NANETS GUIDELINES

2020

NANETS

NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

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INTRODUCTION

Dear NET Community,

It is with great pleasure that we present this inaugural edition of NANETS' Consensus Guidelines.

NANETS is a leader in NET education and is actively involved in the development of consensus guidelines to support the medical treatment and management of NET disease. NANETS' Consensus Guidelines serve as important references for practicing physicians.

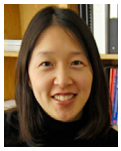
The Guidelines and Publications Committee coordinates the process of developing consensus guidelines using rigorous literature review conducted by content-specific NET experts serving on consensus panels.

Since 2013, NANETS has published 8 guidelines on pancreatic NETs, small bowel NETs, peptide receptor radionuclide therapy with 177Lu-dotatate, and somatostatin receptor PET imaging. Two panels are completing their work on guidelines for pheochromocytoma/paraganglioma and high-grade neuroendocrine neoplasms. We invite you to visit our online library at https://nanets.net/net-guidelines-library as we continue to publish and post new consensus guidelines.

We wish to thank all of the committee members and panelists who have contributed to this important work over the years.

Sincerely,

James R. Howe, MD
Board President
University of Iowa Carver College of Medicine



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NANETS OVERVIEW

The North American Neuroendocrine Tumor Society's (NANETS) mission is to improve outcomes for patients with neuroendocrine tumors through multidisciplinary medical education, NET related medical research, publication of guidelines and the exchange of knowledge and innovation.

The Exchange of Knowledge and Innovation — The Cornerstone of NANETS' Mission

NANETS is committed to furthering neuroendocrine tumor disease diagnosis, treatment and management through research and education. With over 15,000 new patients diagnosed with NETs each year, there is a continuing need to support NET research and advance the dissemination of vital research findings.

NANETS offers a robust educational programming series through regional NET education conferences, an annual symposium, and an online webinars. These educational opportunities are presented by well-known leaders and experts in the field, exclusively for medical professionals.

NANETS supports NET related medical research through annual research grants to early career professionals in basic/translational science, clinical investigation and theranostics. These annual grants support innovative research initiatives and encourage young researchers and scientific clinicians to become NET specialists.

NANETS' Annual Multidisciplinary NET Medical Symposium provides a forum for the exchange of knowledge and innovation among researchers and clinicians within the NET field as well as related fields. NANETS curates abstracts from researchers at institutions in North America and around the world. Through abstract presentations and interactive poster sessions, NANETS showcases cutting edge topics in neuroendocrine tumor research and current clinical trials. Abstracts are compiled in a yearly publication and serve as a comprehensive guide to the latest in NET research.

Guidelines Form the Foundation of NANETS

To begin educating medical professionals on NET disease, founding members of NANETS understood the importance of consensus guidelines. The NANETS Guidelines Working Group was created and from 2008-2010, hours of effort were poured into launching this much-lauded initiative. The first consensus guidelines focused on critical elements of NET disease management by organ – including the development of position papers and collaborative feedback, with the first consensus conference held on October 2, 2008. This meeting generated intense discussions resulting in the publication of NANETS' first consensus guidelines: *The NANETS Consensus Guidelines for the Diagnosis of Neuroendocrine Tumors* (p. 157).[1]

Since that initial meeting and publication, NANETS' has published 7 additional consensus guidelines including joint consensus guidelines with the Society of Nuclear Medicine and Molecular Imaging (SNMMI). Several more guidelines will be published in 2021. The Guidelines and Publications Committee seeks the input from members on guidelines topics through an annual survey. To submit topics, email **staff@nanets.net.**

[1]See p. 195 for more history of the formation of NANETS and the guidelines process.

NANETS
NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Pancreatic Neuroendocrine Tumors

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Abstract

This article is the result of the North American Neuroendocrine Tumor Society consensus conference on the medical management of pancreatic neuroendocrine tumors from July 19 to 20, 2018. The guidelines panel consisted of medical oncologists, pathologists, gastroenterologists, endocrinologists, and radiologists. The panel reviewed a series of questions regarding the medical management of patients with pancreatic neuroendocrine tumors aswell as questions regarding surveillance after resection. The available literature was reviewed for each of the question and panel members voted on controversial topics, and the recommendationswere included in a document circulated to all panel members for a final approval.

Key Words

pancreatic neuroendocrine tumor, islet cell tumors, pancreatic endocrine tumors, pancreatic neuroendocrine carcinoma, insulinoma, gastrinoma, glucagonoma, somatostatinoma, VIPoma, somatostatin analogs, octreotide, lanreotide, peptide receptor radionuclide therapy, PRRT, everolimus, sunitinib, capecitabine, temozolomide, NANETS, North American Neuroendocrine Tumor Society, guidelines

Pancreatic neuroendocrine tumors (pNETs) are heterogeneous neoplasms thought to arise from islet cells of the pancreas.[1,2] The annual incidence of pNETs has increased in the United States over the last 2 decades from 0.3 to 1.0 cases per 100,000 per year.[3,4] Much of this rise can be explained by localized disease identified incidentally through the increased use of imaging and endoscopy,[3] but the incidence of advanced-stage pNETs has also increased. At diagnosis, more than a third of patients have metastatic disease, and an additional 20% have disease that is locally advanced. Moreover, many patients with resected pNETs will develop recurrence with distant metastases.[4]

Along with an increase in incidence of pNETs, there has been an increase in the overall survival (OS) of patients.[3] The improved survival may in part be explained by lead time bias. Although some component of interstage and intrastage migration cannot be excluded, significant advances in diagnosis and therapy of pNETs have occurred in recent years, including somatostatin receptor-based imaging, molecularly targeted therapy, cytotoxic therapy, and peptide receptor radionuclide therapy (PRRT). In addition, the outcomes of large cohorts of patients have been analyzed to quantify the risk of recurrence after surgical resection. Herein, we seek to review the literature and provide guidelines and recommendations for workup, treatment, management, and surveillance in patients with pNETs.

Materials and methods

The medical management panel for the North American Neuroendocrine Tumor Society (NANETS) pNET guidelines consisted of 17 participants, including 9 medical oncologists, 2 pathologists, 2 endocrinologists, 2 radiologists/nuclear medicine physicians, a gastroenterologist, and an interventional radiologist. Similar to previous NANETS guidelines,[5,6] participants debated various topics through a series of short presentations. The key literature was reviewed and presented to the entire group, and participants voted on questions designed to address areas of controversy. Panel members were asked to vote on controversial topics. For these guidelines, we defined “consensus” as no more than 1 oppositional vote and “significant majority” as 75% agreement or greater. The recommendations were included in a document that was circulated to the participants for final approval. Surgical and medical therapy were discussed by separate panels an published independently.[7]

Results

Pathology and Molecular and Clinical Characterization

Minimal Requirements for Diagnosis and Grading

Pancreatic neuroendocrine neoplasms (pNENs) include well-differentiated neuroendocrine tumors (NETs) and poorly differentiated (PD) neuroendocrine carcinomas (NECs).[8] It is essential to confirm the neuroendocrine epithelial nature of pNENs, to correctly distinguish NETs from NECs, to grade NETs, and to attempt to identify the primary site in the setting of a metastasis of occult origin. Reporting of resection specimens should include all of the data elements required in College of American Pathologists Cancer Protocols.[9]

Immunohistochemistry (IHC) for the general neuroendocrine markers, synaptophysin and chromogranin A (CgA), is generally considered mandatory.[10,11] Nearly all pNETs demonstrate diffuse,

strong synaptophysin expression, whereas 80% to 90% express CgA.[12,13] Synaptophysin is less specific for pNENs than CgA, and when faced with a synaptophysin+/CgA− tumor, solid pseudopapillary tumor (ß-catenin-nuclear+), acinar cell carcinoma (trypsin+), and adrenal cortical carcinoma (SF-1+) should be considered. Rates of positivity for these general neuroendocrine markers are significantly lower in PD-NECs (as low as 50%–60%). Insulinoma-associated protein 1 (INSM1) is emerging as a sensitive and specific general neuroendocrinemarker, particularly useful in the diagnosis of NECs.[14,15]

Immunohistochemistry for a broad-spectrum keratin (eg, AE1/AE3 and OSCAR) is highly recommended in diagnostic biopsies of primary/regional disease and is considered mandatory in the distant metastatic setting to confirm the epithelial nature of the neoplasm with positivity distinguishing pNET from paraganglioma/pheochromocytoma and pNEC from lymphoma.[11,16] Broad-spectrum keratin negativity is occasionally (≤5%) encountered in NETs and NECs. In this setting, other broad-spectrum epithelial markers include antibodies to EpCAM (eg, MOC-31 and Ber-EP4) and EMA.

Gastroenteropancreatic (GEP)-NETs should be graded according to the 2019 World Health Organization (WHO) Classification of Digestive System Tumours (**Table 1**).[8,17] Grading incorporates the Ki-67 proliferation index and a mitotic count. For Ki-67 IHC, the WHO recommends evaluation of ≥500 tumor cells in areas of highest nuclear labeling (ie, hotspots). Manual counting of camera-captured digital images is recommended over "eyeball estimates."[18] Digital image analysis may be used if locally validated. For mitotic counting, evaluation of mitotic figures in 50 high-power microscopic fields (HPFs) of highest density is recommended, with the count expressed as the number of mitotic figures per 2 mm^2 (10 HPFs using microscopes with a field diameter of 0.5 mm). For cases in which the grade based on the Ki-67 proliferation index and mitotic count is discrepant, the higher grade is assigned.[19] For NEC, Ki-67 IHC and mitotic counting are not mandatory, although Ki-67 IHC may be useful in the distinction of NEC from NET in small, crushed specimens and is prognostic and predictive.[20]

Ki-67 IHC should be performed on pNET biopsies and resections. In endoscopic ultrasound/fine-needle aspiration specimens, it should be performed on cell block rather than aspirate smear material. Ki-67 proliferation indices may be similar or different in matched primary and metastatic disease. In around one-third of cases assessed simultaneously, the grade is discrepant, with a higher grade in the metastasis in 25% and in the primary in 10%; outcomes in patients with a grade 2 (G2) metastasis/grade 1 (G1) primary are similar to those in patients with a G2 primary.[21] Thus, in pNET resections with concurrently resected liver metastases, it is desirable to assess the Ki-67 proliferation index in one tissue block each of primary and metastatic disease. Because the Ki-67 proliferation index correlates with tumor size, it is recommended to test a block from the largest metastasis.

Minimal Requirements for Pathology Reports in Patients With Grade 3 NENs

Most well-differentiated pNETs are low to intermediate grade (G1, G2). Progression of well-differentiated NETs to a high-grade neoplasm can occur with elevated proliferation demonstrated by either a brisk mitotic rate (>20/10 HPFs) or high Ki-67 index (>20%) grade 3 (G3) well-differentiated pNETs.[22] Poorly differentiated NEC represents a different clinical, pathologic, and genetic entity. It is important to emphasize that although mitotic counting and Ki-67 IHC are applicable for tumor grading, they are not useful in the distinction of G3 NET from NEC in isolation. In the 2017 and 2019 editions of the WHO classification of NENs, formal grading of PD-NEC is no longer necessary because they are invariably high grade.[23] The distinction between G3 well-differentiated NETs and PD-NECs can be challenging, especially in small biopsies, and requires combined clinical, pathological, and molecular correlations.[22]

Pathology reports for high-grade pNENs should include tumor differentiation using the 2019 WHO classification, results of general neuroendocrine marker expression by IHC, mitotic activity (highest area), Ki-67 proliferation index (highest and lowest for NETs with a G3 component), and the presence or absence of tumor necrosis. For resection specimens of pNETs with a G3 component, reports should indicate the relative percentage of the G3 NET component. In instances in which G3 NETand NEC cannot be distinguished based on morphology alone, IHC for DAXX, ATRX (loss of expression of either indicative of NET), p53 (mutant-pattern staining indicative of NEC), and Rb (loss of expression indicative of NEC) should be attempted to facilitate the distinction.[24] Required and recommended reporting elements for all pNENs are summarized in **Table 2**.

The Definition of Functional Tumors

Functional pNETs (F-pNETs) are defined as those that secrete hormones and cause a clinical syndrome (**Table 3**). Nonfunctional pNETs (NF-pNETs) are defined as those tumors that do not cause a clinical syndrome. Nonfunctional pNETs may have stored hormones detected by IHC on the pathology specimen, and the tumor may even secrete some inert substances causing

spurious elevation of biochemical markers; however, by definition, the patient will not have the clinical features of hormone excess. As such, there was consensus that immunohistochemical stains for hormones should not be routinely performed in pNETs. Patients with F-pNETs may benefit from a referral to specialists in endocrinology or gastroenterology depending on the syndrome, as there can be high morbidity and even mortality associated with the hormonal syndrome.

Screening for Multiple Endocrine Neoplasia Type 1 or Other Hereditary Syndromes

Most patients with pNETs have sporadic disease, but a minority of pNETs is associated with a hereditary syndrome. The most common syndromes associated with pNETs are multiple endocrine neoplasia type 1 (MEN1) and von Hippel Lindau (VHL) syndrome, and less commonly, neurofibromatosis type 1 (NF1) and tuberous sclerosis complex type 1 and 2 (TSC1 and TSC2). A population-based study from the Netherlands found that among 905 patients with pNETs, 21 patients (2.3%) had MEN1.[25] A similar study from Japan reported an MEN1 prevalence of 4.3% among pNET patients, slightly higher among F-pNETs (4.9%) than NF-pNETs (4%).[26]

Multiple endocrine neoplasia type 1 is caused by mutations in the MEN1 gene affecting the menin protein, and clinical features include hyperparathyroidism, pNETs, pituitary adenomas, bronchial NETs, adrenal adenomas, and angiofibromas.[27,28] Approximately 30% to 70% of MEN1 patients will develop pNETs, often multifocal, and the prevalence may be higher if sensitive screening methods such as endoscopic ultrasound imaging are used.[27–29] MEN1 can be diagnosed based on the patient having 2 or more features of the disease, the patient having one feature and a first degree relative with MEN1, and/or by genetic testing, which should include sequencing and deletion/duplication analysis of the MEN1 gene.

Pancreatic NETs also are associated with VHL caused by mutations in the VHL gene.[30] Features of VHL include hemangioblastomas of the central nervous system, endolymphatic sac tumors, epididymal cystadenomas, pheochromocytomas, renal cell carcinomas, pancreatic cysts, and pNETs.[31,32] Pancreatic NETs occur in 9% to 17% of VHL patients. Von Hippel Lindau syndrome is diagnosed by the clinical syndrome and genetic testing including sequencing and deletion/duplication analysis of the VHL gene.

Rarely, pNETs are associated with NF1 or TSC1/TSC2. NF1 diagnosis is usually made based on clinical criteria. Patients with NF1 develop cutaneous and/or plexiform neurofibromas, café-au-lait spots, Lisch nodules (benign iris hamartomas), inguinal or axillary freckling, long bone dysplasia, and optic gliomas.[33] Pancreatic NETs are not part of the clinical criteria but occur at increased frequency over the general population. Less than 10% of patients with NF1 develop pNETs. Patients with TSC1 or TSC2 develop facial angiofibromas, ungual fibromas, hypomelanotic macules, renal angiomyolipomas, hamartomas, and neurologic disorders.[34] There are case reports of these patients developing pNETs. The diagnosis of TSC is made by the clinical features and genetic testing including sequencing and deletion/duplication analysis of the TSC1 or TSC2 genes.

We recommend that all patients with pNETs have a thorough history (including family history) and physical examination (including skin examination) to evaluate for symptoms and signs of MEN1, VHL, NF1, or TSC. If there is suspicion for any of these syndromes, the patient should be referred to medical genetics. There was no agreement on the need for checking all new pNET patients for hypercalcemia (with or without measuring parathyroid hormone [PTH]), with a significant majority of panel members agreeing on routinely checking a calcium level in this setting. If there is hypercalcemia or elevated PTH, further evaluation for hyperparathyroidism and consideration for MEN1 testing should occur (especially if the patient is younger than 50 years). We agree with the American College of Medical Genetics and Genomics's recommendations that patients with pNETs should be tested for MEN1 if they also have another MEN1-associated tumor such as a parathyroid adenoma or multigland hyperplasia, a thymic or bronchial NET, a pituitary adenoma, or an adrenal nodule.[35] In addition, the American College of Medical Genetics and Genomics recommends MEN1 testing for all gastrinoma patients and all patients with multifocal pNETs.[35]

We recommend against testing all patients with pNETs for germline MEN1 mutations. First, fewer than 10% of pNET patients will have an associated hereditary syndrome. Second, most patients with MEN1 will develop hypercalcemia by age 30 and certainly by age 50 (with rare exceptions). Third, clinical genetic testing, especially panel gene testing, can uncover variants of undetermined significance, which are not known to cause disease or discover other germline pathologic variants in clinically

sporadic pNETs,[36] which can contribute to excess screening tests, increased health care costs, and high patient anxiety.

In the presence of a hereditary syndrome, previous guidelines recommend frequent (yearly) functional marker panels,[27,37–39] but these recommendations are not borne out by available original data or recent reviews[40–42] and are not endorsed by current National Comprehensive Cancer Network guidelines.

The Role for Routine Use of Tumor Tissue Genomic Analysis Such as Next-Generation Sequencing Panels

At present, routine application of next-generation sequencing panels on pNET tumor tissue is not recommended. These tests do not routinely provide clinically actionable prognostic or predictive information in this tumor type. There may be a possible role for next-generation sequencing analysis in patients with G3 pNENs, as a small minority may harbor potentially actionable alterations (eg, NTRK fusions and microsatellite instability).[43,44]

The Role of Routine Staining for Somatostatin Receptor Type 2A to Determine the Likelihood of Response to Somatostatin Analogs or PRRT

Because ^{111}In-pentetreotide somatostatin receptor (SSTR) scintigraphy (SRS) or SSTR positron emission tomography (SSTR-PET) is the criterion standard for selecting patients for somatostatin analog (SSA) therapy and PRRT, few studies have examined the performance of somatostatin receptor type 2A (SSTR2A) IHC as a predictive marker. These studies have generally been small. Overall, results of functional imaging to evaluate for SSTR presence and SSTR2A IHC are ≥80% concordant, with SSTR2A IHC-positivity in ≥90% of functional imaging-positive tumors.[45–49] The greatest source of discordance are IHC-positive/functional imaging–negative patients (≥50% of patients with negative scintigraphy), although this fraction is shrinking in the SSTR-PET era.[48]

Although SSTR2A IHC is not superior to functional imaging as a predictive marker for response to SSA therapy and PRRT, it is potentially valuable in certain contexts.[50–53] In the recent European Neuroendocrine Tumor Society Pathology Guideline, SSTR2A IHC is included as an optional element, indicated when functional imaging is not available.[53] SSTR2A IHC may also be useful as part of a panel of immunostains to distinguish NET G3 (typically strongly positive) from NEC (usually negative).[24] Most panel members agreed that SSTR2A IHC should not be recommended for routine use as a predictive marker.

Biochemical Markers

Use of Nonspecific Circulating Markers Such as CgA and Pancreastatin at Diagnosis, During Systemic Therapy, and During Follow-up of Completely Resected Tumors

Use of nonspecific tumor markers such as CgA, pancreastatin (PcSt), and others is not recommended for routine use in patients with pNETs. The results of tumor marker analyses rarely, if ever, influence treatment decisions or alter imaging schedules. The sensitivity and specificity of CgA as a diagnostic marker for localized and nonfunctional NETs are insufficient to support routine use.[54–56] Chromogranin A is often significantly elevated in patients on proton pump inhibitors (PPIs) or with coexisting medical conditions including atrophic gastritis and renal insufficiency.[54,55] Multiple studies have shown that higher CgA levels correlate with shorter survival and more advanced disease,[57–66] but the value of CgA when added to imaging studies is likely low. Preoperatively elevated CgA seems to predict higher recurrence risk after resection,[62,67] but there are inadequate data to suggest routinely incorporating CgA measurements in surveillance strategies after resection. Pancreastatin has been suggested as a potentially more sensitive and specific generic NET marker, less likely to be influenced by medications including PPI.[68–71] There are even fewer data available on PcSt, but similar to CgA, higher levels are associated with worse outcomes of therapy and shorter progression-free survival (PFS) and OS.[66,72–75] As with CgA, there are no studies that confirm additional value of PcSt over conventional follow-up with imaging. Although circulating NET markers could in theory influence the frequency of surveillance imaging, prospective studies are needed before adopting markers for that purpose. Use of circulating markers can potentially result in anxiety among patients and providers, as the results can vary substantially without accompanying changes in radiographic appearance.

Use of Circulating Markers for Functional Tumors in Patients With Newly Diagnosed pNETs

Functional hormonal biomarkers (eg, gastrin, glucagon, or vasoactive intestinal peptide [VIP]) should be measured selectively in pNET patients with both sporadic and inherited tumors experiencing appropriate symptoms (**Table 3**). In the absence of a known hereditary predisposition, the decision to obtain functional tumor markers should be driven by the presence of a clinical syndrome. In sporadic pNETs, the pretest probability of finding a clinically significant elevated functional peptide in the absence of syndromic symptoms is too low to justify obtaining any functional marker studies, and their utility in follow-up is unknown.

The Use of Hormone Level Measurements in Patients With Known F-pNETs

More than 80% of pNETs are nonfunctional. The <20% that are functional have plasma elevations of specific neuropeptides/biomarkers and an appropriate constellation of associated symptoms presenting as syndromes or hormone excess specific symptoms. Insulin, gastrin, glucagon, VIP, somatostatin, and adrenocorticotropic hormone (ACTH) are the most common elevated hormones in FpNETs. Other hormones such as PTH-related peptide (PTHrP), cortisol, and ghrelin are rarely produced by pNETs. Once a F-pNET is diagnosed, continued measurement of the specific hormone before and after therapeutic intervention, in conjunction with radiologic testing, can help determine tumor progression, recurrence, and response to therapy. Chronic PPI use can lead to chronically elevated gastrin levels. Stopping the PPI will reverse the hypergastrinemia unless there is underlying atrophic gastritis. As is mentioned hereinafter, however, PPI withdrawal is potentially risky in gastrinoma patients such that routine withdrawal for the purpose of gastrin measurement is not always advisable.

Novel Circulating Markers, Circulating Tumor Cells, and Cell-Free Tumor DNA

Novel markers such as transcriptomic analysis, circulating tumor cells, and cell-free tumor DNA are investigational, and additional data to support their incorporation into practice are needed.

Systemic Therapy of Well-Differentiated pNETs

Systemic Therapy for Patients With G1 and G2 pNETs

There are multiple active systemic treatment options for patients with metastatic well-differentiated pNETs. These include SSAs, everolimus, sunitinib, streptozocin-based cytotoxic regimens, capecitabine/temozolomide, and ^{177}Lu-DOTATATE. A significant majority of panel members agreed that patients with asymptomatic metastatic pNETs, especially those with low-volume disease, can safely be observed with close monitoring using cross-sectional imaging every 3 to 4 months. This is supported by the findings of the CLARINET trial where no difference was seen in OS among the groups.[76]

Evidence for use of SSAs in pNETs derives primarily from the CLARINET trial in which patients with SSTR receptor–positive enteropancreatic NETs with Ki-67 proliferation indices ≤10% were randomized to receive lanreotide 120 mg every 4 weeks versus placebo.[76] Most patients (96%) had stable disease at baseline. Progression-free survival was significantly prolonged with lanreotide (hazard ratio [HR], 0.47; P = 0.0002). Forty-five percent of patients had pNETs, and a 42% improvement in PFS with lanreotide was observed in this subgroup (HR, 0.58; 95% confidence interval [CI], 0.32–1.04; P = 0.06). It is important to emphasize that the study was only powered to demonstrate statistically significant improvement in PFS for the entire study population and not for individual subgroups such as the pNETs subgroup.

Everolimus 10 mg daily was compared with placebo in the RADIANT 3 study of 410 patients with progressing low- and intermediate-grade pNETs; crossover was permitted after progression on placebo.[77] In this trial, prior systemic therapy was allowed, with 50%of subjects having received cytotoxic chemotherapy and 50% SSAs before enrollment. The median PFS improved from 4.6 months on placebo to 11.0 months with everolimus (HR, 0.35; P > 0.0001). The confirmed objective response rate (ORR) was 5%. Overall survival analysis demonstrated a modest trend toward improved OS with median of 37.7 months on placebo versus 44.0 months on everolimus (HR, 0.94; P = 0.3). Common adverse effects included apthous oral ulcers, diarrhea, rash, hyperglycemia, cytopenias, and pneumonitis.

Very similar results were observed in a randomized phase III study comparing sunitinib 37.5 mg daily versus placebo in 181 patients with progressive low- and intermediate-grade pNETs.[78] Median PFS improved from 5.5 months on placebo to 11.4 months with sunitinib. The ORR was 9%. Adverse effects included hypertension, palmar-plantar erythrodysesthesia, diarrhea, fatigue, and cytopenias. The results of these phase III trials of targeted therapy in pNETs are summarized in **Table 4**.

Streptozocin was the first drug approved for pNETs, and data supporting its use have been available since the 1970s, although early trials did not use modern response criteria, and randomized trials were underpowered.[79] A retrospective study of streptozocin, doxorubicin, and 5-fluorouracil (5-FU) demonstrated a response rate of 39% and median PFS of 18 months.[80] Several other retrospective studies support the activity of streptozocin based therapy, in combination with either 5-FU or doxorubicin[81–86] but other studies have not confirmed significant the efficacy of streptozocin with doxorubicin.[87,88]

More recently, oral temozolomide-based regimens have shown significant activity in patients with metastatic pNETs. A retrospective study of 143 consecutively treated

patients with low-, intermediate-, and high-grade pNETs treated with the combination of capecitabine and temozolomide demonstrated an ORR of 54%, median PFS of 17 months, and median OS of 73.2 months.[89]

The randomized phase II Eastern Cooperative Oncology Group 2211 trial compared temozolomide monotherapy with capecitabine and temozolomide in 144 patients with progressive low and intermediate-grade pNETs.[90] Median PFS improved from 14.4 months with temozolomide alone to 22.7 months with the capecitabine/temozolomide combination (HR, 0.58; P = 0.02). Median OS was 38 months with temozolomide and not reached with the combination (HR, 0.41; P = 0.01). The rate of confirmed partial response (PR) with capecitabine/temozolomide was 33%, similar to temozolomide alone (28%). Adverse effects of capecitabine/temozolomide included neutropenia (13% G3/4) and thrombocytopenia (8% G3/4).

Data supporting use of PRRT in SSTR-positive pNETs derive primarily from large institutional registries.[91] In one of the largest series reported thus far, 610 patients with GEP and bronchial NETs were treated with ^{177}Lu-DOTATATE 200 mCi per cycle for a total of 4 cycles[92]; 443 were evaluable for efficacy. Among these, 133 patients had pNETs. The overall response rate in the pNET cohort was 55%, median PFS was 30 months, and median OS was 71 months. It is important to note that not all patients in this study had progressive disease at baseline and that efficacy analysis was limited to patients who received approximated 75% of planned treatment. Adverse effects included cytopenias, which generally resolved within the 8-week cycle. Grade 3/4 hematologic toxicity occurred in 10% (G3/4 thrombocytopenia in 5%, G3/4 leukopenia in 5%, and G3/4 anemia in 4%). The long-term risk of PRRT-induced myeloid neoplasms (t-MN) including myelodysplatic syndrome (MDS) and/or acute leukemia seems to be 2% to 3%, and once PRRT-induced myeloid neoplasm occurs, the prognosis is poor.[93] Treatment-induced MN occurred after a median follow-up of 55 months (range, 32–125 months) for acute myeloid leukemia and after 28 months (range, 9–41 months) for MDS. Other retrospective studies support the use of PRRT for patients with pNETs. In a recent analysis of 12 published reports of retrospective and prospective case series of PRRT with ^{177}Lu-DOTATATE in pNETs,[92,94–105] the median ORR was 58% and the median disease control rate (DCR) was 83%, with median PFS ranging from 25 to 34 months.[91] Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE is associated with significant improvement in quality of life, including symptomatic improvement and more than 80% decrease in plasma hormone levels in patients with F-pNETs.[106,107]

Initial Systemic Therapy in Patients With Positive Receptor Imaging (Octreotide vs Lanreotide)

Somatostatin analogs are generally recommended as a first-line treatment option to slow disease progression in patients with advanced pNETs. Octreotide and lanreotide have similar mechanism of action, and both preferentially bind with similar affinity to somatostatin receptor subtypes 2 and 5.[108] Antitumor activity of lanreotide in patients with pNETs was established in the CLARINET trial, whereas evidence supporting antitumor activity of octreotide in pNET is based on smaller, retrospective, nonrandomized studies.[109] Although there is a higher level of evidence supporting antiproliferative effects of lanreotide in pNET, there was a consensus among panel members that antitumor activity is a class effect of SSAs and that both lanreotide and octreotide are acceptable options for first-line therapy of patients with advanced pNETs.

Initial Therapy for Patients With Negative or Indeterminate Receptor Imaging

When considering the therapeutic options for pNET patients with negative or indeterminant SSTR imaging, 3 important concepts emerge: (1) the type of imaging test matters, (2) G1/2 NETs that are truly SSTR negative by functional imaging are rare, and (3) optimal therapy for true SSTR-negative NETs (by functional imaging) is uncertain. Distinguishing between false- and true-negative SSTR functional imaging is important, as numerous studies suggest that ^{68}Ga-DOTATOC- and DOTATATE-PET/CT (SSTR-PET) imaging has improved diagnostic accuracy compared with SRS (OctreoScan).[110,111] For example, Binnebeek et al[112] studied 53 patients with metastatic NETs (8 pNETs) and showed that the sensitivity of PET/CT was 99.9% (95% CI, 99.3–100.0) compared with 60% with SRS with single-photon emission computed tomorgraphy (SPECT; 95% CI, 48.5–70.2); liver and skeletal lesions were the sites most often detected by PET/CT only. Another study reported a 96% sensitivity with ^{68}Ga-DOTATATE imaging (95% CI, 86%–100%) and 72% sensitivity with SRS-SPECT (95% CI, 58%–84%), and 83% with ^{111}In-pentetreotide SPECT/CT scans specifically (95% CI, 64%–94%).[111] Taken together, these studies suggest that pNETs that are truly negative for SSTR expression by functional imaging are rare (eg, <5%). As such, a negative SRS-SPECT scan should be confirmed by SSTR-PET imaging, if possible. In general, ^{68}Ga-DOTATATE/DOTATOC uptake inversely correlates with grade (eg, higher in G1/G2 NET, lower in G3 NEC).[110,112] Thus, a negative SSTR-PET scan should trigger consideration of a pathology review to rule out G3 or ambiguous morphology.

The optimal treatment of SSTR-negative G1/G2 pNETs is uncertain, as these tumors have likely been underrepresented and unrecognized in recent phase III trials in GEPNETs. The CLARINET study required SSTR(+) tumors by SRS-SPECT for enrollment.[76] As such, use of lanreotide in SRS-negative patients has not been well studied. Becausewe know that a significant portion of SRS-negative GEPNETs are positive on SSTR-PET imaging, the more pressing question is the value of SSA in SSTR-PET– negative NETs. A significant majority of panel members agreed that it would be reasonable to treat patients with negative SRS-SPECT with SSAs in cases where SSTR-PET imaging was not available. In such cases, immunohistochemical staining for SSTR2A could be considered. There was not a consensus among panel members on whether patients with NF-pNET and negative SSTR-PET should receive a trial of SSAs.

In short, depending on the tumor biology and the need for shrinkage (vs stability), chemotherapy, liver-directed therapy, everolimus, and/or sunitinib are reasonable options in SSTR-negative pNETs. The value of SSAs for tumor control in SSTR-negative pNETs is less clear. Because of their relatively benign side-effect profile, SSAs can be considered in indolent, low-volume SSTR-negative pNETs; however, the likelihood of efficacy is probably low.

SSAs Versus Targeted Agents

Randomized trials have not been conducted to compare the efficacy of everolimus and sunitinib to one another or to SSAs. Both everolimus and sunitinib have low radiographic response rates in pNETs. However, based on the more favorable toxicity profile of SSAs, consensus was achieved among panelists that SSAs should be considered as a first-line therapy in patients with SSTR-positive pNETs before use of targeted agents. There may be select situations in which upfront therapy with a targeted agent could be considered, for example, everolimus in cases of advanced insulinoma associated with hypoglycemia.[113,114]

Initial Therapy for Patients With Large-Volume and/or Symptomatic Metastatic pNETs

Generally speaking, when choosing therapy for patients with large-volume and/or symptomatic pNETs, health care providers prioritize treatments that have the potential to shrink, and not just stabilize, tumors. There is no one-size-fits-all approach, but chemotherapy and liver-directed therapy are often considered over cytostatic agents (eg, SSA, sunitinib, and everolimus) in fit patients with large-volume or symptomatic nonfunctional tumors upfront, recognizing that the response rate is <10% with cytostatic agents. A significant majority of panel members considered capecitabine with temozolomide (CAPTEM) to be a reasonable initial treatment choice for patients with large-volume and/or symptomatic, metastatic NF-pNETs. In reality, many patients will eventually be treated with all available agents throughout their disease course, with the sequence varying from one individual to the next.[76–78,90]

Intra-arterial hepatic therapy is typically associated with ~50% response rate in treated lesions[115–118] and therefore is a good choice in patients with liver-dominant bulky disease and intact liver function. Similarly, palliative liver resection or ablation can be considered in selected fit patients, assuming the disease biology is known to be favorable, and radiographic findings demonstrate discrete liver metastases, as opposed to diffuse liver involvement.[119,120] In the setting of relatively rapid growth or newly diagnosed patients, upfront resection for bulky liver disease is not typically recommended over intra-arterial or systemic therapy.

In terms of systemic therapies, temozolomide-based chemotherapy is associated with ~30% response rate.[90] Streptozocin-based therapy is approved for use in pNETs but has yielded conflicting results in more recent studies incorporating modern radiographic response criteria. This, coupled with a relatively unfavorable toxicity profile. had led many providers to switch to temozolomide-based chemotherapy.[79,80,87,88] The role of PRRT in pNETs is evolving.[91] Now Food and Drug Administration (FDA)–approved, preliminary studies suggest that it is associated with higher response in pNETs than the <20% response rate observed in midgut NETs.[92,121] The potentially higher response in pNETs is intriguing but needs to be validated in prospective trials. More information is needed to elucidate if specific factors predict for response to one therapy over another in SSTR-PET (+) tumors (eg, location of metastases, % liver involvement, Ki-67 proliferation index, and max standardized uptake value on SSTR-PET).

In thinking about how best to treat patients with large-volume pNETs, an important consideration is how “large volume” is defined. When assessed by cross-sectional imaging, the definition varies between studies, with some using ≥25% and others using 50% or higher for the cutoff. In addition, advances in image analysis are needed to ensure that assessment of liver involvement is routinely performed and reproducible across institutions and imaging modalities (eg, machine learning).

As an example, in the CLARINET study, lanreotide demonstrated similar cytostatic activity in patients with ≤25% and >25% hepatic tumor volume.[76] However, the impact of liver tumor burden was not described in reports outlining the results of the everolimus and sunitinib

phase III trials in pNET.[77,78] Similarly, tumor bulk was not evaluated in a retrospective analysis of predictors of response to capecitabine/temozolomide in pNETs.[89] In contrast, Kouvaraki et al[80] attempted to assess response to streptozocin-based chemotherapy based on extent of liver involvement by tumor. There were no significant differences in patients with >75% liver involvement and ≤75% liver involvement (although the sample size was very small). The prospective, randomized E2211 study (capecitabine/temozolomide vs temozolomide alone) in pNETs may afford an additional opportunity to explore the impact of tumor burden on response to therapy.[90] The value of PRRT is also uncertain in bulky disease. Brabander et al[92] reported on the use of PRRT in 443 GEPNET patients. Patients with "extensive" disease, as defined by SRS uptake, had a worse prognosis, but the relationship between tumor bulk and response to therapy was not expressly assessed.[122]

Considerations for Sequencing of Therapy (SSAs, Everolimus, Sunitinib, Cytotoxics, and PRRT) Including the Effects of Comorbidities/Tumor Characteristics on Selection of Therapy

Given the lack of randomized data comparing active drugs and relative absence of validated predictive markers, treatment sequencing recommendations cannot be based on evidence. Nevertheless, there are certain general principles that can aid in selection of systemic treatment. Somatostatin analogs are highly effective at delaying tumor growth despite low ORRs and are associated with fewer toxicities and risks than other treatment options. They have been studied primarily in patients with relatively low proliferative activity and stable disease. Somatostatin analogs also have an antisecretory effect and can palliate hormonal syndromes such as gastrinoma, glucagonoma, and VIP-secreting tumor (VIPoma) syndrome. Therefore, for most patients with SSTR-positive tumors, an SSA is the first-line treatment of choice, particularly if disease is relatively nonbulky and unaggressive. Moreover, use of an SSA is imperative for control of certain rare hormonal syndromes such as VIPoma or glucagonoma syndrome.

For patients who have high tumor bulk or have tumor-related symptoms where there is a need for tumor shrinkage, treatment options associated with high response rates include cytotoxic chemotherapy, ^{177}Lu-DOTATATE, or liver-directed therapy. Based on results of the Eastern Cooperative Oncology Group 2211 study, capecitabine/temozolomide can be considered a standard-of-care cytotoxic regimen. First-line use of this regimen is particularly appropriate for patients with aggressive, high-volume tumors. Data on the predictive role of O-6-methylguanine-DNA methyltransferase are conflicting, and O-6-methylguanine-DNA methyltransferase testing therefore cannot be recommended routinely at this time to guide decisions on use of capecitabine/ temozolomide.[89,123]

For most patients who progress on first-line SSAs and have relatively unaggressive and/or low-volume metastatic disease, selection of a particular treatment sequence can be difficult and most panel members felt that there were insufficient data to guide sequencing of subsequent therapy following progression on SSAs. Selection of everolimus versus sunitinib can be quite challenging given similar outcomes of phase III studies. Patient comorbidities can sometimes guide treatment choice. For example, sunitinib may be preferred in patients with preexisting diabetes and underlying lung disease, whereas everolimus may be preferred in patients with history of cardiovascular disease, hypertension, or bleeding diathesis. In patients with SSTR-positive tumors, ^{177}Lu-DOTATATE can be considered after progression on SSAs. There was not a consensus on sequencing of therapy and early use of PRRT after progression on SSAs. Most panel members felt there were insufficient data to suggest superiority of PRRT over other systemic therapy options.

For example, although the response rates and median PFS associated with ^{177}Lu-DOTATATE are favorable, randomized data in pNETs are lacking and risk of MDS/leukemia represents a long-term concern. It is also unclear whether prior alkylating agent chemotherapy increases the risk of long-term bone marrow toxicity. Treatment decisions should be made based on thorough discussions of risks versus benefit and guided by patient preference.

In some cases, transformation of low-intermediate-grade tumors to high-grade results in rapid acceleration of disease growth. In such cases, cytotoxic platinum-based regimens such as carboplatin/etoposide, or 5-FU/oxaliplatin (FOLFOX), or other fluoropyrimidine-based regimens (FOLFIRI, FOLFIRINOX) can be considered, particularly if temozolomide-based chemotherapy has already been used. In cases where individual tumors progress aggressively, locoregional treatments may be effective.

Finally, it is unclear to what degree choice of therapy impacts next line of therapy. For example, although data are lacking, it is theoretically possible that radioembolization or other types of hepatic arterial embolization may increase the risk of PRRT-induced liver toxicity later on (and vice versa).[124] Similarly, use of PRRT and/or alkylator-containing chemotherapy regimens may increase the risk of bone marrow toxicity.[92,121,125]

Use of SSATherapy Beyond First-Line Therapy if Used First-Line?

Functional Tumors

Somatostatin analogs remain the foundation for symptom control of functional small bowel NETs and are currently approved by the FDA for carcinoid syndrome symptomatic control. There is, however, minimal evidence supporting the use of SSAs in F-pNETs. There has been considerable clinical speculation on the possible improvement in hormonal secretions of pNETs with SSAs, particularly with VIPomas, and octreotide is FDA approved for treatment of diarrhea in patients with VIPomas.[126] To date, there are no prospective data on the use of SSAs in pNETs for symptom control, although a large single-institution retrospective series of 191 pancreaticoduodenal NETs described symptomatic improvement with the use of SSAs.[127] Given the considerable symptomatic burden hormonal secretion can have on NET patients,[128] SSAs should be considered in patients with F-pNET, both in first line and beyond largely based on clinical experience of high-volume NET clinicians. This should be considered on a case-by-case basis by discussing with patients the lack of evidence and the possible clinical benefits. Issues such as cost, patient convenience, and preference as well as drug toxicity (however minimal) should be considered.

Nonfunctional Tumors

There have been no randomized trials to date to assess the use of SSAs beyond progression in any type of neuroendocrine neoplasms (NENs). As a result, there is little if any evidence supporting the continuation of SSAs beyond progression of disease in non-functional NETs. There was no consensus among panel members regarding the continuation of SSAs beyond progression.

There is conflicting evidence as to the synergy that may exist with the use of SSAs concurrently with everolimus. The RADIANT-1 trial, which was a nonrandomized phase II trial that included separate cohorts of patients receiving everolimus alone or everolimus with a SSAs, showed a 7-month improvement with the concurrent use of SSAs with everolimus as opposed to everolimus alone.[129] When everolimus alone was compared in a randomized study with everolimus given concurrently with pasireotide (COOPERATE-2), there was no advantage in PFS.[130] The ITMO study was an open-labeled phase II trial that examined the use of everolimus with octreotide in a 50-patient cohort that included 14 patients with pNETs with a higher than expected ORR of 18%.[131]

The role of SSAs maintenance therapy after PRRT treatment remains controversial, especially in pNET patients. The approval for ^{177}Lu-DOTATATE recommends continuing SSAs until disease progression or up to 18 months after treatment initiation.[132] A single-institution nonrandomized retrospective study reported a median PFS of 48 months in patients who continued SSAs post-PRRT versus 27 months for PRRT monotherapy (P = 0.012) along with an improvement in OS and ORR.[133]

There was no consensus regarding the continuation of SSAs beyond first line either concurrently with everolimus or after PRRT treatment in patients with NF-pNETs.

Systemic Therapy for Patients With Well-Differentiated G3 pNETs

Somatostatin Analogs

Well-differentiated G3 pNETs are a relatively new diagnostic entity, and optimal treatment is not known. There are minimal data regarding efficacy of SSA in G3 pNETs, as these patients were not included in the CLARINET trial. A small retrospective study of 14 patients with G3 NETs (7 with G3 pNETs) reported a median PFS of 4.5 months, with 3 patients having stable disease of 24 months or more.[134] Somatostatin analogs can be used in G3 pNETs, particularly under certain circumstances (strong expression of SSTRs by imaging or IHC, slow clinical growth, low volume of disease, or patient preference).

Targeted Therapy

There are no prospective trials regarding the use of sunitinib or everolimus in patients with G3 pNETs. There are limited retrospective data suggesting that everolimus and possibly sunitinib can elicit treatment response in this subgroup of patients.[135,136] Although the use of targeted agents can potentially be considered for treatment of G3 NETs, prospective studies are needed to definitively address optimal therapy in this patient population. There was a consensus among panel members that targeted agents should be considered.

Cytotoxic Therapy

Data on the use of cytotoxic therapy in patients with G3 pNETs are limited and entirely retrospective in nature. Higher response to platinum-based chemotherapy regimens has been reported in tumors with higher Ki-67 proliferation indices. In the NORDIC-NEC study, patients with a Ki-67 index <55% had a lower response rate to platinum-based chemotherapy (15% vs 42%) than did patients with Ki-67 index ≥55%, but DCR was

not significantly different, 62% and 66% respectively.[20] Similarly, a retrospective analysis of 45 patients with G3 pNETs reported ORR to platinum agents in 10% of G3 NETs and in 37% of patients with NECs. Disease control rates were 60% and 74%, respectively.[135]

Most G3 NETs have Ki-67 proliferation indices <55%, which has raised the question regarding the role of alkylating-based chemotherapy in this subgroup of patients. In a retrospective study, use of alkylating agents in 12 patients with G3 pNENs resulted in similar 50% response rates in G3 NETs and G3 NECs. The DCRs were 75% and 67%, respectively.[135] A retrospective analysis of 74 pNETs (including 23 G3 pNETs) treated with streptozocin-based, platinum-based, or dacarbazine/ temozolomide regimens found no difference in PFS between the 3 groups. It was concluded that patients with intermediate or highly proliferative well-differentiated pNETs may benefit from 1 of the 3 chemotherapy regimens.[137] A multicenter retrospective study evaluated the role of temozolomide (combined with capecitabine in 92% of cases) in G3 NENs (75% pancreatic primary). The ORR in G3 pNENs was 41%. The time to treatment failure was 5.8 versus 2.1 months for G3 NETs versus NECs, respectively.[138] Other retrospective studies have also suggested that temozolomide-based therapy is effective for G3 pNETs.[139–141]

For clinically aggressive G3 pNETs, there was agreement among panel members (75%) that the combination of capecitabine and temozolomide (CAPTEM) was a reasonable first-line therapy. For patients with clinically aggressive disease, especially if the disease burden is high, and/or if the tumor is more avid on fluorodeoxyglucose PET than on SSTR-PET, platinum/etoposide is also an option but it is more likely to result in increased patient morbidity than CAPTEM. A randomized phase II trial evaluating first-line platinum/etoposide versus capecitabine/temozolomide in high-grade GEP NENs is ongoing (NCT02595424). Anecdotal evidence and data from retrospective studies also suggest the efficacy of colorectal cancer-like chemotherapy regimens such as FOLFOX or FOLFIRI.[142–144]

Peptide Receptor Radionuclide Therapy

There is limited literature to suggest that ^{177}Lu-DOTATATE PRRT is an effective treatment in G3 pNETs.[94,145–149] Peptide receptor radionuclide therapy cannot be recommended as a first-line therapy. Peptide receptor radionuclide therapy can be used in select patients with positive SSTR-PETwho progress at a slow pace after treatment with SSAs. Most panel members felt that there were inconclusive data to provide treatment recommendations regarding use of PRRT in G3 pNETs. If PRRT is considered for G3 NETs, SSTR-PET should be used to select patients who have SSTR positive disease. The role of concurrent radiosensitizing chemotherapy is not well understood. There is significant concern for the development of marrow toxicity, and the use of radiosensitizing concomitant chemotherapy is not recommended outside a clinical trial.

Therapy of PD-NECs

Choice of Chemotherapy and the Role of SSAs and Targeted Therapy

Cytotoxic chemotherapy is standard therapy for patients with newly diagnosed extrapulmonary NECs. Treatment selection has historically been based on evidence derived from the small cell lung cancer literature given histologic similarities between pulmonary and extrapulmonary tumors, although they are, in fact, different disease entities. In addition to small cell lung cancer trials, there are small prospective and retrospective studies that have identified cisplatin or carboplatin in combination with etoposide as the standard in the first-line setting.[150–152] There was a consensus that platinum and etoposide chemotherapy was an acceptable first-line option. Irinotecan as an alternative to etoposide is also acceptable.[153,154] In the second-line setting, many chemotherapy options have been explored including fluoropyrimidine/platinum combinations (FOLFOX, capecitabine, and oxaliplatin), as well as irinotecan-, temozolomide-, gemcitabine-, and taxane-based regimens, but the data regarding efficacy are extremely limited.[138,139,142,155–162] Most panel members agreed there were insufficient data to support any particular second-line systemic therapy option. A recent retrospective study evaluated the efficacy of second-line cytotoxic chemotherapy for NEC arising at various anatomic sites and reported a disappointingly short PFS of only 2.3 months with no significant difference among different cytotoxic agents.[162] Temozolomide-based regimens should be largely reserved for patients with G3 NETs but would be a reasonable consideration for a pancreatic primary NEC in the second-line setting.

The use of SSAs in NECs has been minimally evaluated and has generally been in combination with cytotoxic chemotherapy. Given the apparent lack of efficacy seen with SSAs in this population, their use is not recommended.[163,164] Targeted therapies, such as everolimus or sunitinib, are also not thought to benefit patients with NECs. A recent small phase II trial reported lack of efficacy of everolimus in pNECs with a very short median PFS of

only 1.2 months.[165] Only small studies and case reports have been reported, and there is a lack of sufficient evidence to demonstrate benefit for patients with PD-NECs.[166–168]

Immunotherapy is being investigated in NECs. Single-agent PD-1/PD-L1 immune checkpoint inhibitor therapy does not seem to provide meaningful treatment benefit,[169,170] and alternative regimens assessing the combination with cytotoxic chemotherapy or dual immune checkpoint blockade remain under investigation.[171] Despite recent advances in small cell lung cancer, in which checkpoint inhibition in combination with cytotoxic chemotherapy has shown some benefit,[172] at this time immunotherapy for pNEC is recommended only in the context of a clinical trial.

Management of Patients With Advanced F-pNETS

Insulin and/or Proinsulin Secreting pNETs (Malignant Insulinoma)

Patients presenting with hypoglycemia from malignant insulinoma are often symptomatic and in urgent need of symptom control. This can be accomplished in 2 complimentary ways: (1) reducing hormone levels by reducing tumor bulk and (2) controlling the hypoglycemia.[173–175] Strategies to decrease tumor bulk are often prioritized in the setting of functional insulinoma, such as resection, liver-directed therapy (50% response rate), and chemotherapy (30% response rate).[80,89,90,115–120] Peptide receptor radionuclide therapy with agents like ^{177}Lu-DOTATATE is associated with major shrinkage in a subset of cases.[92,121] Although shrinkage is by no means guaranteed, there are reports of symptomatic improvement in hypoglycemic patients with insulinoma after 1 cycle of therapy.[176]

Acutely, however, patients should be counseled regarding the symptoms of hypoglycemia and potential precipitating factors (such as exercise and/or prolonged periods between meals).[173–175] A medic alert bracelet is recommended. Frequent glucose monitoring is helpful, as are carbohydrate-rich meals and supplemental cornstarch (every 3 hours around the clock). Diazoxide (200–600 mg/d) controls hypoglycemia in 50% to 60% of patients and works by inhibiting calcium-mediated insulin release. Somatostatin analogs improve hypoglycemia in approximately 50% of patients. However, there is a risk of paradoxical hypoglycemia, so their use should be restricted to SSTR-positive tumors. Some believe a trial subcutaneous octreotide may be a better indicator of the safety of SSA than either SRS or SSTR2/SSTR5 IHC.[177] Of note, although not routinely used, pasireotide may prove to be the optimal SSA in the setting of insulinoma given its relatively high affinity for SSTR3 and SSTR5, and the fact its use is associated with more hyperglycemia than other SSAs.[178] Other treatment options include glucagon injections and corticosteroids.

