PATHOPHYSIOLOGY AND TREATMENT OF PANCREATIC NEUROENDOCRINE TUMORS (PNETs): NEW DEVELOPMENTS

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Updated June 11, 2018

ABSTRACT

Pancreatic neuroendocrine tumors (PNETs) are on the increase. Functional tumors including gastrinoma and insulinoma cause well described clinical syndromes. Non-functional tumors are found incidentally or by direct tumor effects. A third category of tumor secretes hormone(s) at a subclinical level without producing a syndrome. When metastatic PNETs may be indolent for several years but progression is inevitable. In this chapter recent advances in the pathophysiology, diagnosis, and management of these tumors are reviewed and placed in historical context. Tumor markers remain essential in the diagnosis and follow-up of these patients. Major clinical advances have occurred in pathology/classification/staging, imaging (68 Gallium DOTATE PET), the development of additional somatostatin analogues, cytotoxic chemotherapy, targeted therapies (e.g. tyrosine kinase inhibitor sunitinib and mTOR inhibitor everolimus), other modalities (e.g. peptide receptor radiotherapy), and quality of life assessment. These are very hopeful times for patients who have these tumors and their physicians. Issues to be considered when choosing among the plethora of effective treatment options include toxicity and cost, effects on quality of life, and the age and overall health of the patient. Treatment should be coordinated by an experienced multidisciplinary team. Many unanswered questions remain including the optimal treatment sequencing. For complete coverage of this and related aspects of Endocrinology, please visit our FREE web-book, www.endotext.org.

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are an uncommon 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). PNETs are categorized as functional , nonfunctional, or secretory but nonfunctional (4) (Figure 1). An international review showed an increasing incidence over the last few decades, but with differences according to race, gender, and country (5). The improvements in and wider availability of high quality imaging is believed to be a major factor in the increasing incidence of PNETs (6).

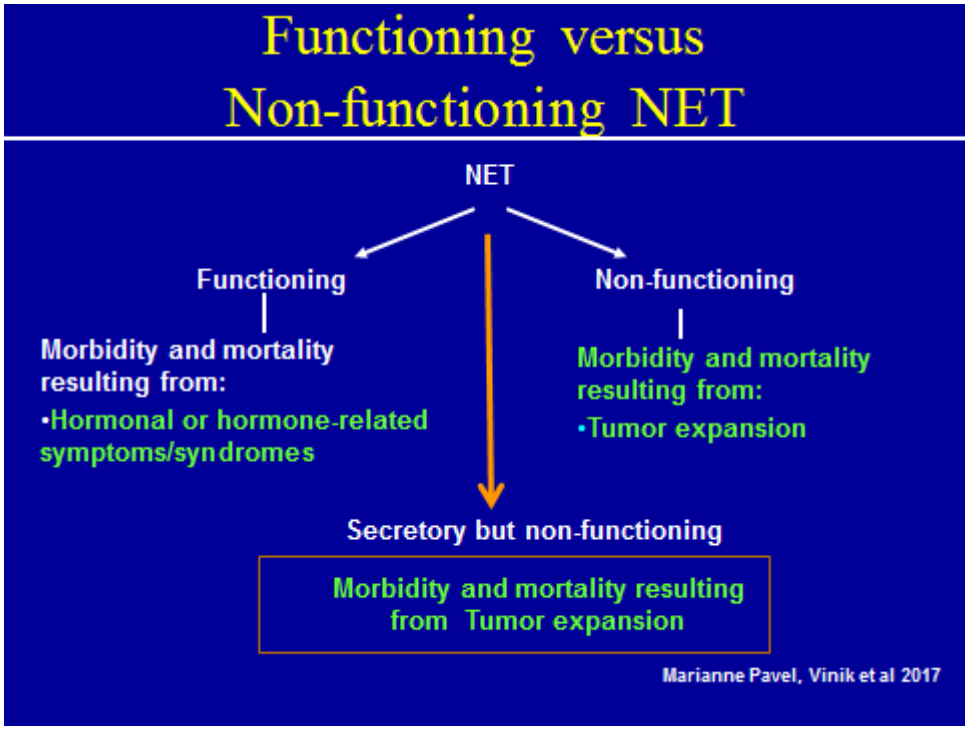

Figure 1. Addition of a Secretory but Non-Functioning Category of NETs

Approximately 10–30% of PNETs are functional (7) (8) with the symptoms and clinical course depending on the specific hormones produced (e.g., insulin, gastrin). The most common clinical syndromes are listed in Table 1. Less common functional PNETs include ACTHomas causing Cushing's syndrome, PNETs causing carcinoid syndrome or hypercalcemia, GRFomas causing acromegaly, and very rare PNETs ectopically secreting luteinizing hormone, renin, erythropoietin or Calcitonin (1) (9;10) (47-50).

Nonfunctional PNETs (NF-PNETs) have been noted traditionally to represent 30-50% of all PNETs. However, more recent series report that non-functional lesions now comprise 60-90% of all PNETs (6). NF-PNETs are intra-pancreatic 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) (7-11) (10). Despite this, the disease course tends to be indolent, with rates of 5-year survival in advanced disease estimated at 30–50% (11) NF-PNETs are either discovered incidentally on imaging studies(1)(43) or presenting with symptoms due to the tumor bulk per se, including abdominal pain (40-60%), weight loss, or jaundice (1) (3) (12) (13) (10). Although NF-PNETS do not secrete peptides causing a clinical syndrome, they characteristically secrete a number of other peptides. These include chromogranins, especially chromogranin A (CGA) (70-100%) and pancreatic polypeptide (PP) (50-100%) (1) (3) (12) (13) (10). However an elevated PP level or CGA level is not specific for NF-PNETS (1) (3) (12) (13) (10).

PNETs most often occur sporadically however they also may occur in patients with various inherited disorders (1) (14). PNETs occur in 80-100% of patients with multiple endocrine neoplasia type I (MEN I); in 10-17% of patients with von Hippel-Lindau syndrome (VHL); in up to 10% of patients with von Recklinghausen's disease (neurofibromatostis-1 [NF-1]), and occasionally in patients with tuberous sclerosis (14). Of these autosomal dominant disorders MEN-1 is the one most frequent in patients with PNETS

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, glossitis, angular cheilitis	CgA, glucagon, glycentin
Somatostatinoma	Pancreatoduodenal groove, ampullary,	Gallstones, diabetes (hyperglycemia),	CgA, somatostatin

	periampullary	steatorrhea	
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.

INDUCTION OF PNETs

Several models of pancreatic regeneration and tumor formation have been established (15) (16-24). Pancreatic duct glandular structures (PDGs) (25) have the capability of transforming into endocrine cells. This has led to the notion that PNETs derive from a tot potential stem cell in the ductal system (Figure 2).

