Recent Progress in the Understanding, Diagnosis, and Treatment of Gastroenteropancreatic Neuroendocrine Tumors

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Abstract

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are relatively rare tumors that arise from the diffuse neuroendocrine system. This heterogeneous group of tumors was often considered a single entity. This belied their biological diversity, and the biggest advance in understanding these tumors over the past decades has been in understanding this diversity. Diagnosis of these tumors has been aided by advances in pathological diagnosis and classification and tumor imaging with endoscopic ultrasound and somatostatin receptor fusion imaging. Genetic and molecular advances have identified molecular targets in the treatment of these tumors. Surgery remains the mainstay of treatment, amply supported by interventional radiological techniques, including embolization. Treatment of metastatic disease has improved significantly with the addition of several new agents, including tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, and yttrium-90–DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and lutetium-177–DOTA octreotate. Despite significant advances in the understanding and management of GEP-NETs, the survival of patients remains largely unchanged and there remains a need for the development of national and international research collaborations to spearhead future efforts. CA Cancer J Clin 2011;61:113–132. © 2011 American Cancer Society, Inc.

Introduction

Several advances in the management of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) have occurred over the last century since Obernourfer coined the term “Karzinoide” in 1907 in his seminal article in the Frankfurt Journal of Pathology.1 A large proportion of these advances were made through sporadic case reports in the latter half of the 20th century given the complexity and heterogeneity of these tumors, in addition to their relative rarity. Recent advances have been triggered through concerted efforts by researchers to participate in collaborative trials in addition to more widespread sharing of information. This review aims to highlight some of the recent advances in the understanding, diagnosis, and management of these interesting tumors.

Epidemiology and Nomenclature

GEP-NETs arise from the diffuse neuroendocrine system in the gastrointestinal tract and include, but are not limited to, carcinoid tumors (from the German “karzinoide” or “cancer-like”). The use of the anatomic term “carcinoid” has been criticized for concerns that it does not convey the malignant potential that some of these tumors have.2 In addition, “carcinoid” was also used quite interchangeably for the syndrome that arises from the release of bioactive amines leading to characteristic symptoms of flushing and diarrhea, among others. However, unlike other functioning tumors, carcinoid tumors were not always characterized by the presence or absence of the syndrome. Hence, the current nomenclature systems such as the European Neuroendocrine Tumor Society

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ENETS and the World Health Organization (WHO) embrace the term “GEP-NETs” for tumors of epithelial origin occurring in the gastrointestinal (GI) tract with neuroendocrine differentiation (Table 1).

Classification of these tumors was attempted by William and Sandler in 1963 based on their embryological origins into foregut, midgut, or hindgut tumors (Fig. 1). Numerous classification systems were used until the WHO classifications in 2000 and subsequently in 2004, which, although a unifying method of classification, still lacked in their abilities to capture the diversity of these tumors. More recently, ENETS proposed the TNM staging, which is based on tumor thickness and/or size, lymph node involvement, and metastatic disease, which is supplemented by the grading system. This has been suggested by some studies to predict outcomes more accurately than the 2000 WHO histological classification and American Joint Committee on Cancer staging system. Recent updates to the WHO classification are underway and the new systems of nomenclature embrace the differentiation and grading features of GEP-NETs (Table 1). Differentiation of NETs refers to the extent that neoplastic cells resemble their non-neoplastic counterparts whereas grade refers to the inherent biologic aggressiveness of the tumor.

### TABLE 1. Nomenclature Systems for GEP-NETs

| GRADE* | ENETS 5,6 | WHO 2010 3 | HOCHWALD 2002 7 |
|--------|----------|------------|-----------------|
| Low grade | Neuroendocrine tumor, grade 1 | Neuroendocrine neoplasm, grade 1 | Well-differentiated pancreatic endocrine neoplasm, low grade |
| Intermediate grade | Neuroendocrine tumor, grade 2 | Neuroendocrine neoplasm, grade 2 | Well-differentiated pancreatic endocrine neoplasm, intermediate grade |
| High grade | Neuroendocrine carcinoma, grade 3, small cell carcinoma | Neuroendocrine carcinoma, grade 3, small cell carcinoma | Poorly differentiated pancreatic endocrine carcinoma, small cell carcinoma |
| | Neuroendocrine carcinoma, grade 3, large cell carcinoma | Neuroendocrine carcinoma, grade 3, large cell carcinoma | Poorly differentiated pancreatic endocrine carcinoma, large cell carcinoma |

GEP-NETs indicates gastroenteropancreatic neuroendocrine tumors; ENETS, European Neuroendocrine Tumor Society; WHO, World Health Organization.

*In which low grade is defined as <2 mitoses/10 high-power fields (HPF) AND <3% Ki-67 index; intermediate grade as 2 to 20 mitoses/10 HPF OR 3% to 20% Ki-67 index; and high grade as ≥20 mitoses/10 HPF OR >20% Ki-67 index for gastroenteropancreatic neuroendocrine tumors. For pancreatic tumors, low grade is defined as <2 mitoses/50 HPF AND no necrosis; intermediate grade as 2 to 50 mitoses/50 HPF OR foci of necrosis; and high grade as ≥50 mitoses/50 HPF.

Adapted with permission from Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010;39:707-712.
Due to the above issues with classification and a lack of consensus, the exact epidemiology of GEP-NETs has been difficult to ascertain. An autopsy series of 16,294 patients conducted between 1958 to 1969 revealed a relatively high incidence of 8.4 carcinoid tumors per 100,000 population per year. Population studies from Europe revealed an incidence of 1.1 per 100,000 person-years, whereas a second series showed the incidence to be 2.0 for men and 2.4 for women. Other reports from Europe showed lower age-adjusted incidence rates (0.7–0.8 from England and 0.6 from Tuscany). A detailed analysis of the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database from Yao
TABLE 2. Epidemiology of Pancreatic Endocrine Tumors

| SUBTYPE       | DISTRIBUTION, % | AGE AT DIAGNOSIS, DECADE | MALE/FEMALE RATIO | 5-YEAR SURVIVAL RATE, % |
|---------------|-----------------|---------------------------|-------------------|-------------------------|
| Insulinoma    | 20-30           | Fifth                     | 0.7:1             | 80-95                   |
| Gastrinoma    | 15-20           | Sixth                     | 1.5:2:1           | 50-70                   |
| Glucagonoma   | 1-3             | Fifth                     | 1:1               | 50-60                   |
| VIPoma        | 2-4             | Fourth to fifth           | 0.3:1             | 40-50                   |
| Somatostatinoma | 0-1           | Sixth                     | 1:1               | 20-40                   |
| Nonfunctioning and PPoma | 10-50      | Fourth to fifth           | 0.86:1            | 30-50                   |

VIPoma indicates rare endocrine tumor that produces vasoactive intestinal peptide; PPoma, neuroendocrine tumor that produces excessive pancreatic polypeptide.