Several reports have provided evidence that everolimus can reverse the symptoms caused by insulin excess, in addition to being cytostatic.[114,174,179] Hyperglycemia is a known adverse effect of everolimus, resulting from its effects on gluconeogenesis and downstream signaling through the insulin/insulin-like growth factor 1 receptor. In one report, 11 of 12 patients experienced an immediate improvement in blood sugars and a reduction in the need for other medications for hypoglycemia within 2 weeks.[180] Importantly, symptom control can last longer than tumor control, so consideration should be given to continuing everolimus beyond disease progression or rechallenging at the time of disease recurrence if control of hypoglycemia is necessary.[179] Future investigations will hopefully clarify the role of SSA (including pasireotide) in treating hypoglycemia from insulinoma, as well as the safety of combining everolimus (for symptom control) with other treatment modalities (for tumor control). At least one study suggests that everolimus can be safely combined with temozolomide.[181] Everolimus combined with ^{177}Lu-DOTATATE (NCT03629847) and everolimus plus liver-directed therapy (NCT01469572) are also under study.

Gastrin Secreting pNETs (Gastrinoma, Zollinger Ellison Syndrome)

Syndromic control of patients with advanced gastrinoma requires twice daily PPI therapy. Oral control of acid output is possible with H2 receptor antagonists, but PPIs are superior (no tachyphylaxis, no need for yearly dose up-titration, less frequent dosing).[182–188] Traditionally, PPIs were started using upward dose titration to acutely control acid output, but this is not routinely done.[189] Moreover, subsequent studies have shown that doses can be reduced with time and maintained for many years without tachyphylaxis and that lower starting doses can be safely used.[183,184,190,191] However, acute loss of control of acid output can be devastating, and twice-daily therapy is recommended to protect against acute absorption problems.[189] Zollinger-Ellison syndrome (ZES) patients who also have MEN-1,[192] gastroesophageal reflux disorder,[193] or prior partial gastric resection[194] are often difficult to control and also require higher doses of PPI twice daily for acid suppression. A medic alert bracelet is recommended.[189] Intravenous control of acid output during periods when patients are fasting is possible with H2 receptor antagonists and PPIs, but PPIs are superior.[195–199] Acid hypersecretion may not completely normalize after successful tumor

resection, and maintenance low-dose acid suppression is often required long term.[200] Before starting maintenance PPI for any indication, physicians should consider the possibility of ZES, as PPI therapy confounds the workup of this condition.[189]

Other Hormone-Secreting pNETs (Vipoma, Glucagonoma, Somatostatinoma, Ectopic ACTH, or PTHrP-Secreting pNETs)

Well before the recognition of the 5 SSTR subtypes and the predominance of SSTR2 overexpression in 90% of NETs, octreotide was approved by the FDA for the secretory diarrhea of carcinoid syndrome and VIP-secretory NETs. Octreotide and lanreotide, now recognized to be predominantly active on SSRT2, are effective at treating glucagonoma syndrome. There are no studies examining the effects of SSA on ACTH-secreting, corticotropin-releasing hormone-secreting, or PTHrP-secreting pNETs. Bilateral adrenalectomy can be considered in the setting of refractory Cushing syndrome from ACTH-secreting tumors. Finding and resecting the tumors seem to be the best way to help lower cortisol and calcium, respectively in these rare F-pNETs.

Peptide Receptor Radionuclide Therapy

PRRT for the Management of Patients With Advanced pNETs

Peptide receptor radionuclide therapy with ^{177}LuDOTATATE, 7.4 GBq per cycle over 4 cycles, is FDA approved for the treatment of SSTR-positive GEP-NETs. The phase III randomized controlled trial of ^{177}Lu-DOTATATE (NETTER-1) was conducted in patients with midgut NETs and reported a significantly better ORR of 18% versus 3% for the control arm (60 mg monthly injection of octreotide) and an estimated PFS of 65.2% at 20 months in the ^{177}Lu-DOTATATE group versus 10.8% in the control group.[121] There are to date no controlled randomized phase III trials of PRRT in pNETs; available data consist of multiple single-arm prospective and retrospective trials, summarized in a recent review article.[91]

In a prospective phase II trial by Sansovini et al,[201] 60 patients with progressive pNETs were treated with 18.5 to 25.9 GBq of ^{177}Lu-DOTATATE for up to 5 treatment cycles. The DCR in this group of progressive pNET patients was 81.7%, with 6.6% achieving complete response, 23.3% PR, and 51.7% stable disease, whereas 18.3% experienced progressive disease. The median PFS was 28.7 months, and median OS was not reached at a median follow-up of 59 months. Similar response rates were also reported by Garske-Roman et al[95] in a prospective study of 49 pNET patients (among 200 NET patients), with pancreaticoduodenal NETs achieving a PR rate of 42.9% and a complete response rate of 2%, while stable disease in 49%. ^{177}Lu-DOTATATE PRRT is generally well tolerated with up to 10% of patients developing G3/4 hematological toxicity, 77% of which normalizes within 3 months. Significant nephrotoxicity with standard administered activities of ^{177}LuDOTATATE is very rare (<1%) with coinfusion of cationic amino acids for renal protection and is significantly less common than previously reported with ^{90}Y-DOTATOC.[92,121,202]

In summary, multiple single-arm studies suggest PRRT with ^{177}Lu-DOTATATE to be an effective treatment modality for unresectable or metastatic pNETs. It is one of the systemic therapy options in addition to SSAs, everolimus, sunitinib, and cytotoxic chemotherapy in this setting. Currently, there are no data to guide sequencing of the systemic therapy options because of lack of randomized trials, although PRRT is generally considered in patients who have progressed on SSAs.[91,203]

Liver-Directed Therapy and Other Locoregional Therapy

Pancreatic NET therapy uses a multimodality approach, often including surgical treatment, liver-directed therapies (ie, embolization), and targeted and cytotoxic systemic treatments. There are no randomized trials to help guide the sequencing of different therapies. In addition to locoregional lymph node metastases, liver metastases are a common feature in the relatively slow-paced natural history of NETs, and progression of liver metastases is the predominant cause of mortality in these patients. For that reason, systemic and regional approaches including hepatic resection, radiofrequency or microwave ablation, and hepatic arterial embolization are often used to control tumor burden.

The Choice of Embolization Therapy for Patients With Liver-Dominant Disease Not Amenable for Resection

Over the last 2 decades, embolotherapy has been a mainstay of treatment of NET metastases isolated to the liver. Response rates have ranged from 40% to 70% by size and necrosis criteria, and the DCR has been very high.[116,204] Until recently, conventional chemoembolization (cTACE) and bland embolization represented the dominant forms of embolotherapy. Two publications on the early experience of drug-eluting beads, DEB-TACE in NETs, demonstrated an unacceptably high rate of bilomas/abscesses, resulting in many centers resorting back to non-DEB-TACE techniques.[205] Recently, in a prospective randomized trial comparing cTACE, bland embolization, and DEB-TACE, concerns of hepatic toxicities with DEB-TACE were confirmed, and this arm has been closed to further accrual. Transarterial radioembolization (TARE)

is the other form of arterial therapy that has garnered significant interest, with its outpatient advantage and similarly high response rate. Although there have been some concerns over long-term toxicities, these mostly originate from centers that have infused supratherapeutic doses above the recommended package label. Most patients treated with TARE have progressed on other forms of treatment, and their median survival is 3 years.[206] In those isolated patients who survive beyond the 4-year mark, a form of pseudocirrhosis can occur that is often not associated with clinical symptoms.[207] In all, the mainstay embolotherapies to date include bland embolization, cTACE and ^{90}Y-TARE, with no recommendation of one over another. DEB-TACE is not recommended. Treatment should be staged in a lobar/sublobar level, limiting normal parenchyma from the effect of embolotherapy. In terms of tumor burden, there was no consensus on maximum percentage that would preclude treatment with embolotherapy or resection. Liver function tests (bilirubin, albumin) were favored to guide therapy choice. High tumor burden with resectable disease should be considered for resection. If not resectable, embolization should be considered.

PRRT and Radioembolization

There has been significant interest in PRRT given contemporary level I evidence. The availability of this treatment option in a pool of patients who may have already been treated with ^{90}Y-TARE calls into question potential radiation toxicities. One study from Germany in 2012 demonstrated no additive toxicity in combining ^{90}Y-TARE to patients after PRRT.[208] Similarly, a Dutch group demonstrated in 2018 that the combination was feasible and safe.[209] Although there is rationale for using PRRT in patients with more widespread metastatic disease and ^{90}Y-TARE in those with liver-only disease, the presence of level I evidence combined with enthusiasm for PRRT has increasingly led to more patients, with liver-only disease being treated with PRRT. Most panel members felt that TARE should be avoided and other embolization methods considered after PRRT or if PRRT was expected to be used in the future. Larger-scale analyses of the combined effects will need to be studied. In patients with bulky liver disease with or without extrahepatic metastases, embolotherapy is recommended.

Impact of Prior Resection (Whipple Procedure) and Portal Vein Occlusion on the Choice of Embolization Therapy

In patients having undergone a prior Whipple procedure or with a stented ampulla, the choice of embolotherapy becomes more nuanced. Although modern antibiotics have lowered the rate abscess formation, this complication still occurs. Because cTACE and bland embolization occlude the vessels at the macroscopic level, there has been interest in ^{90}Y-TARE in this scenario, where microembolization represents the primary mode of action. Indeed, retrospective analyses have shown that, although infections still occur, they are much less common with ^{90}Y-TARE.[210,211] Hence, in patients with violated ampullas, antibiotics before and after procedure combined with ^{90}Y-TARE are recommended to minimize the risk of infection.

Considerations for Using Liver-Directed Therapy Versus Systemic Agents in Patients With Unresectable, Liver-Predominant Disease

As noted previously, there are no prospective, randomized trials comparing the clinical efficacy of these embolization methods, despite apparent substantial differences in potential toxicity and cost. Therefore, there is no evidence to guide the selection of optimal arterial therapy for progressive, unresectable NET liver metastases. Patient selection is important to minimize treatment-related adverse effects, which can include pain, nausea, fever, fatigue, and liver abnormalities. Prophylaxis with SSAs in patients with functional tumors is also important.

In addition, there are no data or trials comparing systemic treatment options to liver-directed approaches. A Cochrane review attempted to compare regional versus systemic therapies and concluded that the absence of randomized and robust data made it impossible to attempt the analysis.[212,213] Valle et al[214] also attempted to compare targeted systemic and liver-directed therapies and also found too much variation between the studies meeting the initial eligibility criteria to complete the analysis.

In general, systemic treatment options should be considered in patients with >50% to 75% hepatic tumor burden.[215,216] Tumor histology, comorbid conditions, and objectives of treatment should be considered to optimize the treatment algorithm. For example, high tumor burden and/or higher-grade tumors may benefit from an antiproliferative systemic treatment such as cytotoxic chemotherapy. As noted, any patient who has undergone a Whipple should be considered for systemic therapy before regional approaches because of the small but serious risk of abscesses and liver infections. In a patient with mild to moderate disease burden and hepatic progression of disease on SSA, regional therapy with embolization should be considered. In low-grade tumors and/or low-volume liver disease, watchful waiting, SSA, or targeted therapies are recommended. Lastly, in patients with symptomatic

disease such as refractory hormone-related symptoms, embolization should be considered for quicker resolution of symptoms.

What Is the Role of External Beam Radiation Therapy in the Management of pNETs?

There are limited data regarding the efficacy of external beam radiation therapy for pNETs.[217] The situations in which radiation therapy has been evaluated include treatment of locally advanced disease, adjuvant therapy after primary tumor resection, and palliative therapy in patients with metastatic disease. Retrospective studies evaluating the role of chemoradiation therapy in patients with locally advanced, unresectable pNET have demonstrated reduction in tumor size and conversion to resectable disease in some patients.[218,219] However, these studies are limited by small numbers of patients evaluated. In addition, other options, including temozolomide- and streptozocin-based chemotherapy and PRRT, can achieve radiographic responses and are supported by more robust data. In the adjuvant setting, retrospective, nonrandomized studies have demonstrated similar or higher rates of local control in patients who have received radiation or chemoradiation for resected disease with high-risk features compared with patients undergoing surgery alone.[220,221] Interpretation of these studies is limited by baseline differences in patient groups, potential selection bias, and small numbers. Therefore, data do not support the routine use of radiation with or without chemotherapy in the adjuvant setting after surgical therapy. In contrast, radiation can be considered as a palliative treatment and can achieve symptom improvement, particularly in patients with bone metastases.[222]

Surveillance

Role of Imaging and Visits in Restaging Patients With Metastatic Disease

A baseline SSTR-PET should be considered to fully stage metastatic disease and assess for SSTR expression; however, SSTR-PET should not be used routinely for surveillance. Exceptions include restaging of patients if there is concern for clinical progression without obvious disease growth on conventional imaging, further evaluation of a new indeterminate lesion, or dominance of lesions that cannot be clearly seen on cross-sectional imaging (eg, bone and peritoneal).[110] A SSTR-PET at initial staging should be used to select the imaging modality used for future follow-up over time. In all circumstances, SSTR-PET is preferred to SRS-SPECT for imaging of pNETs. There was no consensus regarding preference for computed tomography (CT) or magnetic resonance imaging scan for surveillance of disease after resection of metastatic disease. The choice of imaging modality should take into account both tumor and patient characteristics. In patients with liver dominant disease, a hepatobiliary phase magnetic resonance imaging should be considered. In those with nodal dominant disease, contrast-enhanced CT should be used. In patients with bone dominant disease, there are insufficient data to recommend routine use of SSTR-PET for follow-up, but most panel members thought it was a reasonable option, especially if the metastases were difficult to visualize with other imaging modalities. It is important to remember that consistent imaging modalities should be used over time to provide reliable lesion comparison.[223]

The frequency of clinic visits depends on the treatment given, symptoms, tumor burden, and patient preference. Asymptomatic or minimally symptomatic patients with stable metastatic disease on SSA therapy should be seen every 3 to 6 months with imaging with efforts to minimize unnecessary scanning and radiation exposure. Less frequent imaging should be considered in patients with stable disease over time. Patients on cytotoxic chemotherapy and targeted systemic therapy should be seen roughly monthly with a clinical examination and laboratories to evaluate for toxicities, and with imaging every 2 to 3 months. Patients undergoing PRRT should be seen at the time of each treatment with clinical and laboratory evaluation. A contrast-enhanced cross-sectional imaging can be considered before cycle 3 in aggressive tumors or in cases of worsening symptoms and/or worsening laboratory abnormalities, but imaging is not routinely recommended. After PRRT, we recommend imaging within 3 months after the last treatment and again at 6 months and 12 months with further imaging as needed in keeping with the NANETS/Society of Nuclear Medicine and Molecular Imaging Procedure Guidelines for PRRT.[224] A change in the clinical behavior of the malignancy or symptoms may call for more frequent imaging.

Role of Imaging and Visits in Surveillance of pNETs After Resection

Although there was no consensus among panelists regarding the preferred modality for the evaluation of local recurrence, a majority preferred contrast-enhanced CT of the abdomen and pelvis. Imaging of the chest is not recommended in the routine surveillance of patients with pNETs. Somatostatin receptor PET is not indicated for the surveillance of pNETs, but should be used when there is clinical concern for disease progression not observed on

cross-sectional imaging.[110] Magnetic resonance imaging should not be routinely used in surveillance of patients without a history of hepatic metastases, with multiphasic CT preferred.

No consensus was reached regarding the minimal duration of follow-up for patients with resected pNETs (node-negative or node positive) without liver metastases. Fifty percent of panelists felt that patients with resected pNETs should undergo surveillance for at least 10 years as late recurrences can occur. Surveillance imaging may be continued beyond 10 years in select cases, as recurrences beyond 10 years have been reported.[4,225]

Patients with NF-pNETs measuring >2 cm, or tumors <2 cm with positive nodes, should be imaged 3 to 6 months after initial surgical resection (baseline postoperative imaging). The optimal frequency of imaging after resection of primary tumor without metastases is unclear. The recently published Commonwealth Neuroendocrine Tumour research collaborative and NANETS guidelines recommend imaging 12 months after resection and every 12 to 24 months thereafter for 10 years.[225,226] There was not consensus regarding the frequency of imaging after resection among panelists, but a majority recommended imaging every 6 months for 2 years and then annually thereafter, and 25% recommended annual imaging.

There was not a consensus regarding follow-up schedules for patients with resected NF-pNETs less than 2 cm in diameter and without involved lymph nodes. The appropriate imaging duration remains unknown, and there was not a consensus regarding the duration of follow-up (most panelists felt the follow-up should be the same as for larger tumors).

Patients in specific clinical subgroups considered to be at higher risk of recurrence, such as patients with tumors with Ki-67 proliferative index greater than 5%, may need more frequent surveillance, at least initially after surgery. The Commonwealth Neuroendocrine Tumour research collaborative/NANETS guidelines for surveillance suggest imaging every 6 to 12 months for 3 years and then every 1 to 2 years for at least 10 years in patients with Ki-67 >5% and/or patients with positive lymph nodes.[225]

More frequent imaging may be indicated after complete resection of metastatic pNETs. There was no consensus regarding the frequency of imaging studies after resection of metastases. A reasonable imaging schedule would be every 3 to 6 months for the first 2 years after resection and then annually thereafter for at least 10 years.

A significant majority recommended against routine use of biomarkers for surveillance in patients with NF-pNETs. For functional tumors after resection, the frequency of imaging should be adjusted based on serum markers and/or evidence of symptomatic recurrence. In the absence of serum or symptom evidence of recurrence, imaging can performed approximately yearly for up to 10 years. Serial monitoring of the relevant hormone may be useful in surveillance, but nonspecific markers such as CgA are not recommended. Patients with resected insulinomas have a low risk of recurrence, and symptoms are likely to be the first sign of recurrent disease. There was not a consensus regarding the need for imaging after resection of insulinomas (50% in favor of routine surveillance imaging, 50% against). Clinic visits should correspond to the time of imaging with no additional visits recommended because the likelihood of finding a recurrence at a routine visit without imaging is exceedingly low.

Discussion

The annual incidence of pNETs has increased in recent decades, and patients are increasingly diagnosed at earlier stages, possibly reflecting increased use of imaging studies. Many patients are still diagnosed with advanced disease, and many will relapse with metastatic disease requiring therapy. Substantial advances have been made in terms of diagnosis and therapy of NETs in general, but most prospective clinical trials have not specifically focused on pNETs. Longer survival of patients with advanced/metastatic pNETs has been increasingly observed, suggesting improved efficacy of therapy. Unfortunately, high-level evidence is still lacking for most interventions and follow-up. Therefore, there remains considerable debate on many topics, especially regarding sequencing of systemic therapy and surveillance. Given the limitations of the data as well as the heterogeneity of this patient population, optimal management is best determined in the context of multidisciplinary care, including NET-specific tumor boards.

TABLES

Table 1: 2019 WHO Classification of GEP Neuroendocrine Epithelial Neoplasms

Classification/Grade	Ki-67 Proliferation Index,%	Mitotic Count, Per 2 mm^2
Well-differentiated NET		
G1	<3	<2
G2	3–20	2–20
G2	>20	>20
PD-NEC		
G3 (small cell or large cell type)	>20	>20

Table 2: Required and Recommended Reporting Elements for Biopsies and Resections of Pancreatic Neuroendocrine Epithelial Neoplasms

Data Element	Associated Required or Recommended IHC
Required data element	
Diagnosis: well-differentiated NET or PD-NEC (specify small cell or large cell variant if possible)	• Synaptophysin and CgA to establish neuroendocrine nature (required) • Broad-spectrum keratin to confirm epithelial nature (highly recommended in primary and regional disease and required in distant metastasis) • p53, Rb, ATRX, and DAXX are recommended in the distinction of well-differentiated NET G3 from PD-NEC
Ki-67 proliferation index (proliferation index >20% is implied for high grade NEN either well-differentiated NET G3 or a PD-NEC; for known PD-NEC performance is not mandatory)	• Ki-67 on at least one block of tumor (required) • Ki-67 on at least one block of tumor and matched distant metastasis (recommended)
Mitotic count per 10 HPF (in biopsies with <50 HPF to assess, it is reasonable to express the total number of mitotic figures in the total number of microscopic fields; for PD-NEC a mitotic count performance is not mandatory)	
Grade: G1, G2, or G3 for well-differentiated NET (grade for PD-NEC need not be explicitly stated)	
Data elements in CAP Cancer Protocol: for resection specimens	
Recommend data element	
Comment on site of origin (for metastasis of occult origin)	• IHC panel in awell-differentiated NETmay include some combination of polyclonal PAX8, PAX6, PR, islet 1, ATRX, and DAXX for pancreatic origin; CDX2 for midgut origin; TTF-1 (or OTP) for bronchopulmonary origin; and SATB2 for rectal origin • Panel in a PD-NEC may include TTF-1 for visceral origin of small cell carcinoma and CK20 and polyomavirus for cutaneous origin (Merkel cell carcinoma); SMAD4 inactivation suggests a pancreatic origin

Table 3: Types of F-pNETs

Tumor	Hormone	Clinical Syndrome	Laboratories to Evaluate
Insulinoma	Insulin or proinsulin	Hypoglycemia symptoms (especially at night and when fasting and including sweating, shaking, confusion)	Glucose, insulin, proinsulin, C-peptide
Gastrinoma	Gastrin	ZES (severe gastrointestinal reflux; pain, diarrhea, esophageal symptoms)	Gastrin and gastric pH by endoscopy
VIPoma	VIP	Profuse watery diarrhea with hypokalemia	VIP and BMP
Glucagonoma	Glucagon	Glucose intolerance (diabetes mellitus, hyperglycemia), rash, weight loss	Glucagon, HbA_{1c}
Somatostatinoma	Somatostatin	Diabetes mellitus, hyperglycemia, cholelithiasis, diarrhea	Somatostatin, HbA_{1c}
ACTHoma	ACTH (or rarely CRH)	Cushing syndrome	ACTH, cortisol, 1 mg dexamethasone suppression test, 24-h urinary free cortisol, midnight salivary cortisol
GRHoma	Growth hormone–releasing hormone	Acromegaly	IGF1
PTHrPoma	PTHrP	Hypercalcemia	PTHrP, PTH, calcium, albumin, 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D
Other	Serotonin, calcitonin Any hormone	Diarrhea, flushing Symptoms related to hormone production	

BMP, basic metabolic profile; CRH, corticotrophin-releasing hormone; $HbA1^c$, glycated hemoglobin; IGF1, insulin-like growth factor 1.

REFERENCES

References

1. Chan CS, Laddha SV, Lewis PW, et al. ATRX, DAXX or MEN1 mutant pancreatic neuroendocrine tumors are a distinct alpha-cell signature subgroup. *Nat Commun*. 2018;9:4158.
2. Jensen RT, Bodei L, Capdevila J, et al. Unmet needs in functional and nonfunctional pancreatic neuroendocrine neoplasms. *Neuroendocrinology*. 2019;108:26–36.
3. Sonbol MB, Mazza GL, Starr JS, et al. Incidence and survival patterns of pancreatic neuroendocrine tumors over the last two decades: a SEER database analysis. *J Clin Oncol*. 2020;38(Suppl 4):abstr 629.
4. Singh S, Chan DL, Moody L, et al. Recurrence in resected gastroenteropancreatic neuroendocrine tumors. *JAMA Oncol*. 2018;4: 583–585.
5. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical management of midgut neuroendocrine tumors. *Pancreas*. 2017; 46:707–714.
6. Howe JR, Cardona K, Fraker DL, et al. The surgical management of small bowel neuroendocrine tumors: consensus guidelines of the North American Neuroendocrine Tumor Society. *Pancreas*. 2017;46:715–731.
7. Howe JR, Merchant NB, Conrad C, et al. The North American Neuroendocrine Tumor Society consensus paper on the surgical management of pancreatic neuroendocrine tumors. *Pancreas*. 2020;49: 1–33.
8. Klimstra DS, Klöppel G, La Rosa S, et al. Classification of neuroendocrine neoplasms of the digestive system. In: *WHO Classification of Tumours Editorial Board. Digestive System Tumours*. 5th ed. Lyon, France: International Agency for Research on Cancer; 2019:16–19.
9. College of American Pathologists: protocol for the examination of specimens from patients with tumors of the endocrine pancreas, version: PancreasEndocrine 4.0.0.1. June 2017. Available at: https://documents. cap.org/protocols/cp-pancreas-endocrine-17protocol-4001.pdf. Accessed May 6, 2020.
10. Bellizzi AM. Pathologic considerations in gastroenteropancreatic neuroendocrine tumors. *Surg Oncol Clin N Am*. 2020;29:185–208.
11. Bellizzi AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can Brown do for you? *Hum Pathol*. 2020;96:8–33.
12. Tanigawa M, Nakayama M, Taira T, et al. Insulinoma-associated protein 1 (INSM1) is a useful marker for pancreatic neuroendocrine tumor. *Med Mol Morphol*. 2018;51:32–40.
13. Bordi C, Pilato FP, D'Adda T. Comparative study of seven neuroendocrine markers in pancreatic endocrine tumours. *Virchows Arch A Pathol Anat Histopathol*. 1988;413:387–398.
14. Rosenbaum JN, Guo Z, Baus RM, et al. INSM1: a novel Immunohistochemical and molecular marker for neuroendocrine and neuroepithelial neoplasms. *Am J Clin Pathol*. 2015;144:579–591.
15. Kim D, Viswanathan K, Goyal A, et al. Insulinoma-associated protein 1 (INSM1) is a robust marker for identifying and grading pancreatic neuroendocrine tumors. *Cancer Cytopathol*. 2020;128:269–277.
16. Bellizzi AM. Assigning site of origin in metastatic neuroendocrine neoplasms: a clinically significant application of diagnostic immunohistochemistry. *Adv Anat Pathol*. 2013;20:285–314.
17. Klöppel G, Couvelard A, Hruban RH, et al. Neoplasms of the neuroendocrine pancreas: Introduction. In: Lloyd RV, Osamura RY, Klöppel G, et al, eds. *WHO Classification of Tumours of Endocrine Organs*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2017:211–214.
18. Tang LH, Gonen M, Hedvat C, et al. Objective quantification of the Ki67 proliferative index in neuroendocrine tumors of the gastroenteropancreatic system: a comparison of digital image analysis with manual methods. *Am J Surg Pathol*. 2012;36:1761–1770.
19. McCall CM, Shi C, Cornish TC, et al. Grading of well-differentiated pancreatic neuroendocrine tumors is improved by the inclusion of both Ki67 proliferative index and mitotic rate. *Am J Surg Pathol*. 2013;37: 1671–1677.
20. 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;24:152–160.

21. Keck KJ, Choi A, Maxwell JE, et al. Increased grade in neuroendocrine tumor metastases negatively impacts survival. *Ann Surg Oncol*. 2017;24: 2206–2212.
22. Tang LH, Basturk O, Sue JJ, et al. A practical approach to the classification of WHO grade 3 (G3) well-differentiated neuroendocrine tumor (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC) of the pancreas. *Am J Surg Pathol*. 2016;40:1192–1202.
23. Klöppel G, Adsay NV, Couvelard A, et al. Pancreatic neuroendocrine neoplasms: introduction. In: Klimstra DS, Klöppel G, Rosa S, et al, eds. *Classification of Neuroendocrine Neoplasms of the Digestive System, WHO Classification of Tumours. Digestive System Tumours*. 5th ed. Lyon, France: International Agency for Research on Cancer; 2019: 343–346.
24. Konukiewitz B, Schlitter AM, Jesinghaus M, et al. Somatostatin receptor expression related to TP53 and RB1 alterations in pancreatic and extrapancreatic neuroendocrine neoplasms with a Ki67-index above 20. *Mod Pathol*. 2017;30:587–598.
25. Kuiper P, Verspaget HW, van Slooten HJ, et al. Pathological incidence of duodenopancreatic neuroendocrine tumors in the Netherlands: a Pathologisch Anatomisch Landelijk Geautomatiseerd Archief study. *Pancreas*. 2010;39:1134–1139.
26. Ito T, Igarashi H, Nakamura K, et al. Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. *J Gastroenterol*. 2015;50:58–64.
27. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab*. 2012;97:2990–3011.
28. Wasserman JD, Tomlinson GE, Druker H, et al. Multiple endocrine neoplasia and hyperparathyroid-jaw tumor syndromes: clinical features, genetics, and surveillance recommendations in childhood. *Clin Cancer Res*. 2017;23:e123–e132.
29. Wamsteker EJ, Gauger PG, Thompson NW, et al. EUS detection of pancreatic endocrine tumors in asymptomatic patients with type 1 multiple endocrine neoplasia. *Gastrointest Endosc*. 2003;58:531–535.
30. Cassol C, Mete O. Endocrine manifestations of von Hippel-Lindau disease. *Arch Pathol Lab Med*. 2015;139:263–268.
31. What You Need to Know About VHL. *The VHL Handbook*. 5th ed. Boston, MA: VHL Alliance; 2015.
32. Rednam SP, Erez A, Druker H, et al. Von Hippel-Lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetics, and surveillance recommendations in childhood. *Clin Cancer Res*. 2017;23:e68–e75.
33. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J Med Genet*. 2007; 44:81–88.
34. DiMario FJ Jr, Sahin M, Ebrahimi-Fakhari D. Tuberous sclerosis complex. *Pediatr Clin North Am*. 2015;62:633–648.
35. Hampel H, Bennett RL, Buchanan A, et al; Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med*. 2015;17:70–87.
36. Scarpa A, Chang DK, Nones K, et al. Whole-genome landscape of pancreatic neuroendocrine tumours. *Nature*. 2017;543:65–71.
37. Vinik A, Perry RR, Hughes MS, et al. Multiple endocrine neoplasia type 1. In: Feingold KR, Anawalt B, Boyce A, et al, eds. *Endotext*. South Dartmouth, MA: MDText.com, Inc.; 2000.
38. Giusti F, Marini F, Brandi ML. Multiple endocrine neoplasia type 1. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*. Seattle, WA: University of Washington, Seattle;1993 (updated 2017); 2020.
39. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas*. 2013;42:557–577.
40. Modlin IM, Oberg K, Taylor A, et al. Neuroendocrine tumor biomarkers: current status and perspectives. *Neuroendocrinology*. 2014;100:265–277.
41. de Laat JM, Pieterman CR, Weijmans M, et al. Low accuracy of tumor markers for diagnosing pancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1 patients. *J Clin Endocrinol Metab*. 2013;98: 4143–4151.
42. 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;85:400–407.
43. Sigal DS, Bhangoo MS, Hermel JA, et al. Comprehensive genomic profiling identifies novel NTRK fusions in neuroendocrine tumors. *Oncotarget*. 2018;9:35809–35812.
44. Sigal D, Tartar M, Xavier M, et al. Activity of entrectinib in a patient with the first reported NTRK fusion in neuroendocrine cancer. *J Natl Compr Canc Netw*. 2017;15:1317–1322.

45. Asnacios A, Courbon F, Rochaix P, et al. Indium-111-pentetreotide scintigraphy and somatostatin receptor subtype 2 expression: new prognostic factors for malignant well-differentiated endocrine tumors. *J Clin Oncol*. 2008;26:963–970.
46. Sclafani F, Carnaghi C, Di Tommaso L, et al. Detection of somatostatin receptor subtypes 2 and 5 by somatostatin receptor scintigraphy and immunohistochemistry: clinical implications in the diagnostic and therapeutic management of gastroenteropancreatic neuroendocrine tumors. *Tumori*. 2011;97:620–628.
47. Diakatou E, Alexandraki KI, Tsolakis AV, et al. Somatostatin and dopamine receptor expression in neuroendocrine neoplasms: correlation of immunohistochemical findings with somatostatin receptor scintigraphy visual scores. *Clin Endocrinol (Oxf)*. 2015;83:420–428.
48. Alkapalan D, Maxwell JE, O'Dorisio T, et al. Prospective experience with routine SSTR2A immunohistochemistry in neuroendocrine epithelial neoplasms. In: *USCAP 105th Annual Meeting Abstracts. Mod Pathol*. 2016:29(2 suppl):145A.abstract 568.
49. van Adrichem RC, Kamp K, van Deurzen CH, et al. Is there an additional value of using somatostatin receptor subtype 2a immunohistochemistry compared to somatostatin receptor scintigraphy uptake in predicting gastroenteropancreatic neuroendocrine tumor response? *Neuroendocrinology*. 2016;103:560–566.
50. Butturini G, Bettini R, Missiaglia E, et al. Predictive factors of efficacy of the somatostatin analogue octreotide as first line therapy for advanced pancreatic endocrine carcinoma. *Endocr Relat Cancer*. 2006;13: 1213–1221.
51. Qian ZR, Li T, Ter-Minassian M, et al. Association between somatostatin receptor expression and clinical outcomes in neuroendocrine tumors. *Pancreas*. 2016;45:1386–1393.
52. Brunner P, Jörg AC, Glatz K, et al. The prognostic and predictive value of SSTR2-immunohistochemistry and $SSTR_2$-targeted imaging in neuroendocrine tumors. *Eur J Nucl Med Mol Imaging*. 2017;44:468–475.
53. 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;105:196–200.
54. Marotta V, Zatelli MC, Sciammarella C, et al. Chromogranin A as circulating marker for diagnosis and management of neuroendocrine neoplasms: more flaws than fame. *Endocr Relat Cancer*. 2018;25: R11–R29.
55. Gkolfinopoulos S, Tsapakidis K, Papadimitriou K, et al. Chromogranin A as a valid marker in oncology: clinical application or false hopes? *World J Methodol*. 2017;7:9–15.
56. Herrera-Martińez AD, Hofland LJ, Gálvez Moreno MA, et al. Neuroendocrine neoplasms: current and potential diagnostic, predictive and prognostic markers. *Endocr Relat Cancer*. 2019;26:R157–R179.
57. Arnold R, Wilke A, Rinke A, et al. Plasma chromogranin A as marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors. *Clin Gastroenterol Hepatol*. 2008;6:820–827.
58. Ekeblad S, Skogseid B, Dunder K, et al. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res*. 2008;14:7798–7803.
59. Nikou GC, Marinou K, Thomakos P, et al. Chromogranin A levels in diagnosis, treatment and follow-up of 42 patients with non-functioning pancreatic endocrine tumours. *Pancreatology*. 2008;8:510–519.
60. Citterio D, Pusceddu S, Facciorusso A, et al. Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver. *Eur J Surg Oncol*. 2017;43:380–387.
61. Tirosh A, Papadakis GZ, Millo C, et al. Association between neuroendocrine tumors biomarkers and primary tumor site and disease type based on total ^{68}Ga-DOTATATE-Avid tumor volume measurements. *Eur J Endocrinol*. 2017;176:575–582.
62. Nanno Y, Toyama H, Matsumoto I, et al. Baseline plasma chromogranin A levels in patients with well-differentiated neuroendocrine tumors of the pancreas: a potential predictor of postoperative recurrence. *Pancreatology*. 2017;17:291–294.
63. 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;96:3741–3749.
64. Nölting S, Kuttner A, Lauseker M, et al. Chromogranin A as serum marker for gastroenteropancreatic neuroendocrine tumors: a single center experience and literature review. *Cancers (Basel)*. 2012;4:141–155.
65. Walter T, Chardon L, Chopin-laly X, et al. Is the combination of chromogranin A and pancreatic polypeptide serum determinations of interest in the diagnosis and follow-up of gastro-entero-pancreatic neuroendocrine tumours? *Eur J Cancer*. 2012;48:1766–1773.
66. Sharma N, Naraev BG, Engelman EG, et al. Peptide receptor radionuclide therapy outcomes in a North American cohort with metastatic well-differentiated neuroendocrine tumors. *Pancreas*. 2017;46:151–156.

67. Fisher AV, Lopez-Aguiar AG, Rendell VR, et al. Predictive value of chromogranin A and a pre-operative risk score to predict recurrence after resection of pancreatic neuroendocrine tumors. *J Gastrointest Surg*. 2019; 23:651–658.
68. O'Dorisio TM, Krutzik SR, Woltering EA, et al. Development of a highly sensitive and specific carboxy-terminal human pancreastatin assay to monitor neuroendocrine tumor behavior. *Pancreas*. 2010;39:611–616.
69. Raines D, Chester M, Diebold AE, et al. A prospective evaluation of the effect of chronic proton pump inhibitor use on plasma biomarker levels in humans. *Pancreas*. 2012;41:508–511.
70. Ito T, Igarashi H, Jensen RT. Serum pancreastatin: the long sought universal, sensitive, specific tumor marker for neuroendocrine tumors? *Pancreas*. 2012;41:505–507.
71. Rustagi S, Warner RR, Divino CM. Serum pancreastatin: the next predictive neuroendocrine tumor marker. *J Surg Oncol*. 2013;108: 126–128.
72. Strosberg D, Schneider EB, Onesti J, et al. Prognostic impact of serum pancreastatin following chemoembolization for neuroendocrine tumors. *Ann Surg Oncol*. 2018;25:3613–3620.
73. Sherman SK, Maxwell JE, O'Dorisio MS, et al. Pancreastatin predicts survival in neuroendocrine tumors. *Ann Surg Oncol*. 2014;21:2971–2980.
74. 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;11:264–271.
75. 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;45:560–566.
76. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371: 224–233.
77. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:514–523.
78. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:501–513.
79. Moertel CG, Lefkopoulo M, Lipsitz S, et al. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992;326:519–523.
80. Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol*. 2004;22: 4762–4771.
81. Clewemar Antonodimitrakis P, Sundin A, Wassberg C, et al. Streptozocin and 5-fluorouracil for the treatment of pancreatic neuroendocrine tumors: efficacy, prognostic factors and toxicity. *Neuroendocrinology*. 2016;103: 345–353.
82. Aoki T, Kokudo N, Komoto I, et al. Streptozocin chemotherapy for advanced/metastatic well-differentiated neuroendocrine tumors: an analysis of a multi-center survey in Japan. *J Gastroenterol*. 2015;50: 769–775.
83. Cloyd JM, Omichi K, Mizuno T, et al. Preoperative fluorouracil, doxorubicin, and streptozocin for the treatment of pancreatic neuroendocrine liver metastases. *Ann Surg Oncol*. 2018;25:1709–1715.
84. Krug S, Boch M, Daniel H, et al. Streptozocin-based chemotherapy in patients with advanced neuroendocrine neoplasms—predictive and prognostic markers for treatment stratification. *PLoS One*. 2015; 10:e0143822.
85. Dilz LM, Denecke T, Steffen IG, et al. Streptozocin/5-fluorouracil chemotherapy is associated with durable response in patients with advanced pancreatic neuroendocrine tumours. *Eur J Cancer*. 2015;51: 1253–1262.
86. Delaunoit T, Ducreux M, Boige V, et al. The doxorubicin-streptozotocin combination for the treatment of advanced well-differentiated pancreatic endocrine carcinoma; a judicious option? *Eur J Cancer*. 2004;40: 515–520.
87. Cheng PN, Saltz LB. Failure to confirm major objective antitumor activity for streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma. *Cancer*. 1999;86:944–948.
88. McCollum AD, Kulke MH, Ryan DP, et al. Lack of efficacy of streptozocin and doxorubicin in patients with advanced pancreatic endocrine tumors. *Am J Clin Oncol*. 2004;27:485–488.
89. Cives M, Ghayouri M, Morse B, et al. Analysis of potential response predictors to capecitabine/temozolomide in metastatic pancreatic neuroendocrine tumors. *Endocr Relat Cancer*. 2016;23:759–767.
90. Kunz PL, Catalano PJ, Nimeiri H, et al. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: a trial of the ECOG-ACRIN Cancer Research Group (E2211). *J Clin Oncol*. 2018;36(suppl 15):abstr 4004.
91. Ramage J, Naraev BG, Halfdanarson TR. Peptide receptor radionuclide therapy for patients with advanced pancreatic

neuroendocrine tumors. *Semin Oncol*. 2018;45:236–248.
92. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [^{177}Lu-DOTA^{0} ,Tyr^{3}]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res*. 2017;23:4617–4624.
93. Sonbol MB, Halfdanarson TR, Hilal T. Assessment of therapy-related myeloid neoplasms in patients with neuroendocrine tumors after peptide receptor radionuclide therapy: a systematic review. *JAMA Oncol*. 2020 Apr 16. [Epub ahead of print].
94. Nicolini S, Severi S, Ianniello A, et al. Investigation of receptor radionuclide therapy with ^{177}Lu-DOTATATE in patients with GEP-NEN and a high Ki-67 proliferation index. *Eur J Nucl Med Mol Imaging*. 2018; 45:923–930.
95. Garske-Román U, Sandström M, Fröss Baron K, et al. Prospective observational study of ^{177}Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. *Eur J Nucl Med Mol Imaging*. 2018;45:970–988.
96. Ezziddin S, Attassi M, Yong-Hing CJ, et al. Predictors of long-term outcome in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors after peptide receptor radionuclide therapy with 177Lu-octreotate. *J Nucl Med*. 2014;55:183–190.
97. Kwekkeboom DJ, Bakker WH, Kam BL, et al. Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [177Lu-DOTA(0),Tyr3]octreotate. *Eur J Nucl Med Mol Imaging*. 2003;30:417–422.
98. 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: 2124–2130.
99. Bodei L, Cremonesi M, Grana CM, et al. Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: the IEO phase I-II study. *Eur J Nucl Med Mol Imaging*. 2011;38:2125–2135.
100. Sansovini M, Severi S, Ambrosetti A, et al. Treatment with the radiolabelled somatostatin analog Lu-DOTATATE for advanced pancreatic neuroendocrine tumors. *Neuroendocrinology*. 2013;97: 347–354.
101. Ezziddin S, Khalaf F, Vanezi M, et al. Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2014; 41:925–933.
102. Sampaio IL, Luiz HV, Violante LS, et al. [Treatment of gastroenteropancreatic neuroendocrine tumors with 177Lu-DOTA-TATE: experience of the Portuguese Institute of Oncology in Porto]. [Article in Portuguese]. *Acta Med Port*. 2016;29:726–733.
103. Hamiditabar M, Ali M, Roys J, et al. Peptide receptor radionuclide therapy with 177Lu-octreotate in patients with somatostatin receptor expressing neuroendocrine tumors: six years' assessment. *Clin Nucl Med*. 2017;42: 436–443.
104. Demirci E, Kabasakal L, Toklu T, et al. 177Lu-DOTATATE therapy in patients with neuroendocrine tumours including high-grade (WHO G3) neuroendocrine tumours: response to treatment and long-term survival update. *Nucl Med Commun*. 2018;39:789–796.
105. Baum RP, Kulkarni HR, Singh A, et al. Results and adverse events of personalized peptide receptor radionuclide therapy with 90yttrium and ^{177}lutetium in 1048 patients with neuroendocrine neoplasms. *Oncotarget*. 2018;9:16932–16950.
106. Strosberg J, Wolin E, Chasen B, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with ^{177}Lu-Dotatate in the phase III NETTER-1 trial. *J Clin Oncol*. 2018;36: 2578–2584.
107. Zandee WT, Brabander T, Blažević A, et al. Symptomatic and radiological response to 177Lu-DOTATATE for the treatment of functioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab*. 2019;104: 1336–1344.
108. Modlin IM, Pavel M, Kidd M, et al. Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. *Aliment Pharmacol Ther*. 2010;31: 169–188.
109. Jann H, Denecke T, Koch M, et al. Impact of octreotide long-acting release on tumour growth control as a first-line treatment in neuroendocrine tumours of pancreatic origin. *Neuroendocrinology*. 2013; 98:137–143.
110. Hope TA, Bergsland EK, Bozkurt MF, et al. Appropriate use criteria for somatostatin receptor PET imaging in neuroendocrine tumors. *J Nucl Med*. 2018;59:66–74.
111. 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;57:708–714.
112. Van Binnebeek S, Vanbilloen B, Baete K, et al. Comparison of diagnostic accuracy of (111)In-pentetreotide SPECT and (68)Ga-DOTATOC PET/CT: a lesion-by-lesion analysis in patients with metastatic neuroendocrine tumours. *Eur Radiol*. 2016;26:900–909.
113. Fiebrich HB, Siemerink EJ, Brouwers AH, et al. Everolimus induces rapid plasma glucose normalization in insulinoma patients by effects on tumor as well as normal tissues. *Oncologist*. 2011;16:783–787.
114. Kulke MH, Bergsland EK, Yao JC. Glycemic control in patients with insulinoma treated with everolimus. *N Engl J Med*. 2009;360:195–197.

115. Vogl TJ, Naguib NN, Zangos S, et al. Liver metastases of neuroendocrine carcinomas: interventional treatment via transarterial embolization, chemoembolization and thermal ablation. *Eur J Radiol*. 2009;72: 517–528.
116. 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; 31:271–279.
117. Cao CQ, Yan TD, Bester L, et al. Radioembolization with yttrium microspheres for neuroendocrine tumour liver metastases. *Br J Surg*. 2010;97:537–543.
118. de Baere T, Deschamps F, Tselikas L, et al. GEP-NETS update: interventional radiology: role in the treatment of liver metastases from GEP-NETs. *Eur J Endocrinol*. 2015;172:R151–R166.
119. Scott AT, Breheny PJ, Keck KJ, et al. Effective cytoreduction can be achieved in patients with numerous neuroendocrine tumor liver metastases (NETLMs). *Surgery*. 2019;165:166–175.
120. Chakedis J, Beal EW, Lopez-Aguiar AG, et al. Surgery provides long-term survival in patients with metastatic neuroendocrine tumors undergoing resection for non-hormonal symptoms. *J Gastrointest Surg*. 2019;23: 122–134.
121. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125–135.
122. Kwekkeboom DJ, Teunissen JJ, Bakker WH, et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. *J Clin Oncol*. 2005;23: 2754–2762.
123. Raj N, Klimstra DS, Horvat N, et al. O6-methylguanine DNA methyltransferase status does not predict response or resistance to alkylating agents in well-differentiated pancreatic neuroendocrine tumors. *Pancreas*. 2017;46:758–763.
124. Riff BP, Yang YX, Soulen MC, et al. Peptide receptor radionuclide therapy-induced hepatotoxicity in patients with metastatic neuroendocrine tumors. *Clin Nucl Med*. 2015;40:845–850.
125. Goncalves I, Burbury K, Michael M, et al. Characteristics and outcomes of therapy-related myeloid neoplasms after peptide receptor radionuclide/chemoradionuclide therapy (PRRT/PRCRT) for metastatic neuroendocrine neoplasia: a single-institution series. *Eur J Nucl Med Mol Imaging*. 2019;46:1902–1910.
126. Wolin EM. The expanding role of somatostatin analogs in the management of neuroendocrine tumors. *Gastrointest Cancer Res*. 2012;5:161–168.
127. Proye CA, Lokey JS. Current concepts in functioning endocrine tumors of the pancreas. *World J Surg*. 2004;28:1231–1238.
128. Singh S, Granberg D, Wolin E, et al. Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the first global survey of patients with NETs. *J Glob Oncol*. 2016;3:43–53.
129. 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;28:69–76.
130. Kulke MH, Ruszniewski P, Van Cutsem E, 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;28:1309–1315.
131. Bajetta E, Catena L, Pusceddu S, et al. Everolimus in combination with octreotide long-acting repeatable in a first-line setting for patients with neuroendocrine tumors: a 5-year update. *Neuroendocrinology*. 2018;106: 307–311.
132. *LUTATHERA® (Lutetium Lu 177 dotatate) Injection, for Intravenous Use [package insert]*. Millburn, NJ: Advanced Accelerator Applications USA, Inc.; 2018.
133. Yordanova A, Wicharz MM, Mayer K, et al. The role of adding somatostatin analogues to peptide receptor radionuclide therapy as a combination and maintenance therapy. *Clin Cancer Res*. 2018;24: 4672–4679.
134. McGarrah PW, Hobday TJ, Starr JS, et al. Efficacy of somatostatin analog (SSA) monotherapy for well-differentiated grade 3 (G3) gastroenteropancreatic neuroendocrine tumors (NETs). *J Clin Oncol*. 2020;38(suppl 4):abstr 617.
135. Raj N, Valentino E, Capanu M, et al. Treatment response and outcomes of grade 3 pancreatic neuroendocrine neoplasms based on morphology: well differentiated versus poorly differentiated. *Pancreas*. 2017;46: 296–301.
136. Panzuto F, Rinzivillo M, Spada F, et al. Everolimus in pancreatic neuroendocrine carcinomas G3. *Pancreas*. 2017;46:302–305.
137. Roquin G, Baudin E, Lombard-Bohas C, et al. Chemotherapy for well-differentiated pancreatic neuroendocrine tumours with a Ki-67 index ≥10%: is there a more effective antitumour regimen? A retrospective multicentre study of the French Group of Endocrine Tumours (GTE). *Neuroendocrinology*. 2018;106:38–46.
138. Chan D, Chan JA, Halfdanarson TR, et al. Temozolomide in grade 3 neuroendocrine neoplasms (G3 NENs): a multicentre retrospective review. Presented at: the 16th Annual ENETS Conference in March 2019, Barcelona, Spain. 2019.

