Gastrointestinal Cancer: Targets and Therapy

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REVIEW

Neoplastic lesions of endocrine cells in the gastrointestinal tract: ten evolving principles as a basis for clinical understanding

This article was published in the following Dove Press journal:
Gastrointestinal Cancer: Targets and Therapy
27 December 2012

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Abstract: Timely and appropriate diagnosis and treatment of patients with gastroenteropancreatic neuroendocrine neoplasms is a difficult clinical endeavor. The field is particularly dynamic, not only in terms of expanding therapeutic options, but in the classifications and biological principles that underpin good decision-making. Acknowledging the confusion created by past changes and the inevitability of future development, we combine our clinical experience with a review of the literature to frame the current understanding of gastroenteropancreatic neuroendocrine neoplasms in terms of a set of principles that have stabilized in the midst of this change. Firstly, we present five principles that guide classification of neuroendocrine neoplasms; specifically principles of prognostic classification, mechanisms of tumorigenesis, undiagnosed disease burden, clues regarding genetic etiology, and typical clinical presentation. Secondly, we offer five clinical principles upon which to build a therapeutic strategy. Specifically, these treatment principles include the separation of options by tumor cell differentiation, and the site of the primary lesion in well differentiated tumors. Chromogranin A is a moderately useful biomarker. Treatment should only be considered by clinicians in a multidisciplinary team, and in the face of multiple potential therapeutic options without a supporting evidence base, clinical trial enrolment remains imperative. Therefore, we provide a current synopsis of classification of gastroenteropancreatic neuroendocrine neoplasms, and their etiology, clinical presentation, and management in a novel framework of ten relatively stable principles.
Keywords: gastroenteropancreatic neuroendocrine neoplasms, neuroendocrine tumors, epidemiology, molecular targeted therapy, histopathology, grading, staging, carcinoid, tumorigenesis

Introduction

Neuroendocrine neoplasms exhibit marked heterogeneity in terms of location and malignant potential.[1] Neuroendocrine neoplasms arise wherever neuroendocrine cells exist in epithelial linings, most commonly from the epithelium of the gastrointestinal tract or the pancreas, and are labeled gastroenteropancreatic neuroendocrine neoplasms.[2] The term neuroendocrine has been retained because the cells from which gastroenteropancreatic neuroendocrine neoplasms arise have a combined neural and endocrine phenotype; for example, enterochromaffin cells demonstrate neurite outgrowths extending from their base which interact with neural tissue in the gut, yet they also have an endocrine function and secrete measurable levels of serotonin.[3] Both neural and endocrine functions are required to perform their primary function, which is control of gut motility and digestion. Therefore, this epithet "neuroendocrine" has necessarily persisted.

Such difficulties in nomenclature have plagued the field, but even more confusion has arisen due to multiple classification systems, updates following the introduction of new terminology, and the recycling of old terminology into new classifications with new meanings.[4] In addition, the tumor is rare and heterogeneous in its course, making appropriate clinical exposure the exception for the majority.[5–8] Further, many different therapeutic interventions have been reported. Thus, the clinician is faced with a cancer that they might not be able to name, that they will seldom see, that will follow an unknown course, and that could be treated with various combinations of therapy from various medical and surgical specialties.

This paper applies a clinical perspective to recent developments in classification, epidemiology, molecular biology, and clinical trials to integrate clinical decision-making. We combine the themes that are emerging to define principles to guide any clinician faced with a new patient with a neuroendocrine neoplasm. Therefore, we introduce the definitions, etiology, clinical presentation, and current therapeutic strategies for non-neoplastic and neoplastic proliferative lesions of endocrine cells of the gastrointestinal tract in terms of a series of principles that might provide some stability in this constantly changing landscape.

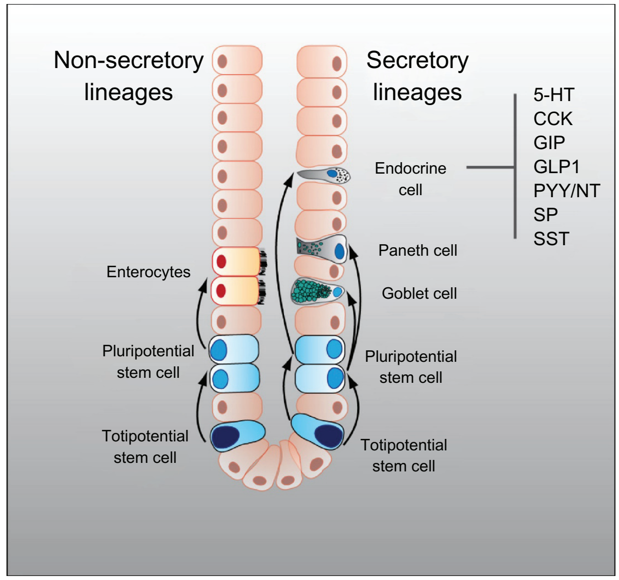

Figure 1 Proposed epithelial cell lineage showing a common precursor for secretory and nonsecretory cells.
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Multiple previous classification systems are now increasingly confluent and emphasize grade, differentiation, and stage

Totipotent stem cells in gastrointestinal crypts will differentiate into typical nonsecretory epithelial cells or several secretory phenotypes (see Figure 1). One class of secretory epithelial cells in the gastrointestinal lumen and pancreas are neuroendocrine cells. These neuroendocrine cells and their precursors give rise to a variety of malignancies currently labeled "neuroendocrine neoplasms".[2] It has been suggested that the poorly differentiated carcinomas derive from less mature precursors, and well differentiated tumors derive from more mature, committed neuroendocrine cells.[9] Perhaps, due to the existence of a common precursor, gastroenteropancreatic neuroendocrine neoplasms can occur associated with an adenocarcinoma in the same location, for example, in the pancreas.[10] Gastroenteropancreatic neuroendocrine neoplasms have proved difficult to classify clinicopathologically, leading to multiple classification schemes over the past several decades, creating diagnostic confusion amongst pathologists and clinicians (Table 1). The reader should note the shifts in principles of categorization; that these lesions were initially all considered benign[11] but are now all considered malignant,[2] that broad embryological groupings[12] have been replaced by organ-specific diagnoses[13] (and further subclassification in gastric neuroendocrine neoplasms[14]), the recent supplementation of differentiation by proliferative index (now the defining measure of "grade"),[15] and the recent validation of a TNM staging system[16] similar to other gastrointestinal malignancies. The current classification is now in accord with other cancers with classification by grade, differentiation, and stage.