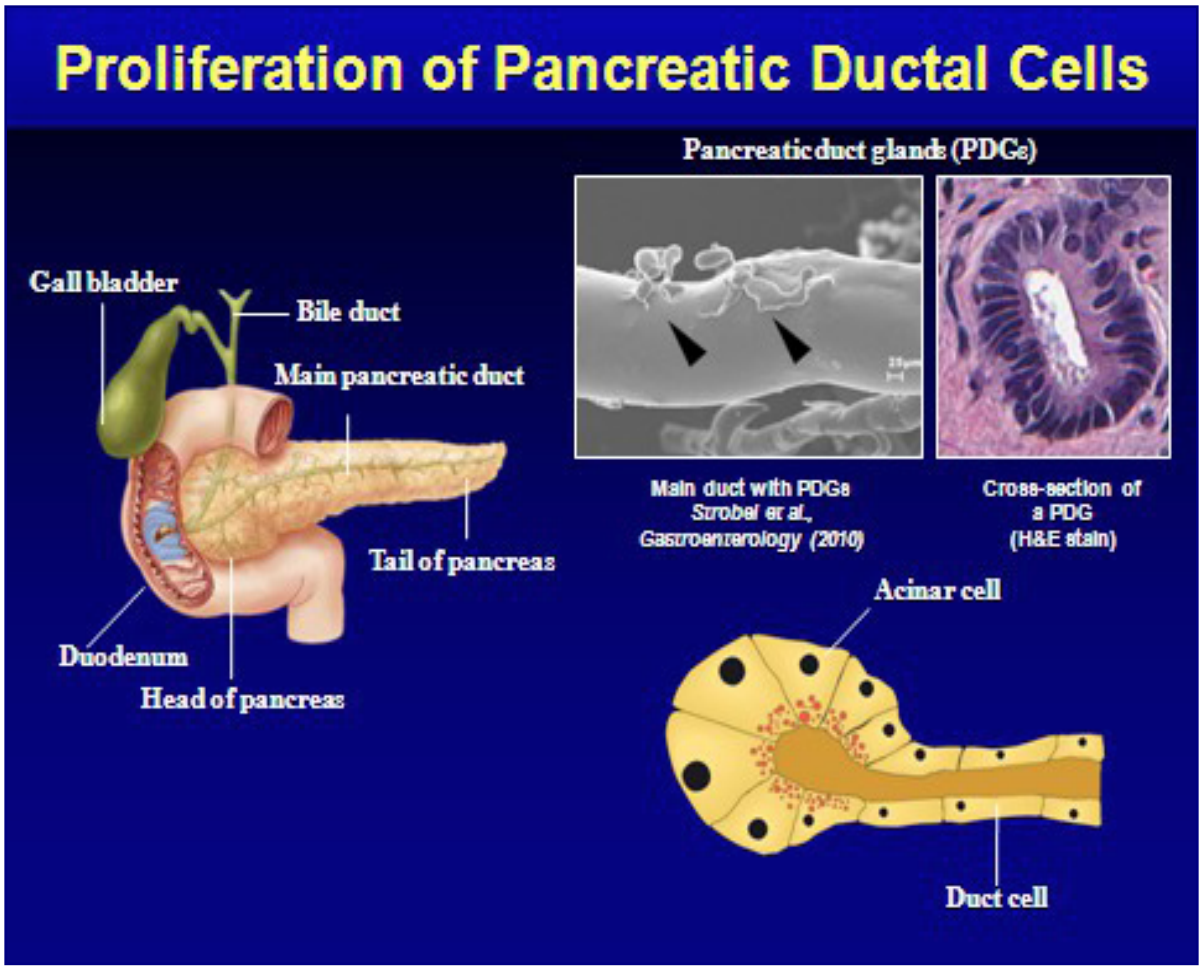

Figure 2. The pancreatic acinar/ductal system contains proto-differentiated stem cells capable of differentiating into a variety of endocrine cells (7). In addition, these cells can grow and proliferate, developing into pancreatic intraductal neoplasms (PANINS) and PNETs.

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 (Figure 3). In a model for new islet formation (i.e., nesidioblastosis) pancreatic ductal cells are capable of differentiating on stimulation into adult endocrine cells that are capable of secreting insulin in a fully regulated manner (30). Treatment of HIP rats with Sitagliptin increases endogenous GLP-1, inducing ductal metaplasia (26). A postmortem study of pancreas specimens obtained from Type 2 diabetics revealed that incretins, Exenatide or GLP-1 markedly increased the expression of GLP-1 receptor in the human pancreatic ductal system leading to expansion of exocrine and endocrine cell mass, with proliferation, dysplasia and hyperplasia (PanIN) (39). Of note, 3/8 incretin-treated patients developed glucagon microadenomas, and one an alpha cell NET. Although there is little clinical evidence in thousands of patients treated with incretins it raises an interesting possibility that GLP-1 may play a role in the formation of adenomas (27). Butler et al reported on the appearance of glucagon cells in the ducts of a patient who had been treated with an incretin (28). This suggests that certain patients may

have a genetic predisposition to incretion-induced neuroendocrine tumors.

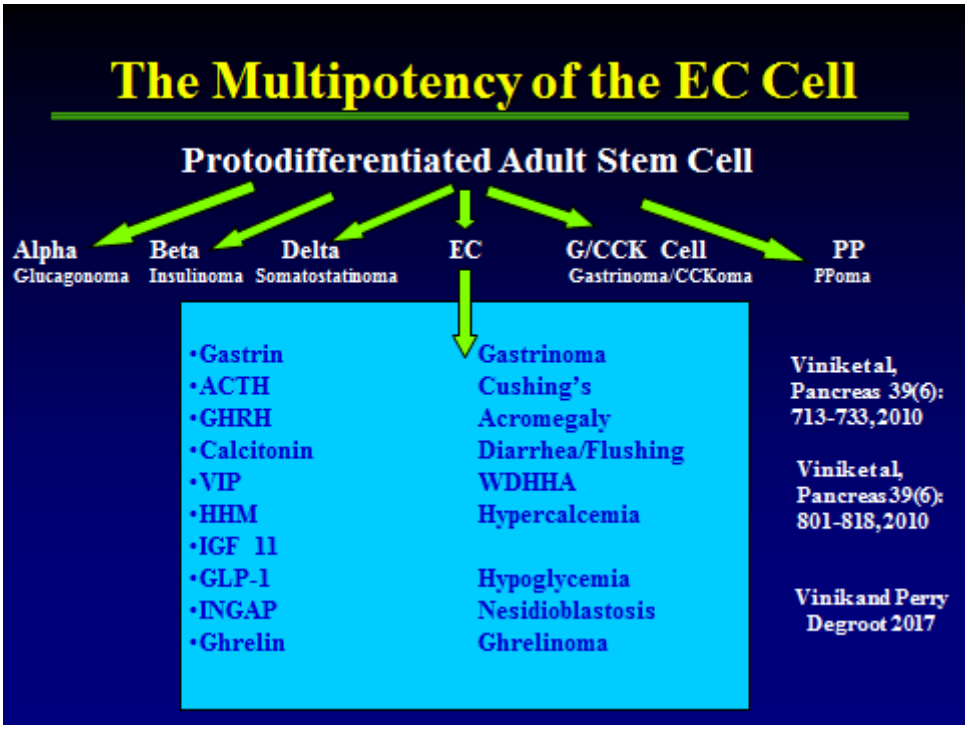

Figure 3 Illustrates the almost totipotentiality of the protodifferentiated pancreatic stem cell to differentiate into a variety of cell types to produce an almost infinite variety of clinical syndromes EC=enterochromaffin, GHRH= growth hormone releasing hormone, VIP = vasoactive intestinal polypeptide, CGRP= calcitonin releasing peptide, HHM = humoral hypercalcemic factor of malignancy, IGF = insulin like growth factor, INGAP = islet neogenesis growth associated peptide.

PATHOLOGY, CLASSIFICATION, AND STAGING

Many PNETs are initially diagnosed or have the diagnosis confirmed using fine needle aspiration (FNA) biopsy obtained during endoscopic ultrasound. Cytologic findings include single, monotonous plasmacytoid cells with fair amounts of cytoplasm and distinctive neuroendocrine chromatin (29). However, FNA biopsy of the primary is less accurate for determining tumor grade than FNA of liver metastases (30). Other PNETs are initially diagnosed using image directed core biopsy, particularly of liver metastases, or on surgical pathology.

The pathology of these lesions remains confusing and controversial with no universally recognized classification system. There are a variety of competing systems, including those developed by the World Health Organization (WHO) (31), and the European Neuroendocrine Tumor Society (ENETS) (32). Measures of cell differentiation include mitotic index, Ki67, presence of angioinvasion, cell size and functional activity (Figure 4). In the ENET consensus guidelines, tumor grade is based on mitotic rate and Ki67 labeling index (44, (33) (32), and has

been shown important in prognostic assessment(15). Data illustrating the value of grade in assessing prognosis is shown in Figure 5.

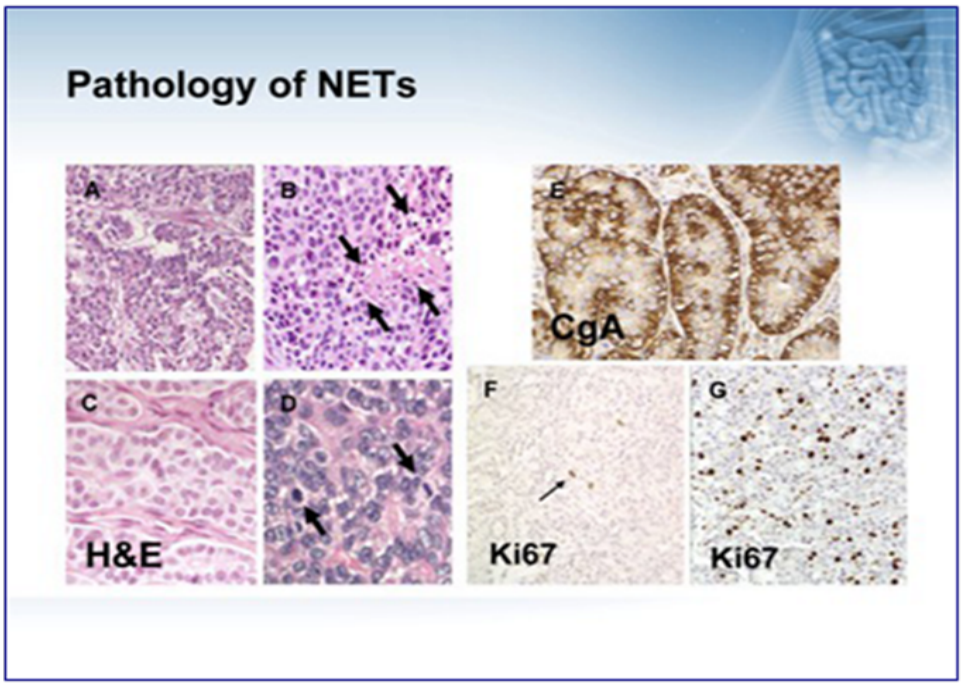

Figure 4. The neuroendocrine nature of a tumor is confirmed by positive staining to Chromogranin A (E). Tumor grade is based on mitotic count and Ki67 index. Mitotic count is measured on standard H and E sections, with examples of low counts (A, higher power C), and high counts (B, higher power D). Also shown are examples of tumors with low (F) and high (G) Ki67 proliferative index.