139. Thomas K, Voros BA, Meadows-Taylor M, et al. Outcomes of capecitabine and temozolomide (CAPTEM) in advanced neuroendocrine neoplasms (NENs). *Cancers (Basel)*. 2020;12:206.
140. Sahu A, Jefford M, Lai-Kwon J, et al. CAPTEM in metastatic well-differentiated intermediate to high grade neuroendocrine tumors: a single centre experience. *J Oncol*. 2019;2019:9032753.
141. Rogowski W, Wachula E, Gorzelak A, et al. Capecitabine and temozolomide combination for treatment of high-grade, well-differentiated neuroendocrine tumour and poorly-differentiated neuroendocrine carcinoma—retrospective analysis. *Endokrynol Pol*. 2019;70:313–317.
142. Hentic O, Hammel P, Couvelard A, et al. FOLFIRI regimen: an effective second-line chemotherapy after failure of etoposide-platinum combination in patients with neuroendocrine carcinomas grade 3. *Endocr Relat Cancer*. 2012;19:751–757.
143. Ferrarotto R, Testa L, Riechelmann RP, et al. Combination of capecitabine and oxaliplatin is an effective treatment option for advanced neuroendocrine tumors. *Rare Tumors*. 2013;5:e35.
144. Apostolidis L, Jäger D, Winkler EC. Treatment outcomes for well differentiated grade 3 neuroendocrine tumors (NET G3). *Ann Oncol*. 2018;29(suppl 8):viii471–viii472.abstract 1317P.
145. Ezziddin S, Opitz M, Attassi M, et al. Impact of the Ki-67 proliferation index on response to peptide receptor radionuclide therapy. *Eur J Nucl Med Mol Imaging*. 2011;38:459–466.
146. Thang SP, Lung MS, Kong G, et al. Peptide receptor radionuclide therapy (PRRT) in European Neuroendocrine Tumour Society (ENETS) grade 3 (G3) neuroendocrine neoplasia (NEN)—a single-institution retrospective analysis. *Eur J Nucl Med Mol Imaging*. 2018;45:262–277.
147. Zhang J, Kulkarni HR, Singh A, et al. Ten-year survival after peptide receptor radionuclide therapy of a metastatic well-differentiated G3 pancreatic neuroendocrine neoplasm. *Clin Nucl Med*. 2018;43:676–678.
148. Carlsen EA, Fazio N, Granberg D, et al. Peptide receptor radionuclide therapy in gastroenteropancreatic NEN G3: a multicenter cohort study. *Endocr Relat Cancer*. 2019;26:227–239.
149. Sorbye H, Kong G, Grozinsky-Glasberg S. PRRT in high-grade gastroenteropancreatic neuroendocrine neoplasms (WHO G3). *Endocr Relat Cancer*. 2020;27:R67–R77.
150. Moertel CG, Kvols LK, O'Connell MJ, et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer*. 1991;68:227–232.
151. Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer*. 1999; 81:1351–1355.
152. Hainsworth JD, Spigel DR, Litchy S, et al. Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: a Minnie Pearl Cancer Research Network Study. *J Clin Oncol*. 2006;24:3548–3554.
153. Yamaguchi T, Machida N, Morizane C, et al. Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. *Cancer Sci*. 2014;105:1176–1181.
154. Zhang P, Li J, Li J, et al. Etoposide and cisplatin versus irinotecan and cisplatin as the first-line therapy for patients with advanced, poorly differentiated gastroenteropancreatic neuroendocrine carcinoma: a randomized phase 2 study. *Cancer*. 2020;126(suppl 9):2086–2092.
155. Bajetta E, Catena L, Procopio G, et al. Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours? *Cancer Chemother Pharmacol*. 2007;59: 637–642.
156. Hadoux J, Malka D, Planchard D, et al. Post–first-line FOLFOX chemotherapy for grade 3 neuroendocrine carcinoma. *Endocr Relat Cancer*. 2015;22:289–298.
157. Olsen IH, Sørensen JB, Federspiel B, et al. Temozolomide as second or third line treatment of patients with neuroendocrine carcinomas. *ScientificWorldJournal*. 2012;2012:170496.
158. Welin S, Sorbye H, Sebjornsen S, et al. Clinical effect of temozolomide-based chemotherapy in poorly differentiated endocrine carcinoma after progression on first-line chemotherapy. *Cancer*. 2011; 117:4617–4622.
159. 159. Rocha-Lima CM, Herndon JE 2nd, Lee ME, et al. Phase II trial of irinotecan/gemcitabine as second-line therapy for relapsed and refractory small-cell lung cancer: Cancer and Leukemia Group B Study 39902. *Ann Oncol*. 2007;18:331–337.
160. Pallis AG, Agelidou A, Agelaki S, et al. A multicenter randomized phase II study of the irinotecan/gemcitabine doublet versus irinotecan monotherapy in previously treated patients with extensive stage small-cell lung cancer. *Lung Cancer*. 2009;65:187–191.
161. Mori K, Kamiyama Y, Kondo T, et al. Pilot phase II study of weekly chemotherapy with paclitaxel and carboplatin for refractory or relapsed small-cell lung cancer. *Cancer Chemother Pharmacol*. 2006;58:86–90.

162. McGarrah PW, Leventakos K, Hobday TJ, et al. Efficacy of second-line chemotherapy in extrapulmonary neuroendocrine carcinoma. *Pancreas*. 2020;49:529–533.
163. Lee SY, Choi YJ, Chang WJ, et al. The role of chemotherapy and/or octreotide in patients with metastatic gastroenteropancreatic and hepatobiliary neuroendocrine carcinoma. *J Gastrointest Oncol*. 2014;5: 457–462.
164. Correale P, Sciandivasci A, Intrivici C, et al. Chemo-hormone therapy of non-well-differentiated endocrine tumours from different anatomic sites with cisplatinum, etoposide and slow release lanreotide formulation. *Br J Cancer*. 2007;96:1343–1347
165. Okuyama H, Ikeda M, Okusaka T, et al. A phase II trial of everolimus in patients with advanced pancreatic neuroendocrine carcinoma refractory or intolerant to platinum-containing chemotherapy (NECTOR trial). *Neuroendocrinology*. 2020 Jan 2. [Epub ahead of print].
166. Pellat A, Dreyer C, Couffignal C, et al. Clinical and biomarker evaluations of sunitinib in patients with grade 3 digestive neuroendocrine neoplasms. *Neuroendocrinology*. 2018;107:24–31.
167. Mizuno Y, Kudo A, Akashi T, et al. Sunitinib shrinks NET-G3 pancreatic neuroendocrine neoplasms. *J Cancer Res Clin Oncol*. 2018;144: 1155–1163.
168. Gilabert M, Rho YS, Kavan P. Targeted therapies provide treatment options for poorly differentiated pancreatic neuroendocrine carcinomas. *Oncology*. 2017;92:170–172.
169. Vijayvergia N, Dasari A, Ross EA, et al. Pembrolizumab (P) monotherapy in patients with previously treated metastatic high grade neuroendocrine neoplasms (HG-NENs). *J Clin Oncol*. 2018; 36(15 suppl):abstract 4104.
170. Yao JC, Strosberg J, Fazio N, et al. Activity & safety of spartalizumab (PDR001) in patients (pts) with advanced neuroendocrine tumors (NET) of pancreatic (Pan), gastrointestinal (GI), or thoracic (T) origin, & gastroenteropancreatic neuroendocrine carcinoma (GEP NEC) who have progressed on prior treatment (Tx). *Ann Oncol*. 2018;29(suppl 8):viii467- viii478.abstract 3442.
171. Patel SP, Othus M, Chae YK, et al. A phase II Basket trial of dual anti–CTLA-4 and anti–PD-1 blockade in rare tumors (DART SWOG 1609) in patients with nonpancreatic neuroendocrine tumors. *Clin Cancer Res*. 2020;26:2290–2296.
172. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220–2229.
173. Öberg K. Management of functional neuroendocrine tumors of the pancreas. *Gland Surg*. 2018;7:20–27.
174. Brown E, Watkin D, Evans J, et al. Multidisciplinary management of refractory insulinomas. *Clin Endocrinol (Oxf)*. 2018;88: 615–624.
175. Baudin E, Caron P, Lombard-Bohas C, et al. Malignant insulinoma: recommendations for characterisation and treatment. *Ann Endocrinol (Paris)*. 2013;74:523–533.
176. Magalhães D, Sampaio IL, Ferreira G, et al. Peptide receptor radionuclide therapy with ^{177}Lu-DOTA-TATE as a promising treatment of malignant insulinoma: a series of case reports and literature review. *J Endocrinol Invest*. 2019;42:249–260.
177. 177. Vezzosi D, Bennet A, Rochaix P, et al. Octreotide in insulinoma patients: efficacy on hypoglycemia, relationships with octreoscan scintigraphy and immunostaining with anti-sst2A and anti-sst5 antibodies. *Eur J Endocrinol*. 2005;152:757–767.
178. Tirosh A, Stemmer SM, Solomonov E, et al. Pasireotide for malignant insulinoma. *Hormones (Athens)*. 2016;15:271–276.
179. Baratelli C, Brizzi MP, Tampellini M, et al. Intermittent everolimus administration for malignant insulinoma. *Endocrinol Diabetes Metab Case Rep*. 2014;2014:140047.
180. Bernard V, Lombard-Bohas C, Taquet MC, et al. Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycemia. *Eur J Endocrinol*. 2013;168:665–674.
181. 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;119:3212–3218.
182. Frucht H, Maton PN, Jensen RT. Use of omeprazole in patients with Zollinger-Ellison syndrome. *Dig Dis Sci*. 1991;36:394–404.
183. Metz DC, Pisegna JR, Ringham GL, et al. Prospective study of efficacy and safety of lansoprazole in Zollinger-Ellison syndrome. *Dig Dis Sci*. 1993;38:245–256.
184. Termanini B, Gibril F, Stewart CA, et al. A prospective study of the effectiveness of low dose omeprazole as initial therapy in Zollinger-Ellison syndrome. *Aliment Pharmacol Ther*. 1996;10:61–71.
185. Metz DC, Soffer E, Forsmark CE, et al. Maintenance oral pantoprazole therapy is effective for patients with Zollinger-Ellison syndrome and idiopathic hypersecretion. *Am J Gastroenterol*. 2003;98:301–307.
186. Metz DC, Comer GM, Soffer E, et al. Three-year oral pantoprazole administration is effective for patients with Zollinger-Ellison syndrome and other hypersecretory conditions. *Aliment Pharmacol Ther*. 2006;23: 437–444.
187. Morocutti A, Merrouche M, Bjaaland T, et al. An open-label study of rabeprazole in patients with Zollinger-Ellison syndrome or

idiopathic gastric acid hypersecretion. *Aliment Pharmacol Ther*. 2006;24:1439–1444.
188. Metz DC, Sostek MB, Ruszniewski P, et al. Effects of esomeprazole on acid output in patients with Zollinger-Ellison syndrome or idiopathic gastric acid hypersecretion. *Am J Gastroenterol*. 2007;102:2648–2654.
189. Metz DC, Cadiot G, Poitras P, et al. Diagnosis of Zollinger-Ellison syndrome in the era of PPIs, faulty gastrin assays, sensitive imaging and limited access to acid secretory testing. *Int J Endocr Oncol*. 2017;4: 167–185.
190. Metz DC, Pisegna JR, Fishbeyn VA, et al. Currently used doses of omeprazole in Zollinger-Ellison syndrome are too high. *Gastroenterology*. 1992;103:1498–1508.
191. Hirschowitz BI, Simmons J, Mohnen J. Clinical outcome using lansoprazole in acid hypersecretors with and without Zollinger-Ellison syndrome: a 13-year prospective study. *Clin Gastroenterol Hepatol*. 2005; 3:39–48.
192. Jensen RT. Management of the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type 1. *J Intern Med*. 1998;243: 477–488.
193. Miller LS, Vinayek R, Frucht H, et al. Reflux esophagitis in patients with Zollinger-Ellison syndrome. *Gastroenterology*. 1990;98:341–346.
194. Maton PN, Frucht H, Vinayek R, et al. Medical management of patients with Zollinger-Ellison syndrome who have had previous gastric surgery: a prospective study. *Gastroenterology*. 1988;94:294–299.
195. Saeed ZA, Norton JA, Frank WO, et al. Parenteral antisecretory drug therapy in patients with Zollinger-Ellison syndrome. *Gastroenterology*. 1989;96:1393–1402.
196. Vinayek R, Frucht H, London JF, et al. Intravenous omeprazole in patients with Zollinger-Ellison syndrome undergoing surgery. *Gastroenterology*. 1990;99:10–16.
197. Vinayek R, Hahne WF, Euler AR, et al. Parenteral control of gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. *Dig Dis Sci*. 1993;38:1857–1865.
198. Lew EA, Pisegna JR, Starr JA, et al. Intravenous pantoprazole rapidly controls gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. *Gastroenterology*. 2000;118:696–704.
199. Metz DC, Forsmark C, Lew EA, et al. Replacement of oral proton pump inhibitors with intravenous pantoprazole to effectively control gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. *Am J Gastroenterol*. 2001;96:3274–3280.
200. Fraker DL, Norton JA, Saeed ZA, et al. A prospective study of perioperative and postoperative control of acid hypersecretion in patients with Zollinger-Ellison syndrome undergoing gastrinoma resection. *Surgery*. 1988;104:1054–1063.
201. Sansovini M, Severi S, Ianniello A, et al. Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with ^{177}Lu-DOTATATE. *Eur J Nucl Med Mol Imaging*. 2017;44:490–499.
202. Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90YDOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol. 2011;29:2416–2423.
203. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Neuroendocrine and Adrenal Tumors. Version 1.2019. March 5, 2019. Available at: https:// www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed May 5, 2020.
204. Chen JX, Rose S, White SB, et al. Embolotherapy for neuroendocrine tumor liver metastases: prognostic factors for hepatic progression-free survival and overall survival. *Cardiovasc Intervent Radiol*. 2017;40: 69–80.
205. Guiu B, Deschamps F, Aho S, et al. Liver/biliary injuries following chemoembolisation of endocrine tumours and hepatocellular carcinoma: lipiodol vs. drug-eluting beads. *J Hepatol*. 2012;56:609–617.
206. Memon K, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for neuroendocrine liver metastases: safety, imaging, and long-term outcomes. *Int J Radiat Oncol Biol Phys*. 2012;83:887–894.
207. Su YK, Mackey RV, Riaz A, et al. Long-term hepatotoxicity of yttrium-90 radioembolization as treatment of metastatic neuroendocrine tumor to the liver. *J Vasc Interv Radiol*. 2017;28:1520–1526.
208. Ezziddin S, Meyer C, Kahancova S, et al. 90Y radioembolization after radiation exposure from peptide receptor radionuclide therapy. *J Nucl Med*. 2012;53:1663–1669.
209. Braat AJAT, Kwekkeboom DJ, Kam BLR, et al. Additional hepatic ^{166}Ho-radioembolization in patients with neuroendocrine tumours treated with ^{177}Lu-DOTATATE; a single center, interventional, non-randomized, non-comparative, open label, phase II study (HEPAR PLUS trial). *BMC Gastroenterol*. 2018;18:84.
210. Cholapranee A, van Houten D, Deitrick G, et al. Risk of liver abscess formation in patients with prior biliary intervention following yttrium-90 radioembolization. *Cardiovasc Intervent Radiol*. 2015;38: 397–400.

211. Devulapalli KK, Fidelman N, Soulen MC, et al. ^{90}Y Radioembolization for hepatic malignancy in patients with previous biliary intervention: multicenter analysis of hepatobiliary infections. *Radiology*. 2018;288: 774–781.
212. Gurusamy KS, Ramamoorthy R, Sharma D, et al. Liver resection versus other treatments for neuroendocrine tumours in patients with resectable liver metastases. *Cochrane Database Syst Rev*. 2009; 2009:CD007060.
213. Gurusamy KS, Pamecha V, Sharma D, et al. Palliative cytoreductive surgery versus other palliative treatments in patients with unresectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours. *Cochrane Database Syst Rev*. 2009;CD007118.
214. Valle JW, Eatock M, Clueit B, et al. A systematic review of non-surgical treatments for pancreatic neuroendocrine tumours. *Cancer Treat Rev*. 2014;40:376–389.
215. Bhagat N, Reyes DK, Lin M, et al. Phase II study of chemoembolization with drug-eluting beads in patients with hepatic neuroendocrine metastases: high incidence of biliary injury. *Cardiovasc Intervent Radiol*. 2013;36:449–459.
216. Yang TX, Chua TC, Morris DL. Radioembolization and chemoembolization for unresectable neuroendocrine liver metastases—a systematic review. *Surg Oncol*. 2012;21:299–308.
217. Chan DL, Thompson R, Lam M, et al. External beam radiotherapy in the treatment of gastroenteropancreatic neuroendocrine tumours: a systematic review. *Clin Oncol (R Coll Radiol)*. 2018;30:400–408.
218. Strosberg J, Hoffe S, Gardner N, et al. Effective treatment of locally advanced endocrine tumors of the pancreas with chemoradiotherapy. *Neuroendocrinology*. 2007;85:216–220.
219. Maidment BW, Ellison T, Herman JM, et al. Radiation in the management of pancreatic neuroendocrine tumors. *J Clin Oncol*. 2012;30(4 suppl): abstract 335.
220. Zagar TM, White RR, Willett CG, et al. Resected pancreatic neuroendocrine tumors: patterns of failure and disease-related outcomes with or without radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;83: 1126–1131.
221. Arvold ND, Willett CG, Fernandez-del Castillo C, et al. Pancreatic neuroendocrine tumors with involved surgical margins: prognostic factors and the role of adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012; 83:e337–e343.
222. Contessa JN, Griffith KA, Wolff E, et al. Radiotherapy for pancreatic neuroendocrine tumors. *Int J Radiat Oncol Biol Phys*. 2009;75:1196–1200.
223. Balthazar P, Shinagare AB, Tirumani SH, et al. Gastroenteropancreatic neuroendocrine tumors: impact of consistent contrast agent selection on radiologists' confidence in hepatic lesion assessment on restaging MRIs. *Abdom Radiol (NY)*. 2018;43:1386–1392.
224. Hope TA, Abbott A, Colucci K, et al. NANETS/SNMMI procedure standard for somatostatin receptor–based peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE. *J Nucl Med*. 2019;60:937–943.
225. Singh S, Moody L, Chan DL, et al. Follow-up recommendations for completely resected gastroenteropancreatic neuroendocrine tumors. *JAMA Oncol*. 2018;4:1597–1604.
226. Shah MH, Goldner WS, Halfdanarson TR, et al. NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. *J Natl Compr Canc Netw*. 2018;16:693–702.

The North American Neuroendocrine Tumor Society Consensus Paper on the Surgical Management of Pancreatic Neuroendocrine Tumors

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INTRODUCTION

The pancreas is an important abdominal organ with multiple functions, and derives from the embryonic foregut. Its exocrine role is important for digestion, while its endocrine effects are carried out through hormones made within pancreatic islet cells, which are released into the bloodstream to affect distant tissues. Hormones produced within the pancreas include insulin, glucagon, somatostatin, ghrelin, and pancreatic polypeptide.[1] Tumors that originate in the islet cells are also known as pancreatic neuroendocrine tumors (PNETs). These account for 1-2% of all pancreatic tumors,[2-4] and their incidence has been increasing, from 3.2 cases per million in 2003 to 8 per million in 2012.[5,6]

Tumors making excess hormones can lead to clinical syndromes, and these tumors are termed functional tumors. These include insulinoma, gastrinoma, vasoactive intestinal polypeptide (VIP) secreting tumors, glucagonoma, somatostatinoma, NETs resulting in carcinoid syndrome due to production of serotonin, as well as even less common tumors making hormones like adrenocorticotrophic hormone (ACTH), calcitonin, growth hormone releasing factor, and parathyroid hormone related peptide (PTHrP). The majority of PNETs (75-90%) are not associated with elevated hormone levels or do not cause a clinical syndrome and these are termed non-functional (NF),[7,8] Some PNETs are associated with elevated levels of pancreatic polypeptide, neurotensin, or HCG, but without a clinical syndrome are still referred to as NF.[9] Functional tumors generally have a more favorable prognosis than their NF counterparts,[7] possibly because of earlier detection.

The median survival of patients with grade 1 and 2 PNETs is 42 months. In all patients with PNETs localized to the pancreas, the median survival is 136 months, which decreases to 77 months when nodal metastases are present. However, 64% of patients present with distant metastases, and in this group the median survival is only 24 months.[5]

Approximately 5% of patients with PNETs have a family history of PNET, while the other 95% are sporadic.[3] Inherited conditions that are associated with PNETs include multiple endocrine neoplasia type 1 (MEN1), von Hippel Lindau syndrome (VHL), tuberous sclerosis complex TSC1 and TSC2, and neurofibromatosis (NF1). The management of familial disease is generally more complex, because tumors are more commonly multifocal, can develop throughout the patient's lifetime, and different tumors may arise in other sites of the body.

Treatment options for patients with PNETs depend upon the anatomic location of the tumor within the gland, size, multifocality, the extent of disease (localized or metastatic), grade, involvement of adjacent structures, and patient co-morbidities. Some management issues in patients with PNETs are clearer than others, such as the appropriate surgical procedures for tumors in different parts of the gland. Many others are not clear at all, and evidence for the correct approaches for specific patient situations is lacking. Furthermore, due to the rarity of these tumors, institutional experiences may be quite variable and clinicians must rely upon their judgement and discussions in multi-disciplinary tumor boards to best serve their patients. In this paper, we have identified a number of controversial areas related to the surgical management of patients with PNETs and assembled a group of expert clinicians to explore the literature in order to present options for dealing with these important clinical questions.

MATERIALS AND METHODS

A list of frequently encountered questions related to the management of patients with PNETs was assembled with special attention to issues of interest to surgeons. Many of these were areas of controversy and where limited data are available. Fourteen surgeons known for their experience in the management of patients with pancreatic and neuroendocrine tumors were invited to be involved with the consensus process, as well as two radiologists with body imaging and nuclear medicine expertise, and one gastroenterologist. The draft questions were submitted to the group for suggestions and edits, and multiple choice questions were created. Prior to the consensus conference, each participant was assigned 2 questions to thoroughly research, identify the most relevant papers from the literature and submit to the project library, and develop a balanced presentation for the group meeting.

The group met in person in Iowa City on July 19-20, 2018 for discussion of these surgical questions related to PNETs, as did a separate group of medical specialists for medical questions related to PNETs. Presentations for each individual question were given to the surgical group followed by discussion of different potential viewpoints in order to seek out consensus based upon the most relevant findings from the literature and experience. On the second day, the surgical group presented their questions and discussed them with the medical group to get their input. Multiple choice questionnaires were filled out by participants before and after the meeting; each was assigned to write a review of the relevant literature pertaining to their assigned questions, followed by a

summary reflecting this literature and consensus opinions of the group. These were edited by the first and senior authors, then distributed to the co-authors and 2 members of the medical group for further review and approval

RESULTS

There were a total of 34 questions, covering the areas of imaging, role of endoscopic ultrasound (EUS), resection based upon size and functionality, strategies for familial tumors, minimally invasive approaches, the role of various techniques (splenic preservation, enucleation, central pancreatectomy, mesenteric vein resection, lymphadenectomy), neoadjuvant treatment, intraoperative and postoperative somatostatin analogue (SSA) therapy, and approaches for metastatic disease and high-grade tumors. Each question appears below and is followed by a review of the relevant literature; as will be clear from the text, the majority of the studies related to these topics are retrospective cohort studies (level 3 evidence), although a few have been addressed by randomized controlled trials (level 1 evidence). Following each review are summary statements with recommendations of the group based upon the best available evidence and expert opinion.

1. How do we optimize the use of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) in the diagnosis of PNETs (sequences/phases, intravenous contrast)?

Imaging plays a central role in the initial staging of patients with PNETs. The best imaging modality for staging of the primary tumor is a pancreatic protocol CT, primarily due to the characterization of vascular involvement and staging of the primary tumor. A typical pancreatic protocol CT uses an arterial phase acquired 45-50 seconds after contrast administration and a portal venous phase acquired 70 seconds after contrast administration.[10,11] This protocol was optimized in the setting of pancreatic ductal adenocarcinoma, but can also be used for neuroendocrine tumors (NETs) as the arterial phase is used to see the arterially enhancing tumor and the portal venous phase allows for good characterization of the portal venous system. On imaging, relevant findings are similar to what is used to report upon in pancreatic adenocarcinomas, and similar templates can be followed.[12] It is important to evaluate the relevant vasculature (encasement and occlusion of the superior mesenteric artery or vein, splenic artery, and celiac axis). The presence of collaterals and varices can be helpful to indicate splenic vein occlusion. CT is also helpful for characterizing aberrant arterial anatomy, biliary and pancreatic ductal abnormalities, as well as invasion into adjacent organs. Although diffusion weighted imaging can be helpful for detection of PNETs and can help indicate the grade of the tumor (i.e. more restricted diffusion=higher grade tumor), EUS with biopsy remains the method of choice for diagnosis.[13,14]

Pancreatic protocol CT does not interfere with the evaluation of hepatic metastases, and the arterial and portal venous phases match that recommended for hepatic imaging.[15] The best imaging modality for the evaluation of hepatic metastases is hepatobiliary phase MRI using gadoxetate disodium (Eovist), which is due both to its increased detection sensitivity and its consistency in measurement.[16-18] For the detection of hepatic metastases, gadoxetate is superior to conventional extracellular contrast agents, although for the characterization of the primary tumor and vascular involvement, extracellular contrast is superior. PNET metastases to the liver are typically fed by the hepatic arteries rather than the portal veins, and therefore are often best seen on the arterial phase. It is also important to evaluate the portal venous phase due to variability in arterial phase timing and vascular supply. Other imaging sequences can be helpful to interpret liver lesions which may be confused for metastatic disease. T2-weighted images and diffusion weighted imaging (DWI) can be helpful to characterize cysts and hemangiomas, which can mimic metastatic disease on hepatobiliary phase imaging. Additionally, DWI can be helpful for the detection of small hepatic metastases although is frequently limited by artifact.

On CT/MRI at time of initial staging, evaluation of lymphadenopathy is important, but with the development of somatostatin receptor (SSTR)-based positron emission tomography (PET) scan (SSTR-PET), the role of conventional imaging to characterize nodal metastases is limited. Both CT and MRI can detect nodal metastases, but are dependent on size criteria for characterization. The finding of enlarged lymph nodes (LNs) may suggest obtaining an SSTR-PET to characterize the extent of metastatic disease. It is also important to use the same imaging technique (CT vs. MRI, and extracellular contrast vs. hepatobiliary contrast) over time. If an SSTR-PET is not obtained, a CT of the chest can be obtained at the time of initial diagnosis to evaluate for metastatic lesions,[19] although imaging of the chest may not be indicated in PNETs without evidence of metastases.[20]

Recommendations: Pancreatic protocol CT is an excellent tool for evaluating primary PNETs and their nodal metastases, and is sufficient for evaluating liver metastases when arterial and venous phases are obtained. MRI is also useful for evaluating primary PNETs and is better than

CT for imaging hepatic metastases. For surgeons, CT has the advantage of being easier to interpret and to find the optimal sequences of interest.

2. What are the appropriate indications for somatostatin receptor imaging at diagnosis and what is the optimal modality?

Somatostatin receptor-PET imaging using ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC is the best imaging modality for the detection of metastatic disease in patients with PNETs at the time of diagnosis.[21,22] In the United States, only ^{68}Ga-DOTATATE (NETSPOT®) has been approved for clinical use. Detection of metastatic disease is helpful for surgical planning. Another important role of SSTR-PET is to localize a primary tumor in patients with a metastatic neuroendocrine tumor; in one study of 40 patients with unknown primary, 15 had their lesions detected by SSTR-PET.[23] As SSTR-PET becomes more widely available, ^{111}In-pentetreotide (Octreoscan) should no longer be used. There are a number of benefits of SSTR-PET over ^{111}In-pentetreotide: shorter scan time (imaging one hour after injection vs. 24 hours after injection), lower radiation dose, improved image quality, decreased bowel activity, improved sensitivity, and the ability to quantify uptake. If possible, SSTR-PET should be performed with intravenous contrast allowing the simultaneous acquisition of an SSTR-PET and a pancreas protocol CT.

In terms of characterizing pancreatic masses detected on MRI or CT, EUS with biopsy is superior to SSTR-PET and can provide important molecular characterization. Of note, SSTR-PET cannot distinguish between a splenule and a small NET and should not be used to distinguish between these two diagnoses. In patients with VHL, the differentiation between microcystic adenomas and small PNETs can be difficult on MRI and CT and in this setting SSTR-PET can be helpful.[24]

The potential for false-positive uptake needs to be carefully considered with SSTR-PET. Physiologic uptake has been well-described in the pancreas, which can be seen in over 50% of patients imaged using SSTR-PET.[25,26] There is significant overlap between physiologic activity and malignant activity in the pancreas and uptake on SSTR-PET cannot be used on its own to characterize uptake, although various cut-offs have been proposed.[27,28] The mechanism by which SSTR analogs are taken up in the pancreas is not well understood, but may be related to pancreatic polypeptide-containing cells.[25] If uptake is seen in the pancreas on SSTR-PET, contrast enhanced CT using a pancreas protocol should be performed in order to determine if there is an underlying lesion. It should also be noted that false positive uptake in the tail of the pancreas has been seen, although less commonly than is found in the uncinate process; as with uncinate process uptake, CT/MRI should be obtained to evaluate for an underlying lesion. Adrenal adenomas can be avid on SSTR-PET, although uptake is typically equivalent or lower than the contralateral adrenal gland. In the case of adrenal nodules that have SSTR-uptake, characterization using CT or MRI should be performed to determine involvement.

Recommendations: Somatostatin receptor-PET imaging should replace ^{111}In-pentetreotide scanning. It is useful for identifying primary tumors and the extent of metastatic disease. One must be aware of the potential for false-positive results, particularly within the uncinate process and the pancreatic tail.

3. What is the role of somatostatin receptor imaging beyond use at diagnosis (monitoring of disease progression, responses to therapy and surveillance)?

Few studies have specifically addressed the role of SSTR-PET/CT imaging in follow-up of NETs after initial therapy and recommendations are based mostly upon consensus of expert opinions. Haug et al retrospectively reviewed 63 patients who were imaged with 68Ga-DOTATATE between 3 to 348 months after initial resection of their NETs; 30 patients were imaged as part of routine surveillance and 33 patients underwent imaging because of concern of recurrence. [29] The sensitivity and specificity of ^{68}Ga-DOTATATE PET/CT in detection of recurrent NET was 92% and 80%, respectively, leading to change in therapy in patients diagnosed with recurrence. In a more recent multicenter study, the clinical utility of SSTR imaging (including ^{68}Ga-DOTA PET and ^{111}In-Octreotide scintigraphy) was analyzed in a multicenter retrospective analysis of patients with metastatic gastroenteropancreatic NETs (GEPNETs). One hundred forty-three patients with metastatic NETs underwent CT imaging every 6 months and SSTR imaging every 12 months as part of oncological follow-up. SSTR imaging detected 75.8% (132/174) of new lesions in follow-up, including 29.3% (51/174) that had been missed by CT.[30] SSTR imaging was considered useful (i.e., for indication to biopsy, choose new therapies or dose escalation, change to surgical treatment, or further radiological examinations as a result of the scan) in 73.4% of patients, more so in patients with grade 2 (G2) tumors. ^{68}Ga-DOTATOC PET imaging, however, has not been shown to add significantly to conventional imaging for assessment of response to peptide receptor radionuclide therapy (PRRT).[31] Recently a committee consisting of experts in surgery, oncology, endocrinology, gastroenterology and radiology reported

on the appropriate use criteria for SSTR-PET in NETs.[21] These indications for SSTR-PET imaging in follow-up of NETs were considered appropriate: (1) monitoring of NETs seen predominantly on SSTR-PET; (2) restaging of the disease at time of clinical or biochemical progression without evidence of progression on conventional imaging; and (3) new indeterminate lesions on conventional imaging with unclear progression.[21] If the disease is seen both on conventional imaging and SSTR-PET, the committee reported that if conventional imaging is stable, intermittent PET (once every 2 to 3 years) may be helpful to evaluate for progression. If the tumor is readily seen on conventional imaging, however, SSTR-PET is not needed for monitoring.[21]

Recommendation: Somatostatin receptor-PET imaging is a highly sensitive and useful adjunct to conventional imaging (CT or MRI) in follow-up of GEPNETs, particularly in monitoring of patients when the extent of disease cannot be reliably evaluated on conventional imaging, and in restaging of NETs at the time of clinical progression that is not supported by conventional imaging.

4. Should all patients with localized tumors have an EUS fine-needle aspiration or biopsy of the primary tumor when feasible?

For several decades, EUS-guided fine needle aspiration (FNA) has been an important tool in our diagnostic armamentarium, particularly in the context of pancreatic neoplasms. Multiple studies have confirmed the high sensitivity and specificity of EUS-FNA. In contrast, fine needle core biopsy (FNB) is not uniformly performed, but may be done more commonly in academic or tertiary medical centers. In particular, FNB may be performed when specifically requested, i.e. for clinical trials. It is also performed more commonly when additional tissue is required for immunohistochemical studies or flow cytometry (e.g. NETs or lymphoma). While FNA and FNB can often be performed with the same device, specimens are submitted separately to cytology and pathology. As with EUS itself, the decision to add FNB is highly operator and practice dependent.

Endoscopic ultrasound-FNA/FNB should be performed in specific situations where it adds to the diagnosis or management of the patient. For instance, if imaging characteristics are equivocal or the diagnosis is in question, EUS-FNA/FNB should be performed to confirm the diagnosis. Similarly, if there is question about the tumor grade, EUS-FNA/FNB can be performed to ascertain tumor grade. However, it is important to recognize that tumor heterogeneity may preclude accurate assessment of tumor grade. In one study of 58 patients with surgically resected PNETs, the variability of the Ki-67 index in different areas of the tumor was higher in G2 tumors as compared to G1 lesions.[32] However, even in G2 tumors, areas with Ki-67 ≤2% were common. Similarly, in a comparison of cytology obtained from EUS-FNA and histology from surgical resection specimens, agreement of tumor grade was poor with less than 50% of G2 and G3 detected on EUS-FNA.[33] This highlights the limitations of EUS-FNA to accurately assess tumor grade in a limited specimen. It remains unknown whether the addition of FNB would change these outcomes. In the only prospective study of EUS-FNB of non-functional PNETs, there was 83% concordance between cytology and histology.[34] This study was limited by its small sample size of 30 patients.

Recommendation: Endoscopic ultrasound-FNA should be performed in patients where making the diagnosis of a PNET would be helpful, or when there is a question about tumor grade. Although FNA is most frequently performed, the addition of FNB can be performed where available.

5. Do the other benefits of evaluation by EUS in potentially resectable PNETs (multifocality, vascular involvement, biopsy of nodes) suggest it should be done in all patients?

As with EUS-FNA, EUS alone plays a specific role in potentially resectable PNETs, but should only be performed where there is potential for added benefit. When there is a question of multifocality, as in MEN1 patients, EUS should be performed. Similarly, if EUS aids in informing surgical strategy, then EUS should be performed. The evidence for EUS alone in MEN1 has been assessed in multiple studies. Barbe and colleagues performed EUS in 90 patients with MEN1; although 268 lesions were detected with EUS, only 158 were detected with MRI.[35] In a prospective study comparing EUS and cross-sectional imaging in 41 MEN1 patients, 101 lesions were detected in 34 patients with a mean size of 9.1mm by EUS.[36] Endoscopic ultrasound demonstrated 83% accuracy and confirmed multiplicity of lesions in this population. Importantly, EUS was positive in patients with negative imaging studies and detected additional lesions beyond conventional imaging.

With regards to EUS for vascular involvement, multiple studies have compared the ability of EUS and cross-sectional imaging techniques for evaluation of pancreatic adenocarcinoma, but none have been performed to evaluate PNET resectability. Extrapolating from

the pancreatic adenocarcinoma literature, EUS has comparable accuracy when compared to CT or MRI, ranging from 61-88%.[37,38]

Recommendation: Endoscopic ultrasound should be performed to identify multifocal disease in MEN1 patients. EUS does not need to be performed to determine surgical resectability.

6. How should NF-PNETs <2 cm be treated?

Management of very small (<1 cm) and relatively small (1-2 cm; collectively T1) PNETs is a significant and increasingly commonly encountered clinical problem. There are no truly prospective or randomized investigations that can inform clinical practice. Recommendations, including prior consensus statements, have been based on retrospective single-institution or collected series and a limited number of systematic reviews. Important issues related to these tumors include the extent of initial evaluation necessary, the criteria to be applied in selecting patients for operation, the approach and extent of surgery that should be performed in those selected for operation, and the follow-up intervals and evaluations recommended for those patients who either do or do not undergo resection. Significant opportunities exist to make progress in our understanding of the natural history, underlying tumor biology, and the outcomes of patients with small PNETs, including through multi-institutional prospective registries and clinical trials. In addition, evaluation of less invasive and more informative diagnostic technologies, including liquid biopsy, FNA molecular diagnostics, and novel imaging will help improve clinical management. Alternative non-surgical management strategies, including targeted medical and tumor ablative therapies will also be important in these patients.

Relevant, representative single-institution investigations that have addressed the issue of treatment of modestly-sized PNETs include the study of Lee and colleagues.[39] In this retrospective study from the Mayo Clinic, clinicopathologic features and outcomes of 77 patients with NF-PNETs <4 cm managed non-operatively were compared to 56 patients treated with surgical resection. Median PNET size in the patients managed non-operatively was 1 cm, median patient age was 67 years, and median follow-up was 45 months. No disease-specific progression or mortality was identified in these patients. Median PNET size in the patients selected for operation was 1.8 cm, median age was 60, and follow-up was 56 months. There was no disease-specific progression or mortality in the patients who underwent operation, although 46% of patients had at least one postoperative complication. The authors concluded that small NF-PNETs are often biologically indolent, and non-operative management may be advocated in patients whose tumors remain stable on imaging.

Sadot and colleagues from Memorial Sloan Kettering Cancer Center performed a retrospective, matched case-control study of patients with asymptomatic PNETs <3 cm in initial size, and compared 104 patients who were observed with 77 patients treated surgically.[40] They noted that the observation group was older than the surgical group (64 vs. 49 years), and that there was significant crossover to surgery in the observation group (25% at a median of 30 months). Among those observed, there was no change in median tumor size (1.2 cm) and no progression. The authors concluded that observation was reasonable in patients with small, stable, and asymptomatic PNETs. Taken together, these and other single-institutional retrospective series suggest that many small, asymptomatic PNETs are biologically very indolent, do not enlarge or progress over time, and may be safely (if selectively) observed.

Haynes et al reported that 8% (3/39) of incidentally discovered, NF-PNETs that were <2 cm and resected developed recurrence or metastases. They concluded that even small tumors can have aggressive behavior and recommended resection.[41] Toste et al reviewed 116 patients having resection of small, NF-PNETs and reported positive nodes in 39% of those with tumors >2 cm and 7% with tumors <2 cm. Furthermore, they demonstrated that negative nodes were associated with better long-term survival (87% vs. 34% 10 year overall survival (OS) for node negative and positive patients, respectively), and concluded that observation was a reasonable option for patients with PNETs <2 cm.[42]

In a study of the National Cancer Database (NCDB), Sharpe and colleagues reported an analysis of 380 patients with non-metastatic PNETs ≤2 cm.[43] Among the patients identified from this administrative database, 71 (18.7%) were observed, while 309 (81.3%) underwent surgical resection. Univariate analysis of survival strongly favored resection (5-year overall survival 82.2% vs. 34.3%, P <0.0001), and multivariable analysis also favored resection (hazards ratio (HR), 2.23). In their discussion of these findings, the authors acknowledged significant limitations, including that NCDB is not structured to capture all patients at reporting institutions under observation and therefore this group might not have been representative. Furthermore, not all patients with small, enhancing pancreatic lesions undergo biopsy and therefore are not entered into the NCDB. Also, a number

of important covariates are not captured by the NCDB, including symptoms, reasons for selecting non-operative management, and disease progression/cause of death.

Finkelstein and colleagues performed a meta-analysis of observation versus surgical resection for PNETs, which analyzed 11 studies.[44] In total, 1607 patients were observed, and 1491 were resected. Overall survival was improved with resection for patients with all sizes of PNET at 1 year (relative risk (RR), 1.28 with non-surgical management), 3 years (RR, 1.84) and 5 years (RR, 2.10). Among patients with PNETs <2 cm, improved OS was seen at 3 years (RR, 1.70) and 5 years (RR, 2.21) for surgical resection. The authors acknowledged limitations of their analysis, including the assumption that significant selection bias was applied within the individual studies in terms of which patients had observation versus resection. Taken together, this study and that of Sharpe et al confirm that surgeons are capable of selecting patients with small PNETs who will potentially benefit from surgical resection, but the reporting and selection biases present suggest that caution should be applied in interpreting these results as a uniform endorsement of surgical resection in such patients.

Other information to consider regarding resection vs. observation in PNETs <2 cm in size is the rate of nodal and liver metastases, and the risk of death from disease. Bettini et al reported on 177 patients with resection of NF-PNETs, of which 90 were <2 cm, 46 were 2-4 cm, and 41 were >4 cm in size. The incidence of nodal and liver metastases were 14% and 0% in those with tumors <2 cm, respectively, 22% and 2% for 2-4 cm PNETs, and 49% and 10% for PNETs >4 cm. None of the patients with tumors <2 cm died of their disease, and the authors suggested that NF-PNETs that were incidentally discovered and <2 cm could be observed because of this low risk counterbalanced by the potential for morbidity, mortality, exocrine and endocrine deficiencies associated with pancreatic resection.[45]

A recent study combining data from 16 European centers reviewed results of 210 patients undergoing surgical resection for sporadic, non-metastatic, NF-PNETs <2 cm.[46] Two-thirds had formal resections while one-third had enucleations performed; 63% of all patients had LNs available for pathologic examination, and 10.6% were positive. Only 3% (4/133) of patients with grade 1 lesions had positive nodes, which increased to 16% (4/25) for grade 2 and 100% (1/1) in grade 3 tumors. Eleven patients (5.9%) developed recurrence at a median of 8 months, with 5 recurrences in the liver, 2 in LNs, 2 in the lung, 1 local, and 1 at multiple sites. The five-year survival rate was 96%, with the one death from PNET in the patient with a grade 3 tumor. All 59 patients with tumors 10mm or smaller were disease-free at 5 years, while those with tumors 11-20 mm had a 95% 5-year disease-free survival rate. On multivariable analysis, tumor size, the presence of biliary obstruction, pancreatic duct obstruction, and grade were all independent predictors of recurrence. They also noted that in 10% of cases the CT scan underestimated the size found on final pathology. The authors concluded that patients with ductal dilatation, grade 2 or 3 tumors should undergo resection, while in other patients with small PNETs <2 cm, surveillance is a reasonable strategy.

Partelli et al performed a systematic search of the literature for studies comparing resection vs. surveillance for small, NF-PNETs.[47] They found 5 studies (several discussed in this section) where 327 patients underwent surveillance and 231 had surgical resection, which included NF-PNETs smaller than 2, 3, or 4 cm in size.[39,40,48-50] In the patients under surveillance, 14% had resection and 41% of these were for tumor growth, 39% due to patient preference, and 15% for physician preference. The median times of surveillance prior to resection was 30-41 months. None of the patients under surveillance died due to their PNET. The authors concluded that surveillance of patients with small NF-PNETs is a reasonable strategy, but identification of factors other than increase in tumor size was limited due to the fact that it included some tumors >2 cm and that grade information was only available in 10% of patients.

There have been several consensus recommendations addressing the issue of management of T1 NF-PNETs. The European Neuroendocrine Tumor Society (ENETS) suggested that incidentally discovered NF-PNETS <2 cm could be selectively observed because of the low risk of malignancy.[51] The Canadian Expert National Group report advised that patients with NF-PNETs ≤2 cm in size demonstrated to have low Ki-67 and no evidence of invasion or metastatic disease could be considered for surveillance.[52] Both anatomic imaging and biochemical evaluation were recommended for such patients initially and every 6 months until stability was confirmed, and then annually thereafter; life-long follow-up for observed patients was implied. It was further suggested that EUS with FNA for histopathologic confirmation of grade/Ki-67, while desirable, was optional Enucleation was considered an acceptable surgical approach for small, low-grade PNETs. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Neuroendocrine and Adrenal Tumors, Version 1.2019 (https://www.nccn.org/professionals/physician_gls/default.aspx#neuroendocrine)[19] also provides recommendations for nonfunctioning PNETs <2 cm. Recommendations for

initial evaluation of patients with known or clinically suspected NF-PNETs regardless of tumor size or stage includes contrast-enhanced multiphasic CT or MRI, consideration for genetic testing, and selective use of ^{68}Ga-DOTATATE PET/CT or SSTR scintigraphy, chest CT, EUS, and biochemical evaluation. NCCN offers that patients with tumors <2 cm may be selectively observed (this recommendation is stronger for those with PNETs <1 cm that are incidentally identified and are of low grade). It is further recommended that surgical risk, site of tumor, and patient co-morbidities be considered in deciding observation vs. resection in such patients. For those selected for surgical resection, either enucleation or formal resection are considered appropriate, with or without regional LN removal based on the details of presentation and surgeon judgment. Mansour et al used a Delphi consensus process to make recommendations on asymptomatic, well-differentiated PNETs.53 There was consensus that tumors <1 cm in size should be observed and that tumors >2 cm should be resected. There was no consensus on whether PNETs 1-2 cm in size should be resected or observed, and it was thought that this decision should be made based upon patient age, co-morbidities, location of the tumor, and change in size over time. In each of these consensus recommendations, limitations of available data constrain the specificity of recommendations that are provided with regards to initial evaluation, extent of follow-up, selection criteria for observation versus resection, and the extent of surgical resection indicated.

Recommendation: Given this background, initial observation without a plan for immediate surgical resection is an acceptable treatment strategy for asymptomatic patients with a pancreatic tumors <1 cm in size and with imaging characteristics consistent with a PNET. In such patients, biopsy is not routinely necessary to confirm the diagnosis prior to making a decision for observation. It is recommended that the decision to observe or resect an asymptomatic PNET 1-2 cm in size be individualized. Criteria that should be considered in decision-making include age and co-morbidities, tumor growth over time, estimated risk of symptom development, details of imaging, grade, the extent of surgical resection required, the patient's wishes, and access to long-term follow-up.

7. Should all functional lesions be resected?

Although numbers vary amongst studies, functional PNETs represent the minority of all PNETs, from 10-40%.[7,54] In the setting of non-metastatic sporadic functional PNETs, the goals of resection are two-fold: (1) management of the endocrine syndrome to control symptoms, and (2) tumor control to improve survival Management rests on proper classification of the tumor by confirming the biochemical diagnosis of a functional endocrine syndrome, ruling out the presence of MEN1, staging via imaging to exclude the presence of distant metastases, and pathologic examination to determine Ki-67 labeling index.[55-59] To confirm the endocrine syndrome diagnosis, consultation with endocrinology should be considered. Once the endocrine diagnosis is established, two scenarios are possible: the PNET may be identified (localized) or not.

In the presence of a localized functional PNET without distant metastases, resection is indicated. This addresses the endocrine syndrome and provides curative-intent therapy of the tumor to prevent metastatic spread. The risk of malignancy varies depending on the type of functional PNET, which ranges from 5-15% for insulinoma, to 60-90% for gastrinoma, glucagonoma, and tumors secreting VIP, PTHrP, or ectopic ACTH.[7,54,60,61] Long-term cure rates after R0 resection of localized disease also vary with the type of tumor. Resection of a localized insulinoma results in a 98% biochemical cure rate with a 6% chance of recurrence at 10 years.[62] Biochemical cure for apparently sporadic gastrinoma is 60% immediately after surgical resection and 30-40% after 5 years, with a 15% 15-year disease-free survival rate. Only rare instances of cure are reported for more aggressive PNETs such as those secreting glucagon, VIP, PTHrP, or ectopic ACTH.[60,61,63-66] When resection is undertaken, removing the regional LNs should be considered, although the prognostic and therapeutic roles of nodal disease have been studied most extensively for NF-PNETs.[67-69] In functional PNETs, this issue has been most closely examined for gastrinoma, where LN resection increases the chances for biochemical cure and improves overall survival[66,70]

When an endocrine functional syndrome associated with PNET has been identified, such as insulinoma or gastrinoma, but a PNET has not yet been localized, further investigations should be pursued prior to operation. Comprehensive investigations should include upper gastrointestinal endoscopy, cross-sectional imaging with pancreatic triphasic thin-sliced CT scan, MRI, and/or EUS. If available, intra-arterial simulation testing or venous sampling should also be considered, if these other studies are unrevealing.[71] Finally, if the PNET is still not localized despite these investigations, exploration with intra-operative ultrasonography should be performed in a center where there is specialized surgical expertise for this procedure and PNETs. SSTR-PET/CT can be useful to identify PNETs, with sensitivity of 100%, specificity of 57%, and accuracy of 94.8% for non-insulinoma PNETs,

including NF tumors.[72] However, its role is limited for insulinoma due to low sensitivity, specificity and accuracy, all which are approximately 25%.[73] In the event where the tumor remains non-localized, patients should be referred to expert centers for functional PNETs prior to embarking on surgical exploration.

The scenario of non-localized functional PNET presents most often with insulinoma and gastrinoma. While surgical exploration had been traditionally part of the management algorithm for those patients, it is not currently recommended routinely.[74,75] In the case of insulinoma, the morbidity associated with an extensive pancreatic mobilization and 10% risk of non-palpable or non-visible tumors outweigh the low-risk of malignancy.[75] Therefore, surgical exploration or blind resection of the tail of the pancreas are not recommended. Symptoms can often be managed effectively with medical therapy, with interval reimaging recommended. For gastrinoma, the surgical data supporting routine exploration for non-localized tumors rely on patients treated at a time when the sensitivity of imaging was limited (most studies were done between 1983-2003).[63,76,77] The majority of gastrinomas identified during surgical exploration were small duodenal lesions with lower gastrin levels, which portend the best prognosis for this type of disease.[78,79] Patients who died from gastrinoma presented with higher gastrin levels, pancreatic primary tumors, and metastases, and were identified preoperatively.[79] The biochemical cure rate in those patients was limited to 46% at a median of 9 years.[74,78] Taking all this into consideration, as well as the efficacy of medical therapy to provide long-term control of acidity-related symptoms, surgical exploration with duodenotomy should not be undertaken routinely.[54] Patients with non-localized gastrinoma should be referred to centers with expertise in gastrinoma and surgical exploration limited to those centers.

Recommendation: Patients with a localized, biochemically confirmed, functional PNET should be resected because clinical syndromes associated with each are significant, even when small in size. Furthermore, with the exception of insulinoma, the majority have significant malignant potential When tumors cannot be localized or the biochemical diagnosis established, patients should be referred to specialized centers for further evaluation.

8. When should one resect PNETs in patients with MEN1?

The unique features of the pancreaticoduodenal tumors that originate in patients with MEN1 include earlier age of onset compared with sporadic tumors, and preneoplastic hyperplasia and multiple microadenomas throughout the target tissue, which precede the asynchronous development of clinically significant tumors. Patients at risk for these familial tumors based on an inherited germline mutation can be identified in most cases by direct DNA mutation testing.[80] This allows for focused surveillance and early intervention in patients in which tumors are detected during prospective screening. However, the natural history and risk of malignant progression for individual PNETs in patients with MEN1 are not well defined.[81,82] The optimal surveillance and surgical intervention strategy would allow management early enough to prevent malignant progression, while minimizing treatment-related morbidity and maximizing preservation of pancreatic endocrine and exocrine function.[83,84] There are limited data available to specifically address all of these issues.

In general, functional PNETs should be resected in patients that can undergo an appropriate surgical procedure for the size and extent of tumor involvement, and who have an acceptably low surgical risk (see additional comments regarding gastrinomas below). The preponderance of evidence supports removal of PNETs >2.0 cm in size in patients with MEN1, while radiographically relatively stable NF-PNETs <1.0 cm in size can be safely observed if an appropriate program of surveillance and follow-up can be implemented.[46,49,85,86]

The available data and therefore the strength of the recommendation regarding appropriate management of PNETs 1.0 to 2.0 cm in size are less clear. The decision to observe or resect 1–2 cm NF-PNETs can be individualized based on additional factors such as the development of symptoms, Ki-67 index or grade if this pathologic information is available, family history, individual patient factors, comorbid conditions, and growth rate or radiographic progression.[85,87,88] An EUS-based study of the growth rate of 226 PNETs in 38 patients with MEN1 over a 13-year period described an annual incidence rate of 0.79

PNETs/year in these patients, and an average growth rate of 0.1 mm/year. Those PNETs that were <10 mm did not grow, whereas PNETs 10mm or larger grew at a rate of 0.44 mm/year. PNETs identified at the time of the initial EUS grew at an overall rate of 0.21 mm/year.[89] A spectrum of mutations has been identified in neuroendocrine tumors.[90] There are no validated significant genotype-phenotype correlation in patients with MEN1 nor are individual patient genotypes routinely used to make surgical decisions. However, patients with MEN1 and mutations in Exon2,[91] the JunD binding domain,[92] or those resulting in loss of interaction with the CHES1 binding domain[93] have been identified as potentially conferring higher risk for the development of primary or metastatic PNETs, and those patients therefore may be candidates for more intensive screening or earlier surgical intervention.