The current prognostic classification of gastroenteropancreatic neuroendocrine neoplasms is most recently summarized in the World Health Organization recommendations.[2] Grade is synonymous with proliferation index. NET-G1 is a low-grade lesion with a Ki-67 $\leq$ 2% and/or a mitotic rate of $<$2 per 10 high-powered fields. NET-G2 is an intermediate-grade lesion with a Ki-67 of 3%–20% and a mitotic count of 2–10 mitoses per 10 high-powered field. NET-G1 and NET-G2 are well differentiated, whereas neuroendocrine carcinoma lesions are poorly differentiated and have a Ki-67 $>$ 20% and/or a mitotic count $>$ 10 per 10 high-powered fields. These criteria are nearly identical in the most recent European Neuroendocrine Tumor Society[2] and North American Neuroendocrine Tumor Society recommendations.[17] It should be noted that these definition cut points are arbitrary and that tumors within these groups may have differing behaviors. Furthermore, assessment of Ki-67 is complicated by intratumoral heterogeneity and

Table 1 Changes in gastrointestinal and pancreatic neuroendocrine tumor classification systems over the past century

Classification system					
Oberndorfer et al[11]	"Karzinoide": cancer-like tumors of the ileum: malignant potential disputed				
Williams et al[12] Based on: embryological origin, histochemistry, secretory products	Foregut Argentaffin- Chromogranin A+ Neuron-specific enolase+ Secretory product	Midgut Argentaffin+ Chromogranin A+ Neuron-specific enolase+ Secretory product	Hindgut Argentaffin- Chromogranin A+ Neuron-specific enolase+ Secretory product		
World Health Organization[20]	Carcinoid	Mucocarcinoid	Mixed forms carcinoid-adenocarcinoma	Pseudotumor lesions	
World Health Organization[13]	Well-differentiated neuroendocrine tumor (benign behavior)	Well-differentiated neuroendocrine carcinoma (low-grade malignant behavior)	Poorly differentiated endocrine carcinoma/small cell carcinoma (high-grade malignant behavior)	Mixed exocrine Endocrine carcinoma	Tumor-like lesion
ENETS[16,18] TNM stage and grade	Site-specific TNM staging Grade 1: Ki67: ≤2 Mitotic count per 10 hpf < 2	Site-specific TNM staging Grade 2: Ki67: 3–20 Mitotic count per 10 hpf 2–20	Site-specific TNM staging Grade 3: Ki67: >20 Mitotic count per 10 hpf > 20		
World Health Organization[2] Focus on cell proliferation markers	Neuroendocrine tumor grade 1 Ki-67 ≤ 2%, ± mitotic count of <2 per 10 hpf	Neuroendocrine tumor grade 2 Ki-67 3%–20%, mitotic count 2–10 per 10 hpf	Neuroendocrine carcinoma grade 3 Ki-67 > 20%, mitotic count > 10 per 10 hpf: large cells and small cells	Mixed adenoneuroendocrine carcinoma	Hyperplastic and preneoplastic lesions

Abbreviations: ENETS, European Neuroendocrine Tumor Society; hpf, high-powered fields.

subject to pathologist-dependent variability. TNM staging has been suggested,[16,18] and undergone initial validation such that the T staging (by size and degree of luminal wall invasion), N staging (by the presence or absence of lymph node involvement), and M staging (based on the presence of distant metastases) appear to contribute to prognostication on initial inspection.[19,20] In keeping with other tumor types, high-grade and metastatic lesions have a worse prognosis; however, there is marked variability within primary tumor sites.[21]

Tumorigenesis by malignant progression from hyperplasia, to dysplasia, to neoplasia occurs in a portion of foregut lesions, but the majority lack etiological explanation

Preneoplastic states have been formally acknowledged in the recent World Health Organization classification[2] (see Table 1). Specifically, the transition from hyperplasia to dysplasia to neoplasia is described in gastric neuroendocrine neoplasms (type 1 and 2), duodenal neuroendocrine neoplasms, and pancreatic neuroendocrine neoplasms,[22] but is rare in the remainder of the gut.[23] This observation is important because it allows a guess at etiology, which is only well defined in the stomach[24] (Figure 2). Type I tumors occur in the presence of achlorhydria (eg, due to atrophic gastritis) which results in compensatory elevation in gastrin which drives enterochromaffin-like cell hyperplasia, dysplasia, and ultimately neoplasia. Type 2 lesions occur in the presence of an elevated gastrin concentration secondary to secretion by a gastrinoma, often causing Zollinger-Ellison syndrome, and occurring in the setting of multiple endocrine neoplasia type 1. Type 3 lesions occur in the absence of a gastrin drive and, as for the majority of gastroenteropancreatic neuroendocrine neoplasms, the cause remains unknown.[25] The appearance and prognosis of each type is distinct and ranges from typically small and multifocal type 1 gastric neuroendocrine neoplasms with excellent prognosis, through to single large type 3 lesions which follow an aggressive course. Therefore, this model of neuroendocrine neoplasm etiology suggests that other well differentiated gastroenteropancreatic neuroendocrine neoplasms with low proliferative indices where the progression from hyperplasia to dysplasia is observed (thus akin to type 1 and 2 lesions) might also undergo malignant transformation due to the presence of an endogenous growth factor. However, to date, this progression has only been observed in sites of active inflammatory bowel