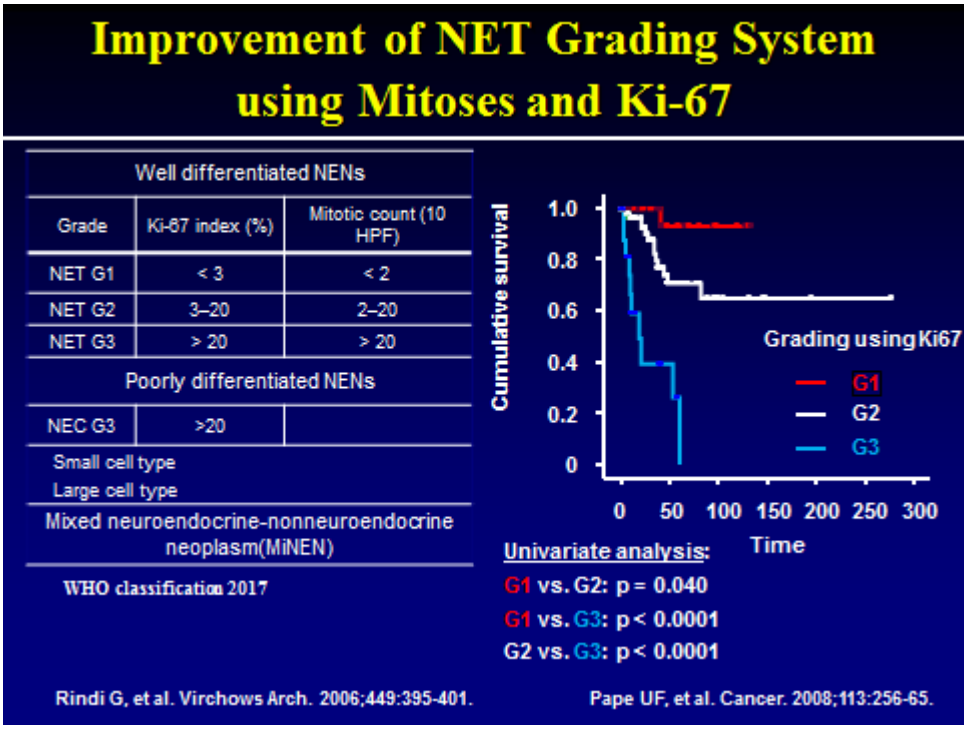

Figure 5 illustrates the value of the grading system based upon mitotic count and the KI67 index given as % of the cells staining positive. Grade has a very marked effect on cumulative survival in months as shown.

Staining for Chromogranin A (CgA) will usually confirm the neuroendocrine nature of the lesion in most cases (Figure 4). However, some high-grade lesions, especially poorly-differentiated NEC, will be negative for CgA. In these cases, staining should be performed for Synaptophysin. Other markers such as NSE or CD56 as less specific, hence less useful. In some cases, it may be difficult to distinguish NEC from poorly differentiated adenocarcinoma (33). Despite the differences among the systems, common elements include distinction of well differentiated (low and intermediate grade) from poorly differentiated (high grade) neuroendocrine tumors. Unfortunately, morphology alone is unable to predict tumor behavior (34). The paradox is that an apparently well-differentiated tumor may metastasize extensively to the lymph nodes, liver and bones.

The landmark WHO 2010 classification (14) was recently updated in 2017 (31). Major changes include alteration of the Ki67 index cutoff from <2% to <3% for G1 tumors, subdivision of G3 tumors into well differentiated NETs and poorly differentiated neuroendocrine carcinomas (NECs) (small and large cell types) and change of the Mixed adenoneuroendocrine carcinoma (MANEC) category to the Mixed endocrine non-endocrine neoplasm(MINEN/MENEN) category (Table 2). The subdivision of G3 tumors into various subgroups based on morphological differentiation reflects the heterogeneity noted in prognosis and response to treatment. Various recommendations were also made to standardize the process of performing and interpreting Ki67 index.

Table 2: Adapted from World Health Organization classification of tumors of endocrine organs, 4th edition, 2017 (31)

Well Differentiated NENs	**Ki67 Index**	**Mitotic Index**
Neuroendocrine tumor (NET) G1	<3%	<2/10HPF
Neuroendocrine tumor (NET) G2	3-20%	2-20/10HPF
Neuroendocrine tumor (NET) G3	>20%	>20/10HPF
Poorly Differentiated NENs		
Neuroendocrine carcinoma (NEC) G3	>20%	
Small cell type		
Large cell type		
Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)		

An experienced pathologist familiar with NETs will likely be able to determine the tumor's grade in the majority of resected specimens. Nonetheless Ki-67 measurements should be obtained, if possible, as such measurements are used in most current classification and grading systems, and have prognostic utility, as shown above. In small biopsy specimens, there may not be sufficient material to differentiate between grade 1 versus 2 neuroendocrine carcinomas with or without Ki-67. A minimum pathology data set has been suggested by the College of American Pathologists(CAP) to standardize the information in pathology reports (35) (36).

Most staging systems have not directly incorporated tumor grade, relying strictly on anatomic tumor extent (TNM). The American Joint Committee on Cancer (AJCC) 7th edition included staging PNETs identical to the staging of adenocarcinoma (37). In the updated AJCC 8th edition, PNET staging is consistent with that of ENETS (38). A modified ENETS (mENETS) classification appears superior to the AJCC 8th edition/ENETS (39). One group has shown that the AJCC 8th edition pancreatic adenocarcinoma staging when applied to PNETs shows better stage separation than AJCC 8th edition/ENETS, and even better than modified mENETS (40).

MOLECULAR GENETICS

Although most PNETs are sporadic, they are unique among NETs in their association with familial syndromes such as 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 (41), with a range of 13-44% depending upon the histologic type (42). The VHL gene is not mutated in sporadic PNETs (42). 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 (43). 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%) (44). Alterations in known oncogenes such as Kras and p53 occur uncommonly in PNETs (45) (46). Regardless of the genetic changes identified in a NET, intra-tumoral and inter-tumoral heterogeneity in the same patient are commonly seen (47).

The three most commonly mutated genes in PNETs are MEN-1, and DAXX/ATRX (25). 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 are noted in 14% of tumors (48). This clearly suggests that genetic factors may determine responsiveness to therapy such as the use of mTOR inhibitors.

A recent landmark study involved whole-genome sequencing of 102 primary PNETs (49). Previously unreported germline mutations in DNA repair genes such as MUTYH, CHECK2, and BRCA2 were noted in sporadic PNETs. Overall, germline mutations, including mutations in MEN-1 and VHL, were noted in 17% of PNETs. Somatic mutations were commonly noted in genes involved in chromatin remodeling, DNA damage repair, mTOR signaling, and telomere maintenance. A subgroup of tumors exhibited HIF signaling (49).

Despite the large increase in knowledge of the genetic changes observed in PNETs, no clear genotype/phenotype correlations have been noted. At this time, identification of specific genetic changes has not proved useful in clinical management. Thus, outside of a clinical syndrome, routine genetic testing is not recommended (6).

BIOCHEMICAL ASSESSMENT AND MONITORING FOR PNETs

Biochemical markers are important in the initial diagnosis of PNETS, monitoring response to treatment and detecting recurrence. Specific hormonal assays are needed to establish the diagnosis of each functional PNET as outlined briefly in Table 1 above. Functional PNETs and NF-PNETs also frequently secrete a number of other substances such as chromogranins, neuron specific enolase (NSE), subunits of human chorionic gonadotropin, neurotensin, and ghrelin (1-3) (12).