In general, patients with MEN1 harboring functional PNETs are candidates for resection. However, surgeons operating on such patients should be aware that the multiplicity of PNETs in MEN1 patients makes definitive preoperative determination that the dominant tumor identified is actually the source of hormone overproduction difficult. Furthermore, hypergastrinemia in MEN1 patients much more commonly arises from duodenal gastrinomas rather than from PNETs. Because gastrinomas in MEN1 patients are commonly small, multiple, and difficult to image, and control of hypergastrinemia with surgical resection has been challenging to achieve, surgical versus medical management of MEN1 patients with hypergastrinemia has been controversial[77,94] Surgical resection for MEN1 patients with hypergastrinemia may be most reasonable in patients with LN metastases, poorly controlled symptoms, or in those with PNET-dominant disease.

The appropriate operative procedure for patients with MEN1 who are selected for surgery should be determined by the size and distribution of PNETs or duodenal NETs, and the desire to preserve pancreatic function.[83,84] The decision to perform enucleation versus major pancreatic resection (pancreaticoduodenectomy [PD], distal pancreatectomy[DP]), or a combination of these procedures, should be individualized. An oncologically sensible and ideally comprehensive operative procedure should be designed with the goal of removing the largest tumors or tumors estimated to have the highest risk of malignant progression, achieving the maximum possible reduction in tumor burden, while minimizing the risk of operative morbidity and maximizing preservation of pancreatic endocrine and exocrine function.[84] The routine use of intraoperative ultrasonography is an important adjunct to surgical exploration for PNETs in patients with MEN1, and consideration should be given to referral of these patients to a high volume Endocrine Surgery center.

Recommendation: In MEN1, NF-PNETs <1 cm can be observed while tumors >2 cm should generally be resected. Functional PNETs should be removed when possible and there is a dominant lesion. Medical management may be considered in many cases of gastrinomas. Multicentricity of PNETs renders surgical decision making complex and unlikely to eliminate all disease in the long term. Therefore, removal of the dominant lesion and potentially other easily accessible lesions that might be present should be the goal, balanced by preservation of pancreatic function and reducing the risk of complications.

9. What is the optimal surgical strategy in patients with familial PNETs?

Pancreatic NETs can also occur in association with other genetic syndromes, including VHL, NF1, TSC1 and TSC2, however the incidence of PNETs in these other syndromes is low in comparison to that in MEN1. Management of PNETs in VHL will be addressed in the next section.

PNETs occur with low frequency in patients with TSC, caused by mutations in the TSC1 or TSC2 genes, which activate the AKT-mTOR oncogenic pathway.[95] Additional endocrine neoplasms such as parathyroid adenomas, pituitary adenomas, adrenomedullary tumors, and gastroenteropancreatic NETs (GEPNETs) may occur with increased frequency in these patients. Most of the reported PNETs in patients with TSC occur in association with TSC2 mutations. The size range of the tumors reported in the literature is 2 to 21 cm; however, the PNETs that occur in association with TSC are typically small, benign, well-differentiated, and functional neoplasms located in the body or tail of the pancreas, with insulin-secreting tumors being common. Malignant tumors have been reported in a few patients, and multiple tumors have also been described. The PNETs that develop in association with TSC may be diagnosed in childhood, but frequently become clinically evident in adults. There appears to be a predilection for male sex in the tumors reported in the literature. Because of the infrequent occurrence and small numbers of tumors described in the literature (only 10 were reported by 2012),[95] it is difficult to make evidence-based surveillance or treatment recommendations. Some have recommended the addition of abdominal imaging in the second decade for patients who are known to be genetically affected with TSC and this recommendation seems reasonable. The management of these tumors

should be based on standard clinical judgment in the context of individual patient factors, such as size, malignant potential of the tumor, and the risk of morbidity associated with the planned intervention. Resection of functional tumors to cure the syndrome of hormone excess (e.g. hypoglycemia due to insulinoma) is indicated when safe and feasible. TSC patients can develop disabling neurologic disorders such as epilepsy, mental retardation, and neurobehaviorial disorders including autism, in addition to multiple hamartomas, and very infrequently, PNETs.[96] Individual comorbid and patient factors may influence the optimal management of PNETs in affected patients. Most of these tumors are curable by complete resection when appropriate, but the rarity of these tumors in TSC does not provide high level evidence to offer management recommendations other than best clinical judgement based on expert opinion.

Neuroendocrine tumors develop in patients with NF1, but are relatively uncommon (0-10%).[97-100] These NETs are almost exclusively duodenal periampullary somatostatinomas, but PNETs occur rarely. By comparison, gastrointestinal stromal tumors occur much more frequently, and are likely the most common NF1-associated gastrointestinal tumor. The NF1-associated duodenal somatostinomas are usually clinically silent and do not result in a functional somatostatinoma syndrome. Nevertheless, they may frequently cause jaundice, biliary obstruction and pancreatitis, and can result in pain, nausea, bleeding, or vomiting. There are limited data to establish surgical management guidelines for these rare tumors. Because these duodenal somatostatinomas are malignant in 30% of patients in the reported series, and may cause early biliary obstruction or symptoms due to their periampullary location, many experts have recommended pancreaticoduodenectomy, particularly for tumors >2 cm. However, local surgical or endoscopic resections are also potentially appropriate for localized tumors <2 cm, if surgically feasible.[101]

Pancreatic NETs may also occur rarely in association with other germline defects, such as mutations in the phosphatase and tensin homolog (PTEN) gene resulting in Cowden syndrome and related disorders.[102] A clear association of these tumors with the underlying genetic defect has not been established and these tumors occur too rarely to allow for evidenced-based diagnostic or treatment recommendations.

The occurrence of PNETs in association with one of these inherited syndromes allows the opportunity for pre-symptomatic screening and focused surveillance for the early detection of tumors when they are small, more amenable to surgical treatment, and ideally prior to malignant spread. Although the rarity of these entities precludes the availability of high level evidence for diagnostic and management algorithms, the unique features of the PNETS that are associated with one of the genetic syndromes do highlight some common treatment concerns and tenets. Familial PNETs tend to occur at an earlier age when compared with sporadic tumors, and may be multifocal within the pancreas. There is variability in the tumor biology and malignant potential between the different syndromes, and often the natural history may not be well-defined. In the absence of sufficient numbers of patients to allow for high level evidence, treatment recommendations must be made based on available series and best expert opinion.

Recommendation: Common themes in the management of PNETs in the familial setting include the desire to intervene prior to the development of significant risk for malignant progression, and the need to minimize treatment-related morbidity and mortality with careful surgical decision making and non-operative surveillance for low-risk tumors.[84] Individual patient factors, co-morbidities, and the potential need for multiple operations over time to treat multifocal or metachronous tumors should be considered when choosing the optimal timing and extent of operation. Broad principles in the management of these familial PNETs include parenchyma-sparing operations aimed at preservation of pancreatic endocrine/exocrine function, watchful surveillance when appropriate for low-risk tumors, enucleation or minimal pancreatic resection for intermediate-risk tumors when feasible and effective, and reserving major pancreatic resection for locally invasive, anatomically difficult, or high-risk lesions.

10. When should one resect PNETs in patients with VHL?

The PNETs that occur in a subset of patients with VHL syndrome are associated with unique features relating to their incidence, natural history, and prognosis. Pancreatic lesions develop in approximately two-thirds of patients, but most of these lesions are cysts (simple pancreatic cysts, serous cystadenomas, or hemangioblastomas).[103] Overall, about half (47%) of VHL patients develop pancreatic cysts that are benign, and do not require surgical or endoscopic intervention unless they are symptomatic, cause pancreatitis, or result in bile duct compression. PNETs are seen in 15-20% of patients with VHL and are therefore less frequent than many of the other common VHL manifestations.[104,105] The PNETs associated with VHL are considered non-functional as there are only

case reports of functional lesions, and larger studies have failed to report evidence of functionality.[103-109] As a result, VHL associated PNETs are asymptomatic and their management is predicated on reducing the risk of distant spread. For those patients with VHL PNETs, distant disease is only seen in 9-12%.[104,105,107] As a result of this low malignant potential, surgical management of primary VHL associated PNETs should be reserved for those patients at greatest risk for developing metastatic disease.

Cross-sectional imaging with CT/MRI should be used to evaluate patients with VHL-associated pancreatic lesions to detect the solid masses which represent PNETs.[103] The addition of functional imaging with ^{68}Ga-DOTATATE-PET–CT and ^{18}F-fluorodeoxyglucose (FDG)-PET–CT may be helpful for evaluating patients with equivocal diagnostic findings on anatomical imaging. EUS with or without fine needle biopsy may be employed in patients with indeterminate pancreatic lesions.[103] Pancreatic NETs in patients with VHL appear to occur more frequently in the head and uncinate process of the pancreas (52%) compared to the pancreatic body (21%) or tail (28%).[106]

Natural history studies with long term follow-up have been conducted in an attempt to correlate clinical and genetic features of these tumors with the risk of developing metastatic disease. Studies have focused on primary tumor size, rate of tumor growth, presence of certain germline VHL mutations and imaging characteristics in an attempt to define specific criteria to inform the decision to operate versus observe.[103-109] While there have been no prospective, randomized studies comparing an operative versus an expectant approach, information gathered from natural history studies have nonetheless been informative.

Tumor size has been shown to correlate with increased risk of developing or presenting with distant disease. There is agreement among studies that lesions 3 cm or larger should be considered for resection and lesions smaller than 2 cm can be safely observed. There has been debate among studies regarding those lesions between 2 and 3 cm.[109] However, the consensus favors <3 cm as the cutoff for observation. Some have recommended that PNETs ≥3 cm in diameter located in the body or tail of the pancreas should be resected, but that those ≥2 cm in the pancreatic head should also be considered for surgical resection to preserve the option of local tumor enucleation, if sufficiently distant from the main pancreatic duct to avoid the need for a pancreaticoduodenectomy.[103,104] Whether different size criteria should be applied based upon the location of the PNETs in VHL is specifically addressed in the next question.

Rate of tumor growth has been shown to be associated with risk of distant disease, with doubling times less than 500 days correlating with increased risk of metastases. This observation has been confirmed in several, but not all studies.[109] It is important to have consistent imaging data using the same imaging modality when calculating changes in tumor size and rate of tumor growth.

There is evidence from several studies that specific hotspots exist with respect to germline mutations that may predict a more aggressive PNET biology.[105,107,109] The most consistent finding has been that mutations in exon 3 are associated with an increased risk of distant disease. Further studies are needed to refine this data to more specific mutations.

Taken as a whole, tumor size 3 cm or larger, doubling time <500 days and germline mutations in exon 3 are each considered poor prognostic factors with respect to metastatic risk.[103,107]

Recommendation: Tumor size, rate of growth and germline mutation should be determined in VHL patients with PNETs. Those with tumors less than 3 cm in size, with doubling times greater than 500 days and mutations outside of exon 3 can be safely observed with serial imaging every 1-2 years. Patients with a single high-risk factor (tumor size 3 cm or larger, doubling time < 500 days or germline mutations in exon 3) should be considered for surgery versus more frequent imaging at 6-12 month intervals depending on other factors and comorbidities unrelated to their PNET. Finally, patients with two or more high-risk factors should be strongly considered for surgical resection.

11. How are size criteria influenced by tumor location in the head versus the body or tail in patients with VHL?

While initial studies recommended resection of lesions in the head when they reach 2 cm or larger in size and resection of body and tail lesions when the reach 3 cm or larger.[104] this was based on a desire to avoid the need to perform a pancreaticoduodenectomy. There is no evidence for any difference in biologic behavior for lesions depending on their anatomic location and therefore no evidence that size criteria for resection should be influenced by location of the tumor.

Recommendation: The decision to resect a PNET in patients with VHL should be based on the criteria described under question 10 regardless of the lesion's location. Location should only be used in decision making

regarding the type of resection employed and should not be interpreted as having any biologic influence on the decision to resect or not to resect.

12. Is laparoscopic distal pancreatectomy equivalent to an open procedure?

Several guidelines have considered approaches for resecting PNETs located in the tail of the pancreas,[110,111] and the laparoscopic approach has been considered to be safe and effective.[112] Experts from the European Association for Endoscopic Surgery concluded that laparoscopic DP is safe and feasible for PNETs with satisfactory postoperative and oncologic outcomes.[113] Conversion rate and intraoperative blood loss were suggested to be indicators of the learning curve. Experts agree that in PNET patients the indication for DP should not be influenced by the fact that a minimally invasive option is available.

Although most reported data demonstrate short-term and oncologic outcomes to be generally equivalent or superior for laparoscopic DP compared to an open approach, these benefits have rarely been reported for PNETs specifically.[112] Extrapolating from the adenocarcinoma literature, the large, case-matched pan-European minimally invasive vs. open DP for ductal adenocarcinoma study (DIPLOMA) study reported favorable blood loss, hospital stay and R0 resection rate for the laparoscopic group, albeit with lower LN retrieval[114] There was no difference in morbidity, 90-day mortality, and overall survival between the two techniques.

There is now level 1 evidence that the minimally-invasive surgical (MIS) approach to DP provides advantages over the open approach for this procedure.[115] De Rooji et al have recently published a randomized trial examining minimally invasive vs. open DP (LEOPARD) for left-sided tumors or pathology, 65% of which were PNETs. In this trial from the Netherlands, 108 subjects were randomized and received open DP or laparoscopic DP. Eligibility included tumors confined to the pancreas (<8 cm), with an intact posterior pancreatic fascial layer not involving any adjacent viscera, at least 1 cm distant from the celiac artery, had not received radiation, and without chronic pancreatitis. The primary endpoint was a novel composite metric of "time to functional recovery" (independently mobile, oral pain medications, taking 50% or more of daily caloric needs, no iv fluids, no infection). Time to functional recovery was 4 days in the laparoscopic DP group versus 6 days for the open ($P < 0.001$). Operative blood loss was also significantly less after MIS DP (150 vs. 400 mL; $P <0.001$). Operative time was longer in the laparoscopic group (217 vs. 179 minutes; $P= 0.005$) and the conversion rate was 8%. Another randomized trial is being conducted in a single center in Sweden (the laparoscopic vs. open DP or LAPOP trial), and the results are expected to be available in 2020.

Although larger retrospective studies and randomized controlled trials report on adenocarcinoma or mixed indications, some studies specifically on PNET are available. Xourafas et al evaluated 171 PNET patients, of whom 73 underwent laparoscopic vs. 98 having open DP.[116] Hospital stay and postoperative complications were significantly reduced in the laparoscopic group ($P=0.008$ and $P=0.028$, respectively) and there was no difference in incidence or grade of pancreatic fistula in the 2 groups. R0 resection rate and OS were similar between the groups as well. A systematic review and meta-analysis of laparoscopic vs. open PNET resections reported a lower overall complication rate, reduced intraoperative blood loss, and decreased length of stay for patients undergoing laparoscopic resection.[117] A frequently discussed topic is the controversy around the costs associated with minimally invasive pancreatic resections. While the up-front costs for surgical supplies and operating room time have been reported to be higher for the laparoscopic group, lower postoperative costs may balance out the total cost, resulting in similar or possibly decreased cost for minimally invasive pancreatic resections.[118]

Recommendations: Level 1 evidence suggests that intra- and post-operative parameters of the laparoscopic approach for DP are improved and long-term outcome are comparable to an open approach for appropriately selected patients when these operations are performed in centers with appropriate expertise. Conflicting data exist regarding relative costs associated with the laparoscopic versus open approach. While patients with T1-T2 lesions may benefit from the laparoscopic approach in a center with appropriate case volume and staff experience, patients requiring multi-visceral resection, those with larger tumors, those with significant lymphadenopathy, or those with significant venous tumor thrombus are currently more likely to be better managed by an open approach. Laparoscopic DP should be considered by surgeons cognizant of their own learning curve and experience in caring for patients with PNETs.

13. When should splenic preservation be employed in DP cases?

While splenic preservation during DP may be technically demanding and carries the risk of hemorrhage or infarction, and may also limit nodal retrieval in patients at risk for regional metastasis, it helps to preserve patients' innate immune responses. Patients with

low risk sporadic PNETs unlikely to have occult nodal metastases, patients predicted to have long survival, and those who develop PNETs at a young age may potentially benefit the most from preserved splenic function and may be considered most appropriate for planned splenic preservation. In this context, Kristinsson et al showed an increased risk of septicemia, pancreas and bladder cancer, as well as pulmonary embolism in a large cohort of American veteran patients in long-term follow up after splenectomy (generally performed after abdominal trauma).[119] A recent meta-analysis evaluating minimally invasive DP with and without splenectomy demonstrated less infections, fewer clinically relevant pancreatic fistulae, shorter operative time, and less blood loss in those with splenic preservation.[120] These results suggest that in carefully selected patients, the added benefits of splenic preservation outweighs its risks. When judged desirable, splenic preservation during DP can be accomplished by two techniques: (1) Warshaw's technique (the splenic vessels are ligated, and the spleen derives its blood supply from the short gastric vessels); and (2) the splenic vessel preservation technique (the splenic artery and vein are dissected out and preserved). While the Warshaw technique can be an important option for preserving splenic function, data suggest that splenic vessel preservation is associated with significantly reduced estimated blood loss, morbidity, clinically relevant pancreatic fistulae, risk of splenic infarctions (5 vs. 39%; P < 0.01), and shorter hospital stay.[121-123] To date, three meta-analyses report significantly lower incidence of splenic infarction, gastric varices, and need for postoperative splenectomy when splenic vessel preservation is employed relative to the Warshaw technique.[120,124,125] In contrast, several studies report longer operative time and higher blood loss in patients with attempted vessel preservation.[123,126] Therefore, the technical approach and decision regarding concomitant splenectomy should be individualized based on a combination of patient factors and surgeon experience. To this end, preoperative predictors of successful splenic vessel preservation during DP have been reported. For example, a tumor cut-off size of <3 cm, especially in pancreatic body tumors, suggests favorability for splenic preservation,[127] whereas preoperative splenomegaly suggests difficulty for vessel preservation due to insufficient blood supply to an increased splenic mass by short gastric vessels alone.[126]

Splenectomy may be necessary in many PNET patients with distal tumors, and it is emphasized that important contraindications arguing against splenic preservation exist. These include large PNETs, chronic pancreatitis, tumors abutting or invading the splenic vasculature, bleeding during attempting vessel preservation, tumor thrombus, and peripancreatic inflammation following the effects of neoadjuvant chemotherapy.[128] In addition, splenic preservation severely limits the ability to harvest splenic hilar lymph nodes, and therefore surgeons should be cautious in performing splenic preservation in PNET patients at significant risk for distal nodal metastasis.

Recommendation: Spleen-preserving DP should be considered when favorable tumor factors are present as discussed above. There is conflicting evidence on the benefits of splenic vessel preservation over the Warshaw technique, which may be employed when vessel ligation during DP becomes necessary or tumors encroach upon the vasculature. [122,123] When PNETs are large or invade the splenic vein and/or surrounding structures, splenic preservation may not be advisable.

14. What is the optimal vaccination strategy if splenectomy is performed?

Splenectomized patients are at risk for severe sepsis, primarily from encapsulated organisms such as Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis.[129,130] In patients undergoing elective splenectomy as part of DP for PNET, a vaccination strategy should be preplanned. Patients undergoing elective splenectomy should receive pneumococcal, meningococcal, and H. influenzae vaccination at least 14 days prior to surgery.[131] If it is not possible to administer these vaccines prior to splenectomy or if a spleen-preserving pancreatectomy is planned but splenectomy is subsequently required, they should be given after the 14th postoperative day, when the patient is able to mount an appropriate immune response. Regarding pneumococcal vaccination, it is recommended that adults in the United States receive 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) in conjunction with splenectomy. While PPSV23 has been recommended for asplenic individuals for many years, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended adding PCV13 for adults with functional or anatomic asplenia in 2012. PCV13 is given first, then PPSV23 8 weeks later to extend the serotype coverage. For N. meningiditis, two vaccines (tetravalent Men ACWY and Men B) are each given twice, 8 weeks apart; for protection against H. influenzae type b, the Hib vaccine is given once. [132]

If postoperative vaccine administration is performed prior to postoperative day 14, it is reasonable to repeat the post-splenectomy vaccines eight weeks after the initial doses. In patients undergoing immunosuppressive chemotherapy or

radiotherapy, immunization should be delayed for at least three months after completion of therapy.[131] Additionally, if compliance concerns exist, surgeons caring for patients who undergo splenectomy should consider vaccination of their patients prior to discharge. Furthermore, while influenza vaccination is recommended for all individuals >6 months of age, it is particularly important for patients with risk factors for influenza complications such as asplenic patients, in whom an inactivated influenza vaccine rather than the live attenuated influenza vaccine should be used. Asplenic patients should receive booster doses of select vaccines (PPSV23, meningococcal ACWY) every 5 years thereafter, and should also receive immunization for influenza yearly.[132] For further information on vaccination of patients undergoing splenectomy and future practice updates, see the vaccination guidelines by the (ACIP) of the Centers for Disease Control and Prevention (CDC).[134,135]

Recommendation: Patients undergoing planned splenectomy should be vaccinated for encapsulated organisms as outlined above at least 14 days prior to operation, or if unplanned splenectomy is performed, at or beyond 14 days postoperatively. Booster doses for pneumococcus and meningococcus should be given to asplenic patients every 5 years.

15. What is the role of robotic surgery for DP in PNETs?

The LEOPARD trial demonstrated the advantages of the MIS over the open approach for DP in appropriately selected patients with left-sided tumors.[115] However, there are currently no randomized controlled trials directly comparing laparoscopic and robotic DP. There are several publications in the literature that retrospectively examined cohorts having robotic and laparoscopic DP. Nearly all of these are included in a recent meta-analysis by Guerrini et al[136] This paper reviewed 10 manuscripts including 813 patients. The analysis demonstrated significantly lower conversion rates using the robotic platform (OR 0.33 P <0.003). Consistent with the lower rate of open conversion, the length of stay was also lower in the robotic group. There were no differences in overall complications or pancreatic fistula. Two recent publications retrospectively compared outcomes of robotic and laparoscopic DP from the National Surgical Quality Improvement Program (NSQIP) database. Zureikat et al examined the 2014 NSQIP Hepatectomy and Pancreatectomy Procedure Targeted database.[137] They reported on 1582 DP performed in this time period, of which 829 were performed open, 571 were laparoscopic and 170 were robotic. They observed statistically significant higher number of DP completed in a pure MIS approach (without hand assist) when the robotic platform was utilized (56% laparoscopic vs. 67% robotic, p=0.017). Similarly, Nassour et al examined this same database from 2014-2015, which included 2926 DP, of which 682 (53.2%) were laparoscopic, 276 (21.5%) laparoscopic with hand assist, 247 (19.3%) robotic, and 76 were robotic with hand assist.[138] They observed that the conversion rate was 17.3% with the laparoscopic and 8.5% with the robotic approach (P <0.001). Of note, this group also found that conversion was independently associated with worse outcome in multivariate analysis.

Recommendations: Level 1 data support that MIS DP is the preferred approach to tumors confined to the distal pancreas (<8 cm, without local invasion) with respect to short-term outcomes (time to recovery, blood loss). Given preliminary data suggesting improved completion rates with the robotic platform, consideration should also be given to this approach in centers with appropriate expertise.

16. What is the role of robotic surgery for Whipple procedures?

The majority of the data regarding robotic PD are from single institutional, small series. One exception is a large, propensity-matched cohort study by Zureikat et al.[139] In this report, the authors examined 1028 patients undergoing PD at 8 high volume institutions, with 2 of these centers contributing robotic cases (RPD) and included only surgeons who were past their learning curve of 80 RPDs. There were 211 RPD (20.5%) and 817 open PD (79.5%). On multivariable analysis, RPD was associated with longer operative times (by 75.4 minutes, P <0.01), reduced blood loss (mean difference 181 mL, P <0.04), and reductions in major complications (odds ratio 0.64, P <0.003). There were no differences in 90-day mortality, clinically relevant postoperative pancreatic fistula (POPF), wound infection, length of stay, or 90-day readmission. In the 522 (51%) patients with pancreatic ductal adenocarcinomas, there was no difference between robotic and open procedures with respect to the number of LNs harvested.

Results with laparoscopic PD may not be as favorable as seen with the robotic approach. The LEOPARD-2 trial randomized patients with tumors requiring PD to laparoscopic or open PD by surgeons who had performed at least 20 laparoscopic PD cases.[140] The data and safety monitoring board terminated the trial early due to high mortality in the laparoscopic group (8/70 patients vs. 1/69 in the open PD group). Furthermore, median time to functional recovery was longer in the laparoscopic group (10 vs. 8 days), as were grade III complications (50% vs. 39%). A recent meta-analysis compared open to

laparoscopic and robotic PD from twenty studies with 2759 patients.[141] There were no differences in postoperative mortality between these techniques. There were improved rates of delayed gastric emptying, length of hospital stay, number of LNs, and postoperative morbidity with the robotic approach. The laparoscopic approach was associated with higher rates of major complications, postoperative bleeding, and biliary leak. Two additional manuscripts examined the NSQIP database from 2014-2015 and found decreased conversion rates for PD when the robotic platform was utilized.[137,141]

Recommendations: Robotic PD has demonstrated equivalent and even improved perioperative outcomes in retrospective series when compared to open PD in the hands of highly experienced surgeons past their learning curve of 80 cases. Robotic PD is associated with decreased conversion rates when compared to laparoscopic PD. At this time robotic (and all MIS PD) should only be attempted at high volume centers by surgeons with extensive open and MIS experience in pancreatic surgery.

17. When should enucleation be employed for PNETs?

Indications for enucleation as compared to resection of PNETs has not been subject to rigorous review, and there have been multiple single institutional, small series examining enucleation versus formal pancreatic resection for PNETs and benign cystic lesions of the pancreas. A systematic literature review of 838 patients having enucleation for "benign" lesions (most of which were PNETs but also including cystic lesions) discussed that tumor size larger than 3 to 4 cm and the proximity of tumors to the main pancreatic duct were the most commonly accepted limitations to using enucleation.[142] Enucleations are considered more frequently for small tumors in the pancreatic head as a means of avoiding pancreaticoduodenectomy, while lesions in the tail are more likely to be resected.[143,144] For functional tumors, insulinomas are more amenable to enucleation than other tumors due to their smaller size at diagnosis and benign behavior.

With respect to perioperative outcomes, a recent meta-analysis including the majority of these studies was performed by Huttner et al[145] In this study, 22 non-randomized, retrospective studies were examined that included 1148 patients. In the final analysis, enucleation demonstrated improved operative times, estimated blood loss, length of stay, and rates of postoperative endocrine (3/215 for enucleation, 39/349 for resection group) and exocrine insufficiency (1/168 for enucleation, 69/291 resection). There were no differences in mortality, overall complications, or return to the operating room. Formal resection demonstrated reduction in POPF (110/432 in the enucleation group, 141/716 in resection group, odds ratio, 2.09). Additional studies have demonstrated that the increased rate of POPF with enucleation was mitigated at high volume centers performing more than 20 cases a year.[87,146]

Recommendation: Enucleation is associated with improved endocrine and exocrine function but at a cost of higher POPF. Criteria for selection of patients for enucleation have not been defined, but expert opinion suggests that enucleation should be reserved for smaller tumors, those more likely to display benign behavior (such as insulinomas or NF-PNETs <2 cm), and that are located >2-3 mm from the main pancreatic duct. Formal resection with lymphadenectomy should generally be considered for larger tumors where there is risk of LN involvement.

18. What type of margin is considered adequate for PNET resection and for enucleations?

There are no randomized trials nor large series examining the impact of margins on local recurrence for PNETs. There are two large population studies where margins were evaluated for impact on survival Bilimoria et al examined 3951 patients who underwent pancreatectomy for PNETs from the NCDB between 1985 and 2004.[147] They examined multiple variables with the primary endpoints of recurrence-free survival and overall survival Five-year overall survival (OS) was significantly worse for patients with grossly positive margins (25.0%) compared to with those with clear (61.3%) or microscopically positive (57.0%) margins (P=0.0001). However, on multivariable analysis margin status was not predictive of survival Factors found to be associated with survival were age, grade, and presence of distant metastasis.

Gratian et al examined 1854 patients with NF-PNETs <2 cm from the NCDB between 1998 and 2011.[148] Five-year OS was significantly reduced for patients not undergoing surgery, but was not different based on the extent of the resection, which was 83.0% for partial pancreatectomy, 72.3% for pancreaticoduodenectomy, and 86.0% for total pancreatectomy. The rate of positive margins was higher for partial pancreatectomy (9.0%) vs. PD (4.1%) and total pancreatectomy (3.5%), which was significant by univariate analysis (P=0.01). The hazard ratio for positive margins was 2.11, but the percentage of patients in the partial pancreatectomy group undergoing enucleation was not specified.

Genc et al reviewed outcomes in 211 patients with NF-PNETs from 3 institutions between 1992 and 2015 to determine factors related to recurrence.[149] Seventeen percent of patients developed recurrence, 69% of which were in the pancreatic remnant and 14% were distant. Three of 29 (10%) patients undergoing enucleation had recurrence, which was below the overall rate of 17%. Factors significantly associated with recurrence on multivariable analysis were grade, positive nodes, and perineural invasion. R1 resections were performed in 15% of patients, and the study did not specify how common this was in the enucleation group. R1 margin status was significantly associated with recurrence on univariate analysis only, and did not reach significance for increased 10-year mortality (P=0.055). Although patients having enucleation had lower rates of recurrence in this study, this was likely related to other favorable factors that allowed these tumors to be enucleated.

A recent review of 1020 PNET patients undergoing resection at 8 centers revealed an R1 rate of 15%.[150] Of these patients, 10.5% had enucleation performed and 22% had R1 resection margins (≤1 mm), slightly higher than in the overall group. In those with R1 margins, the 10-year recurrence-free survival was reduced to 47% from 63% for those with R0 margins (HR 1.8, P=0.02), but was not associated with a reduced 10-year overall survival (71.1% for R1 vs. 71.8% for RO, P=0.392). On multivariable analysis, grade, perineural invasion, vascular invasion but not margin status were significant factors for overall survival The authors concluded that enucleation and parenchymal sparing procedures with minimal margins are reasonable in some patients, as tumor biology rather than margin status appears to be driving survival[150]

Recommendations: Resection with negative margins should be the goal of surgical resection, but there are no data to support that more aggressive resection to obtain wider surgical margins is justified for PNETs, and therefore enucleation is an acceptable option in select patients.

19. What is the role of central pancreatectomy for PNETs?

Pancreatic resections are associated with significant morbidity, therefore there is interest in minimizing the impact of surgical resection. Patients with benign or low grade PNETs have excellent long-term survival, which makes it important to optimize their quality of life in terms of pancreatic function following surgical intervention. Pancreas-sparing resections (PSRs), including central pancreatectomy (CP), have been advocated in select PNET patients in an effort to minimize morbidity and maintain pancreatic endocrine and exocrine function. The primary indication for CP is for deeply located, small, benign or low-grade PNETs in the pancreatic neck or proximal body which are not amenable to enucleation. According to the 2004 World Health Organization (WHO) classification, PNETs were considered likely to exhibit benign behavior if: (1) they are <2 cm; (2) they are confined to the pancreas; (3) they are non-angioinvasive; (4) they have ≤2 mitosis/HPF; and (5) they have Ki67 ≤2%.[151] These would be classified as G1 PNETs in the 2010 and 2017 WHO classifications.[152,153]

A limitation of PSRs, including CP, is the limited LN sampling associated with these procedures, as there remains a significant incidence of nodal metastasis even in small PNETS <1-2 cm in size.[42,146,154,155] However, it is important to note that the routine performance and extent of lymphadenectomy in the management of PNETs is unclear, as the impact of nodal metastasis on survival remains uncertain.[5,156-160]

Crippa et al reported on 100 patients undergoing CP, where the morbidity and mortality was 58% and 0%, respectively, with a POPF rate of 44%.[161] The incidence of new endocrine and exocrine insufficiency was 4% and 5%, respectively, at a median follow-up of 54 months. CP was associated with a higher morbidity rate and a longer postoperative hospital stay compared with DP. In another series of 100 consecutive patients, CP had a low risk for the development of exocrine and endocrine insufficiency (6% and 2%, respectively), however, the morbidity and mortality were 72% and 3% respectively, and the incidence of POPF was up to 66%.[162]

A systematic review and meta-analysis of 636 patients with CP versus DP showed that the overall morbidity and POPF rate following CP was 45% and 31%, respectively, compared to 29% and 14% for DP.[163] While CP was associated with a significantly higher morbidity and POPF rate, it had a lower risk of endocrine insufficiency (relative risk of 0.22, P < 0.001). The risk of exocrine failure was also lower after CP, although this was not significant (relative risk of 0.59, P = 0.082).

A recent systematic review and meta-analysis of 50 studies with 1305 patients undergoing CP compared the clinical outcomes of CP versus DP or PD.[164] Endocrine and exocrine insufficiency occurred in 4% and 5% of patients after CP, while the incidence of endocrine and exocrine insufficiency were 24% and 17% after DP and 17% and 29% after PD, respectively. When CP was compared to DP, it favored CP with regard to less blood loss (P=0.001), lower rates of endocrine (observed risk [OR], 0.13, P <0.001) and exocrine insufficiency (OR, 0.38, P <0.001). There was higher

morbidity with CP than DP (OR, 1.93) as well as a higher POPF rate (OR, 1.5). When compared with PD the same trends persisted, with CP having a lower risk of endocrine (OR, 0.14, P <0.001) and exocrine insufficiency (OR, 0.14, P <0.001), but a higher POPF rate (OR, 1.6, P=0.015). Although the POPF rate of CP was 35%, most cases of POPF were grade A and B.

Recently, the use of minimally invasive approaches for CP have also been advocated. A study comparing laparoscopic versus open CP showed that the laparoscopic approach was associated with a shorter hospital stay, less intra-operative blood loss, shorter diet start time, and a better long-term quality of life.[165] Similarly, a randomized controlled trial of robotic-assisted versus open CP suggested that the robotic approach was associated with a significantly shorter hospital stay, reduced intra-operative time, less intra-operative blood loss, lower clinical PF rate, and expedited postoperative recovery.[166]

Recommendations: CP may be indicated in patients with small, low grade PNETs in the neck or proximal body of the pancreas that cannot be enucleated due to proximity to the main pancreatic duct, and in which the left pancreatic remnant is long enough to maintain sufficient pancreatic function (generally about 5 cm). Patients with larger lesions, diffuse pancreatitis and high-grade malignant tumors are not suitable candidates for CP.[167] Central pancreatectomy has obvious advantages over DP and PD by preserving post-operative pancreatic endocrine and exocrine function. However, this has to be balanced with the higher overall morbidity and risk of POPF associated with CP. Minimally invasive CP is technically feasible and safe, and may have potential advantages over open CP in experienced centers.

20. What is an adequate lymph node dissection for PNETs in the head, body, and tail? Is there a role for extended lymphadenectomy in select patients?

The extent of lymphadenectomy in the management of PNETs remains controversial since the relationship between nodal metastases and survival has been inconsistent.[5,156-159] There are several confounding factors associated with this uncertainty, including: (1) the lack of accurate pre-operative methods to predict which tumors will progress to regional or distant metastases; (2) inadequate or inconsistent LN sampling and lack of consistent pathological evaluation of LNs in reported studies; and (3) studies with small numbers of patients and limited follow-up of an indolent disease. To determine what an adequate LN dissection (LND) for PNETs is, and if extended lymphadenectomy is associated with survival benefit, it is important to understand the factors associated with nodal metastasis and their impact on disease-specific survival (DSS) and OS rates.

There is a clear association with tumor size and LN involvement, with the proportion of patients with LN metastasis rising with increasing tumor size. Tumors >1.5 cm have a >40% incidence and 4.7 times higher risk of nodal metastases than tumors with smaller tumor diameters.[160] Tumors located in the head of the pancreas also have a higher incidence of LN metastasis than tumors located in the body or tail of the pancreas.[160] It is important to note that even in PNETs ≤2 cm, regardless of location, the risk of LN metastasis ranges from 12.9% to 27.3%.[42,146,154,155] While tumor location and size can be reliably identified on preoperative imaging, these two parameters cannot reliably predict patients at low risk for nodal metastasis. Adverse pathological features associated with nodal metastasis are higher grade and Ki-67 levels, lymphovascular invasion, and poor differentiation. These factors are less likely to help determine the extent of surgical resection and extent of LND as they are not reliably available preoperatively. Although Ki-67 proliferative index and differentiation may be obtained on biopsy, it is not always reliable due to tumor heterogeneity.[168]

The clinical significance of nodal metastasis in PNETs remains controversial Some studies have concluded that nodal metastases significantly decrease OS,[169-173] while others have shown no association.[147,174-180] These results warrant caution as many of these studies are plagued by small numbers of patients or do not mention the extent of LN sampling, limiting the ability to identify the association between nodal metastasis and survival Furthermore, most studies have limited follow-up of patients. In 326 PNET patients, Krampitz, et. al failed to find a difference in OS rates between node negative and positive patients. However, a subset analysis with different follow-up (11 years vs 2.7 years) showed a significantly decreased OS rate in patients with nodal metastasis at 11 years of follow-up that was not seen at 2.7 years of follow-up.[70] Based on these discrepancies, debate still exists regarding the value of lymphadenectomy with surgical resection. In contrast to other tumors such as gastric and colon cancer, there are no universally accepted or established threshold for the minimum number of nodes that are required for accurate prognostication of PNETS.[181] In an NCDB study of 999 patients who underwent surgical resection for PNETs, 72.8% of whom had a lymphadenectomy with a median of eight LNs examined, the addition of regional lymphadenectomy was not associated with 2 or 5 year OS rates.[148] Similarly, a Surveillance, Epidemiology and End Results program (SEER) study of 981 PNET patients

did not reveal a survival advantage with sampling of 10 or more nodes.[170] To establish a threshold of examined LNs during pancreatic resection for PNETs, Zhang et. al showed that compared with 1–5 and 6–10 LNs, 11–15 LNs examined significantly increased the likelihood of finding LN metastasis by 2.3 times and 1.5 times, respectively. However, examining 16–20 or more than 20 LNs did not increase the likelihood of identifying LN metastases, suggesting that the best threshold of the number of examined LNs for PNETs appears be 11-15, similar to that reported for pancreatic adenocarcinoma.[182]

In summary, the incidence of LN metastasis in the patients with PNETs, even those ≤2 cm, is not insignificant. The association of nodal metastasis with OS remains controversial and requires longer follow-up time to determine their true prognostic impact. Examination of 11 to 15 lymph nodes is useful to accurately classify N stage, however a survival benefit of extended LND has not been established. In general, when PD or DP with splenectomy are performed, it is not generally difficult to achieve these suggested nodal counts. When CP or spleen-preserving DP are performed (open or laparoscopically), this is more challenging and would require removing the nodal tissue along the hepatic artery, celiac axis, and/or splenic artery. Attention to the same nodes should be given during enucleation of body and tail lesions, and for head lesions, posterior pancreatic and portocaval nodes may be at risk. Whether removing these nodes will positively impact upon survival has not been established, as discussed above. However, reducing tumor burden through LND or at the very least removing suspicious nodes seen on imaging (including other retroperitoneal sites) or at exploration is likely to facilitate future management.

Recommendations: If formal surgical resection (PD or DP) is planned for PNETS, oncologic resection with removal of 11-15 LNs should be performed for accurate nodal staging. If pancreas sparing surgery is planned for smaller PNETS (<2 cm), removal of suspicious nodes seen on preoperative imaging is warranted, and LN sampling may be considered if imaging is negative.

21. Should hepatic cytoreduction be performed for pancreatic NETLMs? If so, what is the appropriate target, more than 70% or more than 90%?

Retrospective studies suggest that cytoreduction of NETLMs may lead to both improvement in symptoms[183,184] and survival[184,185] This is not universally accepted, since retrospective series are at risk for selection bias. Patients with favorable or limited disease are more likely to be offered cytoreduction, while those with more extensive disease, unfavorable tumor biology, or significant comorbidity are more likely to be offered medical therapy or embolotherapy. Despite the shortcomings of these studies, there is little doubt that surgical resection or ablation leads to an immediate tumor response that no other therapy can match. This has the potential to benefit patients through rapid decreases in hormone levels and improvement of symptoms, as well as "resetting the clock" and delaying the leading cause of death in patients with metastatic NETs, liver failure due to hepatic replacement. However, it is important to acknowledge that these patients are rarely cured by hepatic resection or grossly complete cytoreduction. NETLMs are rarely solitary or few in number, and are more commonly bilobar and extensive. Even if effective cytoreduction can be achieved, recurrence rates are 84-95% within 5 years.[184,185] This is because patients with NETLMs likely have many microscopic metastases throughout the liver which are not appreciated even by the most sensitive imaging modalities.[186] Therefore, recurrence is the rule rather than the exception, even adjunctive treatment with SSAs. However, it is also emphasized that results of medical therapy for metastatic disease are not curative and often not durable; benefits have been demonstrated for OS but not progression free survival (PFS; see question 24). In addition, embolotherapy is another option that can be effective for palliation in patients with NETLMs.

Based upon a series of 44 patients with "disabling symptoms" from malignant carcinoid tumors, Foster and colleagues stated that "when less than 95% of the gross liver disease was resected or when the rate of tumor growth was rapid, little palliation was achieved".[187,188] Years later, McEntee et al at the Mayo Clinic reported their experience with hepatic cytoreduction in 24 carcinoid and 13 PNET patients, and concluded that "our experience certainly endorses Foster and Lundy's earlier impression that palliative resection should be considered only when at least 90% of tumor bulk can be removed safely".[189] Of these resections reported, 17 were considered curative and 20 palliative, and clearly these were in highly selected patients, as they comprised only 9% of the total patients with metastatic intestinal or pancreatic NETs seen by Medical Oncology over the reporting period. In 2003, Sarmiento et al described their experience with 170 patients having NETLMs (31% from PNETs) where their objective was to achieve 90% cytoreduction. In symptomatic patients, 96% had partial or complete relief of symptoms. They also included asymptomatic patients (37% of the total), and found no difference in survival between these 2 groups, nor between those with carcinoid vs. islet cell tumors. Although 56% of procedures were considered incomplete resections, they reported a 5-year

OS rate of 61%, which was nearly twice the 30-40% rate quoted for historical controls. This represented a turning point of not just offering cytoreduction to patients for symptom relief, but also to improve survival; since this time, most surgeons have recommended cytoreduction only when they believe they can achieve 90% or greater debulking.

The problem with using 90% as a cytoreduction threshold is that this was chosen not based upon any comparison of response rates or survival with other levels of cytoreduction, but rather arbitrary thresholds that originally began at 95% and then were reduced to 90%. Furthermore, when this level is chosen, only a minority of patients with NETLMs will be candidates for cytoreductive procedures, and it is possible that more patients might derive benefit. One advance in the treatment of NETLMs has been the adoption of parenchymal sparing approaches instead of relying solely on large anatomic resections. The latter approach requires that NETLMs be confined within certain boundaries. Since patients with NETLMs ultimately die of liver replacement, preserving normal liver tissue by performing wedge resections, enucleations, and ablations is becoming more routinely performed, as local recurrence rates at resections sites are low. Mayo et al reported the experience from 8 centers for surgical cytoreduction of NETLMs, which included 339 patients (39.5% with primary PNETs).[184] Most patients had resection performed (77.6%), while 19.5% had resection and ablations performed; 44.5% had >hemihepatectomy and 52.5% had non-anatomic resections. In this series, 54% had R0, 20.4% had R1, and 19.2% had R2 resections. Patients having the greatest survival benefit were those with functional tumors and those with R0/R1 resections, while in NF tumors, survival was the same for patients with R0/R1 and R2 resections. The median overall survival was 125.1 months and the 5-year survival rate was 74%; those having palliative operations had worse survival than those performed with curative intent (77.5 vs. 156.9 months). On multivariate analysis, factors found to negatively influence survival were NF-NETs, synchronous NETLMs, and extrahepatic disease. The value of this study was that it is the largest thus far, and that while only 54% had R0 resections and >20% of patients had ablations, survival was still very good (median OS 125 months) as compared to historical controls, which from SEER was reported in 2008 to be a median of 56 months for SBNETs and 24 months for PNETs.[5] A recent update of SEER from 2017 reported 70 months for SBNET patients with distant disease and 20 months median survival for those with PNETs.[6] In Mayo's study, the number of lesions and degree of liver replacement were not recorded (although 26% of patients were reported to have >50% liver involvement), nor was the volume of disease removed, and therefore this study did not address cytoreduction thresholds beyond margin status.

The first series suggesting using a lower threshold for cytoreduction came from Chambers et al, who looked at 66 patients with metastatic GI NETs (not including PNETs), 45% of whom had hepatic cytoreduction performed.[190] They concluded that cytoreduction of >70% was a reasonable target for palliation of carcinoid syndrome symptoms. Graff-Baker et al studied cytoreduction thresholds in 52 patients with GI NETs having cytoreduction, where it was believed that >70% cytoreduction could be achieved. They found that 27% of patients undergoing 70-89% cytoreduction had progression at a median follow-up of 37.4 months, as compared to 27% in the 90-99% group, and 32% in the 100% cytoreduction group.[191] Of 12 factors examined for correlation with progression-free survival, only age <50 was identified as a significant negative prognostic factor. They concluded that since there was no difference in liver progression-free or DSS in their groups having >70% cytoreduction, that the debulking threshold should be lowered to >70%.

This same group at Oregon Health & Science University (OHSU) also looked at 44 cytoreductive procedures performed on 34 patients with PNETs, 7 with duodenal NETs, and 1 of unknown primary.[192] The timing of resection of the primary and cytoreduction varied, with 36% having the primary removed first, 33% had the cytoreduction first then the primary removed, and 11% had both procedures performed simultaneously; 21% did not have the primary resected due to unresectability or patients declining. For those who needed Whipple procedures, they favored doing the liver cytoreduction first, prior to hepaticojejunostomy which gives free access of bacteria to the biliary tree. They reported that 18% of patients had 70-89% debulking, 27% had 90-99%, and 55% reached 100% cytoreduction. They found that their PFS was only 11 months, in contrast to 72 months for their GI NET patients previously reported by Graff-Baker et al[191] Five-year OS rate remained good at 81%, but no significant differences in PFS or OS were seen between the different cytoreduction groups. The only factor that was significantly associated with poorer survival was metastases 5 cm or larger in size. They concluded that these results were further evidence that the cytoreduction threshold for NET liver metastases should be reduced to >70%.

Maxwell et al studied patients presenting to their institution with metastatic GEPNETs, of whom 108/142 (76%) underwent a cytoreductive procedure; patients

with >70% liver replacement were excluded.[193] There were no requirements that a certain level of cytoreduction could be achieved, because 84% of these patients were also being explored for resection of their primary tumors. There were 80 SBNET and 28 PNET patients, with a median of 10 lesions, and 10% liver replacement in those with SBNETs versus 19% for PNETs. Most patients underwent parenchymal sparing resections or ablations with a median of 6 lesions being treated; 64% of patients achieved >70% cytoreduction by comparison of pre and postoperative CT scans, and 39% achieved >90% cytoreduction. In the PNETs group, 82% achieved a biochemical response (>50% reduction in hormone levels) and both cytoreduction of >70% and >90% were significantly associated with improved PFS relative to less than these levels. For overall survival, only >70% cytoreduction was significantly correlated with improved outcomes, while >90% cytoreduction did not reach significance for OS. The same trends were seen with SBNETs. The authors concluded that >70% was a more appropriate cytoreduction endpoint as it was associated with improved progression-free and overall survival The median PFS in these PNETs patients was 1.6 years and median overall survival was 10.5 years, which was the same as that reported by Mayo et al for their group of GEPNETs. Furthermore, 76% of patients had cytoreduction attempted versus <25% in other series, there were no deaths, and a 13% major complication rate.

An update on this series including 41 PNETs and 128 SBNETs found no difference in PFS or OS rates with respect to whether 1-5, 6-10, or >10 lesions were treated.[194] Major complications remained low at 15% with no deaths, and several trends were identified. The proportion of patients with <70% cytoreduction was 21%, 70-90% cytoreduction was 47%, and >90% was 31%. The median number of lesions and liver replacement were greater in the <70% cytoreduction groups (22 and 30%, respectively) as compared to the 70-90% (11 and 12%) and >90% cytoreduction groups (2 and 2%). This indicated that it is easier to achieve >70% cytoreduction when there are fewer lesions and less liver replacement. PFS between the 3 cytoreduction groups were significantly different (10.8 months for <70%, 20.6 months for 70-90%, and 56.1 months for >90% cytoreduction). The median OS for the <70% cytoreduction group was 37.6 months, versus 134.4 months for 70-90%, and the median was not reached for the >90% cytoreduction group; the latter 2 categories were both significantly different from the <70% cytoreduction group, but not from each other. In multivariate analysis, age, grade, percent liver replacement, and >70% cytoreduction were all found to be significantly associated with OS.

Recommendations: Reports in both GI NETs and PNETs have shown survival benefits of cytoreduction versus historical controls, and recent studies have challenged the previous convention that >90% of liver metastases must be resected in order to either palliate patients with NETLMs or improve their survival Studies specifically evaluating the extent of cytoreduction have shown little difference in PFS or OS once >70% cytoreduction has been achieved. It is easier to achieve higher levels of cytoreduction in patients with fewer liver metastases or liver replacement, but good results have been shown even in patients with >10 lesions. There was no consensus of the group on this question. Over half felt that treatment should be individualized based upon the number and distribution of lesions, patient age and co-morbidities, grade, and rate of progression and believed that symptom control and survival could be improved with >70% cytoreduction. Others felt that cytoreduction might only be effective if all lesions could be removed, and a few others questioned whether the benefits of cytoreduction have even been established, since all studies have been retrospective series prone to selection bias. This is clearly a controversial area where the level of evidence is weak (level III).

22. Should pancreatectomy be combined with major liver debulking if feasible?

Approximately 64% of patients with PNETs present with synchronous liver metastases.[110] A percentage of these patients will be eligible for both liver debulking operations and primary tumor resections. Liver debulking procedures are usually major operations that may be long in duration, may require transfusion, routinely involve immediate acute postoperative care frequently provided in a surgical intensive care unit, and have a risk of major postoperative complications. Similar arguments may be applied to pancreatic resection to remove primary tumors. Therefore, the question arises whether major pancreatectomy can be safely combined with major liver debulking operations within a single procedure. Combining such operations may result in more blood loss, higher postoperative complication rates, and longer hospital stays. Furthermore, combining pancreaticoduodenectomy with hepatic cytoreduction synchronously or done post-Whipple raises the theoretical concern of increased hepatic infections due to free access of bacteria through the biliary tract via the biliary-enteric anastomosis.