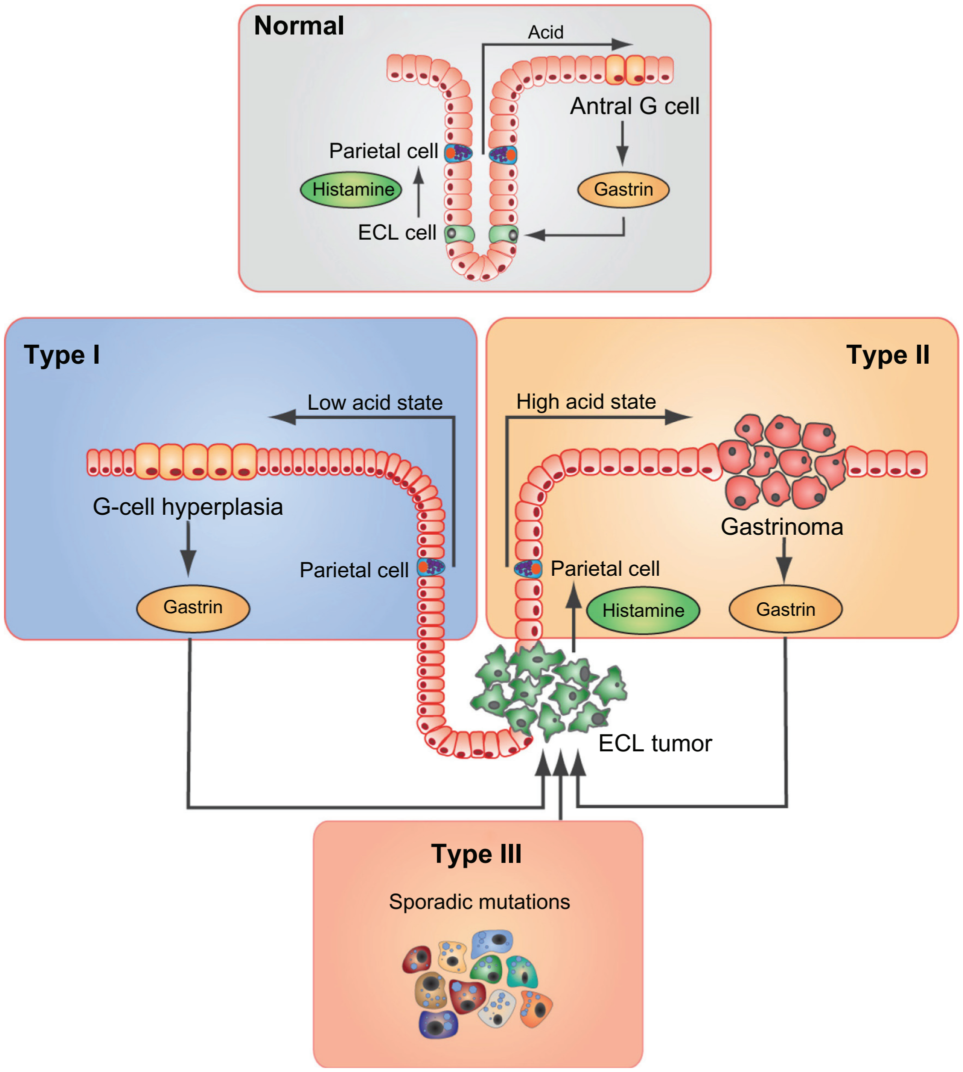

Figure 2 Tumorigenesis in gastric neuroendocrine neoplasms.

Notes: In the normal setting, G cells secrete gastrin which drives production of histamine by enterochromaffin cells, which in turn encourages secretion of acid by parietal cells. In type 1 gastric neuroendocrine tumors, the parietal cells fail to produce acid, resulting in compensatory G cell secretion of gastrin, which drives enterochromaffin cell transition from hyperplasia to dysplasia to neoplasia. Despite this positive feedback loop, the low acid state persists due to pre-existing parietal cell atrophy. In type 2 gastric neuroendocrine tumors, gastrin secretion is autonomous due to gastrin secretion from a gastrinoma. In type 3 gastric neuroendocrine tumors, the cause of malignant transformation is unknown.

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disease in the small intestine and colon, although the driver of tumorigenesis in this setting has not been elucidated.

Majority of lesions are never diagnosed during life and do not contribute to mortality

It is useful to conceive neuroendocrine neoplasms as common tumors, but not tumors that are commonly diagnosed during life. Autopsy studies suggest that approximately 1% of people will have a detectable gastroenteropancreatic neuroendocrine tumor at the time of death, although this is seldom the cause of death. A large series (n = 16,294) in Malmo, Sweden,[26] showed that 1.11% of patients who underwent autopsy had a gastroenteropancreatic neuroendocrine neoplasm, and a similar study in Hong Kong[27] found that 0.1% of patients had a pancreatic neuroendocrine neoplasm. These two figures are complementary because pancreatic neuroendocrine tumors make up approximately 10% of all gastroenteropancreatic neuroendocrine neoplasms in registry data, such as in the Surveillance, Epidemiology and End Results database.[28] These autopsy results indicate a prevalence of approximately 1110 per 100,000 persons, which is considerably more than the prevalence calculated from the registry data (35 per 100,000).[29] This suggests that approximately 3%

of gastroenteropancreatic neuroendocrine neoplasms that are present are actually detected during life, and that the vast majority of gastroenteropancreatic neuroendocrine neoplasms are not directly associated with the death of the person in whom they occur.

This information needs to be borne in mind when considering recent changes in incidence and prevalence. The incidence of neuroendocrine neoplasms is increasing significantly,[28] and is now 3.65 per 100,000 persons. The increases over the past decade are statistically significant, but given the large quantity of undiagnosed disease, a small change in diagnostic acuity is likely to see a large proportional change in diagnostic frequency. Thus, improvements or increased use of diagnostic techniques (colonoscopy, gastroscopy, high-resolution computed tomography imaging) and increased physician awareness probably combine to cause the increased diagnosis.

The extent of undiagnosed disease is also important to consider when seeing a patient with an incidentally diagnosed tumor. A high proportion of incidentally diagnosed tumors might well not impact on survival, making initial observation a reasonable strategy in small, localized, low-grade, well differentiated lesions, especially in older patients.

Finally, the extent of undiagnosed disease and increasing incidence needs to be considered when interpreting survival in tumor registries and institutional series. Epidemiological analysis of survival has noted improvement over the last 20 years. This detection of early cases, or more importantly, cases that will not impact on survival, will cause a lead-time bias where any apparent improvement is in fact due to the relative downstaging related to earlier diagnosis.

Familial syndromes and newly identified sporadic mutations demonstrate genetic alterations in overlapping pathways

The etiology of gastroenteropancreatic neuroendocrine neoplasms is poorly understood, but this appears to be changing, particularly with advances in molecular analyses. Current examinations of the familial syndromes predisposing to gastroenteropancreatic neuroendocrine neoplasms, recently identified sporadic mutations, and epidemiological studies are all beginning to provide compelling evidence of the molecular alterations that occur in this disease.

While most cases (>95%) are sporadic,[30] several familial syndromes are associated with these relatively rare tumors. These include multiple endocrine neoplasia 1, type 1 neurofibromatosis, tuberous sclerosis, von Hippel-Lindau syndrome, and others (Table 2). These syndromes are characterized by loss of function of a tumor suppressor, such as multiple endocrine neoplasia 1 (chromosome 11q13) in the syndrome of the same name,[31] whose gene product, menin, is thought to interact with histone methyltransferase enzymes required for the epigenetic regulation of transcription.[32] Mutations of this gene are also present in a number of sporadic cases.[33] In von Hippel Lindau syndrome, the affected gene is *vHL* (chromosome 3p25.5)[34] which has an important role in angiogenesis, and its encoded protein is involved in the degradation of hypoxia-inducible factor.[35] Loss of *vHL* results in activation of hypoxia-inducible factor and accumulation of proangiogenic growth factors. Other examples are outlined in Table 2. The gene pathways implicated in these disorders (eg, histone modification, angiogenesis) may represent pathways which are crucial for tumorigenesis in gastroenteropancreatic neuroendocrine neoplasms.

