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

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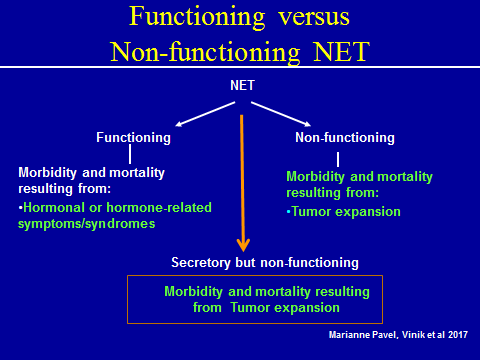
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**ABSTRACT**

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, 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.

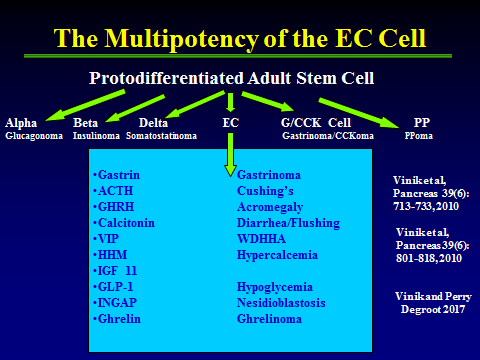
Adapted from *Current Opinions in Oncology*, Milan, S.A. and Yeo, C.J. Neuroendocrine Tumors of the Pancreas, 46–55. © 2012 with permission from Lippincott Williams & Wilkins, Inc. and *Endocrinology and Metabolism Clinics of North America*, Ardill, J.E. and O’Dorisio, T.M., Circulating Biomarkers in 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.

**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.

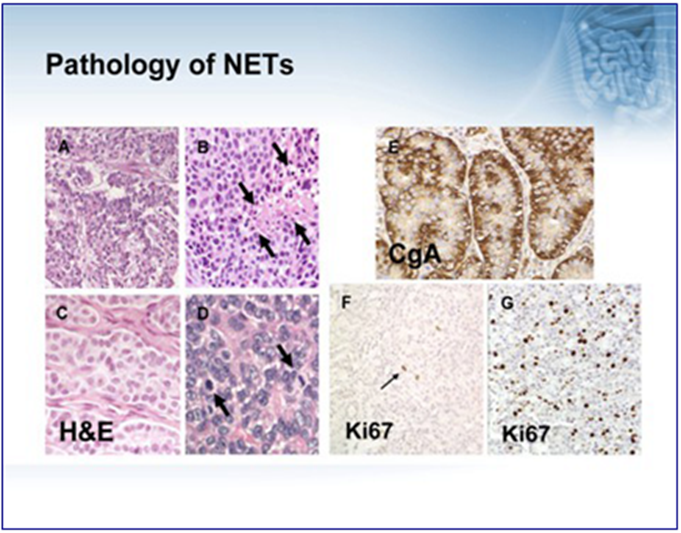
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**Figure 3** **Illustrates the almost totipotentiality of the protodifferentiated pancreatic stem cell to differentiate into a variety of cell types to produce an almost infinite variety of clinical syndromes EC=enterochromaffin, GHRH= growth hormone 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.**

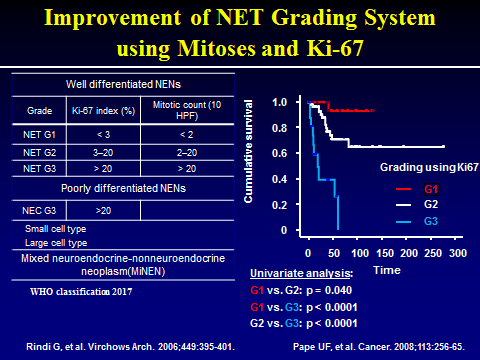
## **PATHOLOGY, CLASSIFICATION, AND STAGING**

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.**

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**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**

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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**

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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.

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## 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 111Indium-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 11C-5 hydroxytryptophan-labeled or 68Gallium-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).

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**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.

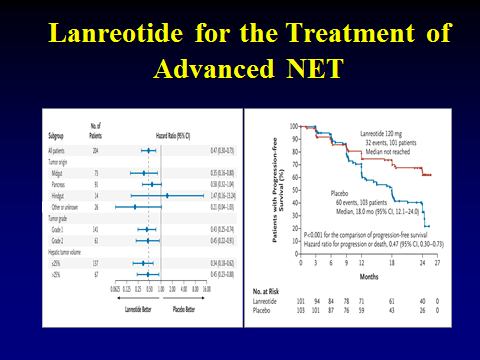
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**Figure 7.** **The current means of targeting the biologic processes promoting cell growth in PNETs. Somatostatin analogs w bind to somatostatin receptors controlling both symptoms and cell growth. Sunitinib is a tyrosine kinase inhibitor which VEGFR 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).