Adapted with permission from Modlin I, Zikusoka M, Kidd M, Latch I, Eick G, Romanyshyn J. The history and epidemiology of neuroendocrine tumors. In: Caplin M, Kvols L, eds. Handbook of Neuroendocrine Tumors. 1st ed. Bristol, UK: BioScientifica; 2006:7-37; Mansour JC, Chen H. Pancreatic endocrine tumors.

et al.14 revealed that the incidence of carcinoid tumors was 5 cases per 100,000 person-years whereas that of GEP-NETs can be estimated at approximately 2.89 cases per 100,000 person-years (incidence of overall cases) — (incidence of lung/thymus/unknown primary site). From 1972 to 2004, the overall age-adjusted incidence of carcinoids of the small intestine and of the digestive system increased by 460% and 720%, respectively. This increase in incidence can be attributed to increased diagnosis by endoscopic and radiological techniques.14 In addition, there has been an increased prevalence in both Caucasian (274%) and African American (500%) populations (Fig. 2). The 5-year survival rate for patients with small intestinal carcinoids remains at 60%, with limited progress reported over the last 30 years, although recent registry data from Spain have revealed a 5-year survival rate of almost 77% for this group of patients.15

The epidemiology of the carcinoid subset of GEP-NETs has been well studied and they occur throughout the GI system. The majority (31%) of these tumors occur in the ileum, with an annual incidence of 0.67 cases per 100,000 person-years.14 The rectum (21%) and the appendix (17% benign and 1% malignant) are the next most frequent sites of GEP-NETs. The colon (12%), stomach (6%), and the remaining small intestine (duodenum, 4% and jejunum, 3%) are other sites of the disease.16 The frequency of appendiceal carcinoid tumors (previously the most frequent tumor) has decreased over time. Earlier surveys such as those compiled by the End Results Group (1950–1969) showed that appendiceal carcinoids comprised 43.9% of all carcinoid tumors, a figure that is now estimated at 12.2% from the SEER data.16

The epidemiology of pancreatic endocrine tumors is poorly understood given the heterogeneous classification, although a synopsis of current data is shown in Table 2. Nonfunctioning tumors and insulinomas are the most common pancreatic NETs.

Advances in Cell Biology of Neuroendocrine Cells

GEP-NETs arise from cells of the diffuse neuroendocrine system (DNES) and until recently were believed to derive from migrated neural crest cells. In fact, they actually derive from local multipotent GI stem cells, rather than by migration of the neural crest cells, and hence are endodermal in origin.17,18 The endocrine cells of the gut are highly specialized and store hormonal substances in suborganelles called secretory vesicles: the large dense core vesicle (LDCV) and the synaptic-like microvesicle (SLMV).19 The gut DNES cells are remarkably heterogeneous and consist of 14 different types of cells (Fig. 1; biochemical classification), making it the largest endocrine organ in the body. The mechanisms that trigger differentiation of the DNES are not well understood, although candidate transcription factors include atonal homolog 1, neurogenin 3, and NeuroD.20

Secretion of peptide hormones packaged inside LDCV is regulated by G-protein–coupled receptors, ion gated receptors, and receptors with tyrosine kinase activity. Chromogranin A (CgA) is an acidic glycoprotein expressed in the secretory granules of most normal and neoplastic neuroendocrine cells. Most commonly assessed neuroendocrine antigens are either located in the cytosol (eg, neuron-specific
enolase and protein gene product 9.5) or are associ-
ated with secretory vesicles (LDCV: chromogranin; and SLMV: synatophysin). Recent studies have
shown vesicular monoamine transporter isoforms
(VMAT-1: LDCV of enterochromaffin cells; VMAT-2: LDCV of enterochromaffin-like cells), neuroen-
ocrine secretory protein 55, synaptic vesicle protein 2, and neural cell adhesion molecule (NCAM) are expressed on cell surfaces of neuroen-
ocrine cells.4

The secretion of bioactive amines is regulated by mechanical and chemical stimuli. Adenyl cyclase, β-adrenoceptors, and pituitary adenylate cyclase-
activating polypeptide are activating pathways whereas somatostatin (via somatostatin receptor 2), acetylcholine (muscarinic acetylcholine receptor M4), and γ-aminobutyric acid (GABA) (via GABA-A receptors) are inhibitory signals. It is the secretion of these bioactive amines that make these tumors unique in their biological characteristics.4,20

**Advances in Molecular Genetics**

The majority of GEP-NETs are sporadic, yet the molecular genetics of tumor susceptibility syndromes in which GEP-NETs occur contribute significantly to the understanding of the genetic underpinnings of the disease.21 Distinct abnormalities such as point mutations, deletions, methylation, and chromosomal losses and gains have been shown to be involved in the development of GEP-NETs.22,23 We discuss some of the molecular and clinical genetics of familial GEP-NETs by characterization of tumor suppressor genes, multiple endocrine neoplasia 1 (MEN-1), Von Hippel-Lindau (VHL), neurofibromatosis 1 (NF-1), tuberous sclerosis (TSC) 1, and TSC-2.

**Multiple Endocrine Neoplasia-1**

MEN-1 is an autosomal dominant endocrine tumor susceptibility syndrome that is associated with tumors of the parathyroid, enteropancreatic endo-
crine tissue, and anterior pituitary.21 GEP-NETs are the second most common manifestation of MEN-1 (a 40% penetrance of gastrinomas and 10% penetrance of gastric carcinoids) after primary hyperparathyroidism and include a spectrum of disease.21 The MEN-1 gene, located at chromosome 11q13, encodes the widely expressed menin protein. Germline mutations of the MEN-1 gene are noted in 70% to 90% of MEN-1 families, whereas some without identifiable mutations may have large deletions or intron mutations not recognized by polymerase chain reaction.21 Recently, in a study of MEN-1 patients undergoing resection of pancreatic endo-
crine tumors, loss of heterozygosity of the MEN-1 locus was noted in 95% (19 of 20) of monohormonal pancreatic endocrine cell clusters and 100% of pancreatic microadenomas.24

**Von Hippel-Lindau Syndrome**

The von Hippel-Lindau syndrome is an autosomal dominant syndrome that occurs from germline mutations in the VHL gene and 11% to 17% of these patients develop endocrine pancreatic tumors.25 Chromosome 3p loss of heterozygosity occurs subsequent to VHL mutation and correlates with malignant progression of VHL-associated GEP-NETs.26

**Neurofibromatosis and Tuberous Sclerosis**

NF-1 and TSC are both autosomal dominant tumor susceptibility syndromes. The occurrence of ampullary carcinoids, duodenal and pancreatic somatostatinomas, and nonfunctioning GEP-NETs have been reported in such families. Both these syndromes are caused by inactivation of tumor suppressor genes such as NF-1 (17q11.2), TSC-1 (9q34), and TSC-2 (16p13.3). Neurofibromin (product of NF-1) also regulates TSC-1 and TSC-2 through the mammalian target of rapa-
mycin (mTOR). Loss of function of NF-1 causes mTOR activation and tumor development.27

**Sporadic GEP-NETs**

Significantly less is known about the genetic mecha-
nism of sporadic GEP-NETs. Hindgut NETs express transforming growth factor α (TGF-α) and the epidermal growth factor receptor (EGFR), whereas foregut NETs have frequent deletions and mutations of the MEN-1 locus.28 The occurrence of chromosomal gains or losses has been studied in pancreatic NETs by loss of heterozygosity, comparative genomic hybridization, and array comparative genomic hybridization analysis. Allelic losses are seen in chromosome loci 1p (23%-75%), 1q (20%-88%), 3p (25%-62%), 11p (29%-52%), 11q (28%-66%), and 22q (38%-93%).29-31 The overall incidence of MEN-1 gene mutations in sporadic primitive neuroectoder-
mal tumors (PNETs) varies between 13% and 38%.30,31 In sporadic GI carcinoids, loss of
chromosome 18 and loci 9p and 16q are the most common genetic alterations.

