Diagnosis and Management of Pancreatic Neuroendocrine Tumors (PNETS)

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Introduction

Pancreatic neuroendocrine tumors (PNETs) are a rare subset of neuroendocrine tumors (NETs) originating from hormone-producing islet cells. Pancreatic neuroendocrine tumors (PNETs) have an estimated incidence of less than 1 per 100,000 individuals and represent 1.3% of all pancreatic neoplasms (1-3). The PNET category encompasses various malignancies, including insulinomas, gastrinomas, and vasoactive intestinal peptidomas (VIPomas) (Table 1), with the symptoms and clinical course depending on the specific hormones produced (e.g., insulin, gastrin). The tumors are categorized as functional or nonfunctional based on hormone production, biological effects, and symptoms. Approximately 10–30% of PNETs are functional (5). Functional PNETs include insulinomas, gastrinomas, VIPomas, somatostatinomas, glucagonomas, growth-hormone releasing factor secreting (GRFomas) and a group of less common PNETs including PNETs secreting ACTH (ACTHomas) and causing Cushing's syndrome, PNETs causing the carcinoid syndrome, PNETS causing hypercalcemia and very rarely PNETs ectopically secreting luteinizing hormone, renin or

erythropoietin (1). Calcitonin secreting PNETs are infinitesimally rare and the largest global case series included 37 patient (6). Functional PNETS are discussed in further detail in separate chapters of this text. Nonfunctional PNETS (NF PNETs) represent 30-50% of all PNETs. Characteristically, NF PNETs are large, and 60% to 85% have liver metastases at the time of diagnosis (1) (3) (7) (8). They differ from functioning PNETS as malignancy occurs in 60-90% (9,10). Tumor size determines malignancy NF PNETs (11). Functional PNETs and NF-PNETs also frequently secrete a number of other substances (chromogranins, neuron specific enolase, subunits of human chorionic gonadotropin, neurotensin, ghrelin (1-3,7).

PNETs can occur both sporadically and in patients with various inherited disorder (1) (12). PNETs occur in 80-100% of patients with multiple endocrine neoplasia type I (MEN I); in 1017% of patients with von Hippel-Lindau syndrome (VHL); up to 10% of patients with von Recklinghausen's disease (neurofibromatostis-1 [NF-1]), and occasionally in patients with tuberous sclerosis (12). Of these autosomal dominant disorders MEN-1 is the one most frequent, in patients with PNETS (12,13). MEN-1 is caused by mutations in chromosome 11q13 region resulting in alterations in the MEN-1 gene, which has important effects on transcriptional regulation, genomic stability, cell division and cell cycle control (12). Patients with MEN-1 develop hyperplasia or tumors of multiple endocrine and non-endocrine tissues including parathyroid adenomas (95-100%) resulting in hyperparathyroidism; pituitary adenomas in 5465%; adrenal adenomas (27-36%); various carcinoid tumors (gastric, lung, thymic) (0-10%); thyroid adenomas (up to 10%), various skin tumors (80-95%); CNS tumors (up to 8%) and smooth muscle tumors (up to 10%) (12). In MEN-1 patients 80-100% develop pancreatic NFPNETS, but in most patients they are small, multifocal and microscopic, causing symptoms in only 0-13% (12). Gastrinomas (>80% duodenal) develop in 54% of MEN-1 patients, insulinomas in 18% and glucagonomas, VIPomas, GRFomas, somatostatinomas in <5% (12). In VHL, 98% of all the PNETs that may develop NF-PNETs. In the 0-10% of NF-1 patients developing a PNET they are characteristically duodenal somatostatinomas which do not cause the somatostatinoma syndrome and in tuberous sclerosis, rare functional and NF-PNETs are reported (12).

Table 1. Recognized functional pancreatic neuroendocrine tumors and their characteristics.

Tumor type and syndrome	Location in pancreas	Signs and symptoms	Circulating biomarkers
Insulinoma (Whipple's triad)	Head, body, tail (evenly distributed)	Hypoglycemia, dizziness, sweating, tachycardia, tremulousness, confusion, seizure	CgA and CgB, insulin inappropriate for blood glucose level, proinsulin, C-peptide
Gastrinoma (Zollinger–Ellison)	Gastrinoma triangle Often extrapancreatic (duodenal); can be found anywhere in gland	Gastric acid hypersecretion, peptic ulcer, diarrhea, esophagitis, epigastric pain	CgA, gastrin, PP (35%)
VIPoma (Verner–Morrison syndrome, WDHA)	Distal pancreas (body and tail) Often spread outside pancreas	Watery diarrhea, hypokalemia, achlorhydria (or acidosis)	CgA, VIP
Glucagonoma	Body and tail of pancreas Often large and spread outside pancreas	Diabetes (hyperglycemia), necrolytic migratory erythema, stomatitis,	CgA, glucagon, glycentin

		glossitis, angular cheilitis	
Somatostatinoma	Pancreatoduodenal groove, ampullary, periampullary	Gallstones, diabetes (hyperglycemia), steatorrhea	CgA, somatostatin
Ppoma	Head of pancreas	None	CgA, PP

Note: CgA is raised only in metastatic tumors.CgA, chromogranin A; CgB, chromogranin B; PP, pancreatic polypeptide; VIP, vasoactive intestinal peptide; WDHA, watery diarrhea, hypokalemia, and achlorhydria.

Adapted from *Current Opinions in Oncology*, Milan, S.A. and Yeo, C.J. Neuroendocrine Tumors of the Pancreas, 46–55. © 2012 with permission from Lippincott Williams & Wilkins, Inc. and *Endocrinology and Metabolism Clinics of North America*, Ardill, J.E. and O'Dorisio, T.M., Circulating Biomarkers in Neuroendocrine Tumors of the Enteropancreatic Tract: Application to Diagnosis, Monitoring Disease, and as Prognostic Indicators, 777–790. © 2010 with permission from Elsevier Inc., Vinik and Raymond. Pancreatic Neuroendocrine Tumors: Approach to treatment with focus on Sunitinib. Therap Adv Gastroenterology 6(5) : 396-411, 2013.

Pathology and Staging

The pathology of these lesions remains confusing and controversial with no universally recognized classification system. There are a variety of competing systems currently in use, including those developed by the World Health Organization (WHO) and the European Neuroendocrine Tumor Society (ENETS). The WHO 2010 classification uses site specific criteria and grade to classify these tumors. For example, low grade gastroenteropancreatic NETs (GEP-NETs) are considered neuroendocrine neoplasms, grade 1, intermediate grade neuroendocrine neoplasms, grade 2, and high grade neuroendocrine carcinoma, grade 3 (14). Despite the differences among the systems, common elements include distinction of well differentiated (low and intermediate grade) from poorly differentiated (high grade) neuroendocrine tumors. Measures of cell differentiation include mitotic index, Ki67, presence of angioinvasion, size and functional activity. Proliferative rate of these lesions also appears important in prognostic assessment (15). A minimum pathology data set has been suggested to standardize the information in pathology reports (16). A detailed discussion of the pathology of these tumors is beyond the scope of this brief review of recent advances. Readers are referred to the excellent coverage of this topic in the NANETS guidelines (15). The AJCC 7^{th} edition now includes staging of pancreatic neuroendocrine tumors. The staging of pancreatic NETs is identical to the staging of adenocarcinoma (17). The paradox is that despite being considered a well-differentiated tumor these may metastasize extensively to the lymph nodes, liver and bones.

Molecular genetics

Although most are sporadic, PNETs are unique among NETs in their association with familial syndromes. The clinical course and prognosis of sporadic PNETs differs from those that occur in MEN-1. For example, surgical resection of sporadic gastrinoma patients result in a better disease free survival compared to patients with MEN-1 (18). MEN-1 has germline mutations in the MEN-1 gene, a tumor suppressor gene, which is located on chromosome 11q13 and encodes the nuclear protein menin that interacts with such nuclear proteins as junD, SMAD3 and NF-kB. In sporadic PNETs, mutations in

the MEN-1 gene are detectable in only 21% of cases (19). Interestingly, over 50% of PNETs exhibit losses at chromosome 11q13 and/or more distal parts on the long arm of the chromosome. This suggests that there may be a tumor suppressor gene distal to the menin gene that may be involved in tumorigenesis of PNETs. Losses on chromosome 1 and gains on 9Q also appear to be important in the development of sporadic PNETs (20). This is in contradistinction to midgut and hindgut NETs which frequently show losses on chromosome 18q (21). Another mechanism of tumor formation in PNETs includes promoter hypermethylation in silencing tumor suppressor gene expression. The most commonly silenced genes are RASSF1A (75%) p16/INK4A (40%) and O6-MGMT (40%) (22). Alterations in known oncogenes such as Kras and p53 occur uncommonly in PNETs (23,24).

A study from Johns Hopkins in patients with pancreatic NETs revealed that the three most commonly mutated genes were MEN-1, and DAXX/ATRX. Patients with these mutations tended to live longer than patients with other mutations. These genes are associated with chromatin remodeling. Mutations in the mTOR pathway were noted in 14% of tumors (25). This clearly suggests that genetic factors may determine responsiveness to therapy such as the use of MTOR inhibitors.

Induction of PNETs

A great deal of interest is now being focused on the factors responsible for the initiation of growth, growth proliferation, differentiation into adult endocrine cells, and, in neuronal systems, for growth cessation and cell maintenance. Several models of pancreatic regeneration and tumor formation have been established (26) (27-36). The developing pancreas appears as a protrusion from the dorsal surface of the embryonic gut (37). The figure shows the normal anatomy of the pancreas and duodenum in the adult. What is also shown is the capability of proliferation of pancreatic duct glandular structures (PDGs) (38) with the capability of transformation in to endocrine cells.