The majority of gastroenteropancreatic neuroendocrine neoplasms do not occur within a familial syndrome, and are considered sporadic.[30] The location of gene mutations in a proportion (about 50%) of these cases has been recently described, and there is some similarity with the familial syndromes. Exome sequencing of ten (nonfamilial) pancreatic neuroendocrine tumors followed by sequence analysis of 58 further pancreatic neuroendocrine neoplasms showed that the most common mutations occurred in mediators of histone organization and chromatin remodeling (multiple endocrine neoplasia 1 44%, DAXX or ATRX 43%) and oncogenic driver pathways such as mammalian target of rapamycin (mTOR, 15%).[36] The mTOR pathway has previously been recognized as important in studies of gene expression in pancreatic neuroendocrine tumors.[37,38] Therefore, it is possible that histone organization and epigenetic changes may be a particularly fruitful area for translational research and therapeutic targeting in the future, although a challenge lies in the recognition that the gene products often have more than one role (eg, DAXX and ATRX also regulate telomeres[39]) making it more difficult to determine which function should be inhibited to prevent tumor growth. Furthermore, expression of genes involved in histone organization are not altered in poorly differentiated neuroendocrine neoplasms,[40] instead typical changes include inactivating p53 and Rb mutations,[41] accompanied by overexpression of Bcl2 (large and small cell neuroendocrine carcinomas were similar in this regard).[40]

Information regarding a genetic predisposition to gastroenteropancreatic neuroendocrine neoplasms from direct gene sequencing and characterization can be supplemented

Table 2 Familial syndromes associated with gastroenteropancreatic neuroendocrine neoplasms

Familial syndrome	Gene	Protein	Pattern of disease
Multiple endocrine neoplasia type 1	*MEN1*	Menin: involved in histone organization of gene transcription	Hyperparathyroidism Pancreatic NENs Pituitary tumors
Multiple endocrine neoplasia type 2	*RET*	RET: tyrosine kinase involved in signal transduction, mutation results in overactivity	Hyperparathyroidism NENs including medullary thyroid cancer and pheochromocytomas
Neurofibromatosis type 1	*NF-1*	Neurofibromin: Ras GTPAse activating protein, regulates TSC2 and hence mTOR pathway	Neurofibromas GEP-NENs (usually duodenal) Pheochromocytomas Glioblastomas Myeloid leukemias
Tuberous sclerosis	*TSC-1+2*	Hamartin and tuberin: inhibitors of mTOR pathway, loss leads to constitutional activation of mTOR	Benign hamartomas Pancreatic NENs
Von Hippel Lindau syndrome	*vHL*	vHL: regulation of HIF, loss leads to accumulation of angiogenic factors	Renal cell carcinomas Hemangioblastomas Pancreatic NENs, pheochromocytomas
Carney complex	*CNC1/PRKAR1A* *CNC2*	Regulatory subunit of cAMP dependent protein kinase A Unknown	Testicular tumors Follicular and papillary thyroid cancers Cardiac myxomas Adrenocortical carcinoma Pancreatic NENs
Cowden syndrome	*PTEN*	PTEN: phosphatase enzyme inhibits Akt signal pathway	Benign mucocutaneous lesions Breast, endometrial and renal cancers, plus a variety of other cancers, including pancreatic NENs

Note: Data from Lindor et al.[30]
Abbreviations: GEP, gastroenteropancreatic; NENs, neuroendocrine neoplasms; mTOR, mammalian target of rapamycin; HIF, hypoxia-inducible factor.

by examining population migration patterns that contribute to epidemiological databases. In the US Surveillance, Epidemiology and End Results registry data, small intestinal neuroendocrine neoplasms are the most common, and similar in incidence to rectal neuroendocrine neoplasms.[28] Other countries with predominantly European populations show a similar pattern (eg, Norway).[42] A striking finding when examining registry data from Europe compared with data from Asia is the different profile of primary tumor sites seen in each population. Asian countries have a higher proportion of rectal primaries, whereas European countries have a higher proportion of small intestinal primaries.[29,43–47] Interestingly, examination of people of Asian and European descent within the US, from one to six generations after population migration, shows that these patterns persist despite the changes in diet and environment that necessarily occur in the US. Asian Americans have higher rates of rectal tumors and European Americans have higher rates of small intestinal tumors (Figure 3). This observation should be interpreted cautiously, because population level data are not ideal for etiological studies, but perhaps shows unexpected stability after migration, suggesting that a component of the predisposition to neuroendocrine neoplasms is, in part, inherent in the germ line. However, using these data, it is not possible to assess persisting culturally specific dietary and cultural practices. Neuroendocrine cells are intimately involved in sensing the luminal environment, and might be expected to be exquisitely sensitive to dietary carcinogens.

The current paradigm of malignant transformation requires cancers to accumulate several mutations/genomic hallmark events,[48] but recent examples of neoplasms driven by single genetic events (eg, chronic myelogenous leukemia, gastrointestinal stromal tumors, granulosa cell tumors[49–51]) suggests that, for some tumors, particularly those with a more indolent clinical course, a single or small number of events might be sufficient to act as a key driver or malignant switch. Potentially, there is some hope that the number of genetic events facilitating neuroendocrine neoplastic transformation might be low, and therefore targetable by a realistic number of antitumor therapies. This will be discussed further in subsequent sections.

Most lesions do not present with hormonal syndromes

Patients present for four common reasons, ie, symptoms related to hormone secretion (functional), an incidental finding of a tumor on a diagnostic test (nonfunctional), symptoms

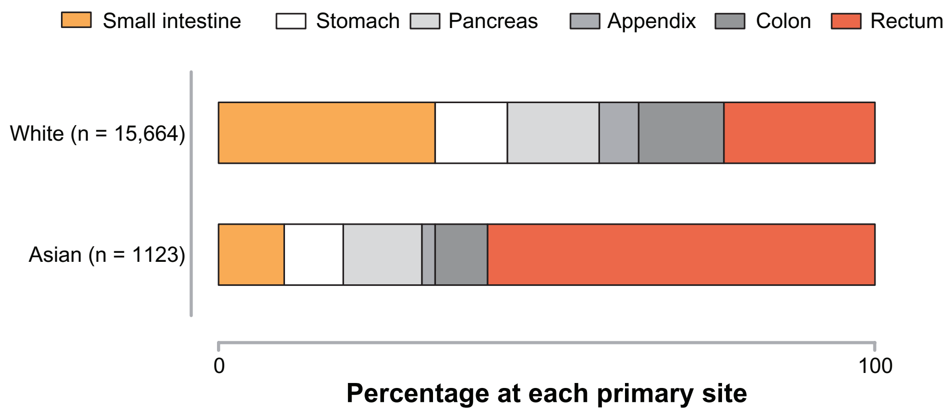

Figure 3 Differences in primary site distribution in Americans of different race and ethnicity SEER 17 2000–2008 (using SEER search terms).
Notes: White Americans have a high proportion of small intestinal tumors and Asian Americans have a high proportion of rectal tumors (Modlin, unpublished data, 2012).
Abbreviation: SEER, Surveillance, Epidemiology and End Results.

of advanced malignancy that cause systemic symptoms, such as cachexia, malaise, and jaundice (nonfunctional), or cause local symptoms, such as pain or biliary obstruction (also nonfunctional).

