CLINICAL
INVESTIGATION

Advances in the management and treatment of gastroenteropancreatic neuroendocrine tumors

Gastroenteropancreatic tumors or pancreatic neuroendocrine tumors (PNETs) are relatively rare tumors, but are being recognized with increasing frequency. They comprise of secretory and nonsecretory tumors. Secretory tumors are recognized by distinct clinical syndromes, such as insulinoma and gastrinoma and nonsecretory tumors present clinically as mass effect and metastases. PNETs occur sporadically or as part of the multiple endocrine neoplasia type and von Hippel–Lindau and von Recklinghausen syndromes. Biomarkers for these tumors include peptides that are known to be secreted, and in addition chromogranins useful for detection, pancreastatin and Neurokinin A. New techniques are being developed for tumor localization, including PET scanning and peptide receptor scanning. Neuroendocrine tumors tend to be more sensitive to containment using somatostatin analogs and the currently available analog that binds the somatostatin receptors 2 and 5 will soon include agonists that also target the 1, 3 and 4 receptors. This at least has the theoretical advantage of greater efficacy, if not specificity, and a wider range of tumor targets. Two new agents have been approved for treating PNETs; a tyrosine kinase inhibitor and an mTOR inhibitor, which have interesting actions on increasing progression-free survival. Perhaps of great interest is the prediction of response to these agents based upon mutations involving the tyrosine kinase or mTOR pathway, the *MEN1* gene and the ret proto-oncogene and the recent recognition of *DAXX* and *ATRX* genes associated with chromatin remodeling. There is emerging concurrence on the pathology and staging of these tumors. Of additional benefit is the use of bone alkaline phosphatase and telopeptide as markers of osteoblasts and osteoclast activation. Surgical excision remains the mainstay of treatment of the primary tumor and somatostatin analogs control symptoms and may have some antitumor activity. Recently there has been interest in health-related quality of life. Of particular interest is the relationship of quality of life to progression-free survival and to the pathophysiology of these tumors. A flurry of interest in the use of combination therapies and interventions based upon known pathophysiology is likely to be rewarded with new and emerging treatment for PNETs in the not too distant future.

EC Feliberti[1], RR Perry[1] & AI Vinik[†1]

[1]Eastern Virginia Medical School, Norfolk, VA, 23510, USA
[†]Author for correspondence:
vinikai@evms.edu

Classification
Pancreatic neuroendocrine tumors (PNETs) are part of a larger group of indolent tumors collectively termed gastroenteropancreatic (GEP) neuroendocrine tumors (NETs). Although rare, there is heterogeneity in their clinical course, histologic appearance, molecular derangements and hormone production. Several classification

FUTURE SCIENCE

part of fsg

schemes have been used to attempt to meaningfully categorize NETs. GEP NETs have been classified based on their embryologic origin in the GI tract as foregut, midgut and hindgut NETs. Midgut NETs are more functionally active in their hormone production, while hindgut NETs tend to be more clinically silent.

Clinically, NETs are also stratified as being functional and nonfunctional tumors, based on their ability to produce clinical syndromes as a result of their hormone secretion. It has become increasingly recognized that PNETs may present with paraneoplastic syndromes in addition to the traditional manifestations due to hormone excess, including fever, myopathies, neuropathies and cachexia amongst others, which are thought to be due to their ability to produce a variety of cytokines and to activate oxidative and nitrosative stresses. For a listing of the clinical presentation, the hormones produced and the common sites see Table 1. The term paraneoplastic refers to the ability of some tumors to produce signs and symptoms at a distance from the site of the primary tumor or metastases, and which may well develop before the tumor becomes apparent. PNETs also have the capability of causing neurological manifestations such as peripheral neuropathy and Eaton–Lambert syndrome, which develop as a result of autoantibodies elicited by malignant cells that crossreact with nerve cells leading to neurological sequelae.

Of particular interest is the emergence of a recently recognized iatrogenic condition, a consequence of the global explosion of gastric bypass procedures, the mechanism of which are still obscure. This condition is termed noninsuloma pancreatogenous hypoglycemia syndrome (NIPHS). This is a recently recognized syndrome occurring in adults who have had gastric bypass. Although not caused by a distinct PNETs, the presenting signs and symptoms may be confused with insulinoma. Therefore, physicians who treat patients with NETs need to be familiar with this syndrome. Initially described in adults as sporadic cases, NIPHS has been reported by Service et al. at the Mayo Clinic developing approximately 1–3 years after a roux-en-Y gastric bypass and presenting with neuroglycopenic symptoms approximately 1–3 h postprandial [1]. With the rising use of gastric bypass in the USA for weight loss management, other institutions have since reported similar cases after gastric bypass [2–4]. Fasting studies are negative for insulinoma and localizing studies, including computed tomography (CT) scan, ultrasound and angiography, are negative for identifying a source of hypoglycemia. Selective arterial calcium stimulation testing can be equivocal in the setting of NIPHS, often showing elevated insulin levels in more than one arterial distribution. Usual sites of elevation include the splenic (the tail and body of pancreas) and superior mesenteric artery (uncinate process) distributions and less often the gastroduodenal artery (head)

distribution. Most cases have been successfully treated with distal pancreatectomy to the level of the superior mesenteric vein even when calcium stimulation studies have shown elevated insulin levels predominantly, in the gastroduodenal artery or superiro mesenteric artery distribution [5]. Most patients have improvement or resolution of postprandial hypoglycemia. Examination of pancreatic specimens with NIPHS have shown β-cell hypertrophy, increased islet cell size with hyperchromatic nuclei and increased periductular islet cells. Findings are characteristic of nesidioblastosis, which is seen in neonates and infants with persistent hyperinsulinemic hypoglycemia. Patients can be medically managed primarily or for recurrence with diazoxide. Other useful agents include acarbose and verapamil. The etiology of NIPHS after roux-en-Y gastric bypass is unknown. Proposals include bypass of the proximal intestine, secretion of GLP-1, decreased ghrelin or hyperinsulinemia with rapid weight loss. It is unclear if this syndrome will also be seen in patients who undergo gastric banding.

PNETs

Pancreatic neuroendocrine tumors have an estimated incidence of less than 1 per 100,000 individuals [6–8]. PNETs are divided into two groups: those associated with a functional syndrome due to ectopic secretion of a biologically active substance, and those that are not associated with a functional syndrome, known as nonfunctional PNETs (NF-PNETs) [6–9]. Functional PNETs include insulinomas, gastrinomas, VIPomas, somatostatinomas, glucagonomas, growth-hormone releasing factor secreting (GRFomas), and a group of less common PNETs including PNETs secreting ACTH (ACTHomas) and causing Cushing's syndrome, PNETs causing carcinoid syndrome, PNETs causing hypercalcemia and, very rarely, PNETs ectopically secreting luteinizing hormone, renin or erythropoietin [6]. Functional PNETs and NF-PNETs also frequently secrete a number of other substances (chromogranins, neuron-specific enolase, subunits of human chorionic gonadotropin, neurotensin and ghrelin [6–9]. In terms of relative frequency, NF-PNETs are, at present, the most frequently found pancreatic endocrine tumors, occurring approximately twice as frequently as insulinomas, which are generally more frequent than gastrinomas followed by glucagonomas, VIPomas and somatostatinomas [6,7,9,10].

