimately promoting protein synthesis, cell-cycle progression, and cell survival, which causes increased cellular proliferation, inhibition of apoptosis, cellular invasion, metastasis, and tumor angiogenesis. This pathway can be inhibited by monoclonal antibodies to growth factor receptors, tyrosine kinase inhibitors with specific activity against various growth factor receptors, or downstream mTOR inhibitors. Although mTOR inhibitors are active against both the tumor directly as well as its blood supply, tyrosine kinase inhibitors or antibodies directed against specific growth factors may predominantly effect the tumor itself or secondarily inhibit tumor cell growth by altering its blood supply.[304–308]

occasional cases of hemorrhage or abscess formation occur. Response rates from 80%–95% are reported and responses have lasted up to 3 years.[248,264–266] Although radiofrequency ablation has not been shown to extend life, its ability to control local metastases with low morbidity has led to it being used increasingly for the treatment of limited small metastases and it may be particularly helpful for patients with limited metastases from a functional PET, especially at the time of surgery.[232,263,266]

Chemotherapy

Traditional chemotherapeutic approaches. If biotherapy fails or the PET is rapidly growing or poorly differentiated, chemotherapy frequently is used.[249,267,268] A large number of regimens have been used in patients with metastatic PETs with some success, in contrast to carcinoid tumors, in which they generally have been unsuccessful.[249] Streptozotocin was the first agent shown to have significant benefit in a prospective study as monotherapy for malignant PETs.[269] However, this approach provided limited benefit with significant renal/hematologic toxicity.[269] Combination therapy with streptozotocin and 5-fluorouracil or doxorubicin subsequently was used to permit lower doses of streptozotocin to potentially limit side effects without sacrificing efficacy. In the 1992 Eastern Cooperative Oncology Group study of 105 patients who received 1 of 3 regimens (streptozotocin-doxorubicin response rate, 70%; streptozotocin-5-fluorouracil response rate, 45%; and chlorozotocin monotherapy response rate, 30%), the streptozotocin-doxorubicin regimen was

shown to improve overall survival with a mean duration of response of 18 months.[270] Later studies using only imaging assessments and better imaging modalities have not found this degree of success. In later studies using streptozotocin in various combinations with 5-fluorouracil and doxorubicin, the overall survival was either not impacted at all or only minimally impacted, the response rate was 6%–40% with no complete responses, and the median response was short (9–18 mo).[249,268,271,272] Particularly poor response rates were seen in patients with replacement of greater than 75% of the liver by tumor or in those who previously had received chemotherapy.[268] Streptozotocin is associated with significant side effects with 74%–100% of patients developing nausea/vomiting, and 20%–40% with long-term treatment developing renal toxicity.[249,268–270] Studies using other chemotherapeutic agents including etoposide, dacarbazine, and cisplatin or carboplatin alone or in combination in general also have been rather disappointing.[9,249,267] In poorly differentiated PETs, chemotherapy with cisplatin, etoposide, or its derivatives is the recommended treatment with response rates of 40%–70% reported; however, the response rates are relatively short.[249,273–275]

Angiogenesis Inhibitors and Other New, Novel Approaches

GI NETs frequently produce multiple growth factors including vascular endothelial growth factor, platelet-derived growth factor, insulin-like growth factor, basic fibroblast growth factor, and transforming growth factor, as well as expressing receptors for these (vascular endothelial growth factor receptor, platelet-derived growth factor receptor, insulin-like growth factor-1 receptor) and other growth factors (epidermal growth factor receptor).[276–280] A number of new, novel therapies are now available that are directed at these growth factors or their receptors and are being investigated in GI NETs including a monoclonal antibody to vascular endothelial growth factor (bevacizumab) as well as small-molecule inhibitors of the intracellular tyrosine kinase domain of vascular endothelial growth factor receptor or other growth factor receptors (sunitinib [SU11248], sorafenib, vatalanib, imatinib [Gleevac; Novartis, East Hanover, NJ], gefitinib)[280–284] (Figure 5). In one study reported in abstract form,[285] sunitinib was evaluated in a phase II study of 61 patients with PETs. The treatment was well tolerated and a response occurred in 13%, tumor stabilization in 68%, and the median time to tumor progression was 33 weeks. In another phase II trial[286] of gefitinib, a tyrosine kinase inhibitor targeting epidermal growth factor receptor, in 31 PET patients a tumor response of only 6% was noted. Other novel approaches to the management of metastatic PETs have focused on targeting downstream targets of tyrosine kinase receptor activation (Figure 5). For example, mammalian target of rapamycin is a threonine kinase that is involved in the regulation of cell-cycle progression and its inhibition has showed promising antitumor activity in a number of neoplasms.[280–282,287] However, temsirolimus, a mammalian target of rapamycin inhibitor, when evaluated in a phase II trial of 15 patients with PETs showed a low response rate of 7%.[287] Another mammalian target of rapamycin inhibitor, everolimus (RAD001), yielded a response rate of 15% when administered in combination with octreotide long-acting release in 13 patients with PETs.[280–282]

Although response rates in these initial studies are low, these agents represent new approaches to treatment. It is hoped that these novel antitumor agents may play a future role alone or in combination with other agents in the management of patients with metastatic PETs.

Palliative Radiotherapy

NET cells are sensitive to standard external beam irradiation. Unfortunately, liver tissue has similar sensitivity such that the therapeutic index for radiation of liver metastases is prohibitive. On the other hand, palliative radiation to bone metastases in the spine and even brain metastases has been shown to be effective.[288,289] Proton-beam radiation holds promise for effective palliation of many different types of cancers. To date, no information is available regarding the use of this potentially promising modality in NET patients.

Liver Transplantation

In contrast to most other neoplasms, liver transplantation continues to be used for selected patients with metastatic PETs.[9,290–293] Conclusions about its potential value or guidelines regarding which patients would most benefit are difficult because the available literature comprises less than 150 patients with malignant PETs treated with liver transplantation, the individual series are small (largest single-center study, 19 cases), and long-term follow-up data are limited.[290] In a recent report involving 15 patients with malignant GI NETs (11-PETs), the 5-year disease-free survival rate was 20% and the total survival rate was 90%, which is in contrast to the results of a review[293] of 103 patients from multiple small series with NETs (including 48 PETs) that showed 2- and 5-year total survival rates of 60% and 47%, respectively. Younger patients (<50 y), patients without extensive other surgical procedures (cluster surgeries), and with disease limited to the liver appeared to fare best.[290,293] Recent reviews suggested that liver transplantation should be considered in selected young patients with metastases limited to the liver and a previously resected primary PET who require relief from incapacitating hormonal or tumor symptoms.[290,291,293]

Future Directions and Unsettled Problems

Even though there have been many advances in recent years in the diagnosis/management of PETs, it is

not clear that survival in patients with advanced disease has improved. In fact, in a recent review[294] of survival for all GI NETs (both carcinoids and PETs), no change in survival was reported over a 30-year period. Numerous factors contribute to this including their continued delay in diagnosis (mean, 4–6 y); the lack of general availability to most patients of the expertise and experience necessary to diagnose and manage them; the lack of good prognostic factors to stage disease extent and tailor treatment accordingly, and the lack of controlled trials, new treatments; and a standardized approach to care so that approaches can be compared in different centers. These problems arise not only because PETs are uncommon, but also because large gaps in our knowledge remain regarding their molecular pathogenesis and there are no widely accepted animal models or PET cell lines that can be used to evaluate innovative treatments. Furthermore, it is difficult for young physicians who may want to acquire the necessary expertise to treat patients with PETs because of a paucity of well-rounded centers that have expertise in all facets of these tumors. Furthermore, comparison of results from study to study is difficult because of a lack of uniformity in the United States in the pathologic classification of these tumors or standardization of the minimum criteria for histologic diagnosis. A number of recent consensus conferences' statements have been published by the European Neuroendocrine Tumor Society,[6,7,295] which attempt to begin to standardize the approach to diagnosis/management including a proposed TNM classification.[19,296] In addition, the National Cancer Institute recently mandated a summit conference on GI NETs and it has been proposed in another recent consensus conference that centers of excellence should be established dealing with all aspects of the diagnosis, management, and basic/clinical research needs related to PETs.[294]