Approximately one-third of neuroendocrine neoplasms produce functional syndromes, but this depends on the series, the site-specific expertise of the referral center, and patterns of referral.[21,47,52] The most commonly recognized syndrome is the diarrhea, flushing, and bronchospasm of classic carcinoid syndrome, produced by tumors which secrete serotonin from enterochromaffin cells (eg, small intestinal neuroendocrine neoplasms). It is important to realize that small intestinal tumors often create a local desmoplastic stroma that precipitates luminal obstruction; however, these are not included in most definitions of functioning tumors, despite the obvious clinical corollary. It is also important to note that biochemically measurable secretion of a secretory product does not equate to a functioning tumor unless symptoms are present. This confusion has led to varying estimates of the incidence of carcinoid syndrome. A number of other functional syndromes are recognized (Table 3), including an "atypical" carcinoid syndrome due to histamine secretion by enterochromaffin-like cell tumors (gastric neuroendocrine neoplasms) which, although very rare, has a subtly different phenotype with a more pronounced urticarial rash.

There is debate over whether symptoms of hormone secretion are prognostic. Several factors would encourage a more positive survival outcome. Functional syndromes can speed recognition of the presence of tumors that might otherwise go unnoticed and cause a lead-time bias compared with tumors that continue to grow while unrecognized. The fact that the secretory machinery of the cell is still intact implies at least some elements of a well differentiated tumor and an expected positive outcome relative to poorly differentiated carcinomas. On the contrary, the presence of a carcinoid syndrome usually indicates liver metastasis as the mechanism by which secreted peptide/amines escape the portal circulation and metabolism by the liver, and thus advanced disease might suggest a poorer prognosis. Complicating this maxim is the observation that the venous drainage of rectal tumors (and even retroperitoneal metastases) can bypass the portal circulation and thus achieve a hormonal syndrome in the absence of liver metastases.

Treatment strategy for poorly differentiated lesions is distinct from that in well differentiated lesions

The treatment algorithms for poorly differentiated neuroendocrine carcinomas and well differentiated neuroendocrine tumors (NET G1 and NET G2) are currently entirely separate. Poorly differentiated neuroendocrine carcinomas have a high proliferative index and metastasize early, with a clinical course akin to small cell lung cancer. Clinical series of poorly differentiated colorectal neuroendocrine neoplasms have reported 3-year survival rates of 13% and 15%,[53,54] and outcomes are similar in the foregut.[14] Surgery is still the standard of care for localized lesions in most centers, but this approach is controversial because even apparently localized lesions are often already metastatic despite negative staging scans. Thus, surgical excision aimed at cure tends to be reserved for small localized lesions where excess morbidity is not expected from the procedure itself. Therapy necessarily focuses on systemic treatment. A platinum drug and etoposide, borrowed from the small cell literature, is the most common treatment approach.[55,56] Many centers substitute carboplatin for cisplatin due to an improved side effect profile, although cisplatin and carboplatin have not been directly compared in

Table 3 Functional syndromes of gastroenteropancreatic neuroendocrine neoplasms[121–123]

Syndrome	Tumor location	Mediator	Symptoms
Carcinoid syndrome	Midgut 75%–87% Pancreas $<$ 1%	Serotonin, tachykinins, motilin, prostaglandins	Flushing, diarrhea, wheeze, cardiac fibrosis
Insulinoma	Pancreas $>$ 99%	Insulin	Hypoglycemia, weight gain
Zollinger-Ellison syndrome: gastrinoma	Duodenum 70% Pancreas 25% Others 5%	Gastrin	Peptic ulceration, abdominal pain, diarrhea
Verner Morrison syndrome: VIPoma	Pancreas $>$ 90% Other 10%	Vasoactive intestinal peptide	Secretory diarrhea, hypokalemia, achlorhydria
Glucagonoma	Pancreas 100%	Glucagon	Diabetes, weight loss, necrolytic migratory erythema, diarrhea, glossitis, angular stomatitis
Somatostatinoma (rare)	Pancreas 55% Small bowel 44%	Somatostatin	Diabetes, diarrhea, jaundice
ACTHoma (rare)	Pancreas	Adrenocorticotrophic hormone	Cushing's syndrome
GRFoma (rare)	Pancreas 30% Lung 54% Jejunum 7% Other 13%	Growth hormone releasing-hormone	Acromegaly
PTHrPoma (rare)	Pancreas	Parathyroid hormone-related peptide	Hypercalcemia

Abbreviations: GEP, gastroenteropancreatic; NEN, neuroendocrine neoplasm.

gastroenteropancreatic neuroendocrine neoplasms. Response rates are high in poorly differentiated tumors, in the order of 50%–80%, but relapse is almost always inevitable.[57,58]

However, recent changes in the use of systemic therapies may lead to overlap between therapies for well and poorly differentiated gastroenteropancreatic neuroendocrine neoplasms. Temozolomide, an alkylating agent,[59] and everolimus, an mTOR inhibitor,[60] have been used in well differentiated pancreatic neuroendocrine neoplasms, but are now also being used in neuroendocrine carcinomas. Some centers use the combination of peptide receptor radionuclide therapy preceded by carboplatin-etoposide to address lower-grade and higher-grade tumor components, respectively, in heterogeneous metastatic gastroenteropancreatic neuroendocrine neoplasms, though the experience of this anecdotal approach has yet to be published. Furthermore, there is clinical acknowledgement of high-grade gastroenteropancreatic neuroendocrine neoplasms (Ki-67 $>$ 20%) that remain well differentiated, and it is not clear whether to treat these as well or poorly differentiated carcinomas.