Chromogranin A (CgA)

CgA is useful as a marker in patients with both functional and non-functional PNETS (1) (50) (51) (52), including less well-differentiated NETs that do not secrete known hormones (53). Elevated CgA levels are noted in 50 to 100% of patients with PNETs (54), depending upon the histologic subtype (65,66). In addition, blood levels depend upon tumor mass, burden or progression and malignant nature of the tumor (55) (56). Small tumors may be associated with normal CgA levels. Common conditions that can falsely elevate CgA levels include decreased renal function , treatment with proton pump inhibitors (57), and even essential hypertension (58); these problems are not seen with Chromogranin B (CgB), with complementary measurement so proposed (57). CgA levels alone or in combination with other biomarkers appears less useful in monitoring MEN1 patients with PNETs (59).

Sensitivity and specificity of CgA depends on many factors including the specific assay and cutoff value used (60). CgA should be interpreted cautiously in patients treated with somatostatin analogs, since these agents significantly reduce plasma CGA levels (51) (61). Response to octreotide has been shown to correlate with patients who have a decrease in CgA levels after octreotide testing (62). 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 progression (50) (51) (52) (63).

Pancreastatin

Pancreastatin is a post-translational processing product of CgA. Multiple studies suggest that pancreastatin is a very useful marker not only for diagnosis but more importantly for monitoring treatment response (71-75). A pre-treatment level > 500pmol/L is an independent indicator of poor outcome. This marker is known to correlate with the number of liver metastasis. An increase in pancreastatin levels following somatostatin analogue therapy is associated with a poor survival (64).

Pancreatic Polypeptide (PP)

PP is another non-specific biochemical marker which when used alone has only a sensitivity of 63% in PNETs. But when combined with CgA the sensitivity increases to 94% in PNETs, better than either marker alone (65).

Neuron-Specific Enolase (NSE)

NSE is highly sensitive (100%), however its use is limited as a blood biochemical marker for NETs due to its very low specificity (32.9%) (66).

Other Markers

Several markers are useful for the detection of boney metastases. Metastases from NETs can be either osteolytic and/or osteoblastic. Markers useful for screening for boney metastases 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 (67). Increased osteoclast activity predicts a poor outcome (68).

Combinations of biomarkers are useful in monitoring response to treatment with targeted agents (Table 4 below). CgA and NSE are useful as prognostic markers in patients with advanced PNETs treated with everolimus (69). However, pancreastatin and Neurokinin A are likely to be better markers of response to therapy as well as prognosis (70). 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 (71).

IMAGING OF PNETs

Regardless of whether a PNET is functional or non–functional, imaging will be critical to assess the extent of disease (1) (10) (72) (73).Imaging modalities include conventional studies (CT, MRI, ultrasound, angiography) (74-77), endoscopic ultrasound (EUS) (1) (78) (79), functional localization studies measuring hormonal gradients (1) (80-82) (94) (102), intra-operative ultrasound (1) (83) (84), somatostatin receptor scintigraphy(SRS), and positron emission tomography (PET) (77) (85-87). Assessment of hormonal gradients is now rarely used, except in occasional patients with insulinomas or gastrinomas not localized by other methods (1, 86-88, 94,102). The other imaging methods are discussed below.

The results with conventional imaging studies are dependent to a large degree on the tumor size (74) (1) (72) (88) (89). 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 and duodenal gastrinomas) and small liver metastases (74) (1) (42)(72)(79) (88) (89). CT scanning with contrast is most frequently the initial imaging modality. Recent data in 55 PNET patients suggests MR criteria may be used to predict tumor grade (90), but this awaits prospective validation.

EUS combined with fine needle aspiration(FNA) biopsy is useful in confirming the diagnosis and localizing occult lesions, distinguishing a PNET from adenocarcinoma or other pancreatic masses (1) (78) (79). EUS is much more effective for localizing intrapancreatic PNETs such as insulinomas than extrapancreatic PNETs such as duodenal gastrinomas or somatostatinomas (1) (10) (78). It has also been proposed that EUS be used to select which MEN1 or VHL patients should have surgery (1) (14) (63) (91-93).

PNETs frequently (>80%) over-express somatostatin receptors (particularly subtypes sst 2, 5), which bind synthetic analogues of somatostatin with high affinity (1) (75-77) (94). An exception is insulinoma where only 40-50% express sst 2 receptors. The most widely used radiolabeled somatostatin analogue for Somatostatin Receptor Scintigraphy (SRS) is ^{111}Indium-DTPA-octreotide (Octreoscan) (1) (75-77) (94). Octreoscan SRS combined with computerized tomography(SPECT imaging) is highly sensitive, detecting 50-70% of primary PNETS (less in insulinomas or duodenal gastrinomas) and >90% of patients with metastatic disease to liver, bone, and other sites (1) (75-77)(96-99) (95). Octreoscan changes management in 24-47% of patients with PNETS (1) (75) (76) (77) (96) (95). False positive localizations can occur in up to 12% of patients. By interpreting the result within the clinical context, the false positive rate can be reduced to 3% (1) (76) (95) (97). Use of a glucagon-like peptide-1(GLP-1) avid radiotracer for SRS (109) may be useful for patients with insulinomas, with a reported sensitivity of 95% (98). This method has not been tried in the U.S.

Conventional FDG-PET is primarily useful in undifferentiated tumors with high proliferative index; it is less useful for well-differentiated PNETs (93) (99). It may have some utility identifying PNETs of increased malignant potential in MEN1 patients (100).The development of newer PET

analogs has been a major breakthrough in imaging. Use of ^{11}C-5 hydroxytryptophan-labeled or ^{68}Gallium-labeled somatostatin PET analogs have been shown to have greater sensitivity for PNETs than Octreoscan SRS or conventional imaging studies (1) (77) (85-87). Figure 6 contrasts the sensitivity of Gallium DOTATOC Octreotide PET with standard Octreoscan. Clearly Gallium PET (right panel) is more sensitive than Octreoscan (left panel).

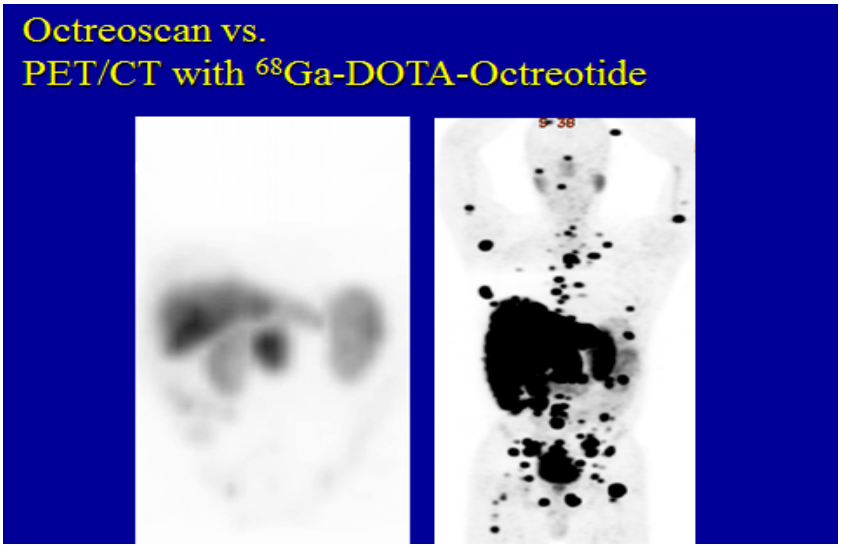

Figure 6. Comparison of Octreoscan SRS (left panel) to Gallium DOTA PET (right panel) in the same patient.

Similar to other imaging studies, false positives may occur with Gallium-DOTATE PET. Reasons for false-positives include pancreatic uncinate process activity, inflammation, osteoblastic activity, and splenosis (101).

The available data show superiority of Gallium PET to conventional imaging studies including CT or MRI, and functional imaging studies including Octreoscan (102) (103) (104) (105) (106). In addition, Gallium-DOTATE PET is highly sensitive in detecting boney metastases, and in many cases may obviate the need for additional radiologic studies (103) (102) (107). Gallium PET has shown utility in finding unknown primary PNETs (102).Gallium PET leads to a change in treatment plans in about 33%-41% of patients (102) (108) (107). Small studies show superiority of Gallium PET imaging in detecting PNETs and other NETS in MEN1 patients (109) (110) (111), but other studies do not (112).

Admittedly, the majority of studies involve heterogeneous populations, but most included a sizable minority of 20-30% PNETs. Many studies are also small, and nearly all are retrospective in nature. Thus, the overall data, although far from perfect, support use of Gallium PET over Octreoscan SRS. In addition to higher sensitivity, other advantages of Gallium PET include patient convenience (requiring only 40 minutes to perform rather that 2-3 days), and lower radiation exposure. Gallium PET may also be better at quantifying somatostatin receptor expression than Octreoscan SRS and thus facilitate targeted therapy such as PRRT (108), as further discussed below.

