REVIEW

Endocrine-Related Cancer (2012) **19** R163–R185

Neuroendocrine tumor disease: an evolving landscape

Andrea Frilling, Goran Åkerström[1]*, Massimo Falconi[2]*, Marianne Pavel[3]*, Jose Ramos[4]*, Mark Kidd[5]* and Irvin Mark Modlin[5]**

Department of Surgery and Cancer, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0HS, UK
[1]Department of Surgery, University Hospital, 75185 Uppsala, Sweden
[2]Department of Surgery University of Verona, Piazzale La Scuro, 37134 Verona, Italy
[3]Department of Gastroenterology and Hepatology, Charite University Medicine, Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany
[4]Department of Surgery, Lower Level Wits University D.G.M.C, 27 Eton Road, Parktown, 2193 Johannesburg, Gauteng, South Africa
[5]Department of Gastroenterological Surgery, Yale University School of Medicine, 333 Cedar Street, PO Box 2088062, New Haven, Connecticut 06520-8062, USA

(Correspondence should be addressed to I M Modlin; Email: imodlin@optonline.net)

*(A Frilling, G Åkerström, M Falconi, M Pavel, J Ramos, M Kidd and I M Modlin contributed equally to this work.)

Abstract

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) represent a heterogenous group of tumors arising from a variety of neuroendocrine cell types. The incidence and prevalence of GEP-NENs have markedly increased over the last three decades. Symptoms are often absent in early disease, or vague and nonspecific even in advanced disease. Delayed diagnosis is thus common. Chromogranin A is the most commonly used biomarker but has limitations as does the proliferative marker Ki-67%, which is often used for tumor grading and determination of therapy. The development of a multidimensional prognostic nomogram may be valuable in predicting tumor behavior and guiding therapy but requires validation. Identification of NENs that express somatostatin receptors (SSTR) allows for SSTR scintigraphy and positron emission tomography imaging using novel radiolabeled compounds. Complete surgical resection of limited disease or endoscopic ablation of small lesions localized in stomach or rectum can provide cure; however, the majority of GEP-NENs are metastatic (most frequently the liver and/or mesenteric lymph nodes) at diagnosis. Selected patients with metastatic disease may benefit from advanced surgical techniques including hepatic resection or liver transplantation. Somatostatin analogs are effective for symptomatic treatment and exhibit some degree of antiproliferative activity in small intestinal NENs. There is a place for streptozotocin, temozolomide, and capecitabine in the management of pancreatic NENs, while new agents targeting either mTOR (everolimus) or angiogenic (sunitinib) pathways have shown efficacy in these lesions.

Endocrine-Related Cancer (2012) **19** R163–R185

Introduction

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are also referred to as neuroendocrine tumors (NETs) or 'carcinoids', although this term is archaic and should be discarded in favor of a nomenclature reflective of specific cellular types and secretory products. These tumors are relatively rare, though increasing rapidly in prevalence (Lawrence *et al.* 2011*a*), tend to be slow-growing (although very aggressive variants exist), and often present a considerable diagnostic and therapeutic challenge. GEP-NENs are mainly found in the small and large intestines ($\sim$80%) with the remainder in the stomach and pancreas. The latter generally exhibit a more aggressive phenotype in comparison with tumors from other sites and, depending on the cell type of origin (α, β, etc.), produce specific symptom complexes such as glucagonoma or insulinoma. The clinical presentation and biological characteristics such as local invasion, fibrosis, and metastatic potential of gut tumors vary considerably depending on anatomical site, neuroendocrine cell(s) of origin (ECL, EC, D, G), and secretory products.

Overall, the primary tumor is usually small and overt clinical symptoms are often absent until metastasis

DOI: 10.1530/ERC-12-0024
1351–0088/12/019–R163 © 2012 Society for Endocrinology *Printed in Great Britain*
Online version via http://www.endocrinology-journals.org

has occurred. Despite considerable improvement in the understanding of GEP-NENs, the diagnosis of these lesions is commonly overlooked and, on average, is delayed for up to 5–7 years following the onset of clinical symptoms. This delay in diagnosis has resulted in a failure to optimize patient outcome because of the development of metastasis or significant local invasion. Some tumor lesions are only apparent when mechanical issues supervene. Tumors release a variety of bioactive products (amines/peptides) that may result in a systemic (carcinoid) syndrome. However, at least 50% of GEP-NENs (~50% of pancreatic and 15–20% of small intestinal (SI)), may be asymptomatic and are characterized as 'nonfunctional' (Schimmack *et al.* 2011). Local (peritoneal ~50%) or distant (cardiac ~25%) fibrosis may be an issue in EC cell small bowel-derived lesions. In general, the most effective, 'commonly' available imaging modality is somatostatin receptor (SSTR) scintigraphy (SRS; Modlin *et al.* 2005). Nevertheless, diagnosis is usually so late in the disease course that the only curative treatment, radical surgical intervention, is rarely an option.

Most surgery in advanced tumor stages reflects an attempt to ameliorate local tumor effects or an endeavor (Sisyphean) to diminish hepatic tumor burden. Somatostatin analogs (SSAs) are effective in ameliorating symptoms in ~80% and may prevent tumor progression with stabilization in ~50% of SI NENs (Rinke *et al.* 2009). Although 'predictably effective' specific tumor-targeted curative treatments are lacking, initial studies on novel agents such as tyrosine kinase inhibitors (TKIs) alone or in combination with the SSA class of agents have been reported to be 'variably' efficacious. This manuscript addresses a series of key areas relevant to the diagnosis and management of GEP-NEN disease.

Epidemiology and incidence

In the USA, the incidence of the disease based on the 2007 National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) database encompassing the period 2003–2007 was 5.76/100 000, and the prevalence was estimated to be ~35/100 000 in 2004. The incidence is increasing at a rate of 3–10% per year depending on the subtype. Furthermore, the overall NEN incidence (1973–2005) has increased from 1.1/100 000 in 1973 to 6.2/100 000 in 2005 (Lawrence *et al.* 2011*a*). Much of this increase probably reflects the introduction of more sensitive diagnostic tools as well as an increased awareness among physicians. Nevertheless, over the last 32 years (1973–2005), the incidence has increased to 520% representing an annual percentage increase of 5.8% (Modlin *et al.* 2008, Yao *et al.* 2008). Using regression analysis, it may conservatively be predicted that by 2015, the incidence and prevalence will be 10.9/100 000, and 65/100 000 respectively. The incidence is equivalent to esophageal cancer (4.5/100 000), testicular cancer (5.4/100 000), and myeloma (5.4/100 000). NENs occur most frequently in the gastrointestinal (GI) tract (60.9%) with the second most common location in the bronchopulmonary system (27.4%), followed by considerably less frequent locations such as the ovaries, testes, hepato-biliary system, and pancreas (Modlin *et al.* 2003). GEP-NENs are most common in the small intestine (30.8%), followed by the rectum (26.3%), colon (17.6%), pancreas (12.1%), stomach (8.9%), and appendix (5.7%) (Fig. 1). Given the overall indolence of the disease, the prevalence renders GEP-NENs the second most common GI cancer after colon cancer (Schimmack *et al.* 2011), and more prevalent than pancreatic, gastric, esophageal, or hepatic cancer or any two of these combined.

Protean symptomatology: late diagnosis: causes and sequelae

An early and accurate diagnosis is often delayed as most GEP-NENs are small, initially asymptomatic, and often misdiagnosed (Modlin *et al.* 2005). When symptoms and signs occur, they may be vague and nonspecific (e.g. intermittent acute abdominal pain in some instances due to intussusceptions; Wilson *et al.* 1974) and misinterpreted as irritable bowel syndrome, asthma, perimenopausal neurotic or part of an anxiety, or food allergy response (Mooney 1985, Jacobs 2009). In bioactive tumors, variable symptoms may develop depending on the tumor cell of origin and the effects of the individual secretory agents (e.g. serotonin (Robiolio *et al.* 1995) among others). The classical carcinoid syndrome is relatively uncommon (10–15%), typically consisting of diarrhea and cutaneous flushing and sweating (Mills 1956, Ringertz 1967). Emergency clinical presentations (~1–5%) such as acute abdomen (obstruction, perforation, bleeding, appendicitis; Brophy & Cahow 1989, Sieren *et al.* 2010) and abdominal angina (major vessel compromise) arise due to either local tumor mass effects or tumor-induced fibrosis (Pellikka *et al.* 1993).

Strategies for identification and biological assessment

The development of sensitive and specific plasma and/or serum assays for peptides and amines produced by GEP-NENs as well as the development of

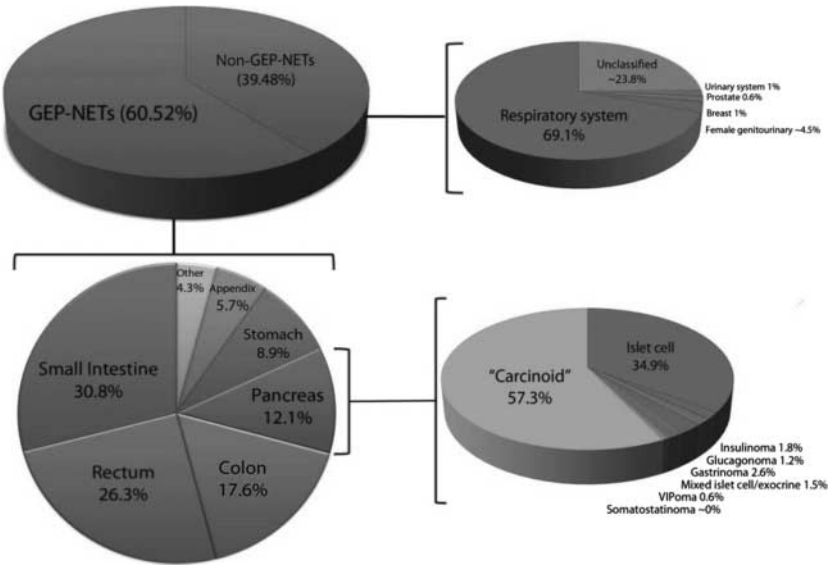

Figure 1 Distribution of 49 012 NENs from the SEER 1973–2007 tumor registry database. Pie charts reflect the distribution of NENs by anatomical site and tumor type. Total NEN distribution (top), GEP-NEN distribution (bottom left), and pancreatic NEN distribution (right). Non-GEP-NENs are predominantly located in the respiratory system (bronchopulmonary NENs ~70%, top right). Pancreatic 'carcinoids' does not reflect serotonin-secreting tumors, but instead reflects SEER-based reporting annotations for the lesions.

immunohistochemistry panels has facilitated both blood and tissue diagnosis. In particular, the measurement of chromogranin A (CgA) has provided a platform to support the diagnosis of the disease (Modlin *et al*. 2010*a*), while the use of a variety of imaging techniques has significantly enhanced the anatomical identification and diagnosis of lesions (Kayani *et al*. 2008).

Circulating and tissue expression of CgA

CgA is a water-soluble acidic glycoprotein stored in the secretory granules of neuroendocrine cells, and its detection in plasma can be used as a general tumor marker for GEP-NENs including 'nonfunctioning' tumors (Lawrence *et al*. 2011*b*). Other markers that are generally less sensitive and specific overall but may be useful in unambiguously identifying lesions include 5-hydroxy tryptophan (HT) (EC cell-derived tumors), histamine (ECL cell-derived tumors), gastrin (gastrinomas), or pancreatic products e.g. insulin (insulinomas). Although plasma CgA levels are sensitive (70–85%) markers of GEP-NENs, they are nonspecific and elevated in other types of NENs as well as pancreatic, small-cell lung, and even some prostate carcinomas (Lawrence *et al*. 2011*b*). In addition to its diagnostic value, plasma CgA levels have some correlation with tumor burden and may, in some circumstances, be used to monitor treatment of NENs (Arnold *et al*. 2008*b*). CgA reduction of >80% following surgery of neuroendocrine hepatic metastases is predictive of subsequent symptom relief and disease control and associated with improved outcome. False-positive elevations of CgA occur in renal impairment and during proton-pump inhibitor therapy.

Urinary 5-hydroxyindole-5-acetic acid

Urinary 5-hydroxyindole-5-acetic acid (5-HIAA; 24 h measurement), the degradation product of 5-HT, is a useful but cumbersome laboratory marker. The specificity of 5-HT-producing NENs is ~85% although tryptophan/serotonin-rich foods (bananas, avocados, plums, eggplant, tomatoes, plantain, pineapples, and walnuts) can provide false elevations. Overnight 5-HIAA collection may be as sensitive as the more burdensome 24-h collection in identifying patients with 5-HT producing tumors (O'Toole *et al*. 2009).

Tissue Ki-67 assessment

The rate of proliferation of a NEN can be quantified by counting the number of mitoses per high powered field on a hematoxylin- and eosin-stained slide, or by counting the percentage of cells that stain positive with the Ki-67 antibody. The defining quality of Ki-67 as a 'proliferative' marker is an exclusive expression by dividing cells in the S, G_2, and M phases of the cell cycle. The percentage of cells that show positive immunohistochemical staining (the Ki-67%)

is 'presumed' to denote the proportion of cells that are actively dividing as viewed on a pathological slide. The Ki-67% has been widely accepted as the cardinal feature of tumor grading. Indeed, in the most recent WHO NEN classification, it is used as a key determinant in tumor grading (Bosman *et al*. 2010).

In NENs, the prognostic value of the Ki-67% separates NENs into NET grade 1 (NET G1), NET grade 2 (NET G2), and neuroendocrine carcinoma (NEC) by Ki-67% of ≤ 2, 3–20, and >20% respectively. Validation of the prognostic ability of Ki-67 has shown differences in 5-year survival using a binary schema of <2 or >2%: pancreatic NENs (PNENs) showed 100 vs 54% survival at 5 years (La Rosa *et al*. 1996); a mixed group of GEP-NENs showed 56 vs 14% and 90 vs 54%, and a mixed group of pancreatic, SI, and colorectal NENs showed 76 vs 29% (Arnold *et al*. 2008*a*). More recently, the use of Ki-67 was defined for PNENs in a study on 1072 patients with at least 2 years of follow-up (Rindi *et al*. 2012). Multivariable modeling indicated curative surgery, TNM staging, and grading were effective predictors of death, and grading was the second best independent predictor of survival in the absence of staging information. A direct comparison of the UICC/AJCC/WHO 2010 TNM and the ENETs TNM staging system identified the latter to be superior (Rindi *et al*. 2012).