Therapeutic options for well differentiated tumors depend on primary site

Gastric neuroendocrine neoplasms

The primary therapy for type 1 gastric neuroendocrine neoplasms is repeated endoscopic mucosal resection.[61] Tumors less than 1 cm may be managed with surveillance and interval resection. Tumors greater than 1 cm require endoscopic ultrasound to assess nodal status, with nodal involvement being an indication for surgery. Local resection and antrectomy is commonly recommended for type 1 lesions larger than 1 cm, invasion of the muscularis propria, or positive margins following endoscopic mucosal resection.[61] The aim of antrectomy is to remove the site of gastrin production, given that chronic gastrin stimulation drives the malignant change. However, there is concern that gastrin production occurs outside the antrum in the majority of patients, so the role of antrectomy is now in question.[62]

Type 2 lesions are also managed by endoscopic mucosal resection and surveillance, but more extensive surgery is seldom indicated unless the source of gastrin production is also localized and can be resected. Similarly, antrectomy is contraindicated in type 2 lesions because the source of gastrin is typically a gastrinoma in the duodenum or pancreas. Type 3 lesions require surgical care in the same manner as a gastric adenocarcinoma.[63] Somatostatin analogs have been shown to reduce the frequency of recurrence of type 1 gastric neuroendocrine neoplasms;[64,65] however, due to the typically benign nature of the disease, their use is not recommended routinely in type 1 or 2 tumors unless a functional syndrome is present.[63] There is also some evidence that stopping this medication may be followed by a more aggressive relapse and so somatostatin analog therapy is not recommended at this time.[66]

Pancreatic neuroendocrine neoplasms

The treatment of pancreatic gastroenteropancreatic neuroendocrine neoplasms is complicated, and multidisciplinary input is essential. Localized tumors should be removed by surgery where feasible.[67] In the absence of metastases outside the liver, resection of unilobar hepatic metastases in a specialist center should be considered, and two-step resection or combination with radiofrequency ablation considered in complex metastatic involvement.[68] Pancreatic lesions with predominantly liver metastases not amenable to surgery can also undergo locally directed therapy such as selective internal radiotherapy, cryotherapy, radiofrequency ablation, and hepatic artery embolization with or without a chemotherapeutic agent. Although experience with these approaches is limited, palliation appears feasible.[69] All have shown radiological and symptomatic improvement, and are usually used for nonoperative situations or when a single large lesion is the cause of significant symptoms not controlled by other therapy.

Metastatic disease can be treated with somatostatin analogs or interferon to achieve symptomatic improvement in functioning tumors, but there is limited evidence of disease control with a pancreatic primary.[69–71] Somatostatin analogs are better tolerated than interferon, and combining the drugs can achieve more effective control of carcinoid syndrome.[72] Trials of somatostatin analogs have included a mixture of gastroenteropancreatic neuroendocrine neoplasm sites, have not included a placebo comparison, and have often not required proof of progressive disease prior to treatment. The results of these studies must therefore be interpreted with caution.[69]

Metastatic pancreatic neuroendocrine neoplasms are more responsive to traditional cytotoxic chemotherapy than other neuroendocrine neoplasms and can benefit from streptozotocin with 5-fluorouracil with or without doxorubicin.[73,74] Response rates to cytotoxic chemotherapy have been approximately 30%–40%, although some studies have included nonradiological criteria for response and also included some higher-grade lesions, possibly overestimating the benefit of these treatments. Early clinical trials with other 5-fluorouracil-based combinations, both in pretreated and treatment-naïve patients, have used oxaliplatin,[75] irinotecan,[76] and temozolomide,[77] and achieved responses in 30%, 5%, and 70%, respectively.

More recently, targeted agents including everolimus,[7] acting through the mTOR pathway and sunitinib,[6] a vascular endothelial growth inhibitor (among other targets), have been tested. Response rates to both therapies are very low (<9%) and the improvements in progression-free survival in both cases is from 5 months for untreated patients to 11 months with treatment, suggesting only modest benefit. Future research will look at how these agents can be combined, as well as with alternative treatment modalities. For example, combining temsirolimus, an mTOR inhibitor, and bevacizumab, a vascular endothelial growth inhibitor, has recently been demonstrated to be effective in an interim analysis of a Phase II trial, with a response rate of 52% by Response Evaluation Criteria In Solid Tumors (RECIST) criteria (n = 25).[78]

An additional consideration for the clinician is the choice of endpoints in the Phase III trials of everolimus and sunitinib. These targeted therapies were trialed with the primary endpoint of progression-free survival which has been criticized, although it is probably not feasible to run a randomized clinical trial with overall survival as an endpoint in these slow-growing tumors. Statistical modeling[79] suggests that the sample size of approximately 2500 patients would be needed to power a study that could detect a significant difference in overall survival using these therapies. Since it has been estimated that only approximately 5000 Americans have a pancreatic net, it is difficult to conceive how this trial could be run. Thus, for the foreseeable future, progression-free survival appears to be the endpoint that we must cautiously accept or tolerate. As an additional consideration, the current emphasis on RECIST criteria may be inadequate to capture clinically meaningful responses to treatment, and to assess potentially cytostatic rather than cytotoxic therapy. Alternatives, such as the Choi criteria, have been developed in soft tissue sarcomas and are beginning to be evaluated in gastroenteropancreatic neuroendocrine neoplasms[80,81] (NCT01525550).

Systemic treatment of advanced gastroenteropancreatic neuroendocrine neoplasms, irrespective of primary site, can also be undertaken with peptide receptor radionuclide therapy. Although used increasingly, there has been relatively little Phase II trial reporting to support this, and importantly peptide receptor radionuclide therapy is yet to be tested against other therapies in a randomized controlled trial. Phase II trials show response rates in the order of 30%, with the peak effect being seen somewhere between 3 and 9 months after therapy.[8,82] The safety of combining peptide receptor radionuclide therapy with the radiosensitizing agent 5-fluorouracil (or capecitabine) has been demonstrated and may achieve additional responses.[83,84] An indirect predictive biomarker for peptide receptor radionuclide therapy is a high level of tracer uptake on radiolabeled octreotide scintigraphy or positron emission tomography. Further attempts to improve on peptide receptor radionuclide therapy will include using combinations of radionuclides,[85,86] novel radionuclides (eg, bismuth), and tailored dosimetry.[87]

Small intestinal neuroendocrine neoplasms

The most significant recent advance is the recognition that cytotoxic chemotherapy, with response rates of zero to 15%,[88] has no role in well differentiated small intestinal neuroendocrine neoplasms.[89] Therefore, therapy in advanced disease should currently focus on surgical debulking, with a current preference for removal of the primary lesion due to the likelihood that the first symptoms will be from bowel obstruction and resection is better undertaken in the elective setting. Curative tumor resection is possible in up to 20% of patients with metastatic disease only in the liver,[90] although whether this correlates with improved survival is unclear and has not been tested in a prospective study. The treatment of liver metastases is the same as described in the previous section concerning pancreatic neuroendocrine neoplasms. There is also a role for peptide receptor radionuclide therapy in metastatic neuroendocrine neoplasms in the small intestine,[91] although as in other primary sites, prospective evaluation is awaited.