Most published series of liver debulking operations for neuroendocrine liver metastases (NETLMs) include a majority of patients with small bowel primary tumors and a minority of patients with pancreatic primary tumors.[183-185,189,193,195] Within these series, data

are sometimes provided about complication rates, the percentage of patients who had simultaneous resection of their primary, or whether a Whipple, distal pancreatectomy, or enucleation was performed. For this reason, the safety of performing these combined procedures is not entirely clear from the literature. A few studies show that the complication rates of combining these procedures may not be much higher than for other series of either just pancreatic resection or hepatic cytoreduction. Maxwell et al described 108 patients having hepatic cytoreduction (28 with PNETs and 80 with SBNETs), and 96% of those with PNETs also had resection of their primary tumor. In PNET patients, there were no deaths and 64% had some complication, the majority (70%) of which were grade I or II; 19% were grade III, 11% were grade IV, and two patients required reoperation.[193] A follow-up study from this group expanded to 41 PNET, 128 SBNETs, and 19 patients with other NETs having hepatic cytoreduction; 74% had simultaneous resection of their primary tumors. They found that there was no difference in complication rates for those having 1-5 lesions treated, 6-10, or >10 lesions treated. Of the entire group, 52% had some complication, with 42-54% having minor (grade I and II) complications, most commonly anemia or infection. Grade III and IV complications occurred in 15% of patients, most commonly hemorrhage and intra-abdominal infections. There were no 30 day mortalities, demonstrating that these combined procedures could be done safely in the majority of patients.[194]

Morgan et al reviewed liver debulking operations in 42 patients with pancreatic or periampullary NETs (17 PNETs in the head, 17 in the body/tail, 7 duodenal, and 1 unknown).[192] Among patients presenting with synchronous metastases, approximately half had simultaneous resections and half had staged procedures. The median American Society of Anesthesiologists class was 3 for both groups. Patients who had simultaneous resections were found to be significantly younger than patients who had staged procedures (mean age 35 years vs. 54 years, respectively, P=0.009). However, no significant differences were found between the groups with respect to blood loss, transfusions, complications (including pancreatic leaks and bilomas), or hospital length of stay. This was true whether the simultaneous operations were compared to either of the two staged procedures, or the values of the variable were combined (e.g. blood loss, hospital length of stay) for the two operations. Therefore, it is concluded that major liver debulking operations may be safely combined with distal pancreatectomy for selected patients at centers experienced in such complex procedures. Additional concerns are raised for patients requiring pancreaticoduodenectomy, and these will be addressed in question 28.

Recommendations: Several reports suggest that combined pancreas resection and liver cytoreduction can be performed safely with acceptable complication and mortality rates in select patients and by experienced surgeons. Combining these procedures during one operation depends on the extent of resection of the pancreas and liver and is a reasonable approach as long as intraoperative factors (blood loss, hypotension) and patient co-morbidities do not contraindicate doing both, especially for distal lesions or in cases suitable for enucleation.

23. Is it safe to perform concurrent ablation or resection of hepatic metastases when performing a Whipple for PNET?

This is a fairly complex issue, as it involves combining 2 major operations, which each have the potential for serious complications. The morbidity of a major Whipple operation (PD) ranges up to 37% and of a liver resection up to 12%.[196] The operative mortality for each of these operations falls between 3-5%. Although several studies have established the safety of performing these operations independently, there are limited data with regards to performing these together, and even fewer for PNETs specifically. Most of these are case controlled series or retrospective analyses that are published with fairly small numbers. In a study by Gaujoux et al, 36 patients underwent synchronous resection of their primary GEPNET and liver metastases.[197] Of these, 13 patients had pancreatic primaries resected (2 PDs, 11 distal pancreatectomies) along with liver resection. One patient undergoing PD and extended right trisectionectomy died from sepsis and respiratory failure. The authors concluded that this combination should be avoided except in highly selected patients in terms of operative risk and favorable tumor biology.

The additional issue associated with concurrent ablation or resection is the concern of bacterial translocation/ migration from the biliary tract into the liver, leading to an increased incidence of liver abscesses. One large study identified 126 patients (out of 5025) undergoing PD who also had liver directed therapy (including resection, ablation, arterial embolization, or liver irradiation), either simultaneously or in a staged fashion, for tumors of various types (35% were PNETs).[198] Liver-directed treatment was performed at the same time as the PD in 45% of patients while 55% had staged procedures, with 90% of these being performed after PD. The most relevant endpoint

was the development of liver abscess, which occurred in 7% of patients undergoing simultaneous PD and liver-directed therapy, and in 14.5% of those having staged procedures (P <0.05). The incidence was even higher (22%) if the subgroup receiving adjuvant hepatic radiation was removed. The authors suggested that simultaneous treatment was preferable, but that if staged procedures were necessary (such as in those with extensive hepatic disease), performing the hepatic resection prior to PD has become their practice.

The judicious use of antibiotics pre- and post-procedurally may also reduce the rate of complications. In a study of 262 patients who underwent 307 percutaneous liver ablation sessions, there were 12 with prior hepaticojejunostomy. Of these, 10 patients received an aggressive prophylactic antibiotic regimen consisting of levofloxacin, metronidazole, neomycin, and erythromycin base. None of the 10 patients developed liver abscess. Two of the 12 received other antibiotic regimens and developed abscesses.[199] Another study of patients having microwave ablation after biliary enteric anastomosis showed that receiving pre-procedural antibiotic bowel preparation and antibiotics after ablation was superior to just peri-procedural antibiotics, with 0/11 and 6/10 patients developing abscesses, respectively.[200]

One also needs to take into account the presence of obstructive jaundice when performing concomitant liver resection and PD. There are higher complication rates with major liver resections in patients with dilated ducts, with increased chances of biliary leakage and postoperative mortality approaching 10%, with the most common cause of death being hepatic failure.[201,202] If the bilirubin is elevated and the ducts are markedly dilated, one might consider decompressing the biliary tree and then attempting the liver resection, but this will also colonize the biliary tree and increase the risk of infection.

Recommendations: The presence of a biliary enteric anastomosis increases the risk of liver abscess in patients having both PD and liver-directed therapy. Simultaneously performing PD and liver treatment reduces the risk of liver abscess relative to doing the PD first and liver therapy later. Judicious use of antibiotics and consideration to performing liver directed treatment prior to biliary enteric anastomosis may further reduce the risk of liver abscess. In the absence of preoperative jaundice, if one is contemplating PD and hepatic cytoreduction, careful consideration of performing the liver cytoreductive therapy first followed by PD staged at a later date is recommended.

24. Is aggressive hepatic cytoreduction indicated for grade 1 tumors? Is this different for grade 2 tumors?

Tumor grade is a significant prognostic factor for survival rates of patients with NETs.[110] Patients with higher grade tumors have worse prognoses. However, how tumor grade affects survival rates specifically within the subgroup of patients eligible for liver debulking operations is not fully known. Data on the heterogeneity of grade between primary NETs and liver metastases, as well as between different liver metastases in the same patient are scant. Most major series of liver debulking operations have reported outcomes for a mixture of patients consisting of a majority with SBNET and a minority with PNET primaries. Therefore, it is difficult to determine from those data how grade impacts outcomes, such as liver progression and survival, specifically among patients with PNETs undergoing liver debulking operations. For example, in the series of Scott et al reporting on 184 patients having cytoreduction procedures, grade was a significant factor for OS and PFS by multivariate analysis, with a relative risk of 2.12 in OS between patients with grade 1 and grade 2 tumors, and 11.69 between those with grade 1 and 3 tumors. Patients with grade 2 tumors still had good OS (mean of ~82 months) relative to that seen in national databases for metastatic NETs (median 56 months for SBNETs and 24 months for PNETs)[5]. However, only 22% of the patients in this series had PNETs.[194]

Two additional series examined clinicopathologic and outcome data for liver debulking operations done for small bowel primary and pancreatic primary tumor groups. Over 200 individual resected metastatic lesions were independently graded from 45 patients with small bowel primary tumors.[191] Although all patients analyzed had a grade 1 primary tumor, 33% of patients had at least one grade 2 liver metastasis. Therefore, considerable heterogeneity may exist both between the primary tumors and liver metastases, and between different liver metastases within individual patients. However, the presence of a grade 2 metastasis did not have any significant effect on liver progression or survival rates. Rather, only younger age was found to be a significant negative prognostic factor for both liver progression and survival Data on tumor grade were considerably different in a subsequent series of 44 operations done specifically for PNETs.[192] Forty-nine percent of patients had at least one liver metastasis that was grade 2, but this was very similar to the percentage of patients whose primary tumors were grade 2. Therefore, although there was a much higher percentage of patients with grade 2 tumors overall, there was considerably less heterogeneity between the primary tumors and liver metastases and between individual liver

metastases within a patient. However, similar to what was seen with SBNETs, the presence of a grade 2 metastasis did not have any statistically significant impact on either liver progression or survival rates. Rather, only the presence of any liver metastasis 5 cm or larger was statistically a significant negative prognostic factor for both liver progression and survival rates in patients with PNETs.

Recommendations: Although patients with grade 2 tumors may do worse than patients with grade 1 tumors, there can be considerable heterogeneity between primary and liver tumors, as well as between metastases themselves. Patients with grade 2 tumors or metastases still have favorable survival after cytoreduction, and therefore the presence of a grade 2 primary or liver metastases should not be considered a contraindication for hepatic cytoreduction.

25. Is there a benefit of resecting the primary tumor where there is unresectable metastatic disease?

There are many factors to consider when contemplating whether to remove a primary PNET when the patient has metastatic disease. If a patient is asymptomatic, will this improve quality of life? Is there evidence that resection of the primary will improve survival, or is survival determined by the current extent of metastases? Pancreatic surgery has morbidity and patients with significant co-morbidities may not tolerate the inevitable complications associated with these operations. Modest benefits in progression-free survival have been found with medical therapy, as revealed in the Controlled study of Lanreotide Antiproliferative Response In NET (CLARINET) study,[203] the third trial of RAD001 in Advanced Neuroendocrine Tumors (RADIANT3),[204] and Sunitinib trials.[205] Even more promising has been an early report of the E2211 trial, where an impressive PFS of 22.7 months was seen in patients with advanced PNETs treated with capecitabine and temozolamide vs. 14.4 months with capecitabine alone (HR, 0.58; P=0.023).[206]

Despite these negatives, there are several arguments in favor of resecting primary PNETs in the setting of metastatic disease. If the patient has symptoms from a functional tumor, resecting the primary may afford some degree of cytoreduction. For asymptomatic patients, the ENETS guidelines suggest that resection should be performed to prevent life-threatening and obstructive complications, which can include hemorrhage, acute pancreatitis, jaundice, or gastroduodenal obstruction.[51] The other reason to remove the primary tumor is to improve survival, presumptively from a reduction in the number of future liver metastases. Another possible benefit is increased sensitivity to systemic therapies, such as peptide receptor radionuclide therapy (PRRT).[207]

There have been a number of SEER studies that have examined the potential benefit of resecting primary PNETs in patients with distant disease. SEER began collecting data from 1973, and some reports have focused on functional tumors, and others non-functional, but there are likely limitations to capturing symptoms and biochemical testing results in the database.[2,208-210] Hill et al included data on whether surgical resection was recommended to patients or not, which could have reduced selection bias. They found a median survival of 60 months for patients with distant disease who underwent resection of the primary vs. 31 months in whom resection was recommended but not performed (P=0.01).[208] One large SEER study looking at NF-PNETs with metastases had 882 patients, and 34% had resection of the primary performed. There was a significant difference in median survival, which was 5.42 yrs. in the group having resection vs. 0.83 yrs. in those not resected. There were differences in the groups, however, and several trends were observed in the resection group: the patients were younger, had more body/tail tumors, and there were more grade 1 and fewer grade 3 tumors.[210] Therefore, the difference in survival between patients with resection of their primaries versus those not resected was clearly influenced by selection bias. In an attempt to improve upon previous SEER studies, Huttner et al used propensity matching to evaluate 442 SEER patients with PNETs and metastases between 2004 and 11. They found a 5 year OS of 52.5% in the group where the primary was resected as compared to 20.6% in the no resection group, which was significant by multivariate analysis.[209] Propensity matching in this study eliminated bias due to age, nodal status, and grade, but they did not stratify by the site of the tumor within the pancreas, which was a source of bias in other studies. Ye et al performed a very similar study using the SEER database for stage IV NF-PNETs between 2004-15, where 392/1974 (19.9%) patients had their primary tumors removed.[211] They found a median OS of 78 months in the resected group vs. 21 months in the unresected group (P <0.0001), which changed very little after propensity matching for 8 factors. Another shortfall of SEER is that it does not capture data on liver tumor burden or co-morbidities, and these could have also been large factors influencing whether resection was performed. SEER also does not record specific details regarding adjuvant therapy, which could influence survival In summary, all of these SEER studies suggested a survival benefit to resecting the primary when there is metastatic disease, but the probability of selection bias makes it difficult to be certain that the benefits seen were due to resection alone. Using the National Cancer Database (NCDB), Tierney et

al evaluated data for patients presenting with metastatic GEPNETs at diagnosis between 2004-14.[212] In the PNET subgroup, they found that only 7.6% (460/6548 patients) underwent primary tumor resection, which occurred more frequently in younger patients, and for grade 1 and 2 tumors. The median OS was 63.6 months for those having resection vs. 14.2 months in those not resected (P <0.001). Comparable results have also been reported from a variety of single institutional series which may have had similar sources of bias.[213-217] These results confirm that surgeons are very good at selecting which patients may benefit from primary tumor resection, but not necessarily that resection itself is the main determinant of improved survival

A study from Milan and Sacre Cuoro Hospital focused upon patients with PNETs of the body and tail and unresectable liver metastases. Of these patients, 63 underwent distal pancreatectomy/splenectomy, 30 were thought to be resectable but refused surgical resection or were getting other treatments instead, and 31 were deemed to be unresectable.[218] Because patients having resection had more tumors in the body, more with <25% liver replacement, fewer grade 3 tumors, and fewer were ^{18}F-fluorodeoxyglucose PET positive, they developed a propensity model. The authors evaluated survival of resected vs. resectable (but not resected) patients using 4 quartiles of propensity matching, and found that by multivariate analysis that the greatest hazard was not having resection (hazard ratio [HR] 6.05), followed by liver tumor burden >25% (HR, 5.03), and Ki-67 (HR, 1.1 for each unit of increase). Median survival of patients that had their primaries resected was 111 months vs. 52 months in patients who were resectable but not resected (P =0.032). They tried to eliminate bias by separating out patients with unresectable tumors and by propensity adjustments, and their findings do suggest a survival benefit to resecting the primary tumor. Limitations to applying these results to all PNET patients are that they avoided inclusion of head lesions and over 90% of patients in each group had received PRRT.

Another study from the same group evaluated whether resection of the primary PNET prior to PRRT would have an impact on response to PRRT, as well as outcome in patients with synchronous, diffuse liver metastases.[207] They excluded patients having resection of both the primary and liver metastases with curative intent, those with G3 tumors, and those with prior PRRT at progression. There were 63 patients who only received PRRT, and 31 who had primary tumor resection then PRRT. Patients having surgical resection had either functional tumors not responding to medical therapy (n=2), a PNET in the head causing life-threatening hemorrhage, obstruction, or pancreatitis (n=5), or underwent resection to facilitate future systemic therapy (n=24). In those receiving PRRT only, 25 were considered inoperable due to SMA or celiac axis encasement, and 38 patients refused resection or started with PRRT according to the wishes of their primary physician. The resection and no resection groups were similar in terms of a variety of clinical factors and American Society of Anesthesiologists (ASA) class, with only 3 patients being excluded for age or comorbidities. Resections included 7 Whipple procedures, 21 distal pancreatectomies, 2 central pancreatectomies, and 1 total pancreatectomy. Overall, 26% of patients had partial response with PRRT, 42% had disease stability, and 32% had progression. Significant factors associated with response or stability after PRRT were primary tumor resection (P =0.014), liver only sites of disease (P =0.024), and being treated with ^{177}Lu-DOTATATE only (P =0.022, as opposed to 90Y or combination of ^{177}Lu and ^{90}Y). The median PFS of patients having resection was 70 months and 30 months for those not having resection (P =0.002). The median OS was 112 months for those having operation vs. 65 months in those not having resection (P=0.011). However, on multivariate analysis including resection, tumor burden, and Ki-67 as variables, Ki-67 was the only one that remained significant (P=0.048). The authors concluded that primary resection may improve prognosis and prevent complications of local tumor progression (the reason for resection in 5 of 31 patients), but primary resection did not hold up on mulitvariate analysis.

A recent study from the group at Bad Berka compared patients with stage IV NETs who had their primary tumors removed before PRRT (486/889 patients, 55%) with those who had PRRT without primary tumor resection (402 patients, 45%).[219] Of these, 38% had PNETs and 32% had small bowel NETs, with a mean of 4 cycles of PRRT given (^{177}Lu- or ^{90}Y-DOTATATE or TOC, or combination of both in 52% of patients). Of the PNET patients, 148/335 (44.2%) presented after resection of their primary tumors (two-thirds were pancreatic head resections, less than one-third distal pancreatectomies) and 55.8% had PRRT only. The median OS in the PNET resection + PRRT group was 140 months vs. 58 months in the PRRT only group (HR, 2.91; P <0.001). This was the greatest difference observed for any of the tumor sites, with a significant benefit also seen in patients with small bowel NETs (HR, 1.86; P=0.002), but not lung, colorectal, or gastroduodenal NETs. The difference in PFS was not as remarkable, which was 18 months for resected PNETs and 14 months for those not resected (HR, 1.21; P=0.012). Although this study had limitations in that it was retrospective and details relating to hepatic cytoreduction were not given, it would appear that there were few barriers to receiving PRRT with respect to

resection status. These remarkable results make a credible argument for combining resection of the primary tumor and giving PRRT to PNET patients with metastases.

Previous consensus recommendations have given us some guidance on this question. In the 2010 NANETS consensus statement, it was stated that resection of PNETs should be attempted if possible and if the patient does not have significant co-morbidities or diffuse liver disease.[110] The 2012 ENETS consensus statement specifically addressing functional PNETs stated that the primary should be resected when there is "limited" metastatic disease to the liver in which 90% is thought to be resectable.[111] For NF-PNETs, the 2012 ENETS consensus paper stated that the survival benefit of primary resection with metastatic disease had not been proven, but advised that resection was justified for significant problems being caused by the tumor, such as hemorrhage, pancreatitis, jaundice, or gastric obstruction.[51] In the 2013 NANETS consensus, it was suggested that resecting the primary tumor could be considered even in those with advanced disease, and that surgical resection of liver metastases should be considered if 90% of disease could be removed.[220]

Recommendations: Even though many studies have suggested a potential benefit to resecting primary PNETs in patients with metastatic disease, all are flawed by virtue of their retrospective nature and the high likelihood of selection bias. Recent studies reporting excellent results with primary resection and PRRT.[219] further highlight the need for prospective, randomized trials. No consensus was reached on this question, but the majority felt that resection of the primary may be beneficial under select circumstances. Factors which should be considered in individual cases are the functional status of the tumor (where those with functional tumors might derive more benefit), the location of the tumor (tail and body lesions being more favorable than those in the head due to lower morbidity from distal pancreatectomy than a Whipple procedure), the patient's age and co-morbidities, to treat or potentially avoid local complications from the tumor, and to possibly improve the response to PRRT.

26. Is extrahepatic disease a contraindication for removing the primary tumor or for hepatic cytoreduction?

Several series have shown a survival benefit for resection of the primary tumor in patients with metastatic pancreatic neuroendocrine tumors, as discussed above. While the results reported in these series were likely affected by selection bias, the findings persisted after propensity matching in one series,[209] so the possibility of a survival benefit is not excluded. However, it is emphasized that these series have focused mainly on patients with unresectable hepatic metastases and in many instances do not specify whether extrahepatic metastases were also present. Therefore, it can be difficult to discern whether a survival benefit for primary tumor resection might also exist among patients with extrahepatic disease.

A series by Lewis et al looked at primary tumor resection in metastatic GI-NETs from the California Cancer Registry and found that 45.4% of all patients had extrahepatic disease (in the lung, bone, peritoneum, and/or retroperitoneal nodes).[221] This included many types of primary NETs, of which 43.6% were PNETs. The median survival was 57 months in those having their PNET primaries removed (27 of 250 patients), and 12 months for those in whom they were not removed ($P < 0.001$). Although it was not specified what percentage of patients with PNETs had extrahepatic disease, it is likely that this would have approached the mean number of 45% and that the survival advantage would have remained. However, in a retrospective, statewide database like this, the bias for selecting the 11% of patients who had their primaries removed could have been significant. The study of Ye et al, which showed a benefit for resection in stage IV PNETs did include patients with distant nodal metastases and carcinomatosis, but the percentage of patients with each was not specified.[211] Kammerer et al reported that in their series of 889 patients with stage IV NETs (38% of which were PNETs), that 71.6% of patients had extrahepatic disease, yet they still derived significant survival benefit from resecting the primary tumor and having PRRT relative to having PRRT alone.[219] None of these studies addressed whether patients with extrahepatic disease had a diminished survival benefit of resecting the primary tumor.

The major cause of death of patients with NETs is liver failure from hepatic replacement by tumor.[6,222,223] This is particularly true for patients with PNETs.[224] Accordingly, the presence of extrahepatic disease (such as the frequently seen small bone metastases with increasing use of SSTR-PET) may not be a contraindication to hepatic cytoreduction of NETLMs. Unfortunately, it has been common among series reporting the results of hepatic cytoreduction to combine patients with PNETs and other types of primary NETs. This can make it difficult to determine the outcomes specific to PNET patients. For example, Mayo et al reported outcomes data combined

from 8 centers for surgical cytoreduction, including 339 patients, but only 39.5% had primary PNETs.[184] Overall median survival for the entire group was 125.1 months. Multivariate analysis found that factors which negatively influenced survival were NF-NETs, synchronous liver metastases, and extrahepatic disease. However, it should be noted that the median survival for the group with extrahepatic disease was still very good, being in excess of 85 months. However, all patients in this series with extrahepatic disease were grouped together, regardless of primary tumor type. Without subgroup analyses, it is not known to what degree or even if the survival of patients with PNETs was adversely affected by extrahepatic disease. Moreover, the majority of patients in the series had SBNETs and a significant percentage of patients with SBNETs die of bowel obstruction from carcinomatosis, which is a form of extrahepatic disease. This may explain some of the poorer prognosis seen among patients with extrahepatic disease. However, carcinomatosis rarely occurs with PNETs, so these patients would not be at much risk of death from that form of extrahepatic disease.

Xiang et al reported reviewed 332 patients undergoing resection of NF-NETLMs (including 149 PNETs), where 37 (11%) patients had extrahepatic disease identified on various imaging tests and 51 (15%) did not have their primaries resected.[225] On multivariate analysis, factors associated with diminished survival included PNET primary (HR, 2.8), synchronous liver lesions (HR, 2.1), grade, extrahepatic disease (HR, 3.9), and R2 resection (HR, 2.5); primary tumor resection was not a significant factor. Although patients with NETLM resection with extrahepatic disease had a favorable 10-year survival of nearly 40%, they still had a 2.5-fold higher risk of death than those without extrahepatic disease, making the benefits of resection less clear in this setting.

Morgan et al reported on the results of 44 hepatic cytoreduction operations specifically among PNET patients, with the caveat that 7 patients had duodenal gastrinomas which have classically been included among PNETs because they also occur in the head of the pancreas.[192] The goal was to determine prognostic factors for liver progression and survival specific to PNET patients. Many variables were analyzed, including age, gender, location of the primary PNET, tumor grade, number of metastases resected, size of metastases resected, and presence of extrahepatic disease. Only having a metastasis 5 cm or greater was significantly correlated with either liver progression or survival Patients with metastases 5 cm or greater were found to have a 5-year survival rate of 61% compared to a 96% 5-year survival rate for patients whose metastases were <5 cm. All deaths in the series were from liver failure from hepatic replacement by tumor, and no patient died of extrahepatic disease. While the series may have been underpowered to detect small differences in survival in PNET patients with extrahepatic disease, if one exists, it can be concluded from this series that any adverse effect of extrahepatic disease is not nearly as significant as the dramatic impact of having any liver metastasis 5 cm or greater.

The vast majority of liver resections are performed for colorectal liver metastases and primary liver tumors. For these types of tumors, a group of classic eligibility and exclusion criteria for hepatic resection have evolved. These include the ability to perform a complete resection of all hepatic disease, to obtain negative margins, and the absence of extrahepatic disease. Given that the incidence of primary liver tumors and colorectal liver metastases are magnitudes greater than the incidence of NETLMs, it is understandable that it has become commonplace to also apply these criteria to NETLMs. However, liver resections for primary liver tumors and colorectal liver metastases are performed with curative intent, which would be precluded by the presence of extrahepatic disease. In contrast, the goals of hepatic cytoreduction of NETLMs are considerably different, chiefly being palliation of symptoms, extension of survival times, and reducing hepatic disease burden to facilitate other forms of treatment (as will be discussed elsewhere in this manuscript and in the accompanying guidelines for medical management).

Recommendation: Some series showing a survival benefit from resection of the primary tumor in the presence of unresectable hepatic metastases likely have included patients with extrahepatic disease, and therefore the decision to resect the primary should be based upon other factors (local complications, symptoms, to improve response to other therapies). Series of hepatic cytoreduction for NETLMs which examined the effects of extrahepatic disease on outcome have been limited and with conflicting results. This group was in agreement that since extrahepatic disease is rarely the cause of death in PNET patients, its presence should not necessarily be a contraindication to removing the primary or to hepatic cytoreduction.

27. Is there a role for an observation period prior to hepatic cytoreduction to allow for more metastases to become evident?

When to perform surgical cytoreduction in patients with stage IV PNETs remains a matter of debate. The rate of disease recurrence or tumor progression after hepatic cytoreduction of PNETs has been reported to

vary between 11 months to over 3 years, depending on hepatic tumor burden, surveillance schedule, and imaging modality.[192,193] There are currently no data advocating for an observation period prior to cytoreduction to allow for new metastases to develop for either neuroendocrine or other GI cancers. However, such an approach has been postulated to be potentially beneficial in patients with metastatic colorectal cancers while on neoadjuvant therapy and prior to extensive cytoreductive operations (and hyperthermic intraperitoneal chemotherapy).[226] Although neoadjuvant therapy can be very effective in colorectal cancer, it has not been widely studied and is probably less effective at reducing hepatic tumor burden in patients with PNETs.[227,228]

Arguments for an observation period prior to cytoreduction include to allow for additional lesions to become visible and thus improve efficacy of future surgical cytoreduction; to allow for tumor biology to declare itself and thus to exclude patients with rapidly progressing metastatic disease from surgical cytoreduction; and that there are likely no major deleterious effect for an observation period in PNETs, since overall survival is significantly longer than in other metastatic GI and pancreatic cancers.

Arguments against an observation period prior to surgical cytoreduction include that there are currently no proven systemic therapies available to effectively and reliably downsize metastatic lesions (although this could change in the future with studies of neoadjuvant PRRT and/or capecitabine/temozolamide); that there is likely little downside to cytoreducing NETLMs up front since future re-resections are safe and often possible due to parenchymal sparing techniques used during the initial cytoreductive surgery;[229] that no data exist to suggest that patients recur more slowly if not surgically cytoreduced; and that patients with synchronous primaries and metastases can have them both dealt with at one operation.

Recommendations: An individualized approach should be considered when evaluating patients with metastatic PNETs for timing of surgical cytoreduction. Both observation and immediate cytoreduction when metastases become evident are acceptable options and there are currently no data to support an impact on PFS or OS for either option. Hepatic tumor burden, tumor grade, previous progression on other therapies, patient age, presence of potentially correctable comorbidities, and access to an experienced hepatic surgeon are factors which should be considered in making this decision.

28. Should PRRT be done before or after hepatic cytoreduction?

Peptide receptor radionucleotide therapy has been shown to be an effective treatment for advanced, unresectable grade 1 and 2 PNETs with objective response rates as high as 70% in some series.[227,228,230,231] Four studies to date have looked at the effect of preoperative PRRT on primary tumor site for borderline or unresectable PNETs, and some patients included in those studies also had liver metastases.[227,228,230,231]

A recent study by Partelli et al compared 23 patients with resectable or potentially resectable PNETs at high risk of recurrence (defined as large tumor size, vascular involvement, liver metastases) who underwent neoadjuvant PRRT (^{90}Y-DOTATOC or ^{177}Lu-DOTATATE) with 23 matched patients who underwent upfront surgical operation.[227] Eight of 23 patients in the PRRT group had primary tumor resection plus liver metastasectomy, of which five had cytoreduction to over 80% and 3 had R0 liver resections. In the 31 patients from both groups who had R0 pancreatic resection, PFS was greater in the 15 patients that received PRRT. The authors also found that 16 patients had a partial response in the PRRT group, and the incidence of nodal metastases and pancreatic fistula were decreased in the PRRT vs. the upfront surgical resection only group.

Van Vliet et al studied the effect of ^{177}Lu-DOTATATE in 29 Dutch patients with borderline or unresectable NF-PNETs (group 1), with oligometastatic disease (defined as ≤3 liver metastases; group 2) or with >3 liver metastases or other distant metastases (group 3). Nine of 29 patients underwent surgery, where eight had regression of their tumors after PRRT. Eleven of the 20 patients that did not undergo surgery also had tumor regression after PRRT. The authors found that median PFS was 69 months for patients undergoing surgical resection vs. 49 months for patients not undergoing surgery, and 29 months for patients in group 3. Only one patient undergoing surgery had ablation of liver metastases. This study suggests that neoadjuvant PRRT treatment may be a valuable option for patients with initially unresectable or borderline resectable PNETs.[228]

Two other studies looked at small case series of patients undergoing PRRT, which included 5 and 6 patients with inoperable GEPNETs, respectively. In both studies PRRT was given to reduce primary tumor size, and significant responses allowing for surgical intervention occurred in one of five and two of six patients, respectively.[230,231] It should be emphasized that the treatment effects of PRRT

specifically on hepatic tumor burden were not reported in any of these studies, and therefore it is difficult to extrapolate the response rates of PRRT on primary tumors to response rates in liver metastases. There are several theoretical advantages to using preoperative PRRT in the setting of hepatic cytoreduction. One is that PRRT could reduce liver tumor burden and therefore make surgical intervention easier or help achieve a higher debulking threshold. Another is that PRRT might increase PFS, time to recurrence, and overall survival in patients having hepatic cytoreduction by treating tumors that might remain, whether this is macroscopic or microscopic disease. Preoperative PRRT is safe and not associated with increased postoperative morbidity or mortality when resecting primary tumors in patients with PNETs, but the potential side effects of PRRT on liver resection still need to be investigated.[227,228] Hypothetical disadvantages to using preoperative PRRT are the potential for significant bone marrow toxicity (thrombocytopenia, leukopenia, anemia), renal dysfunction, or tumor progression after these treatments, which might preclude surgical cytoreduction.

Two studies have examined whether primary resection improves the response to PRRT in metastatic PNETs, but Bertani et al specifically excluded patients having resection of the primary tumor and cytoreduction,[207] while Kaemmerer et al did not report on results or frequency of cytoreductive procedures.[219] Previous studies have suggested that lower tumor burdens result in improved responses with PRRT,[232,233] which may explain why survival benefits were seen after resecting primary tumors then giving PRRT. Performing hepatic cytoreduction prior to PRRT could hypothetically improve the delivery of the isotope to other metastatic sites. Since the number of PRRT treatments patients can receive is limited by their cumulative bone marrow and renal toxicity, one could argue to use them wisely when they may be most effective.

Recommendation: There currently are no data to support routine perioperative use of PRRT in the setting of hepatic cytoreduction. However, PRRT is worth considering in certain situations to reduce liver tumor burden preoperatively or to treat future residual disease. Previous studies using preoperative PRRT for patients with PNETs have shown the potential for size reduction in primary tumors, but whether PRRT makes hepatic cytoreduction easier by shrinking these lesions or whether hepatic cytoreduction could make PRRT more effective by allowing PRRT to work more effectively on smaller tumors needs further study.

29. Is there a role for neoadjuvant treatment of PNETs? What agents are preferred for borderline resectable disease?

Neoadjuvant chemotherapy with or without radiation represents the standard of care for borderline resectable and locally advanced pancreatic adenocarcinoma (PDAC).[234] Comparable to PDAC, neoadjuvant therapy for PNETs may potentially aid down-staging, increase the likelihood of multimodality therapy completion, optimize selection of surgical candidates, potentially decrease postoperative complications, and avoid surgical resection in patients with aggressive disease.[228,235] However, in contrast to PDAC, PNETs generally do not have a predilection for rapid metastatic progression, have less effective systemic treatment options, and more treatment strategies for local and/or distant metastases, including re-operation and hepatectomy.[236] In addition, PNETs may be less likely to directly invade or completely surround major mesenteric vessels (portal vein, superior mesenteric vein) and can undergo successful tumor thrombectomy.[237,238]

Several systemic agents have been described for neoadjuvant use in PNETs, including SSAs, targeted therapy, multi-agent chemotherapy, and PRRT.[236,239-241] A case report has demonstrated successful resection of a previously unresectable PNET after administration of neoadjuvant everolimus.[241] However, results of other studies remain ambiguous.[236,241] A retrospective observational study performed at MD Anderson Cancer Center from 2000-2012 described 29 patients with localized PNETs who received 5-Fluorouracil, doxorubicin, and streptozocin as their first-line therapy. These patients were selected from 356 patients diagnosed with localized PNETs during the study period. According to response evaluation criteria in solid tumors (RECIST), 3% of patients had progression, 90%, had stability, and 7% had partial responses after neoadjuvant therapy. Ultimately, 14 (48%) patients were able to undergo pancreatectomy, with 7 (50%) patients requiring vascular resection, and 9 (64%) patients had negative resection margins. Median overall survival was 112 months for resected patients as compared to 41 months for those not resected.[236]

Several case reports and case series have described successful downstaging of borderline resectable and locally advanced PNETs using capecitabine and temozolomide.[242,243] The recent results from the E2211 trial confirmed the value of this regimen for PFS benefit in patients with advanced PNETs,[206] and this regimen is being used with increasing frequency for neoadjuvant therapy.

A recent NCDB study did not confirm the value of perioperative systemic therapy in patients with stage I-III PNETs undergoing surgery. They compared 301 patients receiving perioperative systemic therapy (21% neoadjuvant, 55% adjuvant, 2% both, 22% unknown) plus surgery to 301 having surgery alone and found no difference in the neoadjuvant group (p=0.21) and actually worse survival in the adjuvant group (p=0.037). This study used propensity matching to reduce differences between the groups, but this does not eliminate the possibility of selection for those receiving systemic therapy. Since the systemic agents used are not recorded in the NCDB, it makes it even harder to draw meaningful conclusions.[244]

In addition to multi-agent chemotherapy, neoadjuvant PRRT consisting of SSAs labeled with ^{90}Y or ^{177}Lu has been used in patients with PNETs. However, although PRRT has been available in Europe, it was not approved by the Food and Drug Administration (FDA) in the United States until January 2018.[245,246] Approval was based on the preliminary results of NETTER-1, a randomized, multicenter, open-label trial performed in 299 patients with well-differentiated, metastatic midgut NETs. Patients were randomized to receive either ^{177}Lu-DOTATATE or 60 mg/month octreotide LAR. This demonstrated that patients receiving ^{177}Lu-DOTATATE had significantly longer PFS than those receiving octreotide LAR (65% at 20 months vs. 10.8%, respectively) with minimal complications and a response rate of 18%.[247] As described in question #27, neoadjuvant ^{177}Lu-DOTATATE in 29 patients with NF-PNETs with borderline/unresectable or oligometastatic (≤3 liver metastases) disease led to successful surgical resection in 31% of these patients, and improved median PFS for resected patients compared to those not resected (69 vs. 49 months, respectively).[228] Partelli et al's comparison of 23 PNET patients treated with neoadjuvant ^{90}Y-DOTATOC or ^{90}Y-DOTATATE versus 23 who had underwent surgical resection alone showed the neoadjuvant group had smaller tumors on pathological examination (59 to 50 mm; p=0.047), and lower risk of developing postoperative pancreatic fistula (0/23 vs. 4/23; P <0.02). Progression-free survival was similar between the 2 groups (52 vs. 37 months; P >0.2). However, the retrospective nature of this study may have resulted in some selection bias.[227] Several case reports and series have demonstrated comparable findings using neoadjuvant PRRT.[230,248-252]

Recommendations: The potential efficacy of neoadjuvant therapy for resectable or borderline resectable PNET remains unclear and further randomized trials are necessary to confirm the safety and oncologic value of this approach. However, neoadjuvant therapy may represent an option for downstaging of selected patients with advanced and metastatic PNETs, especially before cytoreductive surgery.

30. Under what circumstances should patients with tumor thrombus or tumor involvement in the PV/SMV undergo resection?

Venous resection/reconstruction during pancreatectomy for PDAC is performed in approximately one-fourth of patients and generally perceived as safe when carried out in well-selected patients at high-volume centers. Various single-center studies and meta-analyses have demonstrated no significant difference in mortality and morbidity among patients undergoing venous resection/reconstruction compared with standard pancreatectomy for PDAC.[253-257] Patency rates between 70% and 90% after vascular reconstruction have been described using a wide variety of surgical techniques and anticoagulation regimens.[258-261] Although resection remains the only curative therapy for the majority of patients with PNETs, venous resection and/or reconstruction for advanced PNETs has been less commonly described due to the relative rarity of the disease.[239]

Norton et al reported a series of 46 PNETs with major vascular involvement on preoperative CT imaging, including the portal vein in 20, superior mesenteric vein/artery in 16, inferior vena cava in 4, and splenic vein in 4 cases.[262] Intraoperatively, only 15 (36%) patients were found to have invasion or encasement of the major vessels, with 9 (21%) patients requiring vascular reconstruction. Similar to previous findings, these results suggest that PNETs may often encroach, abut, or distort major vascular structures on preoperative imaging, without actually demonstrating encasement or invasion during surgical resection.[237,262,263] None of the patients in this study died postoperatively, but 12 (28%) patients developed postoperative complications. The 10-year survival rate for the overall cohort was 60%, with the presence of liver metastasis being identified as a critical prognostic factor.[262] Similarly, Birnbaum and colleagues reported 127 patients with PNETs who underwent pancreatectomy, with 17 (13%) patients receiving neoadjuvant therapy, 48 (38%) patients having synchronous liver metastases, and 6 (5%) patients requiring portal vein resection. The overall morbidity and mortality rate in this study were 48% and 2.3%, respectively, with synchronous liver metastasis and portal vein resection being found to independently predict poorer prognosis.[264]

Venous tumor thrombi are identified in up to 33% of patients with PNETs on preoperative CT imaging.[26] They can be classified into bland thrombi, resulting from

narrowing of the vessel by external compression of the tumor, and tumor thrombi, which are contiguous with the primary tumor mass and extend locally into the adjacent veins. In contrast to bland thrombi, tumor thrombi will strongly enhance on preoperative imaging after intravenous contrast administration, similar to the primary tumor. Nonetheless, previous studies have demonstrated that tumor thrombi are often underreported on preoperative imaging, leading to significant alteration in surgical planning in 18% of the cases. Prakash et al described 26 patients who underwent pancreatectomy for PNETs involving the portal vein or its tributaries at the MD Anderson Cancer Center.[237] Nine of these patients underwent portal vein tumor thrombectomy, with six (67%) of these patients having received neoadjuvant treatment with streptozocin, 5-fluorouracil with or without doxorubicin. In these patients thrombectomy could safely be performed by extraction of the tumor through the splenic vein orifice after gaining complete control over the venous system. They concluded that tumor thrombectomy is appropriate only when thrombi are mobile and well-demarcated within the venous system. Seven (78%) patients were alive at the median follow-up of 33 months; two patients died within 11 months and 4 years after surgical resection, respectively.

In cases of complete occlusion of the splenic vein by thrombi, sinistral hypertension arises, leading to numerous venous collaterals, including gastric varices, and potential life-threatening upper gastrointestinal hemorrhage.[266] These venous collaterals are frequently thin walled and easily rupture during operations accounting for the higher rates of intraoperative blood loss in these patients.[266] Dedania et al reported their experience at Thomas Jefferson University with distal pancreatectomy in patients with splenic vein thrombosis. Their study demonstrated significantly higher intraoperative blood loss (675 vs. 250 ml; P <0.01) and clinically relevant pancreatic fistula (33% vs. 7%; P <0.01) in patients with thrombosis of the splenic vein.[267]

Recommendations: Isolated major vascular involvement with or without venous tumor thrombus should not be an absolute contraindication to surgical resection for advanced PNETs. Venous resection/reconstruction and thrombectomy may be performed safely at high-volume centers in well-selected patients. As more effective systemic agents for PNETs become available, preoperative therapy may be considered. Rigorous preoperative planning with careful evaluation of the vasculature is important.

31. Under what circumstances should high grade PNETs be resected?

The current state of the literature regarding high-grade PNETs has typically included a heterogenous population of patients, including high-grade well-differentiated tumors mixed with poorly-differentiated pancreatic neuroendocrine carcinomas (NECs),[268,269] and often reported in the context of a broader population of patients with high-grade GEPNETs.[270] The heterogeneity in these reports derives from the 2010 WHO classification of GEPNETs, in which the G3 category includes both well-differentiated tumors with >20 mitoses/10 HPF and/or a Ki-67 index >20%, as well as neuroendocrine carcinoma (large cell or small cell type).[152] Increasingly, it is being recognized that these well-differentiated high-grade tumors have distinct biologic behavior from the poorly-differentiated carcinomas, and therefore should not be considered as one entity.[269-271] In addition to separating the poorly-differentiated large and small cell NECs from the well-differentiated tumors, there may also be important biological and genetic differences between well-differentiated G3 GEPNETs with a Ki-67 of 21-55% versus those with a Ki-67 index >55%.[272,273] These distinct biological behaviors may dictate consideration of tailored treatment pathways for these two groups of patients presenting with G3 GEPNETs.[270,272,274]

Specific to high-grade PNETs, it is important to distinguish poorly-differentiated NEC from poorly-differentiated adenocarcinoma or acinar cell carcinoma. Pancreatic NECs also have a distinct genetic profile with increased frequency of p53 and RB mutations in contrast to well-differentiated high-grade pancreatic NETs,[275] which can aid in sorting these patients into different populations. Patients with poorly-differentiated pancreatic NEC (large or small cell type) typically present with an aggressive course, frequent metastases and poor survival, while those patients presenting with high-grade well-differentiated PNETs can have prolonged survival and a less biologically aggressive course.[269] Further segmenting the G3 well-differentiated PNETs into those with a higher proliferative rate from those with a more moderate rate (Ki-67 20-55%) may delineate an even finer prognostic separation.[272,273]

Results with palliative chemotherapy have revealed moderate response and survival rates. One of the largest series including 252 patients with G3 GI-NETs (23% with PNETs), where 56% were not small or large-cell in morphology (and would have fit the G3 NET rather than G3 NEC category). In PNET patients treated with chemotherapy (most commonly cisplatin/etoposide,

carboplatin/etoposide, or carboplatin/etoposide/vincristine), the partial/complete response rates were 30%, stable disease rate was 40%, and progressive disease occurred in 30%, for a median OS of 15 months.[272] Another study from the Netherlands reported 50 patients with G3 PNETs (12 treated surgically), where 71% had distant metastases, and the 5-year OS was 13% (as compared to 80% for G1 and 67% for G2 tumors).[276]

Surgical treatment of patients with high-grade NET or NECs is not generally carried out owing to their poor survival, as suggested in the European Society of Medical Oncology guidelines.[277] One retrospective, multi-institutional study looking at results after surgical resection began with a careful pathologic review of 107 resected PNETs originally classified as poorly-differentiated NECs, and found that only 44 were actually poorly-differentiated G3 NECs (27 large cell and 17 small cell). In these cases, 88% of patients presented with nodal metastases or distant disease, the majority received cisplatin-based chemotherapy and/or radiotherapy, and the median OS was 11 months.[268] A study from Heidelberg reviewed 310 PNET patients undergoing surgical resection between 2001 and 2012, of which 24 had G3 tumors.[278] Two-thirds of G3 patients had nodal and 58% had liver metastases. The 5-year OS rate was significantly worse for those with G3 tumors (20%; relative risk 13.56 vs. G1) as opposed to G1 (91% 5-year OS) and G2 tumors (71%). Patients with G3 tumors and no metastases had better 5-year survival rates of 43%, while this was 0% in those with metastases (35% 2-year survival). The 5-year survival rate was 29% for those having R0 and R1 resections and 0% for R2 resections. The authors concluded that these results supported potential resection of G3 tumors without distant metastases.

Haugvik et al examined 119 patients with high-grade PNETs (Ki-67 >20%) from 10 Nordic centers between 1998-2012.279 They found that 85% had metastases at diagnosis, and 28 underwent surgical resection, 14 of whom did not have metastases and 9 had small cell morphology. Of those 14, 13 developed metastases, and the other a local recurrence at a median of 7 months from the time of surgical resection. Twelve additional patients had resection of their primaries and liver directed operations (including 1 liver transplant), and 2 others had resection of the primary but not the metastases, for a total of 26 of 28 patients having surgical resection with curative intent; all but one patient also received chemotherapy. Median survival was 23 months for the surgical patients versus 13 months in the chemotherapy only group of 82 patients (78 of whom had metastatic disease). The 3-year survival rate was 69% in those having resection of the primary and metastases, 49% with primary resection without metastases, and 17% for chemotherapy only in those with metastases. Survival was significantly improved in those having resection over chemotherapy alone, and in surgical patients, there was no difference in survival in those with Ki-67 >55% or <55%. The authors concluded that resection of localized high grade PNETs and of those with synchronous liver metastases should be considered on an individual basis, and that this should be combined with chemotherapy.

Partelli et al evaluated patients with PNETs presenting with synchronous metastases from 4 European centers, which included 18 patients undergoing curative resection, 73 having palliative resection, and 75 having no resection.280 There were 13 patients with G3 tumors having resection (1 curative, 12 palliative), and 19 were not resected. In surgically resected patients, the only independent factor associated with failure after surgical resection was being a G3 tumor (median OS of 35 months versus 97 months for G1, G2).

More recently, Feng et al reviewed the SEER database for pancreatic NECs between 1988 and 2014, using the International Classification of Diseases for Oncology (ICD-O-3)/WHO recode function, to capture cases of metastatic large and small-cell NEC as well as NEC.[281] They reported on 350 cases, 83% in which the primary was not resected, and 14% (50 cases) where the primary was resected; in half the latter cases, metastatic disease was also resected. The median OS was 19 months for patients having both the primary and metastases resected, 10 months for primary resection only, and was not reported for the no resection group. The median cancer-specific survival was 12 months for the surgery group and 8 months for those not having surgery (P <0.0001). On multivariate analysis, factors significantly correlated with improved overall survival were location in the pancreatic tail (HR, 0.61), receiving chemotherapy (HR, 0.71), and removal of the primary tumor (HR, 0.48). Although the authors argue that resection for curative intent may improve survival, the median cancer-specific survival was not that much different, and may have also been influenced by selection bias.

In summary, although the available literature is currently too limited to provide an evidence-based approach to precisely answer the question of whether patients with high-grade pancreatic NETs or NECs should undergo resection, there is sufficient emerging evidence from isolated series of high-grade pancreatic neuroendocrine neoplasms and mixed series of high-grade GEPNETs to suggest that these heterogeneous patients cannot be considered with a single uniform algorithm. As

increased genomic analyses become available, there will likely be additional information available to further guide recommendations. In the interim, patients should be carefully stratified between those with poorly differentiated pancreatic NEC and high-grade (G3) well-differentiated PNET, and be managed as distinct patient populations. Resection is reasonable to consider in the latter group in association with multi-modal therapy, while current data (although poor in quality) do not support resection in poorly-differentiated pancreatic NEC. The most recent recommendations from ENETs regarding surgical management are to potentially resect localized tumors followed by platinum-based therapy, but to not perform cytoreduction for metastases.[270]

Recommendations: Patients with poorly-differentiated pancreatic NEC (small or large cell type) should not undergo resection given the aggressive biologic behavior they exhibit and the extremely poor prognosis, which does not appear to be impacted by surgical resection. Conversely, patients with high-grade (G3) well-differentiated PNETs should be evaluated for resection if localized, in the context of multi-modal therapy. Cytoreduction of liver metastases may not be indicated due to high relapse rates and poor survival, and therefore chemotherapy should be considered as first line. Future studies using the 2017 WHO classification are needed to clarify whether patients with G3 NETs and lower Ki-67 (21-55%) may benefit from a more aggressive surgical approach.

32. Should patients have prophylactic octreotide infusion during their operations?

Preoperative preparation with somatostatin analogs to prevent intraoperative carcinoid crisis has been suggested for NETs.[282-285] This consideration focuses mostly on patients with known or high risk of carcinoid syndrome, with typical features of flushing, diarrhea, and wheezing, or elevated serotonin documented via urinary 5-HIAA. While carcinoid syndrome is more frequent with intestinal NETs, it has been reported in 50 cases of PNETs.[286] However, there is now emerging evidence of serotonin secretion in NF-PNETs.[287]

Whether or not SSAs can effectively prevent intraoperative crises has recently been challenged.[288] It is currently uncertain what chemicals mediate intraoperative crisis. Remote studies had suggested a role for serotonin, histamine, and bradykinin in carcinoid syndrome and crisis, but those hypotheses were not subsequently substantiated.[282,283,285] A recent prospective assessment of biochemical and hemodynamic features of intra-operative carcinoid crisis failed to identify a rise in serotonin, histamine, kallikrein, or bradykinin levels during crises.[289] Therefore, it is not surprising that other reports have outlined the lack of effectiveness of SSAs in preventing carcinoid crises.[288,290] Outcomes following intraoperative carcinoid crisis were related to prompt identification and management of hemodynamic instability rather than the preoperative preparation.[290] In light of this new evidence, the role of perioperative SSAs in the prevention of carcinoid crisis is debated for patients with carcinoid syndrome, and even more so for NF-PNETs.

For functional PNETs, preoperative preparation focuses on controlling the endocrine syndrome and its physiologic repercussions in order to optimize patients for surgery. This management should be tailored to the endocrine syndrome. Short or long-acting SSAs may be used to control hypersecretion.[54,291-293] Treatment of insulinoma relies on dietary changes as well as pharmacotherapy with diazoxide that can control hypoglycemia in 50-60% of cases.[54,293] For gastrinoma, hyperacidity and peptic ulcer disease are controlled with high-dose proton pump inhibitors.[291] For glucagonoma and VIP-secreting tumors, correction of diarrhea, electrolyte disturbances, and the catabolic state are necessary, in addition to SSAs.[292]

Recommendations: Patients with functional NETs should undergo preoperative preparation and perioperative monitoring tailored to the diagnosed endocrine syndrome, including consideration for SSAs. The role of SSAs for intraoperative prevention of carcinoid crisis in patients with PNETs remains undefined.