References

1. Duerr EM, Chung DC. Molecular genetics of neuroendocrine tumors. Best Pract Res Clin Endocrinol Metab 2007;21:1–14.
2. Corleto VD, Delle Fave G, Jensen RT. Molecular insights into gastrointestinal neuroendocrine tumors: importance and recent advances. Dig Liver Dis 2002;34:668–680.
3. Arnold R, ed. Endocrine tumors of the gastrointestinal tract: part 11. Best Practice Res Clin Gastroent 2005;19:659–830.
4. Arnold R, ed. Endocrine tumors of the gastrointestinal tract: part 1. Best Practice Res Clin Gastroent 2005;19:489–656.
5. Oberg K, Eriksson BE. Neuroendocrine tumors. Best Pract Res Clin Endocrinol Metab 2007;21:1–172.
6. de Herder WW, O'Toole D, Rindi G, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine tumors part 1-stomach, duodenum and pancreas. Neuroendocrinology 2006;84:151–216.
7. Plockinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology 2004;80:394–424.
8. Oberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol 2005;19:753–781.
9. Jensen RT. Endocrine neoplasms of the pancreas. In: Yamada T, Alpers DH, Kaplowitz N, et al, eds. Textbook of gastroenterology. 5th ed. Oxford: Blackwell; 2008 (in press).
10. Ito T, Tanaka M, Sasano H, et al. Preliminary results of a Japanese nationwide survey of neuroendocrine gastrointestinal tumors. J Gastroenterol 2007;42:497–500.
11. Panzuto F, Nasoni S, Falconi M, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. Endocr Relat Cancer 2005;12:1083–1092.
12. Alexakis N, Connor S, Ghaneh P, et al. Hereditary pancreatic endocrine tumours. Pancreatology 2004;4:417–435.
13. Jensen RT, Berna MJ, Bingham MD, et al. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management and controversies. Cancer 2008 (in press).
14. Kloppel G. Tumour biology and histopathology of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007;21:15–31.
15. Brignardello E, Manti R, Papotti M, et al. Ectopic secretion of LH by an endocrine pancreatic tumor. J Endocrinol Invest 2004;27:361–365.
16. Samyn I, Fontaine C, Van Tussenbroek F, et al. Paraneoplastic syndromes in cancer: case 1. Polycythemia as a result of ectopic erythropoietin production in metastatic pancreatic carcinoid tumor. J Clin Oncol 2004;22:2240–2242.
17. Kawano K, Ushijima K, Fujimoto T, et al. Peptide YY producing strumal carcinoid of the ovary as the cause of severe constipation with contralateral epithelial ovarian cancer. J Obstet Gynaecol Res 2007;33:392–396.
18. Kloppel G, Anlauf M. Epidemiology, tumour biology and histopathological classification of neuroendocrine tumours of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 2005;19:507–517.
19. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006;449:395–401.
20. Rindi G, Bordi C. Aetiology, molecular pathogenesis and genetics. Best Pract Res Clin Gastroenterol 2005;19:519–534.
21. Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia—type 1. Science 1997;276:404–407.
22. Busygina V, Bale AE. Multiple endocrine neoplasia type 1 (MEN1) as a cancer predisposition syndrome: clues into the mechanisms of MEN1-related carcinogenesis. Yale J Biol Med 2006;79:105–114.
23. Goebel SU, Heppner C, Burns AD, et al. Genotype/phenotype correlations of MEN1 gene mutations in sporadic gastrinoma. J Clin Endocrinol Metab 2000;85:116–123.
24. Debelenko LV, Zhuang ZP, Emmert-Buck MR, et al. Allelic deletions on chromosome 11q13 in multiple endocrine neoplasia type-l-associated sporadic gastrinomas and pancreatic endocrine tumors. Cancer Res 1997;57:2238–2243.
25. Perren A, Komminoth P, Heitz PU. Molecular genetics of gastroenteropancreatic endocrine tumors. Ann N Y Acad Sci 2004;1014:199–208.
26. Capurso G, Lattimore S, Crnogorac-Jurcevic T, et al. Gene expression profiles of progressive pancreatic endocrine tumours and their liver metastases reveal potential novel markers and therapeutic targets. Endocr Relat Cancer 2006;13:541–558.
27. Dilley WG, Kalyanaraman S, Verma S, et al. Global gene expression in neuroendocrine tumors from patients with the MEN1 syndrome. Mol Cancer 2005;4:9.
28. Hansel DE, Rahman A, House M, et al. Met proto-oncogene and insulin-like growth factor binding protein 3 overexpression correlates with metastatic ability in well-differentiated pancreatic endocrine neoplasms. Clin Cancer Res 2004;10:6152–6158.

29. Maitra A, Hansel DE, Argani P, et al. Global expression analysis of well-differentiated pancreatic endocrine neoplasms using oligonucleotide microarrays. Clin Cancer Res 2003;9: 5988–5995.
30. Hoffmann KM, Furukawa M, Jensen RT. Duodenal neuroendocrine tumors: classification, functional syndromes, diagnosis and medical treatment. Best Pract Res Clin Gastroenterol 2005;19:675–697.
31. Jensen RT, Niederle B, Mitry E, et al. Gastrinoma (duodenal and pancreatic). Neuroendocrinology 2006;84:173–182.
32. Thom AK, Norton JA, Axiotis CA, et al. Location, incidence and malignant potential of duodenal gastrinomas. Surgery 1991; 110:1086–1093.
33. Jensen RT. Natural history of digestive endocrine tumors. In: Mignon M, Colombel JF, eds. Recent advances in pathophysiology and management of inflammatory bowel diseases and digestive endocrine tumors. Paris, France: John Libbey Eurotext Publishing Co.; 1999:192–219.
34. Gibril F, Doppman JL, Reynolds JC, et al. Bone metastases in patients with gastrinomas: a prospective study of bone scanning, somatostatin receptor scanning, and MRI in their detection, their frequency, location and effect of their detection on management. J Clin Oncol 1998;16:1040–1053.
35. Yu F, Venzon DJ, Serrano J, et al. Prospective study of the clinical course, prognostic factors and survival in patients with longstanding Zollinger-Ellison syndrome. J Clin Oncol 1999;17: 615–630.
36. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology 1995;108: 1637–1649.
37. Sutliff VE, Doppman JL, Gibril F, et al. Growth of newly diagnosed, untreated metastatic gastrinomas and predictors of growth patterns. J Clin Oncol 1997;15:2420–2431.
38. Madeira I, Terris B, Voss M, et al. Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. Gut 1998;43:422–427.
39. Soga J, Yakuwa Y. Vipoma/diarrheogenic syndrome: a statistical evaluation of 241 reported cases. J Exp Clin Cancer Res 1998;17:389–400.
40. Nesi G, Marcucci T, Rubio CA, et al. Somatostatinoma: clinicopathological features of three cases and literature reviewed. J Gastroenterol Hepatol 2008;23:521–526.
41. Chu QD, Hill HC, Douglass HO Jr, et al. Predictive factors associated with long-term survival in patients with neuroendocrine tumors of the pancreas. Ann Surg Oncol 2002;9:855–862.
42. La Rosa S, Sessa F, Capella C, et al. Prognostic criteria in nonfunctioning pancreatic endocrine tumours. Virchows Arch 1996;429:323–333.
43. Hochwald SN, Zee S, Conlon KC, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. J Clin Oncol 2002;20:2633–2642.
44. Maton PN, Gardner JD, Jensen RT. Cushing's syndrome in patients with Zollinger-Ellison syndrome. N Engl J Med 1986;315: 1–5.
45. Jensen RT, Gardner JD. Gastrinoma. In: Go VLW, DiMagno EP, Gardner JD, et al, eds. The pancreas: biology, pathobiology and disease. 2nd ed. New York: Raven Press Publishing Co; 1993: 931–978.
46. Norton JA, Sugarbaker PH, Doppman JL, et al. Aggressive resection of metastatic disease in selected patients with malignant gastrinoma. Ann Surg 1986;203:352–359.
47. Guillausseau PJ, Guillausseau-Scholer C. Glucagonomas: clinical presentation, diagnosis, and advances in management. In: Mignon M, Jensen RT, eds. Endocrine tumors of the pancreas: recent advances in research and management. Series: frontiers in gastrointestinal research. Volume 23. Basel, Switzerland: S. Karger; 1995:183–193.
48. Thompson GB, Van Heerden JA, Grant CS, et al. Islet cell carcinomas of the pancreas: a twenty-year experience. Surgery 1988;104:1011–1017.
49. Lo CY, Van Heerden JA, Thompson GB, et al. Islet cell carcinoma of the pancreas. World J Surg 1996;20:878–884.
50. Norton JA, Fraker DL, Alexander HR, et al. Surgery increases survival in patients with gastrinoma. Ann Surg 2006;244:410–419.
51. Fraker DL, Norton JA, Alexander HR, et al. Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. Ann Surg 1994;220:320–330.
52. de Herder WW. Biochemistry of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007;21:33–41.
53. Gibril F, Jensen RT. Zollinger-Ellison syndrome revisited: diagnosis, biologic markers, associated inherited disorders, and acid hypersecretion. Curr Gastroenterol Rep 2004;6:454–463.
54. Nobels FR, Kwekkeboom DJ, Coopmans W, et al. Chromogranin A as serum marker for neuroendocrine neoplasia: comparison with neuron-specific enolase and the alpha-subunit of glycoprotein hormones. J Clin Endocrinol Metab 1997;82:2622–2628.
55. Campana D, Nori F, Piscitelli L, et al. Chromogranin A: is it a useful marker of neuroendocrine tumors? J Clin Oncol 2007; 25:1967–1973.
56. Zatelli MC, Torta M, Leon A, et al. Chromogranin A as a marker of neuroendocrine neoplasia: an Italian Multicenter Study. Endocr Relat Cancer 2007;14:473–482.
57. Perren A, Anlauf M, Henopp T, et al. Multiple endocrine neoplasia type 1 (MEN1): loss of one MEN1 allele in tumors and monohormonal endocrine cell clusters but not in islet hyperplasia of the pancreas. J Clin Endocrinol Metab 2007;92:1118–1128.
58. Baudin E. Gastroenteropancreatic endocrine tumors: clinical characterization before therapy. Nat Clin Pract Endocrinol Metab 2007;3:228–239.
59. Roy P, Venzon DJ, Feigenbaum KM, et al. Gastric secretion in Zollinger-Ellison syndrome: correlation with clinical expression, tumor extent and role in diagnosis—a prospective NIH study of 235 patients and review of the literature in 984 cases. Medicine (Baltimore) 2001;80:189–222.
60. Soga J, Yakuwa Y. The gastrinoma/Zollinger-Ellison syndrome: statistical evaluation of a Japanese series of 359 cases. J Hepatobiliary Pancreat Surg 1998;5:77–85.
61. Roy P, Venzon DJ, Shojamanesh H, et al. Zollinger-Ellison syndrome: clinical presentation in 261 patients. Medicine (Baltimore) 2000;79:379–411.
62. Jensen RT, Doppman JL, Gardner JD. Gastrinoma. In: Go VLW, Brooks FA, DiMagno EP, et al, eds. The exocrine pancreas: biology, pathobiology and disease. 1st ed. New York: Raven Press; 1986:727–744.
63. Benya RV, Metz DC, Venzon DJ, et al. Zollinger-Ellison syndrome can be the initial endocrine manifestation in patients with multiple endocrine neoplasia-type 1. Am J Med 1994;97:436–444.
64. Gibril F, Schumann M, Pace A, et al. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. A prospective study of 107 cases and comparison with 1009 patients from the literature. Medicine (Baltimore) 2004;83:43–83.
65. Hou W, Schubert ML. Gastric secretion. Curr Opin Gastroenterol 2006;22:593–598.
66. Corleto VD, Annibale B, Gibril F, et al. Does the widespread use of proton pump inhibitors mask, complicate and/or delay the diagnosis of Zollinger-Ellison syndrome? Aliment Pharmacol Ther 2001;15:1555–1561.
67. Berna MJ, Hoffmann KM, Serrano J, et al. Serum gastrin in Zollinger-Ellison syndrome: I. Prospective study of fasting serum

gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. Medicine (Baltimore) 2006;85:295–330.
68. Ruszniewski P, Podevin P, Cadiot G, et al. Clinical, anatomical, and evolutive features of patients with the Zollinger-Ellison syndrome combined with type I multiple endocrine neoplasia. Pancreas 1993;8:295–304.
69. Berna MJ, Hoffmann KM, Long SH, et al. Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the National Institutes of Health and comparison with 537 cases from the literature. evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. Medicine (Baltimore) 2006;85:331–364.
70. Gibril F, Lindeman RJ, Abou-Saif A, et al. Retained gastric antrum syndrome. A forgotten, treatable cause of refractory peptic ulcer disease. Dig Dis Sci 2001;46:610–617.
71. McGuigan JE, Wolfe MM. Secretin injection test in the diagnosis of gastrinoma. Gastroenterology 1980;79:1324–1331.
72. Frucht H, Howard JM, Slaff JI, et al. Secretin and calcium provocative tests in the Zollinger-Ellison syndrome: a prospective study. Ann Intern Med 1989;111:713–722.
73. Norton JA, Cornelius MJ, Doppman JL, et al. Effect of parathyroidectomy in patients with hyperparathyroidism, Zollinger-Ellison syndrome and multiple endocrine neoplasia type I: a prospective study. Surgery 1987;102:958–966.
74. Jensen RT. Management of the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type 1. J Intern Med 1998;243:477–488.
75. Norton JA, Venzon DJ, Berna MJ, et al. Prospective study of surgery for primary hyperaparathyroidism (HPT) in multiple endocrine neoplasia type 1 (MEN1), and Zollinger-Ellison syndrome (ZES): longterm outcome of a more virulent form of HPT. Ann Surgery 2008;247:501–510.
76. Grant CS. Insulinoma. Best Pract Res Clin Gastroenterol 2005; 19:783–798.
77. de Herder WW, Niederle B, Scoazec JY, et al. Well-differentiated pancreatic tumor/carcinoma: insulinoma. Neuroendocrinology 2006;84:183–188.
78. Vezzosi D, Bennett A, Fauvel J, et al. Insulin levels measured with an insulin-specific assay in patients with fasting hypoglycaemia related to endogenous hyperinsulinism. Eur J Endocrinol 2003;149:413–419.
79. Vezzosi D, Bennet A, Fauvel J, et al. Insulin, C-peptide and proinsulin for the biochemical diagnosis of hypoglycaemia related to endogenous hyperinsulinism. Eur J Endocrinol 2007; 157:75–83.
80. Soga J, Yakuwa Y. Glucagonomas/diabetico-dermatogenic syndrome (DDS): a statistical evaluation of 407 reported cases. J Hepatobiliary Pancreat Surg 1998;5:312–319.
81. van Beek AP, de Haas ER, van Vloten WA, et al. The glucagonoma syndrome and necrolytic migratory erythema: a clinical review. Eur J Endocrinol 2004;151:531–537.
82. Kindmark H, Sundin A, Granberg D, et al. Endocrine pancreatic tumors with glucagon hypersecretion: a retrospective study of 23 cases during 20 years. Med Oncol 2007;24:330–337.
83. Wald M, Lawrenz K, Luckner D, et al. Glucagon therapy as a possible cause of erythema necrolyticum migrans in two neonates with persistent hyperinsulinaemic hypoglycaemia. Eur J Pediatr 2002;161:600–603.
84. Case CC, Vassilopoulou-Sellin R. Reproduction of features of the glucagonoma syndrome with continuous intravenous glucagon infusion as therapy for tumor-induced hypoglycemia. Endocr Pract 2003;9:22–25.
85. Mullans EA, Cohen PR. Iatrogenic necrolytic migratory erythema: a case report and review of nonglucagonoma-associated necrolytic migratory erythema. J Am Acad Dermatol 1998;38:866–873.
86. Appetecchia M, Ferretti E, Carducci M, et al. Malignant glucagonoma. New options of treatment. J Exp Clin Cancer Res 2006;25:135–139.
87. Matuchansky C, Rambaud JC. VIPomas and endocrine cholera: clinical presentation, diagnosis, and advances in management. In: Mignon M, Jensen RT, eds. Endocrine tumors of the pancreas: recent advances in research and management. Series: frontiers in gastrointestinal research. Volume 23. Basel, Switzerland: S. Karger; 1995:166–182.
88. Nikou GC, Toubanakis C, Nikolaou P, et al. VIPomas: an update in diagnosis and management in a series of 11 patients. Hepatogastroenterology 2005;52:1259–1265.
89. Ghaferi AA, Chojnacki KA, Long WD, et al. Pancreatic VIPomas: subject review and one institutional experience. J Gastrointest Surg 2008;12:382–393.
90. Jensen RT. Diarrhea in neuroendocrine disorders. In: Domschke W, Stoll R, Brasitus TA, et al, eds. Intestinal mucosa and its diseases: pathophysiology and clinics. 110th ed. Dordrecht, The Netherlands: Kluwer Academic Publishers BV; 1999:61–76.
91. Krejs GJ, Orci L, Conlon JM, et al. Somatostatinoma syndrome. Biochemical, morphologic and clinical features. N Engl J Med 1979;301:285–292.
92. Moayedoddin B, Booya F, Wermers RA, et al. Spectrum of malignant somatostatin-producing neuroendocrine tumors. Endocr Pract 2006;12:394–400.
93. Tanaka S, Yamasaki S, Matsushita S, et al. Duodenal somatostatinoma: a case report and review of 31 cases with special reference to the relationship between tumor size and metastasis. Pathol Int 2000;50:146–152.
94. Losa M, von Werder K. Pathophysiology and clinical aspects of the ectopic GH-releasing hormone syndrome. Clin Endocrinol 1997;47:123–135.
95. Sano T, Asa SL, Kovacs K. Growth hormone-releasing hormone-producing tumors: clinical, biochemical, and morphological manifestations. Endocr Rev 1988;9:357–373.
96. Gola M, Doga M, Bonadonna S, et al. Neuroendocrine tumors secreting growth hormone-releasing hormone: pathophysiological and clinical aspects. Pituitary 2006;9:221–229.
97. Falconi M, Plockinger U, Kwekkeboom DJ, et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology 2006;84:196–211.
98. Plockinger U, Wiedenmann B. Diagnosis of non-functioning neuro-endocrine gastro-enteropancreatic tumours. Neuroendocrinology 2004;80(Suppl 1):35–38.
99. Gullo L, Migliori M, Falconi M, et al. Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. Am J Gastroenterol 2003;98:2435–2439.
100. Eriksson B, Oberg K. PPomas and nonfunctioning endocrine pancreatic tumors: clinical presentation, diagnosis, and advances in management. In: Mignon M, Jensen RT, eds. Endocrine tumors of the pancreas: recent advances in research and management. Series: frontiers in gastrointestinal research. Volume 23. Basel, Switzerland: S. Karger; 1995:208–222.
101. Hochwald SN, Conlon KC, Brennan MF. Nonfunctional pancreatic islet cell tumors. In: Doherty GM, Skogseid B, eds. Surgical endocrinology. Philadelphia: Lippincott Williams & Wilkins; 2001:361–373.
102. Brennan MF, Marx SJ, Doppman J, et al. Results of reoperation for persistent and recurrent hyperparathyroidism. Ann Surg 1981;194:671–676.
103. Plockinger U, Wiedenmann B. Management of metastatic endocrine tumours. Best Pract Res Clin Gastroenterol 2005;19: 553–576.