DNA microarray analysis is now being used to identify gene expression profiles associated with benign and malignant clusters in PNETs, although this approach has yet to be validated prospectively.32

### Advances in Understanding the Clinical Presentation

The presentation of GEP-NETs has been classified based on the anatomical location and cellular functionality, indicating the ability of the tumors to release biologically active substances. However, numerous tumors produce low levels of substances that are clinically insignificant or secrete metabolically inactive or inappropriately processed substances. Most GEP-NETs are nonfunctioning and present fairly late with mass effects, distant metastasis, or both (Table 3).20,33 Delayed diagnosis by 5 to 7 years after the onset of symptoms is common and increases the likelihood of patients presenting with advanced or metastatic disease.20

The classic syndrome associated with functioning GEP-NETs such as carcinoid tumors is the carcinoid syndrome, which is the result of the interaction of tumor factors such as 5-hydroxytryptamine (serotonin) (5-HT), kinins, and kallikrein entering the systemic circulation when not cleared by the portal or pulmonary arterial circulation. In the presence of liver metastasis, serotonin, tachykinins, and other bioactive amines are released into the systemic circulation, leading to flushing, diarrhea, and other features of carcinoid syndrome, which are shown in Table 4. Occasionally, carcinoid crisis, which is an overwhelming release of bioactive amines, can develop in patients with foregut and midgut carcinoids, and can present with hypotension (rarely hypertension), arrhythmias, wheezing, and delirium. This has become of greater relevance in the era of interventional procedures, medications, and anesthesia because these stresses can trigger the carcinoid crisis even in apparently normal patients.

### Table 3. GEP-NETs Tumors: Anatomical, Clinical, and Biochemical Features

| SITE            | PEPTIDE/AMINES               | CLINICAL FEATURES                        | METASTASIS | MEN-1 |
|-----------------|------------------------------|------------------------------------------|------------|-------|
| FOREGUT         |                              |                                          |            |       |
| Bronchi, thymus, stomach, first duodenum | 5-HTP, histamine, ACTH, CRH, GH, gastrin | Pulmonary obstruction, atypical flushing, hormone syndromes | Liver, lymph nodes, bone | 10%   |
| MIDGUT          |                              |                                          |            |       |
| Second duodenum, jejunum, ileum, right colon | 5-HT, tachykinins, prostaglandins, bradykinins, others | Bowel obstruction, typical flushing, wheeze, diarrhea (carcinoid syndrome) | Liver (60%-80%) | Lymph node | — |
| HINDGUT         |                              |                                          |            |       |
| Transverse colon to rectum | Local production somatostatin, peptide YY, glicentin, neurotensin, 5-HTP | Incidental finding, local symptoms | Bone metastasis (5%-40%) | — |
| PANCREATIC      |                              |                                          |            |       |
| Insulinoma      | Insulin, proinsulin          | Neuroglucopenia, Whipple triad           | 10%        | 5%-10%|
| Gastrinoma      | Gastrin                      | ZES (peptic ulcer, epigastric pain, diarrhea) | 60%-90% | 25%   |
| VIPoma          | VIP                          | Watery diarrhea, hypokalemia, achlorhydria | 80%        | 10%   |
| Glucagonoma     | Glucagon                     | Necrotic migratory erythema, diabetes mellitus, cachexia | 80%-90% | 5%-17%|
| Somatostatinoma | Somatostatin                 | Gallstones, diabetes mellitus, steatorrhoea, achlorhydria | 60%-70% | 5%-10%|
| Nonfunctioning tumors | Pancreatic polypeptide | Mass effect                             | 60%        | 20%-30%|
| GRFoma          | Growth hormone-releasing factors | Acromegaly                             | —          | 20%   |

GEP indicates gastroenteropancreatic; MEN-1, multiple endocrine neoplasia 1; 5-HTP, 5-hydroxytryptophan; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; GH, growth hormone; 5-HT, 5-hydroxytryptamine (serotonin); ZES, Zollinger-Ellison syndrome; VIPoma, rare endocrine tumor that produces vasoactive intestinal peptide; GRFoma, neuroendocrine tumors that secrete excessive amounts of growth hormone-releasing factor.

Adapted with permission from Kaltsas G, Grossman A. Clinical features of gastroenteropancreatic tumors. In: Caplin M, Kvols L, eds. Handbook of Neuroendocrine Tumors. 1st ed. Bristol, UK: BioScientifica; 2006:83-101.
symptomatically well-controlled patients. Prophylaxis with octreotide prior to such procedures is recommended in patients at risk of developing carcinoid crisis.

Gastric carcinoids are typically slow-growing with low metastatic potential and are classified based on gastrin production and malignant potential. Tumors presenting as numerous, small localized tumors associated with hypergastrinemia can be either secondary to chronic atrophic gastritis (type 1) or Zollinger-Ellison syndrome (type 2). The Zollinger-Ellison syndrome is characterized by the presence of a gastrinoma classically located in the gastrinoma triangle (defined by the junction of the neck and body of the pancreas, the sweep of the third portion of the duodenum, and the junction of the cystic and common hepatic ducts) in which patients present with intratable ulcer diathesis along with diarrhea. In contrast, sporadic, large gastrinomas not associated with hypergastrinemia occur in type 3 and have significant malignant potential with a likelihood of metastatic disease. Usually lymph node metastases are described in 20% to 50% of patients, whereas liver metastases occur in 66% of the patients.\(^{33,34}\)

Duodenal carcinoids are less common and exhibit lower serotonergic hormone levels, and have a good prognosis.\(^{35}\) Larger tumors (>2 cm) are more often associated with mass effect leading to pancreatitis, obstructive jaundice, or bleeding. Primary pancreatic carcinoids, which are a subgroup of pancreatic NETs or PNETs, are often diagnosed late and are very often associated with the carcinoid syndrome (65%). These tumors metastasize early (69%-88%), which generally precludes surgical resection, and have a poor response to therapy.\(^{35}\)

Small intestinal carcinoids are the most common carcinoids arising from the DNES, and the majority of patients present with abdominal pain, small bowel obstruction, and metastasis. The carcinoid syndrome occurs less frequently (7%-28%).\(^{35}\) Metastatic potential is not reliably predicted by tumor size in this group, although generally tumors >2 cm are more likely to metastasize. An important consideration in small intestinal primaries is their potential to lead to extensive mesenteric reactive fibrosis, which could lead to obstruction or ischemia. Overall prognosis is dictated by the presence of regional and distant disease.