33. Is there a role for Pasireotide or Octreotide after operation to decrease fistulae/leaks?

Pancreatic resection has traditionally been associated with a high incidence of perioperative and postoperative complications.[294] While the morbidity and mortality of pancreatic resection have improved substantially in recent decades, leakage of pancreatic juice from the remaining pancreas following partial pancreatectomy, termed postoperative pancreatic fistula (POPF), is one of the most common and potentially severe complications and remains a persistent challenge.[295] The occurrence of POPF is associated with increased length of stay, the need for further interventions, and mortality.[295-297] The International Study Group for Pancreatic Fistula (ISGPF) has created a grading system for classifying POPFs that has been widely adopted.[298] In this system, modest leaks of amylase rich fluid of no clinical consequence are called “biochemical leaks”, pancreatic leaks of short duration requiring minimal change in perioperative management such as leaving a

drain in place a few additional days are referred to as Type A leaks; leaks requiring more extensive interventions such as percutaneous or endoscopic drainage or intravenous antibiotics are referred to as Type B leaks; and leaks associated with ICU management, return to the operating room, or death are referred to as Type C leaks. Strategies to improve the complications of pancreatic surgery have focused on reducing Type B and C leaks, termed clinically relevant pancreatic fistulas (CR-POPFs).

All surgical approaches to PNETs, including PD, pancreatic body/tail resection, as well as more limited resections such as CP and enucleation are plagued by a relatively high incidence of POPFs.[299,300] Indeed, patients with PNETs are more likely to have CR-POPFs following pancreatic head resection than patients undergoing the same procedure for pancreatic adenocarcinoma.[301,302] This is thought to be related to the relatively normal pancreatic texture and duct size in patients with PNETs of the pancreatic head, as opposed to the increased pancreatic fibrosis and duct diameter in the remnant pancreas commonly observed in patients undergoing PD for pancreatic head adenocarcinoma. It is also important to recognize that in many contemporary series, CR-POPFs occur more frequently in patients undergoing distal pancreatectomy, CP and enucleation than in patients undergoing PD.[299,300,303] Two approaches to minimizing/managing CR-POPFs in patients undergoing surgical resection of PNETs remain controversial and include: 1) the use of SSAs to prevent CR-POPFs and 2) the use of perioperative drains to limit the morbidity of POPFs.

Somatostatin reduces the secretion of pancreatic enzymes and fluid from pancreatic acinar cells.[304] Three distinctive SSAs have been studied in prospective randomized trials to evaluate whether perioperative treatment that reduces pancreatic secretion by agents that activate somatostatin receptors can limit POPFs: somatostatin itself given by continuous infusion, or administration of the longer acting SSAs octreotide and pasireotide.[305-307] Interpretation of the results of these studies is challenging due to varying definitions of POPF (most did not use the ISGPF definitions), variation in the range of pancreatic procedures evaluated, and the relatively small fraction that have focused on the impact of SSA treatment on CR-POPFs.

There is a substantial literature describing prospective randomized trials using somatostatin infusion or bolus octreotide on POPFs. In fact, there are a number of meta-analyses attempting to interpret this literature.[305-307] Not only are the trial results conflicting, but the meta-analyses are also conflicting with regards to whether the use of somatostatin or octreotide is of benefit in preventing CR-POPFs. Somatostatin infusion is of little contemporary interest due to expense and the need for continuous infusion beginning prior to or during the operation. With regards to octreotide, while some studies have suggested a potential benefit, others have shown no benefit or that its use may limit biochemical/type A fistula but may actually enhance the occurrence of CR-POPFs.[305] This latter finding was supported by the results of a non-randomized multi-institutional analysis of subcutaneous (s.c.) octreotide use among high volume pancreatic surgeons.[308] Thus the use of octreotide infusion or s.c. octreotide is not recommended for use in attempting to reduce CR-POPFs in patients undergoing pancreatic resection for PNETs.

Pasireotide is a SSA that has a broader range of activity on somatostatin receptor subtypes and a longer half-life following bolus administration than octreotide. These pharmacokinetic/pharmacodynamic benefits led Allen and colleagues at the Memorial Sloan Kettering Cancer Center to perform a prospective randomized trial of s.c. pasireotide use in patients undergoing pancreatic resection.[309] The effect of pasireotide on CR-POPFs in this trial was strongly beneficial, with an approximately 50% reduction in CR-POPFs. Patients receiving pasireotide had a non-signficant reduction in length of stay and a significant reduction in hospital readmissions. The use of pasireotide was associated with side-effects of hyperglycemia and nausea and vomiting, the latter leading to treatment cessation in 17% of patients.

Although this single institution trial demonstrated evidence of benefit with pasireotide, the expense of its use was substantial and approximated the cost of the CR-POPFs that it prevented.[309,310] Furthermore, the incidence of CR-POPFs in placebo treated patients in the series was higher than that reported in other contemporary series, raising the question of whether routine use of pasireotide would be cost-effective at centers with a lower baseline rate of CR-POPFs.[311] Of greater concern are two reports from high volume pancreatic surgery centers that suggest the routine use of pasireotide in prospective series did not alter CR-POPF rates compared to historical controls from these same institutions.[311,312] While a multi-institutional prospective randomized trial would clearly be of benefit in better defining a role for pasireotide in preventing CR-POPFs, such a study has not thus far been opened. Given the limited evidence of efficacy, side-effects and cost, the routine use of pasireotide to prevent CR-POPFs following PNET resection is not endorsed, though its selective use in high risk patients should not be discouraged.[313]

Recommendations: Intravenous infusion or s.c. octreotide has not shown efficacy for reducing CR-POPFs in patients undergoing pancreatic resection for PNETs. Pasireotide s.c. may decrease CR-POPFs, but its cost and side effects preclude recommending its routine use.

34. Should drains be used after pancreatic resection?

Although the evidence that CR-POPFs are a substantial contributor to the morbidity and mortality of pancreatic tumor resection is beyond dispute, the benefit of drains placed at the time of surgery in reducing the consequences of POPFs remains controversial Arguments in support of routine drainage focus on the experience that undrained pancreatic collections are associated with significant morbidity such as abscess formation and hemorrhage following erosion by pancreatic juice into major blood vessels. On the other hand, surgically placed drains allow bacterial colonization of the peripancreatic space and may themselves erode into tissue thus causing POPFs. Closed suction drains also generate substantial localized negative pressure that may facilitate the development of POPFs. Several prospective randomized trials have addressed this question.

The first prospective randomized trial addressing the use of surgical drains in pancreatic surgery was conducted by Brennan and colleagues at Memorial Sloan Kettering Cancer Center.[314] This study enrolled patients undergoing both PD (78%) and body/tail (22%) resections and randomized 179 patients in total This was approximately 50% of patients undergoing pancreatic resection during the study period, which raised the question of enrollment bias. The study demonstrated that the placement of drains at the time of operation was associated with a POPF rate of 12.5%, but could not be compared to the no drain group since POPF was defined by drain output and amylase level. The study was performed prior to the creation of the ISGPF grading system, and thus CR-POPFs as defined by ISGPF Type B or C could also not be evaluated. However, there was a similar incidence of surgical complications, operative and non-operative interventions, and perioperative mortality in patients regardless of drain placement, suggesting that the occurrence of CR-POPFs was not altered.

A more recent prospective randomized study from two high volume centers in Germany led by Buchler evaluated the role of surgical drainage in patients undergoing pancreatic head resection.[315] This study found a reduced incidence of CR-POPFs in patients who did not have drains placed at the time of operation and no overall differences in hospital length of stay, perioperative morbidity or mortality. This study has been criticized for only enrolling less than 20% of eligible patients, again raising the possibility of enrollment bias, and for including a substantial fraction of patients undergoing surgical resection for chronic pancreatitis (25%). Furthermore, approximately 15% of patients underwent duodenum preserving pancreatic head resections that are not commonly performed in the U.S. It did not address the role of drains in patients undergoing other types of pancreatectomy, such as distal pancreatectomy. With these caveats, a benefit of drain placement in a second prospective randomized trial was not evident.

Both the trials led by Brennan and Büchler were from very high-volume institutions with a small number of pancreatic surgeons and extensive expertise at managing complications of pancreatic operations. A multi-institutional prospective randomized study led by Fisher evaluated the benefit of perioperative drain placement in a larger number of centers for both pancreas head and pancreas body/tail resections in what were essentially two parallel studies that stratified these two types of resections.[316,317] The volume of pancreatic surgery performed, and presumably the experience of participating surgeons at some of the centers enrolling patients in these studies was substantially smaller than that seen in the studies by Brennan and Büchler. A strength of the studies by Fisher and colleagues was that the majority of eligible patients were registered, reducing concerns about enrollment bias. The multi-institutional study of drain placement in pancreatic head resection did not reach its target accrual because of a higher incidence of major morbidity, including gastroparesis, abscess, renal failure, percutaneous drain placement, or reoperation, and a four-fold increase in mortality among patients randomized to the no drainage group.[316] These findings led the data safety monitoring board to stop the pancreatic head resection arm of the study with only 137 total patients randomized.

The study of drain placement in distal pancreatectomy patients was eventually reopened and reached full accrual of over 300 patients.[317] This study showed no difference in the incidence of serious complications, CR-POPF, or length of stay regardless of drain placement. There were only two 90-day mortalities in the study, both of which occurred in the no drain arm, a difference that was not statistically significant but is concerning in light of the results seen by the same investigators in patients who did not have drains placed during PD.

In summary, there have been four prospective randomized trials of drain placement at pancreatectomy. In none of the trials involving patients undergoing PD did patients

with PNETs compose even 10% of enrolled patients; in the trial of DP by Fisher and colleagues PNETs comprised less than 25%. However, DP is essentially an amputation of the tumor-bearing pancreas, in which the tumor pathology has little or no impact on POPF risk from the pancreatic remnant. The studies by Brennan and colleagues and by Fisher and colleagues demonstrate no harm and no benefit in the placement of drains at DP.[314,317]

Brennan's study[314] and the work of Büchler and colleagues[315] suggests that there is no harm to abandoning the routine placement of surgical drains at pancreatic head resection. In contrast, the work by Fisher and colleagues suggests that drain placement substantially reduces morbidity and mortality.[316] While it is not easy to reconcile these findings, the disparate results may in part reflect surgeon and institutional expertise in avoiding and managing POPFs between very high volume centers and those with more moderate experience. It is also worth noting that the study by Fisher was the only one enrolling the majority of eligible patients, and enrollment bias may have reduced the number of participating patients who would have most benefited from drain placement in the studies of Brennan and Büchler.

Studies by Vollmer and colleagues have retroactively examined the benefit of drain placement in pancreatic head resection patients from Fisher's study based on an independently validated fistula risk score.[297] This work suggests that low risk patients were not harmed by lack of drainage and may have even benefited, while those at medium and high risk had even more strikingly negative outcomes due to lack of drainage.[318] The studies of Brennan, Büchler and Fischer included less than 5% PNET patients in total – thus their studies may not be directly applicable to patients undergoing pancreatic head resections for PNETs. Evaluating patients based on their POPF risk is logical and supported by the findings of Bassi and Vollmer's prospective series.[319]

Recommendations: The placement of drains for DP by experienced surgeons in high-volume centers can reasonably be carried out at the surgeon's discretion. In the setting of less surgical and/or institutional experience, the placement of drains is advised. Since most patients undergoing resection of PNETs in the pancreatic head are at higher than average risk for POPFs and will be medium or high risk using the fistula risk score to calculate that risk, the routine use of drains in pancreatic head resection should be considered.

DISCUSSION

The management of patients with PNETs continues to evolve as we develop improved understanding of their incidence, presentation, natural history, and genetic basis. Our ability to treat patients with PNETs has expanded markedly over the past decades. Surgery has become safer with more careful monitoring of outcomes in terms of morbidity and mortality, and options for cytoreduction in patients with metastatic disease have increased. A number of Food and Drug Administration approved systemic therapies have also become available, included targeted agents, chemotherapy, and PRRT. Although we have learned much, there are still a number of vexing clinical problems which clinicians must deal with on a daily basis for which compelling evidence is lacking. In this consensus paper, we have provided the best available evidence for a number of difficult clinical questions commonly presenting to surgeons, and have given suggestions for strategies of patient management. High level evidence is lacking for most of these issues and it is unlikely that randomized trials will be undertaken. Therefore, practitioners must rely upon their experience, patient factors, information from retrospective analyses, and input from multi-disciplinary tumor boards to best serve their patients.

REFERENCES

References

1. Da Silva Xavier G. The Cells of the Islets of Langerhans. *J Clin Med*. 2018;7.
2. Franko J, Feng W, Yip L, et al Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. *J Gastrointest Surg*. 2010;14:541-548.
3. Schimmack S, Svejda B, Lawrence B, et al The diversity and commonalities of gastroenteropancreatic neuroendocrine tumors. *Langenbecks Arch Surg*. 2011;396:273-298.
4. Kuo JH, Lee JA, Chabot JA. Nonfunctional pancreatic neuroendocrine tumors. *Surg Clin North Am*. 2014;94:689-708.
5. Yao JC, Hassan M, Phan A, et al One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26:3063-3072.
6. Dasari A, Shen C, Halperin D, et al Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol*. 2017;3:1335-1342.
7. Halfdanarson TR, Rabe KG, Rubin J, et al Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival *Ann Oncol*. 2008;19:1727-1733.
8. Zerbi A, Falconi M, Rindi G, et al Clinicopathological features of pancreatic endocrine tumors: a prospective multicenter study in Italy of 297 sporadic cases. *Am J Gastroenterol*. 2010;105:1421-1429.
9. O'Toole D, Salazar R, Falconi M, et al Rare functioning pancreatic endocrine tumors. *Neuroendocrinology*. 2006;84:189-195.
10. Lu DS, Vedantham S, Krasny RM, et al Two-phase helical CT for pancreatic tumors: pancreatic versus hepatic phase enhancement of tumor, pancreas, and vascular structures. *Radiology*. 1996;199:697-701.
11. Almeida RR, Lo GC, Patino M, et al Advances in Pancreatic CT Imaging. *AJR Am J Roentgenol*. 2018;211:52-66.
12. Al-Hawary MM, Francis IR, Chari ST, et al Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. *Radiology*. 2014;270:248-260.
13. Lotfalizadeh E, Ronot M, Wagner M, et al Prediction of pancreatic neuroendocrine tumour grade with MR imaging features: added value of diffusion-weighted imaging. *Eur Radiol*. 2017;27:1748-1759.
14. James PD, Tsolakis AV, Zhang M, et al Incremental benefit of preoperative EUS for the detection of pancreatic neuroendocrine tumors: a meta-analysis. *Gastrointest Endosc*. 2015;81:848-856 e841.
15. Kambadakone AR, Fung A, Gupta RT, et al LI-RADS technical requirements for CT, MRI, and contrast-enhanced ultrasound. *Abdom Radiol* (NY). 2018;43:56-74.
16. Balthazar P, Shinagare AB, Tirumani SH, et al Gastroenteropancreatic neuroendocrine tumors: impact of consistent contrast agent selection on radiologists' confidence in hepatic lesion assessment on restaging MRIs. *Abdom Radiol (NY)*. 2018;43:1386-1392.
17. Tirumani SH, Jagannathan JP, Braschi-Amirfarzan M, et al Value of hepatocellular phase imaging after intravenous gadoxetate disodium for assessing hepatic metastases from gastroenteropancreatic neuroendocrine tumors: comparison with other MRI pulse sequences and with extracellular agent. *Abdom Radiol (NY)*. 2018;43:2329-2339.
18. Morse B, Jeong D, Thomas K, et al Magnetic Resonance Imaging of Neuroendocrine Tumor Hepatic Metastases: Does Hepatobiliary Phase Imaging Improve Lesion Conspicuity and Interobserver Agreement of Lesion Measurements? *Pancreas.* 2017;46:1219-1224.
19. Shah MH, Goldner WS, Benson AB, 3rd, et al Neuroendocrine tumors, version 1.2019. J Natl Compr Canc Netw. 2019:1-135.
20. Singh S, Moody L, Chan DL, et al Follow-up Recommendations for Completely Resected Gastroenteropancreatic Neuroendocrine Tumors. *JAMA Oncol*. 2018;4:1597-1604.
21. Hope TA, Bergsland EK, Bozkurt MF, et al Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors. *J Nucl Med*. 2018;59:66-74.
22. Sadowski SM, Neychev V, Millo C, et al Prospective Study of ^{68}Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites. *J Clin Oncol*. 2016;34:588-596.

23. 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;58:1054-1057.
24. Park HS, Kim SY, Hong SM, et al Hypervascular solid-appearing serous cystic neoplasms of the pancreas: Differential diagnosis with neuroendocrine tumours. *Eur Radiol*. 2016;26:1348-1358.
25. Jacobsson H, Larsson P, Jonsson C, et al Normal uptake of ^{68}Ga-DOTA-TOC by the pancreas uncinate process mimicking malignancy at somatostatin receptor PET. *Clin Nucl Med*. 2012;37:362-365.
26. Al-Ibraheem A, Bundschuh RA, Notni J, et al Focal uptake of ^{68}Ga-DOTATOC in the pancreas: pathological or physiological correlate in patients with neuroendocrine tumours? *Eur J Nucl Med Mol Imaging*. 2011;38:2005-2013.
27. Virgolini I, Gabriel M, Kroiss A, et al Current knowledge on the sensitivity of the ^{68}Ga-somatostatin receptor positron emission tomography and the SUVmax reference range for management of pancreatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2016;43:2072-2083.
28. Kroiss A, Putzer D, Decristoforo C, et al ^{68}Ga-DOTA-TOC uptake in neuroendocrine tumour and healthy tissue: differentiation of physiological uptake and pathological processes in PET/CT. *Eur J Nucl Med Mol Imaging*. 2013;40:514-523.
29. Haug AR, Cindea-Drimus R, Auernhammer CJ, et al Neuroendocrine tumor recurrence: diagnosis with ^{68}Ga-DOTATATE PET/CT. *Radiology*. 2014;270:517-525.
30. Merola E, Pavel ME, Panzuto F, et al Functional Imaging in the Follow-Up of Enteropancreatic Neuroendocrine Tumors: Clinical Usefulness and Indications. *J Clin Endocrinol Metab*. 2017;102:1486-1494.
31. Gabriel M, Oberauer A, Dobrozemsky G, et al ^{68}Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. *J Nucl Med*. 2009;50:1427-1434.
32. Hasegawa T, Yamao K, Hijioka S, et al Evaluation of Ki-67 index in EUS-FNA specimens for the assessment of malignancy risk in pancreatic neuroendocrine tumors. *Endoscopy*. 2014;46:32-38.
33. Boutsen L, Jouret-Mourin A, Borbath I, et al Accuracy of Pancreatic Neuroendocrine Tumour Grading by Endoscopic Ultrasound-Guided Fine Needle Aspiration: Analysis of a Large Cohort and Perspectives for Improvement. *Neuroendocrinology*. 2018;106:158-166.
34. Larghi A, Capurso G, Carnuccio A, et al Ki-67 grading of nonfunctioning pancreatic neuroendocrine tumors on histologic samples obtained by EUS-guided fine-needle tissue acquisition: a prospective study. *Gastrointest Endosc*. 2012;76:570-577.
35. Barbe C, Murat A, Dupas B, et al Magnetic resonance imaging versus endoscopic ultrasonography for the detection of pancreatic tumours in multiple endocrine neoplasia type 1. *Dig Liver Dis*. 2012;44:228-234.
36. van Asselt SJ, Brouwers AH, van Dullemen HM, et al EUS is superior for detection of pancreatic lesions compared with standard imaging in patients with multiple endocrine neoplasia type 1. *Gastrointest Endosc*. 2015;81:159-167 e152.
37. DeWitt J, Devereaux B, Chriswell M, et al Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. *Ann Intern Med*. 2004;141:753-763.
38. Ahmad NA, Lewis JD, Siegelman ES, et al Role of endoscopic ultrasound and magnetic resonance imaging in the preoperative staging of pancreatic adenocarcinoma. *Am J Gastroenterol*. 2000;95:1926-1931.
39. Lee LC, Grant CS, Salomao DR, et al Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): role for nonoperative management. *Surgery*. 2012;152:965-974.
40. Sadot E, Reidy-Lagunes DL, Tang LH, et al Observation versus Resection for Small Asymptomatic Pancreatic Neuroendocrine Tumors: A Matched Case-Control Study. *Ann Surg Oncol*. 2016;23:1361-1370.
41. Haynes AB, Deshpande V, Ingkakul T, et al Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. *Arch Surg*. 2011;146:534-538.
42. 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;17:2105-2113.
43. Sharpe SM, In H, Winchester DJ, et al Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. *J Gastrointest Surg*. 2015;19:117-123; discussion 123.
44. Finkelstein P, Sharma R, Picado O, et al Pancreatic Neuroendocrine Tumors (panNETs): Analysis of Overall Survival of Nonsurgical Management Versus Surgical Resection. *J Gastrointest Surg*. 2017;21:855-866.
45. Bettini R, Partelli S, Boninsegna L, et al Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. *Surgery*. 2011;150:75-82.

46. Sallinen VJ, Le Large TYS, Tieftrunk E, et al Prognosis of sporadic resected small (</=2 cm) nonfunctional pancreatic neuroendocrine tumors - a multi-institutional study. *HPB (Oxford)*. 2018;20:251-259.
47. Partelli S, Cirocchi R, Crippa S, et al Systematic review of active surveillance versus surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms. *Br J Surg*. 2017;104:34-41.
48. Gaujoux S, Partelli S, Maire F, et al Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab*. 2013;98:4784-4789.
49. Jung JG, Lee KT, Woo YS, et al Behavior of Small, Asymptomatic, Nonfunctioning Pancreatic Neuroendocrine Tumors (NF-PNETs). *Medicine (Baltimore)*. 2015;94:e983.
50. Rosenberg AM, Friedmann P, Del Rivero J, et al Resection versus expectant management of small incidentally discovered nonfunctional pancreatic neuroendocrine tumors. *Surgery*. 2016;159:302-309.
51. Falconi M, Bartsch DK, Eriksson B, et al ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology*. 2012;95:120-134.
52. Singh S, Dey C, Kennecke H, et al Consensus Recommendations for the Diagnosis and Management of Pancreatic Neuroendocrine Tumors: Guidelines from a Canadian National Expert Group. *Ann Surg Oncol*. 2015;22:2685-2699.
53. Mansour JC, Chavin K, Morris-Stiff G, et al Management of asymptomatic, well-differentiated PNETs: results of the Delphi consensus process of the Americas Hepato-Pancreato-Biliary Association. *HPB (Oxford)*. 2019;21:515-523.
54. Ito T, Igarashi H, Jensen RT. Pancreatic neuroendocrine tumors: clinical features, diagnosis and medical treatment: advances. *Best Pract Res Clin Gastroenterol*. 2012;26:737-753.
55. Cryer PE, Axelrod L, Grossman AB, et al Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94:709-728.
56. Metz DC, Cadiot G, Poitras P, et al Diagnosis of Zollinger-Ellison syndrome in the era of PPIs, faulty gastrin assays, sensitive imaging and limited access to acid secretory testing. *Int J Endocr Oncol*. 2017;4:167-185.
57. Jensen RT, Niederle B, Mitry E, et al Gastrinoma (duodenal and pancreatic). Neuroendocrinology. 2006;84:173-182.
58. Capelli P, Fassan M, Scarpa A. Pathology - grading and staging of GEP-NETs. *Best Pract Res Clin Gastroenterol*. 2012;26:705-717.
59. Klimstra DS. Pathology reporting of neuroendocrine tumors: essential elements for accurate diagnosis, classification, and staging. *Semin Oncol*. 2013;40:23-36.
60. Oberg K. Management of functional neuroendocrine tumors of the pancreas. *Gland Surg*. 2018;7:20-27.
61. Kamp K, Feelders RA, van Adrichem RC, et al Parathyroid hormone-related peptide (PTHrP) secretion by gastroenteropancreatic neuroendocrine tumors (GEP-NETs): clinical features, diagnosis, management, and follow-up. *J Clin Endocrinol Metab*. 2014;99:3060-3069.
62. Mehrabi A, Fischer L, Hafezi M, et al A systematic review of localization, surgical treatment options, and outcome of insulinoma. *Pancreas*. 2014;43:675-686.
63. Fishbeyn VA, Norton JA, Benya RV, et al Assessment and prediction of long-term cure in patients with the Zollinger-Ellison syndrome: the best approach. *Ann Intern Med*. 1993;119:199-206.
64. Grant CS. Insulinoma. *Best Pract Res Clin Gastroenterol*. 2005;19:783-798.
65. Norton JA, Fraker DL, Alexander HR, et al Surgery increases survival in patients with gastrinoma. *Ann Surg*. 2006;244:410-419.
66. Bartsch DK, Waldmann J, Fendrich V, et al Impact of lymphadenectomy on survival after surgery for sporadic gastrinoma. *Br J Surg*. 2012;99:1234-1240.
67. Boninsegna L, Panzuto F, Partelli S, et al Malignant pancreatic neuroendocrine tumour: lymph node ratio and Ki67 are predictors of recurrence after curative resections. *Eur J Cancer*. 2012;48:1608-1615.
68. 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;148:932-939.
69. Tsutsumi K, Ohtsuka T, Mori Y, et al Analysis of lymph node metastasis in pancreatic neuroendocrine tumors (PNETs) based on the tumor size and hormonal production. *J Gastroenterol*. 2012;47:678-685.
70. Krampitz GW, Norton JA, Poultsides GA, et al Lymph nodes and survival in pancreatic neuroendocrine tumors. Arch Surg. 2012;147:820-827.
71. Oberg K. Circulating biomarkers in gastroenteropancreatic neuroendocrine tumours. *Endocr Relat Cancer*. 2011;18 Suppl 1:S17-25.

72. Sharma P, Arora S, Dhull VS, et al Evaluation of ^{68}Ga-DOTANOC PET/CT imaging in a large exclusive population of pancreatic neuroendocrine tumors. *Abdom Imaging*. 2015;40:299-309.
73. Sharma P, Arora S, Karunanithi S, et al Somatostatin receptor based PET/CT imaging with ^{68}Ga-DOTA-Nal3-octreotide for localization of clinically and biochemically suspected insulinoma. *Q J Nucl Med Mol Imaging*. 2016;60:69-76.
74. Norton JA, Alexander HR, Fraker DL, et al Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases, or survival in patients with Zollinger-Ellison syndrome? *Ann Surg*. 2004;239:617-625; discussion 626.
75. O'Grady HL, Conlon KC. Pancreatic neuroendocrine tumours. *Eur J Surg Oncol*. 2008;34:324-332.
76. Fraker DL, Norton JA, Alexander HR, et al Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. *Ann Surg*. 1994;220:320-328; discussion 328-330.
77. Norton JA, Fraker DL, Alexander HR, et al Surgery to cure the Zollinger-Ellison syndrome. *N Engl J Med*. 1999;341:635-644.
78. Norton JA, Fraker DL, Alexander HR, et al Value of surgery in patients with negative imaging and sporadic Zollinger-Ellison syndrome. *Ann Surg*. 2012;256:509-517.
79. Yu F, Venzon DJ, Serrano J, et al Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger-Ellison syndrome. *J Clin Oncol*. 1999;17:615-630.
80. Lairmore TC, Piersall LD, DeBenedetti MK, et al Clinical genetic testing and early surgical intervention in patients with multiple endocrine neoplasia type 1 (MEN 1). *Ann Surg*. 2004;239:637-645; discussion 645-637.
81. Pieterman CR, Conemans EB, Dreijerink KM, et al Thoracic and duodenopancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1: natural history and function of menin in tumorigenesis. *Endocr Relat Cancer*. 2014;21:R121-142.
82. Lowney JK, Frisella MM, Lairmore TC, et al Pancreatic islet cell tumor metastasis in multiple endocrine neoplasia type 1: correlation with primary tumor size. *Surgery*. 1998;124:1043-1048, discussion 1048-1049.
83. Goncalves TD, Toledo RA, Sekiya T, et al Penetrance of functioning and nonfunctioning pancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1 in the second decade of life. *J Clin Endocrinol Metab*. 2014;99:E89-96.
84. Lairmore TC, Chen VY, DeBenedetti MK, et al Duodenopancreatic resections in patients with multiple endocrine neoplasia type 1. *Ann Surg*. 2000;231:909-918.
85. 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*. 2018;268:158-164.
86. Sallinen V, Le Large TY, Galeev S, et al Surveillance strategy for small asymptomatic non-functional pancreatic neuroendocrine tumors - a systematic review and meta-analysis. *HPB (Oxford)*. 2017;19:310-320.
87. Cherenfant J, Stocker SJ, Gage MK, et al Predicting aggressive behavior in nonfunctioning pancreatic neuroendocrine tumors. *Surgery*. 2013;154:785-791; discussion 791-783.
88. Conemans EB, Nell S, Pieterman CRC, et al Prognostic Factors for Survival of Men1 Patients with Duodenopancreatic Tumors Metastatic to the Liver: Results from the Dmsg. *Endocr Pract*. 2017;23:641-648.
89. Kappelle WF, Valk GD, Leenders M, et al Growth rate of small pancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1: results from an endoscopic ultrasound based cohort study. *Endoscopy*. 2017;49:27-34.
90. Scarpa A, Chang DK, Nones K, et al Whole-genome landscape of pancreatic neuroendocrine tumours. *Nature*. 2017;543:65-71.
91. Christakis I, Qiu W, Hyde SM, et al Genotype-phenotype pancreatic neuroendocrine tumor relationship in multiple endocrine neoplasia type 1 patients: A 23-year experience at a single institution. *Surgery*. 2018;163:212-217.
92. Thevenon J, Bourredjem A, Faivre L, et al Higher risk of death among MEN1 patients with mutations in the JunD interacting domain: a Groupe d'etude des Tumeurs Endocrines (GTE) cohort study. *Hum Mol Genet*. 2013;22:1940-1948.
93. Bartsch DK, Slater EP, Albers M, et al Higher risk of aggressive pancreatic neuroendocrine tumors in MEN1 patients with MEN1 mutations affecting the CHES1 interacting MENIN domain. *J Clin Endocrinol Metab*. 2014;99:E2387-2391.
94. Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. *Ann Surg*. 2004;240:757-773.
95. Arva NC, Pappas JG, Bhatla T, et al Well-differentiated pancreatic neuroendocrine carcinoma in tuberous sclerosis--case report and review of the literature. *Am J Surg Pathol*. 2012;36:149-153.
96. Dworakowska D, Grossman AB. Are neuroendocrine tumours a feature of tuberous sclerosis? A systematic review. *Endocr Relat Cancer*. 2009;16:45-58.

97. Dayal Y, Tallberg KA, Nunnemacher G, et al Duodenal carcinoids in patients with and without neurofibromatosis. A comparative study. *Am J Surg Pathol*. 1986;10:348-357.
98. Mao C, Shah A, Hanson DJ, et al Von Recklinghausen's disease associated with duodenal somatostatinoma: contrast of duodenal versus pancreatic somatostatinomas. *J Surg Oncol*. 1995;59:67-73.
99. van Basten JP, van Hoek B, de Bruine A, et al Ampullary carcinoid and neurofibromatosis: case report and review of the literature. *Neth J Med*. 1994;44:202-206.
100. Soga J, Yakuwa Y. Somatostatinoma/inhibitory syndrome: a statistical evaluation of 173 reported cases as compared to other pancreatic endocrinomas. *J Exp Clin Cancer Res*. 1999;18:13-22.
101. Jensen RT, Berna MJ, Bingham DB, et al Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer*. 2008;113:1807-1843.
102. Neychev V, Sadowski SM, Zhu J, et al Neuroendocrine Tumor of the Pancreas as a Manifestation of Cowden Syndrome: A Case Report. *J Clin Endocrinol Metab*. 2016;101:353-358.
103. Keutgen XM, Hammel P, Choyke PL, et al Evaluation and management of pancreatic lesions in patients with von Hippel-Lindau disease. *Nat Rev Clin Oncol*. 2016;13:537-549.
104. Libutti SK, Choyke PL, Bartlett DL, et al Pancreatic neuroendocrine tumors associated with von Hippel Lindau disease: diagnostic and management recommendations. *Surgery*. 1998;124:1153-1159.
105. Libutti SK, Choyke PL, Alexander HR, et al Clinical and genetic analysis of patients with pancreatic neuroendocrine tumors associated with von Hippel-Lindau disease. *Surgery*. 2000;128:1022-1027;discussion 1027-1028.
106. Marcos HB, Libutti SK, Alexander HR, et al Neuroendocrine tumors of the pancreas in von Hippel-Lindau disease: spectrum of appearances at CT and MR imaging with histopathologic comparison. *Radiology*. 2002;225:751-758.
107. Blansfield JA, Choyke L, Morita SY, et al Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). *Surgery*. 2007;142:814-818; discussion 818 e811-812.
108. Turcotte S, Turkbey B, Barak S, et al von Hippel-Lindau disease-associated solid microcystic serous adenomas masquerading as pancreatic neuroendocrine neoplasms. *Surgery*. 2012;152:1106-1117.
109. Krauss T, Ferrara AM, Links TP, et al Preventive medicine of von Hippel-Lindau disease-associated pancreatic neuroendocrine tumors. *Endocr Relat Cancer*. 2018;25:783-793.
110. Kulke MH, Anthony LB, Bushnell DL, et al NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas*. 2010;39:735-752.
111. Jensen RT, Cadiot G, Brandi ML, et al ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology*. 2012;95:98-119.
112. de Rooij T, Klompmaker S, Abu Hilal M, et al Laparoscopic pancreatic surgery for benign and malignant disease. *Nat Rev Gastroenterol Hepatol*. 2016;13:227-238.
113. Edwin B, Sahakyan MA, Abu Hilal M, et al Laparoscopic surgery for pancreatic neoplasms: the European association for endoscopic surgery clinical consensus conference. *Surg Endosc*. 2017;31:2023-2041.
114. van Hilst J, de Rooij T, Klompmaker S, et al Minimally Invasive versus Open Distal Pancreatectomy for Ductal Adenocarcinoma (DIPLOMA): A Pan-European Propensity Score Matched Study. *Ann Surg*. 2019;269:10-17.
115. de Rooij T, van Hilst J, van Santvoort H, et al Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): A Multicenter Patient-blinded Randomized Controlled Trial *Ann Surg*. 2019;269:2-9.
116. Xourafas D, Tavakkoli A, Clancy TE, et al Distal pancreatic resection for neuroendocrine tumors: is laparoscopic really better than open? *J Gastrointest Surg*. 2015;19:831-840.
117. 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;16:397-406.
118. Joechle K, Conrad C. Cost-effectiveness of minimally invasive pancreatic resection. *J Hepatobiliary Pancreat Sci*. 2018;25:291-298.
119. Kristinsson SY, Gridley G, Hoover RN, et al Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up. *Haematologica*. 2014;99:392-398.
120. Nakata K, Shikata S, Ohtsuka T, et al Minimally invasive preservation versus splenectomy during distal pancreatectomy: a systematic review and meta-analysis. *J Hepatobiliary Pancreat Sci*. 2018;25:476-488.
121. Beane JD, Pitt HA, Nakeeb A, et al Splenic preserving distal pancreatectomy: does vessel preservation matter? J Am Coll Surg. 2011;212:651-657; discussion 657-658.

122. Jean-Philippe A, Alexandre J, Christophe L, et al Laparoscopic spleen-preserving distal pancreatectomy: splenic vessel preservation compared with the Warshaw technique. *JAMA Surg*. 2013;148:246-252.
123. Lv GY, Wang GY, Jiang C, et al Laparoscopic spleen-preserving distal pancreatectomy with or without splenic vessel conservation: a retrospective study of 20 cases. *Hepatogastroenterology*. 2013;60:1785-1788.
124. Shi N, Liu SL, Li YT, et al Splenic Preservation Versus Splenectomy During Distal Pancreatectomy: A Systematic Review and Meta-analysis. *Ann Surg Oncol*. 2016;23:365-374.
125. Elabbasy F, Gadde R, Hanna MM, et al Minimally invasive spleen-preserving distal pancreatectomy: Does splenic vessel preservation have better postoperative outcomes? A systematic review and meta-analysis. *Hepatobiliary Pancreat Dis Int*. 2015;14:346-353.
126. Fernandez-Cruz L, Cosa R, Blanco L, et al Curative laparoscopic resection for pancreatic neoplasms: a critical analysis from a single institution. *J Gastrointest Surg*. 2007;11:1607-1621; discussion 1621-1602.
127. Dai MH, Shi N, Xing C, et al Splenic preservation in laparoscopic distal pancreatectomy. *Br J Surg*. 2017;104:452-462.
128. Choi SH, Kang CM, Kim JY, et al Laparoscopic extended (subtotal) distal pancreatectomy with resection of both splenic artery and vein. *Surg Endosc*. 2013;27:1412-1413.
129. Rubin LG, Schaffner W. Clinical practice. Care of the asplenic patient. *N Engl J Med*. 2014;371:349-356.
130. King H, Shumacker HB, Jr. Splenic studies. I. Susceptibility to infection after splenectomy performed in infancy. *Ann Surg*. 1952;136:239-242.
131. Rubin LG, Levin MJ, Ljungman P, et al 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58:309-318.
132. Bonanni P, Grazzini M, Niccolai G, et al Recommended vaccinations for asplenic and hyposplenic adult patients. *Hum Vaccin Immunother*. 2017;13:359-368.
133. Rubin LG, Levin MJ, Ljungman P, et al 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2014;58:e44-100.
134. Robinson CL, Romero JR, Kempe A, et al Advisory Committee on Immunization Practices Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger - United States, 2017. *Am J Transplant*. 2017;17:1136-1138.
135. Kim DK, Riley LE, Harriman KH, et al Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2017. *Am J Transplant*. 2017;17:1132-1135.
136. Guerrini GP, Lauretta A, Belluco C, et al Robotic versus laparoscopic distal pancreatectomy: an up-to-date meta-analysis. *BMC Surg*. 2017;17:105.
137. Zureikat AH, Borrebach J, Pitt HA, et al Minimally invasive hepatopancreatobiliary surgery in North America: an ACS-NSQIP analysis of predictors of conversion for laparoscopic and robotic pancreatectomy and hepatectomy. *HPB (Oxford)*. 2017;19:595-602.
138. Nassour I, Wang SC, Porembka MR, et al Robotic Versus Laparoscopic Pancreaticoduodenectomy: a NSQIP Analysis. *J Gastrointest Surg*. 2017;21:1784-1792.
139. Zureikat AH, Postlewait LM, Liu Y, et al A Multi-institutional Comparison of Perioperative Outcomes of Robotic and Open Pancreaticoduodenectomy. *Ann Surg*. 2016;264:640-649.
140. van Hilst J, de Rooij T, Bosscha K, et al Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial *Lancet Gastroenterol Hepatol*. 2019;4:199-207.
141. Ricci C, Casadei R, Taffurelli G, et al Minimally Invasive Pancreaticoduodenectomy: What is the Best “Choice”? A Systematic Review and Network Meta-analysis of Non-randomized Comparative Studies. *World J Surg*. 2018;42:788-805.
142. Beger HG, Siech M, Poch B, et al Limited surgery for benign tumours of the pancreas: a systematic review. *World J Surg*. 2015;39:1557-1566.
143. Hackert T, Hinz U, Fritz S, et al Enucleation in pancreatic surgery: indications, technique, and outcome compared to standard pancreatic resections. *Langenbecks Arch Surg*. 2011;396:1197-1203.
144. Pitt SC, Pitt HA, Baker MS, et al Small pancreatic and periampullary neuroendocrine tumors: resect or enucleate? *J Gastrointest Surg*. 2009;13:1692-1698.
145. Huttner FJ, Koessler-Ebs J, Hackert T, et al Meta-analysis of surgical outcome after enucleation versus standard resection for pancreatic neoplasms. *Br J Surg*. 2015;102:1026-1036.

146. Kuo EJ, Salem RR. Population-level analysis of pancreatic neuroendocrine tumors 2 cm or less in size. *Ann Surg Oncol*. 2013;20:2815-2821.
147. Bilimoria KY, Talamonti MS, Tomlinson JS, et al Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. *Ann Surg*. 2008;247:490-500.
148. Gratian L, Pura J, Dinan M, et al Impact of extent of surgery on survival in patients with small nonfunctional pancreatic neuroendocrine tumors in the United States. *Ann Surg Oncol*. 2014;21:3515-3521.
149. Genc CG, Jilesen AP, Partelli S, et al A New Scoring System to Predict Recurrent Disease in Grade 1 and 2 Nonfunctional Pancreatic Neuroendocrine Tumors. *Ann Surg*. 2018;267:1148-1154.
150. Zhang XF, Wu Z, Cloyd J, et al Margin status and long-term prognosis of primary pancreatic neuroendocrine tumor after curative resection: Results from the US Neuroendocrine Tumor Study Group. *Surgery*. 2019;165:548-556.
151. Kloppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann N Y Acad Sci*. 2004;1014:13-27.
152. Bosman FT, World Health Organization., International Agency for Research on Cancer. *WHO classification of tumours of the digestive system*. 4th ed. Lyon: International Agency for Research on Cancer; 2010.
153. Lloyd RV, Osamura RY, Klöppel G, et al *Classification of Tumours of Endocrine Organs*. Lyon: IARC Press; 2017.
154. Lombardi M, De Lio N, Funel N, et al Prognostic factors for pancreatic neuroendocrine neoplasms (pNET) and the risk of small non-functioning pNET. *J Endocrinol Invest*. 2015;38:605-613.
155. Sallinen V, Haglund C, Seppanen H. Outcomes of resected nonfunctional pancreatic neuroendocrine tumors: Do size and symptoms matter? *Surgery*. 2015;158:1556-1563.
156. Milan SA, Yeo CJ. Neuroendocrine tumors of the pancreas. *Curr Opin Oncol*. 2012;24:46-55.
157. Falconi M, Plockinger U, Kwekkeboom DJ, et al Well-differentiated pancreatic nonfunctioning tumors/carcinoma. *Neuroendocrinology*. 2006;84:196-211.
158. 158. Wong J, Fulp WJ, Strosberg JR, et al Predictors of lymph node metastases and impact on survival in resected pancreatic neuroendocrine tumors: a single-center experience. *Am J Surg*. 2014;208:775-780.
159. Brunner SM, Weber F, Werner JM, et al Neuroendocrine tumors of the pancreas: a retrospective single-center analysis using the ENETS TNM-classification and immunohistochemical markers for risk stratification. *BMC Surg*. 2015;15:49.
160. Hashim YM, Trinkaus KM, Linehan DC, et al Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). *Ann Surg*. 2014;259:197-203.
161. Crippa S, Bassi C, Warshaw AL, et al Middle pancreatectomy: indications, short- and long-term operative outcomes. *Ann Surg*. 2007;246:69-76.
162. Goudard Y, Gaujoux S, Dokmak S, et al Reappraisal of central pancreatectomy a 12-year single-center experience. *JAMA Surg*. 2014;149:356-363.
163. Iacono C, Verlato G, Ruzzenente A, et al Systematic review of central pancreatectomy and meta-analysis of central versus distal pancreatectomy. *Br J Surg*. 2013;100:873-885.
164. Xiao W, Zhu J, Peng L, et al The role of central pancreatectomy in pancreatic surgery: a systematic review and meta-analysis. *HPB (Oxford)*. 2018;20:896-904.
165. Zhang RC, Zhang B, Mou YP, et al Comparison of clinical outcomes and quality of life between laparoscopic and open central pancreatectomy with pancreaticojejunostomy. *Surg Endosc*. 2017;31:4756-4763.
166. Chen S, Zhan Q, Jin JB, et al Robot-assisted laparoscopic versus open middle pancreatectomy: short-term results of a randomized controlled trial *Surg Endosc*. 2017;31:962-971.
167. Iacono C, Bortolasi L, Facci E, et al The Dagradi-Serio-Iacono operation central pancreatectomy. *J Gastrointest Surg*. 2007;11:364-376.
168. Tatsumoto S, Kodama Y, Sakurai Y, et al Pancreatic neuroendocrine neoplasm: correlation between computed tomography enhancement patterns and prognostic factors of surgical and endoscopic ultrasound-guided fine-needle aspiration biopsy specimens. *Abdom Imaging*. 2013;38:358-366.
169. Postlewait LM, Ethun CG, Baptiste GG, et al Pancreatic neuroendocrine tumors: Preoperative factors that predict lymph node metastases to guide operative strategy. *J Surg Oncol*. 2016;114:440-445.
170. Conrad C, Kutlu OC, Dasari A, et al Prognostic Value of Lymph Node Status and Extent of Lymphadenectomy in Pancreatic Neuroendocrine Tumors Confined To and Extending Beyond the Pancreas. *J Gastrointest Surg*. 2016;20:1966-1974.

171. Ballian N, Loeffler AG, Rajamanickam V, et al A simplified prognostic system for resected pancreatic neuroendocrine neoplasms. *HPB (Oxford)*. 2009;11:422-428.
172. Tomassetti P, Campana D, Piscitelli L, et al Endocrine pancreatic tumors: factors correlated with survival *Ann Oncol*. 2005;16:1806-1810.
173. Bettini R, Boninsegna L, Mantovani W, et al Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. *Ann Oncol*. 2008;19:903-908.
174. Chu QD, Hill HC, Douglass HO, Jr., et al Predictive factors associated with long-term survival in patients with neuroendocrine tumors of the pancreas. *Ann Surg Oncol*. 2002;9:855-862.
175. Hochwald SN, Zee S, Conlon KC, et al Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol*. 2002;20:2633-2642.
176. Fendrich V, Langer P, Celik I, et al An aggressive surgical approach leads to long-term survival in patients with pancreatic endocrine tumors. *Ann Surg*. 2006;244:845-851; discussion 852-843.
177. Fischer L, Kleeff J, Esposito I, et al Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. *Br J Surg*. 2008;95:627-635.
178. Ekeblad S, Skogseid B, Dunder K, et al Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res*. 2008;14:7798-7803.
179. DiNorcia J, Lee MK, Reavey PL, et al One hundred thirty resections for pancreatic neuroendocrine tumor: evaluating the impact of minimally invasive and parenchyma-sparing techniques. *J Gastrointest Surg*. 2010;14:1536-1546.
180. Roland CL, Bian A, Mansour JC, et al Survival impact of malignant pancreatic neuroendocrine and islet cell neoplasm phenotypes. *J Surg Oncol*. 2012;105:595-600.
181. Parekh JR, Wang SC, Bergsland EK, et al Lymph node sampling rates and predictors of nodal metastasis in pancreatic neuroendocrine tumor resections: the UCSF experience with 149 patients. *Pancreas*. 2012;41:840-844.
182. Huebner M, Kendrick M, Reid-Lombardo KM, et al Number of lymph nodes evaluated: prognostic value in pancreatic adenocarcinoma. *J Gastrointest Surg*. 2012;16:920-926.
183. Que FG, Nagorney DM, Batts KP, et al Hepatic resection for metastatic neuroendocrine carcinomas. *Am J Surg*. 1995;169:36-42; discussion 42-33.
184. Mayo SC, de Jong MC, Pulitano C, et al Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol*. 2010;17:3129-3136.
185. Sarmiento JM, Heywood G, Rubin J, et al Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival *J Am Coll Surg*. 2003;197:29-37.
186. Elias D, Lefevre JH, Duvillard P, et al Hepatic metastases from neuroendocrine tumors with a “thin slice” pathological examination: they are many more than you think. *Ann Surg*. 2010;251:307-310.
187. Foster JH, Berman MM. Solid liver tumors. *Major Probl Clin Surg*. 1977;22:1-342.
188. Foster JH, Lundy J. Liver Metastases. Curr Probl Surg. 1981;18:157-202.
189. McEntee GP, Nagorney DM, Kvols LK, et al Cytoreductive hepatic surgery for neuroendocrine tumors. *Surgery*. 1990;108:1091-1096.
190. Chambers AJ, Pasieka JL, Dixon E, et al The palliative benefit of aggressive surgical intervention for both hepatic and mesenteric metastases from neuroendocrine tumors. *Surgery*. 2008;144:645-651; discussion 651-643.
191. Graff-Baker AN, Sauer DA, Pommier SJ, et al Expanded criteria for carcinoid liver debulking: Maintaining survival and increasing the number of eligible patients. *Surgery*. 2014;156:1369-1376; discussion 1376-1367.
192. Morgan RE, Pommier SJ, Pommier RF. Expanded criteria for debulking of liver metastasis also apply to pancreatic neuroendocrine tumors. *Surgery*. 2018;163:218-225.
193. Maxwell JE, Sherman SK, O’Dorisio TM, et al Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy? *Surgery*. 2016;159:320-333.
194. Scott AT, Breheny PJ, Keck KJ, et al Effective cytoreduction can be achieved in patients with numerous neuroendocrine tumor liver metastases (NETLMs). *Surgery*. 2019;165:166-175.
195. Glazer ES, Tseng JF, Al-Refaie W, et al Long-term survival after surgical management of neuroendocrine hepatic metastases. *HPB (Oxford)*. 2010;12:427-433.
196. Brooke-Smith M, Figueras J, Ullah S, et al Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study. *HPB (Oxford)*.

2015;17:46-51.
197. Gaujoux S, Gonen M, Tang L, et al Synchronous resection of primary and liver metastases for neuroendocrine tumors. *Ann Surg Oncol*. 2012;19:4270-4277.
198. De Jong MC, Farnell MB, Sclabas G, et al Liver-directed therapy for hepatic metastases in patients undergoing pancreaticoduodenectomy: a dual-center analysis. *Ann Surg*. 2010;252:142-148.
199. Odisio BC, Richter M, Aloia TA, et al Use of Prophylactic Antibiotics to Prevent Abscess Formation Following Hepatic Ablation in Patients with Prior Enterobiliary Manipulation. *J Gastrointest Surg*. 2016;20:1428-1434.
200. Tan SL, Yu XL, Liang P, et al Preventing intrahepatic infection after ablation of liver tumours in biliary-enteric anastomosis patients. *Int J Hyperthermia*. 2017;33:664-669.
201. Kishi Y, Shimada K, Nara S, et al The type of preoperative biliary drainage predicts short-term outcome after major hepatectomy. *Langenbecks Arch Surg*. 2016;401:503-511.
202. Iacono C, Ruzzenente A, Campagnaro T, et al Role of preoperative biliary drainage in jaundiced patients who are candidates for pancreatoduodenectomy or hepatic resection: highlights and drawbacks. *Ann Surg*. 2013;257:191-204.
203. Caplin ME, Pavel M, Cwikla JB, et al Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371:224-233.
204. Yao JC, Shah MH, Ito T, et al Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:514-523.
205. Raymond E, Dahan L, Raoul JL, et al Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:501-513.
206. Kunz PL, Catalano PJ, Nimeiri H, et al A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211). *J Clin Oncol*. 2018;36:suppl; abstr 4004.
207. Bertani E, Fazio N, Radice D, et al Resection of the Primary Tumor Followed by Peptide Receptor Radionuclide Therapy as Upfront Strategy for the Treatment of G1-G2 Pancreatic Neuroendocrine Tumors with Unresectable Liver Metastases. *Ann Surg Oncol*. 2016;23:981-989.
208. Hill JS, McPhee JT, McDade TP, et al Pancreatic neuroendocrine tumors: the impact of surgical resection on survival *Cancer*. 2009;115:741-751.
209. Huttner FJ, Schneider L, Tarantino I, et al Palliative resection of the primary tumor in 442 metastasized neuroendocrine tumors of the pancreas: a population-based, propensity score-matched survival analysis. *Langenbecks Arch Surg*. 2015;400:715-723.
210. Keutgen XM, Nilubol N, Glanville J, et al Resection of primary tumor site is associated with prolonged survival in metastatic nonfunctioning pancreatic neuroendocrine tumors. *Surgery*. 2016;159:311-318.
211. Ye H, Xu HL, Shen Q, et al Palliative Resection of Primary Tumor in Metastatic Nonfunctioning Pancreatic Neuroendocrine Tumors. *J Surg Res*. 2019.
212. Tierney JF, Chivukula SV, Wang X, et al Resection of primary tumor may prolong survival in metastatic gastroenteropancreatic neuroendocrine tumors. *Surgery*. 2019;165:644-651.
213. 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;130:1078-1085.
214. Nguyen SQ, Angel LP, Divino CM, et al Surgery in malignant pancreatic neuroendocrine tumors. *J Surg Oncol*. 2007;96:397-403.
215. Bertani E, Fazio N, Botteri E, et al Resection of the primary pancreatic neuroendocrine tumor in patients with unresectable liver metastases: possible indications for a multimodal approach. *Surgery*. 2014;155:607-614.
216. Citterio D, Pusceddu S, Facciorusso A, et al Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver. *Eur J Surg Oncol*. 2017;43:380-387.
217. Zhou B, Zhan C, Ding Y, et al 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.
218. Bertani E, Fazio N, Radice D, et al Assessing the role of primary tumour resection in patients with synchronous unresectable liver metastases from pancreatic neuroendocrine tumour of the body and tail. A propensity score survival evaluation. *Eur J Surg Oncol*. 2017;43:372-379.
219. Kaemmerer D, Twrznik M, Kulkarni HR, et al Prior Resection of the Primary Tumor Prolongs Survival After Peptide Receptor Radionuclide Therapy of Advanced Neuroendocrine Neoplasms. *Annals of Surgery*. 2019;Publish Ahead of Print.
220. Kunz PL, Reidy-Lagunes D, Anthony LB, et al Consensus guidelines for the management and treatment of neuroendocrine tumors.