Somatostatin analogs are indicated for symptom control in functioning gastroenteropancreatic neuroendocrine neoplasms and may confer survival benefit. The PROMID study[5] has shown an improvement in progression-free survival extending to some patients with advanced midgut neuroendocrine neoplasms. This fits with anecdotal experience and with preclinical data suggesting an antitumor effect of somatostatin analogs.[92] However, the study was small (n = 85), took a long time to recruit (8 years), and there were some differences between the groups that might have favored the octreotide arm.[93] There is currently debate about how the results of this trial should influence practice. Pasireotide is a somatostatin analog with a broader range of activity at somatostatin receptors than octreotide and has been shown to achieve symptom control in some patients with octreotide-resistant functional syndromes in early phase research[94] as well as inhibit neuroendocrine cell lines in vitro.[95] This agent is currently in clinical trials comparing it with octreotide (NCT00690430) and in combination with everolimus (NCT00804336), although a recent trial in pituitary tumors raised concern regarding iatrogenic hyperglycemia.[96]

Molecular targeted therapies again offer an alternative approach, but have been less promising in small intestinal neuroendocrine neoplasms than in pancreatic neuroendocrine neoplasms. Bevacizumab has shown modest clinical activity,[97] while the antivascular endothelial growth tyrosine kinase inhibitors, sunitinib, sorafenib, and valatanib, have shown almost no responses.[98–100] Similarly, targeting epidermal growth factor with gefitinib has been ineffective.[101] Mixed results were documented after targeting the mTOR pathway. Temsirolimus has produced disappointing results, with a response rate of <5% and with excessive toxicity.[102] Conversely, everolimus showed more clinical activity in early phase trials,[97,103] but the recent Phase III RADIANT2 trial did not achieve statistically significant improvement in progression-free survival in patients with carcinoid syndrome,[104] and is to be repeated in patients with "non-functioning" tumors.

Appendiceal neuroendocrine neoplasms

The treatment of appendiceal neuroendocrine neoplasms is based on clinical series which have suggested that the size of the primary (>1 cm) and invasion of the mesoappendix (by >0.3 cm) are important prognostic variables.[105] Interpretation is made difficult by the often incidental discovery of these tumors at the time of appendectomy for acute appendicitis. However, a small proportion of these lesions do metastasize (about 10% of tumors 1–2 cm, about 40% of tumors > 2 cm) and right hemicolectomy should be considered for tumors with risk factors (>1 cm, mesoappendix invasion > 3 mm, location in base, angioinvasion). They tend not to be associated with symptoms of hormone secretion.[106]

Rectal neuroendocrine neoplasms

For the most part, rectal neuroendocrine neoplasms are small solitary lesions that can be removed endoscopically and do not require further treatment. However, in about 2% of cases, these lesions are metastatic and have a poor prognosis. Surgical resection as for rectal adenocarcinoma should therefore be undertaken for lesions > 2 cm or smaller lesions with muscularis invasion or regional metastases.[107] The primary should be resected in the presence of metastatic disease if there is potential for causing obstruction. Otherwise, metastatic rectal neuroendocrine neoplasms should be managed much as pancreatic lesions, although there is no evidence for this approach.[107]

The complexity of managing gastroenteropancreatic neuroendocrine neoplasms is reflected in the published trials, which are difficult to interpret due to heterogenous trial populations and differing outcome measures. The results of trials of systemic therapy for gastroenteropancreatic

Table 4 Clinical trials currently recruiting or opening soon for gastroenteropancreatic neuroendocrine neoplasms (**A**) and pancreatic neuroendocrine neoplasms (**B**) and registered at ClinicalTrials.gov

	Study	Status	Location
(A) Various gastroenteropancreatic neuroendocrine neoplasms			
Phase I			
NCT01263353	Safety and tolerability of pasireotide LAR in combination with everolimus in advanced metastatic NETs: COOPERATE-1	R	Germany, Novartis
NCT01204476	Cixutumumab, everolimus, and octreotide acetate in treating patients with advanced low-grade or intermediate-grade neuroendocrine cancer	R	MD Anderson Cancer Center, Texas
NCT01364415	Dose escalation study of pasireotide (SOM230) in patients with advanced neuroendocrine tumors (NETs)	R	US, Novartis
Phase II			
NCT00745381	A collection of clinical and epidemiologic data combined with tissue and blood from patients with a diagnosis of neuroendocrine tumors	R	Memorial Sloan-Kettering Cancer Center, New York
NCT01253161	Study of pasireotide long-acting release (LAR) in patients with metastatic neuroendocrine tumors (NETs)	R	H Lee Moffitt Cancer Center and Research Institute, Philadelphia
NCT01237457	^{177}Lutetium-DOTA-octreotate therapy in somatostatin receptor-expressing neuroendocrine neoplasms	R	Excel Diagnostics and Nuclear Oncology Center, Texas
NCT01480986	IPO-NEC trial: study on the efficacy and safety using sequential IP therapy and Oct LAR in the treatment of advanced GI NEC	R	Peking University, China
NCT01203306	Bevacizumab plus somatostatin analogue and metronomic capecitabine in patients with advanced neuroendocrine tumors (XELBEVOCT)	R	University of Turin, Italy
NCT01010126	Temsirolimus and bevacizumab in treating patients with locally advanced, recurrent, metastatic, or progressive endometrial cancer, ovarian epithelial cancer, liver cancer, islet cell cancer, or carcinoid tumor	R	Mayo Clinic
NCT01322542	YF476 in patients with type II gastric carcinoids associated with Zollinger-Ellison syndrome	R	NIDDK
NCT01435122	A study of axitinib in advanced carcinoid tumors	R	H Lee Moffitt Cancer Center and Research Institute, Philadelphia
NCT00688623	RAMSETE: RAD001 in advanced and metastatic silent neuroendocrine tumors in Europe (RAMSETE/CDE16)	R	Europe, Novartis
NCT00869050	Capecitabine and temozolomide for neuroendocrine cancers	R	Columbia University
NCT00843531	RAD001 and erlotinib in patients with neuroendocrine tumors	R	University of California, San Francisco
NCT01280201	Pazopanib as single agent in advanced NETs	R	Spain, GETN
NCT00442533	Safety and efficacy study of In-111 pentetreotide to treat neuroendocrine tumors	R	Radio Isotope Therapy of America, Texas
NCT01466036	Cabozantinib in advanced pancreatic neuroendocrine and carcinoid tumors	P	Massachusetts General Hospital, Boston
Phase III			
NCT01524783	Everolimus plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced neuroendocrine tumors (gastrointestinal or lung origin)	P	International, Novartis
NCT00690430	Safety and efficacy of pasireotide long acting release versus octreotide long acting release in patients with metastatic carcinoid disease	R	US, Novartis
NCT00569127	Octreotide and interferon alfa-2b or bevacizumab in treating patients with metastatic or locally advanced, high-risk neuroendocrine tumors	R	US, SWOG

(*Continued*)

Table 4 (*Continued*)