Topographic and functional localization

Upper GI endoscopy

Upper GI endoscopy can identify lesions to the level of the ligament of Treitz, and colonoscopy can detect colon and rectal NENs as well as some terminal ileal tumors. Enteroscopy, both fiberoptic and capsule, is effective but have limitations. The double balloon or push technique is time consuming and uncomfortable. Endoscopic ultrasonography (EUS) is a highly sensitive method for diagnostic and preoperative evaluation of NENs of the stomach, duodenum, pancreas, and rectum, as it identifies submucosal lesions and facilitates staging. EUS with fine needle aspiration is useful for histological assessment and grading.

Contrast techniques

Contrast techniques such as enteroclysis and barium contrast studies have been widely supplanted by computed tomography (CT) and magnetic resonance imaging (MRI). A small primary tumor is difficult to visualize if a secondary tumor effect due to fibrosis has not developed. Characteristic findings include mass lesions, radiating strands of fibrosis, and spiculation (calcification) with traction or fixation of bowel. Specificity may be as low as 22% for CT, and both MRI and CT can be negative in up to 50% of SRS positive lesions. The advent of multidetector CT and CT enteroclysis techniques may enhance the detection of small primary tumors.

Nuclear imaging techniques

Approximately 70–90% of GEP-NENs express multiple SSTR subtypes with a predominance of $sstr_2$ and $sstr_5$ receptors. Labeling of SSAs with diagnostic radioisotopes enables visualization of SSTR expressing tissues via receptor mediated internalization and consecutive intracellular trapping of the degraded peptide. SRS, based on the use of [indium-111](^{111}In)-diethylenetriamine-pentaacetic acid DTPA)-D-Phe^1-octreotide (^{111}In pentetreotide, OctreoScan, Mallinckrodt Medical BV, Petten, The Netherlands), has proven to be superior to standard imaging modalities in detection of primary tumors and their metastases. A review of over 1200 patients revealed a median detection rate of 89% and median sensitivity of 84% (Modlin *et al*. 2010*c*). This reflects an identification of lesions predominantly expressing high density of $sstr_2$. The role of SRS as a monitor of treatment efficacy and disease progression remains to be verified (Stokkel *et al*. 2011).

Although SRS is very effective, the method is hampered by various factors, such as the necessity of a background ratio of at least 2:1, relatively low spatial resolution particularly for small tumors, and the lack of precise quantification of receptor density and radionuclide biodistribution. These drawbacks have, to some extent, been overcome by the introduction of newer SSAs such as DOTA-D-Phe^1-Try^3-octreotide (DOTATOC), DOTA-D-Phe^1-Try^3-octreotate (DOTATAE), and DOTA-1-NaI Try^3-octreotide (DOTANOC), which exhibit not only a higher $sstr_2$ affinity but also affinity to $sstr_3$ and $sstr_5$ (DOTANOC). Optimization of the profile is achieved when labeled with a generator-derived positron emitter such as ^{68}Ga, which is suitable for positron emission tomography (PET) imaging (Kwekkeboom *et al*. 2010). Precise fusion of functional PET images with a morphological image tools such as CT (PET/CT) has provided additional anatomical information with regard to localization of lesions and definition of lesion boundaries with the added benefit of CT-based attenuation correction of the emission results (Fig. 2). Treatment with SSAs does not markedly reduce binding of tracers to SSTR and does not need to be interrupted before imaging (Haug *et al*. 2011).

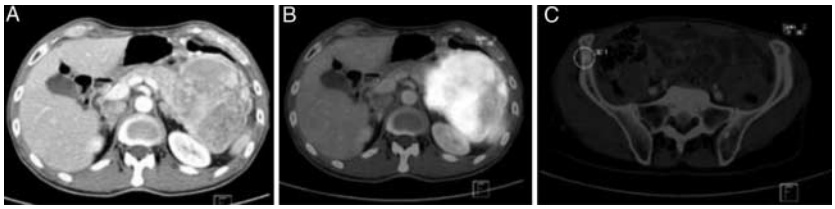

Figure 2 Abdominal CT of a 62-year-old patient with a 20 cm pancreatic neuroendocrine tumor (A). ^{68}Ga-DOTATOC PET/CT confirmed the location and dimensions of the primary lesion (B) and in addition disclosed a solitary bone metastasis (C). The skeletal deposit was identifiable only on the PET sequence.

Comparison of OctreoScan with PET using ^{68}Ga-DOTA reveals the potential of this novel technique. Thus, additional evidence of metastatic lesions was evident in >30%, particularly when localized within the skeletal system (Buchmann *et al.* 2007), and localization of unknown primary NENs was established in 39% of cases (Prasad *et al.* 2010). The superiority of ^{68}Ga-DOTA-based PET/CT over anatomic imaging using CT or MRI and its impact on treatment were demonstrated in a recent study on 52 NEN patients who underwent both standard morphological imaging and ^{68}Ga-DOTATOC PET/CT (Frilling *et al.* 2010). The primary treatment decision, based solely on CT and/or MRI results, was altered in 59.6% of patients when ^{68}Ga-DOTATOC PET/CT results were considered.

Given the low metabolic rate of most well-differentiated NENs, standard PET imaging using ^{18}F-fluorodeoxyglucose is relatively ineffective, but positivity denotes highly aggressive lesions (poorly differentiated NENs). ^{11}C-5-HT and ^{18}F-DOPA may have a role in patients with pancreatic and intestinal NENs that have negative or inconclusive results on SSTR-based imaging (Koopmans *et al.* 2008).

Predictive indices of tumor behavior

Gastric NENs

For gastric NENs, the important predictors of tumor behavior are type, size, and histology. When a gastric NEN is detected, it is crucial to determine serum gastrin levels, obtain a tumor biopsy, as well as multiple biopsies from the gastric body and fundic mucosa, to reveal signs of atrophic gastritis vs hypertrophy, and also to determine pH of the gastric aspirate. This will reveal the type of gastric NEN and guide the treatment approach, and provide information in regard to prognosis.

Type 1

Type 1 gastric NENs occur in patients with chronic atrophic gastritis (CAG), with hypergastrinemia due to the absence of gastric acid, as multiple, small gastric body and fundus polyps, together with mucosal atrophy and ECL-cell hyperplasia (Borch *et al.* 2005, Ruszniewski *et al.* 2006, Akerstrom & Hellman 2009, Åkerström *et al.* 2009). Polyps <1 cm are generally indolent and can be followed with yearly endoscopic surveillance. Tumors >1 cm, or multiple lesions without invasion can be treated with endoscopic mucosal resection or multiple band mucosectomy (Hopper *et al.* 2009), a few larger invasive tumors require local surgical excision, and only rare larger, multifocal lesions need gastric resection (Burkitt & Pritchard 2006). The CAG–NENs have low incidence of lymph node metastases, exceptionally liver metastases (LM), and disease-related deaths are rare. As an alternative, SSA therapy has been used. This was associated with regression of these lesions and occasionally reductions in circulating gastrin (Fykse *et al.* 2004, Campana *et al.* 2008), but the effects are short term (~1 year) and disease progression has been noted at 5 years following the termination of therapy (Jianu *et al.* 2011).

Type 2

Type 2 gastric NENs occur in multiple endocrine neoplasia type 1 (MEN1) Zollinger–Ellison syndrome (ZES) patients, as multiple polyps in the gastric body and fundus, with hypertrophic surrounding mucosa, and low pH in the gastric aspirate (pH<2; Borch *et al.* 2005, Ruszniewski *et al.* 2006, Akerstrom & Hellman 2009, Åkerström *et al.* 2009). The malignant potential is intermediate, with lymph node metastases in ~30% and LM in 10–20%. Polyps >1 cm are treated with local excision, whereas gastric resection is required for larger lesions. Removal of the source of hypergastrinemia is the critical aim of surgery; regression of type 2 lesions may be encountered following successful gastrinoma excision (Richards *et al.* 2004). SSAs may have efficacy in treatment of these lesions (Tomassetti *et al.* 2000) and have been used to control hypergastrinemia and ulceration (Campana *et al.* 2005), although proton-pump inhibitors are the treatment of choice (Lew *et al.* 2000).

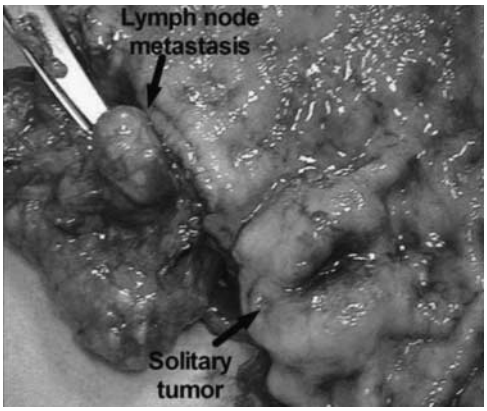

Figure 3 Sporadic, solitary type 3 gastric NEN with lymph node metastasis treated with a partial gastric resection. Reproduced, with permission, from Åkerström G, Hellman P & Hessman O 2009 Gastrointestinal carcinoids. In *Endocrine Surgery*, 4th edn, pp 147–176. Ed T Lennard. Copyright 2009 Elsevier.

Type 3

Type 3 sporadic gastric NENs occur in patients with normal serum gastrin, as often large (>2 cm), clearly invasive gastric body and fundus tumors (Fig. 3; Borch *et al*. 2005, Ruszniewski *et al*. 2006, Akerstrom & Hellman 2009, Åkerström *et al*. 2009). The tumors are aggressive and often infiltrated the entire gastric wall, with regional lymph node metastases in 20–50% and LM ultimately in two-thirds of patients. Large tumors with a high mitotic rate and high Ki-67% are even more aggressive. In general, the type 3 gastric NEN requires partial gastric resection with regional lymph node clearance or gastrectomy for metastasized tumors comparable to procedures for gastric adenocarcinoma. Only occasionally endoscopic resection may be performed for small nonmetastasized tumors (Kaehler *et al*. 2006). The 5-year survival rate is ~50% in locoregional disease and ~10% with distant metastases.

Midgut NENs

While in gastric, appendiceal, and colorectal NENs the risk for metastases relates to tumor size, midgut NENs have regional and ultimately distant metastases irrespective of primary tumor size. Most midgut NENs have a low proliferation rate with Ki-67% of <2% and can present with LM, although Ki-67%-based staging appears to have prognostic significance (Jann *et al*. 2011). Some tumors have higher proliferation rate and tend to progress more rapidly. Midgut NENs often originate in the distal small intestine as either a small, submucosal tumor or as multicentric lesions. The incidence of mesenteric lymph node metastases is as high as 70–90% irrespective of tumor size (Makridis *et al*. 1996, 1997, Ohrvall *et al*. 2000, Hellman *et al*. 2002, Akerstrom & Hellman 2009, Åkerström *et al*. 2009). Large mesenteric tumors mass together with marked surrounding fibrosis may encase the mesenteric root and cause intestinal obstruction or vascular impairment (Fig. 4). Venous ischemia may occur in part of the intestine, causing diarrhea, or functional obstruction, and ultimately, intestinal angina and malnutrition. Mesenteric metastases may often be removed by dissection of the mesenteric root, with preservation of main mesenteric vessels, and collateral circulation along the intestine, allowing limited intestinal resection (Ohrvall *et al*. 2000, Akerstrom & Hellman 2009). Studies on survival have revealed favorable outcome in patients subjected to radical resection of mesenteric metastases, with survival benefit also in presence of LM (Makridis *et al*. 1997, Hellman *et al*. 2002). Several authors have reported marked palliation of abdominal symptoms after removal of the mesenteric tumor burden (Makridis *et al*. 1996, 1997, Wangberg *et al*. 1996, Ohrvall *et al*. 2000, Hellman *et al*. 2002, Boudreaux *et al*. 2005). Early surgical intervention may avoid abdominal complications and should be done before mesenteric tumor growth exacerbates and renders local inoperability (Makridis *et al*. 1996). The midgut NEN, however, is tenacious and, in almost all patients, is often associated with synchronous or metachronous LM with delayed manifestation of up to 10 years or even more (Makridis *et al*. 1997, Åkerström *et al*. 2009).

Pancreatic NENs

PNENs consist of functioning lesions related to syndromes of hormone excess and of nonfunctioning tumors. All these entities may be sporadic or associated with inherited neoplasia syndromes such as MEN1

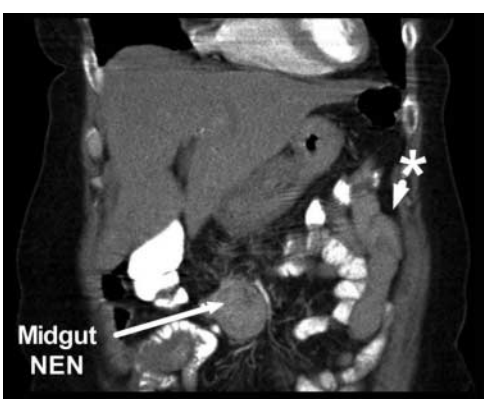

Figure 4 CT image of mesenteric metastasis of midgut NEN, the distal intestine is edematous due to venous stasis (indicated by *).

(Akerstrom & Hellman 2009) or VHL (Oberg 2010). Apart from sporadic insulinomas, which are in general benign, PNENs are frequently malignant with tumor size as an important predictor of progression in both, sporadic and MEN1-related tumors.

Insulinomas

Insulinomas are sporadic, benign small tumors in 90% of cases, whereas the malignant forms should be suspected when tumor size exceeds 4 cm. In contrast to the sporadic type, the MEN1-associated insulinomas may be malignant also when small in size (Akerstrom & Hellman 2009). According to the benign nature of the disease, the vast majority of insulinomsa are amendable to parenchyma-sparing types of resection.