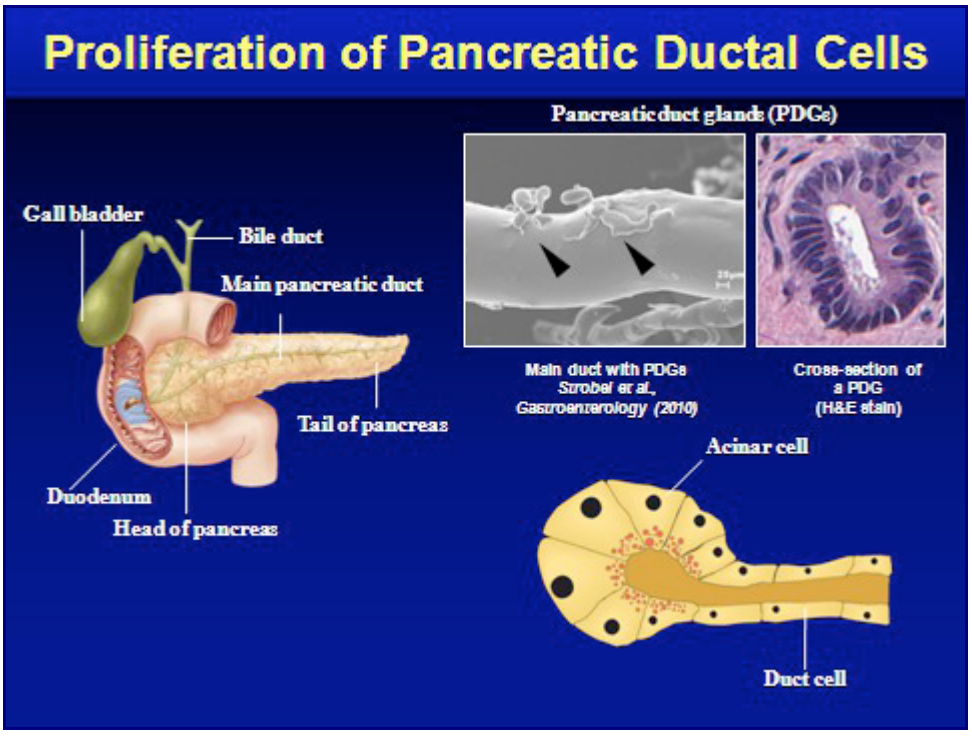

Figure 1. This Figure illustrates the pancreato-biliary complex including the ductular system. The acina/ductal system contains proto-differentiated stem cells capable of differentiating into a variety of endocrine cells (4). In addition the pancreatic duct glands can grow and proliferate developing

pancreatic Intraductal neoplasms (PANINS) forming the basis of PNETs and NFPNETS with different levels of differentiation and dedifferentiation.

The different islet-cell types appear sequentially during development in vivo. Therefore, it seems reasonable to propose that coordinated growth depends on the specificity of growth factors. Rosenberg and Vinik (4) used a model for new islet formation (i.e., nesidioblastosis) and showed that pancreatic ductal cells are capable of differentiating on stimulation into adult endocrine cells that are capable of secreting insulin in a fully regulated manner. This has led to the notion that endocrine tumors derive from a potential stem cell in the gut that is capable of differentiating into any one of a variety of cells that may be responsible for the clinical syndrome. (Figure 1) In HIP rats treated with Sitagliptin, a peptidyl peptidase 1V inhibitor thus preventing the catalytic breakdown of glucagon like peptide 1(GLP1) thereby increasing endogenous GLP-1 inducing ductal metaplasia (39). Human GLP-1 receptor is expressed in the ductal system in human and upon stimulation with incretins , Exenatide or GLP-1 markedly increase the expression of gLP-1 receptor leading to the formation of intraductal neoplasms called PanINs) (40) showed expansion of exocrine and endocrine pancreas with Incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon producing tumors. Pancreata from Type 2 Diabetes organ donors on Incretin therapy (n=8), other RX (n=12) and Diabetic Controls (n=14) were obtained. In DM beta cell mass was reduced 60%. Incretin treatment increased islet mass by 40%. However (3/8) developed glucagon microadenomas and 1 an alpha cell NET accompanied by exocrine cell proliferation and pancreatic intraepithelial neoplasia (Panins). Co-staining for insulin and glucagon increased in DM and was even greater in Incretin treated patients. They concluded that Incretins expand exocrine and endocrine pancreas with proliferation, dysplasia and a cell hyperplasia with possible adenoma formation. While this data was found in postmortem specimens and there is little clinical evidence in thousands of patients treated with incretins it raises an interesting possibility on the formation of adenomas and the role that GLP-1 may play (40). FButler et al reported on the appearance of glucagon cells in the ducts of a patient who had been treated with an incretin (41). The suggestion being that with the correct genetic predisposition use of incretins may have the capacity to induce malignant transformation of cells with formation of neuroendocrine tumors.

Nonfunctioning Pancreatic endocrine tumors (NF-PNETS)

NF-PNETS are intrapancreatic in location, characteristically large (70% >5cm), and at an advanced stage when first diagnosed with 60-85% having liver metastases in most series(1),(3), (7),(42),(8). NF-PNETS are not associated with a clinical hormonal syndrome presenting with symptoms due to the tumor per se which include abdominal pain (40-60%), weight loss, or jaundice (1),(3),(7),(42),(8). In recent years, they are increasingly being discovered by chance on imaging studies performed for nonspecific abdominal symptoms (1),(43). Although NFPNETS do not secrete peptides causing a clinical syndrome, they characteristically secrete a number of other peptides, which are helpful in their diagnosis. These include chromogranins, especially chromogranin A (CGA) (70-100%) and pancreatic polypeptide (PP) (50-100%) (1) (3) (7) (42) (8). The presence of an NF-PET is suggested by the presence of a pancreatic mass in a patient without hormonal symptoms, with an elevated serum PP or CGA level or a positive octreoscan (somatostatin receptor scintigraphy. However an elevated PP level or CGA level is not specific for NF-PNETS (1) (3) (7) (42) (8).

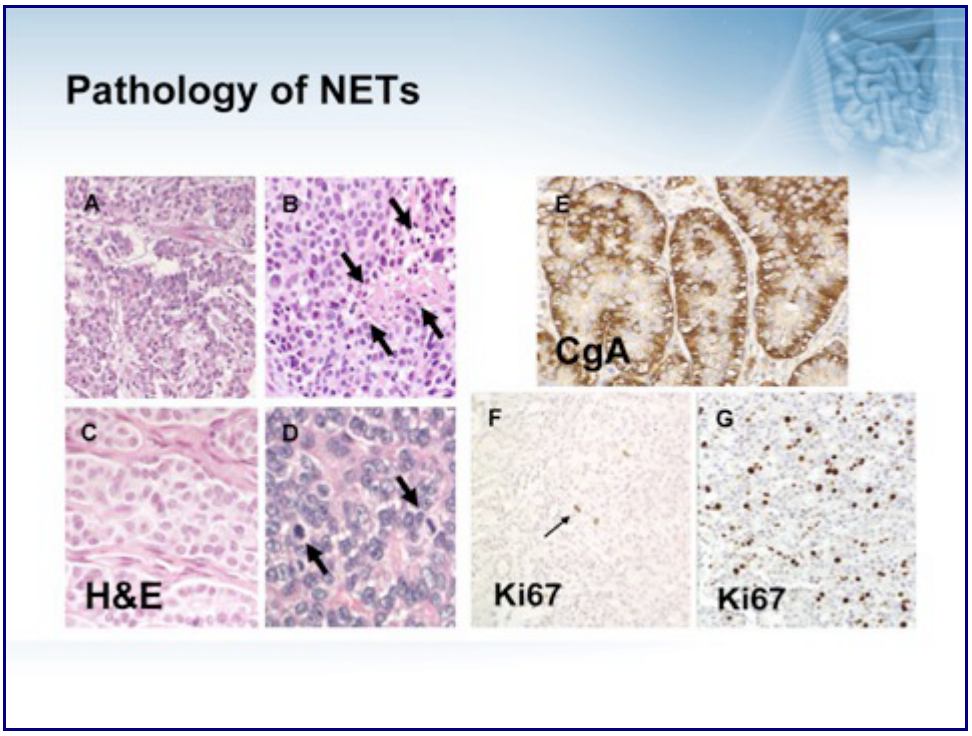

Figure 2. Shows the histological findings supporting the neuroendocrine nature of the tumor with positive CGA staining and the degree of dedifferentiation illustrated by the number of mitotic figures shown on H and E in the top left and a blow up bottom right. The proliferative index is shown in F and G indicating a low level in F and a high KI67 indexes in G.

They are also classified by degree of differentiation, with well-differentiated tumors generally considered low-grade and poorly differentiated tumors considered high-grade. In the European Neuroendocrine Tumor Society (ENETS) consensus guidelines, the grading of proliferative rate of the tumor cells based on combination of the mitotic rate and Ki67 labeling index is advocated (44) Figure 2. The World Health Organization (WHO) classification incorporates both grading and staging, and provides a basis for prognostic prediction (14). These grading systems are helpful to assess the predictive malignant potential in the patients with pancreatic NETs. It would be expected to apply more practically at each disease stage Figure 3. The value of the grading system in determining prognosis is illustrated in Figure 4.

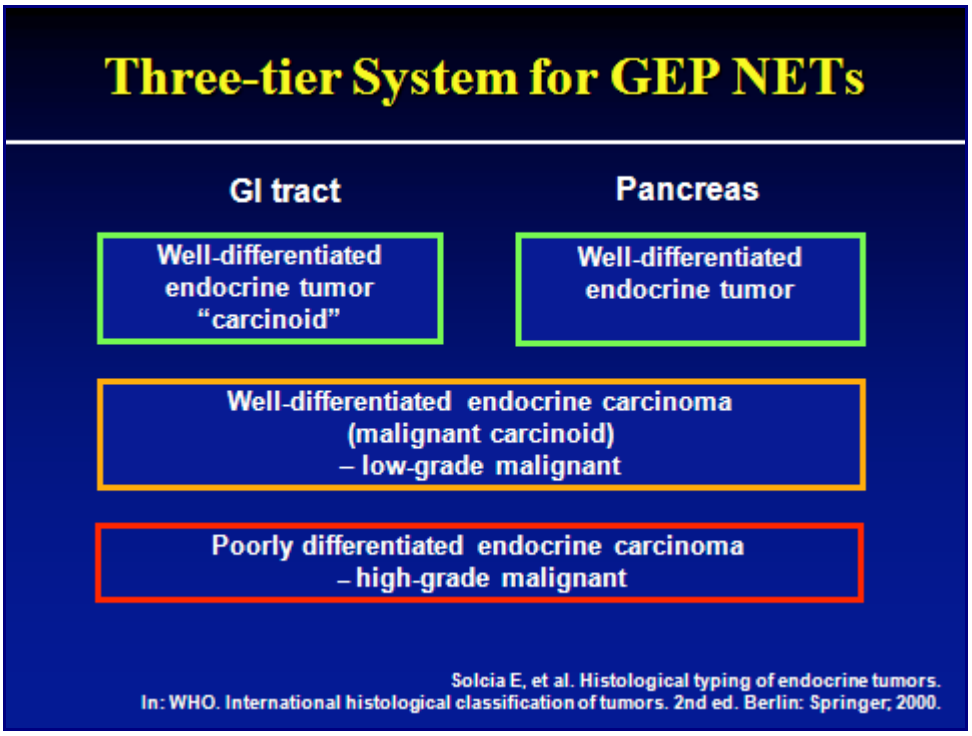

Figure 3. This figure is a compilation of reports by Solcia et al and agreed upon by the WHO international registry that divides Gastroenteropancreatic NETs into the GI tract and pancreas NETs. There are three tiers starting with a well-differentiated pancreatic tumor, a second tier of a well differentiated endocrine carcinoma which is really still a low grade level of malignancy and the a poorly differentiated endocrine carcinoma which has a high grade of malignancy.