The appendix was once considered the most common location of carcinoids, but carcinoids of the small bowel and rectum are now thought to be more frequent.\(^{14}\) This change in incidence may be due to better diagnosis of both primary and metastatic disease, although the reasons for this phenomenon have not been clearly studied. The majority of these tumors occur in the distal one-third of the appendix and have excellent prognosis in the absence of histological atypia, mesoappendiceal invasion, and size <2 cm. The 5-year survival rate is 94% for patients with local disease and 84% for those with regional disease.\(^{14,35}\) Goblet cell carcinoids are a special subtype that show glandular differentiation and generally behave more aggressively than conventional carcinoid tumors with a 20% to 56% incidence of metastasis.\(^{36,37}\)

Colon carcinoids occur most frequently in the cecum and ileocecal region and generally have a poor prognosis, and a low incidence of the carcinoid syndrome.\(^{14}\)

| TABLE 4. Putative Mediators and Manifestations of the Carcinoid Syndrome |
|-----------------------------|-----------------|---------------------------------|
| **CLINICAL FEATURES**       | **INCIDENCE, %** | **CHARACTERISTICS**             |
| Flushing                    | 90              | Foregut tumors: prolonged fit,  |
|                            |                 | red-purple, localized to face   |
|                            |                 | and trunk                      |
|                            |                 | Midgut tumors: quick fit, pink-|
|                            |                 | red                          |
| Diarrhea                    | 70              | Secretory                      |
| Abdominal pain              | 40              | Long lasting                    |
| Profuse sweating            | 15              | Face                           |
| Telangiectasia              | 25              | Valvulopathies (tricuspid and  |
|                            |                 | pulmonary), right heart failure|
|                            |                 | and dyspnea                    |
| Heart disease               | 30 (right)      | Substance P, serotonin         |
|                            | 10 (left)       | Telangiectasia                 |
| Pellagra                    | 5               | Dermatitis                      |

VIP indicates vasoactive intestinal peptide. Reprinted with permission from Massironi S, Sciola V, Peracchi M, Ciafardini C, Spampatti MP, Conte D. Neuroendocrine tumors of the gastro-entero-pancreatic system. World J Gastroenterol. 2008;14:5377-5384.
syndrome. Unlike gastric and small intestinal carcinoids, which present with carcinoid syndrome 10% to 50% of the time (usually with the development of liver metastases), colonic carcinoids more often present with pain (50%), bleeding (10%–50%), and mass (10%–50%) and with the carcinoid syndrome less than 10% of the time.\textsuperscript{36} The lower frequency of carcinoid syndrome is due to the decreased production of serotonin and other bioactive amines by hindgut tumors. The 5-year survival rates are 70% for local disease and 20% for distant disease. Rectal carcinoids contain glucagon, pancreatic polypeptide, and glcinent-like peptide rather than 5-HT. Prognostic features usually include tumor size, infiltration of muscularis propria, and atypical histology, in which case patients have a poor prognosis. Overall, however, the patients fare better than those with colon carcinoids, with a 5-year survival rate of 81% for those initially diagnosed with local disease.\textsuperscript{35}

Carcinoids of unknown primary consist of a group of tumors that are biochemically similar to midgut carcinoids with metastasis, with similar 5-year survival rates.\textsuperscript{37} Carcinoids can arise from the genitourinary tract but their clinical presentation can include hematuria, pain, and constitutional symptoms.\textsuperscript{37}

Most pancreatic NETs are large and approximately 50% have metastatic disease at diagnosis.\textsuperscript{33,38} Functional tumors produce numerous bioactive substances with a varied clinical presentation (Table 3). Insulinomas are the most common tumors, and are typically hypervascular, solitary, small tumors. Successful excision of these tumors leads to normal life expectancy. Gastrinomas are typically highly malignant tumors (70%–80% of patients have liver metastasis at presentation), which are most frequently (eg, 78% of explorations\textsuperscript{39}) localized to the gastrinoma triangle described above, with 40% of them being located in the duodenum. Glucagonomas have been associated with a pathognomonic rash, necrotic migratory erythema, which is a red blistering rash that spreads over the lower abdomen, buttocks, perineum, and groin. They can also be associated with dystrophic nails, cheilitis, and atrophic glossitis. Diabetes mellitus in patients with glucagonomas is usually hard to control, but the most important complication that accounts for almost 50% of mortality is thromboembolic disease.\textsuperscript{33} Patients have very good survival rates after surgery, with 85% survival reported at 5.7 years of follow up, and 60% reported for those with metastatic disease.\textsuperscript{37} VIPomas (rare endocrine tumors that produce vasoactive intestinal peptide) and somatostatinomas are generally characterized by the effects of hypersecretion of vasoactive intestinal polypeptide and somatostatin, respectively, and have a good prognosis with surgery. VIPomas are associated with secretory watery diarrhea, hypokalemia, and achlorhydria (Verner-Morrison syndrome), whereas somatostatinomas can present with steatorrhea, achlorhydria, diabetes mellitus, and cholelithiasis (Table 3). Extrapancreatic somatostatinomas can occur in the duodenum, cystic duct, colon, and rectum. These tumors present more often due to the mass effect, with obstruction and pancreatitis, although occasionally diabetes and cholelithiasis have been described. Duodenal tumors are often associated with NF-1. Almost 40% of pancreatic NETs are nonfunctioning, unifocal tumors unless associated with MEN-1, when they are multifocal.\textsuperscript{37}

**Advances in Biochemical and Tissue Markers**

Diagnosis of GEP-NETs relies heavily on their biochemical markers in addition to the clinical presentation and pathological features. Several markers are indicative of specific tumor types, whereas some, such as chromogranin, are nonspecific but sensitive (Fig 3). CgA is an acidic glycoprotein expressed in the secretory granules of most normal and neoplastic neuroendocrine cell types. The technique used for determination of CgA might affect its sensitivity because GEP-NETs might have a higher cleavage of CgA; therefore, enzyme-linked immunoadsorbent assay might be more sensitive than immunoradiometric assay.\textsuperscript{40} Levels of circulating CgA are increased in 60% to 80% of patients with GEP-NETs but are nonspecific due to elevation in renal failure, proton pump inhibitor use, and chronic atrophic gastritis.\textsuperscript{20} Carcinoid tumors of the GI tract can be diagnosed with measurement of the breakdown product of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), and for pancreatic tumors, specific bioactive markers may be used (Fig. 3).

**Advances in Pathology**

In addition to serum biochemical markers, there have been new immunohistochemical markers suggested for the diagnosis and prognostication of these tumors. These include synaptic vesicle glycoprotein
2, synaptobrevin 1, NCAM-1, CDX2, transcription termination factor 1 (TTF-1), and peptide hormone receptors, which augment diagnosis with conventional stains such as synatophysin and neuron-specific enolase (Table 5). Advances in cell biology have triggered the increasing use of NCAM-1 as previously mentioned, whereas CDX2 and TTF-1 are more reliable markers of enterochromaffin cells in the gut and surfactant production in the lung, respectively. Interpretation of these immunohistochemical stains has to be made within the clinical context of the patient, especially in patients with metastatic tumors with an unknown primary. For well-differentiated NETs, TTF-1 labeling favors a pulmonary origin, CDX2 is typical of intestinal or pancreatic primaries, and PDX1 or Isl1 are commonly expressed in pancreatic NETs.2,41

The classification of GEP-NETs has been clarified somewhat since the adoption of the WHO classification in 2000 and the subsequent TNM staging with the (ENETS) modification (Table 1).5 The WHO classification was grouped on the basis of clinical-pathological criteria into 1) well-differentiated endocrine tumors, with benign and uncertain behavior; 2) well-differentiated endocrine carcinoma with low-grade malignant behavior; and 3) poorly differentiated endocrine carcinomas with high-grade malignant behavior and mixed endocrine-exocrine carcinomas (Table 1). The TNM staging system uses the size, lymph node metastasis, and systemic metastasis to stage tumors. Modifications to the TNM system have been proposed by the ENETS in which the Ki-67 index and mitotic index are used to classify tumors into grade 1 (<2 mitoses/10 high-powered fields [HPF] and Ki-67 index of ≤2%), grade 2 (2–20 mitoses/HPF and/or Ki-67 index of 3%–20%), and grade 3 (>20 mitoses/HPF or Ki-67 index >20%).5 There still remains significant disagreement between experts concerning the prognostic significance of this classification and the lack of features to capture dysplasia. To improve consistency between pathologists, a recent consensus conference using the Delphi consensus process was used to establish criteria reportable for a NET.43 CgA and synatophysin were recognized as universal stains applicable for all NETs, but the applicability of immunohistochemistry for well-differentiated tumors and the use of CgB, NCAM, CD57, neuron-specific enolase, and keratins was not routinely recommended.43 The role of CDX2 and TTF-1 in determining the site of origin and the role of Ki-67 in determining proliferative potential are recognized, yet uniform guidelines for reporting them are currently being developed.