Gastrinomas

Gastrinomas occur in most instances within the head of the pancreas and/or duodenum either as sporadic or MEN1-associated lesions (~30%) with comparable rates of malignancy in both sites (Metz & Jensen 2008, Akerstrom & Hellman 2009). They have a low tendency to grow; however, 60–70% are malignant at initial manifestation (Jensen *et al*. 2008, Goudet *et al*. 2010). Resection of the primary tumor should be anticipated in all patients suitable for surgery, as it was shown to improve prognosis in both, sporadic and hereditary cases due to lower rate of LM when compared with conservatively managed patients (Norton *et al*. 2006). During the last decades, duodenal gastrinomas have been increasingly recognized and are now known to account for ~60% of sporadic and ~90% of MEN1-associated ZES case. In this location, the tumors are often small with diameters of 5–10 mm or even less but are associated with lymph node metastases, which often have grown larger than the primary tumor themselves and are easily be mistaken as such.

Most pancreatic gastrinomas are suitable for limited, locally focused resections in combination with peripancreatic lymphadenectomy. In the absence of locoregional lymph node metastasis, preoperative location can be extremely difficult and precise localization depends on the adept fingers of the surgeon during duodenectomy. Depending on the localization, pylorus-preserving pancreatoduodenectomy or distal pancreatic resection and lymph node dissection may be the procedure of choice for larger or invasively growing lesions. A duodenal gastrinoma tumor can be managed with local excision via longitudinal duodenotomy and regional lymph node resection. Survival is excellent for small duodenal gastrinomas (~90% at 3 years) (Mortellaro *et al*. 2009) but worse for pancreatic and large duodenal tumors, particularly when LM are present (Norton 2005).

The extent of surgery is a controversial debate in MEN1-ZES. More conservative approaches encompass duodenotomy with excision of duodenal wall tumors, enucleation of any lesion localized within the pancreatic head, peripancreatic lymph node dissection, and concomitant distal pancreatic resection (Thompson procedure) (Thompson 1998, Gauger *et al*. 2009). For tumors regionalized mainly in the pancreatic head and with the presumption that virtually all MEN1-ZES patients also have duodenal lesions, several groups now favor pylorus-preserving pancreaticoduodenectomy, a radical approach that can achieve biochemical cure but is associated with a higher morbidity risk and may complicate consecutive surgery for recurrent tumors in the pancreatic remnant (Norton & Jensen 2004, Tonelli *et al*. 2006, Fendrich *et al*. 2007). Pancreas-preserving total duodenectomy as reported by Imamura *et al*. (2005) is an effective technique to entirely remove multiple duodenal gastrinomas in selected patients.

Glucagonomas and VIPomas

Glucagonomas and VIPomas are rare tumors, often presenting with metastases at initial diagnosis (~70%) and requiring aggressive treatment to alleviate the severe hormonal symptoms (Doherty 2005, Akerstrom & Hellman 2009). In both tumor types formal, oncological pancreatic resection with peripancreatic lymph node dissection is mandatory to attempt favorable survival (Akerstrom *et al*. 2004). Slow tumor progression may necessitate repeated surgical interventions for lymph node and/or LM during the course of the disease (Madeira *et al*. 1998). Prophylactic cholecystectomy to facilitate later SSA therapy significantly ameliorated symptoms in a series of patients with VIPoma and glucagonoma and may be considered (Nikou *et al*. 2005, Kindmark *et al*. 2007). Overall survival is ~4 years and may extend to 15 years in single cases (Smith *et al*. 1998). In a series of six patients with glucagonoma treated during a period of 25 years, Eldor *et al*. (2011) achieved a median survival time of 6.25 years (range 2–11) from diagnosis and 8 years (range 8–16) from initial symptoms by following a multimodal treatment concept including SSAs, surgery (in three/six patients), peptide receptor radiotherapy (two responses in three/six patients), and chemotherapy (two responses in three/six patients. Ghaferi *et al*. reported on four patients with VIPomas. Of them, two patients were tumor-free 17–22 months

after surgery and one patient, 68 months postoperatively after adjuvant SSA treatment and radiofrequency ablation of LM (Ghaferi *et al*. 2008).

Nonfunctioning PNENs

Nonfunctioning PNENs are often large when detected, although smaller lesions are being increasingly recognized due to the widespread use of cross-sectional imaging techniques (Vagefi *et al*. 2007). Sporadic nonfunctioning PNENs >2 cm are more likely malignant and are often associated with lymph node or LM (Ekeblad *et al*. 2008, Bettini *et al*. 2011) as tumors originating from *MEN1* deletions (Falconi *et al*. 2006). In these larger tumors, a standard oncological pancreatic resection with peripancreatic lymphadenectomy is recommended, whereas parenchyma-preserving resections (i.e. enucleation or central pancreatectomy) could be advocated for PNENs <2 cm (Aranha & Shoup 2005, Falconi *et al*. 2010). In a series of 177 patients, Bettini *et al*. (2011) showed a clear correlation between tumor size and malignancy and recommended nonsurgical management of incidentally detected lesions <2 cm in size. Patients with well-differentiated PNENs have favorable prognosis after radical surgical removal, whereas those with poorly differentiated tumors have a poor survival despite surgery. These patients appear to benefit from chemotherapy as an up front treatment (Ekeblad *et al*. 2008). Survival is clearly related to the Ki-67%, nodal status, and evidence of LM (Bettini *et al*. 2008). Patients with Ki-67 <2% have a 5-year survival rate of 80% compared with 40% for those with Ki-67 >2% (Ekeblad *et al*. 2008). Results of surgery in PNENs with vascular involvement, of mainly the portal vein, are encouraging and surgery should also be considered for the treatment of LM (Bartsch *et al*. 2000, Hellman *et al*. 2000, Kouvaraki *et al*. 2005, Akerstrom & Hellman 2009, Capurso *et al*. 2011). In general, surgical approach is recommended in well-differentiated NENs (WHO groups I and II), whereas patients with poorly differentiated NEC (WHO group III) should primarily be treated with chemotherapy.

Pancreaticoduodenal tumors account for the major cause of death in patients with MEN1 syndrome. Elevated serum hormone biomarkers indicate development of functioning lesions even before a clinical hormonal syndrome has occurred (Bartsch *et al*. 2005, Kouvaraki *et al*. 2006, You *et al*. 2007, Ekeblad *et al*. 2008, Akerstrom & Hellman 2009). When such a syndrome has developed, 30–50% of patients already have metastases. Up to 80% of patients affected by MEN1 develop synchronous or metachronous pancreatic islet cell or duodenal tumors, of them gastrinomas in 54%, insulinomas in 18%, and nonfunctional tumors in 80–100% (Triponez & Cadiot 2007). As occurrence of metastases in nonfunctioning PNENs rises markedly with tumor size (>10 mm), several groups consequently recommend surgical removal of lesions exceeding this size (Bartsch *et al*. 2005, Kouvaraki *et al*. 2006, Triponez *et al*. 2006, You *et al*. 2007, Ekeblad *et al*. 2008, Akerstrom & Hellman 2009). Others claim a tumor size >2 cm as indication for surgery, but it is clear that a large proportion of these patients already have metastases (Bartsch *et al*. 2005, Kouvaraki *et al*. 2006, Triponez *et al*. 2006, Triponez & Cadiot 2007, You *et al*. 2007, Ekeblad *et al*. 2008, Akerstrom & Hellman 2009). Clearly this remains an open question as outlined in current guidelines and deserves a prospective analysis (Falconi *et al*. 2012, Ramage *et al*. 2012). Due to the high rate of multicentric lesions, intraoperative ultrasound is mandatory. In most instances, distal pancreas resection for the removal of tumors localized within the tail combined with enucleation of pancreatic head lesions is performed. Total pancreatectomy may be needed for recurrent, rapidly growing, or unusually large multicentric tumors but is avoided as long as possible due to diabetes that will follow.

Options for surgical management of LM

The propensity of GEP-NENs to commonly metastasize to the liver represents an important adverse prognostic factor in the advance of the disease. At the time of diagnosis, $\sim$75% of GEP-NENs (excluding appendix and stomach) exhibit synchronous LM (Saxena *et al*. 2010). Under such circumstances, 5-year survival has been reported to be 13–54% in historical series (McDermott *et al*. 1994). This outcome is worse than that for localized or locally advanced disease but is better in respect of ductal adenocarcinoma. Moreover, individuals with synchronous LM also often present with debilitating symptoms related both to the extent of the hepatic tumor mass and the sequel of excessive production of bioactive products by the tumor.

There are a number of invasive options available for the treatment of GEP-NEN LM, with either curative or palliative intent for decreasing the tumor burden. These include resective strategies as well as locally ablative techniques (e.g. radio frequency ablation, cryoablation, and microwave ablation), percutaneous liver-directed interventions (transcatheter arterial bland embolization or chemoembolization and selective internal radiation therapy), and liver transplantation (LT). Surgery is of

specific benefit in that it is effective in relieving symptoms and is the only potentially curative treatment if complete resection (R0/R1 resection) of the primary tumor and liver lesions is achieved. Unfortunately, given the late stage presentation and the high incidence of multifocal and bilobar deposits, radical liver resection is possible in <20% of patients (Steinmuller *et al*. 2008). In order to facilitate better patient selection for treatment, a classification system for neuroendocrine LM based on morphological extent of hepatic involvement has been proposed: type I, a single metastasis of any size; type II, an isolated metastatic bulk accompanied by smaller deposits, with both liver lobes always involved, and type III, disseminated metastatic spread, with both liver lobes always involved, with single lesions of varying size and virtually no normal liver parenchyma (Frilling *et al*. 2009). Significant differences in Ki-67% and in outcome among the three types suggest that not only the tumor grade but also the growth type reflects the biological aggressiveness of the disease (Hentic *et al*. 2010). Of note is that intratumoral heterogeneity causing discrepant proliferative rates, as reported in nearly 50% of cases, has to be considered (Yang *et al*. 2011).

Under ideal circumstances, resection is associated with a low mortality rate (0–5%) while an acceptable morbidity is ~30% (Steinmuller *et al*. 2008). Irrespective of the primary tumor site and in absence of nonresectable extrahepatic disease, surgery should therefore be proposed in all well-differentiated GEP-NEN patients with LM in whom complete resection is feasible. It should be noted that individuals with high-grade NENs probably represent a separate disease entity and are unsuitable for surgical treatment as they exhibit a median overall survival of only 6 months after partial hepatectomy (Cho *et al*. 2008). It is therefore critical that a core needle biopsy or laparoscopically guided biopsy is undertaken before the decision for surgery to establish tumor grading. This preemptive strategy will optimize patient management by excluding those with poorly differentiated tumors who will not benefit from surgical treatment.

The extent of hepatic resection is defined by variables including the number and size of LM, intrahepatic location of disease, and the hepatic reserve itself. It ranges from a limited, nonanatomical resection to hepatectomy, in some instances in combination with locally ablative measures (Elias *et al*. 2003, Sarmiento *et al*. 2003). Ideally, these patients should be treated in units with extensive experience in advanced hepatic surgery in order to achieve complete disease elimination particularly when the metastatic spread is primarily assessed as nonresectable (Kianmanesh *et al*. 2008). Postresectional overall 5-year survival rates range from 46% in earlier series (Dousset *et al*. 1996) to 85–94% in more recent reports (Mazzaferro *et al*. 2007, Kianmanesh *et al*. 2008, Frilling *et al*. 2009, Scigliano *et al*. 2009). Early recurrence however is to be expected with 5-year disease-free survival of <50% in most series (Sarmiento *et al*. 2003, Mazzaferro *et al*. 2007, Kianmanesh *et al*. 2008, Scigliano *et al*. 2009). The limited number of patients suitable for hepatic resection and the high postresectional recurrence rate highlight the need for neo-adjuvant and adjuvant strategies, such as in approaches for colorectal LM. While TACE (Touzios *et al*. 2005) has been shown to have the potential to increase the number of patients eligible for hepatic surgery, adjuvant therapy with streptozotocin and 5-fluorouracil (FU) has failed to demonstrate the benefit in terms of longer recurrence-free survival (Maire *et al*. 2009).

In contrast to liver secondaries of adenocarcinomas, nonresectable neuroendocrine LM are an indication for LT under consideration of strict evaluation process (Lerut *et al*. 2007, Bonaccorsi-Riani *et al*. 2010, Gedaly *et al*. 2011). While nonresectable extrahepatic tumor manifestation, Ki-67% >15%, and severe carcinoid heart disease are generally accepted as exclusion criteria for LT, patient age (<50 vs >50 years), the dynamics of the hepatic tumor growth (stable disease vs rapid tumor progress), the extent of hepatic involvement, and timing of transplantation (first-line treatment vs an ultima ratio approach after unsuccessful previous treatment) remain controversial (Olausson *et al*. 2002, Rosenau *et al*. 2002, Le Treut *et al*. 2008). Although encouraging overall 5-year survival rates of 50–90% have been reported in newer series, disease recurrence within 2–3 years after LT is to be expected (Frilling *et al*. 2006, van Vilsteren *et al*. 2006, Olausson *et al*. 2007). The availability of novel effective targeted therapies for pretransplant tumor downstaging or for post-transplant tumor recurrence and immunosuppressive regiments with antineoplastic components, e.g. rapamycin, justify LT for neuroendocrine LM even when realistically considered as a palliative rather than a curative treatment modality.

The clinical and biological rationale for SSA treatment

Somatostatin (SS), a cyclic tetradecapeptide first identified in 1972 in the hypothalamus and subsequently detected in several other central and

peripheral tissues including the GI tract and endocrine system, plays a key role in regulating physiological functions of NENs. Two bioactive forms of this ubiquitous inhibitor are known, a 14-amino acid form (SST-14) and a carboxyl terminally extended and more active 28-amino acid form (SST-28; Yamada *et al.* 1992). The various endocrine and paracrine functions of SST are triggered through G-protein-coupled receptors with seven transmembrane domains. In humans, five SSTR subtypes ($sstr_{1-5}$) have been cloned and characterized (Lamberts *et al.* 1990). The presence of SSTRs has been demonstrated to a different degree of distribution and a regionally heterogenous subtype-specific expression is evident in over 80% of well-differentiated GEP-NENs. Overall, there is a clear predominance of $sstr_2$ (Taylor *et al.* 1994). Tumor dedifferentiation is usually associated with diminution of receptor density and changes in receptor subtype profile; thus, the presence of SSTRs serves as a tumor-specific predictor of prognosis. It remains unclear if only numeric reduction of SSTRs or also their downregulation occurs with tumor dedifferentiation (Modlin *et al.* 2010*c*).