Diagnosis of NF PNETs often occurs at an advanced stage because the symptoms are nonspecific and the disease course tends to be indolent (45). Even at an advanced stage, the tumors are slow to progress, with rates of 5-year survival in advanced disease estimated at 30–50% [Lepage et al. disease, debulking surgery may be useful and in instances where metastases are limited to the liver, palliative benefits may result from loco-regional treatments, including chemoembolization, radiofrequency ablation, and percutaneous ethanol injection (48).

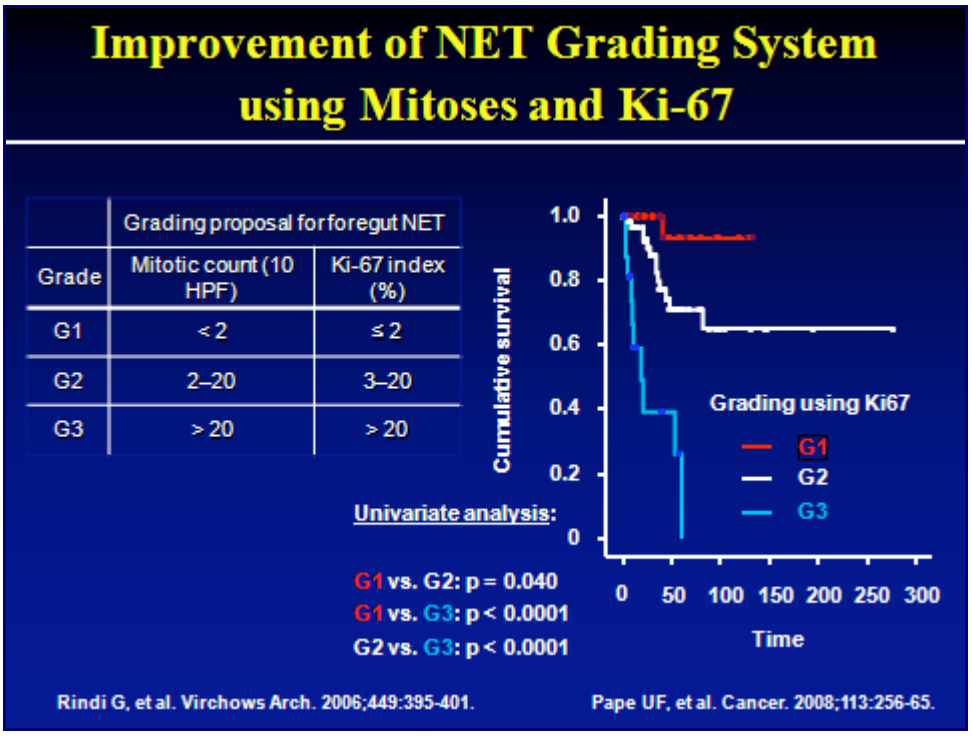

Figure 4 illustrates the value of the grading system based upon mitotic count per 10 high power fields and the KI67 index given as % of the cells staining positive immunohistochemically. Dividing the pathology into the three grades has very marked effect on cumulative survival in months as shown in the graph on the right.

Immunohistochemistry

While most agree that a mitotic rate or Ki-67 is necessary in specific cases, whether Ki-67 staining is needed in all cases remains hotly debated. An experienced pathologist familiar with

NETs will likely be able to determine the tumor's grade in the majority of resected specimens and a Ki-67 can be obtained as needed in difficult cases. In small biopsy specimens, there may not be sufficient material to differentiate between grade 1 versus 2 neuroendocrine carcinomas with or without Ki-67. (See Figure 2)

Other Rare Functional PNETS

GRFomas ectopically secrete growth hormone-releasing factor, which results in acromegaly, that is clinically indistinguishable from that caused by pituitary adenomas (1) (42) (49). GRFomas in the pancreas are generally single, large tumors at diagnosis; one-third have liver metastases and they are found in the pancreas in 30% of cases, 54% in the lung and the remainder primarily in other abdominal locations (1) (42) (49)}. PNETS causing hypercalcemia usually secrete PTH-related peptide (PTH-rP) as well as other biologically active peptides and are usually large tumors at diagnosis with 80-90% associated with liver metastases (1) (42) (50,51).

Miscellaneous PNETs

Acromegaly or Gigantism: Can present when any NET secretes GH or GHRH. Basal levels of GH and

IGF-1 are usually enough to make a diagnosis; but in 15 to 20% of the patients further investigation is needed to show nonsuppressibility of GH to an oral glucose tolerance test (OGTT), a somatostatin inhibition test or a bromocriptine suppression test. In the case of the OGTT, lipids and insulin, which should also be suppressed. Other pituitary and hypothalamic hormones should also be measured, such as prolactin, the α and ß -subunits of gonadotropins and thyroid stimulating hormone (TSH) (52).

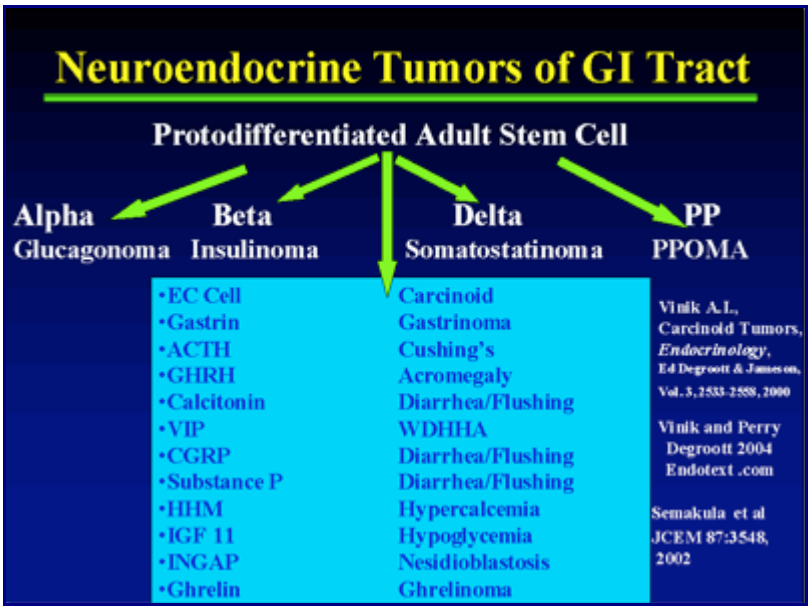

Figure 5 Illustrates the almost totipotentiality of the protodifferentiated pancreatic stem cell to differentiate into a variety of either cell types to produce an almost infinite variety of clinical syndromes EC=enterochromaffin, GHRH= growth hormone releasing hormone, VIP = vasoactive intestinal polypeptide, CGRP= calcitonin releasing peptide, HHM = humoral hypercalemic factor of malignancy, IGF = insulin like growth factor, INGAP = islet neogenesis growth associated peptide.

Cushing's Syndrome: A pituitary tumor, small cell carcinoma of the lung (known to produce ACTH) or an ACTH secreting NET will present clinically as the Cushing syndrome from over secretion of cortisol, adrenal androgens and 11-deoxycorticosterone. To reach the diagnosis several steps should be followed. New guidelines for the diagnosis of Cushing's syndrome have been published, though some of the recommendations are based on low quality evidence. Their proposed approach is as follows.

After excluding exogenous glucocorticoid use (iatrogenic Cushing's syndrome) patients with age-unusual features like osteoporosis or hypertension, other features predictive of Cushing's syndrome (easy bruising, facial plethora, proximal myopathy or muscle weakness, reddish/purple striae, weight gain in children with decreasing growth velocity) and those with adrenal incidentaloma compatible with adenoma should undergo testing for Cushing's syndrome starting with one test with high diagnostic accuracy: Urine free cortisol (at least two measurements), late night salivary cortisol (two measurements), 1mg overnight dexamethasone suppression test (DST) or longer low-dose DST (2mg/d for 48 hours). If the test is negative and the pretest probability was low then follow up in 6 months is recommended if progression of symptoms; in case of a negative test but with a high pretest probability then more than 1 test should be performed. In some cases a serum midnight cortisol or dexamethasone-CRH test should be done (53).

Biochemical Assessment and Monitoring for PNETS

Specific hormonal assays are needed to establish the diagnosis of each functional PNET as outlined in

the discussion of each tumor type in Section B above. Specifically, for insulinomas an assessment of plasma insulin, proinsulin and C-peptide are needed at the time of glucose determinations, usually during a fast (1) (54,55). For gastrinoma, serum gastrin is needed either alone or during a secretin provocation test (1) (54) (56) (57) (55). For VIPomas a plasma VIP level is needed; for glucagonoma plasma glucagon levels; for GRFomas plasma GH and GRF levels; for Cushing's syndrome urinary cortical, plasma ACTH and appropriate ACTH suppression studies; for hypercalcemia with PNET both serum PTH levels and PTH-rP levels are indicated and for a PNET with carcinoid syndrome, urinary 5-H1AA should be measured (1) (58) (42) (55) (59).