104. Gibril F, Jensen RT. Diagnostic uses of radiolabelled somatostatin-receptor analogues in gastroenteropancreatic endocrine tumors. Dig Liver Dis 2004;36:S106–S120.
105. Rockall AG, Reznek RH. Imaging of neuroendocrine tumours (CT/MR/US). Best Pract Res Clin Endocrinol Metab 2007;21: 43–68.
106. Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007;21: 69–85.
107. Noone TC, Hosey J, Firat Z, et al. Imaging and localization of islet-cell tumours of the pancreas on CT and MRI. Best Pract Res Clin Endocrinol Metab 2005;19:195–211.
108. Wiedenmann B, Jensen RT, Mignon M, et al. Preoperative diagnosis and surgical management of neuroendocrine gastroenteropancreatic tumors: general recommendations by a consensus workshop. World J Surg 1998;22:309–318.
109. Orbuch M, Doppman JL, Strader DB, et al. Imaging for pancreatic endocrine tumor localization: recent advances. In: Mignon M, Jensen RT, eds. Endocrine tumors of the pancreas: recent advances in research and management. Frontiers of gastrointestinal research. Volume 23. Basel, Switzerland: S. Karger; 1995:268–281.
110. Krudy AG, Doppman JL, Jensen RT, et al. Localization of islet cell tumors by dynamic CT: comparison with plain CT, arteriography, sonography and venous sampling. AJR Am J Roentgenol 1984;143:585–589.
111. Frucht H, Doppman JL, Norton JA, et al. Gastrinomas: comparison of MR imaging with CT, angiography and US. Radiology 1989;171:713–717.
112. Orbuch M, Doppman JL, Jensen RT. Localization of pancreatic endocrine tumors. Pancreatic endocrine tumors. Semin Gastrointest Dis 1995;6:90–101.
113. Akerstrom G, Hellman P. Surgery on neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007;21:87–109.
114. Ho JM, Darcy SJ, Eysselein VE, et al. Evolution of fine needle aspiration cytology in the accurate diagnosis of pancreatic neoplasms. Am Surg 2007;73:941–944.
115. Nichols MT, Russ PD, Chen YK. Pancreatic imaging: current and emerging technologies. Pancreas 2006;33:211–220.
116. Pausawasdi N, Scheiman J. Endoscopic evaluation and palliation of pancreatic adenocarcinoma: current and future options. Curr Opin Gastroenterol 2007;23:515–521.
117. McLean AM, Fairclough PD. Endoscopic ultrasound in the localisation of pancreatic islet cell tumours. Best Pract Res Clin Endocrinol Metab 2005;19:177–193.
118. DeAngelis C, Carucci P, Repici A, et al. Endosonography in decision making and management of gastrointestinal endocrine tumors. Eur J Ultrasound 1999;10:139–150.
119. Chang F, Chandra A, Culora G, et al. Cytologic diagnosis of pancreatic endocrine tumors by endoscopic ultrasound-guided fine-needle aspiration: a review. Diagn Cytopathol 2006;34: 649–658.
120. Stelow EB, Woon C, Pambuccian SE, et al. Fine-needle aspiration cytology of pancreatic somatostatinoma: the importance of immunohistochemistry for the cytologic diagnosis of pancreatic endocrine neoplasms. Diagn Cytopathol 2005;33:100–105.
121. Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. Ann Surg 2004;240:757–773.
122. Zimmer T, Stolzel U, Bader M, et al. Endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localisation of insulinomas and gastrinomas. Gut 1996;39: 562–568.
123. Vezzosi D, Bennet A, Rochaix P, et al. Octreotide in insulinoma patients: efficacy on hypoglycemia, relationships with Octreoscan scintigraphy and immunostaining with anti-sst2A and anti-sst5 antibodies. Eur J Endocrinol 2005;152:757–767.
124. Bertherat J, Tenenbaum F, Perlemoine K, et al. Somatostatin receptors 2 and 5 are the major somatostatin receptors in insulinomas: an in vivo and in vitro study. J Clin Endocrinol Metab 2003;88:5353–5360.
125. Langer P, Kann PH, Fendrich V, et al. Prospective evaluation of imaging procedures for the detection of pancreaticoduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. World J Surg 2004;28:1317–1322.
126. Wamsteker EJ, Gauger PG, Thompson NW, et al. EUS detection of pancreatic endocrine tumors in asymptomatic patients with type 1 multiple endocrine neoplasia. Gastrointest Endosc 2003;58:531–535.
127. Kann PH, Balakina E, Ivan D, et al. Natural course of small, asymptomatic neuroendocrine pancreatic tumours in multiple endocrine neoplasia type 1: an endoscopic ultrasound imaging study. Endocr Relat Cancer 2006;13:1195–1202.
128. Hellman P, Hennings J, Akerstrom G, et al. Endoscopic ultrasonography for evaluation of pancreatic tumours in multiple endocrine neoplasia type 1. Br J Surg 2005;92:1508–1512.
129. Langer P, Wild A, Celik I, et al. Prospective controlled trial of a standardized meal stimulation test in the detection of pancreaticoduodenal endocrine tumours in patients with multiple endocrine neoplasia type 1. Br J Surg 2001;88:1403–1407.
130. Kann PH, Kann B, Fassbender WJ, et al. Small neuroendocrine pancreatic tumors in multiple endocrine neoplasia type 1 (MEN1): least significant change of tumor diameter as determined by endoscopic ultrasound (EUS) imaging. Exp Clin Endocrinol Diabetes 2006;114:361–365.
131. Lonser RR, Glenn GM, Walther M, et al. von Hippel-Lindau disease. Lancet 2003;361:2059–2067.
132. Hammel PR, Vilgrain V, Terris B, et al. Pancreatic involvement in von Hippel-Lindau disease. Gastroenterology 2000;119:1087–1095.
133. Libutti SK, Choyke PL, Alexander HR, et al. Clinical and genetic analysis of patients with pancreatic neuroendocrine tumors associated with von Hippel-Lindau disease. Surgery 2000;128: 1022–1027.
134. Binkovitz LA, Johnson CD, Stephens DH. Islet cell tumors in von Hippel-Lindau disease: increased prevalence and relationship to the multiple endocrine neoplasias. AJR Am J Roentgenol 1990;155:501–505.
135. Libutti SK, Choyke PL, Bartlett DL, et al. Pancreatic neuroendocrine tumors associated with von Hippel Lindau disease: diagnostic and management recomendations. Surgery 1998;124: 1153–1159.
136. Marcos HB, Libutti SK, Alexander HR, et al. Neuroendocrine tumors of the pancreas in von Hippel-Lindau disease: spectrum of appearances at CT and MR imaging with histopathologic comparison. Radiology 2002;225:751–758.
137. Blansfield JA, Choyke L, Morita SY, et al. Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). Surgery 2007;142:814–818.
138. Wermer P. Genetic aspects of adenomatosis of endocrine glands. Am J Med 1954;16:363–371.
139. Strader DB, Doppman JL, Orbuch M, et al. Functional localization of pancreatic endocrine tumors. In: Mignon M, Jensen RT, eds. Endocrine tumors of the pancreas: recent advances in research and management. Series: frontiers of gastrointestinal research. Volume 23. Basel, Switzerland: Karger Publishing Co.; 1995:282–297.
140. Jackson JE. Angiography and arterial stimulation venous sampling in the localization of pancreatic neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2005;19:229–239.
141. Gibril F, Doppman JL, Chang R, et al. Metastatic gastrinomas: localization with selective arterial injection of secretin. Radiology 1996;198:77–84.