The clinical use of native SST is limited in the therapeutic setting because of its short half-life (~90 s) and a postadministration hypersecretion rebound phenomenon. In contrast, bioactive synthetic SSAs, which are less sensitive to serum peptidases, evade these drawbacks and have therefore opened the conduit to various diagnostic and therapeutic purposes. The analog, octreotide, and a long-acting formulation of octreotide, lanreotide, exhibit high affinity to $sstr_2$ and lower affinity to $sstr_3$ and $sstr_5$. Multi-SSTR-targeted analog SOM230 (pasireotide) activates $sstr_{1-5}$, while Try^0-(cyclo-D-Dab-Arg-Phe-Phe-D-Trp-Lys-Thr-Phe (KE108) binds avidly to all five known receptor subtypes (Reubi *et al.* 2002).

Symptomatic and antiproliferative effects of SSAs

Numerous studies on tolerability and efficacy of octreotide and lanreotide have demonstrated a mean symptomatic response rate of 73.2% (range 50–100%). Mean biochemical response rates (partial and complete response) for octreotide, octreotide long-acting release (LAR), and for long-acting lanreotide were 50.9% (range 28–77%), 51.4% (31.5–100%), and 39.0% (17.9–58%) respectively (Toumpanakis *et al.* 2009, Modlin *et al.* 2010*c*; Table 1).

Clinical objective evidence of the antiproliferative effect of octreotide was first described with a high level of evidence in the PROMID phase III trial of midgut NENs (Rinke *et al.* 2009). Treatment with octreotide LAR 30 mg/day achieved a median time to tumor progression of 14.3 months compared with 6.0 months in the placebo group. After 6 months of treatment, the disease remained stable in 66.7% of patients in the treatment arm and in 37.2% in the placebo group. Patients with NENs poorly responsive to treatment with octreotide or lanreotide may benefit from combining SSAs with interferon (IFN)-α although there is no clear evidence for a beneficial effect of the combination. While an additive effect has been reported in nonrandomized trials, in three randomized trials no significant survival benefit was evident (Fazio *et al.* 2007). In a presently recruiting phase III trial, patients with advanced low- or intermediate-grade non-islet cell NENs are randomized to treatment with depot octreotide and IFN-α or depot octreotide and bevacizumab (www.clinicaltrials.gov, NCT00569127). This trial has the potential to further elucidate the effect of combination therapy.

Peptide receptor radionuclide therapy

Adequate density of SSTRs quantifiable on SRI is a prerequisite for the evaluation of patient eligibility

Table 1 Clinical studies on the efficacy (biochemical response) of different somatostatin analogs adapted, with permission, from Modlin IM, Pavel M, Kidd M & Gustafsson BI 2010*c* Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. *Alimentary Pharmacology & Therapeutics* **31** 169–188

Author (year)	***n***	**SSA**	**SD** (%)	**PR** (%)	**CR** (%)	**BR** (%)
Kvols *et al.* (1986)	25	OCT		72		
Arnold *et al.* (1996)	103	OCT	38.5	28.2	5.1	33.3
Ricci *et al.* (2000)	15	OCT LAR	33	8	33	41
Eriksson *et al.* (1997)	19	LAN				58
Wymenga *et al.* (1999)	55	LAN SR	52	27		47
Bajetta *et al.* (2006)	30	LAN AG	18.5	29.6	11.1	40.7

OCT, octreotide; LAR, long-acting repeatable; LAN, lanreotide; SR, slow release; AG, autogel; SSA, somatostatin analog; SD, stable disease; PR, partial response; CR, complete response; BR, overall biochemical response (PR+CR).

for PRRT. In the initial phase, [^{111}In-DTPA-D-Phe^{1}]octreotide was the isotope of choice. Due to its short-range radiotoxicity and limited antiproliferative effect, this analog has been supplanted in favor of more suitable beta-emitting ^{90}Yttrium (^{90}Y)- or ^{177}Lutetium (^{177}Lu)-coupled analog. These have proven to be efficacious both for symptom relief and tumor remission (Kwekkeboom *et al*. 2008). Adverse events associated with PRRT using the new generation radiopharmaceuticals are, for the most part, uncommon and mild. They include hematological and renal deleterious effects that can, however in a minority of patients, be severe. Maximum tolerated dose per cycle and administration of nephroprotective agents are implemented in treatment protocols.

In a study on 504 patients who underwent 1772 treatment sessions, Kwekkeboom *et al*. (2008) documented the efficacy of PRRT with (^{177}Lu-octreotate). The treatment protocol comprised four treatment cycles with intervals of 6–10 weeks and a cumulative activity of up to 750–800 mCi (27.8–29.6 GBq). While complete and partial tumor remissions were documented in 2 and 28% of patients, respectively, minor tumor response was seen in 16%. Uptake of OctreoScan and Karnofsky performance status >70 proved to be significant predictors of tumor remission. Twenty-five percent developed nausea within 24 h of the treatment initiation, and hematological toxicity was evident in 9.5%. In nine patients, serious delayed side effects occurred. Temporary hair loss was evident in 62%. An overall survival benefit from the time of initial diagnosis of 40–72 months was evident when the outcome was compared with the historical experience of the group. Imhof *et al*. (2010) obtained encouraging results in a phase II study on 1109 patients treated with (^{90}Y-octreotide). Morphological, biochemical, and clinical responses were seen in 34.1, 15.5, and 29.7% respectively. Results of initial functional imaging were predictive for overall survival and for severe renal toxicity. Efficacy of PRRT in a neoadjuvant setting for downstaging either of unresectable primary tumor or hepatic metastases has also recently been reported (Stoeltzing *et al*. 2010). There exist some general reservations in respect of the outcome data of PRRT as, to date, there are no prospective randomized studies, and the long-term toxicities remain unknown. Nevertheless, there is compelling clinical logic for the use of this therapeutic modality given the limited treatment options available when other treatments fail.

Novel targeted therapeutic strategies

The choice of the appropriate treatment for GEP-NENs represents a challenge due to the variety of different NET types, the absence of comparative data for many of the therapeutic approaches, and the numerous disciplines involved in the development of a personalized management strategy. Ideally, therefore, it is commonly and most effectively undertaken in a tumor board comprised experts in the field. Treatment is highly individualized and based on data gathered over decades from smaller clinical studies. In recent times, data have become available from placebo-controlled studies, which support the value of specific drugs with its use in individual tumor types based on the identification of specific molecular targets (Table 2).

The current status of medical therapy in GEP-NENs

Until recently, the only approved drugs for the treatment of NENs were the SSAs (octreotide and lanreotide). The main indication for therapy was the presence of the carcinoid syndrome. These two classes of agents act as secretory inhibitors by targeting tumor cell receptors and may also inhibit tumor cell proliferation. Their antiproliferative efficacy, however, is limited and rarely associated with objective tumor remissions (8–11%). Nevertheless, these drugs have a value in tumor growth stabilization and prolongation of time to tumor progression (Dahan *et al*. 2009, Rinke *et al*. 2009, Modlin *et al*. 2010*c*). Although there is no

Table 2 Molecular targeted medical therapies and agents in neuroendocrine tumors adapted, with permission, from Gupta S, Engstrom PF & Cohen SJ 2011 Emerging therapies for advanced gastroenteropancreatic neuroendocrine tumors. *Clinical Colorectal Cancer* **10** 298–309. Copyright 2011 Elsevier.

Inhibition of somatostatin receptors
Octreotide, lanreotide, pasireotide
Inhibition of angiogenesis
Anti-VEGF monoclonal antibody
Bevacizumab
Receptor tyrosine kinase inhibitors
Sunitinib, Soarafenib, Pazopanib, Imatinib, Vatalinib
Other
Thalidomide
Signal transduction inhibitors
Inhibition of PIK-3/Akt/mTOR pathway
Everolmus, temsirolimus
Inhibition of insulin-like growth factor receptor
Cixitumumab
Dalotuzumab
Inhibition of epidermal growth factor receptor
Gefitinib
Immune-modulators
Interferon-α

Table 3 Current clinical trials using agents that target growth factor receptors and signaling pathways for the treatment of GEP-NENs

Drug	Target	Cotreatment	Phase	Reference/trial no.
Bevacizumab	VEGF	Peg IFN-α depot	Phase II	Carcinoid SWOG:S50518
		Octreotide	Phase III	
		2-Methoxy-estradiol	Phase I/II	Carcinoid NCT00328497
		FOLFOX	Phase I/II	Advanced GEP-NEN NCT00227617
		Oxaliplatin, capecitabine	Phase II	Advanced GEP-NEN NCT00398320
		Temozolomide	Phase II	PNEN, SI NEN ('carcinoid')
Pazopanib	Pan-VEGFR, PDGF-R, c-KIT		Phase II	Low-grade GEP-NEN NCT00454363
Motesanib	VEGFR, PDGF-R, c-KIT	Octreotide	Phase II	GEP-NEN NCT00427349
Bortezomid	Proteasome inhibitor		Phase II, completed	GEP-NEN NCT00017199

regulatory approval for antiproliferative indications in all GEP-NENs (except for midgut NENs), SSAs especially are frequently used as first-line therapy in G1/G2 NENs. This usage is based on the evidence derived from a placebo-controlled trial with octreotide in therapy-naïve patients with midgut NENs (Rinke *et al*. 2009). The antiproliferative value of lanreotide in nonfunctioning GEP-NENs is currently under evaluation in a placebo-controlled trial (CLARINET study). Although systemic chemotherapy can be of value in some PNENs, the vast majority of midgut NENs are slow proliferating and are nonresponsive to cytotoxic drugs (Sun *et al*. 2005, Dahan *et al*. 2009). Data supporting the use of streptozotocin-based chemotherapy either with 5-FU and/or doxorubicin mainly come from older studies using a variety of nonstandard endpoints (Moertel *et al*. 1992). Despite the limitations of the latter study, recent retrospective and small prospective studies have demonstrated the efficacy of this regimen with reports of tumor remissions of ~40% (Kouvaraki *et al*. 2005, Turner *et al*. 2010). Smaller, phase II trials support the efficacy of temozolomide-based chemotherapy in PNENs (Kulke *et al*. 2009). In a retrospective study on patients with metastatic PNENs treated with first-line chemotherapy with a combination of capecitabine and temozolamide, a response rate of 70% and a median progression-free survival of 18 months were achieved compared with a response rate of 39% and a median progression-free survival of 9.3 months achieved with a triple combination of streptozotocin, doxorubicin, and 5-FU (Strosberg *et al*. 2011). These data warrant further confirmation in prospective trials. Nevertheless, it remains unclear in which group of patients this regimen might be used and if determination of the (*O*-6-methylguanine-DNA methyltransferase) expression or methylation status is helpful in preselecting patients for this therapy. For poorly differentiated tumors, platinum-based chemotherapy is still the sole available treatment.

Molecular targets in GEP-NENs

The recent availability of novel drugs (e.g. small molecule TKIs) has provided new treatment opportunities and holds promise given the expression in GEP-NENs of a variety of targets including angiogenic factors and their receptors (e.g. VEGF(R), PDGF(R)), peptide receptors (e.g. $sstr_{1-5}$, EGFR, IGF1(R)), or intracellular molecules (e.g. mTOR; Hofland & Lamberts 1996, Welin *et al*. 2006, Srirajaskanthan *et al*. 2010; Tables 3 and 4). The mTOR pathway is especially activated in PNENs (Missiaglia *et al*. 2010, Kasajima *et al*. 2011) and somatic mutations have been

Table 4 Current clinical trials for the treatment of GEP-NENs (from www.clinicaltrials.gov)

Drug combination	Target(s)	Phase	GEP-NEN targeted
Sorafenib + bevacizumab	VEGF, PDGF, Raf, c-KIT	Phase II	SI NEN ('carcinoid') PNEN
Sorafenib + metronomic cyclophosphamide	VEGFR, PDGF, Raf, c-KIT, mTOR	Phase II	GEP-NEN
Sorafenib + RAD001	VEGFR, PDGF, Raf, c-KIT, mTOR	Phase I	SI NEN ('carcinoid') PNEN
RAD001 (RAMSETE)	mTOR	Phase II	NF NEN other than PNEN
RAD001 + pasireotide	mTOR, SSTR	Phase I	SI NEN ('carcinoid') PNEN
RAD001 + bevacizumab	mTOR, VEGF	Phase II	Low-grade NEC
RAD001 + temozolomide	mTOR, cytotox.	Phase I/II	PNEN
IMC-12 + octreotide LAR	IGF1-R	Phase II	SI NEN ('carcinoid') Islet cell
AMG-479	IGF1-R	Phase II	SI NEN ('carcinoid') Islet cell

identified in ~14% (Jiao *et al*. 2011). To date there has been limited efficacy of current therapy in the long-term management of GEP-NENs in respect of syndrome and tumor control as well as limited survival (Surveillance Epidemiology 2009). Thus, a key unmet need has been the development of novel drugs and drug combinations to improve overall response rates and progression-free survival. A variety of targeted agents have been explored in GEP-NENs including angiogenesis inhibitors (e.g. PTK787/ZK, bevacizumab, thalidomide, and endostatin), single and multiple TKIs (imatinib, gefitinib, sorafenib, and sunitinib), mTOR inhibitors (temsirolimus and everolimus), novel SSAs (universal ligand pasireotide, chimeric molecule dopastatin targeting dopamine, and SSTR), and others (e.g. tryptophan hydroxylase inhibitors (LX1606) for carcinoid syndrome control, histone deacetylase inhibitors, and IGF receptor antibodies for tumor growth control). Overall, the objective response rates achieved with targeted drug monotherapy is <10% and may reach ~25% with drug combinations in phase II trials. Among the angiogenesis inhibitors, bevacizumab is the only agent that is currently under evaluation in other clinical trials, while sorafenib and everolimus are being investigated with various drug combinations (www.clinicaltrials.gov).