Chromogranin A (CgA) and Chromogranin B (CgB): Both are part of the granin family. They are stored and secreted from vesicles present in the neuroendocrine cells, together with other peptides, amines and neurotransmitters (60). CgA can be used as a marker in patients with both functional and non-functional pancreatic endocrine tumors (1) (55) (59) (61). CgA is the best studied (62) and most used but is not perfect. Stridsberg et al reported common conditions that can increase the levels of this marker and give false positive measurements including: decreased renal function and treatment with proton pump inhibitors (63) and even essential hypertension (64); these problems are not seen with CgB, with complementary measurement so proposed (63).

The most important characteristic of these markers is that they are not only secreted by the functional tumors but also by those less well-differentiated NETs that do not secrete known hormones (65). High CgA has been shown to be increased in 50 to 100% of patients with NETs (66). CgA levels may be associated with the primary tumor (gastrinomas 100%, pheochromocytomas 89%, carcinoid tumors 80%, nonfunctioning tumors of the endocrine pancreas 69% and medullary thyroid carcinomas 50%). In addition blood levels depend upon tumor mass, burden or progression and malignant nature of the tumor (67) (68). Small tumours may be associated with normal CgA levels.

Sensitivity and specificity of CgA depends on many factors. For example, sensitivity varies from 77.8 to 84% and specificity from 71.3 to 85.3% depending on the assay used, and of great importance is to establish the cutoff value that gives the highest sensitivity without compromising the specificity (69). Another utility of CgA is to discriminate between patients with or without metastasis, which also depends on the assay and the cut-off values used, with a sensitivity of 57-63.3% and specificity 55.6-71.4% (69). CgA should be used cautiously in patients treated with somatostatin analogs, since these agents significantly reduce plasma CGA levels (59) (70). In patients on stable doses of somatostatin analogs, consistent increases in plasma CGA levels over time may reflect loss of secretory control and/or tumor growth (55) (59) (61) (71) (72).

Pancreatic Polypeptide (PP): Is considered another non-specific biochemical marker. In a study conducted by Panzuto et al. in Rome, Italy in 2004, PP sensitivity was 54% in functioning tumors, 57% in non-functioning, 63% in pancreatic tumors and 53% in gastrointestinal tumors. Specificity was 81% compared with disease free patients, and 67% compared to non-endocrine tumors' patients. But when combined with CgA the sensitivity increased compared to either of the markers alone. When used in combination, the sensitivity of these markers is: for gastro entero-pancreatic neuroendocrine tumors (GEP NETs) 96%; for non-functioning tumors 95% and for pancreatic tumors 94% (73).

Neuron-Specific Enolase (NSE): Are enzymes that occur mainly in cells of neuronal and neuroectodermal origin. NSE has been found in thyroid and prostatic carcinomas, neuroblastomas, small-cell lung carcinoma, carcinoids, GEP NETs and pheochromocytomas. Despite its high sensitivity (100%), its use is limited as a blood biochemical marker for neuroendocrine tumors due to its very low specificity (32.9%) (74).

Imaging of PNETs

General

Imaging of the primary tumor location and the extent of the disease is needed for all phases of management of patients with PNETs. It is needed to stage extent of disease, to determine whether surgical resection for possible cure or possible cytoreductive surgery is needed, whether treatment for advanced metastatic disease is appropriate and during follow-up to assess the effects of any anti-tumor treatment as well as the need for deciding whether additional treatments directed at the PNETs are indicated (1) (42) (75) (76). Functional PNETs (especially insulinomas, duodenal gastrinomas) are often small in size, and localization may be difficult (1) (42) (75,76). A number of different imaging modalities have been widely used including conventional imaging studies (CT, MRI, ultrasound, angiography) (77-80) endoscopic ultrasound (EUS) (1) (81,82) functional localizations studies measuring hormonal gradients; (1) (83-85) intra-operative methods particularly intra-operative ultrasound (1) (86,87) and recently, the use of positron emission tomography preoperatively (80) (88-90). A few important points in regard to each will be made below.

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

Even though PNETs are highly vascular tumors and most of these studies are now performed with contrast agents, the results with conventional imaging studies are dependent to a large degree on the tumor size (77),(1),(75),(91),(92). While conventional imaging studies detect >70% of PNETs>3 cm, they detect <50% of most PNETs<1 cm, therefore frequently miss small primary pNETs (especially insulinomas, duodenal gastrinomas) and small liver metastases (77), (1),(75),(91),(92). At least one of these modalities is generally available in most centers with CT scanning with contrast being most frequently used as the first imaging modality.

Somatostatin receptor scintigraphy (SRS)

PNETs, similar to carcinoid tumors, frequently (>80%, except insulinomas) over-express somatostatin receptors (particularly subtypes sst 2, 5), which bind various synthetic analogues of somatostatin (Octreotide, lanreotide) with high affinity (1) (78-80) (93). A number of radiolabeled somatostatin analogues have been developed to take advantage of this finding to image PNETS, with the most widely used worldwide and the only one available in the US, being ^{111}Indium-DTPA-octreotide (octreoscan) (1) (78-80) (93) SRS combined with computerized tomographic detection (SPECT imaging) is more sensitive than conventional imaging for detection of both the primary (except insulinomas) PET and metastatic PNETS to liver, bone or other distant sites (94) (78-80) (93) (95). This sensitivity allows SRS to detect 50-70% of primary PNETS (less frequent with insulinomas or duodenal gastrinomas) and >90% of patients with metastatic disease (1) (78-80) (96) (97). It has the advantage of allowing total body scanning quickly at one time and its use has resulted in a change in management of 24-47% of patients with PNETS (1) (78) (79) (80) (96) (97). False positive localizations can occur in up to 12% of patients so it is important to interpret the result within the clinical context of the patient and by doing this, the false positive rate can be reduced to 3% (1) (79) (97) (98).

Endoscopic ultrasound (EUS)

EUS combined with fine needle aspiration can be useful in distinguishing a NF-PET from adenocarcinoma or some other cause of a pancreatic mass (1) (81,82). Fine needle aspiration is rarely used to diagnose functional PNETS because they are suggested by symptoms and the diagnosis is established by hormonal assays (1) (42). EUS is much more effective for localizing intrapancreatic PNETs than extrapancreatic PNETs such as duodenal gastrinomas or somatostatinomas (1) (42) (81) (42). EUS is particularly helpful in localizing insulinomas, which are small, almost always intrapancreatic and frequently missed by conventional imaging studies and SRS (1) (42) (81) (42). EUS can identify an intrapancreatic PET in about 90% of cases (1) (81). EUS can also play an important role in the management of patients with MEN1 who contain NF-PNETs in 80-100% of cases or in patients with NF-PNETS with VHL syndrome which occur in 10-17%, which are often small and whose management is controversial (1) (12) (71) (99) (100) (101). EUS can detect many of these small NF-PNETS and it has been proposed that serial evaluations with EUS be used to select which MEN1 or VHL patients should have surgery (1) (12) (71) (100-102).

Functional localization (assessing hormonal gradients) and Positron Emission Tomographic scanning for PNETs

Assessment of hormonal gradients is now rarely used except in occasional patients with insulinomas or gastrinomas not localized by other imaging methods (1) (91) (83-85) (103). When used it is now usually performed at the time of angiography and combined with selective intra-arterial injections of calcium for primary insulinomas or secretin for a primary gastrinoma or possible metastatic gastrinoma in the liver with hepatic venous hormonal sampling (1) (91) (8385) (103). Positron Emission Tomographic scanning for PNETs is receiving increasing attention because of its increased sensitivity (1) (91) (88-90). With PNETS ^{11}C-5 hydroxytryptophan or ^{68}Gallium-labeled somatostatin analogs have been shown to have greater sensitivity than SRS or conventional imaging studies and therefore may be clinically useful in the future. At present neither of these methods is approved for use in the US and are not available in the US at the current time (1) (80) (88-90).

Intraoperative localization of PNETs

During surgery the routine use of intraoperative ultrasound is recommended especially for pancreatic PNETS (1) (86,87) and for small duodenal tumors (especially duodenal gastrinomas) endoscopic transillumination (1) (104,105) in addition to routine duodenotomy are recommended (1) (18) (81) (105) (106,107). These will be discussed in more detail in the surgical section below.

Diagnosis of Bone Metastasis

Metastases from NETs can be either lytic and/or osteoblastic. There may be an increased osteoclast activity contributing to lytic lesions and or an increase osteoblastic activity responsible for blastic metastases. Bone markers in lytic and osteoblastic metastases therapy include bone alkaline phosphatase (bAP), an indicator of osteoblast function, and urinary N – telopeptide, which reflects osteoclast activity or bone resorption. Somewhat paradoxically only blastic metastases show an increase in both markers (108).

Increased osteoclast activity predicts a poor outcome, with a Relative Risk (RR) for high N–telopeptide (> 100 nmol BCE/mM creatinine) of: skeletal related events RR: 3.3 ($p<0.001$); disease

progression RR: 2.0 ($p<0.001$); death RR: 4.6 ($p<0.001$) (109).

Summary of Imaging for NETs

The preliminary work-up of a neuroendocrine tumor often starts in the emergency department with plain abdominal X rays done to work up an abdominal pain syndrome. Any abnormal finding leads to CT scanning and the discovery of liver metastasis inevitably leads to CT guided liver biopsy. These tests are often used non-specifically because of the presence of vague symptom complexes. Once the NET diagnosis is suspected, more specific means of imaging are typically employed. For detecting the primary NET tumor, a multimodality approach is best and may include CT, MRI, somatostatin receptor scintigraphy (SRS), endoscopic ultrasound (EUS), endoscopy, and less commonly digital selective angiography or venous sampling. CT is probably superior for localizing the primary tumor, mesenteric invasion, and thoracic lesions, whereas gadolinium enhanced MRI is superior in characterizing liver lesions. Technique is critical and meticulous attention to detail is necessary and MDCT and MRI gradients have enhanced diagnostic performance. While some investigators in Europe advocate the use of enteroclysis with CT imaging, this techniques is not readily available in most US hospitals and thus is rarely done here in the US.