**Advances in Diagnostic Imaging Modalities**

The diagnosis of GEP-NETs has been facilitated with the development of numerous imaging techniques over the last few decades. Nevertheless, almost 20% to 50% of primary tumors are not localized and gastrinomas and midgut carcinoids are generally elusive and detected only once metastatic disease develops.20 The conventional imaging modalities such as transabdominal ultrasound, computed tomography (CT) scans, and magnetic resonance imaging (MRI) have been tailored to enhance their sensitivity in the diagnosis of GEP-NETs. Dynamic ultrasound testing remains highly dependent on the operator, but the development of endoscopic ultrasound (EUS) and intraoperative ultrasound (IOUS) and laparoscopic ultrasound have greatly improved the diagnostic yield of this...
technique. Ultrasound has the added advantage of no radiation exposure, repeatability, and being a dynamic test to assess response in vascularity to assess therapeutic response. EUS can detect 45% to 60% of duodenal lesions and 90% to 100% of pancreatic lesions, whereas laparoscopic ultrasound correlates well with core needle biopsies of liver metastasis, especially after previous radiofrequency ablation (RFA). The use of IOUS has been described for gastrinomas and insulinomas especially in MEN-1 patients to evaluate multifocal disease, but has not been studied extensively.

Advances in CT scan imaging with dynamic and multiphase CT scans have improved the diagnostic yield of this technique and remains the most common initial test for the evaluation of GEP-NETs. Conventional CT scan imaging has a detection frequency of 22% to 45%, although with multidetector row CT scan imaging, the sensitivity can be as high as 80% for insulin-producing tumors. Similarly, the use of dynamic contrast-enhanced MRI contrast agents including ultrasmall superparamagnetic iron oxide particles is sensitive to the vascular phase of contrast medium delivery and can demonstrate vascular permeability and assess lymph nodes. New agents including gadolinium-EOB-DTPA (gadoxetate [EOVIST]) and SHU-555A (RESOVIST) are being used for liver imaging. Gadoxetate is selectively taken up by hepatocytes, which increases the signal intensity on T1-weighted images, leading to better lesion-to-liver contrast, whereas SHU-555A in the reticuloendothelial system causes a decrease in the signal intensity of the liver parenchyma on both T2- and T1-weighted images, although it is unchanged in metastatic tumors, improving the lesion-to-liver contrast. Molecular MRI with antibodies or gadolinium-labeled peptides can detect receptors on tumors and identify tumoral antigens such as ErbB2 and can assess the efficacy of antitumor agents. Conventional angiography with selective sampling, including portal vein sampling plus pentagastrin stimulation, was widely used before, but has lost utility in the era with more advanced diagnostic imaging techniques due to its cumbersome and invasive nature.

Somatostatin receptor scintigraphy (SRS) uses the affinity of the radioactive–labeled somatostatin analogues to G-protein–coupled glycoproteins, which are expressed in 70% to 90% of carcinoid tumors and 50% to 80% of endocrine pancreatic tumors. SRS is the most sensitive modality for the identification of hepatic metastases for all GEP-NETs (and not only SRS-positive tumors) (81%–96% compared with 50%–90% for angiography, 55%–70% for MRI, 32%–34% for CT, and 10%–11% for ultrasound).TABLE 5. Tissue Markers Used in the Diagnosis and Prognosis of GEP-NETs

| ROLE | USE | SENSITIVITY |
|------|-----|-------------|
| Chromogranin, synaptophysin, neuron-specific enolase | Histopathological identification and classification | Identification of neuroendocrine neoplasia | High |
| Ki-67 antigen | Proliferation index | Assessment of rate of cell proliferation | High |
| Protein families of transforming growth factor-α, transforming growth factor-β, vascular endothelial growth factor, and epidermal growth factor | Growth factors and regulators of proliferation | Assessment of regulatory mechanisms and potential targets of novel therapeutic agents | Intermediate |
| Receptors for somatostatin (subtypes 1-5), cholecystokinin, vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide, tachykinins, serotonin, and dopamine | Hormone receptors | Assessment of receptor-specific treatment for somatostatin, assessment of therapeutic effectiveness with somatostatin analogues (cold or radioisotope labeled) | Somatostatin receptors: high; Serotonin receptors: intermediate; Others: low to unproven |
| AF-10, insulin-like growth factor binding protein 3, p21 (cyclin-dependent kinase inhibitor 1), p27, CD99 antigen, transcription factor jun-D | Oncoproteins or cell cycle control proteins | Indicators of proliferation and potential for aggressive behavior and metastasis | Low to unproven |
| Neural cell adhesion molecule 1, CDX2, transcription termination factor 1, synaptic vesicle glycoprotein | Regulators of cell function | Identification of neuroendocrine differentiation and potential for aggressive behavior | Low to unproven |

GEP-NETs indicates gastroenteropancreatic neuroendocrine tumors.

Reprinted from Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9:61-72 with permission from Elsevier.
and 14%-63% for ultrasonography). SRS has a sensitivity of 55% to 77% for noninsulinomas and 25% for insulinomas and a negative SRS is associated with worse prognosis. The worse prognosis for SRS-negative tumors may be due to the lack of antiproliferative effects of somatostatin analogue therapy, the delay in prognosis, or other as yet unexplained behavior. The combination of SRS with CT fusion improves anatomical localization while retaining functional information.

Positron emission tomography (PET)-CT scan imaging and single photon emission computed tomography-CT hybrid systems have been used in several malignancies with high uptake of 18F-fluorodeoxyglucose but are not useful for NETs except for the aggressive tumors. Recent advances in PET imaging using 18F-levodopa for carcinoid tumors and carbon-11(11C) tryptophan for recurrences and visually occult tumors provide complimentary diagnostic information to other imaging modalities. Advances in the use of gallium-68 labelled agents ([68Ga-DOTA]-D-Phe(1)-Tyr(3)-octreotide) to identify metastatic NETs, while allowing for the performance of scans one hour after injection, has been particularly exciting given the lack of need of an in-house cyclotron. This technology also holds promise for the possible detection of primary tumors.

Aggressive use of enteroclysis, video endoscopy, EUS, and double-balloon enteroscopy for detection of primary tumors is currently investigational but holds significant promise. A summary of currently available diagnostic techniques is provided in Figure 4.