Sunitinib and everolimus (RADIANT-3) have been evaluated in phase III placebo-controlled trials in progressive NENs of pancreatic origin, while everolimus in combination with octreotide LAR has also been assessed in NENs associated with the carcinoid syndrome (RADIANT-2). These studies were large, international prospective trials and used progression-free survival (PFS) as the primary endpoint given the low remission rates noted in the phase II clinical trials.

Sunitinib (37.5 mg/day) was evaluated in patients ($n=171$) with well-differentiated nonresectable progressive PNENs. The majority received prior antitumor drug treatment (66% in the sunitinib arm and 72% in the placebo arm). Significant prolongation of PFS by 5.9 months compared with placebo was achieved with tumor remissions of <10% (Raymond *et al*. 2011*a*). Based on the trial results, sunitinib was approved (2011) for the treatment of progressive PNENs by the US FDA and European health authorities. The study exhibited some weaknesses including low recruitment (50% of preplanned patients), low number of patients at risk beyond 10 months, high death rate indicating inclusion of highly advanced patients, and lack of central radiology. The initially reported survival benefit was not evident with further follow-up (Raymond *et al*. 2011*b*). Most frequent side effects included diarrhea (59%), nausea (45%), asthenia (34%), and vomiting (34%).

In a similar study design, everolimus (10 mg/day) was compared with placebo in a large number of patients ($n=410$) with progressive well to moderately differentiated PNENs. Everolimus significantly prolonged PFS by 6.4 months compared with placebo, and this effect was long lasting (35% stable at 18 months). Tumor remissions were rare (5%; Yao *et al*. 2011). Everolimus was approved (2011) by the US FDA for the treatment of progressive PNENs, and European approval is pending. The most frequent adverse events included stomatitis (64%), rash (49%), diarrhea (34%), and fatigue (31%), while infections (23%) or pulmonary infiltrates (17%) require careful monitoring.

Everolimus has also been evaluated in a large placebo-controlled phase III trial ($n=429$) in different types of NENs (SI and lung) associated with the carcinoid syndrome. Although PFS was prolonged by 5.1 months, the primary endpoint was not determined by central reading. This has been suggested to reflect different judgments of tumor progression by local radiologists, leading to a loss of events in the central analysis and imbalances between study arms (e.g. WHO performance status, lung as primary tumor site) favoring the placebo arm (Pavel *et al*. 2010). Results of local and central analysis were, nevertheless, consistent. Further studies are required to clarify which subgroup might benefit from everolimus.

Although targeted agents such as everolimus and sunitinib have broadened the spectrum of available agents in GEP-NEN therapy, there future treatment issues that require consideration remain. Thus, in the case of a multiple TKIs such as sunitinib, activation of mechanisms of resistance, development of angiogenic rescue, potential acceleration of tumor growth, and incompatibility with surgery and other drugs in sequential therapy have to be evaluated. Potential side effects with broader and long-term use are reported in other types of cancers (including bleeding, cardiac events, among others).

Similar concerns occur with the mTOR inhibitors including the development of mechanisms of resistance, such as reactivation of PI3K Akt and MAP kinase pathways (Carracedo *et al*. 2008, Carew *et al*. 2011, Svejda *et al*. 2011). In addition, the question of compatibility with other drug treatments needs further clarification. A further consideration is the risk posed by surgery for which withdrawal of the mTOR agent may be required to lower the subsequent risk associated with a drug-induced chronic immunosuppressive state. The most important potential side effects, however, appear to be infections and

pneumonitis, which may occur more frequently with broader and long-term use.

The specific role of targeted drugs in the management of GEP-NENs remains to be defined (Fig. 5). Most data are available for low- or intermediate-grade PNENs. Everolimus and sunitinib were evaluated in patients with PNENs mostly after failure of SSAs and/or systemic chemotherapies. Thus, there is a place for these agents after failure of chemotherapy, which is considered as a standard palliative therapy for PNENs in many centers, before tumor progression is required. Both drugs may be considered earlier in the treatment algorithm under special circumstances (e.g. intolerability or contraindication for chemotherapy). As in the placebo-controlled trial with everolimus (RADIANT-3), 40% of the patients were therapy-naïve, the potential long-term risks have to be considered if these drugs are used as a first-line treatment. There are currently insufficient data to support the use of sunitinib in patients with other GEP-NENs (Kulke *et al*. 2008). Everolimus may, however, be considered in patients with progressive NENs of the lung or midgut, if available or approved. Given the current lack of evidence of superiority of single drugs and combinations, the treatment approach remains a very individualized one. Combination therapies with targeted drugs are probably required in the future to improve response rates and overcome mechanisms of resistance. Clearly, further comparative clinical trials are required to clarify the precise therapeutic strategy.

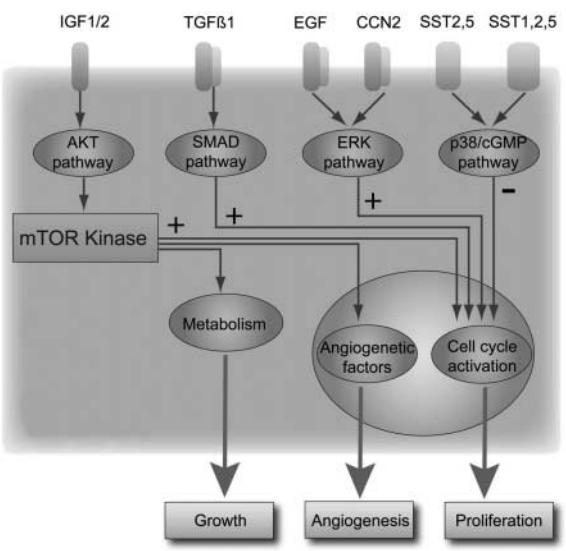

Figure 5 Molecular targets in GEP-NENs. Proliferation is regulated by a number of different growth factors (e.g. TGFβ) through activation of AKT/ERK/SMAD and mTOR pathways. Negative regulators include somatostatin (SS), which target cell cycle activators through the P38/cGMP pathways. Targeting mTOR kinase or SS receptors are currently considered the most effective approach for inhibiting cell growth.

Future directions

Two areas that have begun to be explored are identification of known or novel markers that can be identified in tissue peripheral blood as well as the development of a nomogram as an adjunct in the clinical setting.

Identification and use of tissue or circulating markers

A panel of gene markers have been identified from microarray studies and used to develop a classification system for midgut NENs. This has been used with success to differentiate the subtypes and can accurately predict metastasis (Drozdov *et al*. 2009). Detection of CgA using real-time PCR is more sensitive than conventional histochemical and immunohistochemical techniques to identify micrometastases (Kidd *et al*. 2006). PCR-based approached for different target genes may be of use in more accurately defining management strategy.

As an alternative to tissue analyses, the detection of circulating tumor-derived mRNA transcripts by PCR, either alone or in combination with detection of circulating peptides and amines by standard immunoassay, represents a novel approach to the diagnosis of GEP-NENs (Modlin *et al*. 2009). The identification of a gene panel of NEN transcripts encoding secreted markers, indicators of cell proliferation, and markers of metastasis has enabled the development of a mathematical predictive algorithm by which transcripts expressed in GEP-NEN tissue can be identified in blood with an accuracy that allows prediction of metastasis and determination of the pathological character of the NEN. For example, using real-time PCR to measure plasma or tissue levels of mRNA for a variety of neuroendocrine markers (e.g. 5-HT, CgA, ghrelin, and connective tissue growth factor) and using a predictive mathematical model for GEP-NEN diagnosis, various types of NENs can be distinguished from normal cells solely based on their molecular signature. This are still under development and are not currently in clinical use. Circulating tumor cells have also been detected (Khan *et al*. 2011), but their relevance is not known.

Prognostic nomogram

Approximately 18 000 cases and 8200 deaths attributable to this disease are predicted for 2011 in the USA

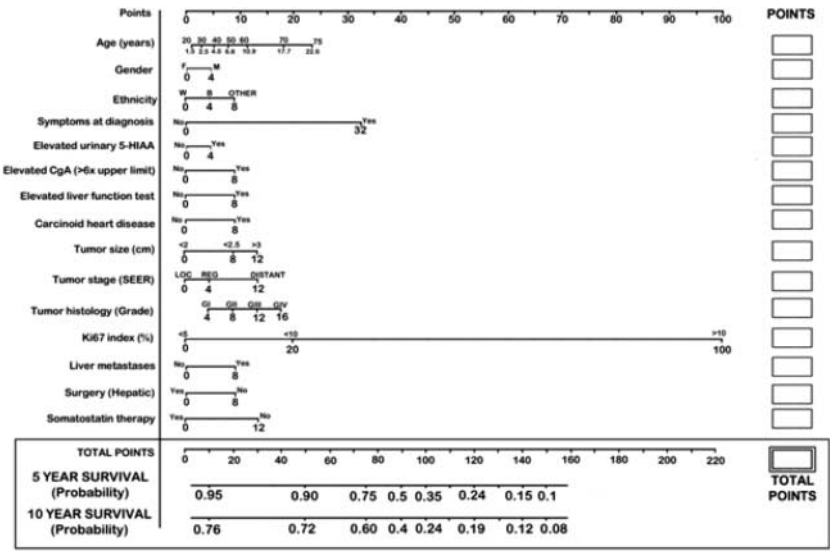

Figure 6 Five- and 10-year probability survival nomogram for SI NENs based on the overall literature review ($n=12\,412$) and additional analysis of 7445 patients in the NCI-SEER database. F, female; M, male; W, white; B, black; O, other.

based on the NCI SEER data. Given the wide range of the 5-year survival rates of 41–95% depending on disease extent, grade, and tumor site, patients with a NEN require a precise prognosis. With accurate prediction, patients at low risk of disease-specific death can be safely reassured, whereas patients at high risk can be considered for appropriate surgery and systemic therapy.

The recent description of an objective multivariate analysis of indices that defines SI NEN prognosis provides a rigorous mathematical-based tool – a nomogram – for the assessment of parameters that define progress, determine prognosis, and can guide therapy (Modlin *et al*. 2010*b*). The NEN nomogram is designed for prognosis prediction, patient group comparisons, and a guide for stratification of treatment and surveillance. It uses hazard ratio (HR), Cox and Kaplan–Meier analyses of published data, and the current SEER database to provide a nomogram from 15 variables that are demonstrated to provide significant multivariate HRs. These include age, gender, ethnicity, symptoms, urinary 5-HIAA, plasma CgA, liver function tests, tumor size, invasion, metastasis, histology, the Ki-67%, carcinoid heart disease, and therapy (surgery or long-acting SSAs). Internal validation enabled development of a GEP-NEN nomoscore using HR weighting and stratification into low (<75), medium (75–95), and high risk (>95). This enabled identification of significant differences in survival (15.5 ± 4.3, 9.7 ± 2.5, and 6.4 ± 1.1 years respectively). The nomoscore was significantly elevated ($P<0.01$) in deceased compared with alive patients. The introduction of a nomogram represents an optimized construct based on the currently analyzable data and its application will facilitate accurate stratification for comparison in clinical trials (Fig. 6). In addition, the development of a mathematically validated nomogram provides a platform for objective assessment of SI NEN disease, a finite basis for precise prognostication and a tool to guide management strategy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors would like to thank Dr Panagiotis Drymousis for his excellent assistance in preparation of this manuscript. The work was presented at the 9th Congress of the European–African Hepato-Pancreato-Biliary Association, 12–16 April 2011, Cape Town, South Africa.

References

Akerstrom G & Hellman P 2009 Surgical aspects of neuroendocrine tumours. *European Journal of Cancer* **45** (Suppl 1) 237–250. (doi:10.1016/S0959-8049(09)70039-5)

Akerstrom G, Hellman P, Hessman O & Osmak L 2004 Surgical treatment of endocrine pancreatic tumours. *Neuroendocrinology* **80** 62–66. (doi:10.1159/000080744)

Åkerström G, Hellman P & Hessman O 2009 Gastrointestinal carcinoids. In *Endocrine Surgery*, 4th edn, pp 147–176. Ed T Lennard. London: Saunders Elsevier.

Aranha GV & Shoup M 2005 Nonstandard pancreatic resections for unusual lesions. *American Journal of Surgery* **189** 223–228. (doi:10.1016/j.amjsurg.2004.11.005)

Arnold R, Trautmann ME, Creutzfeldt W, Benning R, Benning M, Neuhaus C, Jurgensen R, Stein K, Schafer H, Bruns C *et al.* 1996 Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut* **38** 430–438. (doi:10.1136/gut.38.3.430)

Arnold CN, Nagasaka T, Goel A, Scharf I, Grabowski P, Sosnowski A, Schmitt-Graff A, Boland CR, Arnold R & Blum HE 2008*a* Molecular characteristics and predictors of survival in patients with malignant neuroendocrine tumors. *International Journal of Cancer* **123** 1556–1564. (doi:10.1002/ijc.23690)

Arnold R, Wilke A, Rinke A, Mayer C, Kann PH, Klose KJ, Scherag A, Hahmann M, Muller HH & Barth P 2008*b* Plasma chromogranin A as marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors. *Clinical Gastroenterology and Hepatology* **6** 820–827. (doi:10.1016/j.cgh.2008.02.052)

Bajetta E, Procopio G, Catena L, Martinetti A, De Dosso S, Ricci S, Lecchi AS, Boscani PF, Iacobelli S, Carteni G *et al.* 2006 Lanreotide autogel every 6 weeks compared with Lanreotide microparticles every 3 weeks in patients with well differentiated neuroendocrine tumors: a Phase III Study. *Cancer* **107** 2474–2481. (doi:10.1002/cncr.22272)

Bartsch DK, Schilling T, Ramaswamy A, Gerdes B, Celik I, Wagner HJ, Simon B & Rothmund M 2000 Management of nonfunctioning islet cell carcinomas. *World Journal of Surgery* **24** 1418–1424. (doi:10.1007/s002680010234)

Bartsch DK, Fendrich V, Langer P, Celik I, Kann PH & Rothmund M 2005 Outcome of duodenopancreatic resections in patients with multiple endocrine neoplasia type 1. *Annals of Surgery* **242** 757–764 (discussion 764-756). (doi:10.1097/01.sla.0000189549.51913.d8)

Bettini R, Boninsegna L, Mantovani W, Capelli P, Bassi C, Pederzoli P, Delle Fave GF, Panzuto F, Scarpa A & Falconi M 2008 Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. *Annals of Oncology* **19** 903–908. (doi:10.1093/annonc/mdm552)

Bettini R, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P, Scarpa A & Falconi M 2011 Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. *Surgery* **150** 75–82. (doi:10.1016/j.surg.2011.02.022)

Bonaccorsi-Riani E, Apestegui C, Jouret-Mourin A, Sempoux C, Goffette P, Ciccarelli O, Borbath I, Hubert C, Gigot JF, Hassoun Z *et al.* 2010 Liver transplantation and neuroendocrine tumors: lessons from a single centre experience and from the literature review. *Transplant International* **23** 668–678. (doi:10.1111/j.1432-2277.2010.01086.x)

Borch K, Ahren B, Ahlman H, Falkmer S, Granerus G & Grimelius L 2005 Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. *Annals of Surgery* **242** 64–73. (doi:10.1097/01.sla.0000167862.52309.7d)

Bosman FT, Carneiro F, Hruban RH & Theise ND (Eds) 2010 *WHO Classification of Tumours of the Digestive System*, 4th edn. World Health Organization Press: Geneva, Switzerland.