These advantages led the FDA in 2016 to approve Gallium PET in the U.S., after being available in Europe for a number of years (113). Furthermore, with the development of an FDA approved Gallium 68 DOTATE generator, an on-site cyclotron is no longer required, thus making this technology more widely available. A multisociety workgroup has recommended that Gallium PET replace use of Octreoscan SRS, unless Gallium PET is not available. Appropriate use criteria have also been developed by this workgroup and recently published (114) (115) (102) (116). We proposed that the American Association of Clinical Endocrinology endorse the application of this new technology to the evaluation of certain patients with neuroendocrine tumors or suspected of having such on the basis of symptoms or biochemical abnormalities compatible with a neuroendocrine tumor.

No doubt other PET agents will follow since PNETs express a variety of receptors for which there are potential ligands. One such target is GLP-1 for insulin producing tumors (98).

MANAGEMENT OF PNETs

The management of these patients has increased in complexity, with better understanding of the heterogeneity of the disease, and the increasing number of treatment options. Unfortunately, there is a lack of head to head comparison data. Treatment must be individualized, considering the age and overall health of the patient, the specific toxicities of the potential treatment(s), cost, and potential impact on quality of life. These are decisions that cannot be made in isolation. The importance of an experienced, multidisciplinary team coordinating the management of these patients, together with their primary care physician, cannot be overemphasized

Nonetheless, there are several general management principles to consider. It is usually helpful to distinguish functional from non-functional tumors, even though this long-standing principle has been questioned (114). Functioning tumors should be medically controlled to decrease symptoms and morbidity and must be achieved prior to any invasive or surgical procedure, lest there be disastrous consequences for the patient! For a more detailed discussion the reader is referred to various guidelines such as the Vienna Consensus Conference (6).

The grade/differentiation, and stage/extent of the tumor must be considered. Different treatment schemes are evolving based on these factors. For example, surgical resection is usually advocated for functional, early stage tumors. A wait and see attitude is often appropriate for non-functional, small(<2cm), low grade(G1/G2) early stage tumors, given the indolent nature of most of these tumors.

For patients with metastatic disease, the treatment options are many, and include surgical debulking, systemic therapy including chemotherapy or targeted therapy, liver directed therapy, and peptide receptor radionuclide therapy (PRRT). There are no head-to-head randomized trials comparing the various modalities. Most patients will receive multiple modalities during the course of their disease. There are no data on optimal treatment sequencing. The European SEQTOR trial is examining streptozotocin(STZ)/5-FU followed by everolimus compared to the

reverse (117). There are also few data on relative cost. A U.S modeling study showed a non-significant trend favoring the cost-effectiveness of everolimus compared to sunitinib (118).

It is not unusual for the management plan to change, based on treatment response and disease progression. Current consensus guidelines do not specifically address the indications for rebiopsy. However, it would seem reasonable to consider rebiopsy (if feasible) when there is a failure to respond to treatment, or an unexpected change in the tempo of disease, as tumor dedifferentiation and tumor heterogeneity are well described in PNETs. The various treatment modalities are discussed below.

SURGICAL MANAGEMENT

Surgery continues to play a major role in the management of patients with PNETs. Experienced pancreatic surgeons are able resect PNETs with low morbidity and mortality. Indications for surgery include direct tumor related complications such as bleeding, bowel obstruction, or severe pain, to assist in the control of the biochemical syndrome, and in many cases to achieve cure (119).

Surgical resection of a functioning PNET should be considered whenever possible (1) (3) (120) (117). This includes MEN 1 patients with functioning PNETs (other than gastrinoma), as these generally have a high cure rate (121). Surgery for MEN 1 patients with gastrinoma remains controversial, as they are almost never cured (14) (122) (78) (123) (121), and even aggressive resection has not been shown to improve survival (119).

The positive impact of resection on survival in patients with NF-PNETs has been repeatedly demonstrated (124) (125) (126) (127) (128). Small tumors (< 2 cm) have an indolent course and may be amenable to observation (129) (130) (131). Factors to be considered in deciding upon surgery include tumor size, tumor grade and differentiation, and overall health of the patient (128) (132) (133). Nodal metastases occur in 30% of patients with NF PNETs, are associated with radiological nodal status and tumor grade, and decreased disease-free survival. (134). Thus, some have advocated resection of even small NF PNETs in patients who are otherwise in excellent health.

Indications for surgery in MEN1 patients with NF-PNETs are similar to those with sporadic disease. Patients with MEN 1 and NF-PNETs 2cm or smaller in diameter, who have a low disease specific mortality, may be managed conservatively (135). Others have suggested resection in MEN1 patients with NF-PNETs more than 1 cm in size and/or demonstrate significant growth over 6-12 months (136).

The traditional surgical approach is open laparotomy. Thorough abdominal exploration including bimanual palpation and intraoperative ultrasound of the pancreas and liver are performed (1) (83) (84). For small duodenal tumors (especially duodenal gastrinomas) endoscopic trans illumination (1) (137) (138) and routine duodenotomy are recommended (1) (122) (78) (138-140).

It appears that certain lesions, particularly those amenable to enucleation or to distal pancreatectomy, may be approached with laparoscopic or robotic techniques, generally with comparable or slightly better results than open resection (141) (119). Gastrinomas are an exception, as duodenotomy and palpation remain important to detect these often small lesions. Adopting a pure laparoscopic or robotic approach to these tumors will depend upon improvements in haptic feedback technology. For tumors requiring pancreatic head/duodenal resection, laparoscopic and/or robotic pancreaticoduodenectomy (Whipple resection) is being performed at several centers with thus far similar results to open procedures (142), but at generally increased costs. This technology continues to evolve.

The most common site of distant metastases is the liver (128) (143) (144;145), with synchronous metastases noted in about 30% (132,135). There are multiple options available for the patient with hepatic metastases, including surgical resection which in selected patients appears to improve survival (146). Cytoreductive hepatic surgery in patients with functioning PNETs may improve the clinical symptoms by reducing hormone levels and may increase long-term survival (147-149). NANETS guidelines suggest that debulking surgery should be considered in carefully selected patients particularly those with functional tumors where the tumors may be removed safely (150) (151). Surgical debulking may be associated with improved responses to concomitant therapy such as embolization and overall survival (152).

Resection of the primary tumor in the setting of liver metastases remains controversial, given the number of non-surgical options available to treat liver metastases. Both National Comprehensive Cancer Network (NCCN) guidelines (153) and ENETS consensus guidelines (154) 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 complications which may occur with disease progression (155) (156), and may improve survival (157). An analysis of the SEER database showed a benefit to resecting the primary tumor in all disease stages, including stage 4 (118).

Important considerations include the extent of resection required for the primary, the extent of the liver metastases and their planned treatment, as well as the age and overall health of the patient. Aggressive surgical resection of both primary and metastatic lesions has been reported in selected patients with good results (130-34) (147,148,149), even when the primary is locally advanced requiring vascular resection (158).

To summarize, multiple surgical controversies persist including the role of surgery in patients with MEN1 and gastrinoma (we would argue few or none, except perhaps for lesions>3cm), the extent of the surgical resection, the role and extent of lymphadenectomy, the role of resection of the primary in patients with metastatic disease, and the role of surgical debulking when complete resection cannot be achieved. For further details the reader is referred elsewhere (119).

SYSTEMIC THERAPY OF PNETs

Use of systemic therapy is limited to those with locally advanced or metastatic disease. Some of the current targets of systemic therapy are shown in Figure 7. There is no recognized role for adjuvant therapy in patients who have successfully undergone complete resection, outside of a clinical trial.