	Study	Status	Location
(B) Pancreatic NETs only			
Phase II			
NCT01229943	Everolimus and octreotide with or without bevacizumab in treating patients with locally advanced or metastatic pancreatic neuroendocrine tumors that cannot be removed by surgery	R	US, Cancer and Leukemia Group B
NCT01525082	Capecitabine, temozolomide and bevacizumab for metastatic or unresectable pancreatic neuroendocrine tumors	P	Stanford University, Palo Alto
NCT01465659	Temozolomide and pazopanib hydrochloride in treating patients with advanced pancreatic neuroendocrine tumors that cannot be removed by surgery	R	Northwestern University

Abbreviations: R, recruiting; P, pending; GETN, Grupo Espanol de Tumores Neuroendocrinos; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; SWOG, Southwestern Oncology Group.

neuroendocrine neoplasms are well reported in published reviews.[108–110]

Chromogranin A is the most useful biomarker in diagnosis and monitoring of lesions but has some notable limitations

The secretory capability of gastroenteropancreatic neuroendocrine neoplasms lends itself to the use of biochemical markers in diagnosis and monitoring of response, and early responses to chromogranin A after treatment may correlate with progression-free survival.[111] Potential biomarkers include chromogranin A, 5-hydroxyindoleacetic acid, and neuron-specific enolase. Chromogranin A, a glycoprotein stored in secretory vesicles, is almost ubiquitous in well differentiated and secretory neuroendocrine tumor cells, although is not always so easily detected in plasma.[112] Chromogranin A is useful in both functioning and nonfunctioning neuroendocrine neoplasms and is more sensitive than other biochemical markers.[113,114] However, there are many caveats when using chromogranin A. Chromogranin A becomes elevated after eating, and even exercise and anxiety can cause false positive results. Chromogranin A levels are elevated in hepatic and renal dysfunction, as well as in atrophic gastritis and chronic proton pump inhibition (which predispose to enterchromaffin-like cell hyperplasia). Several cardiovascular (eg, hypertension, heart failure), endocrine (eg, hyperthyroidism), and gastrointestinal disorders (eg, inflammatory bowel disease, liver cirrhosis) also cause chromogranin A elevation. Further, non-neuroendocrine cancers have been associated with increases in chromogranin A, including cancers of the breast, pancreas, colon, ovary, and prostate, and thus chromogranin A should not be used as a diagnostic tool.[115]

5-Hydroxyindoleacetic acid, the end product of serotonin metabolism, and most reliably measured in the urine over 24 hours, and neuron-specific enolase are both highly specific, approaching 100% for some functioning neuroendocrine neoplasms. However, they lack sensitivity; in one study of mixed neuroendocrine neoplasms, 5-hydroxyindoleacetic acid and neuron-specific enolase showed a sensitivity of 33% and 35%, respectively, compared with 68% for chromogranin A.[114] The sensitivity of 5-hydroxyindoleacetic acid is highest (up to 73%) in midgut carcinoids (mostly small intestinal neuroendocrine neoplasms) especially in the presence of carcinoid syndrome.[116] 5-Hydroxyindoleacetic acid false-positives can occur with tryptophan-containing foods and some medicines.[117] Neuron-specific enolase may be useful in poorly differentiated neuroendocrine carcinomas where other markers are often negative.[56] Chromogranin A and 5-hydroxyindoleacetic acid also have prognostic value, with higher levels associated with a poor outcome.[118]

Treatment should only be considered by clinicians in a multidisciplinary team

The treatment of gastroenteropancreatic neuroendocrine neoplasms is predominantly not evidence-based, and is shaped more by the local skill set and funding restrictions than by clear scientific recommendations. This makes treatment decisions particularly difficult for clinicians and impossible for clinicians acting alone. The number of treatment modalities now available is growing and the potential permutations and combinations of surgery, systemic therapy, nuclear medicine, and liver-directed therapies is enormous, and the ideal combination remains a crucial question for each patient.

All patients should consider participating in a clinical trial, since treatment strategies have not been directly compared, leading to large interpractice variability

The current state of knowledge regarding the management of gastroenteropancreatic neuroendocrine neoplasms leads to a final inescapable conclusion. A coordinated international clinical trials program is essential.[119] Further, there is a genuine possibility that gastroenteropancreatic neuroendocrine neoplasms will be more suitable to molecular targeted therapies than many other malignancies, making this an optimistic time for patients with these heterogeneous tumors. Many trials are currently recruiting (Table 4) and the authors would strongly encourage the reader to refer patients for trial participation.

Conclusion

The clinician considering a new diagnosis of gastroenteropancreatic neuroendocrine neoplasm could be well served by considering the following etiological and epidemiological principles:

- Classification systems are becoming increasingly confluent across transnational (World Health Organization), European (European Neuroendocrine Tumor Society) and US American Joint Committee on Cancer) systems, and more similar to other cancers in the use of grading, differentiation, and staging.
- There is a progression from hyperplasia to dysplasia to neoplasia in some gastroenteropancreatic neuroendocrine neoplasms of the foregut, but this transition has not yet been observed at more distal sites.
- The majority of gastroenteropancreatic neuroendocrine neoplasms are never diagnosed and do not contribute to mortality. Therefore, a high proportion of lesions discovered incidentally will not impact on mortality, and so initial or long-term observation may be warranted.
- The genetic cause of gastroenteropancreatic neuroendocrine neoplasms is beginning to be uncovered, and relevant pathways that might facilitate therapeutic inhibition have started to be identified.
- Most gastroenteropancreatic neuroendocrine neoplasms do not present with hormonal syndromes, eg, carcinoid syndrome, despite this being the best known symptom in this group of tumors.
- Treatment strategies for poorly differentiated gastroenteropancreatic neuroendocrine neoplasms are divergent from those of well differentiated gastroenteropancreatic neuroendocrine neoplasms. The cornerstone of therapy for well differentiated gastroenteropancreatic neuroendocrine neoplasms is surgery, but is chemotherapy for poorly differentiated gastroenteropancreatic neuroendocrine neoplasms.
- The therapeutic options for well differentiated gastroenteropancreatic neuroendocrine neoplasms depend on the primary site of the lesion. Resection of the primary is recommended in metastatic luminal neuroendocrine neoplasms because obstruction is often the initial complication.
- Chromogranin A is a modestly effective biomarker that is more useful in well differentiated tumors. The clinical should note limitations of both sensitivity and specificity.
- Treatment should only be considered by clinicians who consider themselves part of a multidisciplinary team. There are too many options to be assessed by a single clinician.
- Clinical trials are essential, and international collaboration will be required to obtain the necessary sample sizes. Treatment strategies for well differentiated gastroenteropancreatic neuroendocrine neoplasms are protean and have not been compared with each other. There is no head-to-head comparison of therapies in gastroenteropancreatic neuroendocrine neoplasms, and recommendations are mostly based on expert opinion rather than clinical trials.

Disclosure

The authors report no conflicts of interest in this work.

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