Boudreaux JP, Putty B, Frey DJ, Woltering E, Anthony L, Daly I, Ramcharan T, Lopera J & Castaneda W 2005 Surgical treatment of advanced-stage carcinoid tumors: lessons learned. *Annals of Surgery* **241** 839–845 (discussion 845-836). (doi:10.1097/01.sla.0000164073.08093.5d)

Brophy C & Cahow CE 1989 Primary small bowel malignant tumors. Unrecognized until emergent laparotomy. *American Surgeon* **55** 408–412.

Buchmann I, Henze M, Engelbrecht S, Eisenhut M, Runz A, Schafer M, Schilling T, Haufe S, Herrmann T & Haberkorn U 2007 Comparison of ^{68}Ga-DOTATOC PET and ^{111}In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. *European Journal of Nuclear Medicine and Molecular Imaging* **34** 1617–1626. (doi:10.1007/s00259-007-0450-1)

Burkitt MD & Pritchard DM 2006 Review article: pathogenesis and management of gastric carcinoid tumours. *Alimentary Pharmacology & Therapeutics* **24** 1305–1320. (doi:10.1111/j.1365-2036.2006.03130.x)

Campana D, Piscitelli L, Mazzotta E, Bonora M, Serra C, Salomone L, Corinaldesi R & Tomassetti P 2005 Zollinger–Ellison syndrome. Diagnosis and therapy. *Minerva Medica* **96** 187–206.

Campana D, Nori F, Pezzilli R, Piscitelli L, Santini D, Brocchi E, Corinaldesi R & Tomassetti P 2008 Gastric endocrine tumors type I: treatment with long-acting somatostatin analogs. *Endocrine-Related Cancer* **15** 337–342. (doi:10.1677/ERC-07-0251)

Capurso G, Bettini R, Rinzivillo M, Boninsegna L, Delle Fave G & Falconi M 2011 Role of resection of the primary pancreatic neuroendocrine tumour only in patients with unresectable metastatic liver disease: a systematic review. *Neuroendocrinology* **93** 223–229. (doi:10.1159/000324770)

Carew JS, Kelly KR & Nawrocki ST 2011 Mechanisms of mTOR inhibitor resistance in cancer therapy. *Targeted Oncology* **6** 17–27. (doi:10.1007/s11523-011-0167-8)

Carracedo A, Ma L, Teruya-Feldstein J, Rojo F, Salmena L, Alimonti A, Egia A, Sasaki AT, Thomas G, Kozma SC *et al.* 2008 Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. *Journal of Clinical Investigation* **118** 3065–3074.

Cho CS, Labow DM, Tang L, Klimstra DS, Loeffler AG, Leverson GE, Fong Y, Jarnagin WR, D'Angelica MI, Weber SM *et al.* 2008 Histologic grade is correlated with outcome after resection of hepatic neuroendocrine neoplasms. *Cancer* **113** 126–134. (doi:10.1002/cncr.23523)

Dahan L, Bonnetain F, Rougier P, Raoul JL, Gamelin E, Etienne PL, Cadiot G, Mitry E, Smith D, Cvitkovic F *et al.* 2009 Phase III trial of chemotherapy using 5-fluorouracil and streptozotocin compared with interferon alpha for advanced carcinoid tumors: FNCLCC-FFCD 9710. *Endocrine-Related Cancer* **16** 1351–1361. (doi:10.1677/ERC-09-0104)

Doherty GM 2005 Rare endocrine tumours of the GI tract. *Best Practice & Research. Clinical Gastroenterology* **19** 807–817. (doi:10.1016/j.bpg.2005.05.004)

Dousset B, Saint-Marc O, Pitre J, Soubrane O, Houssin D & Chapuis Y 1996 Metastatic endocrine tumors: medical treatment, surgical resection, or liver transplantation. *World Journal of Surgery* **20** 908–914 (discussion 914-905). (doi:10.1007/s002689900138)

Drozdov I, Kidd M, Nadler B, Camp RL, Mane SM, Hauso O, Gustafsson BI & Modlin IM 2009 Predicting neuroendocrine tumor (carcinoid) neoplasia using gene expression profiling and supervised machine learning. *Cancer* **115** 1638–1650. (doi:10.1002/cncr.24180)

Ekeblad S, Skogseid B, Dunder K, Oberg K & Eriksson B 2008 Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clinical Cancer Research* **14** 7798–7803. (doi:10.1158/1078-0432.CCR-08-0734)

Eldor R, Glaser B, Fraenkel M, Doviner V, Salmon A & Gross DJ 2011 Glucagonoma and the glucagonoma syndrome – cumulative experience with an elusive endocrine tumour. *Clinical Endocrinology* **74** 593–598. (doi:10.1111/j.1365-2265.2011.03967.x)

Elias D, Lasser P, Ducreux M, Duvillard P, Ouellet JF, Dromain C, Schlumberger M, Pocard M, Boige V, Miquel C *et al.* 2003 Liver resection (and associated extrahepatic resections) for metastatic well-differentiated endocrine tumors: a 15-year single center prospective study. *Surgery* **133** 375–382. (doi:10.1067/msy.2003.114)

Eriksson B, Renstrup J, Imam H & Oberg K 1997 High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. *Annals of Oncology* **8** 1041–1044. (doi:10.1023/A:1008205415035)

Falconi M, Bettini R, Boninsegna L, Crippa S, Butturini G & Pederzoli P 2006 Surgical strategy in the treatment of pancreatic neuroendocrine tumors. *Journal of the Pancreas* **7** 150–156.

Falconi M, Zerbi A, Crippa S, Balzano G, Boninsegna L, Capitanio V, Bassi C, Di Carlo V & Pederzoli P 2010 Parenchyma-preserving resections for small non-functioning pancreatic endocrine tumors. *Annals of Surgical Oncology* **17** 1621–1627. (doi:10.1245/s10434-010-0949-8)

Falconi M, Bartsch DK, Eriksson B, Kloppel G, Lopes JM, O'Connor JM, Salazar R, Taal BG, Vullierme MP, O'Toole D *et al.* 2012 ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology* **95** 120–134. (doi:10.1159/000335587)

Fazio N, de Braud F, Delle Fave G & Oberg K 2007 Interferon-alpha and somatostatin analog in patients with gastroenteropancreatic neuroendocrine carcinoma: single agent or combination? *Annals of Oncology* **18** 13–19. (doi:10.1093/annonc/mdl144)

Fendrich V, Langer P, Waldmann J, Bartsch DK & Rothmund M 2007 Management of sporadic and multiple endocrine neoplasia type 1 gastrinomas. *British Journal of Surgery* **94** 1331–1341. (doi:10.1002/bjs.5987)

Frilling A, Malago M, Weber F, Paul A, Nadalin S, Sotiropoulos GC, Cicinnati V, Beckebaum S, Bockisch A, Mueller-Brand J *et al.* 2006 Liver transplantation for patients with metastatic endocrine tumors: single-center experience with 15 patients. *Liver Transplantation* **12** 1089–1096. (doi:10.1002/lt.20755)

Frilling A, Li J, Malamutmann E, Schmid KW, Bockisch A & Broelsch CE 2009 Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. *British Journal of Surgery* **96** 175–184. (doi:10.1002/bjs.6468)

Frilling A, Sotiropoulos GC, Radtke A, Malago M, Bockisch A, Kuehl H, Li J & Broelsch CE 2010 The impact of ^{68}Ga-DOTATOC positron emission tomography/computed tomography on the multimodal management of patients with neuroendocrine tumors. *Annals of Surgery* **252** 850–856. (doi:10.1097/SLA.0b013e3181fd37e8)

Fykse V, Sandvik AK, Qvigstad G, Falkmer SE, Syversen U & Waldum HL 2004 Treatment of ECL cell carcinoids with octreotide LAR. *Scandinavian Journal of Gastroenterology* **39** 621–628. (doi:10.1080/00365520410005225)

Gauger PG, Doherty GM, Broome JT, Miller BS & Thompson NW 2009 Completion pancreatectomy and duodenectomy for recurrent MEN-1 pancreaticoduodenal endocrine neoplasms. *Surgery* **146** 801–806 (discussion 807–808). (doi:10.1016/j.surg.2009.06.038)

Gedaly R, Daily MF, Davenport D, McHugh PP, Koch A, Angulo P & Hundley JC 2011 Liver transplantation for the treatment of liver metastases from neuroendocrine tumors: an analysis of the UNOS database. *Archives of Surgery* **146** 953–958. (doi:10.1001/archsurg.2011.186)

Ghaferi AA, Chojnacki KA, Long WD, Cameron JL & Yeo CJ 2008 Pancreatic VIPomas: subject review and one institutional experience. *Journal of Gastrointestinal Surgery* **12** 382–393. (doi:10.1007/s11605-007-0177-0)

Goudet P, Murat A, Binquet C, Cardot-Bauters C, Costa A, Ruszniewski P, Niccoli P, Menegaux F, Chabrier G, Borson-Chazot F *et al.* 2010 Risk factors and causes of death in MEN1 disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. *World Journal of Surgery* **34** 249–255. (doi:10.1007/s00268-009-0290-1)

Gupta S, Engstrom PF & Cohen SJ 2011 Emerging therapies for advanced gastroenteropancreatic neuroendocrine tumors. *Clinical Colorectal Cancer* **10** 298–309. (doi:10.1016/j.clcc.2011.06.006)

Haug AR, Rominger A, Mustafa M, Auernhammer C, Goke B, Schmidt GP, Wangler B, Cumming P, Bartenstein P & Hacker M 2011 Treatment with octreotide does not reduce tumor uptake of (68)Ga-DOTATATE as measured by PET/CT in patients with neuroendocrine tumors. *Journal of Nuclear Medicine* **52** 1679–1683. (doi:10.2967/jnumed.111.089276)

Hellman P, Andersson M, Rastad J, Juhlin C, Karacagil S, Eriksson B, Skogseid B & Akerstrom G 2000 Surgical strategy for large or malignant endocrine pancreatic tumors. *World Journal of Surgery* **24** 1353–1360. (doi:10.1007/s002680010224)

Hellman P, Lundstrom T, Ohrvall U, Eriksson B, Skogseid B, Oberg K, Tiensuu Janson E & Akerstrom G 2002 Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. *World Journal of Surgery* **26** 991–997. (doi:10.1007/s00268-002-6630-z)

Hentic O, Couvelard A, Rebours V, Zappa M, Dokmak S, Hammel P, Maire F, O'Toole D, Levy P, Sauvanet A *et al.* 2010 Ki-67 index, tumor differentiation, and extent of liver involvement are independent prognostic factors in patients with liver metastases of digestive endocrine carcinomas. *Endocrine-Related Cancer* **18** 51–59. (doi:10.1677/ERC-09-0319)

Hofland LJ & Lamberts SW 1996 Somatostatin receptors and disease: role of receptor subtypes. *Baillière's Clinical Endocrinology and Metabolism* **10** 163–176. (doi:10.1016/S0950-351X(96)80362-4)

Hopper AD, Bourke MJ, Hourigan LF, Tran K, Moss A & Swan MP 2009 En-bloc resection of multiple type 1 gastric carcinoid tumors by endoscopic multi-band mucosectomy. *Journal of Gastroenterology and Hepatology* **24** 1516–1521. (doi:10.1111/j.1440-1746.2009.05909.x)

Imamura M, Komoto I, Doi R, Onodera H, Kobayashi H & Kawai Y 2005 New pancreas-preserving total duodenectomy technique. *World Journal of Surgery* **29** 203–207. (doi:10.1007/s00268-004-7585-z)

Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, Macke HR, Rochlitz C, Muller-Brand J & Walter MA 2010 Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [^{90}Y-DOTA]-TOC in metastasized neuroendocrine cancers. *Journal of Clinical Oncology* **29** 2416–2423. (doi:10.1200/JCO.2010.33.7873)

Jacobs C 2009 Neuroendocrine tumors a rare finding: part I. *Clinical Journal of Oncology Nursing* **13** 21–23. (doi:10.1188/09.CJON.21-23)

Jann H, Roll S, Couvelard A, Hentic O, Pavel M, Muller-Nordhorn J, Koch M, Rocken C, Rindi G, Ruszniewski P *et al.* 2011 Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. *Cancer* **117** 3332–3341 (doi: 3310.1002/cncr.25855). (doi:10.1002/cncr.25855)

Jensen RT, Berna MJ, Bingham DB & Norton JA 2008 Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer* **113** 1807–1843. (doi:10.1002/cncr.23648)

Jianu CS, Fossmark R, Syversen U, Hauso O, Fykse V & Waldum HL 2011 Five-year follow-up of patients treated for 1 year with octreotide long-acting release for enterochromaffin-like cell carcinoids. *Scandinavian Journal of Gastroenterology* **46** 456–463. (doi:10.3109/00365521.2010.539255)