The most sensitive imaging modality for detecting widespread metastatic disease in NET's is somatostatin receptor scintigraphy (SRS; OctreoScan®). However, SRS is less sensitive for metastatic insulinomas because only 40-50% express type 2 somatostatin receptors (sst 2) needed for SRS. Recent finding using glucagon receptor (110) imaging suggest that this may replace Octreoscans when insulinomas have not been identified but this has not been done in the US. Octreoscans are extremely useful in confirming the diagnosis and evaluating tumor distribution and burden. The use of PET scanning in undifferentiated tumors or small cell like lesions of the bronchus or thymus is highly effective. The role of PET scanning for well-differentiated NETs is less delineated. Only tumors with high proliferative activity and dedifferentiation show FDG-PET uptake. PET with tracers based upon metabolic features (5 HTP) and receptor characteristics (DOTATOC) have shown promising results in a limited number of studies.

Recently ^{123}I MIGB scanning has been added to the diagnostic tools of US for the physician working up NETS. This scan offers information that is additive to the information gained by SRS imaging. In some patients SRS scanning is negative and other lesions light up on MIBG scanning. In other patients SRS imaging and MIBG scans both are positive or negative. In the case where both scans are positive patients may be candidates for future therapy with ^{131} I MIBG or PRRT with radiolabeled somatostatin analogs.

Management of PNETs

Although the clinical relevance of the distinction between functioning and nonfunctioning PNETs has recently been questioned as the treatment of these tumors follow the same general principles (111), the distinction is sometimes important for clinical presentation, diagnosis, and treatment of these tumors and the appropriate choice for medical management and if one addresses only the mass the surgical removal of a mass may fail to recognize the offending tumor with disastrous consequences for the patient! For medical management of functioning PNETS see the individual sections on for e.g. gastrinoma, insulinoma etc.

Surgical Management

Surgical resection of a functioning PNET should be considered whenever possible (1) (3) (112), except in patients with MEN 1 with the presence of ZES. The reason of this exception is that patients with MEN 1 and gastrinoma are almost never cured without extensive resections due to multifocal tumors in the pancreas (12) (18,81,113). In patients with sporadic gastrinomas, pancreatectomies with lymphadenectomy are recommended for possible cure due to their high incidence of nodal involvement (114).

The positive impact of resection on survival in patients with NF PNETs has been repeatedly demonstrated (115-119). The extent of surgery and lymphadenectomy should be limited because NF PNETs are often indolent neoplasms without lymph node metastasis. Small tumors (< 2 cm) have an indolent course and may be amenable to observation (11) (120,121). In addition to size of tumor, tumor grade and differentiation are candidates of indicators of biologic behavior and are associated with survival (119) (122,123). Nodal metastases occurred in 30% of patients with NF PNETs and were associated with decreased 5-year disease-free survival. Independent factors associated with nodal metastasis were radiological nodal status and tumor grade (124). Tumor characteristics are a central consideration for treatment decisions of PNETs.

Surgical Treatment of PNETs with resectable synchronous metastases

Most of the PNETs already have metastases at the time of diagnosis (125). Liver metastases are the most common (126) (127) and account for 90% of metastases in patients with PNETs (128). Aggressive surgical resection of both primary and metastatic lesions have been reported (129) (130). More than half of the patients with liver metastases from NETs underwent a major hepatic resection and 40% of them had concurrent resection of the primary tumor (131). Norton JA, et al. reported that aggressive surgery including pancreatectomy, splenectomy, superior mesenteric vein reconstruction, and liver resection can be done with acceptable morbidity and low mortality rates in well selected patients with advanced PNETs (132,133).

Surgical Treatment of PNETs with unresectable synchronous liver metastases and no extrahepatic metastases

The incident rate of synchronous liver metastases from all PNETs is approximately 30% (129) (134). Cytoreductive hepatic surgery in patients with functioning PNETs may be indicated to reduce the amount of hormone and improve the clinical symptoms and prognosis, and may be associated with increased long-term survival (135-137). Cytoreductive surgery can be performed safely with minimal morbidity and mortality and results in regression of symptoms and prolonged survival in the majority of patients (138). Patients with metastatic disease may also benefit from an aggressive surgical approach. Some authors have also shown that resecting the primary tumor in these patients improves survival (139). Such an approach is supported by the NANETS guidelines (140). Even in the face of malignant metastatic disease some patients with PNETs may benefit from an aggressive surgical approach with resection of the primary tumor. This was demonstrated by a recent study of P NETs which analyzed the SEER database and showed an odds ratio of 0.48 (95% confidence limits 0.35-0.66) for those who underwent surgical resection of the primary, compared to those who were recommended for surgery but did not proceed with surgery (115). The benefit of resecting the primary tumor was seen in all disease stages, including stage 4 (140) (141). Both the National Comprehensive

Cancer Network (NCCN) guideline for PNETs (133) and ENETs consensus guidelines for unresectable liver metastases from digestive NETs (142) recommend hepatic regional therapy with systemic treatment, but do not provide guidelines for managing the primary tumor concurrently. Resection of the primary tumor may prevent some of complications which are developed on disease progression (130) (143) and may be associated with improved responses to concomitant therapy and overall survival (144).

Chemotherapy of PNETS Figure 6

For metastases hepatic regional therapy such as trans-catheter arterial embolization (TAE), trans-catheter arterial chemoembolization (TACE), radioembolization, or ablative therapy, in combination with resection of primary pancreatic tumor is possible to be considered (130) (145).

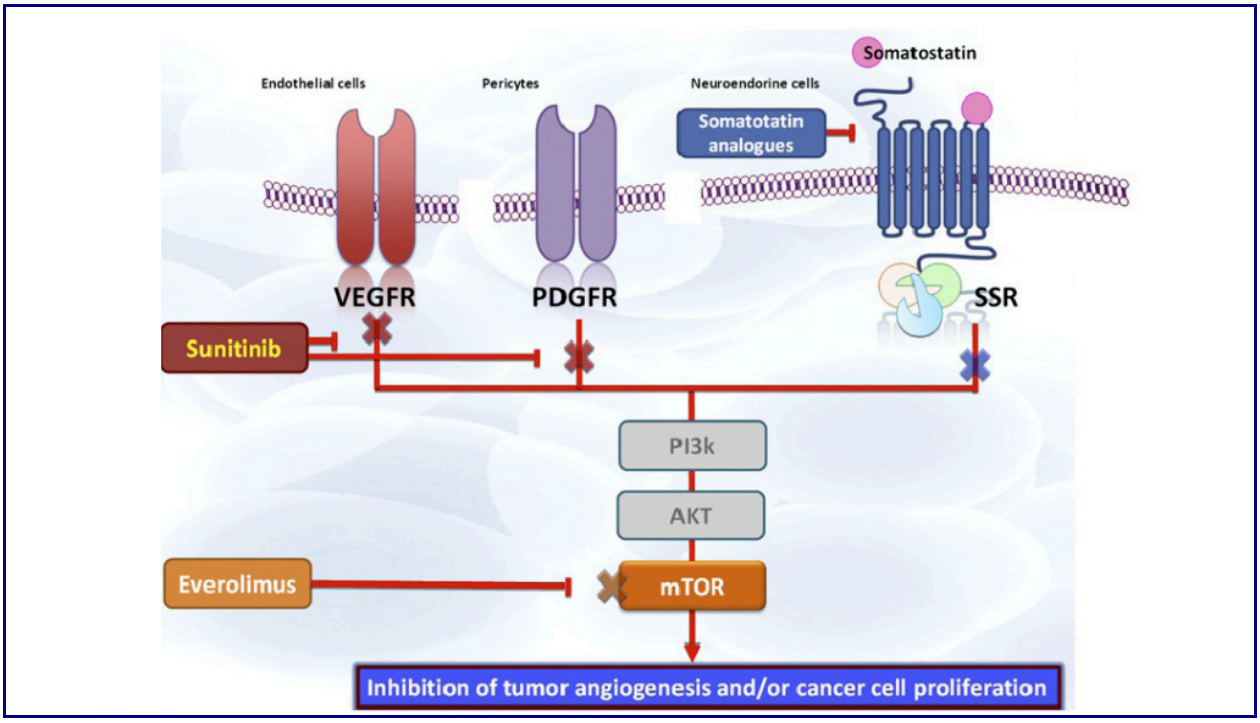

Figure 6. This figure illustrates the current means of targeting the biologic processes promoting cell growth in PNETs. The mainstay of treatment has been the use of somatostatin analogs which bind to somatostatin receptors controlling both symptoms and cell growth. Sunitinib is a tyrosine kinase inhibitor and inhibits vasoendothelial derived growth factor (VEGFR) as well as platelet derived growth factor (PDGFR) and everolimus is an MTOR inhibitor . These are designed to inhibit tumor angiogenesis and or cancer cell proliferation. Figure 6 mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; SSR, somatostatin receptors; VEGFR, vascular endothelial growth receptor. Reprinted from Endocrinology and Metabolism Clinics of North America, Faivre, S., Sablin, M. P., Dreyer, C. and Raymond, E., Novel Anticancer Agents in Clinical Trials for Well-Differentiated

Recurrence of PNETs may benefit from aggressive surgical approaches and achieve long-term survival or long-term palliation (146) (147). Somatostatin analogs have long been a mainstay in the treatment of metastatic NET's. Somatostatin is effective in reducing the symptoms of NETs including flushing, and diarrhea. Indeed, response to octreotide has been shown to correlate with patients who have a decrease in chromogranin A levels after octreotide testing (148). Faiss et al. reported in a prospective multicenter trial evaluating the efficacy of lanreotide, interferon alpha and their combination in

metastatic neuroendocrine tumors a partial response or stable disease in 32% patients treated with lanreotide compared to 29.6% for interferon alpha and 25% for the combination (149). This study found that foregut tumors, of which PNETs comprised 72%, had a statistically shorter time to progression as compared to midgut tumors. Symptoms (diarrhea, flushing) were more significantly reduced with combination treatment than either monotherapy, but combination therapy had a higher incidence of side effects and lead to a 25% (7 of 28 pts) interruption of therapy compared to 14.8% and 12% for interferon alpha and lanreotide respectively. The lower response rate of the somatostatin arm compared to prior studies is thought due to the nonrandom and nonblinded prior reports as well as the high number of foregut tumors which are less responsive to somatostatin therapy. The PROMID trial evaluated the efficacy of somatostatin monotherapy in the form of octreotide 30 mg intramuscular injection every 28 days versus placebo on time to progression in metastatic midgut neuroendocrine tumors (150). Octreotide showed a 66.7% stable disease at 6 months compared to 37.2% for placebo. This effect was similar in functional and nonfunctional carcinoid tumors. The time to progression was longer in the octreotide group at 14.3 months versus 6 months. There was no significant reduction in symptoms (diarrhea or flushing). A similar study for PNETs has not been done. More recently the use of other somatostatin analogs Somatuline (Lanreotide) in the Clarinet trial (151) and the Excel Trial (152) as well as Som 230 (Pasireotide) (153) have shown promise with the former binding to somatostatin receptors 2 and 5 and Som 230 binding to 1,3 and 4 with the prospects of greater avidity for these tumors .