142. Miller DL, Doppman JL, Metz DC, et al. Zollinger-Ellison syndrome: technique, results and complications of portal venous sampling. Radiology 1992;182:235–241.
143. Thom AK, Norton JA, Doppman JL, et al. Prospective study of the use of intraarterial secretin injection and portal venous sampling to localize duodenal gastrinomas. Surgery 1992; 112:1002–1008.
144. Doppman JL, Miller DL, Chang R, et al. Gastrinomas: localization by means of selective intraarterial injection of secretin. Radiology 1990;174:25–29.
145. Lo CY, Chan FL, Tam SC, et al. Value of intra-arterial calcium stimulated venous sampling for regionalization of pancreatic insulinomas. Surgery 2000;128:903–909.
146. Piovesan A, Pia A, Visconti G, et al. Proinsulin-secreting neuroendocrine tumor of the pancreas. J Endocrinol Invest 2003; 26:758–761.
147. Doppman JL, Chang R, Fraker DL, et al. Localization of insulinomas to regions of the pancreas by intra-arterial stimulation with calcium. Ann Intern Med 1995;123:269–273.
148. Defreyne L, Konig K, Lerch MM, et al. Modified intra-arterial calcium stimulation with venous sampling test for preoperative localization of insulinomas. Abdom Imaging 1998;23:322–331.
149. Baba Y, Miyazono N, Nakajo M, et al. Localization of insulinomas. Comparison of conventional arterial stimulation with venous sampling (ASVS) and superselective ASVS. Acta Radiol 2000;41:172–177.
150. Guillermet-Guibert J, Lahlou H, Pyronnet S, et al. Somatostatin receptors as tools for diagnosis and therapy: molecular aspects. Best Pract Res Clin Gastroenterol 2005;19:535–551.
151. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [^{111}In-DTPA-D-Phe^{1}]- and [^{123}I-Tyr^{3}]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med 1993;20:716–731.
152. Papotti M, Bonjiovanni M, Volante M, et al. Expression of somatostatin receptor types 1-5 in 81 cases of gastrointestinal and pancreatic endocrine tumors. Virchows Arch 2002;440: 461–475.
153. Jensen RT. Peptide therapy. Recent advances in the use of somatostatin and other peptide receptor agonists and antagonists. In: Lewis JH, Dubois A, eds. Current clinical topics in gastrointestinal pharmacology. Malden, MA: Blackwell Science, Inc.; 1997:144–223.
154. Virgolini I, Traub-Weidinger T, Decristoforo C. Nuclear medicine in the detection and management of pancreatic islet-cell tumours. Best Pract Res Clin Endocrinol Metab 2005;19:213–227.
155. Gibril F, Reynolds JC, Doppman JL, et al. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas: a prospective study. Ann Intern Med 1996;125:26–34.
156. Termanini B, Gibril F, Doppman JL, et al. Distinguishing small hepatic hemangiomas from vascular liver metastases in patients with gastrinoma: use of a somatostatin-receptor scintigraphic agent. Radiology 1997;202:151–158.
157. Schillaci O, Spanu A, Scopinaro F, et al. Somatostatin receptor scintigraphy in liver metastasis detection from gastroenteropancreatic neuroendocrine tumors. J Nucl Med 2003;44:359–368.
158. Lebtahi R, Cadiot G, Delahaye N, et al. Detection of bone metastases in patients with endocrine gastroenteropancreatic tumors: bone scintigraphy compared with somatostatin receptor scintigraphy. J Nucl Med 1999;40:1602–1608.
159. Schillaci O, Corleto VD, Annibale B, et al. Single photon emission computed tomography procedure improves accuracy of somatostatin receptor scintigraphy in gastro-entero pancreatic tumours. Ital J Gastroenterol Hepatol 1999;31:S186–S189.
160. Lebtahi R, Cadiot G, Sarda L, et al. Clinical impact of somatostatin receptor scintigraphy in the management of patients with neuroendocrine gastroenteropancreatic tumors. J Nucl Med 1997;38:853–858.
161. Termanini B, Gibril F, Reynolds JC, et al. Value of somatostatin receptor scintigraphy: a prospective study in gastrinoma of its effect on clinical management. Gastroenterology 1997;112: 335–347.
162. Cadiot G, Bonnaud G, Lebtahi R, et al. Usefulness of somatostatin receptor scintigraphy in the management of patients with Zollinger-Ellison syndrome. Gut 1997;41:107–114.
163. Alexander HR, Fraker DL, Norton JA, et al. Prospective study of somatostatin receptor scintigraphy and its effect on operative outcome in patients with Zollinger-Ellison syndrome. Ann Surg 1998;228:228–238.
164. Eriksson B, Orlefors H, Oberg K, et al. Developments in PET for the detection of endocrine tumours. Best Pract Res Clin Endocrinol Metab 2005;19:311–324.
165. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med 2007;48: 508–518.
166. Orlefors H, Sundin A, Garske U, et al. Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. J Clin Endocrinol Metab 2005;90:3392–3400.
167. Metz DC, Jensen RT. Advances in gastric antisecretory therapy in Zollinger-Ellison syndrome. In: Mignon M, Jensen RT, eds. Endocrine tumors of the pancreas: recent advances in research and management. Series: frontiers of gastrointestinal research. Volume 23. Basel, Switzerland: S. Karger; 1995:240–257.
168. Berna MJ, Jensen RT. Role of CCK/gastrin receptors in gastrointestinal/metabolic diseases and results of human studies using gastrin/CCK receptor agonists/antagonists in these diseases. Curr Top Med Chem 2007;7:1211–1231.
169. Jensen RT. Use of omeprazole and other proton pump inhibitors in the Zollinger-Ellison syndrome. In: Olbe L, ed. Milestones in drug therapy. Basel, Switzerland: Birkhauser Verlag AG Publish. Co.; 1999:205–221.
170. Metz DC, Strader DB, Orbuch M, et al. Use of omeprazole in Zollinger-Ellison: a prospective nine-year study of efficacy and safety. Aliment Pharmacol Ther 1993;7:597–610.
171. Metz DC, Pisegna JR, Ringham GL, et al. Prospective study of efficacy and safety of lansoprazole in Zollinger-Ellison syndrome. Dig Dis Sci 1993;38:245–256.
172. Hirschowitz BI, Simmons J, Mohnen J. Clinical outcome using lansoprazole in acid hypersecretors with and without Zollinger-Ellison syndrome: a 13-year prospective study. Clin Gastroenterol Hepatol 2005;3:39–48.
173. Metz DC, Comer GM, Soffer E, et al. Three-year oral pantoprazole administration is effective for patients with Zollinger-Ellison syndrome and other hypersecretory conditions. Aliment Pharmacol Ther 2006;23:437–444.
174. Morocutti A, Merrouche M, Bjaaland T, et al. An open-label study of rabeprazole in patients with Zollinger-Ellison syndrome or idiopathic gastric acid hypersecretion. Aliment Pharmacol Ther 2006;24:1439–1444.
175. Metz DC, Sostek MB, Ruszniewski P, et al. Effects of esomeprazole on acid output in patients with Zollinger-Ellison syndrome or idiopathic gastric acid hypersecretion. Am J Gastroenterol 2007;102:2648–2654.
176. Raufman JP, Collins SM, Pandol SJ, et al. Reliability of symptoms in assessing control of gastric acid secretion in patients with Zollinger-Ellison syndrome. Gastroenterology 1983;84: 108–113.
177. Miller LS, Vinayek R, Frucht H, et al. Reflux esophagitis in patients with Zollinger-Ellison syndrome. Gastroenterology 1990;98:341–346.