Jiao Y, Shi C, Edil BH, de Wilde RF, Klimstra DS, Maitra A, Schulick RD, Tang LH, Wolfgang CL, Choti MA *et al.* 2011 DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science* **331** 1199–1203. (doi:10.1126/science.1200609)

Kaehler G, Grobholz R, Langner C, Suchan K & Post S 2006 A new technique of endoscopic full-thickness resection using a flexible stapler. *Endoscopy* **38** 86–89. (doi:10.1055/s-2005-921181)

Kasajima A, Pavel M, Darb-Esfahani S, Noske A, Stenzinger A, Sasano H, Dietel M, Denkert C, Rocken C, Wiedenmann B *et al.* 2011 mTOR expression and activity patterns in gastroenteropancreatic neuroendocrine tumours. *Endocrine-Related Cancer* **18** 181–192. (doi:10.1677/ERC-10-0126)

Kayani I, Bomanji JB, Groves A, Conway G, Gacinovic S, Win T, Dickson J, Caplin M & Ell PJ 2008 Functional imaging of neuroendocrine tumors with combined PET/CT using ^{68}Ga-DOTATATE (DOTA-D-Phe^{1},Tyr^{3}-octreotate) and ^{18}F-FDG. *Cancer* **112** 2447–2455. (doi:10.1002/cncr.23469)

Khan MS, Tsigani T, Rashid M, Rabouhans JS, Yu D, Luong TV, Caplin M & Meyer T 2011 Circulating tumor cells and EpCAM expression in neuroendocrine tumors. *Clinical Cancer Research* **17** 337–345. (doi:10.1158/1078-0432.CCR-10-1776)

Kianmanesh R, Sauvanet A, Hentic O, Couvelard A, Levy P, Vilgrain V, Ruszniewski P & Belghiti J 2008 Two-step surgery for synchronous bilobar liver metastases from digestive endocrine tumors: a safe approach for radical resection. *Annals of Surgery* **247** 659–665. (doi:10.1097/SLA.0b013e31816a7061)

Kidd M, Modlin IM, Mane SM, Camp RL & Shapiro MD 2006 QRT-PCR detection of chromogranin A: a new

standard in the identification of neuroendocrine tumor disease. *Annals of Surgery* **243** 273–280. (doi:10.1097/01.sla.0000197734.28551.0f)

Kindmark H, Sundin A, Granberg D, Dunder K, Skogseid B, Janson ET, Welin S, Oberg K & Eriksson B 2007 Endocrine pancreatic tumors with glucagon hypersecretion: a retrospective study of 23 cases during 20 years. *Medical Oncology* **24** 330–337. (doi:10.1007/s12032-007-0011-2)

Koopmans KP, Neels OC, Kema IP, Elsinga PH, Sluiter WJ, Vanghillewe K, Brouwers AH, Jager PL & de Vries EG 2008 Improved staging of patients with carcinoid and islet cell tumors with ^{18}F-dihydroxy-phenyl-alanine and ^{11}C-5-hydroxy-tryptophan positron emission tomography. *Journal of Clinical Oncology* **26** 1489–1495. (doi:10.1200/JCO.2007.15.1126)

Kouvaraki MA, Solorzano CC, Shapiro SE, Yao JC, Perrier ND, Lee JE & Evans DB 2005 Surgical treatment of non-functioning pancreatic islet cell tumors. *Journal of Surgical Oncology* **89** 170–185. (doi:10.1002/jso.20178)

Kouvaraki MA, Shapiro SE, Cote GJ, Lee JE, Yao JC, Waguespack SG, Gagel RF, Evans DB & Perrier ND 2006 Management of pancreatic endocrine tumors in multiple endocrine neoplasia type 1. *World Journal of Surgery* **30** 643–653. (doi:10.1007/s00268-006-0360-y)

Kulke MH, Lenz HJ, Meropol NJ, Posey J, Ryan DP, Picus J, Bergsland E, Stuart K, Tye L, Huang X *et al.* 2008 Activity of sunitinib in patients with advanced neuroendocrine tumors. *Journal of Clinical Oncology* **26** 3403–3410. (doi:10.1200/JCO.2007.15.9020)

Kulke MH, Hornick JL, Frauenhoffer C, Hooshmand S, Ryan DP, Enzinger PC, Meyerhardt JA, Clark JW, Stuart K, Fuchs CS *et al.* 2009 *O*-6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. *Clinical Cancer Research* **15** 338–345. (doi:10.1158/1078-0432.CCR-08-1476)

Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J & Hahn RG 1986 Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. *New England Journal of Medicine* **315** 663–666. (doi:10.1056/NEJM198609113151102)

Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, Feelders RA, vanAken MO & Krenning EP 2008 Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr^3]octreotate: toxicity, efficacy, and survival. *Journal of Clinical Oncology* **26** 2124–2130. (doi:10.1200/JCO.2007.15.2553)

Kwekkeboom DJ, Kam BL, van Essen M, Teunissen JJ, van Eijck CH, Valkema R, de Jong M, de Herder WW & Krenning EP 2010 Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. *Endocrine-Related Cancer* **17** R53–R73. (doi:10.1677/ERC-09-0078)

Lamberts SW, Bakker WH, Reubi JC & Krenning EP 1990 Somatostatin receptor imaging *in vivo* localization of tumors with a radiolabeled somatostatin analog. *Journal of Steroid Biochemistry and Molecular Biology* **37** 1079–1082. (doi:10.1016/0960-0760(90)90469-2)

La Rosa S, Sessa F, Capella C, Riva C, Leone BE, Klersy C, Rindi G & Solcia E 1996 Prognostic criteria in non-functioning pancreatic endocrine tumours. *Virchows Archiv* **429** 323–333.

Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M & Modlin IM 2011*a* The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinology and Metabolism Clinics of North America* **40** 1–18, vii. (doi:10.1016/j.ecl.2010.12.005)

Lawrence B, Gustafsson BI, Kidd M, Pavel M, Svejda B & Modlin IM 2011*b* The clinical relevance of chromogranin A as a biomarker for gastroenteropancreatic neuroendocrine tumors. *Endocrinology and Metabolism Clinics of North America* **40** 111–134, viii. (doi:10.1016/j.ecl.2010.12.001)

Lerut JP, Weber M, Orlando G & Dutkowski P 2007 Vascular and rare liver tumors: a good indication for liver transplantation? *Journal of Hepatology* **47** 466–475. (doi:10.1016/j.jhep.2007.07.005)

Le Treut YP, Gregoire E, Belghiti J, Boillot O, Soubrane O, Mantion G, Cherqui D, Castaing D, Ruszniewski P, Wolf P *et al.* 2008 Predictors of long-term survival after liver transplantation for metastatic endocrine tumors: an 85-case French multicentric report. *American Journal of Transplantation* **8** 1205–1213. (doi:10.1111/j.1600-6143.2008.02233.x)

Lew EA, Pisegna JR, Starr JA, Soffer EF, Forsmark C, Modlin IM, Walsh JH, Beg M, Bochenek W & Metz DC 2000 Intravenous pantoprazole rapidly controls gastric acid hypersecretion in patients with Zollinger–Ellison syndrome. *Gastroenterology* **118** 696–704. (doi:10.1016/S0016-5085(00)70139-9)

Madeira I, Terris B, Voss M, Denys A, Sauvanet A, Flejou JF, Vilgrain V, Belghiti J, Bernades P & Ruszniewski P 1998 Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. *Gut* **43** 422–427. (doi:10.1136/gut.43.3.422)

Maire F, Hammel P, Kianmanesh R, Hentic O, Couvelard A, Rebours V, Zappa M, Raymond E, Sauvanet A, Louvet C *et al.* 2009 Is adjuvant therapy with streptozotocin and 5-fluorouracil useful after resection of liver metastases from digestive endocrine tumors? *Surgery* **145** 69–75. (doi:10.1016/j.surg.2008.08.007)

Makridis C, Rastad J, Oberg K & Akerstrom G 1996 Progression of metastases and symptom improvement from laparotomy in midgut carcinoid tumors. *World Journal of Surgery* **20** 900–906 (discussion 907). (doi:10.1007/s002689900137)

Makridis C, Ekbom A, Bring J, Rastad J, Juhlin C, Oberg K & Akerstrom G 1997 Survival and daily physical activity in patients treated for advanced midgut carcinoid tumors. *Surgery* **122** 1075–1082. (doi:10.1016/S0039-6060(97)90211-7)

Mazzaferro V, Pulvirenti A & Coppa J 2007 Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *Journal of Hepatology* **47** 460–466. (doi:10.1016/j.jhep.2007.07.004)

McDermott EW, Guduric B & Brennan MF 1994 Prognostic variables in patients with gastrointestinal carcinoid tumours. *British Journal of Surgery* **81** 1007–1009. (doi:10.1002/bjs.1800810725)

Metz DC & Jensen RT 2008 Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* **135** 1469–1492. (doi:10.1053/j.gastro.2008.05.047)

Mills GY 1956 The syndrome of intestinal carcinoid, pulmonary valvular stenosis and cutaneous flush. *Annals of Internal Medicine* **45** 1213–1221.

Missiaglia E, Dalai I, Barbi S, Beghelli S, Falconi M, della Peruta M, Piemonti L, Capurso G, Di Florio A, delle Fave G *et al.* 2010 Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. *Journal of Clinical Oncology* **28** 245–255. (doi:10.1200/JCO.2008.21.5988)

Modlin IM, Lye KD & Kidd M 2003 A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* **97** 934–959. (doi:10.1002/cncr.11105)

Modlin IM, Kidd M, Latich I, Zikusoka MN & Shapiro MD 2005 Current status of gastrointestinal carcinoids. *Gastroenterology* **128** 1717–1751. (doi:10.1053/j.gastro.2005.03.038)

Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle Fave G, Kaltsas GA, Krenning EP *et al.* 2008 Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncology* **9** 61–72. (doi:10.1016/S1470-2045(07)70410-2)

Modlin IM, Gustafsson BI, Drozdov I, Nadler B, Pfragner R & Kidd M 2009 Principal component analysis, hierarchical clustering, and decision tree assessment of plasma mRNA and hormone levels as an early detection strategy for small intestinal neuroendocrine (carcinoid) tumors. *Annals of Surgical Oncology* **16** 487–498. (doi:10.1245/s10434-008-0251-1)

Modlin IM, Gustafsson BI, Moss SF, Pavel M, Tsolakis AV & Kidd M 2010*a* Chromogranin A – biological function and clinical utility in neuro endocrine tumor disease. *Annals of Surgical Oncology* **17** 2427–2443. (doi:10.1245/s10434-010-1006-3)

Modlin IM, Gustafsson BI, Pavel M, Svejda B, Lawrence B & Kidd M 2010*b* A nomogram to assess small-intestinal neuroendocrine tumor ('carcinoid') survival. *Neuroendocrinology* **92** 143–157. (doi:10.1159/000319784)

Modlin IM, Pavel M, Kidd M & Gustafsson BI 2010*c* Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. *Alimentary Pharmacology & Therapeutics* **31** 169–188.

Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG & Klaassen D 1992 Streptozocin–doxorubicin, streptozocin–fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *New England Journal of Medicine* **326** 519–523. (doi:10.1056/NEJM199202203260804)

Mooney E 1985 The flushing patient. *International Journal of Dermatology* **24** 549–554.

Mortellaro VE, Hochwald SN, McGuigan JE, Copeland EM, Vogel SB & Grobmyer SR 2009 Long-term results of a selective surgical approach to management of Zollinger–Ellison syndrome in patients with MEN-1. *American Surgeon* **75** 730–733.

Nikou GC, Toubanakis C, Nikolaou P, Giannatou E, Safioleas M, Mallas E & Polyzos A 2005 VIPomas: an update in diagnosis and management in a series of 11 patients. *Hepatogastroenterology* **52** 1259–1265.

Norton JA 2005 Surgical treatment and prognosis of gastrinoma. *Best Practice & Research. Clinical Gastroenterology* **19** 799–805. (doi:10.1016/j.bpg.2005.05.003)

Norton JA & Jensen RT 2004 Resolved and unresolved controversies in the surgical management of patients with Zollinger–Ellison syndrome. *Annals of Surgery* **240** 757–773. (doi:10.1097/01.sla.0000143252.02142.3e)

Norton JA, Fraker DL, Alexander HR, Gibril F, Liewehr DJ, Venzon DJ & Jensen RT 2006 Surgery increases survival in patients with gastrinoma. *Annals of Surgery* **244** 410–419.

Oberg K 2010 Pancreatic endocrine tumors. *Seminars in Oncology* **37** 594–618. (doi:10.1053/j.seminoncol.2010.10.014)

Ohrvall U, Eriksson B, Juhlin C, Karacagil S, Rastad J, Hellman P & Akerstrom G 2000 Method for dissection of mesenteric metastases in mid-gut carcinoid tumors. *World Journal of Surgery* **24** 1402–1408. (doi:10.1007/s002680010232)

Olausson M, Friman S, Cahlin C, Nilsson O, Jansson S, Wangberg B & Ahlman H 2002 Indications and results of liver transplantation in patients with neuroendocrine tumors. *World Journal of Surgery* **26** 998–1004. (doi:10.1007/s00268-002-6631-y)

Olausson M, Friman S, Herlenius G, Cahlin C, Nilsson O, Jansson S, Wangberg B & Ahlman H 2007 Orthotopic liver or multivisceral transplantation as treatment of metastatic neuroendocrine tumors. *Liver Transplantation* **13** 327–333. (doi:10.1002/lt.21056)

O'Toole D, Grossman A, Gross D, Delle Fave G, Barkmanova J, O'Connor J, Pape UF & Plockinger U 2009 ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: biochemical markers. *Neuroendocrinology* **90** 194–202. (doi:10.1159/000225948)

Pavel M, Hainsworth J, Baudin E, Peeters M, Hoersch D, Anthony L, Hoosen S, St Peter J, Jehl V & Yao J 2010 A randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus/octreotide LAR vs placebo/octreotide LAR in patients with advanced neuroendocrine tumors (NET) (Radiant-2). *Annals of Oncology* **21** (Suppl 8) 853. Abstract LBA8.