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**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)  Phase III, RCT  (173) (182) | 66 PNET  41 carcinoid  171 [86 SU; 85 placebo] | 50 mg daily, Schedule 4/2\*  37.5 mg daily, CDD‡ | No  Yes | PR 17%†  SD 68%†  **Sunitinib**:  CR 2.3%  PR 7%  SD 62.8%  **Placebo**:  ORR 0%  SD 60% | 7.7  **Sunitinib**: 11.4/12.6  **Placebo**: 5.5/5.8 | Grade 3-4 fatigue: 25%  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 (RADIANT-3) (177) | 410 [207 everolimus, 203 placebo] | 10 mg daily | Yes | **Everolimus**: PR 5.0%  SD 73%  **Placebo**: PR 2.0%  SD 51% | **Everolimus:** 11.  **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% |

\*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  IL-8  sVEGFR-2  SDF=1α | Reductions in sVEGFR-3 correlated with objective responses and improved PFS [*p*=0.04]  Lower baseline sVEGFR-2 with radiologically stable disease for > 6 months [*p*=0.009]  Elevated baseline sVEGFR-2 correlated with improved OS [HR 0.22; 95% CI 0.06-0.78; *p*=0.01]  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  NSE | 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 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 90Yttrium embedded either in a resin microsphere (Sir-Sphere) or a glass microsphere (TheraSphere). Acute toxicities associated with 90Yttrium 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](https://link.springer.com/article/10.1007%2Fs11864-017-0461-5#CR64)], promising results have been observed in carcinoid patients enrolled in early-phase studies of PD-1-blocking mAbs [[65](https://link.springer.com/article/10.1007%2Fs11864-017-0461-5#CR65), [66](https://link.springer.com/article/10.1007%2Fs11864-017-0461-5#CR66)]. 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 COMME****NTARY**

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.

**REFERENCES**

1. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology 2008; 135(5):1469-1492.

2. Kloppel G, Anlauf M. Epidemiology, tumour biology and histopathological classification of neuroendocrine tumours of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 2005; 19(4):507-517.

3. Oberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol 2005; 19(5):753-781.

4. Pavel ME, Phan AT, Wolin EM et al. Biomarker and Treatment Response With Lanreotide in Gastroenteropancreatic Neuroendocrine Tumors From CLARINET. J Clin Endocrinol Metab 2017; In Press.

5. Fraenkel M, Kim M, Faggiano A, de Herder WW, Valk GD. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. Endocr Relat Cancer 2014; 21(3):R153-R163.

6. Falconi M, Eriksson B, Kaltsas G et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology 2016; 103(2):153-171.

7. Vinik AI. Advances in diagnosis and treatment of pancreatic neuroendocrine tumors. Endocr Pract 2014; 20(11):1222-1230.

8. Liakakos T, Roukos DH. Everolimus and sunitinib: from mouse models to treatment of pancreatic neuroendocrine tumors. Future Oncol 2011; 7(9):1025-1029.

9. Schneider R, Waldmann J, Swaid Z et al. Calcitonin-secreting pancreatic endocrine tumors: systematic analysis of a rare tumor entity. Pancreas 2011; 40(2):213-221.

10. Jensen RT. Endocrine Neoplasms of the Pancreas. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, editors. In Textbook of Gastroenterology. Oxford, England: Wiley-Blackwell, 2009: 1875-1920.

11. Lepage C, Bouvier AM, Phelip JM, Hatem C, Vernet C, Faivre J. Incidence and management of malignant digestive endocrine tumours in a well defined French population. Gut 2004; 53(4):549-553.

12. Falconi M, Plockinger U, Kwekkeboom DJ et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology 2006; 84(3):196-211.

13. Plockinger U, Wiedenmann B. Diagnosis of non-functioning neuro-endocrine gastro-enteropancreatic tumours. Neuroendocrinology 2004; 80 Suppl 1:35-38.

14. Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. Cancer 2008; 113(7 Suppl):1807-1843.

15. Miyaura C, Chen L, Appel M et al. Expression of reg/PSP, a pancreatic exocrine gene: relationship to changes in islet beta-cell mass. Mol Endocrinol 1991; 5:226-234.

16. Brockenbrough JS, Weir GC, Bonner-Weir S. Discordance of exocrine and endocrine growth after 90% pancreatectomy in rats. Diabetes 1988; 37:232-236.

17. Pour P, Mohr U, Cardesa A, Althoff J, Kruger FW. Pancreatic neoplasms in an animal model: morphological, biological, and comparative studies. Cancer 1975; 36:379-389.

18. Rosenberg L, Duguid WP, Brown RA, Vinik AI. Induction of nesidioblastosis will reverse diabetes in Syrian golden hamster. Diabetes 1988; 37:334-341.

19. Rosenberg L, Duguid WP, Vinik AI. Cell proliferation in the pancreas of the Syrian golden hamster. Dig Dis Sci 1987; 32:1185.

20. Sarvetnick N. Islet cell destruction and regeneration in IFN-gamma transgenic mice. J Cell Biochem 1991; CB019:49.

21. Smith DB, Scarffe JH, Wagstaff J, Johnston RJ. Phase II trial of rDNA alfa 2b interferon in patients with malignant carcinoid tumor. Cancer Treat Rep 1987; 71(12):1265-1266.

22. Takasawa S, Yamamoto H, Terazono K, Okamoto H. Novel gene activated in rat insulinomas. Diabetes 1986; 35:1178-1180.

23. Terazono K, Yamamoto H, Takasawa S et al. A novel gene activated in regenerating islets. J Biol Chem 1988; 263:2111-2114.

24. Watanabe T, Yonekura H, Terazono K, Yamamoto H, Okamoto H. Complete nucleotide sequence of human reg gene and its expression in normal and tumoral tissues. The reg protein, pancreatic stone protein, and pancreatic thread protein are one and the same product of the gene. J Biol Chem 1990; 265:7432-7439.

25. Strobel O, Rosow DE, Rakhlin EY et al. Pancreatic duct glands are distinct ductal compartments that react to chronic injury and mediate Shh-induced metaplasia. Gastroenterology 2010; 138(3):1166-1177.

26. Elashoff M, Matveyenko A, Gier B, Elashoff R, Butler P. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology 2011; 141(1):150-156.

27. Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked Expansion of Exocrine and Endocrine Pancreas with Incretin Therapy in Humans with increased Exocrine Pancreas Dysplasia and the potential for Glucagon-producing Neuroendocrine Tumors. Diabetes 2013; 62(7):2595-2604.

28. Butler PC, Dry S, Elashoff R. GLP-1-based therapy for diabetes: what you do not know can hurt you. Diabetes Care 2010; 33(2):453-455.

29. Reid MD, Balci S, Saka B, Adsay NV. Neuroendocrine tumors of the pancreas: current concepts and controversies. Endocr Pathol 2014; 25(1):65-79.

30. Rebours V, Cordova J, Couvelard A et al. Can pancreatic neuroendocrine tumour biopsy accurately determine pathological characteristics? Dig Liver Dis 2015; 47(11):973-977.

31. World Health Organization. WHO Classification of Tumours of Endocrine Organs. Fourth Edition ed. 2017.

32. Perren A, Couvelard A, Scoazec JY et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pathology: Diagnosis and Prognostic Stratification. Neuroendocrinology 2017; 105(3):196-200.

33. Garcia-Carbonero R, Sorbye H, Baudin E et al. ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. Neuroendocrinology 2016; 103(2):186-194.

34. Salaria SN, Shi C. Pancreatic Neuroendocrine Tumors. Surg Pathol Clin 2016; 9(4):595-617.

35. Klimstra DS, Modlin IR, Adsay NV et al. Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. Am J Surg Pathol 2010; 34(3):300-313.

36. Protocol for the examination of specimens from patients with tumors of the endocrine pancreas. College of the American Pathologists (CAP). 2017.

37. Kwekkeboom DJ, Krenning EP, Lebtahi R et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. Neuroendocrinology 2009; 90(2):220-226.

38. AJCC. Cancer Staging Manual. 2017.

39. Luo G, Javed A, Strosberg JR et al. Modified Staging Classification for Pancreatic Neuroendocrine Tumors on the Basis of the American Joint Committee on Cancer and European Neuroendocrine Tumor Society Systems. J Clin Oncol 2017; 35(3):274-280.

40. Li X, Gou S, Liu Z, Ye Z, Wang C. Assessment of the American Joint Commission on Cancer 8th Edition Staging System for Patients with Pancreatic Neuroendocrine Tumors: A Surveillance, Epidemiology, and End Results analysis. Cancer Med 2018; 7(3):626-634.

41. Gortz B, Roth J, Krahenmann A et al. Mutations and allelic deletions of the MEN1 gene are associated with a subset of sporadic endocrine pancreatic and neuroendocrine tumors and not restricted to foregut neoplasms. Am J Pathol 1999; 154(2):429-436.

42. Oberg K. The genetics of neuroendocrine tumors. Semin Oncol 2013; 40(1):37-44.

43. Speel EJ, Scheidweiler AF, Zhao J et al. Genetic evidence for early divergence of small functioning and nonfunctioning endocrine pancreatic tumors: gain of 9Q34 is an early event in insulinomas. Cancer Res 2001; 61(13):5186-5192.

44. House MG, Herman JG, Guo MZ et al. Aberrant hypermethylation of tumor suppressor genes in pancreatic endocrine neoplasms. Ann Surg 2003; 238(3):423-431.

45. Moore PS, Orlandini S, Zamboni G et al. Pancreatic tumours: molecular pathways implicated in ductal cancer are involved in ampullary but not in exocrine nonductal or endocrine tumorigenesis. Br J Cancer 2001; 84(2):253-262.

46. Pellegata NS, Sessa F, Renault B et al. K-ras and p53 gene mutations in pancreatic cancer: ductal and nonductal tumors progress through different genetic lesions. Cancer Res 1994; 54(6):1556-1560.

47. Crona J, Skogseid B. GEP- NETS UPDATE: Genetics of neuroendocrine tumors. Eur J Endocrinol 2016; 174(6):R275-R290.

48. Jiao Y, Shi C, Edil BH et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science 2011; 331(6021):1199-1203.

49. Scarpa A, Chang DK, Nones K et al. Whole-genome landscape of pancreatic neuroendocrine tumours. Nature 2017; 543(7643):65-71.

50. de Herder WW. Biochemistry of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007; 21(1):33-41.

51. Oberg K, Eriksson B. Best Practice & Resaerch Clinical Endocrinology Metabolism. Elsevier, Ltd., 2007.

52. Ardill JE. Circulating markers for endocrine tumours of the gastroenteropancreatic tract. Ann Clin Biochem 2008; 45(Pt 6):539-559.

53. Eriksson B, Oberg K, Stridsberg M. Tumor markers in neuroendocrine tumors. Digestion 2000; 62 Suppl 1:33-38.

54. Oberg K. Biochemical diagnosis of neuroendocrine GEP tumor. Yale J Biol Med 1997; 70(5-6):501-508.

55. Nobels FR, Kwekkeboom DJ, Coopmans W et al. Chromogranin A as serum marker for neuroendocrine neoplasia: comparison with neuron-specific enolase and the alpha-subunit of glycoprotein hormones. J Clin Endocrinol Metab 1997; 82(8):2622-2628.

56. Bilek R, Safarik L, Ciprova V, Vlcek P, Lisa L. Chromogranin A, a member of neuroendocrine secretory proteins as a selective marker for laboratory diagnosis of pheochromocytoma. Physiol Res 2008; 57 Suppl 1:S171-S179.

57. Stridsberg M, Eriksson B, Fellstrom B, Kristiansson G, Tiensuu JE. Measurements of chromogranin B can serve as a complement to chromogranin A. Regul Pept 2007; 139(1-3):80-83.