178. Maton PN, Frucht H, Vinayek R, et al. Medical management of patients with Zollinger-Ellison syndrome who have had previous gastric surgery: a prospective study. Gastroenterology 1988; 94:294–299.
179. Metz DC, Pisegna JR, Fishbeyn VA, et al. Currently used doses of omeprazole in Zollinger-Ellison syndrome are too high. Gastroenterology 1992;103:1498–1508.
180. Termanini B, Gibril F, Stewart CA, et al. A prospective study of the effectiveness of low dose omeprazole as initial therapy in Zollinger-Ellison syndrome. Aliment Pharmacol Ther 1996;10: 61–71.
181. Termanini B, Gibril F, Sutliff VE III, et al. Effect of long-term gastric acid suppressive therapy on serum vitamin B_{12} levels in patients with Zollinger-Ellison syndrome. Am J Med 1998;104: 422–430.
182. Stewart CA, Termanini B, Sutliff VE, et al. Assessment of the risk of iron malabsorption in patients with Zollinger-Ellison syndrome treated with long-term gastric acid antisecretory therapy. Aliment Pharmacol Ther 1998;12:83–98.
183. Peghini PL, Annibale B, Azzoni C, et al. Effect of chronic hypergastrinemia on human enterochromaffin-like cells: insights from patients with sporadic gastrinomas. Gastroenterology 2002; 123:68–85.
184. Maton PN, Lack EE, Collen MJ, et al. The effect of Zollinger-Ellison syndrome and omeprazole therapy on gastric oxyntic endocrine cells. Gastroenterology 1990;99:943–950.
185. Berna MJ, Annibale B, Marignani M, et al. A prospective study of gastric carcinoids and enterochromaffin-like cells changes in multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: identification of risk factors. J Clin Endocrinol Metab 2008;93:1582–1591.
186. Lehy T, Cadiot G, Mignon M, et al. Influence of multiple endocrine neoplasia type 1 on gastric endocrine cells in patients with the Zollinger-Ellison syndrome. Gut 1992;33:1275–1279.
187. Bordi C, Azzoni C, Ferraro G, et al. Sampling strategies for analysis of enterochromaffin-like cell changes in Zollinger-Ellison syndrome. Am J Clin Pathol 2000;114:419–425.
188. Lew EA, Pisegna JR, Starr JA, et al. Intravenous pantoprazole rapidly controls gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. Gastroenterology 2000;118:696–704.
189. Schumacher B, Lubke HJ, Frieling T, et al. Prospective study on the detection of insulinomas by endoscopic ultrasonography. Endoscopy 1996;28:273–276.
190. Creutzfeldt W. Insulinomas: clinical presentation, diagnosis, and advances in management. In: Mignon M, Jensen RT, eds. Endocrine tumors of the pancreas: recent advances in research and management. Series: frontiers of gastrointestinal research. Volume 23. Basel, Switzerland: S. Karger; 1995:148–165.
191. Gill GV, Rauf O, MacFarlane IA. Diazoxide treatment for insulinoma: a national UK survey. Postgrad Med J 1997;73:640–641.
192. Pless J, Bauer W, Briner U, et al. Chemistry and pharmacology of SMS 201-995, a long-acting octapeptide analogue of somatostatin. Scand J Gastroenterol Suppl 1986;119:54–64.
193. Maton PN, Gardner JD, Jensen RT. Use of the long-acting somatostatin analog, SMS 201-995 in patients with pancreatic islet cell tumors. Dig Dis Sci 1989;34:28S–39S.
194. McKeage K, Cheer S, Wagstaff AJ. Octreotide long-acting release (LAR): a review of its use in the management of acromegaly. Drugs 2003;63:2473–2499.
195. Bajetta E, Procopio G, Catena L, et al. Lanreotide autogel every 6 weeks compared with Lanreotide microparticles every 3 weeks in patients with well differentiated neuroendocrine tumors: a phase III study. Cancer 2006;107:2474–2481.
196. Newman CB, Melmed S, Snyder PJ, et al. Safety and efficacy of long-term octreotide therapy of acromegaly: results of a multicenter trial in 103 patients—a clinical research center study. J Clin Endocrinol Metab 1995;80:2768–2775.
197. Norton JA, Alexander HR, Fraker DL, et al. Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Ann Surg 2001;234:495–506.
198. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999;341:635–644.
199. Fishbeyn VA, Norton JA, Benya RV, et al. Assessment and prediction of long-term cure in patients with Zollinger-Ellison syndrome: the best approach. Ann Intern Med 1993;119:199–206.
200. Hiramoto JS, Feldstein VA, LaBerge JM, et al. Intraoperative ultrasound and preoperative localization detects all occult insulinomas. Arch Surg 2001;136:1020–1026.
201. Norton JA. Surgical treatment of neuroendocrine metastases. Best Pract Res Clin Gastroenterol 2005;19:577–583.
202. Que FG, Sarmiento JM, Nagorney DM. Hepatic surgery for metastatic gastrointestinal neuroendocrine tumors. Adv Exp Med Biol 2006;574:43–56.
203. Norton JA, Doherty GD, Fraker DL, et al. Surgical treatment of localized gastrinoma within the liver: a prospective study. Surgery 1998;124:1145–1152.
204. Norton JA, Warren RS, Kelly MG, et al. Aggressive surgery for metastatic liver neuroendocrine tumors. Surgery 2003;134: 1057–1065.
205. Levy-Bohbot N, Merle C, Goudet P, et al. Prevalence, characteristics and prognosis of MEN 1-associated glucagonomas, VIPomas, and somatostatinomas: study from the GTE (Groupe des Tumeurs Endocrines) registry. Gastroenterol Clin Biol 2004;28: 1075–1081.
206. Norton JA, Fang TD, Jensen RT. Surgery for gastrinoma and insulinoma in multiple endocrine neoplasia type 1. J Natl Compr Canc Netw 2006;4:148–153.
207. Cougard P, Goudet P, Peix JL, et al. [Insulinomas in multiple endocrine neoplasia type 1. Report of a series of 44 cases by the multiple endocrine neoplasia study group]. Ann Chir 2000; 125:118–123.
208. MacFarlane MP, Fraker DL, Alexander HR, et al. A prospective study of surgical resection of duodenal and pancreatic gastrinomas in multiple endocrine neoplasia-type 1. Surgery 1995; 118:973–980.
209. Akerstrom G, Hessman O, Hellman P, et al. Pancreatic tumours as part of the MEN-1 syndrome. Best Pract Res Clin Gastroenterol 2005;19:819–830.
210. Sheppard BC, Norton JA, Doppman JL, et al. Management of islet cell tumors in patients with multiple endocrine neoplasia: a prospective study. Surgery 1989;106:1108–1117.
211. Anlauf M, Garbrecht N, Henopp T, et al. Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinico-pathological and epidemiological features. World J Gastroenterol 2006;12:5440–5446.
212. Triponez F, Cadiot G. Non-functioning tumours of the pancreas in MEN1 patients. J Gastrointestin Liver Dis 2007;16:295–296.
213. Fendrich V, Langer P, Waldmann J, et al. Management of sporadic and multiple endocrine neoplasia type 1 gastrinomas. Br J Surg 2007;94:1331–1341.
214. Mignon M, Cadiot G, Rigaud D, et al. Management of islet cell tumors in patients with multiple endocrine neoplasia type 1. In: Mignon M, Jensen RT, eds. Endocrine tumors of the pancreas: recent advances in research and management. Series: frontiers in gastrointestinal research. Volume 23. Basel, Switzerland: S. Karger; 1995:342–359.
215. Triponez F, Goudet P, Dosseh D, et al. Is surgery beneficial for MEN1 patients with small ($<$ or $=$ 2 cm), nonfunctioning pan-