PNETs can occur both sporadically and in patients with various inherited disorders [6,11]. PNETs occur in 80–100% of patients with multiple endocrine neoplasia type I (MEN I); in 10–17% of patients with von Hippel–Lindau syndrome (VHL); up to 10% of patients with von Recklinghausen's disease (neurofibromatostis-1 [NF-1]), and occasionally in patients with tuberous sclerosis [11]. Of these autosomal dominant disorders MEN1

Table 1. The clinical presentations, syndromes, tumor types, sites and hormones of gastroenteropancreatic neuroendocrine tumors.				
Clinical presentation	Syndrome	Tumor type	Sites	Hormones
Flushing	Carcinoid, medullary carcinoma of thyroid and pheochromocytoma	Carcinoid, C cell tumor and tumor of chromaffin cells	Mid/ foregut, adrenal medulla, gastric, thyroid, C cells, adrenal and sympathetic nervous system	Serotonin, CGRP, calcitonin, metanephrine and normetanephrine
Diarrhea abdominal pain and dyspepsia	Carcinoid, WDHA, ZE, PP and MCT	Carcinoid, VIPoma, gastrinoma, PPoma, medullary carcinoma, thyroid and mastocytoma	As above, pancreas, mast cells and thyroid	As above, VIP, gastrin, PP and calcitonin
Diarrhea/ steatorrhea	Somatostatin, bleeding and GI tract	Somatostatinoma and neurofibromatosis	Pancreas and duodenum	Somatostatin
Wheezing	Carcinoid	Carcinoid	Gut, pancreas and lung	SP, CGRP and serotonin
Ulcer/dyspepsia	ZE	Gastrinoma	Pancreas and duodenum	Gastrin
Hypoglycemia	Whipple's triad	Insulinoma, sarcoma and hepatoma	Pancreas and retroperitoneal liver	Insulin, IGF1 and IGF11
Dermatitis	Sweet syndrome, pellagra	Glucagonoma and carcinoid	Pancreas and midgut	Glucagon and serotonin
Dementia	Sweet syndrome	Glucagonoma	Pancreas	Glucagon
Diabetes	Glucagonoma and somatostatin	Glucagonoma and somatostatinoma	Pancreas	Glucagon and somatostatin
DVT, steatorrhea, cholelithiasis, neurofibromatosis	Somatostatin	Somatostatinoma	Pancreas and duodenum	Somatostatin
Silent, liver metastases	Silent	PPoma	Pancreas	PP
Acromegaly	Acromegaly, gigantism	NET, PNET, Pheo	Pancreas islet	GHRH
Cushing's syndrome	Cushing's	NET, PNET, Pheo	Pancreas islet, lung, pheo, MTC	CRH and ACTH
Pigmentation	Pigmentation	NET	Pancreas islet	MSH
Anorexia, nausea, vomiting, abdominal pain	Hypercalcemia	NET, PNET, Pheo	Pancreas islet and pheo	PthRP, Pth,TGFβ, IL, 25O-HD, 1:25 OHD– bone alk phos, NTx
Hypoglycemia	Autonomic and CNS symptoms of hypoglycemia	NET, PNET	Pancreas and carcinoid	IGF, IGF2 and proIGF, GLP-1, GLP-2
Weakness, lethargy, apathy	Hyponatremia, SIADH	NET, PNET, Pheo	Lung, pancreas and pheo	ADH, ANP
Hyperandrogenism, gynecomastia, hyperthyroidism		PET	Pancreas	LH, FSH, prolactin and TSH
Hypertension	Malignant hypertension	PET, pheo- and para-ganglioma	Paraganglioma and NET	Renin, prorenin and aldosterone

25-OHD: 25-hydroxyvitamin D; ACTH: Adrenocorticotropic hormone; ADH: Antidiuretic hormone; ANP: Atrial natriuretic peptide; CGRP: Calcitonin gene-related peptide; CRH: Corticotropin-releasing hormone; DVT: Deep vein thrombosis; FSH: Follicle-stimulating hormone; GHRH: Growth hormone releasing growth hormone; GLP: Glucagon-like peptide; LH: Luteinizing hormone; MCT: Medullary carcinoma of the thyroid; MSH: Melanocyte-stimulating hormone; MTC: Medullary thyroid carcinoma; NET: Neuroendocrine tumor; NTx: N-telopeptide; Pheo: Pheochromocytoma; PNET: Pancreatic neuroendocrine tumor; PP: Pancreatic polypeptide; PTH: Parathyroid hormone; PTH-rp: Parathyroid hormone-related peptide; SIADH: Syndrome of inappropriate secretion of antidiuretic hormone; SP: Substance P; TSH: Thyrotropin-stimulating hormone; VIP: Vasoactive intestinal peptide; WDHA: Watery diarrhea, hypokalemia and achlorhydria; ZE: Zollinger–Ellison.
Adapted from [106,107].

is the most frequent in patients with PNETs [11,12]. MEN1 is caused by mutations in chromosome 11q13 resulting in alterations in the *MEN1* gene, which has important effects on transcriptional regulation, genomic stability, cell division and cell cycle control [11]. Patients with MEN1 develop hyperplasia or tumors of multiple endocrine and nonendocrine tissues including parathyroid adenomas (95–100%) resulting in hyperparathyroidism; pituitary adenomas (54–65%), adrenal adenomas (27–36%), various carcinoid tumors (gastric, lung, thymic; 0–10%), thyroid adenomas (≤10%), various skin tumors (80–95%), CNS tumors (≤8%) and smooth muscle tumors (≤10%) [11]. In MEN1 patients, 80–100% develop pancreatic NF-PNETs, but in most patients they are small or microscopic, causing symptoms in only 0–13% [11]. Gastrinomas (>80% duodenal) develop in 54% of MEN1 patients, insulinomas in 18% and glucagonomas, VIPomas, GRFomas and somatostatinomas in <5% [11]. In VHL, 98% of all the PNETs that develop in 10–17% of the patients are NF-PNETs, in the 0–10% of NF-1 patients developing a pancreatic endocrine tumors, they are characteristically duodenal somatostatinomas that do not cause the somatostatinoma syndrome. In tuberous sclerosis, rare functional and NF-PNETs are reported [11].

NF-PNETs

NF-PNETs are intrapancreatic in location, characteristically large (70% >5 cm), and at an advanced stage when first diagnosed with 60–85% having liver metastases in most series [6,9,13,14]. NF-PNETs are not associated with a clinical hormonal syndrome, presenting with symptoms due to the tumor including abdominal pain (40–60%), weight loss or jaundice [6,8,9,13,14]. In recent years, they are increasingly being discovered by chance on imaging studies performed for nonspecific abdominal symptoms [6,15]. Although NF-PNETs do not secrete peptides that cause clinical syndromes, they characteristically secrete a number of other peptides, which are helpful in their diagnosis. These include chromogranins, especially chromogranin A (CgA; 70–100%) and pancreatic polypeptide (PP; 50–100%) [6,8,9,13,14]. The presence of an NF-PNET is suggested by the presence of a pancreatic mass in a patient without hormonal symptoms, with an elevated serum PP or CgA level or a positive octreoscan (somatostatin receptor scintigraphy [SRS]; discussed in the next section). However an elevated PP level or CgA level is not specific for NF-PNETs [6,8,9,13,14].

■ Incidence

PNETs have traditionally been described as rare tumors. Although the incidence of these tumors is low, because patients often live for many years the prevalence of the disease is higher. An accurate assessment of the incidence and prevalence of NETs has been challenging since these tumors can be classified under multiple names from carcinoid to NETs to functional tumors. A recent study of the US SEER database by Yao *et al.* sought to overcome this challenge by querying the database for all NETs using multiple International Clasification of Disease for Oncology, 3rd Edition, codes [16]. This included codes for functional NETs, islet cell carcinomas, enterochromaffin cell carcinoids, atypical carcinoids, goblet cell carcinoids, composite carcinoids and neuroendocrine carcinoids. This analysis showed that the incidence of NETs has increased from 1.09 per 100,000 of the population in 1973 to 5.25 in 2004. The most common NETs of the gut are carcinoid tumors, with an incidence of approximately 1.5 cases per 100,000 of the general population. Another common site of NETs is the lung, with an incidence of 1.35 per 100,000, whilst the incidence of PNETs in 2004 was 0.32. NETs occur more commonly in African–Americans compared with whites. The most common sites in African–Americans are the rectum (1.8 per 100,000), small bowel (0.88) and pancreas (0.36). The estimated 29-year limited duration prevalence of carcinoids in the USA was 103,312 cases, making carcinoids more prevalent than pancreatic, gastric or esophageal cancer. In comparison with other sites of NETS, PNETs were most likely to present with distant metastases (64%), while presenting with localized disease in only 14% of cases. This was associated with one of the lowest median survivals of NETs by site of primary, with a median survival of 42 months.