58. Takiyyuddin MA, Cervenka JH, Hsiao RJ, Barbosa JA, Parmer RJ, O'Connor DT. Chromogranin A. Storage and release in hypertension. Hypertension 1990; 15(3):237-246.

59. Qiu W, Christakis I, Silva A et al. Utility of chromogranin A, pancreatic polypeptide, glucagon and gastrin in the diagnosis and follow-up of pancreatic neuroendocrine tumours in multiple endocrine neoplasia type 1 patients. Clin Endocrinol (Oxf) 2016; 85(3):400-407.

60. Zatelli MC, Torta M, Leon A et al. Chromogranin A as a marker of neuroendocrine neoplasia: an Italian Multicenter Study. Endocr Relat Cancer 2007; 14(2):473-482.

61. Oberg K, Kvols L, Caplin M et al. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol 2004; 15(6):966-973.

62. Massironi S, Conte D, Sciola V et al. Plasma chromogranin A response to octreotide test: prognostic value for clinical outcome in endocrine digestive tumors. Am J Gastroenterol 2010; 105(9):2072-2078.

63. Kann PH, Balakina E, Ivan D et al. Natural course of small, asymptomatic neuroendocrine pancreatic tumours in multiple endocrine neoplasia type 1: an endoscopic ultrasound imaging study. Endocr Relat Cancer 2006; 13(4):1195-1202.

64. Stronge RL, Turner GB, Johnston BT et al. A rapid rise in circulating pancreastatin in response to somatostatin analogue therapy is associated with poor survival in patients with neuroendocrine tumours. Ann Clin Biochem 2008; 45(Pt 6):560-566.

65. Panzuto F, Severi C, Cannizzaro R et al. Utility of combined use of plasma levels of chromogranin A and pancreatic polypeptide in the diagnosis of gastrointestinal and pancreatic endocrine tumors. J Endocrinol Invest 2004; 27(1):6-11.

66. Bajetta E, Ferrari L, Martinetti A et al. Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. Cancer 1999; 86(5):858-865.

67. Lipton A, Costa L, Ali S, Demers L. Use of markers of bone turnover for monitoring bone metastases and the response to therapy. Semin Oncol 2001; 28(4 Suppl 11):54-59.

68. Brown JE, Cook RJ, Major P et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. J Natl Cancer Inst 2005; 97(1):59-69.

69. Yao JC, Pavel M, Phan AT et al. Chromogranin A and neuron-specific enolase as prognostic markers in patients with advanced pNET treated with everolimus. J Clin Endocrinol Metab 2011; 96(12):3741-3749.

70. Woltering EA, Hilton RS, Zolfoghary CM et al. Validation of serum versus plasma measurements of chromogranin a levels in patients with carcinoid tumors: lack of correlation between absolute chromogranin a levels and symptom frequency. Pancreas 2006; 33(3):250-254.

71. Vinik AI, Raymond E. Pancreatic neuroendocrine tumors: approach to treatment with focus on sunitinib. Therap Adv Gastroenterol 2013; 6(5):396-411.

72. Noone TC, Hosey J, Firat Z, Semelka RC. Imaging and localization of islet-cell tumours of the pancreas on CT and MRI. Best Pract Res Clin Endocrinol Metab 2005; 19(2):195-211.

73. Kloppel G, Couvelard A, Perren A et al. ENETS Guidelines for the Standards of Care in Patients with Neuroendocrine Tumors: Towards a Standardized Approach to the Diagnosis of Gastroenteropancreatic Neuroendocrine Tumors and Their Prognostic Stratification. Neuroendocrinology 2008.

74. Rockall AG, Reznek RH. Imaging of neuroendocrine tumours (CT/MR/US). Best Pract Res Clin Endocrinol Metab 2007; 21(1):43-68.

75. Virgolini I, Traub-Weidinger T, Decristoforo C. Nuclear medicine in the detection and management of pancreatic islet-cell tumours. Best Pract Res Clin Endocrinol Metab 2005; 19(2):213-227.

76. Gibril F, Jensen RT. Diagnostic uses of radiolabelled somatostatin receptor analogues in gastroenteropancreatic endocrine tumours. Dig Liver Dis 2004; 36 Suppl 1:S106-S120.

77. Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007; 21(1):69-85.

78. Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. Ann Surg 2004; 240(5):757-773.

79. McLean AM, Fairclough PD. Endoscopic ultrasound in the localisation of pancreatic islet cell tumours. Best Pract Res Clin Endocrinol Metab 2005; 19(2):177-193.

80. Doppman JL, Miller DL, Chang R et al. Gastrinomas: localization by means of selective intraarterial injection of secretin. Radiology 1990; 174(1):25-29.

81. Doppman JL, Chang R, Fraker DL et al. Localization of insulinomas to regions of the pancreas by intra-arterial stimulation with calcium. Ann Intern Med 1995; 123(4):269-273.

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

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

84. Shin LK, Brant-Zawadzki G, Kamaya A, Jeffrey RB. Intraoperative ultrasound of the pancreas. Ultrasound Q 2009; 25(1):39-48.

85. Orlefors H, Sundin A, Garske U et al. Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. J Clin Endocrinol Metab 2005; 90(6):3392-3400.

86. Gabriel M, Decristoforo C, Kendler D et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med 2007; 48(4):508-518.

87. Eriksson B, Orlefors H, Oberg K, Sundin A, Bergstrom M, Langstrom B. Developments in PET for the detection of endocrine tumours. Best Pract Res Clin Endocrinol Metab 2005; 19(2):311-324.