creaticoduodenal endocrine tumor? An analysis of 65 patients from the GTE. World J Surg 2006;30:654–662.
216. Norton JA, Alexander HR, Fraker DL, et al. Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases or survival in patients with Zollinger-Ellison syndrome (ZES)? Ann Surg 2004;239:617–626.
217. Sugg SL, Norton JA, Fraker DL, et al. A prospective study of intraoperative methods to diagnose and resect duodenal gastrinomas. Ann Surg 1993;218:138–144.
218. Norton JA. Surgery and prognosis of duodenal gastrinoma as a duodenal neuroendocrine tumor. Best Pract Res Clin Gastroenterol 2005;19:699–704.
219. Norton JA, Jensen RT. Current surgical management of Zollinger-Ellison syndrome (ZES) in patients without multiple endocrine neoplasia-type 1 (MEN1). Surg Oncol 2003;12:145–151.
220. Norton JA. Intraoperative methods to stage and localize pancreatic and duodenal tumors. Ann Oncol 1999;10:182–184.
221. Maton PN, Mackem SM, Norton JA, et al. Ovarian carcinoma as a cause of Zollinger-Ellison syndrome. Natural history, secretory products and response to provocative tests. Gastroenterology 1989;97:468–471.
222. Furihata M, Tagaya N, Kubota K. Laparoscopic enucleation of insulinoma in the pancreas: case report and review of the literature. Surg Laparosc Endosc Percutan Tech 2001;11:279–283.
223. Ayav A, Bresler L, Brunaud L, et al. Laparoscopic approach for solitary insulinoma: a multicentre study. Langenbecks Arch Surg 2005;390:134–140.
224. Toniato A, Meduri F, Foletto M, et al. Laparoscopic treatment of benign insulinomas localized in the body and tail of the pancreas: a single-center experience. World J Surg 2006;30:1916–1919.
225. Frucht H, Norton JA, London JF, et al. Detection of duodenal gastrinomas by operative endoscopic transillumination: a prospective study. Gastroenterology 1990;99:1622–1627.
226. Norton JA, Doppman JL, Jensen RT. Curative resection in Zollinger-Ellison syndrome: results of a 10-year prospective study. Ann Surg 1992;215:8–18.
227. Norton JA, Doppman JL, Collen MJ, et al. Prospective study of gastrinoma localization and resection in patients with Zollinger-Ellison syndrome. Ann Surg 1986;204:468–479.
228. Kato M, Imamura M, Hosotani R, et al. Curative resection of microgastrinomas based on the intraoperative secretin test. World J Surg 2000;24:1425–1430.
229. Norton JA. Surgical treatment and prognosis of gastrinoma. Best Pract Res Clin Gastroenterol 2005;19:799–805.
230. Nikfarjam M, Warshaw AL, Axelrod L, et al. Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital. Ann Surg 2008;247:165–172.
231. Butturini G, Bettini R, Missiaglia E, et al. Predictive factors of efficacy of the somatostatin analogue octreotide as first line therapy for advanced pancreatic endocrine carcinoma. Endocr Relat Cancer 2006;13:1213–1221.
232. Shah T, Caplin M. Biotherapy for metastatic endocrine tumours. Best Pract Res Clin Gastroenterol 2005;19:617–636.
233. Plockinger U, Wiedenmann B. Biotherapy. Best Pract Res Clin Endocrinol Metab 2007;21:145–162.
234. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 2004;25:458–511.
235. Delaunoit T, Rubin J, Neczyporenko F, et al. Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumors. Mayo Clin Proc 2005;80:502–506.
236. Panzuto F, Di Francesco V, Iannicelli E, et al. Long-term clinical outcome of somatostatin analogues for treatment of progressive, metastatic, well-differentiated entero-pancreatic endocrine carcinoma. Ann Oncol 2006;17:461–466.
237. Fallucca P, Delle Fave G, Giangrande L, et al. Effect of somatostatin on gastrin, insulin and glucagon secretion in two patients with Zollinger-Ellison syndrome. J Endocrinol Invest 1981;4:451–453.
238. Faiss S, Pape UF, Bohmig M, et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors—the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 2003;21:2689–2696.
239. Fazio N, de Braud F, Delle Fave G, et al. Interferon-alpha and somatostatin analog in patients with gastroenteropancreatic neuroendocrine carcinoma: single agent or combination? Ann Oncol 2007;18:13–19.
240. Forrer F, Valkema R, Kwekkeboom DJ, et al. Neuroendocrine tumors. Peptide receptor radionuclide therapy. Best Pract Res Clin Endocrinol Metab 2007;21:111–129.
241. Van Essen M, Krenning EP, de Jong M, et al. Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours. Acta Oncol 2007;46:723–734.
242. Kwekkeboom DJ, Teunissen JJ, Kam BL, et al. Treatment of patients who have endocrine gastroenteropancreatic tumors with radiolabeled somatostatin analogues. Hematol Oncol Clin North Am 2007;21:561–573.
243. Virgolini I, Traub T, Novotny C, et al. Experience with indium-111 and yttrium-90-labeled somatostatin analogs. Curr Pharm Des 2002;8:1781–1807.
244. Kaltsas GA, Papadogias D, Makras P, et al. Treatment of advanced neuroendocrine tumours with radiolabelled somatostatin analogues. Endocr Relat Cancer 2005;12:683–699.
245. Kwekkeboom DJ, Mueller-Brand J, Paganelli G, et al. Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. J Nucl Med 2005;46(Suppl 1):62S–66S.
246. Valkema R, Pauwels S, Kvols LK, et al. Survival and response after peptide receptor radionuclide therapy with [(90)Y-DOTA(0),Tyr(3)]octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. Semin Nucl Med 2006;36:147–156.
247. Kwekkeboom DJ, Teunissen JJ, Bakker WH, et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol 2005;23:2754–2762.
248. O'Toole D, Ruszniewski P. Chemoembolization and other ablative therapies for liver metastases of gastrointestinal endocrine tumours. Best Pract Res Clin Gastroenterol 2005;19:585–594.
249. Toumpanakis C, Meyer T, Caplin ME. Cytotoxic treatment including embolization/chemoembolization for neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007;21:131–144.
250. Arnold R, Trautmann ME, Creutzfeldt W, et al. Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. Gut 1996;38:430–438.
251. Ruszniewski P, O'Toole D. Ablative therapies for liver metastases of gastroenteropancreatic endocrine tumors. Neuroendocrinology 2004;80(Suppl 1):74–78.
252. Ramage JK, Davies AH, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. Gut 2005;54(Suppl 4):iv1–16.
253. Venook AP. Embolization and chemoembolization therapy for neuroendocrine tumors. Curr Opin Oncol 1999;11:38–41.
254. Gupta S, Johnson MM, Murthy R, et al. Hepatic arterial embolization and chemoembolization for the treatment of patients