■ Pathology & staging

The pathology of these lesions remains confusing and controversial and there is no universally recognized classification system. There are a variety of competing systems currently in use, including those developed by the WHO and ENETS. The WHO's 2010 classification uses site-specific criteria and grade to classify these tumors. For example, low-grade GEP-NETs are considered neuroendocrine neoplasms, grade 1, intermediate-grade neuroendocrine neoplasms, grade 2, and high-grade neuroendocrine carcinomas, grade 3 [17]. Despite the differences among the systems, common elements include distinction of well differentiated (low and intermediate grade) from poorly differentiated (high grade) NETs. Measures of cell differentiation include mitotic index, Ki67, presence of angioinvasion, size and functional activity. Proliferative rate of these lesions also appears important in prognostic assessment [18]. A minimum pathology dataset has been suggested to standardize the information in pathology reports [19]. A detailed discussion of the pathology of these tumors is beyond the scope of this review and, therefore, readers

are referred to the excellent coverage of this topic in the NANETS guidelines [18]. The AJCC 7th Edition now includes staging of PNETs. The staging of PNETs is identical to the staging of adenocarcinoma [20].

■ Molecular genetics

Although NETs of the gastroenteropancreatic system appear histologically similar, there is heterogeneity in the hormones produced based on their site of origin and in association with familial syndromes. Although most are sporadic, PNETs are unique among NETs in their association with familial syndromes. The clinical course and prognosis of sporadic PNETs differs from PNETs that occur in MEN1. For example, surgical resection of sporadic gastrinoma patients results in better disease-free survival compared with patients with MEN1 [21]. PNETs may arise in the setting of MEN1, NF1, VHL and tuberous sclerosis complex. MEN1 has germline mutations in the *MEN1* gene which is located on chromosome 11q13 and encodes the nuclear protein menin that interacts with such nuclear proteins such as junD, SMAD3 and NF-κB. *MEN1* is a tumor-suppressor gene. As with all tumor-suppressor genes, loss of heterozygosity is required for the mutated gene to be inactivated. In sporadic PNETs, mutations in the *MEN1* gene are detectable in only 21% of cases [22]. Interestingly, over 50% of PNETs exhibit losses at chromosome 11q13 and/or more distal parts on the long arm of the chromosome. This suggests that there may be a tumor-suppressor gene distal to the menin gene that may be involved in tumorigenesis of PNETs. Losses on chromosome 1 and gains on 9Q also appear to be important in the development of sporadic PNETs [23]. This is in contradistinction to midgut and hindgut NETs, which frequently show losses on chromosome 18q [24]. Another mechanism of tumor formation in PNETs includes promoter hypermethylation in silencing tumor-suppressor gene expression. The most commonly silenced genes are *RASSF1A* (75%) *p16/INK4A* (40%) and *O6-MGMT* (40%) [25]. Alterations in known oncogenes such as *Kras* and *p53* occur uncommonly in PNETs [26,27].

A study from Johns Hopkins in patients with PNETs revealed that the three most commonly mutated genes were *MEN1*, *DAXX* and *ATRX*, which are associated with chromatin remodeling. Patients with these mutations tended to live longer than patients with other mutations. Mutations in the mTOR pathway were noted in 14% of tumors [28].

■ Tumor markers

Diagnosis of PNETs is based on clinical presentation and symptoms, biochemical assays and pathology. Serum markers relate to specific clinical syndromes. Such markers include serum insulin and pro-insulin levels for insulinoma, plasma gastrin levels for gastrinoma, vas-active intestinal peptide levels in VIPoma and glucagon levels in glucagonoma. Markers common to GEP–NETs and useful for NF–NETs include CgA, which can be elevated in 60–80% of GEP–NETs. Indeed, CgA remains the most useful and widely available tumor marker in NETs. However, there are certain pitfalls in the use of CgA. False elevations may occur in a variety of conditions including renal insufficiency, uncontrolled hypertension, pregnancy, steroid treatment and treatment with proton pump inhibitors [29]. A recent finding indicates that breakdown products of CgA can also be elevated in NETs and can be prognostic. One such product is pancreastatin, which is derived from the protein CgA. Its effects are thought to counteract those of insulin. It can be elevated in insulin-resistant states such as gestational diabetes and has also been found to be elevated in NETs. Calhoun *et al.* reported that in 31 carcinoid patients, pancreastatin levels were elevated in 81% and it was the only elevated hormone in 57% [30]. Elevated pancreastatin levels in the setting of carcinoid tumor can provide prognostic information. Bloomston *et al.* reported that in metastatic carcinoid patients undergoing hepatic arterial chemoembolization, a pretherapy pancreastatin level greater than 5000 pg/ml was associated with a decreased survival [31]. A decrease of at least 20% of pancreastatin levels after chemoembolization was associated with a radiologic reduction of tumor bulk.

Determining prognosis

Chromogranin A

Other than the applications of CgA previously discussed, this marker can be used for prognosis and follow-up. Jensen *et al.* found that a reduction on CgA levels >80% after cytoreductive surgery for carcinoid tumors predicts symptom relief and disease control; it is associated with improved patient outcomes, even after incomplete cytoreduction [32].

Pancreastatin

One of the post-translational processing products of CgA has been found to be an indicator of poor outcome when its concentration in plasma is elevated before treatment in patients with NETs. A level of >500 pmol/l is an independent indicator of poor outcome. This marker is also known to correlate with the number of liver metastases, so it would be appropriate to use it in the follow-up of NET patients. Furthermore, Stronge *et al.* found that an increase in pancreastatin levels following somatostatin analogue therapy is associated with poor survival [33]. Other studies have shown that pancreastatin should be measured prior to, during and after treatment. Plasma levels of this marker >5000 pg/ml at

pretreatment were associated with increased periprocedure mortality in patients with NETs who underwent hepatic artery chemoembolization [31].

These observations suggest that pancreastatin is potentially very useful as a marker, not only for diagnosis but, more importantly, for monitoring treatment response.

Neurokinin A

Neurokinin A (NKA) has been shown to have strong prognostic value. In 2006, Turner *et al.* showed that, in patients with midgut carcinoid who had raised plasma NKA, a reduction of NKA after somatostatin analogue therapy was associated with an 87% survival at 1 year compared with 40% if it increased. They also concluded that alteration in NKA can predict improved or worsening survival [34].

Diagnosis of bone metastasis

Metastases from NETs can be either lytic and/or osteoblastic. There may be an increased osteoclast activity contributing to lytic lesions and/or an increase in osteoblastic activity responsible for blastic metastases. Bone markers in lytic and osteoblastic metastases therapy include bone alkaline phosphatase (an indicator of osteoblast function) and urinary N-telopeptide, which reflects osteoclast activity or bone resorption. Somewhat paradoxically, only blastic metastases show an increase in both markers [35].

Increased osteoclast activity predicts a poor outcome, with a relative risk (RR) for high N-telopeptide (>100 nmol BCE/mM creatinine) of skeletal-related events (RR = 3.3; p <0.001); disease progression (RR = 2.0; p < 0.001) and death (RR = 4.6; p < 0.001) [36].

A detailed discussion of biochemical testing for specific clinical syndromes is beyond the scope of this review. The 72 h fast remains the gold standard for the diagnosis of insulinoma. The presence of elevated fasting gastrin and low gastric pH, with confirmation by a secretin stimulation test, remains the standard for the diagnosis of gastrinoma. Table 1 provides a summary of the clinical syndromes and the hormone/cytokines produced. For a more detailed discussion, the reader is referred to the ENETS consensus guidelines [29].

Imaging & localization: imaging of PNETs
◼ General

Imaging of the primary tumor location and the extent of the disease is needed for all phases of management of patients with PNETs. It is needed to determine whether surgical resection for possible cure or possible cytoreductive surgery is needed, if treatment for advanced metastatic disease is appropriate and, during follow-up, to assess the effects of any antitumor treatment as well as the need for deciding whether additional treatments directed at the PNETs are indicated [6,13,37,38].

Functional PNETs (especially insulinomas and duodenal gastrinomas) are often small in size and localization may be difficult [6,13,37,38]. A number of different imaging modalities have been widely used including conventional imaging studies (CT, MRI, ultrasound and angiography) [39–42]; endoscopic ultrasound (EUS) [6,43,44] functional localizations studies measuring hormonal gradients [6,45–47]; intraoperative methods (particularly intraoperative ultrasound) [6,48,49] and, recently, the use of PET scanning preoperatively [42,50–52]. A few important points in regard to each will be made below.