Until recently, no safe and effective systemic treatment was available for advanced PNETs. Conventional chemotherapy consisting of streptozocin with or without doxorubicin was associated with only modest response and considerable toxicity. For functional tumors, somatostatin analogues (SSAs) provide symptomatic relief but have limited anti-tumor activity Liakakos 2011 (5) (48). Newly developed targeted treatments, such as sunitinib malate (SUTENT®; Pfizer Inc., New York, NY, USA) and everolimus (AFINITOR®; Novartis Pharmaceuticals, East Hanover, NJ, USA), have changed treatment practices for advanced, metastatic pNETs. These new drugs act by targeting key pathways involved in tumor proliferation and angiogenesis, and have demonstrated clear clinical benefits in phase III trials, including prolonged progression-free survival (PFS).

In view of the limited activity of systemic chemotherapy, a variety of other agents have been examined. Recent interest has included studies of tyrosine kinase inhibitors such as sunitinib. In a study examining 107 patients with advanced neuroendocrine tumors, (carcinoid n=41, pancreatic endocrine tumor n=66) the overall response rate to sunitinib was 16.7% and 68% had stable disease. Median time to progression was 7.7 months in pancreatic neuroendocrine tumor patients and 10.2 months in carcinoid patients (154). A recently reported multi-national randomized double blind placebo controlled trial confirmed the activity of sunitinib in patients with advanced well differentiated pancreatic neuroendocrine tumors. A total of 171 patients were entered on this study. Median progression free survival was 11.4 months in the sunitinib group, compared with 5.5 months in the placebo group. 9 deaths were reported in the sunitinib group (10%) versus 21 deaths in the placebo group (25%) (155). Of great importance was the impact on improved quality of life (156) and the recent demonstration on the relationship between quality of life, tumor burden and biochemical markers of NETs (157) (158).

Additional excitement has been generated by study of mTOR inhibitors, either alone or combined with octreotide therapy. Mammalian target of rapamycin (mTOR) is a serine-threonine kinase involved in the regulation of cell growth and death through apoptosis. It transduces signals mediated through PI3K/Akt pathway and activates downstream protein kinases involved in ribosomal biosynthesis and translation of key mRNA's of proteins vital for cell cycle progression. Upstream mTOR can be regulated by tumor suppressors NF1, PTEN and the protein complex TSC1/TSC2. Since neurofibromatosis type 1 and tuberous sclerosis are associated with development of pancreatic NETs,

mTOR may be a potential target for medical therapy in patients with pancreatic NETs. A multinational phase 2 study, the RADIANT 1 trial, has reported the efficacy of everolimus alone and in combination with octreotide in patients with metastatic pancreatic neuroendocrine tumors that have progressed on chemotherapy (159). Monotherapy with everolimus produced stable disease in 67.8% of patients and a partial response in 9.6%, while combination therapy resulted in 80% stable disease and 4.4% partial response. Everolimus also resulted in a decrease in chromogranin A and neuron specific enolase levels 50.7% and 68.2% of patients. An early tumor marker response (> 50% decrease by 4 weeks) was associated with a significantly longer progression-free survival. The RADIANT 3 trial studied everolimus as first line therapy in patients with advanced PNETs. Four hundred and ten patients with radiologic progression of disease were randomized to everolimus 10 mg. once daily or placebo. The median progression free survival was 11 months with everolimus compared to 4.6 months with placebo, representing a 65% reduction in estimated risk of progression or death. The proportion of patients alive and progression free at 18 months was 34% with everolimus compared with 9% with placebo. Toxicities were mostly grade I or II (160) Figure 7.

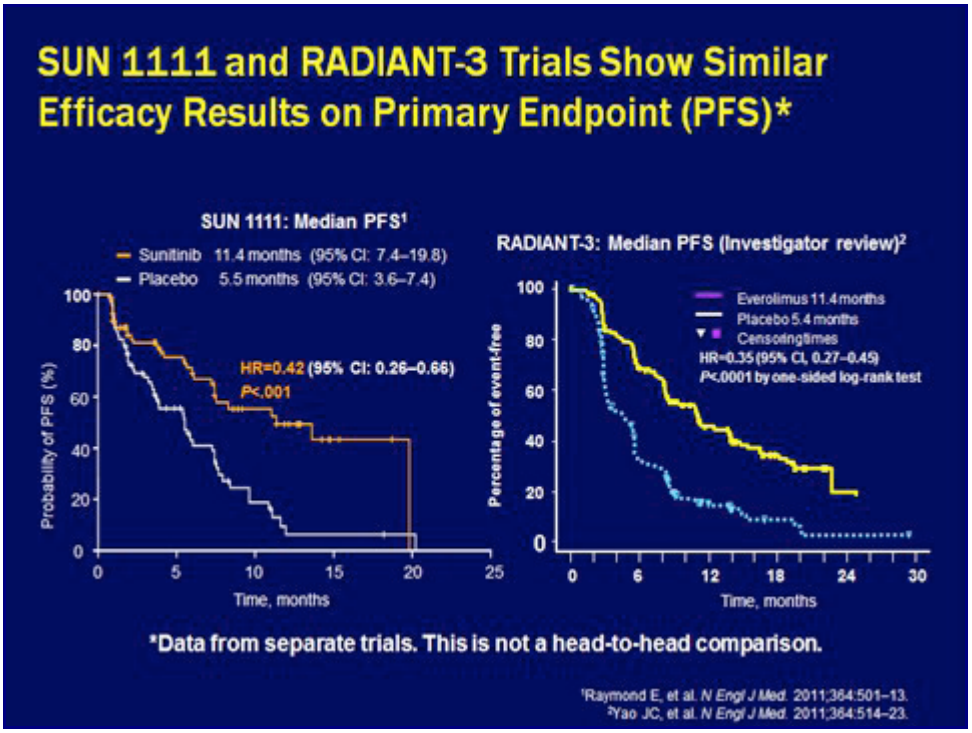

Figure 7 This figure compares the progression free survival in response to sunitinib in the SUN 1111 trial (Raymond et al) with the percent of patients with advanced metastatic PNETs in response to everolimus in the Radiant 3 trial.(Yao et al). While the efficacy measures a PFS are similar the are significant differences in the side effects and choices need to be individualized.

Targeted anticancer agents sunitinib and everolimus both act against signaling pathways that are instrumental to tumor growth and survival. Sunitinib inhibits activation of VEGFR and PDGFR, resulting in apoptosis of endothelial cells and pericytes and inhibition of tumor angiogenesis. Everolimus binds to mTOR, blocking signal transduction in tumor cells and inhibiting tumor growth and angiogenesis. Everolimus and sunitinib are now registered worldwide for the treatment of pancreatic NETs. These two agents have similar tumor-stabilizing effects in pancreatic NETs. Since there has been no trial that compared the two agents directly, choice of the agent in each case could be suggested in perspective of side-effects. For example, in patients with poorly controlled hormonal symptoms, congestive heart failure, poorly controlled hypertension, high risk of gastrointestinal bleed, or a history of myocardial infarction or stroke, everolimus is thought be the preferred choice agent. In

patients with poorly controlled diabetes mellitus, pulmonary disease, or high risk of infection, sunitinib would be a more appropriate choice (156) (161). To evaluate of response these agents, several biomarkers are investigated. It has been suggested that chromogranin A and neuron-specific enolase are useful as prognostic markers in patients with advanced PNET treated with everolimus (162). However we have shown that pancreastatin and Neurokinin A are likely to be better markers of response to therapy as well as prognosis (163). Soluble vascular endothelial growth factor receptor 2 and 3, interleukin-8, and stromal cell-derived factor 1alpha have been reported to have a potential as biomarkers associated with response to sunitinib (156). Based on recent data, treatment algorithms for PNETS are expected to evolve . For studies in progress or currently being carried out see tables below. Of particular concern is the impact of treatment on quality of life and a comparison of response to intervention are shown in relation to tumor burden reduction and the reduction in biomarkers (157). Nonetheless, with malignant hyperinsulinism rapamycin (164) or everolimus are the drugs of choice because of induction if insulin resistance and suppression of insulin secretion reducing the incidence and severity of hypoglycemia. There does not appear to be any significant difference in the remaining secretory NETS (156) but no case of calcitonin over production was included.

Tumor grading is paramount for selecting patients who should receive chemotherapy, and platinum-based chemotherapy is recommended in patients with NEC G3 (165). In some patients with NET G1/G2, molecular-targeted treatment or chemotherapy may provide a great benefit. The European Society for Medical Oncology (ESMO) guidelines 2012 recommended use of molecular-targeted agents in advanced pancreatic NETs G1/G2 (166). According to the North American Neuroendocrine Tumor Society (NANETS) guidelines, the level of recommendation is listed as “consider” to use of everolimus in metastatic functioning NETs because there has been no sufficient evidence to recommend routine use of it (167) (see Tables 2 and 3).

Other Forms of Treatment

Hepatic artery chemoembolization or bland embolization with gel foam remains a mainstay in the management of patients with liver metastases. A recent study of chemoembolization combined with somatostatin therapy resulted in relief of systems in 78% of patients. Monitoring of serum pancreastatin levels predicted a response to this therapy in which radiographic improvement or stability were seen in 45% of patients (168). Very good results have also been seen in radioembolization using resin 90Y-microspheres. A total of 148 patients were treated in 185 separate procedures. A complete response was seen in 2.7%, partial response 60.5%, stable disease 22.7%, and progressive disease in 4.5%. No radiation liver failure occurred and median survival was 70 months (169). This appears to be a promising approach. The use of radio labeled somatostatin analogs has also been studied. In a study of 504 patients, treatment with the analog 177Lu-DOTA 0,TYR3 octreotate showed complete response in 2%, partial response in 28%, and minor responses in 16%. Median time to progression was 40 months, and toxicity was minor (170).