Pancreas. 2013;42:557-577.
221. Lewis A, Raoof M, Ituarte PHG, et al Resection of the Primary Gastrointestinal Neuroendocrine Tumor Improves Survival with or without Liver Treatment. *Ann Surg*. 2018.
222. Lawrence B, Gustafsson BI, Chan A, et al The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am.* 2011;40:1-18, vii.
223. Hallet J, Law CH, Cukier M, et al Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer*. 2015;121:589-597.
224. Pommier RF. Re-evaluating resection of primary pancreatic neuroendocrine tumors. *Surgery*. 2019;165:557-558.
225. Xiang JX, Zhang XF, Beal EW, et al Hepatic Resection for Non-functional Neuroendocrine Liver Metastasis: Does the Presence of Unresected Primary Tumor or Extrahepatic Metastatic Disease Matter? *Ann Surg Oncol*. 2018;25:3928-3935.
226. Simkens GA, Rovers KP, Nienhuijs SW, et al Patient selection for cytoreductive surgery and HIPEC for the treatment of peritoneal metastases from colorectal cancer. *Cancer Manag Res*. 2017;9:259-266.
227. Partelli S, Bertani E, Bartolomei M, et al Peptide receptor radionuclide therapy as neoadjuvant therapy for resectable or potentially resectable pancreatic neuroendocrine neoplasms. *Surgery*. 2018;163:761-767.
228. van Vliet EI, van Eijck CH, de Krijger RR, et al Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [177Lu-DOTA0,Tyr3]Octreotate. *J Nucl Med*. 2015;56:1647-1653.
229. Mise Y, Aloia TA, Brudvik KW, et al Parenchymal-sparing Hepatectomy in Colorectal Liver Metastasis Improves Salvageability and Survival *Ann Surg*. 2016;263:146-152.
230. Barber TW, Hofman MS, Thomson BN, et al The potential for induction peptide receptor chemoradionuclide therapy to render inoperable pancreatic and duodenal neuroendocrine tumours resectable. *Eur J Surg Oncol*. 2012;38:64-71.
231. Sowa-Staszczak A, Pach D, Chrzan R, et al Peptide receptor radionuclide therapy as a potential tool for neoadjuvant therapy in patients with inoperable neuroendocrine tumours (NETs). *Eur J Nucl Med Mol Imaging*. 2011;38:1669-1674.
232. Campana D, Capurso G, Partelli S, et al Radiolabelled somatostatin analogue treatment in gastroenteropancreatic neuroendocrine tumours: factors associated with response and suggestions for therapeutic sequence. *Eur J Nucl Med Mol Imaging*. 2013;40:1197-1205.
233. Ezziddin S, Attassi M, Yong-Hing CJ, et al Predictors of long-term outcome in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors after peptide receptor radionuclide therapy with ^{177}Lu-octreotate. *J Nucl Med*. 2014;55:183-190.
234. Khorana AA, Mangu PB, Katz MHG. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update Summary. *J Oncol Pract*. 2017;13:388-391.
235. Tsai S, Erickson BA, Dua K, et al Evolution of the Management of Resectable Pancreatic Cancer. *J Oncol Pract*. 2016;12:772-778.
236. Prakash L, Bhosale P, Cloyd J, et al Role of Fluorouracil, Doxorubicin, and Streptozocin Therapy in the Preoperative Treatment of Localized Pancreatic Neuroendocrine Tumors. *J Gastrointest Surg*. 2017;21:155-163.
237. Prakash L, Lee JE, Yao J, et al Role and Operative Technique of Portal Venous Tumor Thrombectomy in Patients with Pancreatic Neuroendocrine Tumors. *J Gastrointest Surg*. 2015;19:2011-2018.
238. Pommier RF. Editorial: peptide receptor radionuclide therapy as neoadjuvant therapy for resectable or potentially resectable pancreatic neuroendocrine neoplasms. *Surgery*. 2018;163:768-769.
239. Kulke MH, Shah MH, Benson AB, 3rd, et al Neuroendocrine tumors, version 1.2015. *J Natl Compr Canc Netw*. 2015;13:78-108.
240. Basu S, Ranade R, Thapa P. Metastatic Neuroendocrine Tumor with Extensive Bone Marrow Involvement at Diagnosis: Evaluation of Response and Hematological Toxicity Profile of PRRT with ^{177}Lu-DOTATATE. *World J Nucl Med*. 2016;15:38-43.
241. Sato A, Masui T, Sankoda N, et al A case of successful conversion from everolimus to surgical resection of a giant pancreatic neuroendocrine tumor. *Surg Case Rep*. 2017;3:82.
242. Devata S, Kim EJ. Neoadjuvant chemotherapy with capecitabine and temozolomide for unresectable pancreatic neuroendocrine tumor. *Case Rep Oncol*. 2012;5:622-626.
243. Ambe CM, Nguyen P, Centeno BA, et al Multimodality Management of "Borderline Resectable" Pancreatic Neuroendocrine Tumors: Report of a Single-Institution Experience. *Cancer Control*. 2017;24:1073274817729076.
244. Xie H, Liu J, Yadav S, et al The role of perioperative systemic therapy in localized pancreatic neuroendocrine neoplasms. *Neuroendocrinology*. 2019.

245. Frilling A, Clift AK. Therapeutic strategies for neuroendocrine liver metastases. *Cancer*. 2015;121:1172-1186.
246. FDA. FDA approves lutetium Lu 177 dotatate for treatment of GEP-NETS. 2018.
247. Strosberg J, El-Haddad G, Wolin E, et al Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. 2017;376:125-135.
248. 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;26:2124-2130.
249. Kaemmerer D, Prasad V, Daffner W, et al Neoadjuvant peptide receptor radionuclide therapy for an inoperable neuroendocrine pancreatic tumor. *World J Gastroenterol*. 2009;15:5867-5870.
250. Stoeltzing O, Loss M, Huber E, et al Staged surgery with neoadjuvant ^{90}Y-DOTATOC therapy for down-sizing synchronous bilobular hepatic metastases from a neuroendocrine pancreatic tumor. *Langenbecks Arch Surg*. 2010;395:185-192.
251. Ezziddin S, Lauschke H, Schaefers M, et al Neoadjuvant downsizing by internal radiation: a case for preoperative peptide receptor radionuclide therapy in patients with pancreatic neuroendocrine tumors. *Clin Nucl Med*. 2012;37:102-104.
252. da Silva TN, van Velthuysen MLF, van Eijck CHJ, et al Successful neoadjuvant peptide receptor radionuclide therapy for an inoperable pancreatic neuroendocrine tumour. *Endocrinol Diabetes Metab Case Rep*. 2018;2018.
253. Yekebas EF, Bogoevski D, Cataldegirmen G, et al En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. *Ann Surg*. 2008;247:300-309.
254. Zhou Y, Zhang Z, Liu Y, et al Pancreatectomy combined with superior mesenteric vein-portal vein resection for pancreatic cancer: a meta-analysis. *World J Surg*. 2012;36:884-891.
255. Yu XZ, Li J, Fu DL, et al Benefit from synchronous portal-superior mesenteric vein resection during pancreaticoduodenectomy for cancer: a meta-analysis. *Eur J Surg Oncol*. 2014;40:371-378.
256. Ravikumar R, Sabin C, Abu Hilal M, et al Portal vein resection in borderline resectable pancreatic cancer: a United Kingdom multicenter study. *J Am Coll Surg*. 2014;218:401-411.
257. Kasumova GG, Conway WC, Tseng JF. The Role of Venous and Arterial Resection in Pancreatic Cancer Surgery. *Ann Surg Oncol*. 2018;25:51-58.
258. Smoot RL, Christein JD, Farnell MB. Durability of portal venous reconstruction following resection during pancreaticoduodenectomy. *J Gastrointest Surg*. 2006;10:1371-1375.
259. Lee DY, Mitchell EL, Jones MA, et al Techniques and results of portal vein/superior mesenteric vein reconstruction using femoral and saphenous vein during pancreaticoduodenectomy. *J Vasc Surg*. 2010;51:662-666.
260. Meniconi RL, Ettorre GM, Vennarecci G, et al Use of cold-stored vein allografts for venous reconstruction during pancreaticoduodenectomy. *J Gastrointest Surg*. 2013;17:1233-1239.
261. Krepline AN, Christians KK, Duelge K, et al Patency rates of portal vein/superior mesenteric vein reconstruction after pancreatectomy for pancreatic cancer. *J Gastrointest Surg*. 2014;18:2016-2025.
262. 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;146:724-732.
263. Glebova NO, Hicks CW, Piazza KM, et al Technical risk factors for portal vein reconstruction thrombosis in pancreatic resection. *J Vasc Surg*. 2015;62:424-433.
264. Birnbaum DJ, Turrini O, Ewald J, et al Pancreatic neuroendocrine tumor: A multivariate analysis of factors influencing survival *Eur J Surg Oncol*. 2014;40:1564-1571.
265. Balachandran A, Tamm EP, Bhosale PR, et al Venous tumor thrombus in nonfunctional pancreatic neuroendocrine tumors. *AJR Am J Roentgenol*. 2012;199:602-608.
266. McDermott VG, England RE, Newman GE. Case report: bleeding gastric varices secondary to splenic vein thrombosis successfully treated by splenic artery embolization. *Br J Radiol*. 1995;68:928-930.
267. Dedania N, Agrawal N, Winter JM, et al Splenic vein thrombosis is associated with an increase in pancreas-specific complications and reduced survival in patients undergoing distal pancreatectomy for pancreatic exocrine cancer. *J Gastrointest Surg*. 2013;17:1392-1398.
268. Basturk O, Tang L, Hruban RH, et al Poorly differentiated neuroendocrine carcinomas of the pancreas: a clinicopathologic analysis of 44 cases. *Am J Surg Pathol*. 2014;38:437-447.
269. Basturk O, Yang Z, Tang LH, et al The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol*.

2015;39:683-690.
270. Garcia-Carbonero R, Sorbye H, Baudin E, et al ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. *Neuroendocrinology*. 2016;103:186-194.
271. Nunez-Valdovinos B, Carmona-Bayonas A, Jimenez-Fonseca P, et al Neuroendocrine Tumor Heterogeneity Adds Uncertainty to the World Health Organization 2010 Classification: Real-World Data from the Spanish Tumor Registry (R-GETNE). *Oncologist*. 2018;23:422-432.
272. 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;24:152-160.
273. Galleberg RB, Knigge U, Tiensuu Janson E, et al Results after surgical treatment of liver metastases in patients with high-grade gastroenteropancreatic neuroendocrine carcinomas. *Eur J Surg Oncol*. 2017;43:1682-1689.
274. Sorbye H, Baudin E, Borbath I, et al Unmet Needs in High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms (WHO G3). *Neuroendocrinology*. 2019;108:54-62.
275. Yachida S, Vakiani E, White CM, et al Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. *Am J Surg Pathol*. 2012;36:173-184.
276. Genc CG, Klumpen HJ, van Oijen MGH, et al A Nationwide Population-Based Study on the Survival of Patients with Pancreatic Neuroendocrine Tumors in The Netherlands. *World J Surg*. 2018;42:490-497.
277. Oberg K, Knigge U, Kwekkeboom D, et al Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23 Suppl 7:vii124-130.
278. Fischer L, Bergmann F, Schimmack S, et al Outcome of surgery for pancreatic neuroendocrine neoplasms. *Br J Surg*. 2014;101:1405-1412.
279. Haugvik SP, Janson ET, Osterlund P, et al Surgical Treatment as a Principle for Patients with High-Grade Pancreatic Neuroendocrine Carcinoma: A Nordic Multicenter Comparative Study. *Ann Surg Oncol*. 2016;23:1721-1728.
280. Partelli S, Inama M, Rinke A, et al Long-Term Outcomes of Surgical Management of Pancreatic Neuroendocrine Tumors with Synchronous Liver Metastases. *Neuroendocrinology*. 2015;102:68-76.
281. Feng T, Lv W, Yuan M, et al Surgical resection of the primary tumor leads to prolonged survival in metastatic pancreatic neuroendocrine carcinoma. *World J Surg Oncol*. 2019;17:54.
282. Kinney MA, Warner ME, Nagorney DM, et al Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. *Br J Anaesth*. 2001;87:447-452.
283. Roy RC, Carter RF, Wright PD. Somatostatin, anaesthesia, and the carcinoid syndrome. Peri-operative administration of a somatostatin analogue to suppress carcinoid tumour activity. *Anaesthesia*. 1987;42:627-632.
284. Seymour N, Sawh SC. Mega-dose intravenous octreotide for the treatment of carcinoid crisis: a systematic review. *Can J Anaesth*. 2013;60:492-499.
285. Woltering EA, Wright AE, Stevens MA, et al Development of effective prophylaxis against intraoperative carcinoid crisis. *J Clin Anesth*. 2016;32:189-193.
286. Chiruvella A, Kooby DA. Surgical Management of Pancreatic Neuroendocrine Tumors. *Surg Oncol Clin N Am*. 2016;25:401-421.
287. Mirakhur B, Pavel ME, Pommier RF, et al Biochemical Responses in Symptomatic and Asymptomatic Patients with Neuroendocrine Tumors: Pooled Analysis of 2 Phase 3 Trials. *Endocr Pract*. 2018.
288. Condron ME, Pommier SJ, Pommier RF. Continuous infusion of octreotide combined with perioperative octreotide bolus does not prevent intraoperative carcinoid crisis. *Surgery*. 2016;159:358-365.
289. Condron ME, Jameson NE, Limbach KE, et al A prospective study of the pathophysiology of carcinoid crisis. *Surgery*. 2019;165:158-165.
290. Massimino K, Harrskog O, Pommier S, et al Octreotide LAR and bolus octreotide are insufficient for preventing intraoperative complications in carcinoid patients. *J Surg Oncol*. 2013;107:842-846.
291. Ito T, Igarashi H, Uehara H, et al Pharmacotherapy of Zollinger-Ellison syndrome. *Expert Opin Pharmacother*. 2013;14:307-321.
292. Nightingale KJ, Davies MG, Kingsnorth AN. Glucagonoma syndrome: survival 24 years following diagnosis. *Dig Surg*. 1999;16:68-71.
293. Mansour JC, Chen H. Pancreatic endocrine tumors. *J Surg Res*. 2004;120:139-161.
294. Strobel O, Neoptolemos J, Jager D, et al Optimizing the outcomes of pancreatic cancer surgery. *Nat Rev Clin Oncol*. 2019;16:11-26.
295. Nahm CB, Connor SJ, Samra JS, et al Postoperative pancreatic fistula: a review of traditional and emerging concepts. *Clin Exp Gastroenterol*. 2018;11:105-118.

296. Veillette G, Dominguez I, Ferrone C, et al Implications and management of pancreatic fistulas following pancreaticoduodenectomy: the Massachusetts General Hospital experience. *Arch Surg*. 2008;143:476-481.
297. Callery MP, Pratt WB, Vollmer CM, Jr. Prevention and management of pancreatic fistula. *J Gastrointest Surg*. 2009;13:163-173.
298. Bassi C, Marchegiani G, Dervenis C, et al The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*. 2017;161:584-591.
299. Zhou YM, Zhang XF, Wu LP, et al Pancreatic fistula after central pancreatectomy: case series and review of the literature. *Hepatobiliary Pancreat Dis Int*. 2014;13:203-208.
300. Jilesen AP, van Eijck CH, Busch OR, et al Postoperative Outcomes of Enucleation and Standard Resections in Patients with a Pancreatic Neuroendocrine Tumor. *World J Surg*. 2016;40:715-728.
301. Inchauste SM, Lanier BJ, Libutti SK, et al Rate of clinically significant postoperative pancreatic fistula in pancreatic neuroendocrine tumors. *World J Surg*. 2012;36:1517-1526.
302. Fendrich V, Merz MK, Waldmann J, et al Neuroendocrine pancreatic tumors are risk factors for pancreatic fistula after pancreatic surgery. *Dig Surg*. 2011;28:263-269.
303. McMillan MT, Christein JD, Callery MP, et al Comparing the burden of pancreatic fistulas after pancreatoduodenectomy and distal pancreatectomy. *Surgery*. 2016;159:1013-1022.
304. Chalabi M, Duluc C, Caron P, et al Somatostatin analogs: does pharmacology impact antitumor efficacy? *Trends Endocrinol Metab.* 2014;25:115-127.
305. Connor S, Alexakis N, Garden OJ, et al Meta-analysis of the value of somatostatin and its analogues in reducing complications associated with pancreatic surgery. *Br J Surg*. 2005;92:1059-1067.
306. Koti RS, Gurusamy KS, Fusai G, et al Meta-analysis of randomized controlled trials on the effectiveness of somatostatin analogues for pancreatic surgery: a Cochrane review. *HPB (Oxford)*. 2010;12:155-165.
307. Jin K, Zhou H, Zhang J, et al Systematic review and meta-analysis of somatostatin analogues in the prevention of postoperative complication after pancreaticoduodenectomy. *Dig Surg*. 2015;32:196-207.
308. McMillan MT, Christein JD, Callery MP, et al Prophylactic octreotide for pancreatoduodenectomy: more harm than good? *HPB (Oxford)*. 2014;16:954-962.
309. Allen PJ, Gonen M, Brennan MF, et al Pasireotide for postoperative pancreatic fistula. *N Engl J Med*. 2014;370:2014-2022.
310. Ma LW, Dominguez-Rosado I, Gennarelli RL, et al The Cost of Postoperative Pancreatic Fistula Versus the Cost of Pasireotide: Results from a Prospective Randomized Trial *Ann Surg*. 2017;265:11-16.
311. Dominguez-Rosado I, Fields RC, Woolsey CA, et al Prospective Evaluation of Pasireotide in Patients Undergoing Pancreaticoduodenectomy: The Washington University Experience. *J Am Coll Surg*. 2018;226:147-154 e141.
312. Elliott IA, Dann AM, Ghukasyan R, et al Pasireotide does not prevent postoperative pancreatic fistula: a prospective study. *HPB (Oxford)*. 2018;20:418-422.
313. Denbo JW, Slack RS, Bruno M, et al Selective Perioperative Administration of Pasireotide is More Cost-Effective Than Routine Administration for Pancreatic Fistula Prophylaxis. *J Gastrointest Surg*. 2017;21:636-646.
314. Conlon KC, Labow D, Leung D, et al Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. *Ann Surg*. 2001;234:487-493; discussion 493-484.
315. Witzigmann H, Diener MK, Kienkotter S, et al No Need for Routine Drainage After Pancreatic Head Resection: The Dual-Center, Randomized, Controlled PANDRA Trial (ISRCTN04937707). *Ann Surg*. 2016;264:528-537.
316. Van Buren G, 2nd, Bloomston M, Hughes SJ, et al A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. *Ann Surg*. 2014;259:605-612.
317. Van Buren G, 2nd, Bloomston M, Schmidt CR, et al A Prospective Randomized Multicenter Trial of Distal Pancreatectomy With and Without Routine Intraperitoneal Drainage. *Ann Surg*. 2017;266:421-431.
318. McMillan MT, Fisher WE, Van Buren G, 2nd, et al The value of drains as a fistula mitigation strategy for pancreatoduodenectomy: Something for everyone? Results of a randomized prospective multi-institutional study. *J Gastrointest Surg*. 2015;19:21-30; discussion 30-21.
319. McMillan MT, Malleo G, Bassi C, et al Multicenter, Prospective Trial of Selective Drain Management for Pancreatoduodenectomy Using Risk Stratification. *Ann Surg*. 2017;265:1209-1218.

NANETS/SNMMI Consensus Statement on Patient Selection and Appropriate Use of 177Lu-DOTATATE Peptide Receptor Radionuclide Therapy

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Background

With the growing use of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT), there are many unanswered questions regarding patient selection. In this document, we review the literature on the use of ^{177}Lu-DOTATATE in neuroendocrine tumors (NETs) of different primary origin, discuss issues of controversy, and review potential contraindications to treatment.

The present consensus statement was developed collaboratively by NANETS and the SNMMI. The North American Neuroendocrine Tumor Society (NANETS) is a multidisciplinary professional society of neuroendocrine specialists in North America that was founded in 2005. NANETS mission is to improve neuroendocrine tumor disease management through increased research and educational opportunities. NANETS is committed to a multidisciplinary approach and consists of doctors and scientists involved in different specialties of NETs. The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology and practical application of nuclear medicine. In addition to publishing journals, newsletters, and books, the SNMMI also sponsors international meetings and workshops designed to increase the competencies of nuclear medicine practitioners and to promote new advances in the science of nuclear medicine.

Materials and methods

Systematic Review

To inform the development of these guidelines, a systematic review of evidence was performed. We followed the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) guidelines (1). A literature search of Pubmed and the CENTRAL database resulted in 1,195 potentially relevant articles using the following search string: ("peptide receptor radionuclide therapy" OR "radioisotope therapy" OR "radionuclide therapy" OR "radiolabeled therapy" OR Yttrium-90 OR 90Y OR Y-90 OR "(90)Y" OR "Y(90)" OR "(177)Lu" OR "Lu(177)" OR Lutetium-177 OR 177Lu OR Lu-177 OR PRRT) AND (neuroendocrine OR carcinoid OR paraganglioma OR pheochromocytoma OR neuroblastoma OR somatostatin). Papers that were excluded included those in non-NET patients, duplications, studies including Indium-111, non-original articles, and those without reported outcomes (Figure 1). After a review of the abstracts and titles, 153 articles were determined to meet the criteria for inclusion in this review. Given the focus of this work, reports using ^{177}Lu-DOTATATE were prioritized. Articles were then selected and grouped according to the primary site of tumor.

Scoring of appropriateness

In developing these guidelines, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: "The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics". The workgroup scored each scenario as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9. Scores 7–9 indicate that the use of the procedure is appropriate for the specific scenario and is generally considered acceptable. Scores 4–6 indicate that the use of the procedure may be appropriate for the specific scenario. This implies that more research is needed to classify the scenario definitively. Scores 1–3 indicate that the use of the procedure is rarely appropriate for the specific scenario and generally is not considered acceptable.

Definition of somatostatin-receptor positivity

^{177}Lu-DOTATATE PRRT should only be used to treat somatostatin receptor (SSTR)-positive tumors. Typically, positivity is defined as intensity of uptake in sites of disease that exceeds the normal liver, a threshold that was originally defined for use with ^{111}In-pentetreotide planar scintigraphy. Nevertheless, the same threshold is often applied to ^{68}Ga-DOTATATE PET imaging despite the fact that the PET scan tends to overestimate uptake compared to scintigraphy (2). Although the FDA approval of ^{177}Lu-DOTATATE limits its use to gastroenteropancreatic (GEP)- NETs, there are other indications where SSTR-PRRT may be beneficial. Consideration of the site of primary tumor is important in determining if a patient should be treated with PRRT. Below we discuss the evidence for the use of ^{177}Lu-DOTATATE for the treatment of NET subtypes assuming that the disease is SSTR-positive on SSTR-PET or scintigraphy. SSTR-negative disease should not be treated using ^{177}Lu-DOTATATE.

Evidence for use based on primary site

Midgut NET

The NETTER-1 study is the only randomized phase III clinical study offering high level evidence of efficacy with ^{177}Lu-DOTATATE. This study was performed in midgut NETs and is discussed in more detail below. Additionally, numerous single-arm studies and clinical series provide additional data on risk and benefit, some in patients receiving only ^{177}Lu-DOTATATE (3,4) and others with combinations of ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC (5,6) (**Table 1**).

NETTER-1 Trial

The NETTER-1 trial, a double-blind, randomized, controlled study of ^{177}Lu-DOTATATE versus high dose octreotide, enrolled grade 1 or 2 midgut NET patients with metastatic or locally advanced progressive tumors during treatment with octreotide (7). Of note, patients had well- differentiated histology with a proliferative index (Ki-67) of 20% or less and positive uptake on SSTR-scintigraphy. The NETTER-1 trial demonstrated an improvement of progression-free survival (PFS) for ^{177}Lu-DOTATATE compared to the control arm (8.4 months for the control arm vs not reached for ^{177}Lu-DOTATATE; HR of 0.21 - 95% CI, 0.13-0.33). Objective response rate with ^{177}Lu-DOTATATE was 18%, versus 3% with high dose octreotide. Preliminary analysis of overall survival (OS) demonstrated a hazard ratio of 0.4 (p=0.004) favoring 177Lu-DOTATATE; final OS is pending. Analysis of health-related quality of life demonstrated that ^{177}Lu-DOTATATE significantly delayed decline in clinically relevant endpoints such as global health, physical functioning, role functioning, and in symptoms such as pain, fatigue and diarrhea (8). Overall, in patients with midgut NET, ^{177}Lu-DOTATATE should be considered in SSTR-positive patients at time of progression after treatment with first line somatostatin analog therapy (Appropriateness Score 9).

Pancreatic NET

Pancreatic NET (pNET) is the second most common site of origin for metastatic GEP-NETs, and a number of retrospective studies have reported results with ^{177}Lu-DOTATATE in this population. Compared to midgut NETs, pNETs appear to have a slightly higher ORR which ranges from 45- 60%, although OS and PFS are consistent with or slightly shorter than seen with midgut (4-6,9,10) (**Table 1**). Outside of the NETTER-1 trial, there are two prospective studies in pNETs: the first is the IEO Phase 1-2 trial, which included 14 pNET patients and reported an overall response rate of 57% (8/14) (11), and the second is a study of 60 pNET patients with an overall response rate of 30% (18/60) (12). Based on registry data, the Food and Drug Administration (FDA) included pNET within the indication for ^{177}Lu-DOTATATE, and PRRT should be considered for treatment of progressive pNET patients (Appropriateness Score 8).

Bronchial NET

Several papers have reported the use of PRRT in pulmonary neuroendocrine tumors, treated with both ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE (**Table 1**). Overall response rates ranged from 13- 30%, while progression free survival ranged from 19-28 months and overall survival ranged from 32-59 months. Bronchial NETs are categorized into two groups, typical and atypical carcinoid tumors, which are considered distinct from the more aggressive large-cell and small- cell neuroendocrine carcinoma. Not unexpectedly, typical bronchial carcinoids appear to be more responsive to PRRT, although the majority of papers do not distinguish response rates between the subsets. One issue concerning bronchial NETs is the relatively small percentage of tumors which express sufficient somatostatin receptors to be candidates for therapy, although in one recent manuscript, 76% of 143 bronchial NETs were positive on somatostatin receptor scintigraphy (13). Although the literature is not definitive, there appear to be significantly higher levels of SSTR expression in typical bronchial carcinoids compared to atypical carcinoids (14). In patients with SSTR-positive tumors, ^{177}Lu-DOTATATE therapy can be considered as a potential therapeutic option after progression on everolimus (Appropriateness Score 7).

Treatment with ^{177}Lu-DOTATATE prior to everolimus is considered less appropriate (Appropriateness Score 6).

Tumors of Unknown Primary

Tumors of unknown primary are becoming less common since the introduction of SSTR-PET. To date, there are no studies performed only in patients with tumors of unknown primaries, although a number of studies report results for a subset of patients with unknown primaries (**Table 1**). Efficacy seems to be comparable to what is reported with a known gastrointestinal or pancreatic primary. Therefore, decisions to treat with PRRT in unknown primaries should mirror those in patients with GEP-NETs and ^{177}Lu-DOTATATE therapy should be considered in patients who progress despite treatment with first-line somatostatin analog therapy (Appropriateness Score 8).

Paraganglioma / Pheochromocytoma

Paraganglioma and pheochromocytoma (para/pheo) constitute a heterogeneous group of tumors with varying underlying genomic variations and variable SSTR expression. SDHB- associated subtype has been well evaluated and has a high expression of SSTRs (15). There are several small single-center retrospective studies evaluating PRRT in para/pheo (some in the context of larger series including other neuroendocrine tumors) that demonstrate ORR ranging from 7-29% (16,17), with the highest reported response rate from a manuscript that described a combination of chemotherapy and PRRT (18) (**Table 1**). Currently there

is an ongoing prospective clinical trial evaluating the efficacy of ^{177}Lu-DOTATATE in patients with advanced para/pheo (NCT03206060). It should be noted that ^{131}I-iobenguane (MIBG) was approved by the Food and Drug Administration for the treatment of MIBG-positive para/pheo (19). While ^{177}Lu-DOTATATE may be promising in this disease, treatment at this time should be limited to patients whose tumors are MIBG-negative (Appropriateness Score 7). Treatment of MIBG- positive patients with ^{177}Lu-DOTATATE in place of therapeutic ^{131}I-iobenguane is considered less appropriate (Appropriateness Score 6).

Special circumstances

Renal insufficiency

To inform the development of these guidelines, a Clinical experience and trial evidence accumulated over the past two decades have demonstrated that PRRT with ^{177}Lu-DOTATATE is generally well-tolerated. Chronic and permanent toxicity affecting the kidneys is rare if necessary precautions and attention to specific risk factors are undertaken. Renal irradiation, and consequently the risk of toxicity, is significantly decreased when positively charged amino acids, such as lysine and arginine, are co- infused with the treatment, due to the competitive inhibition of reabsorption at the proximal tubule. Examining the outcomes of more than 2,500 patients (20-27), it is apparent that PRRT with ^{90}Y-peptides is associated with a significant risk for reduction of renal function. In subjects treated with ^{177}Lu-DOTATATE, the incidence of severe, end-stage renal damage is very rare, with only sporadic cases reported in the literature (23,26), mainly in patients with compromised renal function at baseline. Indeed, the NETTER-1 study demonstrated no evidence of clinically significant worsening of renal dysfunction among 11 patients with baseline mild renal dysfunction (GFR 50-59) and 13 patients with moderate renal dysfunction (GFR<50) treated on the ^{177}Lu-DOTATATE arm of the study (28).

Severe renal dysfunction has generally been considered a contraindication to treatment with ^{177}Lu-DOTATATE. Many institutional series have required a minimum glomerular-filtration rate (GFR) of 50 cc/hour. Based on available data, we do not consider a GFR <50 to be a contraindication to 177Lu-DOTATATE use. For patients with severe baseline renal dysfunction defined as GFR <30, ^{177}Lu-DOTATATE should be used only in exceptional circumstances. Of note, hydronephrosis represents a particular concern as it impairs renal excretion and increases exposure to radiation. As much as possible, hydronephrosis should be corrected prior to initiation of ^{177}Lu-DOTATATE treatment. Patients on dialysis may be treated with ^{177}Lu-DOTATATE but, as with other radiopharmaceutical therapies, this should be done very carefully, with consideration for dose reduction and dosimetry.

Prior chemotherapy

It is still unclear whether prior cytotoxic chemotherapy increases risk of myelodysplatic syndrome (MDS) or acute leukemia (AL) associated with ^{177}Lu-DOTATATE. In one small series of 20 patients treated with an alkylating agent (primarily streptozocin) and subsequently treated with ^{177}Lu-DOTATATE, 4 cases of MDS/AL were observed (29). Compared to typical patients treated with PRRT in the same institution (4), these 20 patients had more cycles of chemotherapy, more cycles of alkylating agents, had experienced more frequent early high-grade hematotoxicity, and tended to more frequently have bone metastases. Conversely, the largest series of patients treated with ^{90}Y- and/or ^{177}Lu-peptides, identified an incidence of 2.3% for MDS and 1.8% for leukemia (of which 75% evolved from MDS), with a median latency from exposure of 4.4 years (26). In these patients, only 29% of MDS and 22% of leukemia could be correlated to prior chemotherapy. Therefore, it remains uncertain whether prior chemotherapy, and temozolomide-based treatment in particular, is associated with increased risk of MDS/AL after ^{177}Lu-DOTATATE therapy or not.

Mesenteric and peritoneal disease

In certain clinical circumstances, we recommend caution prior to consideration of ^{177}Lu-DOTATATE. Mesenteric tumors are often characterized by substantial surrounding desmoplasia. There are theoretical concerns that radiation may exacerbate the desmoplatic process, thus leading to increase in symptoms. Similar theoretical concerns pertain to patients with extensive peritoneal carcinomatosis in whom radiation may lead to bowel obstruction. Certain centers prescribe short courses of prophylactic steroids (e.g. 1-2 weeks) starting immediately after each dose of ^{177}Lu-DOTATATE.

High-grade disease

^{177}Lu-DOTATATE has been studied almost exclusively in patients with low or intermediate-grade neuroendocrine neoplasms (NENs). Consequently, there is limited evidence to support the use of ^{177}Lu-DOTATATE in grade 3 disease (30-32). Several studies demonstrate that very high proliferative indexes (ie Ki-67 > 35-55%) are associated with inferior outcomes. Zhang, et al reported the largest retrospective study to date of 69

patients with SSTR-expressing G3 NENs with a Ki-67 > 20% who received PRRT (33). The median PFS was 9.6 months and median OS was 19.9 months. Notably, patients with Ki-67 > 55% had the shortest survival (PFS 4 months, OS 7 months). Due to the potential heterogeneity of disease in this patient population, confirmation of SSTR expression across all metastases is essential. Additional imaging with 18F- FDG PET may also be of use to fully characterize all sites of disease.

Pediatric patients

Neuroendocrine tumors (NETs) are rare in pediatric patients (34). In addition to NETs, PRRT may be useful in neuroblastoma and paraganglioma/pheochromocytoma, particularly if ^{131}I- MIBG therapy is not an option or if patients have progressed after MIBG therapy. However, there are limited data on PRRT in children. The largest study to date evaluated ^{90}Y-DOTATOC in 17 patients with various NETs and demonstrated minimal or partial response in 41% of patients. (35). Two smaller studies which included a total of 10 patients demonstrated efficacy, but also demonstrated marrow toxicity in those patients previously treated with MIBG (36,37). In patients with neuroblastoma, it is not clear whether ^{177}Lu-DOTATATE should be used given the extensive experience with MIBG. Overall, PRRT appears promising in pediatric patients with NETs and neuroblastoma, although at this time ^{177}Lu-DOTATATE use should be limited to tumors that are negative on MIBG imaging.

Timing of treatment

In nearly all cases described in the literature, patients treated with ^{177}Lu-DOTATATE had already progressed on a first-line SSA. While progression is typically defined radiographically, select patients may be treated based on symptomatic progression. Due to the long-term safety and efficacy of SSAs, first-line treatment with ^{177}Lu-DOTATATE is generally not appropriate. Certain exceptions to this rule include patients with very high tumor burden where any further growth would entail significant risk. The decision to treat with ^{177}Lu-DOTATATE, in the second-line or beyond, needs to be considered in the context of the larger systemic treatment landscape.

For patients with typical, hormone-secreting midgut NETs, systemic treatment options beyond first-line SSA are limited. In this population, the RADIANT-2 study compared everolimus combined with octreotide to placebo plus octreotide, and did not demonstrate a significant improvement in PFS (38). Therefore, ^{177}Lu-DOTATATE should be considered the 2nd-line systemic treatment of choice for most patients with functional somatostatin-receptor positive midgut NETs.

In advanced non-functioning GI and bronchial NETs, everolimus was shown to significantly improve PFS compared to placebo (39). Decisions regarding sequencing of ^{177}Lu-DOTATATE versus everolimus must be individualized, with SSTR expression levels factored into the decision, although in bronchial NETs everolimus should be considered prior to ^{177}Lu-DOTATATE.

For patients with pancreatic NETs, multiple systemic treatment options exist including everolimus, sunitinib, and capecitabine/temozolomide chemotherapy. The latter is likely most appropriate for patients with relatively aggressive or symptomatic tumors, irrespective of SSTR expression. Further research is needed to develop evidence-based recommendations on sequencing of ^{177}Lu-DOTATATE with respect to these alternative treatment options.

Liver targeted therapy

Hepatic arterial embolization is a common approach to patients with unresectable, liver- dominant midgut NETs. Meta-analyses suggest a radiographic response rate of approximately 50%, with a higher rate of symptomatic response. There are no completed clinical trials comparing various embolization modalities, and thus significant controversy exists regarding the optimal embolic approach: bland embolization versus chemoembolization or 90Y- radioembolization. However, despite the lack of prospective evidence, liver embolization remains an appropriate, guidelines-endorsed alternative to ^{177}Lu-DOTATATE in patients with liver-dominant metastases, and offers the potential for rapid symptom palliation among patients with carcinoid syndrome or other secretory symptoms (40,41).
There exist some concerns regarding interaction between ^{177}Lu-DOTATATE and prior liver-directed therapies. In one small series, increased hepatotoxicity with PRRT was observed in patients who had undergone prior liver-directed therapy (42). Of particular concern is the risk of cumulative hepatic radiation toxicity in patients who have undergone prior radioembolization, a procedure itself associated with risk of long-term radiation-induced hepatic injury. Patients with extensive hepatic disease are potentially at risk of developing radiation hepatitis, although there is little evidence of chronic hepatic toxicity with ^{177}Lu-DOTATATE, even among patients with high liver tumor burden (43).

Surgery

Surgical resection of the primary tumor and subtotal resection of metastatic disease plays an important role in NET patients. Limited retrospective data suggests that debulking prior to PRRT can result in improved response to PRRT and PFS (44).

Overall considerations

Due to lack of trials comparing the numerous treatment options, selection and sequencing of treatments are not evidence based, and must be made based on cross-trial comparisons, and assessments of risk versus benefit in individual patients.

Future Directions

With the clinical approval of ^{177}Lu-DOTATATE, there are many possibilities for future research and optimizing clinical care with PRRT. These include optimizing the number of therapy cycles and administered activity, consideration of repeat therapy, delivering the therapy intra- arterially, the use of different radionuclides, and using novel peptides to bind SSTRs.
Although the NETTER-1 trial used four treatments at a fixed activity, optimizing the number of treatments or the administered activity of each administration may allow for decreased toxicity and improved efficacy. By measuring treatment effect during therapy or measuring lesional/organ dose, it may be possible to adjust the treatment schedule to increase efficacy. Currently, it is unclear how and even whether one should use patient specific dosimetry to adjust the administered activity, and many feel that giving a fixed activity works well for the majority of patients. This idea of repeat-PRRT has been evaluated in retrospective studies (45-47). If a patient responds well to one complete course of ^{177}Lu-DOTATATE, then it is reasonable to conclude that they may respond well to another course of ^{177}Lu-DOTATATE when they subsequently progress. These studies showed that repeat-PRRT is safe and effective, although the PFS is not as long compared to the initial PRRT course. Many patients have liver dominant disease , and in these patients intra-arterial ^{177}Lu-DOTATATE administered via the hepatic artery has been proposed (48,49). In theory, this provides higher delivery to the tumor, while reducing the systemic circulation and associated side effects.

Both ^{90}Y and ^{177}Lu have been used for PRRT, and each may provide different benefits given their different physical properties (50). The electron emitted from ^{90}Y has a higher energy and would be beneficial for bulkier tumors. Conversely, the longer path length of 90Y will also have a greater bystander effect on normal tissues such as the bone marrow and kidneys resulting in higher toxicity. The relative benefits of ^{90}Y vs ^{177}Lu have not been studied. Similarly, the use of alpha-emitters is another area of active research. DOTATATE is a SSTR analog, which becomes internalized after activating the receptor. SSTR antagonists have been developed that have a higher binding specificity to the SSTR such that even though they do not activate the receptor nor get internalized into the cell, they potentially deliver a high dose of radiation (51,52). famotidine). When increasing the amino acid rate to the target of 320 mL/hour, additional doses of 5-HT3 antagonist may be required with the addition of a D2 receptor antagonist (e.g. prochlorperazine). Benzodiazepines may also be required for anticipatory nausea and vomiting (8). Steroids, such as dexamethasone can also be administered after infusion of ^{177}Lu-DOTATATE.

Additionally, cooling and pressure aids may also be beneficial to help with the possible side effects of the amino acid solution infusion. Patient education is highly important at the beginning of the procedure to ensure the patient understands the importance of where and how to contain emesis under these circumstances.

Conclusion

The decision to initiate ^{177}Lu-DOTATATE therapy in a patient with progressive neuroendocrine tumor is complex and should be made within the setting of a multidisciplinary discussion. ^{177}Lu-DOTATATE should be considered when treating GEP-NETs, and tumors of unknown origin, generally after progression on somatostatin analog. In patients with bronchial carcinoids, ^{177}Lu-DOTATATE should be considered after everolimus, and in patients with para/pheo, therapy should be limited primarily to patients with MIBG-negative disease.

REFERENCES

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. Public Library of Science. 2009. p. e1000097.
2. Hope TA, Calais J, Zhang L, Dieckmann W, Millo C. 111In-pentetreotide scintigraphy vs. 68Ga-DOTATATE PET: Impact on Krenning Scores and Effect of Tumor Burden. J Nucl Med. 2019.
3. Sabet A, Dautzenberg K, Haslerud T, et al. Specific efficacy of peptide receptor radionuclide therapy with (177)Lu-octreotate in advanced neuroendocrine tumours of the small intestine. Eur J Nucl Med Mol Imaging. 2015;42:1238–1246.
4. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-Term Efficacy, Survival, and Safety of [(177)Lu-DOTA(0),Tyr(3)]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. Clin Cancer Res. 2017;23:4617–4624.
5. Hörsch D, Ezziddin S, Haug A, et al. Effectiveness and side-effects of peptide receptor radionuclide therapy for neuroendocrine neoplasms in Germany: A multi-institutional registry study with prospective follow-up. Eur J Cancer. 2016;58:41–51.
6. Baum RP, Kulkarni HR, Singh A, et al. Results and adverse events of personalized peptide receptor radionuclide therapy with 90Yttrium and 177Lutetium in 1048 patients with neuroendocrine neoplasms. Oncotarget. Impact Journals. 2018;9:16932–16950.
7. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017;376:125–135.
8. Strosberg J, Wolin E, Chasen B, et al. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With 177Lu-Dotatate in the Phase III NETTER-1 Trial. J Clin Oncol. 2018;36:2578–2584.
9. Garske-Román U, Sandström M, Fröss Baron K, et al. Prospective observational study of 177Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. Eur J Nucl Med Mol Imaging. Springer Berlin Heidelberg. 2018;45:970–988.
10. Ezziddin S, Khalaf F, Vanezi M, et al. Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2014;41:925–933.
11. Bodei L, Cremonesi M, Grana CM, et al. Peptide receptor radionuclide therapy with ^{177}Lu- DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging. 2011;38:2125–2135.
12. Sansovini M, Severi S, Ambrosetti A, et al. Treatment with the radiolabelled somatostatin analog Lu-DOTATATE for advanced pancreatic neuroendocrine tumors. Neuroendocrinology. 2013;97:347–354.
13. Robelin P, Hadoux J, Forestier J, et al. Characterization, Prognosis, and Treatment of Patients With Metastatic Lung Carcinoid Tumors. J Thorac Oncol. 2019.
14. Lococo F, Perotti G, Cardillo G, et al. Multicenter comparison of 18F-FDG and 68Ga- DOTA-peptide PET/CT for pulmonary carcinoid. Clin Nucl Med. 2015;40:e183–e189.
15. Janssen I, Blanchet EM, Adams K, et al. Superiority of [68Ga]-DOTATATE PET/CT to Other Functional Imaging Modalities in the Localization of SDHB-Associated Metastatic Pheochromocytoma and Paraganglioma. Clin Cancer Res. 2015;21:3888–3895.
16. van Essen M, Krenning EP, Kooij PP, et al. Effects of therapy with [177Lu-DOTA0, Tyr3]octreotate in patients with paraganglioma, meningioma, small cell lung carcinoma, and melanoma. Journal of Nuclear Medicine. 2006;47:1599–1606.
17. Forrer F, Riedweg I, Maecke HR, Mueller-Brand J. Radiolabeled DOTATOC in patients with advanced paraganglioma and pheochromocytoma. Q J Nucl Med Mol Imaging. 2008;52:334–340.
18. Kong G, Grozinsky-Glasberg S, Hofman MS, et al. Efficacy of Peptide Receptor Radionuclide Therapy for Functional Metastatic Paraganglioma and Pheochromocytoma. J Clin Endocrinol Metab. 2017;102:3278–3287.
19. Pryma DA, Chin BB, Noto RB, et al. Efficacy and Safety of High-Specific-Activity I-131 MIBG Therapy in Patients with Advanced Pheochromocytoma or Paraganglioma. J Nucl Med. 2018.
20. Waldherr C, Pless M, Maecke HR, et al. Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq (90) Y-DOTATOC. Journal of Nuclear Medicine. 2002;43:610–616.

21. Bodei L, Cremonesi M, Zoboli S, et al. Receptor-mediated radionuclide therapy with 90Y- DOTATOC in association with amino acid infusion: a phase I study. Eur J Nucl Med Mol Imaging. 2003;30:207–216.
22. Valkema R, Pauwels S, Kvols LK, et al. Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0,Tyr3] octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. YSNUC. 2006;36:147–156.
23. 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;26:2124–2130.
24. Sabet A, Ezziddin K, Pape U-F, et al. Accurate assessment of long-term nephrotoxicity after peptide receptor radionuclide therapy with (177)Lu-octreotate. Eur J Nucl Med Mol Imaging. 2014;41:505–510.
25. Sabet A, Ezziddin K, Pape U-F, et al. Long-term hematotoxicity after peptide receptor radionuclide therapy with 177Lu-octreotate. J Nucl Med. 2013;54:1857–1861.
26. Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging. 2015;42:5–19.
27. Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol. 2011;29:2416– 2423http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=215556 92&retmode=ref&cmd=prlinks.
28. Strosberg JR, Wolin EM, Chasen BA, Kulke MH, Bushnell DL, Caplin ME. Clinical outcomes in patients with baseline renal dysfunction in the NETTER-1 study: 177Lu-Dotatate vs. high dose octreotide in progressive midgut neuroendocrine tumors. Journal of Clinical Oncology. 2018;36:–4102.
29. Brieau B, Hentic O, Lebtahi R, et al. High risk of myelodysplastic syndrome and acute myeloid leukemia after 177Lu-octreotate PRRT in NET patients heavily pretreated with alkylating chemotherapy. Endocr Relat Cancer. 2016;23:L17–L23.
30. Ezziddin S, Opitz M, Attassi M, et al. Impact of the Ki-67 proliferation index on response to peptide receptor radionuclide therapy. Eur J Nucl Med Mol Imaging. 2nd ed. 2011;38:459–466.
31. Thang SP, Lung MS, Kong G, et al. Peptide receptor radionuclide therapy (PRRT) in European Neuroendocrine Tumour Society (ENETS) grade 3 (G3) neuroendocrine neoplasia (NEN) - a single-institution retrospective analysis. Eur J Nucl Med Mol Imaging. 2017;23:vii124.
32. Nicolini S, Severi S, Ianniello A, et al. Investigation of receptor radionuclide therapy with 177Lu-DOTATATE in patients with GEP-NEN and a high Ki-67 proliferation index. Eur J Nucl Med Mol Imaging. 2018;45:923–930.
33. Zhang J, Kulkarni HR, Singh A, Niepsch K, Müller D, Baum RP. Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms: Safety and Survival Analysis in 69 Patients. J Nucl Med. 2018.
34. Navalkele P, O'Dorisio MS, O'Dorisio TM, Zamba GKD, Lynch CF. Incidence, survival, and prevalence of neuroendocrine tumors versus neuroblastoma in children and young adults: nine standard SEER registries, 1975-2006. Pediatr Blood Cancer. 2011;56:50
35. Menda Y, O'Dorisio MS, Kao S, et al. Phase I trial of 90Y-DOTATOC therapy in children and young adults with refractory solid tumors that express somatostatin receptors. J Nucl Med. 2010;51:1524–1531.
36. Gains JE, Bomanji JB, Fersht NL, et al. 177Lu-DOTATATE molecular radiotherapy for childhood neuroblastoma. J Nucl Med. 2011;52:1041–1047.
37. Kong G, Hofman MS, Murray WK, et al. Initial Experience With Gallium-68 DOTA- Octreotate PET/CT and Peptide Receptor Radionuclide Therapy for Pediatric Patients With Refractory Metastatic Neuroblastoma. J Pediatr Hematol Oncol. 2016;38:87–96.
38. Pavel ME, Baudin E, Öberg KE, et al. Efficacy of everolimus plus octreotide LAR in patients with advanced neuroendocrine tumor and carcinoid syndrome: final overall survival from the randomized, placebo-controlled phase 3 RADIANT-2 study. Annals of Oncology. 2017;28:1569–1575.
39. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968–977.
40. Neuroendocrine and Adrenal Tumors. National Comprehensive Cancer Network. 2018;:1–133.
41. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors. 2017. pp. 707– 714http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=2860935 6&retmode=ref&cmd=prlinks.
42. Riff BP, Yang Y-X, Soulen MC, et al. Peptide Receptor Radionuclide Therapy-Induced Hepatotoxicity in Patients With Metastatic Neuroendocrine Tumors. Clin Nucl Med. 2015;40:845–850.