with metastatic neuroendocrine tumors: variables affecting response rates and survival. Cancer 2005;104:1590–1602.
255. Osborne DA, Zervos EE, Strosberg J, et al. Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors. Ann Surg Oncol 2006;13:572–581.
256. Ho AS, Picus J, Darcy MD, et al. Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors. AJR Am J Roentgenol 2007; 188:1201–1207.
257. Sarmiento JM, Que FG. Hepatic surgery for metastases from neuroendocrine tumors. Surg Oncol Clin North Am 2003;12: 231–242.
258. Falconi M, Bettini R, Boninsegna L, et al. Surgical strategy in the treatment of pancreatic neuroendocrine tumors. JOP 2006;7: 150–156.
259. Carty SE, Jensen RT, Norton JA. Prospective study of aggressive resection of metastatic pancreatic endocrine tumors. Surgery 1992;112:1024–1031.
260. Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 2003;197:29–37.
261. House MG, Cameron JL, Lillemoe KD, et al. Differences in survival for patients with resectable versus unresectable metastases from pancreatic islet cell cancer. J Gastrointest Surg 2006;10:138–145.
262. Musunuru S, Chen H, Rajpal S, et al. Metastatic neuroendocrine hepatic tumors: resection improves survival. Arch Surg 2006;141:1000–1004.
263. Moug SJ, Leen E, Horgan PG, et al. Radiofrequency ablation has a valuable therapeutic role in metastatic VIPoma. Pancreatology 2006;6:155–159.
264. Mazzaglia PJ, Berber E, Milas M, et al. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. Surgery 2007;142: 10–19.
265. Gillams A, Cassoni A, Conway G, et al. Radiofrequency ablation of neuroendocrine liver metastases: the Middlesex experience. Abdom Imaging 2005;30:435–441.
266. Elvin A, Skogseid B, Hellman P. Radiofrequency ablation of neuroendocrine liver metastases. Abdom Imaging 2005;30: 427–434.
267. Arnold R, Rinke A, Schmidt C, et al. Chemotherapy. Best Pract Res Clin Gastroenterol 2005;19:649–656.
268. Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004;22:4762–4771.
269. Moertel CG, Hanley JA, Johnson LA. Streptozotocin alone compared with streptozotocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Engl J Med 1980;303:1189–1194.
270. Moertel CG, Lefkopoulo M, Lipsitz S, et al. Streptozotocin-doxorubicin, streptozotocin-flourouracil or chlorozotocin in the treatment of advanced islet cell carcinoma. N Engl J Med 1992; 326:519–523.
271. von Schrenck T, Howard JM, Doppman JL, et al. Prospective study of chemotherapy in patients with metastatic gastrinoma. Gastroenterology 1988;94:1326–1334.
272. Cheng PN, Saltz LB. Failure to confirm major objective antitumor activity for streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma. Cancer 1999;86: 944–948.
273. Ron D, Kazanietz MG. New insights into the regulation of protein kinase C and novel phorbol ester receptors. FASEB J 1999;13: 1658–1676.
274. Moertel CG, Kvols LK, O'Connell MJ, et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer 1991;68:227–232.
275. Hainsworth JD, Spigel DR, Litchy S, et al. Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: a Minnie Pearl Cancer Research Network Study. J Clin Oncol 2006;24:3548–3554.
276. Fjallskog ML, Lejonklou MH, Oberg KE, et al. Expression of molecular targets for tyrosine kinase receptor antagonists in malignant endocrine pancreatic tumors. Clin Cancer Res 2003; 9:1469–1473.
277. Wulbrand U, Wied M, Zofel P, et al. Growth factor receptor expression in human gastroenteropancreatic neuroendocrine tumours. Eur J Clin Invest 1998;28:1038–1049.
278. Peghini PL, Iwamoto M, Raffeld M, et al. Overexpression of epidermal growth factor and hepatocyte growth factor receptors in a proportion of gastrinomas correlates with aggressive growth and lower curability. Clin Cancer Res 2002;8: 2273–2285.
279. Furukawa M, Raffeld M, Mateo C, et al. Increased expression of insulin-like growth factor I (IGF-1) and/or its receptor (IGF-1R) in gastrinomas is associated with low curability, increased growth and development of metastases. Cancer Res 2005;11:3233–3242.
280. Yao JC. Molecular targeted therapy for carcinoid and islet-cell carcinoma. Best Pract Res Clin Endocrinol Metab 2007;21: 163–172.
281. Strosberg JR, Kvols LK. A review of the current clinical trials for gastroenteropancreatic neuroendocrine tumours. Expert Opin Investig Drugs 2007;16:219–224.
282. Chan JA, Kulke MH. Emerging therapies for the treatment of patients with advanced neuroendocrine tumors. Expert Opin Emerg Drugs 2007;12:253–270.
283. Yao JC, Zhang JX, Rashid A, et al. Clinical and in vitro studies of imatinib in advanced carcinoid tumors. Clin Cancer Res 2007; 13:234–240.
284. Hopfner M, Sutter AP, Gerst B, et al. A novel approach in the treatment of neuroendocrine gastrointestinal tumours. Targeting the epidermal growth factor receptor by gefitinib (ZD1839). Br J Cancer 2003;89:1766–1775.
285. Kulke M, Lenz HJ, Meropol NJ, et al. A phase 2 study to evaluate the efficacy and safety of SU11248 in patients with unresectable neuroendocrine tumors (NET): a phase 11 consortium (P2C) study. J Clin Oncol 2005;23:310s.
286. Hobday TJ, Holen K, Donehower R, et al. A phase II trial of gefitinib in patients with progressive metastatic neuroendocrine tumors: a phase II consortium study. J Clin Oncol 2006;24: A4043.
287. Duran I, Kortmansky J, Singh D, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. Br J Cancer 2006;95:1148–1154.
288. Kimmig BN. Radiotherapy for gastroenteropancreatic neuroendocrine tumors. Ann N Y Acad Sci 1994;733:488–495.
289. Strosberg J, Hoffe S, Gardner N, et al. Effective treatment of locally advanced endocrine tumors of the pancreas with chemoradiotherapy. Neuroendocrinology 2007;85:216–220.
290. Pascher A, Klupp J, Neuhaus P. Transplantation in the management of metastatic endocrine tumours. Best Pract Res Clin Gastroenterol 2005;19:637–648.
291. Olausson M, Friman S, Herlenius G, et al. Orthotopic liver or multivisceral transplantation as treatment of metastatic neuroendocrine tumors. Liver Transpl 2007;13:327–333.
292. Le Treut YP, Delpero JR, Dousset B, et al. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. Ann Surg 1997; 225:355–364.

293. Lehnert T. Liver transplantation for metastatic neuroendocrine carcinoma. Transplantation 1998;66:1307–1312.
294. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61–72.
295. de Herder WW, O'Toole D, Rindi G, et al. ENETS consensus guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumors: part 2—midgut and hindgut tumors. Neuroendocrinology 2008;87:1–63.
296. Rindi G, Kloppel G, Couvelard A, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2007;451:757–762.
297. Kaplan EL, Horvath K, Udekwu A, et al. Gastrinomas: a 42-year experience. World J Surg 1990;14:365–375.
298. Farley DR, Van Heerden JA, Grant CS, et al. The Zollinger-Ellison syndrome. A collective surgical experience. Ann Surg 1992; 215:561–569.
299. Mignon M, Cadiot G. Diagnostic and therapeutic criteria in patients with Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1. J Intern Med 1998;243:489–494.
300. Galbut DL, Markowitz AM. Insulinoma: diagnosis, surgical management and long-term follow- up. Review of 41 cases. Am J Surg 1980;139:682–690.
301. Dizon AM, Kowalyk S, Hoogwerf BJ. Neuroglycopenic and other symptoms in patients with insulinomas. Am J Med 1999;106:307–310.
302. Soga J, Yakuwa Y, Osaka M. Insulinomas/hypoglycemic syndrome: a statistical evaluation of 1085 reported cases of a Japanese series. J Exp Clin Cancer Res 1998;17:379–388.
303. Fajans SS, Vinik AI. Insulin-producing islet cell tumors. Endocrinol Metab Clin North Am 1989;18:45–74.
304. Wiedmann MW, Caca K. Molecularly targeted therapy for gastrointestinal cancer. Curr Cancer Drug Targets 2005;5:171–193.
305. Smolewski P. Recent developments in targeting the mammalian target of rapamycin (mTOR) kinase pathway. Anticancer Drugs 2006;17:487–494.
306. Dancey JE. Therapeutic targets: MTOR and related pathways. Cancer Biol Ther 2006;5:1065–1073.
307. Rocha-Lima CM, Soares HP, Raez LE, et al. EGFR targeting of solid tumors. Cancer Control 2007;14:295–304.
308. Harari PM. Epidermal growth factor receptor inhibition strategies in oncology. Endocr Relat Cancer 2004;11:689–708.

Received February 4, 2008. Accepted May 12, 2008.

Address reprint requests to: Robert T. Jensen, MD, Building 10, Room 9C-103, National Institutes of Health, Bethesda, Maryland 20892. e-mail: RobertJ@bdg10.niddk.nih.gov; fax: (301) 402-0600.

The authors disclose the following: this work is partially supported by the Intramural Program of the NIDDK, National Institutes of Health.