A novel approach to hepatic metastases involves embolization of ^{90}Yttrium embedded either in a resin microsphere (Sir-Sphere) or a glass microsphere (TheraSphere). This technique (also known as selective intrahepatic radiotherapy; (SIRT) enables direct delivery of a radionuclide to hepatic metastases. Acute toxicities associated with ^{90}Yttrium microsphere embolization appear to be lower than other embolization techniques, primarily due to the fact that the procedure does not induce ischemic hepatitis. Thus, the procedure can be performed on an outpatient basis. A rare, but potentially serious complication is radiation enteritis, which can occur if particles are accidentally infused into arteries supplying the GI tract. Chronic radiation hepatitis is another potential toxicity. Response rates associated with radioembolization in metastatic neuroendocrine tumors have been encouraging. In one

retrospective multi-center study of 148 patients treated with SirSpheres, the objective radiographic response rate was 63% with a median survival of 70 months (169). Another study of 42 patients treated with either TheraSpheres or SirSpheres reported a response rate of 51%; however only 29 of the 42 enrolled patients were evaluable for response (171).

Peptide Receptor Radionuclide Therapy (PRRT) (Figure 8) is an abbreviation of peptide receptor radionuclide therapy. A compound that is attracted to receptors on the tumor cells is combined with radioactive compounds to deliver the killing effect of radioactivity directly to the tumor, avoiding the destruction of healthy cells often found in external beam radiation treatment. Currently there are no FDA-approved PRRT therapies available in the United States, though it has been used in Europe since 1996. There are two clinical trials of PRRT underway in the US at Excel Diagnostics in Houston Texas with Lutera (Lu 177) currently preparing for phase 3 trial at 14 sites. PRRT is currently offered at several sites in Europe at Basel Switzerland , Rotterdam Holland and Bad Berka in Germany. Information on the Lutathera trial can be found at Clinical Trials.gov. Currently third party payers do not support the cost of treatment which is considered investigational. A summary of the findings reported a 6% complete response and a 36% partial response in non function PNETs and no complete responses and 47% partial responses in functioning PNETs (170). More recently a review of 68 patients with PNETs treated with PRRT provided a more salutary picture (172). Treatment responses (SWOG criteria) consisted of a partial response in 41 patients (60.3 %), a minor response in 8 (11.8 %), stable disease in 9 (13.2 %), and progressive disease in 10 (14.7 %). Median progression-free survival (PFS) and overall survival (OS) were 34 (95 % CI 26 – 42) and 53 months (95 % CI 46 – 60), respectively. A G1 proliferation status was associated with longer PFS (p=0.04) and OS (p=0.044) in the multivariate analysis. Variables linked to impaired OS, on the other hand, were a reduced performance status (Karnofsky score =70 %, p=0.007), a high hepatic tumor burden (=25 % liver volume, p=0.017), and an elevated plasma level of neuron-specific enolase (NSE >15 ng/ml, p=0.035). The authors concluded that the outstanding response rates and survival outcomes suggest that PRRT is highly effective in advanced G1/2 PNET when compared to data of other treatment modalities. Independent predictors of survival are the tumor proliferation index, the patient’s performance status, tumor burden and baseline plasma NSE level.

However, a striking improvement in quality of life in those who respond has been demonstrated (173) not unlike that found in this case of a calcitonima and similar to that found by Vinik and Raymond with treatment with sunitinib in functioning and nonfunctioning well differentiated but metastatic PNETs (156).

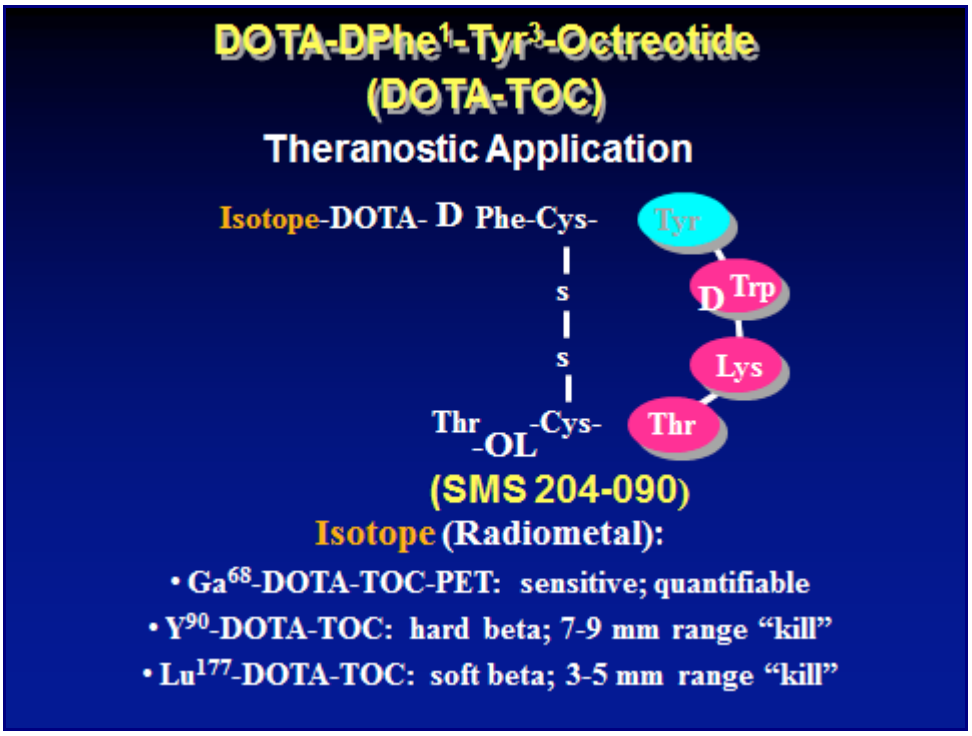

Figure 8 illustrates the use of somatostatin which binds to specific receptors on malignant cells when linked with a spacer (DOTA) TOC or NOC and be synthesized and combine with Gallium 68 and used a s a sensitive and quantifiable tracer for scanning with many advantages over the Octreoscan and combined with Ytrium 90 or Lutetium 177 can be used of peptide receptor radiotherapy with a 3-9 mm kill range depending on being a hard or soft beta emitter.

Thus, new techniques are being developed for tumor localization which includes PET scanning (for ^{68}Ga-DOTATATE PET in patients with negative or equivocal somatostatin receptor scintigraphy) and peptide receptor scanning has been extended from Octreoscans to include scans using GLP-1 which targets for e.g. insulin producing tumors. NO doubt other will follow since PNETs express a variety of receptors for which there are potential ligands. NETS tend to be more sensitive to containment using somatostatin analogs and the currently available analog that binds the SSTR 2 and 5 will soon include agonists which target in addition the 1, 3 and 4 receptors. This at least has the theoretical advantage of greater efficacy if not specificity and a wider range of tumor targets. Two new agents have been approved for treating PNETs, a tyrosine kinase inhibitor and an MTOR inhibitor which have interesting actions on increasing progression free survival. Perhaps of great interest is the prediction of response to these agents based upon the mutations involving the TK or MTOR pathway, the MEN1 gene and the ret proto-oncogene and the recent recognition of DAXX/ATRX genes associated with chromatin remodeling. There is emerging concurrence on the pathology and staging of these tumors which is dependent on the mitotic index and the Ki67 index of cell proliferation sites and spread and angioinvasion. Of additional benefit is the use of bone alkaline phosphatase and NTelopeptide as markers of osteoblasts and osteoclast activation.Surgical excision remains the mainstay of treatment of the primary tumor and somatostatin analogs control symptoms and may have some anti-tumor activity. The use of radio labeled somatostatin analogs has also been studied, e.g. ^{177}Lu-DOTA 0, TYR3 octreotate and is expensive and still in the research arena. There is now a flurry of interest in health related quality of life. Of particular interest is the relationship of QOL to PFS and to the pathophysiology of these tumors. An increased interest in the use of combination therapies and interventions based upon known pathophysiology is likely to be rewarded with new and emerging treatment for PNETs in the not too distant future.

Table 2. Results from phase II and III studies of sunitinib and everolimus in pNETs.

Study	Patients	Active treatment	PD at entry	ORR	PFS/TTP (months)	Safety and other comments
Sunitinib						
Phase II, open-label [Kulke et al. 2008]	66 pNET 41 carcinoid	50 mg daily, Schedule 4/2*	No	PR: 17%† SD: 68%†	7.7†	G 3–4 fatigue: 25%
Phase III, RCT [Raymond et al. 2011]	171 (86 SU; 85 placebo)	37.5 mg daily, CDD‡	Yes	SU, CR: 2.3%; PR: 7%; SD: 62.8%; Placebo, CR: 0%; PR: 0%; SD: 60%	SU: 11.4 Placebo: 5.5	Most common AEs associated with SU ≥30%: diarrhea, nausea, asthenia, vomiting, and fatigue G 3–4 neutropenia and hypertension: 10–12%
Everolimus						
Phase II, open-label [Yao et al. 2008a]	30 pNET 30 carcinoid	10 mg daily + octreotide LAR 30 mg	No	PR: 27%† SD: 60%†	12.5†	G 3/4 fatigue and diarrhea: 11% G 3/4 thrombocytopenia and leukopenia: 5%
Phase II, open-label in 2 strata (RADIANT-1) [Yao et al. 2010]	160	Stratum I: 10 mg daily Stratum II: 10 mg daily + octreotide LAR 30 mg	Yes	Stratum I PR: 9.6% SD: 67.8% Stratum II: PR: 4.4% SD: 80%	Stratum I: 9.7% Stratum II: 16.7%	Most common AEs ≥30% (in both strata, all grades): stomatitis, rash, diarrhea, fatigue, and nausea Stratum I G 3/4 asthenia: 5.2% Stratum II G 3/4 thrombocytopenia: 8.9%
Phase III, RCT (RADIANT-3) [Yao et al. 2011b]	410 (207 EV, 203 placebo)	10 mg daily	Yes	EV: 5.0 Placebo: 2.0	EV: 11.04 Placebo: 4.6	Most common AEs: stomatitis, 64%; rash, 49%; diarrhea, 34%; fatigue, 31%; infections, 23% AEs of clinical concern: pneumonitis, 12%; interstitial lung disease, 2%

CDD, continuous daily dosing; CR, complete response; EV, everolimus; G, grade; LAR, long-acting release; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor; PR, partial response; RADIANT, RAD001 in Advanced Neuroendocrine Tumors; RCT, randomized, controlled trial; SD, stable disease; SU, sunitinib; TTP, time to progression.*Concomitant use of SSA in 27% of pNET patients and 54% of carcinoid patients. †In pNET patients. ‡Concomitant use of SSA in 26.7% of patients.