88. Jackson JE. Angiography and arterial stimulation venous sampling in the localization of pancreatic neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2005; 19(2):229-239.

89. Sundin A, Vullierme MP, Kaltsas G, Plockinger U. ENETS Guidelines for the Standards of Care in Patients with Neuroendocrine Tumours: Radiological Examinations in Patients with Neuroendocrine Tumours. Neuroendocrinology 2008.

90. De RR, Cingarlini S, Tinazzi MP et al. Pancreatic neuroendocrine neoplasms: Magnetic resonance imaging features according to grade and stage. World J Gastroenterol 2017; 23(2):275-285.

91. Libutti SK, Choyke PL, Bartlett DL et al. Pancreatic neuroendocrine tumors associated with von Hippel Lindau disease: diagnostic and management recommendations. Surgery 1998; 124(6):1153-1159.

92. Langer P, Kann PH, Fendrich V et al. Prospective evaluation of imaging procedures for the detection of pancreaticoduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. World J Surg 2004; 28(12):1317-1322.

93. Manfredi S, Pagenault M, de Lajarte-Thirouard AS, Bretagne JF. Type 1 and 2 gastric carcinoid tumors: long-term follow-up of the efficacy of treatment with a slow-release somatostatin analogue. Eur J Gastroenterol Hepatol 2007; 19(11):1021-1025.

94. Krenning EP, Kwekkeboom DJ, Oei HY et al. Somatostatin-receptor scintigraphy in gastroenteropancreatic tumors. An overview of European results. Ann N Y Acad Sci 1994; 733:416-424.

95. Berna M, Jensen R. Use of radiolabeled somatostatin receptor analogues in diagnosis of gastrointestinal neuroendocrine tumors. In: Modlin IM, Oberg K, ., editors. In A Century of Advances in Neuroendocrine Tumor Biology and Treatment. Hanover: Felstein C.C.C.P., 2007: 328-339.

96. Termanini B, Gibril F, Reynolds JC et al. Value of somatostatin receptor scintigraphy: a prospective study in gastrinoma of its effect on clinical management. Gastroenterology 1997; 112(2):335-347.

97. Gibril F, Reynolds JC, Chen CC et al. Specificity of somatostatin receptor scintigraphy: a prospective study and effects of false-positive localizations on management in patients with gastrinomas. J Nucl Med 1999; 40(4):539-553.

98. Christ E, Wild D, Ederer S et al. Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: a prospective multicentre imaging study. Lancet Diabetes Endocrinol 2013; 1(2):115-122.

99. Panagiotidis E, Alshammari A, Michopoulou S et al. Comparison of the Impact of 68Ga-DOTATATE and 18F-FDG PET/CT on Clinical Management in Patients with Neuroendocrine Tumors. J Nucl Med 2017; 58(1):91-96.

100. Kornaczewski Jackson ER, Pointon OP, Bohmer R, Burgess JR. Utility of FDG-PET Imaging for Risk Stratification of Pancreatic Neuroendocrine Tumors in MEN1. J Clin Endocrinol Metab 2017; 102(6):1926-1933.

101. Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. Radiographics 2015; 35(2):500-516.

102. Sadowski SM, Neychev V, Millo C et al. Prospective Study of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites. J Clin Oncol 2016; 34(6):588-596.

103. Etchebehere EC, de Oliveira SA, Gumz B et al. 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: a prospective trial. J Nucl Med 2014; 55(10):1598-1604.

104. Deppen SA, Blume J, Bobbey AJ et al. 68Ga-DOTATATE Compared with 111In-DTPA-Octreotide and Conventional Imaging for Pulmonary and Gastroenteropancreatic Neuroendocrine Tumors: A Systematic Review and Meta-Analysis. J Nucl Med 2016; 57(6):872-878.

105. Yang J, Kan Y, Ge BH, Yuan L, Li C, Zhao W. Diagnostic role of Gallium-68 DOTATOC and Gallium-68 DOTATATE PET in patients with neuroendocrine tumors: a meta-analysis. Acta Radiol 2014; 55(4):389-398.

106. Mojtahedi A, Thamake S, Tworowska I, Ranganathan D, Delpassand ES. The value of (68)Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. Am J Nucl Med Mol Imaging 2014; 4(5):426-434.

107. Skoura E, Michopoulou S, Mohmaduvesh M et al. The Impact of 68Ga-DOTATATE PET/CT Imaging on Management of Patients with Neuroendocrine Tumors: Experience from a National Referral Center in the United Kingdom. J Nucl Med 2016; 57(1):34-40.

108. Deppen SA, Liu E, Blume JD et al. Safety and Efficacy of 68Ga-DOTATATE PET/CT for Diagnosis, Staging, and Treatment Management of Neuroendocrine Tumors. J Nucl Med 2016; 57(5):708-714.

109. Lastoria S, Marciello F, Faggiano A et al. Role of (68)Ga-DOTATATE PET/CT in patients with multiple endocrine neoplasia type 1 (MEN1). Endocrine 2016; 52(3):488-494.

110. Sadowski SM, Millo C, Cottle-Delisle C et al. Results of (68)Gallium-DOTATATE PET/CT Scanning in Patients with Multiple Endocrine Neoplasia Type 1. J Am Coll Surg 2015; 221(2):509-517.

111. Froeling V, Elgeti F, Maurer MH et al. Impact of Ga-68 DOTATOC PET/CT on the diagnosis and treatment of patients with multiple endocrine neoplasia. Ann Nucl Med 2012; 26(9):738-743.