◼ Conventional imaging studies for PNETs (CT, MRI, ultrasound & angiography)

Even though PNETs are highly vascular tumors and most of these studies are now performed with contrast agents, the results with conventional imaging studies are, to a large degree, dependent on the tumor size [6,37,39,53,54]. While conventional imaging studies detect >70% of PNETs of >3 cm, they detect <50% of most PNETs of <1 cm, therefore these studies frequently miss small primary PNETs (especially insulinomas and duodenal gastrinomas) and small liver metastases [6,37,39,53,54]. At least one of these modalities is generally available in most centers, with CT scanning with contrast most frequently used as the first imaging modality.

◼ Somatostatin receptor scintigraphy

PNETs frequently overexpress somatostatin receptors (>80% except insulinomas), particularly subtypes SST 2 and 5, which bind various synthetic analogues of somatostatin (octreotide and lanreotide) with high affinity [6,40–42,55]. A number of radiolabeled somatostatin analogues have been developed to take advantage of this finding in order to image PNETs, with the most widely used worldwide, and the only one available in the US, being [111]Indium-DTPA-octreotide (Octreoscan™) [6,40–42,55]. SRS combined with computerized tomographic detection (SPECT imaging) is more sensitive than conventional imaging for detection of both the primary (except insulinomas) pancreatic endocrine tumors and metastatic PNETs to liver, bone or other distant sites [40–42,55–57]. This sensitivity allows SRS to detect 50–70% of primary PNETs (less frequent with insulinomas or duodenal gastrinomas) and >90% of patients with metastatic disease [6,40–42,58,59]. SRS also has the advantage of allowing total body scanning to be carried out quickly and at one time, and its use has resulted in a change in management of 24–47% of patients with PNETs [6,40–42,58,59]. False-positive localizations can occur in up to 12% of patients, thus it is important to interpret the result within the clinical context of the patient and by doing so, the false-positive rate can be reduced to 3% [6,41,59,60].

■ Endoscopic ultrasound

Endoscopic ultrasound combined with fine needle aspiration can be useful in distinguishing a PNET from adenocarcinoma or some other cause of a pancreatic mass [6,43,44]. Fine needle aspiration is rarely used to diagnose functional PNETs because they are suggested by symptoms and the diagnosis is established by hormonal assays [6,13]. EUS is much more effective for localizing intrapancreatic PNETs than extrapancreatic PNETs, such as duodenal gastrinomas or somatostatinomas [6,13,43]. EUS is particularly helpful in localizing insulinomas, which are small, almost always intrapancreatic and frequently missed by conventional imaging studies and SRS [6,13,43]. EUS can identify intrapancreatic primary pancreatic endocrine tumors in approximately 90% of cases [6,43]. EUS can also play an important role in the management of patients with MEN1 who have NF-PNETs in 80–100% of cases or, in patients with NF-PNETs with VHL syndrome, which occurs in 10–17% of cases. These NF-PNETs are often small and their management is controversial [6,11,61–63]. EUS can detect many of these small NF-PNETs and it has been proposed that serial evaluations with EUS be used to select which MEN1 or VHL patients should have surgery [6,11,61–64].

■ Functional localization (assessing hormonal gradients) & PET scanning for PNETs

Assessment of hormonal gradients is now rarely used, except occasionally in patients with insulinomas or gastrinomas not localized by other imaging methods [6,45–47,53,65]. When used it is now usually performed at the time of angiography and combined with selective intra-arterial injections of calcium for primary insulinomas or secretin for a primary gastrinoma or possible metastatic gastrinoma in the liver with hepatic venous hormonal sampling [6,45–47,53,65]. PET scanning for PNETs is receiving increasing attention because of its increased sensitivity [6,50–53]. With PNETs, ^{11}C-5 hydroxytryptophan or ^{68}Gallium-labeled somatostatin analogues have been shown to have greater sensitivity than SRS or conventional imaging studies and, therefore, may be clinically useful in the future. At present neither of these methods are approved for use in the USA and are therefore not available at the current time [6,42,50–52].

■ Intraoperative localization of PNETs

During surgery the routine use of intraoperative ultrasound is recommended, especially for PNETs [6,48,49], and for small duodenal tumors (especially duodenal gastrinomas) endoscopic transillumination [6,66,67] in addition to routine duodenotomy is recommended [6,21,43,67–69].

Standard imaging for these tumors include anatomic and morphologic imaging, such as CT or MRI, and functional imaging such as SRS. The lack of radiation exposure is a potential advantage of MRI in younger patients. SRS may provide better staging than conventional imaging techniques and may also provide particularly useful information prior to patients undergoing exploration. SRS will also occasionally reveal occult primary lesions not detected on other imaging modalities. It may also reveal unsuspected metastatic disease and provide information on somatostatin-receptor status, which is important if octreotide treatment is a consideration. For patients with PNETs, endoscopic ultrasound combined with fine needle aspiration biopsy is often useful. For patients with tumors in certain sites, such as liver metastases, image-guided core biopsy may be useful; however conventional 18 FDG-PET has limited utility in the routine management of these patients. In difficult-to-localize insulinomas, their ability to bind GLP-1 has recently led to the development of GLP-1 receptor imaging techniques [70].

Imaging and localization techniques continue to evolve. A number of studies have shown a potential role for ^{68}Ga-DOTATATE PET in patients with negative or equivocal SRS. ^{68}Ga-DOTATATE PET identified more lesions than SRS and changed management in nearly 71% of patients [71]. These results are similar to those seen with ^{68}Ga-DOTATOC PET [51]. A number of studies have shown that EUS has a high sensitivity (80%) for detection of PNETs [72]. Contrast enhancement during EUS can improve the detection of PNETs, and allow distinction between these tumors and conventional adenocarcinoma [73,74]. Indeed, such contrast enhancement has also been shown to be beneficial in conventional trans-abdominal ultrasound [75].

The standard imaging scheme of anatomic and functional imaging is useful for most patients with functional and nonfunctional PNETs. More invasive modalities, such as selective angiography and/or transhepatic portal venous sampling, are required much less often than in the past due to the improvements in cross-sectional imaging and the development of SRS. These more invasive modalities do remain useful in certain patients, such as those with gastrinoma and insulinoma in whom conventional noninvasive imaging has failed to localize the lesion.

Readers interested in more information on imaging and localization are referred to the ENETS guidelines on somatostatin receptor imaging [76], and the ENETS guidelines for radiologic examination [77].

Treatment
■ Surgical management

Surgical resection remains one of the cornerstones of PNETs management. Surgical treatment should be individualized, based on the extent of the disease and

the overall medical condition of the patient. A multi-disciplinary team is essential in devising the treatment strategy and sequencing of treatments.

Resection of the primary tumor can be curative in patients who have localized nonmetastatic disease. Primary tumor size and location are important criteria in helping decide appropriate surgical management. PNETs >3 cm in size are more often malignant. Patients with PNETs who undergo surgery should, in general, have the entire pancreas explored with a combination of palpation and intraoperative ultrasound. Patients with gastrinoma should also undergo duodenotomy and resection of any identified abnormalities, as originally recommended by Thompson *et al.* [78].

Patients with metastatic disease may also benefit from an aggressive surgical approach. For example, resection of primary small bowel carcinoid tumors should be considered even in the presence of distant metastases to prevent future intestinal obstruction [79]. Some authors have also shown that resecting the primary tumor in these patients improves survival [80]. Such an approach is supported by the NANETS guidelines [81].

Even in the face of malignant metastatic disease, some patients with PNETs may benefit from an aggressive surgical approach with resection of the primary tumor. Similar results are seen in patients with PNETs. This was demonstrated by a recent study of PNETs that analyzed the SEER database and showed an odds ratio of 0.48 (95% CI: 0.35–0.66) for those who underwent surgical resection of the primary tumor compared with those who were recommended for, but did not proceed with, surgery [82]. The benefit of resecting the primary tumor was seen in all disease stages, including stage 4.