Advances in Treatment

The treatment of GEP-NETs encompasses the diverse fields of surgery, interventional radiology, radiation oncology, and medical oncology and requires close collaboration between all specialists to tailor therapy specific to the patient.

Surgery

Surgery has been the focus of therapy for GEP-NETs and includes curative, cytoreductive, and palliative surgical approaches for these tumors. It remains the primary modality of cure in those with limited disease. The role of cytoreductive surgery has been studied previously by our group and others, and has been shown to improve survival and palliation of disease, although it needs to be studied in a prospective fashion. Palliative surgery can obviate bowel and other organ (ureter) obstruction from fibrosis and relieve intestinal ischemia, helping with symptom control.

The role of curative surgery in metastatic disease is usually beneficial when margin-negative resection (for both primary and metastatic tumors) is achieved. Benefits in survival (overall and progression-free survival) have been noted from cytoreduction alone but not all studies report the same benefits. Almost 80% of patients with GEP-NETs have lymph node and hepatic metastases and it is usually difficult to identify these metastases, even with intraoperative radionuclide detection with prior SRS scanning.

Tumor-Specific Surgery

The role of surgery is greater than conventional modalities in patients with insulinomas, of whom 85% to 95% are cured with surgery. The use of sophisticated intraoperative tools such as IOUS facilitates intraoperative exploration.

In patients with gastrinomas, only 45% to 65% remain disease free after surgery and 35% remain so at 5 years. The role of preoperative EUS has contributed to the improved identification of these tumors (and pancreatic NETs) preoperatively, although the percentage of gastrinomas found by duodenotomies alone was almost 26%.
In patients with functioning pancreatic tumors such as insulinomas, regional localization techniques such as arterial stimulation with calcium and hepatic venous sampling are less frequently used given the use of IOUS, which is 95% accurate in detecting insulinomas.46,47

The use of radiation detectors to detect micrometastasis with the use of radiolabeled somatostatin receptor antibodies or other tumor-specific molecules holds promise yet is currently in the early stages of development.68 The use of nanoparticles for ablation of metastasis has also been studied but has not been implemented for NETs.69

**Resection of Metastatic Disease**

Simultaneous resection of primary and metastatic disease can be performed safely in a select group of patients, with a 5-year actuarial survival rate of 73%.58 Occasionally intraoperative RFA can be used in conjunction with resection of the primary tumor with an almost 90% lesion control rate.70,71

The majority of resections of metastatic disease are performed for GEP-NETs with liver metastasis, which can occur in 50% to 75% of small bowel NETs, 5% to 70% of foregut NETs, 14% of hindgut NETs, and 30% to 85% of PNETs.20 The survival varies from 40% to 83% at 5 years, with a relatively low operative mortality (0%-5.3%).72 However, in studies with longer follow up, it is clear that most patients develop disease recurrence, with a recurrence rate of almost 94% at 10 years.58 Nevertheless, the reported survival rates after surgical resection of metastases remain higher than those reported for medical therapy alone, but the data are not conclusive.58 Surgery does offer palliation of symptomatic disease and is recommended for patients with poorly controlled symptoms with resectable/debulking disease.73

**Neoadjuvant Therapy**

Trials of cytotoxic chemotherapy have shown response rates of 39% to 69%, and this approach is often employed in a neoadjuvant fashion to achieve resectability of metastatic tumors. The role of peptide receptor radiotherapy with yttrium-90(90Y)–DOTA-TOC has been reported in isolated case reports with impressive responses.74 Currently, data suggest a possible benefit of aggressive surgical debulking, and to this end, chemotherapy agents such as temozolomide, capecitabine, and tyrosine kinase inhibitors in combination with other agents are used to convert previously unresectable patients to surgical candidates.58

**Liver Transplantation**

The role of liver transplantation in GEP-NETs remains controversial and to date approximately 150 patients with metastatic liver NETs have received such a transplant. The only current indication is unresectable tumors or for symptom palliation. The 5-year survival rate varies from 36% to 47%,75 although isolated series have reported a 5-year survival rate of almost 83%.76 The use of Milan criteria (which includes a single tumor 5 cm or less in diameter, 3 or fewer tumors <3 cm each, no extrahepatic extension, and no macrovascular invasion) for the selection of patients has been proposed yet has not been studied prospectively.77

**Interventional Therapeutics**

**Hepatic Artery Embolization**

The rationale for hepatic artery embolization is based on the observation that these hypervascular tumors derive the majority of their blood supply from the hepatic artery.78,79 Typically, each lobe of the liver is embolized selectively. Thus, the entire liver can be treated in 2 to 3 stages, depending on the extent of disease. Chemotherapeutic agents are often added to the embolic material (doxorubicin, streptozocin); however, it is still uncertain whether the addition of chemotherapy improves outcomes.

The technique of an embolization involves performing a diagnostic celiac angiogram to identify the hepatic vasculature, the patency of the portal vein, and the number and location of hepatic metastases (Fig. 5 Top). The presence of portal vein occlusion and ascites are considered relative contraindications for the procedure.

Various particulate materials, including 250- to 355-μm polyvinyl alcohol (Contour particles; Boston Scientific-Target Vascular, Boston, Mass) and 500- to 700-μm microspheres (Embosphere microsphere; BioSphere Medical, Inc, Rockland, Mass) have been used. For chemoembolization, an emulsion of a cytotoxic drug such as doxorubicin (50 mg/m²) or streptozocin (1.5 g/m²) is used until complete stasis
Symptomatic responses occur as a result of reduction in hepatic tumor burden as well as a decrease in hormonal output in functional tumors. For example, major decreases in 5-HIAA levels (>50% reduction) occur in 51% to 91% of patients with carcinoid syndrome.

Objective tumor responses have been noted in 33% to 80% of patients with advances being made over the last decade (Table 6). This is a heterogeneous rate due to variation in the type of tumors, the choice of cytotoxic agent, and the concomitant use of somatostatin analogues. The extent of liver involvement has been proposed to be predictive of tumor response. Limitations in future randomized trials include the heterogeneity of disease, prior therapies provided, and lack of strong collaborations between high-volume centers.

**Hepatic Artery Radioembolization**

Radioembolization using 90Y as a source of beta energy is currently approved in the United States for the treatment of hepatocellular carcinoma (Therasphere; Theragenics Corporation, Buford, Ga) and colorectal cancer (SIR-Spheres; Sirtex Medical, Inc, Lake Forest, Ill). The goal of radioembolization is to cause tumor necrosis through radiation exposure. Cell death by radiation requires normal oxygen tension. Therefore, stasis of flow is avoided during radioembolization. Infusion of radioembolic agent is typically performed to both lobes rather than staged using a unilobar approach.

In a retrospective multi-institution study, radioembolization demonstrated complete imaging response in 2.7% of patients, a partial response in 60.5% of patients, stable disease in 22.7% of patients, progression of disease in 4.9% of patients, and a median survival of 70 months. The post-embolization syndrome is suggested to be much less than that noted with traditional chemoembolization (18%), which may be due to limited macroscopic arterial embolization and hence, limited tissue ischemia.

**Cryoablation**

Cryoablation involves freezing and thawing of tumors, resulting in tumor ablation. The drawbacks include the large size of the probe leading to increased risk of hemorrhage and higher rates of complications than RFA for larger metastases. More recently, smaller gauge cryoprobes for percutaneous ablation with the ability to place multiple probes
simultaneously have been introduced (PerCryo; Endocare Inc, Austin, Tex).