112. Albers MB, Librizzi D, Lopez CL et al. Limited Value of Ga-68-DOTATOC-PET-CT in Routine Screening of Patients with Multiple Endocrine Neoplasia Type 1. World J Surg 2017; 41(6):1521-1527.

113. Food and Drug Administration. FDA approves lutetium Lu 177 dotatate for treatment of GEP-NETS. https://www accessdata fda/drugs/informationdrugs/approveddrugs/ucm594105 htm 2018.

114. Hope TA, Bergsland EK, Bozkurt MF et al. Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors. J Nucl Med 2018; 59(1):66-74.

115. Menda Y, O'Dorisio TM, Howe JR et al. Localization of Unknown Primary Site with (68)Ga-DOTATOC PET/CT in Patients with Metastatic Neuroendocrine Tumor. J Nucl Med 2017; 58(7):1054-1057.

116. Strosberg J, El-Haddad G, Wolin E et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017; 376(2):125-135.

117. Krug S, Gress TM, Michl P, Rinke A. The Role of Cytotoxic Chemotherapy in Advanced Pancreatic Neuroendocrine Tumors. Digestion 2017; 96(2):67-75.

118. Casciano R, Chulikavit M, Perrin A, Liu Z, Wang X, Garrison LP. Cost-effectiveness of everolimus vs sunitinib in treating patients with advanced, progressive pancreatic neuroendocrine tumors in the United States. J Med Econ 2012; 15 Suppl 1:55-64.

119. Perry R, Feliberti E, Vinik A. Pancreatic Surgery for Endocrine Tumors. In: Clark O, Duh Q-Y, Kebebew E, Gosnell J, Shen W, editors. Textbook of Endocrine Surgery. New Delhi, India: Jaypee Brothers Medical Publishers, Inc., 2016: 1209-1220.

120. Akerstrom G, Hellman P. Surgery on neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007; 21(1):87-109.

121. Jensen RT, Norton JA. Treatment of Pancreatic Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type 1: Some Clarity But Continued Controversy. Pancreas 2017; 46(5):589-594.

122. Norton JA, Fraker DL, Alexander HR et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999; 341(9):635-644.

123. Jensen RT, Niederle B, Mitry E et al. Gastrinoma (duodenal and pancreatic). Neuroendocrinology 2006; 84(3):173-182.

124. Hill JS, McPhee JT, McDade TP et al. Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. Cancer 2009; 115(4):741-751.

125. Gomez-Rivera F, Stewart AE, Arnoletti JP, Vickers S, Bland KI, Heslin MJ. Surgical treatment of pancreatic endocrine neoplasms. Am J Surg 2007; 193(4):460-465.

126. Zerbi A, Capitanio V, Boninsegna L et al. Surgical treatment of pancreatic endocrine tumours in Italy: results of a prospective multicentre study of 262 cases. Langenbecks Arch Surg 2011; 396(3):313-321.

127. Franko J, Feng W, Yip L, Genovese E, Moser AJ. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. J Gastrointest Surg 2010; 14(3):541-548.

128. Martin RC, Kooby DA, Weber SM et al. Analysis of 6,747 pancreatic neuroendocrine tumors for a proposed staging system. J Gastrointest Surg 2011; 15(1):175-183.

129. Bettini R, Partelli S, Boninsegna L et al. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery 2011; 150(1):75-82.

130. Lee LC, Grant CS, Salomao DR et al. Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): role for nonoperative management. Surgery 2012; 152(6):965-974.

131. Gaujoux S, Partelli S, Maire F et al. Observational study of natural history of small sporadic non-functioning pancreatic neuroendocrine tumors. J Clin Endocrinol Metab 2013.

132. Scarpa A, Mantovani W, Capelli P et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. Mod Pathol 2010; 23(6):824-833.

133. Toste PA, Kadera BE, Tatishchev SF et al. Nonfunctional Pancreatic Neuroendocrine Tumors <2 cm on Preoperative Imaging are Associated with a Low Incidence of Nodal Metastasis and an Excellent Overall Survival. J Gastrointest Surg 2013; 17(12):2105-2113.

134. Partelli S, Gaujoux S, Boninsegna L et al. Pattern and clinical predictors of lymph node involvement in nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs). JAMA Surg 2013; 148(10):932-939.

135. Triponez F, Sadowski SM, Pattou F et al. Long-term Follow-up of MEN1 Patients Who Do Not Have Initial Surgery for Small </=2 cm Nonfunctioning Pancreatic Neuroendocrine Tumors, an AFCE and GTE Study: Association Francophone de Chirurgie Endocrinienne & Groupe d'Etude des Tumeurs Endocrines. Ann Surg 2017.

136. Thakker RV, Newey PJ, Walls GV et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012; 97(9):2990-3011.

137. Frucht H, Norton JA, London JF et al. Detection of duodenal gastrinomas by operative endoscopic transillumination. A prospective study. Gastroenterology 1990; 99(6):1622-1627.

138. Norton JA, Doppman JL, Jensen RT. Curative resection in Zollinger-Ellison syndrome. Results of a 10-year prospective study. Ann Surg 1992; 215(1):8-18.

139. Norton JA, Alexander HR, Fraker DL, Venzon DJ, Gibril F, Jensen RT. Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases, or survival in patients with Zollinger-Ellison syndrome? Ann Surg 2004; 239(5):617-625.

140. Sugg SL, Norton JA, Fraker DL et al. A prospective study of intraoperative methods to diagnose and resect duodenal gastrinomas. Ann Surg 1993; 218(2):138-144.