As always, the aggressiveness of the surgery needs to be balanced with the potential morbidity and mortality of surgery. Enucleation of small primary PNETs is equivalent, and often superior to, pancreatic resection, particularly for lesions of the pancreatic head [83]. It must be recognized that these more limited procedures may understage some patients, but the effect of such understaging on long-term outcomes is unknown. To address this potential problem, lymph node sampling has been recommended in patients who undergo pancreas-sparing procedures [84]. Liver transplantation is a controversial option in highly selected patients with neuroendocrine liver metastases. For further information on surgical debulking and the role of liver transplantation, readers are referred to the NANETS guidelines [81,85].

■ **Systemic treatment**
Systemic treatment is generally reserved for patients with advanced disease, particularly in patients with poorly differentiated tumors with high ki67 index.

Conventional systemic chemotherapy, predominantly streptozotocin often combined with other agents, has shown disappointing results. A recent study of 79 chemo-naive patients with locally advanced or metastatic NETs at various sites examined the response to a combination of 5-FU, cisplatin and streptozotocin. An overall response rate of 33%, stable disease in 51% and progression in 16% were noted. Grade and mitotic index were the best predictors of response. Median time-to-progression was 9.1 months, and median overall survival was 31.5 months [86].

Somatostatin analogues have long been a mainstay in the treatment of metastatic NETs. Somatostatin is effective in reducing the symptoms of NETs including flushing and diarrhea. Indeed, response to octreotide has been shown to correlate with patients who have a decrease in CgA levels after octreotide testing [87]. Faiss *et al.* reported in a prospective multicenter trial evaluating the efficacy of lanreotide, IFNα and their combination in metastatic NETs, a partial response or stable disease in 32% of patients treated with lanreotide compared with 29.6% for IFNα and 25% for the combination [88]. This study found that foregut tumors, of which PNETs comprised 72%, had a statistically shorter time-to-progression compared with midgut tumors. Symptoms (diarrhea, flushing) were more significantly reduced with combination treatment than either monotherapy, but combination therapy had a higher incidence of side effects and led to a 25% (seven of 28 patients) interruption of therapy compared with 14.8 and 12% for IFNα and lanreotide respectively. The lower response rate of the somatostatin arm compared with prior studies is thought to be due to the nonrandom and nonblinded prior reports, as well as the high number of foregut tumors, which are less responsive to somatostatin therapy. The PROMID trial evaluated the efficacy of somatostatin monotherapy in the form of octreotide 30 mg intramuscular injection every 28 days versus placebo on time-to-progression in metastatic midgut NETs [89]. Octreotide showed 66.7% stable disease at 6 months compared with 37.2% for placebo. This effect was similar in functional and nonfunctional carcinoid tumors. The time-to-progression was longer in the octreotide group at 14.3 versus 6 months. There was no significant reduction in symptoms (diarrhea or flushing). A similar study for PNETs has not yet been conducted.

In view of the limited activity of systemic chemotherapy, a variety of other agents have been examined. Recent interest has included studies of tyrosine kinase inhibitors such as sunitinib. In a study examining 107 patients with advanced NETs, (carcinoid n = 41; pancreatic endocrine tumor n = 66) the overall response

rate to sunitinib was 16.7% and 68% had stable disease. Median time-to-progression was 7.7 months in pancreatic neuroendocrine tumor patients and 10.2 months in carcinoid patients [90]. A recently reported multinational, randomized, double-blind, placebo-controlled trial confirmed the activity of sunitinib in patients with advanced, well-differentiated pancreatic neuroendocrine tumors. A total of 171 patients were entered on this study. Median progression-free survival was 11.4 months in the sunitinib group, compared with 5.5 months in the placebo group. Nine deaths were reported in the sunitinib group (10%) versus 21 in the placebo group (25%) [91]. A small study with temozolimide as monotherapy in 36 patients with advanced malignant NETs of multiple sites revealed radiologic response in 14%, stable disease in 53%, and overall time-to-progression of 7 months [92]. One small study of 29 patients with metastatic carcinoid, pheochromocytoma or pancreatic endocrine tumors showed somewhat better results with the combination of temozolimide and thalidomide, with a biochemical response rate of 40%, radiologic response of 25%, and a median duration of response of 13.5 months. Results were somewhat better in pancreatic endocrine tumors than in carcinoid tumors [93].

Additional excitement has been generated by a study of mTOR inhibitors, either alone or combined with octreotide therapy. mTOR is a serine–threonine kinase involved in the regulation of cell growth and death through apoptosis. It transduces signals mediated through the PI3K/Akt pathway and activates downstream protein kinases involved in ribosomal biosynthesis and translation of mRNAs vital for cell cycle progression. Upstream mTOR can be regulated by the tumor suppressors NF1 and PTEN and the protein complex TSC1/TSC2. Since neurofibromatosis type 1 and tuberous sclerosis are associated with development of PNETs, mTOR may be a potential target for medical therapy in patients with PNETs. Everolimus is an orally available mTOR inhibitor shown to be effective in inhibiting tumor growth in preclinical models [94]. A single institutional study of 30 patients with carcinoid and 30 patients with islet cell tumors treated with everolimus 5 and 10 mg daily combined with octreotide LAR 30 mg every 28 days showed a partial response rate of 22%, stable disease in 70% and progressive disease in 8% of patients with advanced carcinoid and islet cell carcinomas [95]. A subsequent multinational Phase II study, the RADIANT 1 trial, has reported the efficacy of everolimus alone and in combination with octreotide in patients with metastatic PNETs that have progressed on chemotherapy [96]. Monotherapy with everolimus produced stable disease in 67.8% of patients and a partial response in 9.6%, while combination

therapy resulted in 80% stable disease and 4.4% partial response. Everolimus also resulted in a decrease in CgA and neuron-specific enolase levels in 50.7 and 68.2% of patients, respectively. An early tumor marker response (>50% decrease by 4 weeks) was associated with a significantly longer progression-free survival. Further trials evaluating the efficacy of everolimus in NETs are planned. A randomized Phase III, double-blind, multicenter trial (the RADIANT 2 trial), will compare the combination of everolimus plus octreotide LAR with octreotide LAR plus placebo in patients with advanced carcinoid tumors. The RADIANT 3 trial is a Phase III trial studying everolimus as first-line therapy in patients with advanced PNETs. The results of this trial were recently reported [96]. A total of 410 patients with radiologic progression of disease were randomized to everolimus 10 mg once daily or placebo. The median progression-free survival was 11 months with everolimus compared with 4.6 months with placebo, representing a 65% reduction in estimated risk of progression or death. The proportion of patients alive and progression-free at 18 months was 34% with everolimus compared with 9% with placebo. Toxicities were mostly grade I or II [97]. A Phase II clinical trial (CALGB-80701) of everolimus with or without bevacizumab in patients with advanced or metastatic PNETs has recently been opened.

It remains difficult to assert that one form of systemic therapy is superior to another, due to the relatively small size of the available studies, the heterogenous group of tumors included in the studies, as well as the different degrees of pretreatment of the patients in these studies. Agents such as the tyrosine kinase inhibitor sunitinib and mTOR inhibitor everolimus appear to give response rates similar or better to conventional systemic therapy with less toxicity. In addition, some studies suggest that the mTOR inhibitors have a higher response rate in chemo-naive patients and appear useful in the multimodality treatment of these patients.

■ Other forms of treatment

The use of conventional external beam radiation therapy is little discussed; however, external beam radiation therapy can be useful for palliation of painful lesions including bony metastases. A study from the University of Michigan (MI, USA), that examined 36 patients treated at 49 tumor sites, showed effective palliation in 90% of patients and a 3-year local freedom-from-progression rate of 49%. A greater benefit was observed in those patients who received more than the median of 2 Gy per fraction biologically equivalent dose of 49.6 Gy [98].

Hepatic artery chemoembolization or bland embolization with gel foam remains a mainstay in the

management of patients with liver metastases. A recent study of chemoembolization combined with somatostatin therapy resulted in relief of systems in 78% of patients. Monitoring of serum pancreastatin levels predicted a response to this therapy in which radiographic improvement or stability were seen in 45% of patients [99]. Very good results have also been observed in radioembolization using resin ^{90}Y-microspheres. A total of 148 patients were treated in 185 separate procedures. A complete response was seen in 2.7%, partial response in 60.5%, stable disease in 22.7% and progressive disease in 4.5% of patients. No radiation-induced liver failure occurred and median survival was 70 months [100]. This appears to be a promising approach.