**Laser Interstitial Thermotherapy**

The use of a neodymium-doped yttrium aluminium garnet (Nd-YAG) laser to create coagulative necrosis has been proposed for the management of hepatic metastasis from NETs. The advantage of the laser application system is that it can be done under MRI guidance; this is of great value because the efficacy of the therapy can be evaluated simultaneously under MRI. Nevertheless, outcomes from this therapy are still being investigated.

**Radiofrequency Ablation**

Complete or significant symptom response has been demonstrated in 69% to 80% of patients treated with RFA and local control was achieved in 74% of the symptomatic patients. Complications from RFA are usually restricted to complications from the site of needle entry such as pneumothorax and neuritis, in addition to liver abscesses. The use of large umbrella RFA probes may increase tumor cell destruction for larger tumors and the combination of RFA with other intratumoral agents including alcohol may increase the antitumor potential of this technique.

**Medical Therapy**

The role of medical therapy is paramount in symptom control and in the suppression of tumor growth and spread.

**Somatostatin and Analogues**

Somatostatin is a 14-amino acid peptide that inhibits the secretion of a broad range of hormones and has been used for symptom control in NETs since the early 1980s and remains the mainstay of symptomatic control of GEP-NETs. In earlier studies, subcutaneous injection of 150 μg of somatostatin 3 times a day improved the symptoms of 88% of patients, but this has since been replaced with long-acting octreotide (10 mg, 20 mg, or 30 mg) or lanreotide autogel (60 mg, 90 mg, or 120 mg). The patient is initially started on 20 mg of long-acting octreotide administered intramuscularly after sensitivity testing with the subcutaneous formulation and the dosage is adjusted according to symptomatology. Lanreotide SR (sustained release) is also equally efficacious, and has been shown to be as effective as octreotide in a randomized study of 33 patients.

Somatostatin analogs (octreotide, lanreotide, and vapreotide) are believed to have direct and indirect tumor effects in addition to symptom control. Direct

| STUDY            | TUMOR HISTOLOGY | THERAPY | CR+PR, % |
|------------------|-----------------|---------|----------|
| Dominguez 2000   | Carcinoid       | TACE    | 50 (4 of 8) |
| Roche 2003       | Carcinoid       | TACE    | 43 (6 of 14) |
| Gupta 2003       | Carcinoid       | TACE    | 44 (12 of 27) |
| Desai 2001       | Carcinoid/ICC   | TACE    | 53 (18 of 34) |
| Kress 2003       | Carcinoid/ICC   | TACE    | 8 (2 of 26) |
| Fiorentini 2004  | Carcinoid/ICC   | TACE    | 70 (7 of 10) |
| Marrache 2007    | Carcinoid/ICC   | TACE    | 37 (14 of 38) |
| Artinyan 2008    | Carcinoid/ICC   | TACE    | 22 (6 of 27) |
| Dominguez 2000   | ICC             | TACE    | 57 (4 of 7) |
| Gupta 2003       | ICC             | TACE    | 50 (11 of 22) |
| Loewe 2003       | Carcinoid       | TAE     | 73 (16 of 22) |
| Gupta 2003       | Carcinoid       | TAE     | 81 (34 of 42) |
| Gupta 2003       | ICC             | TAE     | 28 (9 of 32) |
| Ho 2007          | Carcinoid/ICC   | TACE/TAE| 46 (15 of 33) |
| Ruddai nen 2007  | Carcinoid/ICC   | TACE/TAE| 49       |
| Christante 2008  | Carcinoid/ICC   | TACE+chemoinfusion | 81 (62 of 77) |
| McStay 2005      | Carcinoid/ICC   | Y-90 radioembolization | 16 (3 of 19) |
| King 2008        | Carcinoid/ICC   | Y-90 radioembolization | 50 (17 of 34) |
| Kennedy 2008     | Carcinoid/ICC   | Y-90 radioembolization | 63 (93 of 148) |
| Murthy 2008      | Carcinoid/ICC   | Y-90 radioembolization | 13 (1 of 8) |

CR indicates complete response; PR, partial response; TACE: transarterial chemoembolization; ICC, islet cell tumors; TAE, transarterial (bland) embolization; Y-90, yttrium-90.

Adapted with permission from Kvols LK, Turaga KK, Strosberg J, Choi J. Role of interventional radiology in the treatment of patients with neuroendocrine metastases in the liver. J Natl Compr Canc Netw. 2009;7:765-772.
effects such as arrest of tumor growth and stimulation of apoptosis and indirect effects such as antiangiogenesis and immunomodulatory effects are postulated to be dependent somewhat on the receptor subtype present in the tumor and the relative percentage expressed by the tumor cell type.\textsuperscript{115} To stimulate the immunomodulatory effects, the combination therapy of lanreotide with interferon-\(\alpha\) was studied in a randomized controlled trial of 80 therapy naive patients, with a higher overall partial response noted (7\% in the combined arm vs 4\% with lanreotide vs 4\% with interferon-\(\alpha\)) but with a high rate of stable disease in each arm (18\%, 28\%, and 26\%, respectively).\textsuperscript{116} There are however data that suggest that the addition of interferon might increase median survival (51 months vs 35 months) with a lower risk of progressive disease reported in a separate trial.\textsuperscript{117}

The recently reported PROMID study used octreotide LAR (octreotide acetate suspension for injection) at a dose of 30 mg intramuscularly every month until tumor progression and found that the median time to progression, which was the study endpoint, was 15.6 months compared with 5.9 months (\(P < .001\)), especially in patients with a low hepatic tumor load and resected primary tumors. The study included only patients with inoperable metastatic NETs with well-differentiated tumor histology.\textsuperscript{118}

**Cytotoxic Chemotherapy**

Cytotoxic chemotherapy remains the first-line treatment of widely metastatic unresectable disease in patients with GEP-NETs. However, despite the early use of cytotoxic chemotherapy agents, the response rates have remained somewhat low (0\%-33\%).\textsuperscript{119,120} Single-agent therapy has shown response rates of 20\% to 30\% for fluorouracil (5-FU), streptozocin, or doxorubicin and subsequent Eastern Cooperative Oncology Group trials comparing combination 5-FU or cyclophosphamide with streptozocin, streptozocin with 5-FU versus doxorubicin alone, and 5-FU versus doxorubicin in combination with streptozocin showed no significant durable survival advantage.\textsuperscript{119}

A multidrug Southwest Oncology Group trial showed a slightly higher response with 5-FU, cyclophosphamide, doxorubicin, and streptozocin in combination (31\%) than previously reported, but this was not significant between the 2 arms.\textsuperscript{121} Dacarbazine has shown some promise as salvage therapy after previously failing chemotherapy agents with an 8\% response rate; the addition of 5-FU and epirubicin to this agent has resulted in response rates of almost 25\%.\textsuperscript{122}

Temozolomide and 5-FU/capecitabine in combination have yielded significantly higher response rates (70\%) in recently reported data, which is an improvement from earlier reports of response rates of 45\% with temozolomide combined with thalidomide.\textsuperscript{123-125}