141. Drymousis P, Raptis DA, Spalding D et al. Laparoscopic versus open pancreas resection for pancreatic neuroendocrine tumours: a systematic review and meta-analysis. HPB (Oxford) 2014; 16(5):397-406.

142. Kendrick ML, van HJ, Boggi U et al. Minimally invasive pancreatoduodenectomy. HPB (Oxford) 2017; 19(3):215-224.

143. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97(4):934-959.

144. Chamberlain RS, Canes D, Brown KT et al. Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg 2000; 190(4):432-445.

145. Gaujoux S, Gonen M, Tang L et al. Synchronous resection of primary and liver metastases for neuroendocrine tumors. Ann Surg Oncol 2012; 19(13):4270-4277.

146. Partelli S, Cirocchi R, Rancoita PMV et al. A Systematic review and meta-analysis on the role of palliative primary resection for pancreatic neuroendocrine neoplasm with liver metastases. HPB (Oxford) 2018; 20(3):197-203.

147. McEntee GP, Nagorney DM, Kvols LK, Moertel CG, Grant CS. Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery 1990; 108(6):1091-1096.

148. Modlin IM, Lewis JJ, Ahlman H, Bilchik AJ, Kumar RR. Management of unresectable malignant endocrine tumors of the pancreas. Surg Gynecol Obstet 1993; 176(5):507-518.

149. Wessels FJ, Schell SR. Radiofrequency ablation treatment of refractory carcinoid hepatic metastases. J Surg Res 2001; 95(1):8-12.

150. Kulke MH, Anthony LB, Bushnell DL et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas 2010; 39(6):735-752.

151. Kunz PL, Reidy-Lagunes D, Anthony LB et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas 2013; 42(4):557-577.

152. Gupta S, Johnson MM, Murthy R et al. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. Cancer 2005; 104(8):1590-1602.

153. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. 1.2012. 2012. <http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf>. Neuroendocrine tumors of the pancreas. Ref Type: Report

154. Pavel M, Baudin E, Couvelard A et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012; 95(2):157-176.

155. Hodul PJ, Strosberg JR, Kvols LK. Aggressive surgical resection in the management of pancreatic neuroendocrine tumors: when is it indicated? Cancer Control 2008; 15(4):314-321.

156. Solorzano CC, Lee JE, Pisters PW et al. Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. Surgery 2001; 130(6):1078-1085.

157. Zhou B, Zhan C, Ding Y, Yan S, Zheng S. Role of palliative resection of the primary pancreatic neuroendocrine tumor in patients with unresectable metastatic liver disease: a systematic review and meta-analysis. Onco Targets Ther 2018; 11:975-982.

158. Norton JA, Harris EJ, Chen Y et al. Pancreatic endocrine tumors with major vascular abutment, involvement, or encasement and indication for resection. Arch Surg 2011; 146(6):724-732.

159. Faiss S, Pape UF, Bohmig M et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors--the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 2003; 21(14):2689-2696.

160. Pavel M, O'Toole D, Costa F et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology 2016; 103(2):172-185.

161. Caplin ME, Pavel M, Cwikla JB et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014; 371(3):224-233.

162. Wolin EM, Hu K, Hughes G, Bouillaud E, Giannone V, Resendiz KH. Safety, tolerability, pharmacokinetics, and pharmacodynamics of a long-acting release (LAR) formulation of pasireotide (SOM230) in patients with gastroenteropancreatic neuroendocrine tumors: results from a randomized, multicenter, open-label, phase I study. Cancer Chemother Pharmacol 2013; 72(2):387-395.

163. Mueller D, Krug S, Majumder M, Rinke A, Gress TM. Low dose DTIC is effective and safe in pretreated patients with well differentiated neuroendocrine tumors. BMC Cancer 2016; 16:645.

164. Velayoudom-Cephise FL, Duvillard P, Foucan L et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? Endocr Relat Cancer 2013; 20(5):649-657.

165. Rinke A, Gress TM. Neuroendocrine Cancer, Therapeutic Strategies in G3 Cancers. Digestion 2017; 95(2):109-114.

166. Sorbye H, Welin S, Langer SW et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol 2013; 24(1):152-160.

167. Strosberg JR, Fine RL, Choi J et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer 2011; 117(2):268-275.

168. Chan JA, Stuart K, Earle CC et al. Prospective study of bevacizumab plus temozolomide in patients with advanced neuroendocrine tumors. J Clin Oncol 2012; 30(24):2963-2968.

169. Koumarianou A, Antoniou S, Kanakis G et al. Combination treatment with metronomic temozolomide, bevacizumab and long-acting octreotide for malignant neuroendocrine tumours. Endocr Relat Cancer 2012; 19(1):L1-L4.

170. Kulke MH, Stuart K, Enzinger PC et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol 2006; 24(3):401-406.

171. Chan JA, Blaszkowsky L, Stuart K et al. A prospective, phase 1/2 study of everolimus and temozolomide in patients with advanced pancreatic neuroendocrine tumor. Cancer 2013; 119(17):3212-3218.

172. Kulke MH, Lenz HJ, Meropol NJ et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol 2008; 26(20):3403-3410.

173. Raymond E, Dahan L, Raoul JL et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011; 364(6):501-513.

174. Vinik E, Carlton CA, Silva MP, Vinik AI. Development of the norfolk quality of life tool for assessing patients with neuroendocrine tumors. Pancreas 2009; 38(3):e87-e95.

175. Vinik A, Vinik E, Diebold A, Woltering E. Measuring the relationship of quality of life (QOL) and health status - including tumor burden, symptoms and biochemical measures in patients with neuroendocrine tumors. In: Raymond E, Faivre S, Ruszniewski P, editors. Management of Neuroendocrine Tumors of the Pancreas & the Digestive Tract. Springer- Verlag, France, 2014: 199-220.