The use of radiolabeled somatostatin analogues has also been studied. In a study of 504 patients, treatment with the analogue ^{177}Lu-DOTA 0, TYR3 octreotate showed complete response in 2%, partial response in 28% and minor responses in 16% of patients. Median time-to-progression was 40 months and toxicity was minor [101]. A more detailed discussion of this topic is beyond the scope of this review. For details interested readers are referred to the ENETS consensus guidelines on peptide-receptor radionuclide therapy [20]. It should be noted that this therapy in general is quite costly and, in the USA, this form of therapy is usually not covered by third party insurance companies.

■ Prognosis

A variety of prognostic factors have been identified. In patients with metastatic disease, grade, mitotic rate and Ki67 indexes correlated with survival in the metastatic setting [102]. In patients undergoing resection, a study of the National Cancer Database revealed that age, grade and distant metastasis could be used to develop a post-resection prognostic score [103]. Similar results were shown by analyzing the SEER database, where advanced stage, higher grade and age were the strongest predictors of survival [104].

Patients with metastatic NETs frequently have prolonged survival. Due to the multiplicity of treatments that are available, and the apparent similarity in response rates and outcomes, assessment of quality of life (QOL) is critical. The Norfolk QOL tool is a seven-domain tool that has been shown to be reliable and reproducible [105]. Information on the effects of the various treatments on QOL will be important when it comes to selecting treatment.

Future perspective

Of critical importance in PNETs is the development and validation of biomarkers that will allow earlier recognition and detection as well as enhancement in the sophistication of techniques for relatively noninvasive tumor localization. Better biomarkers are needed for prediction of success of therapy as well as projected morbidity and mortality. While the role of TK and mTOR have recently drawn attention, a number of other pathways are coming to the fore with a great deal of promise for new therapeutics. The likelihood is that pharmacodynamics and pharmacotherapeutic efficacy will be greatly enhanced by the emergence of proteomics, metabolomics and genomics, which have already shown promise in predicting outcomes. Ultimately, PNETs have arrived with the need to enhance QOL and tools have been developed that relate outcomes, progression-free survival and hormonal and cytokine expression to the impact on QOL, clearly a highly desirable outcome for treatment of these tumors.

Financial & competing interests disclosure

Executive summary

- Pancreatic neuroendocrine tumors are uncommon, but the incidence is increasing.
- Advances in molecular genetics have increased the understanding of this diverse group of diseases and identified several new potential targets for therapy.
- In addition to Chromogranin A, recent data demonstrate that measurement of pancreastatin levels is useful in assessing response to therapy and prognosis.
- Imaging and localization techniques continue to improve and evolve.
- More cases of noninsulinoma pancreatogenous hypoglycemia syndrome are expected due to the increasing popularity of gastric bypass surgery. Surgical treatment remains a cornerstone of the management of the patients with neuroendocrine tumors.
- The use of newer agents such as tyrosine kinase inhibitors and mTOR inhibitors have shown promising results in patients with metastatic disease. Radiologic management of these tumors also continues to evolve.
- Due to the the long disease course, assessment of quality of life will be important in helping select among the various treatments.

Bibliography

1   Service GJ, Thompson GB, Service FJ *et al.* Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *N. Engl. J. Med.* 353, 249–254 (2005).

2   Won JG, Tseng HS, Yang AH *et al.* Clinical features and morphological characterization of 10 patients with noninsulinoma pancreatogenous hypoglycaemia syndrome (NIPHS). *Clin. Endocrinol. (Oxf).* 65, 566–578 (2006).

3   Patti ME, McMahon G, Mun EC *et al.* Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. *Diabetologia.* 48, 2236–2240 (2005).

4   Mathavan VK, Arregui M, Davis C *et al.* Management of postgastric bypass noninsulinoma pancreatogenous hypoglycaemia. *Surg. Endosc.* 24, 2547–2555 (2010).

5   Thompson GB, Service FJ, Andrews JC *et al.* Noninsulinoma pancreatogenous hypoglycemia syndrome: an update in 10 surgically treated patients. *Surgery* 128, 937–944 (2000).

6   Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* 135, 1469–1492 (2008).

7   Kloppel G, Anlauf M. Epidemiology tumour biology and histopathological classification of neuroendocrine tumours of the gastrointestinal tract. *Best Pract. Res. Clin. Gastroenterol.* 19, 507–517 (2005).

8   Oberg K, Eriksson B. Endocrine tumours of the pancreas. *Best Pract. Res. Clin. Gastroenterol.* 19, 753–781 (2005).

9   Falconi M, Plockinger U, Kwekkeboom DJ *et al.* Well-differentiated pancreatic nonfunctioning tumors/carcinoma. *Neuroendocrinology* 84, 196–211 (2006).

10   O'Toole D, Salazar R, Falconi M *et al.* Rare functioning pancreatic endocrine tumors. *Neuroendocrinology* 84, 189–195 (2006).

11   Jensen RT, Berna MJ, Bingham DB *et al.* Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer* 113, 1807–1843 (2008).

12   Gibril F, Schumann M, Pace A *et al.* Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. *Medicine (Baltimore)* 83, 43–83 (2004).

13   Jensen RT. Endocrine neoplasms of the pancreas. In: *Atlas of Gastroenterology.* Yamada T, Alpers DH, Kalloo AN *et al.* (Eds). Wiley-Blackwell, Oxford, England, 1875–1920 (2009).

14   Plockinger U, Wiedenmann B. Diagnosis of non-functioning neuro-endocrine gastro-enteropancreatic tumours. *Neuroendocrinology* 80(Suppl. 1), S35–S38 (2004).

15   Gullo L, Migliori M, Falconi M *et al.* Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. *Am. J. Gastroenterol.* 98, 2435–2439 (2003).

16   Yao JC, Hassan M, Phan A *et al.* One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J. Clin. Oncol.* 26, 3063–3072 (2008).

17   Bosman F, Carneiro F, Hruban R *et al. WHO Classification of Tumors of the Digestive System.* Bosman F, Carneiro F, Hruban R *et al.* (Eds). IARC Press, Lyons, France (2010).

18   Klimstra DS, Modlin IR, Coppola D *et al.* The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 39, 707–712 (2010).

19   Klimstra DS, Modlin IR, Adsay NV *et al.* Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. *Am. J. Surg. Pathol.* 34, 300–313 (2010).

20   Kwekkeboom DJ, Krenning EP, Lebtahi R *et al.* ENETS consensus guidelines for the standards of care in neuroendocrine tumors: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. *Neuroendocrinology* 90, 220–226 (2009).

21   Norton JA, Fraker DL, Alexander HR *et al.* Surgery to cure the Zollinger–Ellison syndrome. *N. Engl. J. Med.* 341, 635–644 (1999).

22   Gortz B, Roth J, Krahenmann A *et al.* Mutations and allelic deletions of the *MEN1* gene are associated with a subset of sporadic endocrine pancreatic and neuroendocrine tumors and not restricted to foregut neoplasms. *Am. J. Pathol.* 154, 429–436 (1999).

23   Speel EJ, Scheidweiler AF, Zhao J *et al.* Genetic evidence for early divergence of small functioning and nonfunctioning endocrine pancreatic tumors: gain of 9Q34 is an early event in insulinomas. *Cancer Res.* 61, 5186–5192 (2001).

24   Lollgen RM, Hessman O, Szabo E *et al.* Chromosome 18 deletions are common events in classical midgut carcinoid tumors. *Int. J. Cancer* 92, 812–815 (2001).

25   House MG, Herman JG, Guo MZ *et al.* Aberrant hypermethylation of tumor suppressor genes in pancreatic endocrine neoplasms. *Ann. Surg.* 238, 423–431 (2003).

26   Moore PS, Orlandini S, Zamboni G *et al.* Pancreatic tumours: molecular pathways implicated in ductal cancer are involved in ampullary but not in exocrine nonductal or endocrine tumorigenesis. *Br. J. Cancer* 84, 253–262 (2001).