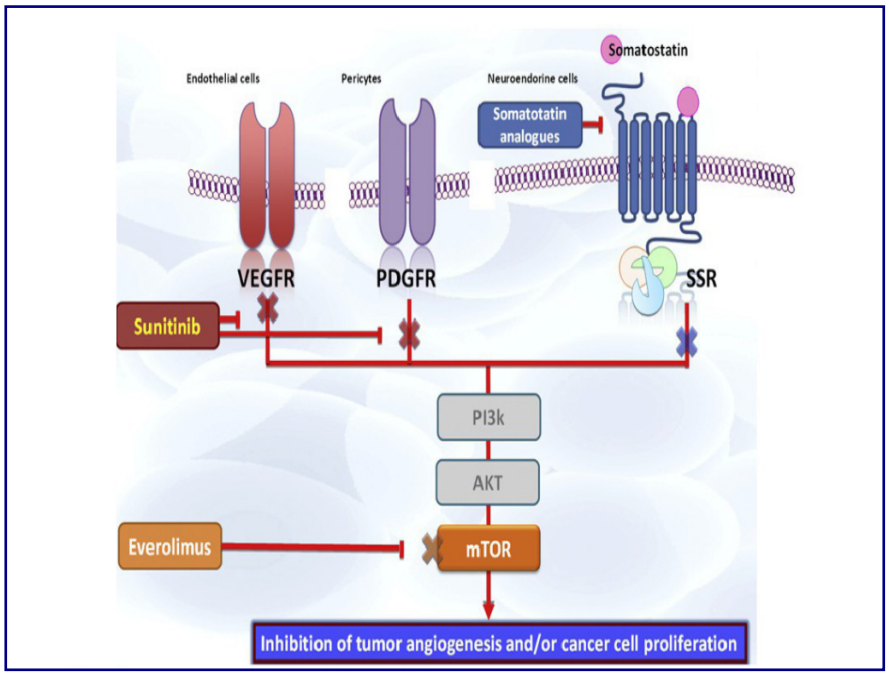

Figure 7. The current means of targeting the biologic processes promoting cell growth in PNETs. Somatostatin analogs w bind to somatostatin receptors controlling both symptoms and cell growth. Sunitinib is a tyrosine kinase inhibitor which VEGFR and PDGFR. Everolimus is an mTOR inhibitor. The result is inhibition of tumor angiogenesis and or cancer cell proliferation. Legend: mTOR, mammalian target of Rapamycin; PDGFR, platelet-derived growth factor receptor; SSR, somatostatin receptors; VEGFR, vascular endothelial growth receptor. Reprinted from Faivre, S., et al. Novel anticancer agents in clinical trials for well-differentiated NETS Endocrinol Metab Clin North Am 2010,31(4)-811-26.

SOMATOSTATIN ANALOGS

Somatostatin analogs (SSAs) have long been a mainstay in the treatment of advanced and metastatic NETs including PNETs. Although much of the data are from mixed populations of NET patients, it is possible to glean data regarding PNETs. A prospective multicenter trial evaluated the efficacy of lanreotide, interferon alpha, and their combination in metastatic NETs. Comparable response/stable disease rates of 25-32% were noted in all 3 treatment arms, and results were similar in functional and nonfunctional tumors (159). PNETs comprised 32.5% of tumors. This study suggested that foregut tumors including PNETs are less responsive to

somatostatin therapy than midgut NETs. The CLARINET trial (155) showed that in the lanreotide treatment group similar progression–free survival was noted in the PNET (Hazard ratio 0.58(0.32-1.04)) and midgut subgroups (0.35 (0.16-0.80)). Studies limited to midgut NETS such as the PROMID trial (154) showed a disease stabilization rate of 67% in the octreotide LAR group (Figure 9). Thus, whether or not PNETS have a lower response rate than midgut NETS to somatostatin analogs remains an unanswered question. Hopefully ongoing clinical trials will help answer this question. If there is a difference, it is likely modest.

The FDA approved Lanreotide (Somatuline depot) for GEP-NETs including PNETs on 12/16/2014. ENETS guidelines support the use of SSAs for advanced PNETs, particularly those with a high burden of liver metastases (160).

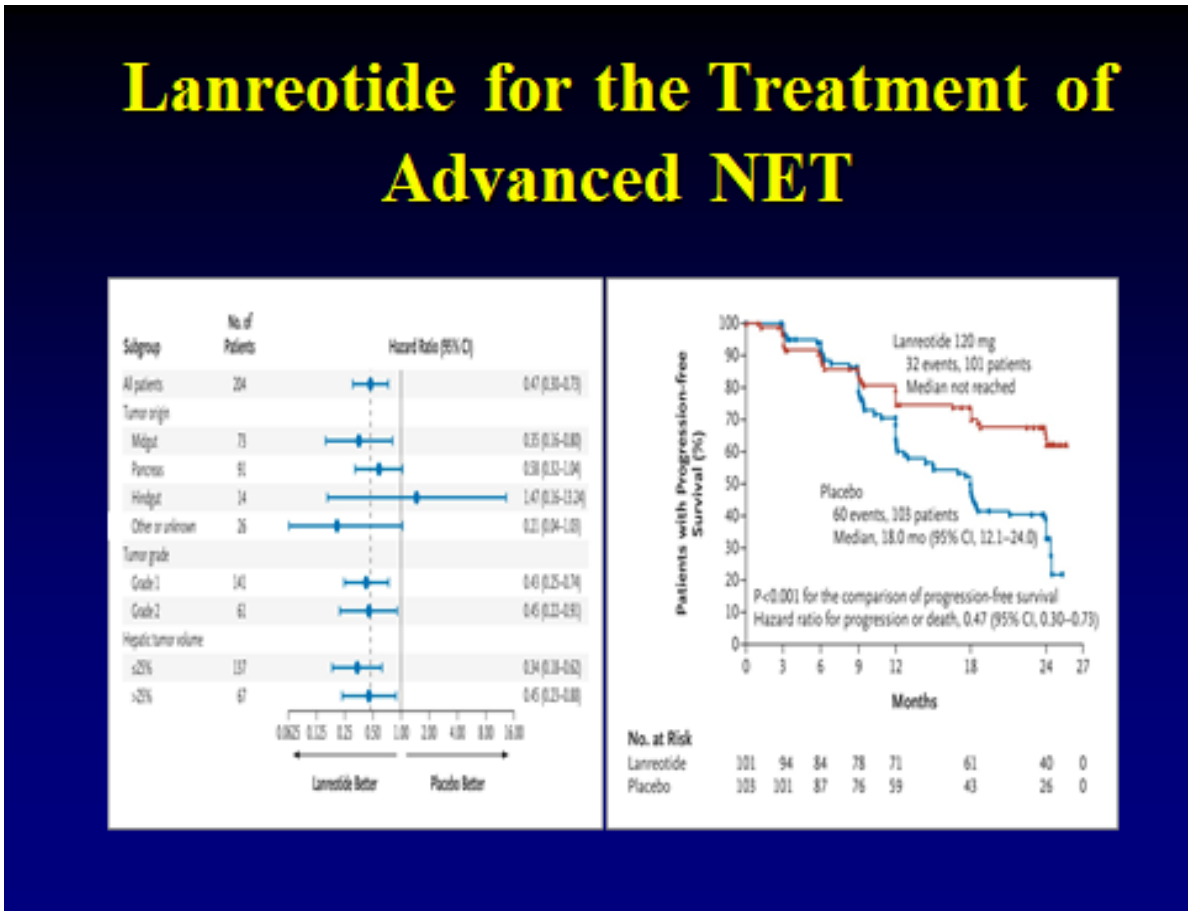

Figure 8. **CLARINET trial in a mixed group including PNETs**

Various SSAs including Octreotide LAR (PROMID trial) (154), Somatuline (Lanreotide) (CLARINET trial) (161), ELECT trial (155) and Som 230 (Pasireotide) (162) have shown promise in NETs and PNETs (Figure 8), but since the studies had different designs, and looked at different patient populations and endpoints, it is difficult at this juncture to say definitively that one agent is superior to the others in PNETs. Hopefully prospective trials in progress will help

answer this question.

CYTOTOXIC CHEMOTHERAPY

Patient selection for conventional cytotoxic chemotherapy should include factors such as primary tumor site and stage, tumor differentiation, and proliferation index (166). ENETS guidelines include indications such as progression while under SSA treatment, worsening symptoms, and/or Ki67 values >10% (160). Currently the standard regimen is streptozotocin (STZ) and 5-FU rather than STZ and doxorubicin (117). Recent studies show that treatment of advanced PNETs with STZ/5-FU is associated with good objective response rates of 28-43% and disease control rates of 66-92%, albeit with considerable toxicity (117). Limited data show that monotherapies with Dacarbazine (DTIC) has a similar response rate but less toxicity (163).

Other regimens have shown activity as well. Recent data show that platinum-based chemotherapy has significant activity in GI-NEC G3 (164), and should be considered first line therapy in patients with metastatic disease (165) (166). Temozolomide (TMZ) appears to have significant activity against advanced PNETs, especially when combined with various agents including capecitabine (167), bevacizumab (168), bevacizumab and octreotide LAR (169), thalidomide (170), and everolimus (171).

MOLECULAR-TARGETED AGENTS

Newly developed molecular-targeted treatments include the tyrosine kinase(TK) inhibitor sunitinib malate (SUTENT®; Pfizer Inc., New York, NY, USA) and the mammalian target of Rapamycin (mTOR) inhibitor everolimus (AFINITOR®; Novartis Pharmaceuticals, East Hanover, NJ, USA) (Figure 7). These agents have changed treatment practices for advanced, metastatic PNETs (Table 3).