176. Yao JC, Lombard-Bohas C, Baudin E et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol 2010; 28(1):69-76.

177. Yao JC, Shah MH, Ito T et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011; 364(6):514-523.

178. Lombard-Bohas C, Yao JC, Hobday T et al. Impact of prior chemotherapy use on the efficacy of everolimus in patients with advanced pancreatic neuroendocrine tumors: a subgroup analysis of the phase III RADIANT-3 trial. Pancreas 2015; 44(2):181-189.

179. Kulke MH, Ruszniewski P, Van CE et al. A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. Ann Oncol 2017; 28(6):1309-1315.

180. Oberg K, Knigge U, Kwekkeboom D, Perren A. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 Suppl 7:vii124-vii130.

181. Yao JC, Phan AT. Optimising therapeutic options for patients with advanced pancreatic neuroendocrine tumours. European Oncology and Haematology 2012; 8(4):217-223.

182. Faivre S, Niccoli P, Castellano D et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. Ann Oncol 2017; 28(2):339-343.

183. Yao JC, Phan A, Hoff PM et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. J Clin Oncol 2008; 26(8):1316-1323.

184. Bello C, Deprimo S, Friece C et al. Analysis of circulating biomarkers of sunitinib malate in patients with unresectable neuroendocrine tumors (NET): VEGF, IL-8, and soluble VEGF receptors 2 and 3. ASCO Meeting Absracts 24, 4045. 2006. Ref Type: Abstract

185. Zurita A, Heymach J, Khajavi M et al. Circulating protein and cellular biomarkers of sunitinib in patients with advanced neuroendocrine tumors. 47th Annual Meeting of the American Society of Clinical Oncology June 3-7[Chicago, IL]. 2011. Ref Type: Abstract

186. Desai DC, O'Dorisio TM, Schirmer WJ et al. Serum pancreastatin levels predict response to hepatic artery chemoembolization and somatostatin analogue therapy in metastatic neuroendocrine tumors. Regul Pept 2001; 96(3):113-117.

187. Bloomston M, Al-Saif O, Klemanski D et al. Hepatic artery chemoembolization in 122 patients with metastatic carcinoid tumor: lessons learned. J Gastrointest Surg 2007; 11(3):264-271.

188. Kennedy AS, Dezarn WA, McNeillie P et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. Am J Clin Oncol 2008; 31(3):271-279.

189. Rhee TK, Lewandowski RJ, Liu DM et al. 90Y Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. Ann Surg 2008; 247(6):1029-1035.

190. Kwekkeboom DJ, de Herder WW, Kam BL et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008; 26(13):2124-2130.

191. Strosberg J, Wolin E, Chasen B et al. QOL improvements in NETTER-1 phase III trial in patients with progressive midgut neuroendocrine tumors. NANETS 2017 Annual Symposium Philadelphia, October 19-21, 2017. 2017. Ref Type: Abstract

192. Bodei L, Mueller-Brand J, Baum RP et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013; 40(5):800-816.

193. McGranahan N, Furness AJ, Rosenthal R et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 2016; 351(6280):1463-1469.

194. Naing A, Papadopoulos KP, Autio KA et al. Safety, Antitumor Activity, and Immune Activation of Pegylated Recombinant Human Interleukin-10 (AM0010) in Patients With Advanced Solid Tumors. J Clin Oncol 2016; 34(29):3562-3569.

195. Patnaik A, Kang SP, Rasco D et al. Phase I Study of Pembrolizumab (MK-3475; Anti-PD-1 Monoclonal Antibody) in Patients with Advanced Solid Tumors. Clin Cancer Res 2015; 21(19):4286-4293.

196. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85(5):365-376.

197. Yadegarfar G, Friend L, Jones L et al. Validation of the EORTC QLQ-GINET21 questionnaire for assessing quality of life of patients with gastrointestinal neuroendocrine tumours. Br J Cancer 2013; 108(2):301-310.

198. Vinik E, Silva MP, Vinik AI. Measuring the relationship of quality of life and health status, including tumor burden, symptoms, and biochemical measures in patients with neuroendocrine tumors. Endocrinol Metab Clin North Am 2011; 40(1):97-109, viii.

199. Jimenez-Fonseca P, Carmona-Bayonas A, Martin-Perez E et al. Health-related quality of life in well-differentiated metastatic gastroenteropancreatic neuroendocrine tumors. Cancer Metastasis Rev 2015; 34(3):381-400.

200. Meng Y, McCarthy G, Berthon A, Dinet J. Patient-reported health state utilities in metastatic gastroenteropancreatic neuroendocrine tumours - an analysis based on the CLARINET study. Health Qual Life Outcomes 2017; 15(1):131.

201. Pavel M, Unger N, Borbath I et al. Safety and QOL in Patients with Advanced NET in a Phase 3b Expanded Access Study of Everolimus. Target Oncol 2016; 11(5):667-675.

202. Marinova M, Mucke M, Mahlberg L et al. Improving quality of life in patients with pancreatic neuroendocrine tumor following peptide receptor radionuclide therapy assessed by EORTC QLQ-C30. Eur J Nucl Med Mol Imaging 2018; 45(1):38-46.

203. Martini C, Gamper EM, Wintner L et al. Systematic review reveals lack of quality in reporting health-related quality of life in patients with gastroenteropancreatic neuroendocrine tumours. Health Qual Life Outcomes 2016; 14(1):127.