Pellikka PA, Tajik AJ, Khandheria BK, Seward JB, Callahan JA, Pitot HC & Kvols LK 1993 Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. *Circulation* **87** 1188–1196.

Prasad V, Ambrosini V, Hommann M, Hoersch D, Fanti S & Baum RP 2010 Detection of unknown primary neuroendocrine tumours (CUP-NET) using (68)Ga-DOTA-NOC receptor PET/CT. *European Journal of Nuclear Medicine and Molecular Imaging* **37** 67–77. (doi:10.1007/s00259-009-1205-y)

Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, Corrie P, Davar J, Davies AH, Lewington V *et al.* 2012 Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* **61** 6–32. (doi:10.1136/gutjnl-2011-300831)

Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, Valle J, Metrakos P, Smith D, Vinik A *et al.* 2011*a* Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *New England Journal of Medicine* **364** 501–513. (doi:10.1056/NEJMoa1003825)

Raymond E, Niccoli P, Raoul J, Bang Y, Borbath I, Lombard-Bohas C, Valle J, Metrakos P, Smith D, Vinik A *et al.* 2011*b* Updated overall survival (OS) and progression-free survival (PFS) by blinded independent central review (BICR) of sunitinib (SU) versus placebo (PBO) for patients (Pts) with advanced unresectable pancreatic neuroendocrine tumors (NET). *Journal of Clinical Oncology* **29**.

Reubi JC, Eisenwiener KP, Rink H, Waser B & Macke HR 2002 A new peptidic somatostatin agonist with high affinity to all five somatostatin receptors. *European Journal of Pharmacology* **456** 45–49. (doi:10.1016/S0014-2999(02)02651-1)

Ricci S, Antonuzzo A, Galli L, Ferdeghini M, Bodei L, Orlandini C & Conte PF 2000 Octreotide acetate long-acting release in patients with metastatic neuroendocrine tumors pretreated with lanreotide. *Annals of Oncology* **11** 1127–1130. (doi:10.1023/A:1008383132024)

Richards ML, Gauger P, Thompson NW & Giordano TJ 2004 Regression of type II gastric carcinoids in multiple endocrine neoplasia type 1 patients with Zollinger–Ellison syndrome after surgical excision of all gastrinomas. *World Journal of Surgery* **28** 652–658. (doi:10.1007/s00268-004-7345-0)

Rindi G, Falconi M, Klersy C, Albarello L, Boninsegna L, Buchler MW, Capella C, Caplin M, Couvelard A, Doglioni C *et al.* 2012 TNM staging of neoplasms of the endocrine pancreas: results from a large International Cohort Study. *Journal of the National Cancer Institute* **104** 764–777. (doi:10.1093/jnci/djs208)

Ringertz N 1967 The gastrointestinal carcinoid and the carcinoid syndrome. *National Cancer Institute Monographs* **25** 299–315.

Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Blaker M *et al.* 2009 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. *Journal of Clinical Oncology* **27** 4656–4663. (doi:10.1200/JCO.2009.22.8510)

Robiolio PA, Rigolin VH, Wilson JS, Harrison JK, Sanders LL, Bashore TM & Feldman JM 1995 Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. *Circulation* **92** 790–795.

Rosenau J, Bahr MJ, von Wasielewski R, Mengel M, Schmidt HH, Nashan B, Lang H, Klempnauer J, Manns MP & Boeker KH 2002 Ki67, E-cadherin, and p53 as prognostic indicators of long-term outcome after liver transplantation for metastatic neuroendocrine tumors. *Transplantation* **73** 386–394. (doi:10.1097/00007890-200202150-00012)

Ruszniewski P, Delle Fave G, Cadiot G, Komminoth P, Chung D, Kos-Kudla B, Kianmanesh R, Hochhauser D, Arnold R, Ahlman H *et al.* 2006 Well-differentiated gastric tumors/carcinomas. *Neuroendocrinology* **84** 158–164. (doi:10.1159/000098007)

Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM & Que FG 2003 Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *Journal of the American College of Surgeons* **197** 29–37. (doi:10.1016/S1072-7515(03)00230-8)

Saxena A, Chua TC, Bester L, Kokandi A & Morris DL 2010 Factors predicting response and survival after yttrium-90 radioembolization of unresectable neuroendocrine tumor liver metastases: a critical appraisal of 48 cases. *Annals of Surgery* **251** 910–916. (doi:10.1097/SLA.0b013e3181d3d24a)

Schimmack S, Svejda B, Lawrence B, Kidd M & Modlin IM 2011 The diversity and commonalities of gastroenteropancreatic neuroendocrine tumors. *Langenbeck's Archives of Surgery* **396** 273–298. (doi:10.1007/s00423-011-0739-1)

Scigliano S, Lebtahi R, Maire F, Stievenart JL, Kianmanesh R, Sauvanet A, Vullierme MP, Couvelard A, Belghiti J, Ruszniewski P *et al.* 2009 Clinical and imaging follow-up after exhaustive liver resection of endocrine metastases: a 15-year monocentric experience. *Endocrine-Related Cancer* **16** 977–990. (doi:10.1677/ERC-08-0247)

Sieren LM, Collins JN, Weireter LJ, Britt RC, Reed SF, Novosel TJ & Britt LD 2010 The incidence of benign and malignant neoplasia presenting as acute appendicitis. *American Surgeon* **76** 808–811.

Smith SL, Branton SA, Avino AJ, Martin JK, Klingler PJ, Thompson GB, Grant CS & van Heerden JA 1998 Vasoactive intestinal polypeptide secreting islet cell tumors: a 15-year experience and review of the literature. *Surgery* **124** 1050–1055. (doi:10.1067/msy.1998.92005)

Srirajaskanthan R, Shah T, Watkins J, Marelli L, Khan K & Caplin ME 2010 Expression of the HER-1–4 family of

receptor tyrosine kinases in neuroendocrine tumours. *Oncology Reports* **23** 909–915. (doi:10.3892/or_00000714)

Steinmuller T, Kianmanesh R, Falconi M, Scarpa A, Taal B, Kwekkeboom DJ, Lopes JM, Perren A, Nikou G, Yao J *et al.* 2008 Consensus guidelines for the management of patients with liver metastases from digestive (neuro)-endocrine tumors: foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* **87** 47–62. (doi:10.1159/000111037)

Stoeltzing O, Loss M, Huber E, Gross V, Eilles C, Mueller-Brand J & Schlitt HJ 2010 Staged surgery with neoadjuvant ^{90}Y-DOTATOC therapy for down-sizing synchronous bilobular hepatic metastases from a neuroendocrine pancreatic tumor. *Langenbeck's Archives of Surgery* **395** 185–192. (doi:10.1007/s00423-009-0520-x)

Stokkel MP, Rietbergen DD, Korse CM & Taal BG 2011 Somatostatin receptor scintigraphy and chromogranin A assay in staging and follow-up of patients with well-differentiated neuroendocrine tumors. *Nuclear Medicine Communications* **32** 731–737. (doi:10.1097/MNM.0b013e328347a895)

Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, Helm J & Kvols L 2011 First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer* **117** 268–275. (doi:10.1002/cncr.25425)

Sun W, Lipsitz S, Catalano P, Mailliard JA & Haller DG 2005 Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. *Journal of Clinical Oncology* **23** 4897–4904. (doi:10.1200/JCO.2005.03.616)

Surveillance Epidemiology aERPwscg 2009 SEER*Stat Database. In *Incidence – SEER 17 Regs Limited-Use + Hurricane Katrina Impacted Louisiana Cases, Nov 2008 Sub (1973–2006 varying) – Linked To County Attributes – Total U.S., 1969–2006 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch.*

Svejda B, Kidd M, Kazberouk A, Lawrence B, Pfragner R & Modlin IM 2011 Limitations in small intestinal neuroendocrine tumor therapy by mTor kinase inhibition reflect growth factor-mediated PI3K feedback loop activation via ERK1/2 and AKT. *Cancer* **117** 4141–4154. (doi:10.1002/cncr.26011)

Taylor JE, Theveniau MA, Bashirzadeh R, Reisine T & Eden PA 1994 Detection of somatostatin receptor subtype 2 (SSTR2) in established tumors and tumor cell lines: evidence for SSTR2 heterogeneity. *Peptides* **15** 1229–1236. (doi:10.1016/0196-9781(94)90146-5)

Thompson NW 1998 Current concepts in the surgical management of multiple endocrine neoplasia type 1 pancreatic-duodenal disease. Results in the treatment of 40 patients with Zollinger–Ellison syndrome, hypoglycaemia or both. *Journal of Internal Medicine* **243** 495–500. (doi:10.1046/j.1365-2796.1998.00307.x)

Tomassetti P, Migliori M, Caletti GC, Fusaroli P, Corinaldesi R & Gullo L 2000 Treatment of type II gastric carcinoid tumors with somatostatin analogues. *New England Journal of Medicine* **343** 551–554. (doi:10.1056/NEJM200008243430805)

Tonelli F, Fratini G, Nesi G, Tommasi MS, Batignani G, Falchetti A & Brandi ML 2006 Pancreatectomy in multiple endocrine neoplasia type 1-related gastrinomas and pancreatic endocrine neoplasias. *Annals of Surgery* **244** 61–70. (doi:10.1097/01.sla.0000218073.77254.62)

Toumpanakis C, Garland J, Marelli L, Srirajaskanthan R, Soh J, Davies P, Buscombe J & Caplin ME 2009 Long-term results of patients with malignant carcinoid syndrome receiving octreotide LAR. *Alimentary Pharmacology & Therapeutics* **30** 733–740. (doi:10.1111/j.1365-2036.2009.04083.x)

Touzios JG, Kiely JM, Pitt SC, Rilling WS, Quebbeman EJ, Wilson SD & Pitt HA 2005 Neuroendocrine hepatic metastases: does aggressive management improve survival? *Annals of Surgery* **241** 776–783 (discussion 783-775). (doi:10.1097/01.sla.0000161981.58631.ab)

Triponez F & Cadiot G 2007 Non-functioning tumours of the pancreas in MEN1 patients. *Journal of Gastrointestinal and Liver Diseases* **16** 295–296.

Triponez F, Dosseh D, Goudet P, Cougard P, Bauters C, Murat A, Cadiot G, Niccoli-Sire P, Chayvialle JA, Calender A *et al.* 2006 Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. *Annals of Surgery* **243** 265–272. (doi:10.1097/01.sla.0000197715.96762.68)

Turner NC, Strauss SJ, Sarker D, Gillmore R, Kirkwood A, Hackshaw A, Papadopoulou A, Bell J, Kayani I, Toumpanakis C *et al.* 2010 Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours. *British Journal of Cancer* **102** 1106–1112. (doi:10.1038/sj.bjc.6605618)

Vagefi PA, Razo O, Deshpande V, McGrath DJ, Lauwers GY, Thayer SP, Warshaw AL & Fernandez-Del Castillo C 2007 Evolving patterns in the detection and outcomes of pancreatic neuroendocrine neoplasms: the Massachusetts General Hospital experience from 1977 to 2005. *Archives of Surgery* **142** 347–354. (doi:10.1001/archsurg.142.4.347)

van Vilsteren FG, Baskin-Bey ES, Nagorney DM, Sanderson SO, Kremers WK, Rosen CB, Gores GJ & Hobday TJ 2006 Liver transplantation for gastroenteropancreatic neuroendocrine cancers: defining selection criteria to improve survival. *Liver Transplantation* **12** 448–456. (doi:10.1002/lt.20702)

Wangberg B, Westberg G, Tylen U, Tisell L, Jansson S, Nilsson O, Johansson V, Schersten T & Ahlman H 1996 Survival of patients with disseminated midgut carcinoid tumors after aggressive tumor reduction. *World Journal of Surgery* **20** 892–899 (discussion 899). (doi:10.1007/s002689900136)

Welin S, Fjallskog ML, Saras J, Eriksson B & Janson ET 2006 Expression of tyrosine kinase receptors in malignant midgut carcinoid tumors. *Neuroendocrinology* **84** 42–48. (doi:10.1159/000096294)

Wilson JM, Melvin DB, Gray GF & Thorbjarnarson B 1974 Primary malignancies of the small bowel: a report of 96 cases and review of the literature. *Annals of Surgery* **180** 175–179. (doi:10.1097/00000658-197408000-00008)

Wymenga AN, Eriksson B, Salmela PI, Jacobsen MB, Van Cutsem EJ, Fiasse RH, Valimaki MJ, Renstrup J, de Vries EG & Oberg KE 1999 Efficacy and safety of prolonged-release lanreotide in patients with gastro-intestinal neuroendocrine tumors and hormone-related symptoms. *Journal of Clinical Oncology* **17** 1111.

Yamada Y, Post SR, Wang K, Tager HS, Bell GI & Seino S 1992 Cloning and functional characterization of a family of human and mouse somatostatin receptors expressed in brain, gastrointestinal tract, and kidney. *PNAS* **89** 251–255. (doi:10.1073/pnas.89.1.251)

Yang Z, Tang LH & Klimstra DS 2011 Effect of tumor heterogeneity on the assessment of Ki67 labeling index in well-differentiated neuroendocrine tumors metastatic to the liver: implications for prognostic stratification. *American Journal of Surgical Pathology* **35** 853–860. (doi:10.1097/PAS.0b013e31821a0696)

Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A *et al.* 2008 One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of Clinical Oncology* **26** 3063–3072. (doi:10.1200/JCO.2007.15.4377)

Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG *et al.* 2011 Everolimus for advanced pancreatic neuroendocrine tumors. *New England Journal of Medicine* **364** 514–523. (doi:10.1056/NEJMoa1009290)

You YN, Thompson GB, Young WF Jr, Larson D, Farley DR, Richards M & Grant CS 2007 Pancreatoduodenal surgery in patients with multiple endocrine neoplasia type 1: operative outcomes, long-term function, and quality of life. *Surgery* **142** 829–836 (discussion 836 e821). (doi:10.1016/j.surg.2007.09.010)

Received in final form 25 May 2012
Accepted 29 May 2012
Made available online as an Accepted Preprint
29 May 2012