**Peptide Receptor Radionuclide Therapy**

GEP-NETs overexpress somatostatin subtype 2 receptors, which are targets for this safe and effective therapy. SRS can identify the tumors that overexpress these receptors and these are then targeted with radionuclide therapy. Indium-111–labeled octreotide has not shown very promising results but the ability to couple\(^{90}\)Y (a high-energy beta emitter) and lutetium-177 (\(^{177}\)Lu) (a medium-energy beta emitter) with the high-affinity chelator DOTA has allowed the development of specific targeted therapies. \(^{177}\)Lu DOTATE has a favorable affinity profile to the subtype receptor 2, and data on efficacy analysis have been reported for 310 patients with a survival benefit of 40 months to 72 months from diagnosis. Complete and partial tumor responses occurred in 2\% and 28\%, respectively, of the tumors, with minor tumor responses in 16\%.\textsuperscript{126} Additional molecules such as edotreotide have been shown to be effective in tumors refractory to octreotide treatment when coupled with \(^{90}\)Y.\textsuperscript{127} Early phase 2 trials of \(^{90}\)Y-coupled peptide receptor radiotherapies showed 23\% response rates but long-term efficacy was hampered due to hematological and renal toxicity.\textsuperscript{128}

**Newer Targets for Therapy**

Traditional medical therapies have been somewhat limited in the therapy for GEP-NETs and this has stimulated research into newer targeted therapies. GEP-NETs are highly vascular tumors and express proangiogenic molecules such as vascular endothelial growth factor. In addition, the surface of GEP-NET cells presents several growth factor receptors and their downstream effectors, including receptor tyrosine kinases such as EGFR, the stem cell factor receptor c-Kit, insulin-like growth factor (IGF) 1 receptor, phosphoinositide-3-kinase, RAC-\(\alpha\) serine/threonine protein kinase (AKT), mTOR, and the platelet-derived growth factor receptor. This lends
### TABLE 7. Molecular Targeted Mechanisms and Outcomes for Antineoplastic Drugs in the Treatment of GEP-NETs

| DRUG | MECHANISM | STUDY | OUTCOME | COMMENTS |
|------|-----------|-------|---------|----------|
| **Targeting Angiogenesis** | | | | |
| Bevacizumab | Humanized clonal antibody that blocks VEGF | PEG-IFN+BEV\textsuperscript{129} | PFS: 95% vs 68% | N = 44 |
| | | TEM+BEV\textsuperscript{125} | PR: 14% | N = 34 |
| | | Capecitabine-oxaliplatin+BEV\textsuperscript{130} | PR: 30% | N = 13 |
| | | FOLFOX6+BEV\textsuperscript{131} | PR: 30% | N = 13 |
| Sunitinib | Multitargeted tyrosine kinase inhibitor | Sunitinib\textsuperscript{132} | PR: 13.5% (PNET) | N = 109 |
| | | | PR: 5% (carcinoid) | |
| | | Sunitinib: phase 2 trial | — | Ongoing |
| | | Sunitinib+hepatic artery embolization: phase 2 trial | — | Closed to accrual |
| Sorafenib | Multitargeted anti-Raf kinase | Sorafenib\textsuperscript{133} | PR: 10% | N = 93 |
| | | | Side effects: 43% | |
| Valatanib | Inhibitor of VEGF tyrosine kinase | Valatanib\textsuperscript{134} | SD: 50% | N = 20 |
| | | | SD: 27% (at 12 mo) | |
| Thalidomide | Inhibition of TNF-\(\alpha\) | Thalidomide+TEM\textsuperscript{125} | CR: 25% | N = 29 |
| Endostatin | Inhibition of vascular endothelial cell migration and proliferation | Recombinant human endostatin: phase 2 trial\textsuperscript{135} | SD: 80% (no regression/cytotoxic effect) | N = 42 |
| **Tyrosine Kinase Receptor Inhibitors** | | | | |
| Her2-Neu inhibitors | Increased expression of Her2 in aggressive gastrinomas | No current trial | — | — |
| Gefitinib | Inhibitor of EGFR | Phase 2 trial for metastatic GEP-NETs with progressive disease\textsuperscript{136} | PR: 2.5% (carcinoid) | N = 96 |
| | | | PET: | |
| | | | SD: 32% (carcinoid); 14% PET at 4 mo | |
| Imatinib | Inhibitor of growth independently of c-kit expression, possibly other tyrosine kinases, or independent of the tyrosine kinase pathway | Phase 2 study; 800 mg/d\textsuperscript{137} | 0% response | N = 15 |
| | | | Phase 2 study\textsuperscript{138} | PR: 3.7% | N = 27 |
| | | | SD: 63% | |
| **Blocking mTOR** | | | | |
| Temsirolimus | Derivative of sirolimus, specific inhibitor of mTOR | Phase 2 study\textsuperscript{139} | PR: 4.8% (carcinoid) | N = 37 |
| | | | TEM, 25 mg iv every wk | PR: 6.7% (PET) |
| | | | | SD: 64% |
| Everolimus | Oral mTOR inhibitor, synergistic with octreotide | Phase 2 study\textsuperscript{140} | PR: 22% | N = 60 |
| | | | Everolimus, 5 mg/10 mg orally every d | SD: 72% |
| | | | Octreotide, 30 mg im every 28 d | PFS: 60 wk |
| | | | 69% patients with PD | |
| | | | Phase 2 study | PR: 7.8% and 4.4% | N = 160 |
| | | | Everolimus, 10 mg/d or everolimus +octreotide, 10 mg/d\textsuperscript{141} | PR+SD: 76.5%+82.2% | |

GEP-NETs indicates gastroenteropancreatic neuroendocrine tumors; VEGF, vascular endothelial growth factor; PEG-IFN, pegylated interferon; BEV, bevacizumab; PFS, progression-free survival; TEM, temozolomide; PR, partial response; SD, stable disease; FOLFOX6, leucovorin, fluorouracil, and oxaliplatin; PNET, primitive neuroectodermal tumor; TNF, tumor necrosis factor; CR, complete response; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; PET, positron emission tomography; mTOR, mammalian target of rapamycin; iv, intravenously; im, intramuscularly; PD, progressive disease.

Adapted from Capurso G, Fazio N, Festa S, Panzuto F, De Braud F, Delle Fave G. Molecular target therapy for gastroenteropancreatic endocrine tumours: biological rationale and clinical perspectives. *Crit Rev Oncol Hematol.* 2009;72:110-124 with permission from Elsevier.
itself to several therapeutic targets that are currently being investigated (Table 7).\textsuperscript{125,129-141}

There remain exciting possibilities in drug development for NETs with therapeutic realms ranging from IGF inhibitors, Src-kinase inhibition, cyclooxygenase-2 inhibitors, histone deacetylase inhibitors, nelfinavir (a protease inhibitor antiviral agent), and bortezomib (a reversible inhibitor of the 26S proteasome).\textsuperscript{142}

**Conclusions**

GEP-NETs are a fascinating group of tumors that have been studied for over a century with several markers helping identify subsets of tumors, yet much progress needs to be made to understand the pathological characteristics, including the classification systems. Diagnostic modalities including SRS with CT fusion imaging, EUS, and MRI have vastly improved the understanding of these tumors. The aggressive use of curative and cytoreductive surgery as well as interventional radiological techniques including embolization and ablation in conjunction with symptom control with somatostatin analogues is the frontline of treatment. For the vast majority of patients with unresectable metastatic disease, older chemotherapeutic agents have shown disappointing results, yet new regimens and new classes of drugs hold great promise.

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