Table 3. Soluble biomarkers and correlations with outcomes with targeted therapies in pNETs.

Study	Biomarker	Results

Sunitinib		
[Bello et al. 2006]	sVEGFR-3	– Reductions in sVEGFR-3 correlated with objective responses and improved PFS (p = 0.04)
	IL-8	– Lower baseline IL-8 correlated with radiologically stable disease for >6 months (p = 0.009)
	sVEGFR-2	– Elevated baseline sVEGFR-2 correlated with improved OS (HR, 0.22; 95% CI, 0.06–0.78; p = 0.01)
[Zurita (2011)]	SDF-1α	– Elevated baseline SDF-1α correlated with significantly shorter TTP (p = 0.05), PFS (p = 0.005) and OS (p = 0.02) (in combined group of pNETs and carcinoid tumors) – Lower baseline SDF-1a correlated with improved CBR (objective response or SD ≥6 months; p = 0.004)
Everolimus		
RADIANT1 and MDACC US-52 [Yao et al. 2011a]	CgA	– Elevated CgA at baseline (>2-fold upper normal limits) correlated with decreased PFS (HR, 0.55; p = 0.03) and OS (HR, 0.3; p = 0.01) – Early decreases in CgA (>30% reduction after 4 weeks vs. baseline) correlated with increased PFS (HR 0.25; p < 0.001) and OS (HR 0.4; p = 0.01)
	NSE	– Elevated NSE (over upper normal limits) at baseline correlated with decreased PFS (HR, 0.52; p = 0.01) and OS (HR, 0.44; p = 0.005) – Early reductions in NSE (>30% reduction after 4 weeks vs. baseline) correlated with improved PFS (HR, 0.25; p < 0.001)
RADIANT2* [Baudin et al. 2011]	CgA	– Baseline elevated CgA (>2-fold upper normal limits) correlated with reduced PFS (HR 0.43; p = 0.001) in the overall trial population. – PFS benefit for everolimus + octreotide vs. placebo + octreotide was significant in the subgroup with baseline elevated CgA levels (HR, 0.66; p = 0.003)
	5-HIAA	– Significant PFS benefit for everolimus + octreotide vs. placebo + octreotide in patients with elevated 5-HIAA levels (>2-fold upper normal limits) at baseline (HR, 0.66; p = 0.007)

***Patients randomized to everolimus + SSA or placebo + SSA.**

5-HIAA, 5-hydroxy indole acetic acid; CBR, clinical benefit rate; CgA, chromogranin A; HR, hazard ratio; IL-8, interleukin-8; MDACC, MD Anderson Cancer Center; NET, neuroendocrine tumor; NSE, neuron-specific enolase; OS, overall survival; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor; RADIANT, RAD001 in Advanced Neuroendocrine Tumors; SDF-1α, stromal cell-derived factor-1α; SSA, somatostatin analogue; sVEGFR, soluble VEGF receptor; VEGF, vascular endothelial growth factor.

Determining prognosis

CgA: Other than the applications of CgA previously discussed, this marker can be used for prognosis and follow up. Jensen et al. found that a reduction on CgA levels > 80% after cytoreductive surgery for carcinoid tumors predicts symptom relief and disease control; it is associated with improved patient outcomes, even after incomplete cytoreduction (174).

Pancreastatin: One of the post-translational processing products of CgA has found to be an indicator of poor outcome when its concentration in plasma is elevated before treatment in patients with NETs. A level > 500pmol/L is an independent indicator of poor outcome. This marker is also known to correlate with the number of liver metastasis, so it would be appropriate to use it in the follow-up of NET patients. Furthermore, Stronge et al. found that an increase in pancreastatin levels following somatostatin analogue therapy is associated with a poor survival (175). Other studies have shown that pancreastatin should be measured prior to treatment and monitored during and after it. Plasma levels of this marker above 5000 pg/ml pre-treatment were associated with increased peri-procedure mortality in patients with NETs that underwent hepatic artery chemoembolization (HACE) (176).

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

Neurokinin A: Has been shown to have strong prognostic value. Turner et al. in 2006 showed that in patients with midgut carcinoid that have raised plasma NKA, a reduction of this biochemical marker after somatostatin analog (SSA) therapy, was associated with an 87% survival at one year compared with 40% if it increased. They also concluded that any alteration in NKA predicts improved or worsening survival (177).

Quality of Life in patients with NETS

The measurement of health-related quality of life (HRQOL) has become essential for evaluating the impact of neuroendocrine tumors (NETs) on symptoms, social, emotional, psychological and physical functioning of patients who harbor these tumors. Here we describe instruments that have been developed to capture the spectrum of symptoms and to measure the impact of the disease on their overall well-being. Two specific tools have been developed and validated using classical test theory. There are distinct similarities between these tools, the EORTC-QLQ-GI. NET-21 and the Norfolk QOLNET but the unique differences favor the use of the Norfolk QOL-NET for clinical trials. These instruments provide us with the ability to discriminate patients with tumors from those people who are free of the disease. Shown below in the table is a comparison of the two NET specific tools that have been developed. Both have now been shown to have adequate sensitivity, specificity and reproducibility and the value of psychometric factor analysis to explore the domains that embrace the manifestations of these tumors as well as aspects of the instruments that reflect tumor burden, biochemical and hormonal status. There is a striking impact of tumor burden, and specific biochemical and clinical features on the impact on total QOL as well as the specific domains of these tools (157) (158) (178). Both tools have been shown to be useful in clinical trials and the Norfolk QOL NET has greater sensitivity for certain features. (Table 4).

Table 4. Norfolk QOL-NET QOL total scores, Norfolk QOL-NET domains, tumor burden, biochemical markers, and Norfolk carcinoid symptom scores with . ORTC QLQ-C30 GI.NET-21.

	Total Norfolk QOL		**Total European QOL**		**Domain 1 Depression**		**Domain 2 Flushing**		**Domain 3 Respiratory**		**Domain 4 Gastrointestinal**		**Domain 5 Cardiovascular**		**Domain 6 Physical Functioning**		**Domain 7 Positive Attitude**	
	R	P	r	P	r	P	r	P	r	P	r	P	r	P	r	P	r	P
Total Norfolk QOL			0.94	<.001	0.73	<.0001	0.62	.0003	0.65	.0002	0.78	<.0001	0.46	.012	0.96	<.0001	0.52	.004
Tumor burden	0.52	.004	0.5	.005	0.42	.023	0.24	.216	0.02	.935	0.58	.001	0.18	.343	0.56	.002	0.18	.346
Serotonin	0.62	.013	0.71	.003	0.56	.03	0.08	.78	0.32	.25	0.62	.013	0.29	.3	0.62	.013	0.12	.67
CgA	0.06	.764	0.06	.765	–0.15	.433	0.26	.176	0.08	.663	0.03	.891	0.34	.07	0.07	.735	0.12	.55
Carcinoid symptom score	0.67	<.001	0.67	<.001	0.37	.051	0.58	.001	0.53	.003	0.66	.0006	0.55	.0018	0.71	<.0001	0.59	.0009

EORTC, European Organization for Research and Treatment of Cancer; Norfolk QOL-NET, Norfolk quality of life – neuroendocrine tumor.Reprinted from Endocrinology and Metabolism Clinics of North America, Vinik, E., Silva, M.P. and Vinik, A.I., Measuring the Relationship of Quality of Life and Health Status, Including Tumor Burden, Symptoms, and Biochemical Measures in Patients with Neuroendocrine Tumors, 97–109. © 2011 with permission from Elsevier Inc.

Summary and Conclusion:

Pancreatic neuroendocrine tumors (pNETs) are relatively rare malignancies. With secretory tumors such as insulinomas, vasoactive intestinal peptidomas, and gastrinomas, the hormone produced causes the symptom complex (eg, hypoglycemia, peptic ulcer disease). With non-secretory NETs, the clinical condition is determined by tumoral growth and metastasis. The course of metastatic pNETs may be indolent for several years but progression is often more rapid at later stages, leading to significant disability and a markedly negative impact on quality of life. Until recently, there were few effective systemic treatments for pNETs. Standard chemotherapy produces limited responses and has considerable toxicity. Somatostatin analogues control symptoms in some types of pNETs, but have not

yet demonstrated anti-tumor activity. The recent introduction of targeted therapies, including the tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus, yielded new opportunities for patients with advanced/metastatic pNETs. These drugs, which target key pathways in tumor proliferation and angiogenesis, provided clear clinical benefits in phase III clinical trials, including delayed tumor progression. The pivotal sunitinib phase III trial was discontinued prematurely due to higher rates of death and serious adverse events with placebo and greater progression-free survival (PFS) with sunitinib. In this trial, sunitinib demonstrated encouraging long-term responses as well as PFS and overall survival benefits, and an acceptable safety profile that allowed patients to preserve their quality of life. In every patient subgroup, including secretory and non-secretory tumors, the hazard ratio for progression or death favored sunitinib. Circulating biomarkers are being investigated for the prediction and monitoring of responses to therapy. Of particular interest are Chromogranin A, Pancreastatin and NeurokininA. Based on recent data, treatment algorithms have been updated for advanced and metastatic pNETs.

When the tumor is localized then surgery is clearly indicated. Even with metastases reduction of tumor bulk, removal of the primary and targeted therapy for the hepatic metastases appears to be the favored approach.

The ability to use peptide receptor radiotherapy using somatostatin as the peptide a DOTA linker and lutetium, Yttrium or Gallium now provides for enhanced tumor identification and reduction of tumor mass. While this is frequently done in Europe it is still in the investigational phase in the USA.

Recently, several guidelines for the management of pancreatic NETs have been established and help to devise clinical strategy. In the treatment algorithms, however, a lot of uncertainties remain and practical treatment decisions of pancreatic NETs are still made in a patient-and/or physicians-oriented manner.

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