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 PNETs and 10.2 months in carcinoid patients (172). A recently reported multi-national randomized double-blind placebo-controlled trial (SUN 1111) confirmed the activity of sunitinib in patients with advanced well differentiated PNETs (Figure 9). 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%) (173). Of great importance was the impact on improved quality of life (71) and the recent demonstration on the relationship between quality of life, tumor burden and biochemical markers of NETs (174) (175) (Table 4).

Additional excitement has been generated by study of mTOR inhibitors, either alone or combined with octreotide therapy. 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 PNETs that have progressed on chemotherapy (176). 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 in 50.7% and 68.2% of patients (Table 4). An early tumor marker response (> 50% decrease by 4 weeks) was associated with a significantly longer progression-free survival (161). The RADIANT 3 trial studied everolimus as first line therapy in patients with advanced PNETs (Figure 9). 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 (177). Similar progression free survival was noted regardless of whether patients were chemo-naïve or had received prior chemotherapy (178). Addition of pasireotide LAR to everolimus did not improve PFS compared to everolimus alone (179).

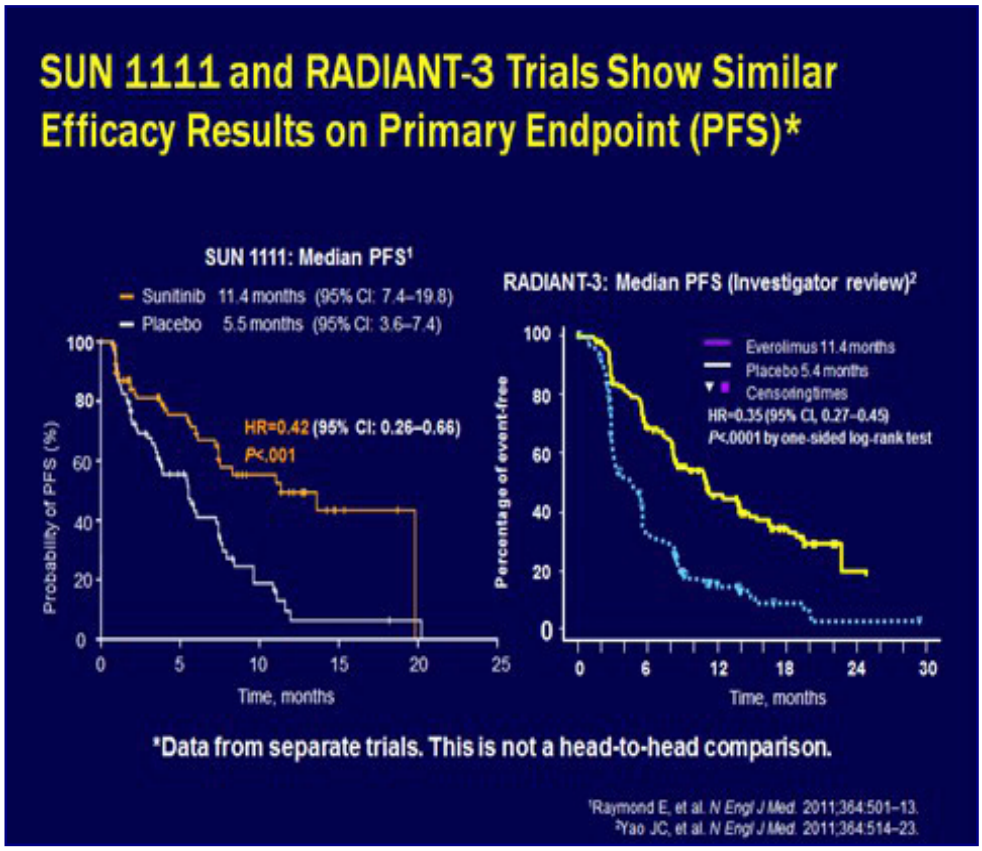

Figure 9. This figure compares the progression free survival (PFS) in patients with advanced metastatic PNETs treated with sunitinib in the SUN1111 trial (173) compared to everolimus in the RADIANT- 3 trial (177). While the PFS are similar, there are significant differences in the side effects; thus, choices need to be individualized.

Based on recent data, treatment algorithms for PNETs are expected to evolve. The European Society for Medical Oncology (ESMO) guidelines 2012 recommended use of molecular-targeted

agents such as everolimus or sunitinib in advanced pancreatic NETs G1/G2 (180). The North American Neuroendocrine Tumor Society (NANETS) guidelines similarly recommend sunitinib or everolimus for progressive metastatic PNETs (168). Looking at separate trials, the PFS (Figure 9) and response rates (Table 3) appear comparable. Correlation of biomarkers and outcomes is shown in Table 4. Since there has been no trial comparing the two agents directly, choice of the agent may be based on the potential side-effects and the patient's health. For example, in patients with poorly controlled hormonal symptoms especially hyperinsulinism, 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 (165). In patients with poorly controlled diabetes mellitus, pulmonary disease, or high risk of infection, sunitinib would be a more appropriate choice (71) (181).

Table 3. **Results from selected 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 (172)	66 PNET 41 carcinoid	50 mg daily, Schedule 4/2*	No	PR 17%† SD 68%†	7.7	Grade 3-4 fatigue: 25%
Phase III, RCT (173) (182)	171 [86 SU; 85 placebo]	37.5 mg daily, CDD‡	Yes	**Sunitinib**: CR 2.3% PR 7% SD 62.8% **Placebo**: ORR 0% SD 60%	**Sunitinib**: 11.4/12.6 **Placebo**: 5.5/5.8	Most common AEs associated with sunitinib ≥30%: diarrhea, nausea, asthenia, vomiting, and fatigue Grade 3-4 neutropenia and hypertension: 10-12%
Everolimus						
Phase II, open label (183) Ella check the ref	30 PNET 30 carcinoid	10 mg daily + octreotide LAR 30 mg	No	PR 27%† SD 60%†	12.5†	Grade 3-4 fatigue and diarrhea: 11% Grade 3-4 thrombocytopenia and leukopenia: 5%
Phase II, open label in two strata [RADIANT-1] (176)	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 grade 3-4 asthenia: 5.2% Stratum II grade 3-4 thrombocytopenia: 8.9%
Phase III, RCT	410 [207	10 mg daily	Yes	**Everolimus**:	**Everolimus:**	Most common AEs:

(RADIANT-3) (177)	everolimus, 203 placebo]			PR 5.0% SD 73% **Placebo**: PR 2.0% SD 51%	11. **Placebo**: 4.6	stomatitis 64%; rash 49%; diarrhea 34%; fatigue 31%; infections 23% AEs of clinical concern: pneumonitis 12%' interstitial lung disease 2%

*Concomitant use of SSA in 27% of patients with PNET and 54% of patients with carcinoid tumors

†In patients with PNET

‡Concomitant use of SSA in 26.7% of patients

AE, adverse event; CDD, continuous daily dosing; CR, complete response; 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; SSA, somatostatin analogue; TTP, time to progression.

Table 4. **Soluble biomarkers and correlations with outcomes with targeted therapies in PNETs.**

Study	Biomarker	Results
Sunitinib (184)(185)	sVEGFR-3	Reductions in sVEGFR-3 correlated with objective responses and improved PFS [p=0.04]
	IL-8	Lower baseline sVEGFR-2 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]
	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-1α correlated with improved CBR (objective response or SD ≥ 6 months; p=0.004]
Everolimus RADIANT-1(161) and MDACC US-52 (69)	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 versus baseline] correlated with increased PFS [HR 0.25; p<0.001] and

	NSE	OS [HR 0.4; *p*=0.01] Elevated NSE [over range 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 versus baseline] correlated with improved PFS [HR 0.25; p<0.001]

*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
Adapted from Molecular Diagnosis and Therapy, Mateo, J., Heymach, J.V. and Zurita, A.J., Biomarkers of Response to Sunitinib in Gastroenteropancreatic Neuroendocrine Tumors: Current Data and Clinical Outlook, 151–161. © 2012 with permission from Springer.

LIVER DIRECTED THERAPY

Multiple methods of liver directed therapy are available for the treatment of patients with liver metastases. These methods include hepatic artery chemoembolization or bland embolization with gel foam, or radioembolization as discussed below. Given the lack of randomized data, it is difficult to determine with certainty which method is preferred.

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 (186) in carcinoid patients that underwent hepatic artery chemoembolization (HACE) (187). Plasma levels of Pancreastatin above 5000 pg/ml pre-treatment were associated with increased peri-procedure mortality.

Radioembolization (also known as selective intrahepatic radiotherapy, SIRT) involves embolization of ^{90}Yttrium embedded either in a resin microsphere (Sir-Sphere) or a glass microsphere (TheraSphere). 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, with no radiation-induced liver failure (188). 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 (189).