27   Pellegata NS, Sessa F, Renault B *et al.* K-ras and p53 gene mutations in pancreatic cancer: ductal and nonductal tumors progress through different genetic lesions. *Cancer Res.* 54, 1556–1560 (1994).

28   Jiao Y, Shi C, Edil BH *et al. DAXX/ATRX, MEN1,* and *mTOR* pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science* 331, 1199–1203 (2011).

29   O'Toole D, Grossman A, Gross D *et al.* ENETS consensus guidelines for the standards of care in neuroendocrine tumors: biochemical markers. *Neuroendocrinology* 90, 194–202 (2009).

30   Calhoun K, Toth-Fejel S, Cheek J *et al.* Serum peptide profiles in patients with carcinoid tumors. *Am. J. Surg.* 186, 28–31 (2003).

31   Bloomston M, Al-Saif O, Klemanski D *et al.* Hepatic artery chemoembolization in 122 patients with metastatic carcinoid tumor: lessons learned. *J. Gastrointest. Surg.* 11, 264–271 (2007).

32   Jensen EH, Kvols L, McLoughlin JM *et al.* Biomarkers predict outcomes following cytoreductive surgery for hepatic metastases from functional carcinoid tumors. *Ann. Surg. Oncol.* 14, 780–785 (2007).

33   Stronge RL, Turner GB, Johnston BT *et al.* A rapid rise in circulating pancreastatin in response to somatostatin analogue therapy is associated with poor survival in patients with neuroendocrine tumours. *Ann. Clin. Biochem.* 45, 560–566 (2008).

34   Turner GB, Johnston BT, McCance DR *et al.* Circulating markers of prognosis and response to treatment in patients with midgut carcinoid tumours. *Gut* 55, 1586–1591 (2006).

35   Lipton A, Costa L, Ali S *et al.* Use of markers of bone turnover for monitoring bone metastases and the response to therapy. *Semin. Oncol.* 28, 54–59 (2001).

36   Brown JE, Cook RJ, Major P *et al.* Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. *J. Natl. Cancer Inst.* 97, 59–69 (2005).

37   Noone TC, Hosey J, Firat Z *et al.* Imaging and localization of islet-cell tumours of the pancreas on CT and MRI. *Best Pract. Res. Clin. Endocrinol. Metab.* 19, 195–211 (2005).

38   Kloppel G, Couvelard A, Perren A *et al.* ENETS consensus guidelines for the standards of care in patients with neuroendocrine tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. *Neuroendocrinology* 90(2), 162–166 (2009).

39   Rockall AG, Reznek RH. Imaging of neuroendocrine tumours (CT/MR/US). *Best Pract. Res. Clin. Endocrinol. Metab.* 21, 43–68 (2007).

40   Virgolini I, Traub-Weidinger T, Decristoforo C. Nuclear medicine in the detection and management of pancreatic islet-cell tumours. *Best Pract. Res. Clin. Endocrinol. Metab.* 19, 213–227 (2005).

41   Gibril F, Jensen RT. Diagnostic uses of radiolabelled somatostatin receptor analogues in gastroenteropancreatic endocrine tumours. *Dig. Liver Dis.* 36(Suppl. 1), S106–S120 (2004).

42   Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. *Best Pract. Res. Clin. Endocrinol. Metab.* 21, 69–85 (2007).

43   Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. *Ann. Surg.* 240, 757–773 (2004).

44   McLean AM, Fairclough PD. Endoscopic ultrasound in the localisation of pancreatic islet cell tumours. *Best Pract. Res. Clin. Endocrinol. Metab.* 19, 177–193 (2005).

45   Doppman JL, Miller DL, Chang R *et al.* Gastrinomas: localization by means of selective intraarterial injection of secretin. *Radiology* 174, 25–29 (1990).

46   Doppman JL, Chang R, Fraker DL *et al.* Localization of insulinomas to regions of the pancreas by intra-arterial stimulation with calcium. *Ann. Intern. Med.* 123, 269–273 (1995).

47   Strader D, Doppman J, Orbuch M *et al.* Functional localization of pancreatic endocrine tumors. In: *Endocrine Tumors of the Pancreas: Recent Advances in Research and Management. Series: Frontiers of Gastrointestinal Research.* Mignon M, Jensen RT (Eds). Karger Publishing Co, Basel, Switzerland, 282–297 (1995).

48   Norton JA. Surgical treatment of islet cell tumors with special emphasis on operative tumors. In: *Endocrine Tumors of the Pancreas: Recent Adances in Research and Management.* Mignon M, Jensen RT (Eds). Karger S, Basel, Switzerland, 309–332 (1995).

49   Shin LK, Brant-Zawadzki G, Kamaya A *et al.* Intraoperative ultrasound of the pancreas. *Ultrasound Q.* 25, 39–48 (2009).

50   Orlefors H, Sundin A, Garske U *et al.* Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. *J. Clin. Endocrinol. Metab.* 90, 3392–3400 (2005).

51   Gabriel M, Decristoforo C, Kendler D *et al.* 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J. Nucl. Med.* 48, 508–518 (2007).

52   Eriksson B, Orlefors H, Oberg K *et al.* Developments in PET for the detection of endocrine tumours. *Best Pract. Res. Clin. Endocrinol. Metab.* 19, 311–324 (2005).

53   Jackson JE. Angiography and arterial stimulation venous sampling in the localization of pancreatic neuroendocrine tumours. *Best Pract. Res. Clin. Endocrinol. Metab.* 19, 229–239 (2005).

54   Sundin A, Vullierme MP, Kaltsas G *et al.* ENETS guidelines for the standards of care in patients with neuroendocrine tumours: radiological examinations in patients with neuroendocrine tumours. *Neuroendocrinology* 90(2), 167–183 (2009).

55   Krenning EP, Kwekkeboom DJ, Oei HY *et al.* Somatostatin-receptor scintigraphy in gastroenteropancreatic tumors. An overview of European results. *Ann. NY Acad. Sci.* 733, 416–424 (1994).

56   Gibril F, Doppman JL, Reynolds JC *et al.* Bone metastases in patients with gastrinomas: a prospective study of bone scanning, somatostatin receptor scanning, and magnetic resonance image in their detection, frequency, location, and effect of their detection on management. *J. Clin. Oncol.* 16, 1040–1053 (1998).

57   Gibril F, Reynolds JC, Doppman JL *et al.* Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas. A prospective study. *Ann. Intern. Med.* 125, 26–34 (1996).

58   Termanini B, Gibril F, Reynolds JC *et al.* Value of somatostatin receptor scintigraphy: a prospective study in gastrinoma of its effect on clinical management. *Gastroenterology* 112, 335–347 (1997).

59   Berna M, Jensen R. Use of radiolabeled somatostatin receptor analogues in diagnosis of gastrointestinal neuroendocrine tumors. In: *A Century of Advances in Neuroendocrine Tumor Biology and Treatment.* Modlin IM, Oberg K (Eds). Felstein C.C.C.P., Hanover, Germany, 328–339 (2007).

60   Gibril F, Reynolds JC, Chen CC *et al.* Specificity of somatostatin receptor scintigraphy: a prospective study and effects of false-positive localizations on management in patients with gastrinomas. *J. Nucl. Med.* 40, 539–553 (1999).

61   Kann PH, Balakina E, Ivan D *et al.* Natural course of small, asymptomatic neuroendocrine pancreatic tumours in multiple endocrine neoplasia type 1: an endoscopic ultrasound imaging study. *Endocr. Relat. Cancer* 13, 1195–1202 (2006).

62   Libutti SK, Choyke PL, Bartlett DL *et al.* Pancreatic neuroendocrine tumors associated with von Hippel Lindau disease: diagnostic and management recommendations. *Surgery* 124, 1153–1159 (1998).

63   Langer P, Kann PH, Fendrich V *et al.* Prospective evaluation of imaging procedures for the detection of pancreaticoduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. *World J. Surg.* 28, 1317–1322 (2004).

64   Manfredi S, Pagenault M, de Lajarte-Thirouard AS *et al.* Type 1 and 2 gastric carcinoid tumors: long-term follow-up of the efficacy of treatment with a slow-release somatostatin analogue. *Eur. J. Gastroenterol. Hepatol.* 19, 1021–1025 (2007).