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)

Peptide receptor radionuclide therapy (PRRT) is a novel therapy whereby a radiolabeled somatostatin analog is used to treat somatostatin–receptor positive locally advanced and/or metastatic GEP-NETs, including PNETs.

In a study of 504 patients, treatment with the analog 177Lu-DOTA 0,TYR3 octreotide showed activity in GE-NETs (190). Looking specifically at the PNET subgroup, there was a 6% complete response and a 36% partial response in NF-PNETs, and no complete responses and 47% partial responses in functioning PNETs (190). Striking improvements in quality of life of responders was also noted (174). A more recent study of 68 patients with PNETs treated with PRRT showed partial responses in 41 patients (60.3 %), minor responses in 8 (11.8 %), stable disease in 9 (13.2 %), and progressive disease in 10 (14.7%) (173). The authors concluded that the outstanding response rates and survival outcomes suggest that PRRT is highly effective in advanced G1/2 PNETs when compared to other treatment modalities. Independent predictors of survival were the tumor proliferation index, the patient's performance status, and tumor burden and baseline plasma NSE level. The results of the recently reported NETTER-1 trial demonstrates improvements in PFS compared to octreotide in midgut NETs (191).

Thus, there is an increasing body of evidence demonstrating the efficacy and safety of PRRT in PNETs and midgut NETs. Recently the FDA approved use of 177 Lu DOTATATE based on the results of the NETTER-1 trial in midgut carcinoids (113). Thus, the number of centers where this treatment is available is expected to increase in the United States, though it has been used in Europe since 1996. Joint society practice guidelines have been developed (192). There are a number of ongoing international clinical trials listed on Clinical Trials.gov. Third party payer reimbursement is an ongoing issue which hopefully will be resolved.

NOVEL TARGETS FOR THE TREATMENT OF NETS

While there has been a quantum leap in the ability to treat NETS successfully we have a long way to go to "cure" the disease. Fortunately, there are a number of agents in preclinical or phase 2 trials with promise. Inhibitors of PI3 kinase, inhibitors of the growth factors VEGFR/FGFR/PDGFR, Burton's tyrosine kinase inhibitor(BTK), Cyclin dependent kinases (CDKs) inhibition of CDK4/6, Ubiquitin-proteasome, Inhibition of PD1 and CTLA-4. Although a high mutational burden is thought to be one of the main drivers of response to immune checkpoint inhibitor therapy [64], promising results have been observed in carcinoid patients enrolled in early-phase studies of PD-1-blocking mAbs [65, 66]. On this basis, several trials of immunotherapy specifically designed for NET patients are currently underway (NCT02939651, NCT02955069). There is much speculation that PRRT cytotoxic drugs will induce genotoxicity and increase the neoantigen load thereby enhance the efficacy of immunotherapy (193) (194) (195).

QUALITY OF LIFE IN PATIENTS WITH PNETs

The measurement of health-related quality of life (HRQOL) has become essential for evaluating the impact of the disease process and the treatment on patient symptoms, social, emotional, psychological and physical functioning. The EORTC QLQ-C30 tool was developed for oncology patients (196), and the EORTC QLQ-GINET21 tool was developed in a spectrum of NET patients (28% PNETs) (197). The Norfolk QOLNET was specifically developed and may have some advantages for midgut NETS(carcinoid) (174) (175) (198).

The most commonly used QOL tool in GEP-NETS (including PNETs) is the EORTC QLQ-C30 (199). Somatostatin analogues and sunitinib have shown improved HRQOL in diverse groups of GEP-NET patients (199). In the CLARINET study, QLC-C30 data were mapped to EQ-5D utilities, and not surprisingly, worse utility values were noted with progressive disease compared to stable disease. Of note, tumor location (midgut vs pancreas, did not affect utility (200). PNET patients treated with everolimus showed stable HRQOL scores, as opposed to worse scores in non-PNET patients (201). PRRT treatment of PNET patients resulted in significantly improved global health status, social functioning, and mitigation of physical complaints (202).

Thus, data are emerging on HRQOL in PNET patients. However, most studies are too heterogeneous in terms of patient populations and treatment interventions to draw firm conclusions (203). Moving forward, it will be important for HRQOL to be measured as a key component of clinical trials.

EXPERT COMMENTARY

Increasing knowledge of the biology and pathophysiology have led to marked improvements in imaging, with the development of 68 Gallium DOTATE PET, and targeted treatments such as the tyrosine-kinase inhibitor sunitinib, and the mTOR inhibitor everolimus. The genetics of these tumors is increasingly understood, but thus far has not led to gene-based therapies, and there are no clear genotype-phenotype correlations. Imaging will continue to advance as more tumor specific imaging agents are developed. Other effective treatments for patients with advanced disease will also be developed. Biomarkers that are better able to predict response to a particular therapy are required.

After many years of frustration, there are finally effective treatments for patients with advanced and metastatic disease. Unfortunately, the optimal treatment(s) and treatment sequencing have yet to be defined. The relatively uncommon nature of PNETs has made designing and completing randomized studies of adequate power challenging, but nonetheless can be accomplished as demonstrated by several recent successful trials. The relatively indolent nature of many or most of these tumors requires long term follow-up to assess differences in treatment related outcomes. Lack of treatment standardization, the plethora of treatments that most patients receive, and different treatment sequencing makes it difficult to assess the effectiveness of a particular treatment relative to other treatments. Lacking are head to head randomized comparisons.

Available consensus guidelines establish broad principles but are generally not helpful in managing a specific patient. Management has become even more complex giving the multiplicity of effective treatments for advanced disease, none of which has convincingly been shown to be superior to the others. Thus, an experienced multidisciplinary team is essential in helping guide management of these patients. Given relative parity of effectiveness, decisions regarding choice of treatment need to be based on multiple considerations, including patient's overall health, disease burden, symptomatology, rate of progression, treatment toxicity and effect on QOL, and cost. These considerations will usually lead to one treatment being favored over another.

The uncommon nature of these tumors makes it difficult for a single institution to see a sufficient number of patients to carry out a study of adequate power. Thus, we applaud the recent trend of multi-institutional multinational studies in more homogeneous patient populations. The recent refinements in tumor categorization and staging should lead to better study design going forward. We strongly agree with the recommendation of NANETS, ENETS and other groups that all of these patients should be entered onto clinical trials whenever feasible. Determining study availability and patient eligibility has been greatly facilitated by Clinical trials.gov as well as institutional and organizational websites. Enrolling more patients in clinical trials by overcoming barriers to participation will be required to move patient care forward.

5 YEAR VIEW

Knowledge of the biology and genetics will continue to accumulate. This will lead to further refinements in classification, staging, and personalized treatment. Additional PET analogs will come into limited clinical use for certain tumors such as insulinomas. Genetic profiling will become clinically useful. Data will accumulate on treatment effectiveness in patient subgroups leading to more tailored therapies. Biomarkers will be developed that better predict response to a particular therapy. Results of ongoing clinical trials on newer somatostatin analogs and targeted agents will add to the number of available treatments. There will be increased knowledge as to optimal treatment sequencing. Designing randomized clinical trials of adequate power will remain a challenge for many reasons including the scarcity and indolent growth of these tumors. Consensus guidelines will evolve, but patient management will continue to require an experienced multidisciplinary team.

KEY ISSUES

- Increasing knowledge about the biology, pathophysiology, and genetics of PNETs has led to major improvements in classification and staging, imaging, and treatment.
- Classification systems including WHO 2017 have been refined to recognize tumor heterogeneity.
- Circulating biomarkers remain key in diagnosis, assessing response to treatment, and detecting recurrence. Needed are biomarkers better predictive of therapy response.
- 68 Gallium DOTATE PET is a major advance in imaging and has recently been approved by

the FDA.

- Surgery remains the initial form of treatment for many/most early stage tumors. Aggressive resection of primary tumor and its metastases may be of benefit in highly selected patients with advanced disease.
- Multiple somatostatin analogues are available for clinical use. The primary benefit is disease stabilization. Combination of somatostatin with other bioactive compounds can enhance the biologic responsiveness.
- Platinum-based chemotherapy may be of benefit in a subgroup of metastatic G3 tumors. Targeted therapies such as sunitinib and everolimus play an increasing role in the treatment of metastatic G1/G2 tumors.
- Peptide receptor radiotherapy with 177 Lu DOTA adds another treatment option for patients with advanced SRS-positive PNETs and has recently been FDA approved.
- Improvement of quality of life is still possible even when the treatment has been drastic.
- All patients should be considered for clinical trials whenever possible.
- Updated consensus guidelines are useful for providing a general management framework. However, given the multiplicity of treatments and major unresolved questions, an experienced multidisciplinary team is essential to coordinate care.

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