65   Gibril F, Doppman JL, Chang R *et al.* Metastatic gastrinomas: localization with selective arterial injection of secretin. *Radiology* 198, 77–84 (1996).

66   Frucht H, Norton JA, London JF *et al.* Detection of duodenal gastrinomas by operative endoscopic transillumination. A prospective study. *Gastroenterology* 99, 1622–1627 (1990).

67   Norton JA, Doppman JL, Jensen RT. Curative resection in Zollinger-Ellison syndrome. Results of a 10-year prospective study. *Ann. Surg.* 215, 8–18 (1992).

68   Norton JA, Alexander HR, Fraker DL *et al.* Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases, or survival in patients with Zollinger–Ellison syndrome? *Ann. Surg.* 239, 617–625 (2004).

69   Sugg SL, Norton JA, Fraker DL *et al.* A prospective study of intraoperative methods to diagnose and resect duodenal gastrinomas. *Ann. Surg.* 218, 138–144 (1993).

70   Christ E, Wild D, Reubi JC. Glucagon-like peptide-1 receptor: an example of translational research in insulinomas: a review. *Endocrinol. Metab. Clin. North Am.* 39, 791–800 (2010).

71   Srirajaskanthan R, Kayani I, Quigley AM *et al.* The role of ⁶⁸Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on ¹¹¹In-DTPA-octreotide scintigraphy. *J. Nucl. Med.* 51, 875–882 (2010).

72   Pais SA, Al-Haddad M, Mohamadnejad M *et al.* EUS for pancreatic neuroendocrine tumors: a single-center, 11-year experience. *Gastrointest. Endosc.* 71, 1185–1193 (2010).

73   Ishikawa T, Itoh A, Kawashima H *et al.* Usefulness of EUS combined with contrast-enhancement in the differential diagnosis of malignant versus benign and preoperative localization of pancreatic endocrine tumors. *Gastrointest. Endosc.* 71, 951–959 (2010).

74   Napoleon B, Alvarez-Sanchez MV, Gincoul R *et al.* Contrast-enhanced harmonic endoscopic ultrasound in solid lesions of the pancreas: results of a pilot study. *Endoscopy* 42, 564–570 (2010).

75   Malago R, D'Onofrio M, Zamboni GA *et al.* Contrast-enhanced sonography of nonfunctioning pancreatic neuroendocrine tumors. *AJR Am. J. Roentgenol.* 192, 424–430 (2009).

76   Kwekkeboom DJ, Krenning EP, Scheidhauer K *et al.* ENETS consensus guidelines for the standards of care in neuroendocrine tumors: somatostatin receptor imaging with (111) In-pentetreotide. *Neuroendocrinology* 90, 184–189 (2009).

77   Sundin A, Vullierme MP, Kaltsas G *et al.* ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: radiological examinations. *Neuroendocrinology* 90, 167–183 (2009).

78   Thompson NW, Vinik AI, Eckhauser FE. Microgastrinomas of the duodenum. A cause of failed operations for Zollinger-Ellison syndrome. *Ann. Surg.* 209, 396–404 (1989).

79   Boudreaux JP, Putty B, Frey DJ *et al.* Surgical treatment of advanced-stage carcinoid tumors: lessons learned. *Ann. Surg.* 241, 839–845 (2005).

80   Giva B, Pommier S, Thompson A *et al.* Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival. *Surgery* 140, 891–898 (2006).

81   Boudreaux JP, Klimstra DS, Hassan MM *et al.* The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas* 39, 753–766 (2010).

82   Hill JS, McPhee JT, McDade TP *et al.* Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. *Cancer* 115, 741–751 (2009).

83   Pitt SC, Pitt HA, Baker MS *et al.* Small pancreatic and periampullary neuroendocrine tumors: resect or enucleate? *J. Gastrointest. Surg.* 13, 1692–1698 (2009).

84   Falconi M, Zerbi A, Crippa S *et al.* Parenchyma-preserving resections for small nonfunctioning pancreatic endocrine tumors. *Ann. Surg. Oncol.* 17, 1621–1627 (2010).

85   Kulke MH, Anthony LB, Bushnell DL *et al.* NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas* 39, 735–752 (2010).

86   Turner NC, Strauss SJ, Sarker D *et al.* Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours. *Br. J. Cancer* 102, 1106–1112 (2010).

87   Massironi S, Conte D, Sciola V *et al.* Plasma chromogranin A response to octreotide test: prognostic value for clinical outcome in endocrine digestive tumors. *Am. J. Gastroenterol.* 105, 2072–2078 (2010).

88   Faiss S, Pape UF, Bohmig M *et al.* Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors – the International Lanreotide and Interferon Alfa Study Group. *J. Clin. Oncol.* 21, 2689–2696 (2003).

89   Rinke A, Muller HH, Schade-Brittinger *C et al.* Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J. Clin. Oncol.* 27, 4656–4663 (2009).

90   Kulke MH, Lenz HJ, Meropol NJ *et al.* Activity of sunitinib in patients with advanced neuroendocrine tumors. *J. Clin. Oncol.* 26, 3403–3410 (2008).

91   Raymond E, Dahan L, Raoul JL *et al.* Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N. Engl. J. Med.* 364, 501–513 (2011).

92   Ekeblad S, Sundin A, Janson ET *et al.* Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. *Clin. Cancer Res.* 13, 2986–2991 (2007).

93   Kulke MH, Stuart K, Enzinger PC *et al.* Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J. Clin. Oncol.* 24, 401–406 (2006).

94   Moreno A, Akcakanat A, Munsell MF *et al.* Antitumor activity of rapamycin and octreotide as single agents or in combination in neuroendocrine tumors. *Endocr. Relat. Cancer* 15, 257–266 (2008).

95   Yao JC, Phan AT, Chang DZ *et al.* Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a Phase II study. *J. Clin. Oncol.* 26, 4311–4318 (2008).

96   Yao JC, Lombard-Bohas C, Baudin E *et al.* Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a Phase II trial. *J. Clin. Oncol.* 28, 69–76 (2010).

97   Yao JC, Shah MH, Ito T *et al.* Everolimus for advanced pancreatic neuroendocrine tumors. *N. Engl. J. Med.* 364, 514–523 (2011).

98   Contessa JN, Griffith KA, Wolff E *et al.* Radiotherapy for pancreatic neuroendocrine tumors. *Int. J. Radiat. Oncol. Biol. Phys.* 75, 1196–1200 (2009).

99   Desai DC, O'Dorisio TM, Schirmer WJ *et al.* Serum pancreastatin levels predict response to hepatic artery chemoembolization and somatostatin analogue therapy in metastatic neuroendocrine tumors. *Regul. Pept.* 96, 113–117 (2001).

100   Kennedy AS, Dezarn WA, McNeillie P *et al.* Radioembolization for unresectable neuroendocrine hepatic metastases using resin ⁹⁰Y-microspheres: early results in 148 patients *Am. J. Clin. Oncol.* 31, 271–279 (2008).

101   Kwekkeboom DJ, de Herder WW, Kam BL *et al.* Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0, Tyr3] octreotate: toxicity, efficacy, and survival. *J. Clin. Oncol.* 26, 2124–2130 (2008).

102   Strosberg J, Nasir A, Coppola D *et al.* Correlation between grade and prognosis in metastatic gastroenteropancreatic neuroendocrine tumors. *Hum. Pathol.* 40, 1262–1268 (2009).

103   Billimoria K, Talamonti M, Tomlinson J *et al.* Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. *Ann. Surg.* 247, 490–500 (2008).

104   Halfdanarson TR, Rabe KG, Rubin J *et al.* Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann. Oncol.* 19, 1727–1733 (2008).

105   Vinik E, Carlton CA, Silva MP *et al.* Development of the norfolk quality of life tool for assessing patients with neuroendocrine tumors. *Pancreas* 38, e87–e95 (2009).

106   Vinik A, O'Dorisio T, Woltering E *et al.* Neuroendocrine tumors: a comprehensive guide to diagnosis and management. interscience institute, (2006).

107   Vinik AI, Gonzales MR. New and emerging syndromes due to neuroendocrine tumors. *Endocrinol. Metab. Clin. N. Am.* 40, 19–63 (2011).