43. Strosberg J, Wolin E, Yao J, et al. Impact of baseline liver tumor burden on treatment outcomes with 177Lu-Dotatate in the NETTER-1 study. Eur J Nucl Med Mol Imaging. 2018;45:S60–S60.
44. Bertani E, Fazio N, Radice D, et al. Resection of the Primary Tumor Followed by Peptide Receptor Radionuclide Therapy as Upfront Strategy for the Treatment of G1-G2 Pancreatic Neuroendocrine Tumors with Unresectable Liver Metastases. Annals of surgical oncology. 1st ed. 2016;23:981–989.
45. Sabet A, Haslerud T, Pape U-F, et al. Outcome and toxicity of salvage therapy with 177Lu- octreotate in patients with metastatic gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. Springer Berlin Heidelberg. 2014;41:205–210
46. Vaughan E, Machta J, Walker M, Toumpanakis C, Caplin M, Navalkissoor S. Retreatment with peptide receptor radionuclide therapy in patients with progressing neuroendocrine tumours: efficacy and prognostic factors for response. Br J Radiol. 2018;91:20180041.
47. van der Zwan WA, Brabander T, Kam BLR, et al. Salvage peptide receptor radionuclide therapy with [177Lu-DOTA,Tyr3]octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. Springer Berlin Heidelberg. 2019;46:704–717.
48. Kratochwil C, Giesel FL, López-Benítez R, et al. Intraindividual comparison of selective arterial versus venous 68Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine tumors. Clin Cancer Res. 2010;16:2899–2905.
49. Kratochwil C, López-Benítez R, Mier W, et al. Hepatic arterial infusion enhances DOTATOC radiopeptide therapy in patients with neuroendocrine liver metastases. Endocr Relat Cancer. BioScientifica. 2011;18:595–602.
50. Gabriel M, Andergassen U, Putzer D, et al. Individualized peptide-related-radionuclide- therapy concept using different radiolabelled somatostatin analogs in advanced cancer patients. Q J Nucl Med Mol Imaging. 2010;54:92–99.
51. Wild D, Fani M, Fischer R, et al. Comparison of Somatostatin Receptor Agonist and Antagonist for Peptide Receptor Radionuclide Therapy: A Pilot Study. J Nucl Med. 2014.
52. Krebs S, Pandit-Taskar N, Reidy D, et al. Biodistribution and radiation dose estimates for 68Ga-DOTA-JR11 in patients with metastatic neuroendocrine tumors. Eur J Nucl Med Mol Imaging. Springer Berlin Heidelberg. 2018;40:1–9.
53. Sansovini M, Severi S, Ianniello A, et al. Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with 177Lu-D OTATATE. Eur J Nucl Med Mol Imaging. Springer Berlin Heidelberg. 2017;44:490–499.
54. Mariniello A, Bodei L, Tinelli C, et al. Long-term results of PRRT in advanced bronchopulmonary carcinoid. Eur J Nucl Med Mol Imaging. 2016;43:441–452.
55. Ianniello A, Sansovini M, Severi S, et al. Peptide receptor radionuclide therapy with (177)Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18)F-FDG PET. Eur J Nucl Med Mol Imaging. 2016;43:1040– 1046.
56. Parghane RV, Talole S, Prabhash K, Basu S. Clinical Response Profile of Metastatic/Advanced Pulmonary Neuroendocrine Tumors to Peptide Receptor Radionuclide Therapy with 177Lu-DOTATATE. Clin Nucl Med. 2017;42:428–435.
57. Sabet A, Haug AR, Eiden C, et al. Efficacy of peptide receptor radionuclide therapy with 177Lu-octreotate in metastatic pulmonary neuroendocrine tumors: a dual-centre analysis. Am J Nucl Med Mol Imaging. 2017;7:74–83.
58. Delpassand ES, Samarghandi A, Zamanian S, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE for patients with somatostatin receptor-expressing neuroendocrine tumors: the first US phase 2 experience. Pancreas. 2014;43:518–525.

TABLES

Table 1: Experience with PRRT by site of primary tumor.

Author	Year	Patients*	Treatment	ORR	PFS	OS
Midgut Neuroendocrine Tumors (Grade 9)						
Strosberg (7)	2017	116	^{177}Lu-DOTATATE	18% 18/101	NR	NR
Sabet (3)	2015	61	^{177}Lu-DOTATATE	13% 8/61	33	61
Horsch (5)	2016	138	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	51	NR
Brabander (4)	2017	181	^{177}Lu-DOTATATE	31% 57/181	30	60
Baum (6)	2018	315	^{177}Lu-DOTATATE	NR	22	69
Pancreatic Neuroendocrine Tumors (Grade 8)						
Baum (6)	2018	315	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	20	44
Horsch (5)	2016	172	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	39	53
Brabander (4)	2017	133	^{177}Lu-DOTATATE 72/133	55%	30	71
Ezziddin (10)	2014	68	^{177}Lu-DOTATATE 41/68	60%	34	53
Sansovini (53)	2017	60	^{177}Lu-DOTATATE 18/60	30%	29	NR
Garske-Román (9)	2018	48	^{177}Lu-DOTATATE 22/49	45%	NR	NR
Bronchial Carcinoid (before everolimus Grade 6; after everolimus Grade 7)						
Mariniello (54)	2016	114	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	13% 15/114	28	59
Baum (6)	2018	75	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	11	40
Ianniello (55)	2017	34	^{177}Lu-DOTATATE	15% 4/32	19	49
Brabander (4)	2017	23	^{177}Lu-DOTATATE	30% 7/23	20	52
Parghane (56)	2017	22	^{177}Lu-DOTATATE	11% 2/19	NR	40
Sabet (57)	2017	22	177Lu-DOTATATE	27% 6/22	27	42

Table 1, continued

Unknown Primary Tumor (Grade 8)						
Baum (6)	2018	151	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	NR	13	53
Brabander (4)	2017	82	177Lu-DOTATATE	35% 29/82	29	53
Delpassand (58)	2014	7	^{177}Lu-DOTATATE	NR	11	NR
Bodei (11)	2011	3	^{177}Lu-DOTATATE	0% 0/3	NR	NR
Paraganglioma / Pheochromocytoma (MIBG positive Grade 5; MIBG negative Grade 7)						
Forrer (17)	2008	28	^{177}Lu-DOTATATE ^{90}Y-DOTATOC	7% 2/28	NR	NR
Kong (18)	2017	20	^{177}Lu-DOTATATE	29% 5/17	39	NR
van Essen (16)	2006	12	^{177}Lu-DOTATATE	17% 2/12	NR	NR

* only within NET subtype (n), ORR = overall response rate, PFS = progression free survival (in months), OS = overall survival (in months), NR = not reported/reached

NANETS/SNMMI Procedure Standard for Somatostatin Receptor Based Peptide Receptor Radionuclide Therapy with ^{177}Lu-DOTATATE

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With the recent approval of 177Lu-DOTATATE for use in gastroenteropancreatic neuroendocrine tumors, access to peptide receptor radionuclide therapy is increasing. Representatives from the North American Neuroendocrine Tumor Society and the Society of Nuclear Medicine and Molecular Imaging collaborated to develop a practical consensus guideline for the administration of 177Lu-DOTATATE. In this paper, we discuss patient screening, maintenance somatostatin analog therapy requirements, treatment location and room preparation, drug administration, and patient release as well as strategies for radiation safety, toxicity monitoring, management of potential complications, and follow-up. Controversies regarding the role of radiation dosimetry are discussed as well. This document is designed to provide practical guidance on how to safely treat patients with this therapy.

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Preamble

The present guidelines/standards were developed collaboratively by THE North American Neuroendocrine Tumor Society (NANETS) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI). NANETS is a multidisciplinary professional society of neuroendocrine specialists in North America that was founded in 2005. NANETS' mission is to improve neuroendocrine tumor disease management through increased research and educational opportunities. NANETS is committed to a multidisciplinary approach and consists of doctors and scientists involved in different specialties of neuroendocrine tumors (NETs). SNMMI is an international scientific and professional organization founded in 1954 to promote the science, technology and practical application of nuclear medicine. In addition to publishing journals, newsletters, and books, the SNMMI also sponsors international meetings and workshops designed to increase the competencies of nuclear medicine practitioners and to promote new advances in the science of nuclear medicine. This collaboration between NANETS and SNMMI aims to define new procedure standards for peptide receptor radionuclide therapy (PRRT) to improve the quality of service to patients. Existing practice guidelines will be reviewed for revision or renewal as appropriate, on their fifth anniversary or sooner, if indicated. Each practice standard has undergone a thorough consensus process in which it has been subjected to extensive review. Much of the content within the guidelines are based on working group experience. These procedure standards are intended to assist practitioners in providing appropriate nuclear medicine care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, NANETS and SNMMI caution against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question. The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by medical professionals taking into account the unique circumstances of each case. Thus, there is no implication that an approach differing from the guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the guidelines. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these procedure standards is to assist practitioners in achieving this objective.

Background

NETS are a heterogeneous group of malignancies that frequently overexpress somatostatin receptors (SSTRs) (1). NETs can be imaged using somatostatin analogs (SSAs) labeled with ^{68}Ga (^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC) (2). β-emitting radionuclides such as ^{177}Lu (^{177}Lu) can be used for PRRT (3). The NETTER-1 trial demonstrated prolonged progression-free survival in mid-gut NET patients treated with four cycles of ^{177}Lu-DOTATATE, which subsequently led to the approval of this therapy (4).

Treatment Overview

^{177}Lu-DOTATATE is administered at an activity of 7.4 GBq (200 mCi)every 8±1 wk for four cycles. Combined with prophylactic amino acid infusions and antiemetics, each treatment visit can last approximately 5 –8 hours (Fig. 1). Before starting PRRT treatments, each treatment site must ensure that ^{177}Lu is included in their institutional radioactive materials license. A detailed review of procedures surrounding ^{177}Lu-DOTATATE therapy is provided below.

Patient Screening

Patients should be evaluated by a multidisciplinary NET team, including a cancer specialist with expertise in the medical management of NETs as well as a nuclear medicine physician or appropriate authorized user to decide on the appropriateness and timing of PRRT in individual patients. Potential candidates should undergo an SSTR PET scan or a SSTR scintigraphy (^{111}In-pentetreotide) to demonstrate adequate SSTR expression (2). Traditionally, SSTR expression on ^{111}In-pentetreotide greater than background hepatic uptake has been considered an eligibility requirement for PRRT (5). Necessary levels of SSTR expression on ^{68}Ga-based SSTR PET have not been clearly defined, but lesion uptake should exceed background hepatic uptake. Laboratory values should be checked shortly before the treatment is ordered (typically 2 wk prior to each cycle). These should include blood urea nitrogen, creatinine, albumin,

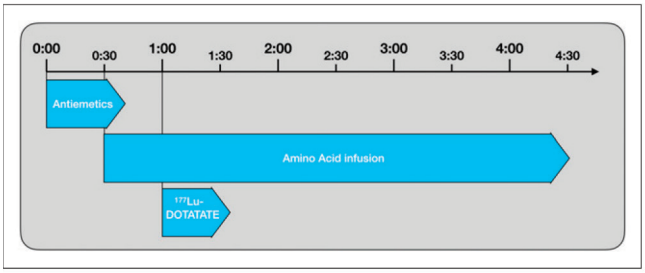

FIGURE 1. Timeline of administration of antiemetics, amino acids, and ^{177}Lu-DOTATATE during PRRT. Antiemetics can be repeated during amino acid infusion as needed.

alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, white blood cell with differential, hemoglobin, and platelet counts. The threshold values provided in Table 1 should be taken as general eligibility guidelines for therapy.

Somatostatin Analog Therapy

SSA therapy is used frequently to treat NET patients, and SSAs are typically administered in depot formulations every 4 wk. It is recommended that PRRT treatments be scheduled at least 4 wk after the last long-acting SSA therapy to prevent interference with SSTR binding For symptomatic patients, short-acting SSAs being used as a bridge should be stopped at least 24 h before treatment. Subsequent SSA doses can be administered as soon as several hours after the completion of the radiopharmaceutical therapy. During and after completion of PRRT, it is generally agreed that syndromic patients should remain on SSA therapy. It is unclear whether patients with non-functional tumors should remain on SSA treatment regardless of whether or not they had progressed on SSA therapy before initiation of PRRT. In the NETTER-1 study, all patients remained on lobg-acting release octreotide despite prior progression on this drug, and the ^{177}Lu-DOTATATE package insert suggests that patients should remain on SSAs for up to 18 mo after treatment (6). However, there are no clear data to support or refute this recommendation.

Treatment Location

Sites have the option to provide PRRT in an inpatient or outpatient setting, within the oncology infusion clinic or nuclear medicine department, or a combination of both locations. Most sites in the United States treat in the outpatient setting. Oncology nursing staff are often more accustomed to the complexities of required concomitant medication infusions and patient monitoring than nuclear medicine staff, but nuclear medicine staff are well trained in radiation safety and the necessary precautions required

TABLE 1
Recommended Laboratory Thresholds for PRRT Treatment

Laboratory	Acceptable value before first treatment
Hemoglobin (HGB)	>8 g/dL
White blood cell count (WBC)	>2K/mm^3
Platelet count (PLT)	>70K/mm^3
Estimated glomerular filtration rate (eGFR)	>50 mL/min
Total bilirubin	≤3 × ULN
Serum albumin	>3.0 g/dL

ULN = upper limits of normal.

during administration of radioactivity. If a combination approach is taken (i.e., the patient is transported between departments for specific components of the procedure), extra caution regarding radiation protection is required for patient travel. When treated as an outpatient, a patient should be forewarned of the uncommon possibility of an overnight hospital stay should a complication such as a neuroendocrine hormonal crisis or severe emesis occur (6).

Room Preparation

Because body fluids (primarily urine) are radioactive after ^{177}Lu-DOTATATE administration, room preparation is essential to reduce potential contamination. For example, patient stretchers, chairs, floors, and lower walls can be covered with a prophylactic protective covering (Fig. 2). Furthermore, whereas a treatment suite with an attached toilet is ideal, having a dedicated toilet nearby is acceptable as the patient will need to void frequently on the completion of the 177Lu-DOTATATE infusion and may need assistance. Local rules related to radioactive waste materials should be followed under the guidance of a local radiation safety officer.

Patient Preparation

It may be helpful to have patients change into hospital scrubs or gowns on arrival in order to avoid potential contamination of personal belongings. If stress urinary incontinence is a concern, disposable undergarments are also recommended. For some patients, a Foley catheter with acrylic shielding of the Foley bag may be necessary. However, routine bladder catheterization is not recommended.

A peripheral vein in the antecubital fossa is the preferred location for venous access, and intravenous lines in both arms are preferred, one to administer the radioactivity and one to administer the amino acid solution. If 2 lines

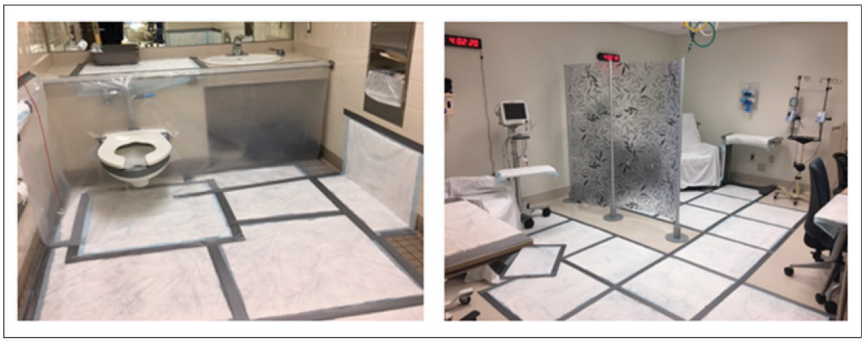

FIGURE 2. Example room preparation for therapy. A dedicated bathroom should be used and wrapped in order to prevent urine contamination.

are not possible, the amino acids and radiotherapy may be infused through the same line. Central lines may be used for the administration of the premedications and the amino acid solution in the case of patients with difficult peripheral venous access; however, a peripheral line is the recommended route for the administration of the ^{177}Lu-DOTATATE infusion, as the use of a central line has not been studied. Intermittent assessment of ongoing vascular access is necessary throughout the procedure due to the high osmolarity of the amino acid solutions, and local reactions at the infusion site may occur. Additionally, patency of the peripheral intravenous site should be monitored continuously throughout the infusion of the ^{177}Lu-DOTATATE.

Amino Acid Solutions

Administration of an amino acid solution with the appropriate lysine and arginine concentration (Table 2) before, during, and after the ^{177}Lu-DOTATATE infusion is required to decrease reabsorption of ^{177}Lu-DOTATATE via the proximal renal tubules and thereby decrease the radiation dose to the kidneys (7). Several high concentration commercial amino acid solutions are currently available with the correct concentration of arginine and lysine (Table 3); however, they also include additional amino acids, which raise the osmolality of the solution and are associated with significant nausea and vomiting during infusion. The target infusion rate of the commercial amino acid solutions should reach 320 mL/h. 177Lu-DOTATATE should generally not be administered until this rate is reached or until one eighth of the total volume of amino acid solution has been infused. The amino acid solution should infuse concurrently with the 177Lu-DOTATATE, and continue at 320 mL/h or greater until the total volume has been administered. Commencing at a low rate of 100 mL/h for the high concentration amino acid solution and increasing slowly (e.g., by 20–50 mL/h every 15 –20 min) has been somewhat successful at reducing side effects relating to nausea or vomiting.

An alternative compounded amino acid formulation consisting solely of 25 g of lysine and 25 g of arginine diluted in 1L of normal saline for injection should be considered (8). The compounded two amino acid solution is substantially less emetogenic and can generally be infused over a shorter period of time.The use of arginine-lysine formulations may be preferred due to improved tolerability; however, due to licensing requirements and compounding regulations, compounded arginine-lysine formulations may not be available at many institutions. When using the compounded arginine-lysine solution, it should be infused at a rate of 250 mL/h for 4 h, commencing 30 min before the treatment with the radiopharmaceutical.

Antiemetic Medications

Nausea and vomiting are common during the administration of commercial amino acid solutions when infusion rates are above 250 mL/h. Therefore, it is recommended to use an intravenous premedication regime consisting of a 5-HT3 antagonist (e.g., granisetron, ondansetron, or palonosetron), an NK1 receptor antagonist (e.g., fosaprepitant), and anH2 receptor antagonist (e.g., famotidine). When increasing the amino acid rate to the target of 320 mL/h, additional doses of the 5-HT3 antagonist may be required with the addition of a D2 receptor antagonist (e.g., prochlorperazine). Benzodiazepines may also be required for anticipatory nausea and vomiting (9). Steroids, such as dexamethasone, can also be administered after infusion of ^{177}Lu-DOTATATE.

Additionally, cooling and pressure aids may also be beneficial to help with the possible side effects of the amino acid solution infusion. Patient education is highly important at the beginning of the procedure to ensure the patient understands the importance of where and how to contain emesis under these circumstances.

Patients receiving compounded arginine/lysine generally require only a 5-HT3 antagonist as prophylactic medication.

Radiopharmaceutical Administration

Treatment centers can choose among different infusion methods for 177Lu-DOTATATE administration, including the gravity method, the saline infusion method, the pump method with a vial, and the pump method with a

TABLE 2
Content Requirements for the Amino Acid Solution

Item	Specification
Lysine HCl content	Between 18 and 24 g
Arginine HCl content	Between 18 and 24 g
Volume	1.5 to 2.2 L for commercial (1.0 L for compounded)
Osmolarity	<1,050 mOsmol

syringe (Fig. 3) (6). Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org) provides step-by-step instructions for each method (10). The saline infusion method may result in leakage from the vial, and care should be taken to prevent contamination. The pump method with a syringe can result in extra radiation exposure to the technologists when drawing the activity from the vial and higher residual values. The pump method with the vial requires the availability of an automated infusion pump. Regardless of the method used, one should use appropriate radiation shielding and aseptic technique when preparing and administering the radiopeptide solution, including wearing appropriate personal protective equipment, using tongs when handling the vial to minimize radiation exposure, confirming the amount of the radioactivity of the radiopeptide vial (and syringe if applicable) with an appropriate dose calibrator dose administration, and inspecting the product visually for particulate matter and discoloration under a shielded screen (the vial should not be used if particulates or discoloration are present). The therapy dosage should be administered over 30 min and should not be administered as a bolus.

Dosage Modifications for Adverse Reactions

In patients who have baseline renal, liver, or bone marrow dysfunction, or in those who develop toxicity while on treatment, modification of the administered ^{177}Lu-DOTATATE activity can be considered (6). In patients with preexisting toxicity, decreased administered activity or longer intervals between administrations can be considered. Bone marrow toxicity is the most common adverse event to develop during treatment. In patients experiencing myelosuppression greater than grade 1, one can delay treatment, allowing bone marrow function to recover, administer a lower administered activity (i.e., 3.7 GBq [100 mCi]) during the next treatment, or permanently stop therapy. Oftentimes thrombocytopenia will resolve with a delay. Renal and liver toxicity rarely occur during treatment, but if patients develop toxicity that is attributable to ^{177}Lu-DOTATATE (e.g., elevated bilirubin or reduction in kidney function), therapy should be withheld until toxicity resolves. Because of issues related to differential reimbursement based on the administered activity, it may be difficult to administer at half the normal activity. Therefore, it may only be feasible to prolong the delay between treatments.

Patient Monitoring and Potential Reactions

Hormonal Crisis (Carcinoid Crisis)

Neuroendocrine hormonal crises due to excessive release of hormones or bioactive substances develop in 1% of patients and typically occur during treatment or within 2 d after the initial treatment (6,11). Typical clinical manifestations include cutaneous flushing, diarrhea, bronchospasm, and hypertension. Hormonal crises can be treated with intravenous high-dose SSAs, intravenous fluids, corticosteroids, and correcting of electrolyte disturbances in patients with diarrhea or vomiting. Pretreating patients at high risk for crisis has been suggested, although this is not done at the majority of centers (12).

Infiltration of ^{177}Lu-DOTATATE

Prevention of infiltration is critical and includes testing the intravenous line patency before administration of the radiopharmaceutical, direct observation of the site during

TABLE 3
Currently Available Commercial Amino Acid Solutions

Formulation	Amino acid concentration	Dilution
Aminosyn II 10%	21 g of lysine, 20.4 g of arginine in 2 L	
Aminosyn II 15%	23.6 g of lysine, 22.9 g of arginine in 1.5 L	Dilute to approximately 2 L
Clinisol 15%	18 g of lysine, 18 g of arginine in 1.6 L	Dilute to approximately 2.2 L
Plenamine 15%	18.8 g of lysine, 23.5 g of arginine in 1.6 L	Dilute to approximately 2.1 L
Trophamine 10%	18 g of lysine, 26 g of arginine in 2.2 L	Consult*
Premasol 10%	16.4 g of lysine, 24 g of arginine in 2 L	Consult*

*Consult with treating physician as lysine–arginine concentration may be outside specifications, which may increase adverse events.

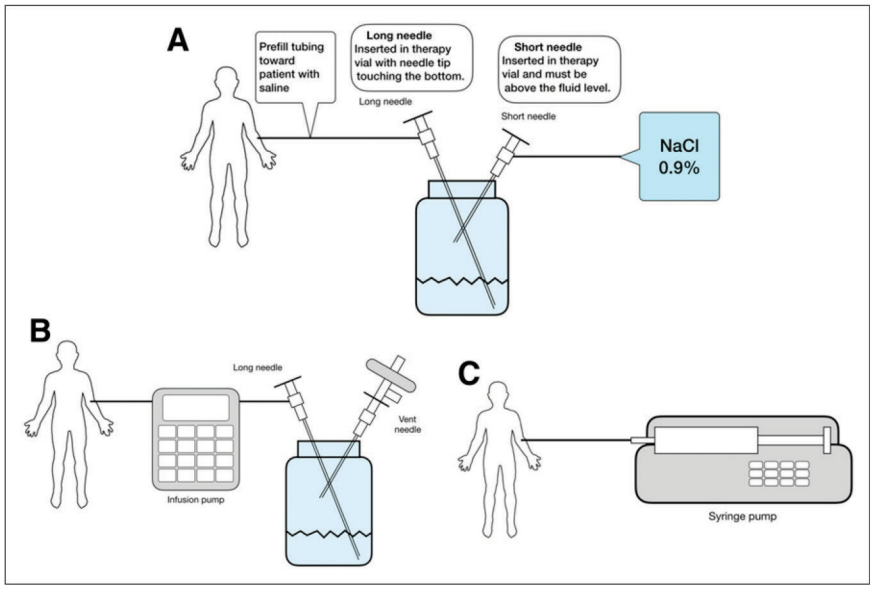

FIGURE 3. Administration techniques. (A) Gravity method. (B) Pump method with vial. (C) Pump method with syringe. Please see Supplemental Table 2 for further details on the administration techniques.

swelling or pain develop. If infiltration occurs, clearance of the radiotracer from the site can be facilitated with warm packs, compression, and elevation (13). Infiltration must be reported to radiation safety for monitoring and calculation of skin dose.

Radiation Safety

Contamination

With a half-life of 6.6 d, ^{177}Lu raises the possibility of prolonged contamination. Blood and urine are the main sources of contamination during and after radionuclide administration. Because ^{177}Lu-DOTATATE is primarily excreted in urine, with a cumulative excretion of 44% within 5 h, 58% within 24 h and 65% within 48 h AFTER administration, the main focus for individual patients for the first 3 d after therapy is on preventing urinary contamination (6). Of note, when produced by neutron activation, there is a long-lived 177Lu contaminant, ^{177}mLu, which has a half-life of 160 d and needs to be surveyed for before disposal of radioactive waste from the treatment center. This issue is of greater importance in locations that treat patients in an inpatient setting. Emesis can contain small amounts of radioactive material and should be treated as contaminated and disposed of appropriately.

Preparation for Inpatient Therapy

For patients who require an overnight stay, typically due to medical complications, the recommendations largely follow those already in place for ^{131}I inpatients, noting that the external dose rate from ^{177}Lu is significantly lower than ^{131}I given the lower energy and abundance of its γ emissions. Nursing personnel will need to be instructed in pertinent radiation safety precautions (i.e., potential for contamination related primarily to the patient's blood and urine), but also be advised that nausea and vomiting related to the administration of the amino acid solution may occur. Universal precautions (e.g., gloves, gowns, shoe covers) should be used to avoid contact with patient bodily fluids. If blood or urine specimens are needed for laboratory testing, nursing staff should be advised to collect the smallest amount necessary for testing. Nursing staff should be provided with radiation monitoring devices (passive dosimeter, direct-reading dosimeter). Ideally, radiation safety staff should help prepare the patient's bed, floor, and bathroom to minimize potential radioactive contamination from patient bodily fluids. Institutional radiation safety guidelines should be developed for general nursing care of ^{177}Lu-DOTATATE inpatients including approaches to medical emergencies or patient deaths before a ^{177}Lu-DOTATATE therapy program is established.

Release Criteria

To ensure that radiation dose to members of the public remains less than 5 mSv (500 mrem), the patient should be provided with instructions (Table 4) at discharge. Each center should determine its own recommendations based each patient's specific circumstances and local regulations, but we have provided a basic guidance in Table 4 for minimizing exposure to others and potential urine contamination (14). The average exposure at one m immediately after treatment is 1.8 ± 0.5 mrem/h, and at time of discharge is 0.9 ± 0.4 mrem/h (combined institutional experiences from more than 100 therapies). This exposure is less than that from ^{131}I therapy and below release criteria from published Nuclear Regulatory Commission guidelines (15). The time periods for following various instructions will vary, but 3 d should be sufficient for resumption of most public activities, given the physical half-life of 6.7 d, the mean effective blood elimination half-life of 3.5 ± 1.4 h and the mean terminal blood half-life of 71 ± 28 h (6). Extra precautions should be taken to minimize exposure of young children and pregnant women. The mathematics of release criteria for any nuclear medicine therapy patients have been addressed comprehensively

(14). The RADAR website has an online tool that allows for calculation of cumulative doses to family members or members of the public from exposure to patients treated with ^{177}Lu-DOTATATE (16).

Pregnancy

Radiopharmaceutical therapy is almost universally contraindicated during pregnancy. Therapy must be delayed until childbirth or termination of pregnancy. Breast feeding should be stopped for treatment and not be restarted until 2.5 mo after the final therapy. Future children may be breastfed. Contraception should be used for 6 mo after completion of the final treatment.

Issues with Cremation and Patient Death

It is important to notify the local radiation safety officer of a death involving a radioactive patient. Deceased patients should be appropriately labeled and the death certificate should note that the patient is radioactive. If possible the radiation safety officer should appropriately train the medical examiners and the mortuary personnel, as well as perform radiation surveys. Please refer to the National Council on Radiation Protection and Measurements (NCRP) Report No. 161 (NCRP 2008) for additional guidance on the management of radiation accident victims, regarding guidelines for the medical examiner and mortuary personnel (17).

Dosimety and Post-Treatment Imaging

Although dosimetry was not a part of the Phase III NETTER-1 trial, there may be a role for patient specific dosimetry when considering cumulative renal and bone marrow dose. There is a large variability in tumor and organ uptake of radiolabeled SSAs across patients, which suggests that tailored dosimetry may be useful for ^{177}Lu-DOTATATE therapy (18). For example, 1 study showed a Biologically effective dose to the kidneys ranging from 9 to more than 40 Gy (19). Please see Supplemental Table 2 for standardized dose estimates for the reference adult for ^{177}Lu-DOTATATE (20). Although 68Ga-DOTATATE may be used for diagnostic evaluation of tracer uptake, it cannot be used for dosimetry planning due to its short (68 min) half-life. However, ^{177}Lu gamma-rays are suitable for gamma camera imaging (Supplemental Table 3), and imaging for dosimetry may be performed after the initial therapy cycle (Fig. 4).

Further details about potential imaging protocols for dosimetry can be found in the supplemental materials.

TABLE 4
Radiation Safety Recommendations After ^{177}Lu-DOTATATE Treatment

Duration	Recommendations
	Sleep
3 d	Sleep in separate bed, avoid intimate contact. For infants/children or pregnant partner, the time period should be extended.
	Urination
3 d	Flush toilet twice with the lid closed after each use (all patients should be advised to sit down when urinating to minimize/avoid splashing), and to use separate towels and washcloths.
	General recommendations
3 d	Use a general distance guideline of no closer than 3 feet for not more than 1 h per day. Try to maintain a distance of 6 feet from others. Minimize public transportation and use of public facilities. Return to work in 3 d, depending on patient tolerance.

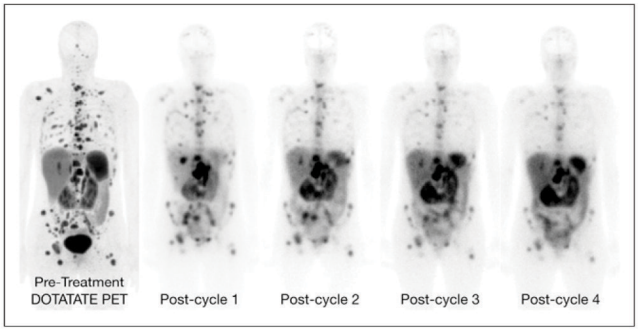

FIGURE 4. Whole-body images acquired after administration of ^{177}Lu-DOTATATE in different therapy cycles.

Toxicity

Rates of toxicity vary between patients, and heavily pretreated patients have higher rates of PRRT-associated toxicity. In particular, liver toxicity has been reported in patients who have had extensive prior liver-directed therapy or who are treated with 90Y-based PRRT (21). The following sections focus on bone marrow and kidney toxicity in more detail.

Bone Marrow Toxicity

Grade 3 and 4 thrombocytopenia and neutropenia occur in ≤5% of patients and resolve within 8 wk (4,22). Grade 3 and 4 lymphopenia is more common, but is rarely of clinical significance since opportunistic infections are not observed in association with ^{177}Lu-DOTATATE. The most significant long-term hematological risk is myelodysplastic syndrome or acute leukemia, which occurs in roughly 2%

TABLE 5
Recommended Monitoring Interval After Completion of PRRT

Time after treatment*	Clinical evaluation	Laboratory tests†	Markers‡	Diagnostic imaging
2–4 wk	X	X		
2 mo		X		X¶
3 mo	X	X	Per team	
6 mo	X	X	Per team	X
12 mo	X	X	Per team	X
Long term	Per team	Per team	Per team	Per team

*Increase monitoring based on clinical presentation, symptoms, concern for progressive disease, or posttreatment sequelae.
†Complete blood count with differential, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, albumin, and serum creatinine/GFR
‡Monitoring of markers should be based on clinical indication/presentation.
¶Imaging is recommended once between one and three months after therapy.

- 3% of patients at a median of 2 y after therapy. Although little can be done during treatment to minimize marrow toxicity, there are possible risk factors for the development of toxicity such as prior chemotherapy (6,23,24).

Renal Toxicity

Due to the high exposure to the kidneys from the renal excretion of the radiotracer, renal toxicity is possible. With the introduction of concurrent amino acids for renal protection and the use of ^{177}Lu-labeled compounds in place of ^{90}Y-labeled compounds, the rates of renal toxicity are low, with long-term grade 3-4 renal toxicity less than 2% (4,23). Variations in individual kidney sensitivity to radiation may explain the variability seen between renal dose and the subsequent development of renal toxicity. For example, there is evidence that patients with long-standing diabetes or hypertension may be at higher risk for renal dysfunction after ^{177}Lu-DOTATATE treatment (19). Nevertheless, severe renal toxicity is rare (<5%) when using the current administration guidelines (4,19).

Follow-Up

Monitoring of patients after PRRT treatment is an essential part of the treatment plan. The recommended monitoring should include clinical evaluation to assess symptoms and detection of possible treatment sequelae, laboratory, and imaging tests (Table 5).

Clinical Evaluation

Clinical evaluation by the treating or primary team should ideally be conducted at 1 mo, 3 mo, 6 mo, and 12 mo after PRRT. If there are no laboratory abnormalities or clinical symptoms concerning for posttreatment sequelae, patients can resume clinical follow-up per the primary team. National Comprehensive Cancer Network (NCCN) guidelines recommend follow up intervals of 3-12 mo based on clinical presentation (25). Clinical symptoms and presentations that could reflect possible progression, increased symptoms from carcinoid syndrome, or posttreatment sequelae warrant closer monitoring.

Laboratory Tests and Markers

Blood tests including complete blood count with differential, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, albumin, and serum creatinine/GFR should be monitored at roughly 1 mo, 3 mo, 6 mo, and 12 mo after treatment. If all blood tests are within normal limits, a complete blood count and serum creatinine should be monitored at least yearly or sooner if clinically indicated or per primary team. If there are any abnormalities in blood tests, more frequent monitoring is recommended.

Both secondary myelodysplastic syndrome and acute leukemia are known toxicities of PRRT. Increased monitoring is recommended for those patients with persistent cytopenias with blood tests until recovery. In addition, hematology consult should be considered for patients with persistent cytopenias.

Patients with mild to moderate renal impairment after PRRT treatment warrant closer monitoring with serum creatinine measurements. In addition, nephrology consult should be considered for patients with persistent or worsening renal impairment.

There are no formal recommendations for following tumor markers after PRRT. NCCN NET guidelines recommend following markers if clinically applicable every 3-12 mo (25).

Diagnostic Imaging Evaluation

In most cases, diagnostic imaging should be done at 1 – 3 mo, 6 mo, and 12 mo after the completion of all treatment cycles. Thereafter, patients should undergo diagnostic imaging based on treatment response. It is important to remain consistent with imaging modalities. NCCN guidelines recommend following patients with contrast-enhanced abdominal and pelvic CT or MRI with contrast along with chest CT with or without contrast (if clinically indicated) every 3-12 mo (25). MRI of the liver with gadoxetate disodium (Eovist) should be considered for those patients with liver dominant disease (26,27). Increased monitoring is recommended for clinical presentation concerning for possible progressive disease, clinical worsening, or possible posttreatment sequel. If there is evidence of progression or equivocal findings on CT or MRI, SSTR-based imaging with ^{68}Ga-DOTATATE PET should be considered and is preferred over SSTR scintigraphy (^{111}In-pentetreotide) (2).

It should be noted that the first imaging study performed after the completion of PRRT can be complicated by pseudoprogression (28). In nearly 10% of patients with stable disease, metastatic disease can increase in volume transiently, presumably due to edema from radiation to the tumor. Diagnostic imaging during the course of PRRT can be considered in patients with relatively aggressive tumors, or patients with clinical evidence of progression.

Conclusion

^{177}Lu-DOTATATE is an effective treatment for patients with NETs. The above guidelines provide information on how to safely administer this novel treatment to patients.

REFERENCES

1. Kulke MH, Mayer RJ. Carcinoid tumors. *N Engl J Med*. 1999;340:858–868.
2. Hope TA, Bergsland EK, Bozkurt MF, et al. Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors. *J Nucl Med.* 2018;59:66–74.
3. Kwekkeboom DJ, Kam BL, van Essen M, et al. Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. *Endocr Relat Cancer.* 2010;17:R53–R73.
4. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. 2017;376:125–135.
5. 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;26:2124–2130.
6. Lutathera [Package Insert]. New York, NY: Advanced Accelerator Applications; 2018.
7. de Jong M, Krenning E. New advances in peptide receptor radionuclide therapy. *Journal of Nuclear Medicine.* 2002;43:617–620.
8. 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; 40:800–816.
9. Roscoe JA, Morrow GR, Aapro MS, Molassiotis A, Olver I. Anticipatory nausea and vomiting. *Support Care Cancer.* 2011;19:1533–1538.
10. Abbott A, Sakellis C, Andersen E. Nuts and Bolts of 177Lu-DOTATATE Administration in the Nuclear Medicine Division: Guidance from a Single Institute's Experience. *J Nucl Med Technol.* August 3, 2108 [Epub ahead of print].
11. de Keizer B, van Aken MO, Feelders RA, et al. Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. *Eur J Nucl Med Mol Imaging.* 2008;35:749–755.
12. Tapia Rico G, Li M, Pavlakis N, Cehic G, Price TJ. Prevention and management of carcinoid crises in patients with high-risk neuroendocrine tumours undergoing peptide receptor radionuclide therapy (PRRT): Literature review and case series from two Australian tertiary medical institutions. *Cancer Treatment Reviews.* 2018;66:1–6.
13. Bonta DV, Halkar RK, Alazraki N. Extravasation of a therapeutic dose of 131I-metaiodobenzylguanidine: prevention, dosimetry, and mitigation. *J Nucl Med.* 2011;52:1418–1422.
14. Siegel JA, Marcus CS, Stabin MG. Licensee over-reliance on conservatisms in NRC guidance regarding the release of patients treated with 131I. *Health Phys.* 2007;93:667–677.
15. Regulatory Guide 8.39: Release of Patients Administered Radioactive Materials. U.S. Nuclear Regulatory Commission website, https://www.nrc.gov/docs/ML0833/ML083300045.pdf. Accessed February 21, 2019.
16. Stabin MG. RADAR Patient Exposure Radiation Dose Calculator. RADAR website. http://www.doseinfo-radar.com/ExposureCalculator.html. Accessed February 21, 2019.
17. National Council on Radiation Protection and Measurements. *Management of Persons Contaminated with Radionuclides.* Bethesda, MD: National Council on Radiation; 2008.
18. Cremonesi M, Botta F, Di Dia A, et al. Dosimetry for treatment with radiolabelled somatostatin analogues: A review. Q *J Nucl Med* Mol Imaging. 2010;54:37–51.
19. Bodei L, Cremonesi M, Grana CM, et al. Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: the IEO phase I-II study. *Eur J Nucl Med Mol Imaging.* 2011;38:2125–2135.
20. Sandström M, Garske-Román U, Granberg D, et al. Individualized dosimetry of kidney and bone marrow in patients undergoing 177Lu-DOTA-octreotate treatment. *J Nucl Med.* 2013;54:33–41.
21. Riff BP, Yang Y-X, Soulen MC, et al. Peptide receptor radionuclide therapy-induced hepatotoxicity in patients with metastatic neuroendocrine tumors. *Clin Nucl Med.* 2015;40:845–850.
22. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [177Lu-DOTA(0),Tyr(3)]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res.* 2017;23:4617–4624.
23. Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *Eur J Nucl Med Mol Imaging.* 2015;42:5–19.
24. Bergsma H, van Lom K, Raaijmakers MHGP, et al. Persistent hematologic dysfunction after peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: incidence, course, and predicting factors in patients with gastroenteropancreatic neuroendocrine tumors. *J Nucl Med.* 2018;59:452–458.

25. Kulke MH, Shah MH, Benson AB, et al. Neuroendocrine tumors, version 1.2015. *J Natl Compr Canc Netw.* 2015. pp. 78–108.
26. Tirumani SH, Jagannathan JP, Braschi-Amirfarzan M, et al. Value of hepatocellular phase imaging after intravenous gadoxetate disodium for assessing hepatic metastases from gastroenteropancreatic neuroendocrine tumors: comparison with other MRI pulse sequences and with extracellular agent. *Abdom Radiol.* 2018;43: 2329-2339.
27. Morse B, Jeong D, Thomas K, Diallo D, Strosberg JR. Magnetic resonance imaging of neuroendocrine tumor hepatic metastases: does hepatobiliary phase imaging improve lesion conspicuity and interobserver agreement of lesion measurements? *Pancreas.* 2017;46:1219–1224.
28. Brabander T, van der Zwan WA, Teunissen JJM, et al. Pitfalls in the response evaluation after peptide receptor radionuclide therapy with [177Lu-DOTA0,Tyr3]octreotate. *Endocr Relat Cancer.* 2017;24:243–251.

NANETS
NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

The Surgical Management of Small Bowel Neuroendocrine Tumors

Consensus Guidelines of the North American Neuroendocrine Tumor Society

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Abstract

Small bowel neuroendocrine tumors (SBNETs) have been in- creasing in frequency over the past decades, and are now the most common type of small bowel tumor. Consequently, general surgeons and surgical oncologists are seeing more patients with SBNETs in their practices than ever before. The management of these patients is often complex, owing to their secretion of hormones, frequent presentation with advanced disease, and difficulties with making the diagnosis of SBNETs. Despite these issues, even patients with advanced disease can have long-term survival. There are a number of scenarios which commonly arise in SBNET patients where it is difficult to determine the optimal management from the published data. To address these challenges for clinicians, a consensus conference was held assembling experts in the field to review and discuss the available literature and patterns of practice pertaining to specific management issues. This paper summarizes the important elements from these studies and the recommendations of the group for these questions regarding the management of SBNET patients.

Key Words

small bowel tumors, liver metastases, carcinoid tumors, hepatic debulking, unknown primary NET, carcinomatosis, video capsule endoscopy, DOTATATE, octreotide prophylaxis

Neuroendocrine tumors (NETs) arise from specialized cells that are dispersed throughout the body, and one convention for categorizing these tumors is their division into foregut (bronchial, gastric, duodenal, and pancreas), midgut (jejunal, ileal, appendiceal, and ascending/transverse colon), and hindgut (distal colon and rectum) tumors. Midgut NETs of the jejunum and ileum (small bowel NETs or small bowel neuroendocrine tumors [SBNETs]) are the third most common site of NETs after the lung and rectum, but are the most common site of NETs that develop distant metastases. Their incidence has increased 4-fold between 1973 and 2004.[1] With respect to all small bowel malignancies, NETs have recently surpassed adenocarcinoma as the most frequent type,[2,3] accounting for 37% of cases. Because of their increasing incidence, now reaching 0.67 cases per 100,000 population in the United States,[1] patients with these tumors are no longer a rarity for general surgeons and surgical oncologists.

It is often difficult to make the diagnosis of midgut NETs at an early stage, because the primary tumors tend to be small and generally do not lead to symptoms until they cause partial obstruction, abdominal pain, or bleeding or become metastatic and initiate carcinoid syndrome. As a result, patients often present with metastatic disease, which has been estimated to occur in 35% of cases in large population-based studies[1] and more than 60% of cases from larger referral centers.[4,5] However, despite this advanced presentation at the time of diagnosis, patients with metastatic SBNETs have a median survival of 56 months,[1] which can be improved further by cytoreduction.[6,7] Therefore, the optimal treatment of SBNET patients is complicated by the fact that long-term survival is common, and there may be benefits to aggressive management that would not be contemplated in comparable stage patients with other gastrointestinal (GI) malignancies.

Not surprisingly, there has been much confusion and controversy surrounding the management of patients with SBNETs, and there are no randomized studies that define their optimal surgical treatment. Therefore, in treating these patients, clinicians must rely on their experience and the results of retrospective studies, both of which are subject to bias. Furthermore, there may be significant differences in opinion among the physicians taking care of these patients, depending on whether they are surgical oncologists, medical oncologists, endocrinologists, gastroenterologists, interventional radiologists, or nuclear medicine physicians. Both the European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumor Society (NANETS) have published consensus guidelines for the diagnosis and management of SBNETs,[8,9] but there remain many clinical scenarios for which the ideal approach is unclear. The objective of this article was to assemble a group of physicians specializing in the treatment of patients with SBNETs and to specifically address many of the most frequent questions that arise regarding their surgical management.

Materials and methods

A list of topics was created summarizing important areas of ongoing controversy or uncertainty regarding the surgical management of SBNETs. Ten surgeons with recognized expertise in these tumors were invited to participate in the guidelines process, as well as a gastroenterologist, body

imaging radiologist, and a nuclear medicine physician. The questions to be discussed were reviewed by the group in advance, and each participant was assigned 1 to 2 specific questions to research and present the results of the most relevant studies to the group. All references were collected and distributed to each member, and the group met on August 11 and 12, 2016. Each participant communicated his/her findings to the assembly, followed by discussion to explore consensus on each question based on the best available evidence. The broad topics included the perioperative use of octreotide, open versus laparoscopic resection of SBNETs, the management of nodal metastases, the role of surgical exploration in various situations (high-grade tumors, tumors of unknown primary site, and metastatic disease), the role of liver-directed surgery, and prophylactic cholecystectomy. The utility of cross-sectional and functional imaging and capsule endoscopy in the preoperative evaluation was also discussed. An audience response system was used to survey the opinions of the group on a series of multiple-choice questions tailored to different clinical scenarios, followed by discussion to attempt to reach consensus. After this, a joint meeting was convened with a parallel group assembled to explore issues pertaining to the medical management of SBNET patients. The information and opinions of the surgical group were presented to the medical group to gather further perspective. The responses to each question were summarized then distributed to each participant several months later for final voting. Consensus was defined as unanimous agreement, near consensus as 1 or 2 oppositional votes, and less than 80% agreement was defined as lack of consensus. The final recommendations of the surgical group were then reviewed by 2 medical oncologist members from the medical group for their perspectives and comments.

Results

There were 8 broad topics and a total of 19 specific questions that were addressed concerning the surgical management of patients with SBNETs, which appear in the sections that follow. Each question is accompanied by a review of the relevant information pertaining to each subject, followed by the summary of the recommendations of the group; some questions (1a + b; 2a + b; 3a + b + c) are grouped together with a common recommendation at the end of that section. Consensus was reached with full agreement of the group on the majority of the recommendations, with the exception of near consensus (one dissent) on questions 1a/b, 5a and 5c.

Preoperative and Postoperative Delivery/ Management of Octreotide

1a. When Is Perioperative Treatment With Octreotide Needed and What Is the Optimal Dose?

Carcinoid crisis is the sudden onset of hemodynamic instability that can occur during anesthesia, operations, or other invasive procedures performed on patients with SBNETs. It can have serious sequelae of organ dysfunction and may lead to complete circulatory collapse and death. It is generally believed that administration of octreotide, either before or during induction of anesthesia and/or invasive procedures, prevents carcinoid crises. Recommendations on how to administer octreotide vary widely from treating patients with long-acting octreotide prior to operation, to preoperative doses of subcutaneous octreotide, to intraoperative intravenous boluses of octreotide, to continuous intravenous infusion of octreotide. Furthermore, there is considerable variation in the recommended doses, infusion rates, and duration of infusions. Generally, prophylaxis is recommended only for patients with carcinoid syndrome, whereas some also extend this to those with asymptomatic neuroendocrine tumor liver metastases (NETLMs) and/or elevation of preoperative serotonin, chromogranin A, or urinary 5′-hydroxyindoleacetic (5′-HIAA).

However, outcome data supporting the efficacy of these various octreotide regimens are scant. The only data for effective perioperative octreotide prophylaxis come from a publication by Kinney et al.10 In their series of 119 patients with metastatic carcinoid tumors undergoing abdominal operations, intraoperative complications were defined as flushing, dysrhythmias, bronchospasm, hypertension, acidosis (pH <7.2), hypotension (systolic blood pressure <80 mm Hg), and need for vasopressor support (systolic blood pressure <80mmHg for >10minutes). The overall rate of intraoperative complications was 7%, with events occurring in 7 (10%) of 67 patients who received no octreotide and 1 (17%) of 6 patients who received only a preoperative dose. In 45 patients who received intraoperative octreotide, either alone or with a preoperative dose, no intraoperative complications occurred (P = 0.023, relative to those not receiving intraoperative octreotide). Carcinoid heart disease and elevated preoperative 5′-HIAA levels were significant risk factors for complications and death. Despite these findings, the authors concluded that their “study was not able to evaluate the efficacy of intraoperative octreotide therapy to prevent intraoperative carcinoid crises.” Thus, the case for octreotide prophylaxis in the literature is

based on these 45 patients who received intraoperative octreotide. However, the doses used in those patients ranged from 30 to 4000 µg (median, 350 µg intravenously or subcutaneously); hence, the proper prophylactic dose is unclear. Furthermore, the optimal time in the course of an operation that the dose should be given and under what circumstances remain undefined.

Massimino et al[11] studied 97 consecutive patients at Oregon Health & Science University undergoing abdominal operations for GI carcinoid tumors and used the same criteria for intraoperative events as did Kinney et al.[10] They gave patients a preoperative intravenous bolus of 500 µg of octreotide and 250- to 500-µg intravenous boluses intraoperatively as needed. The event rate was 24% in their patients, with liver metastases being the strongest predictor of events, but events also occurred in asyndromic patients. However, neither preoperative octreotide LAR nor a preoperative dose of 500 µg of octreotide significantly decreased the incidence of these events. Fifty-six patients also received intraoperative doses of octreotide, and 46% of those patients still had a subsequent event. Patients who had intraoperative events in their series were significantly more likely to have serious postoperative complications.[11]

Woltering et al[12] retrospectively reviewed the anesthesia records of 150 patients undergoing 179 cytoreductive procedures for SBNETs. Eighty-five percent of patients had some component of carcinoid syndrome preoperatively, and a similar number were treated with long-acting somatostatin analogs (SSAs) at baseline. All patients were given an octreotide infusion at 500 µg/h preoperatively, intraoperatively, and postoperatively, and they used similar criteria to define carcinoid crisis as described by Massimino et al.[11] Their review found that only 6 (3.4%) of 179 patients had carcinoid crisis, and this group felt that the continuous infusion of octreotide was better than a preoperative bolus, because the half-life of octreotide is 90 to 120 minutes.

A follow-up study from Oregon Health & Science University examined 127 patients having 150 operations for GI carcinoids.[13] All patients received a preoperative intravenous bolus of 500 µg followed by a continuous infusion at 500 µg/h. However, the rate of events in this series was still 30%. The presence of carcinoid syndrome or hepatic metastases was significantly associated with intraoperative carcinoid crises, whereas preoperative 5′-HIAA and serum chromogranin were not. Because of the association of sustained hypotension and serious postoperative complications observed in their previous series, the investigators modified their treatment protocol such that if the systolic blood pressure was less than 80 mm Hg, and the surgeon and anesthesiologist agreed that there was no other plausible explanation for the hypotension, they would declare it to be a crisis and immediately treat the hypotension with vasopressors. With earlier initiation of treatment for hypotension, events were no longer associated with complications, except when hypotension persisted for more than 10 minutes. The authors concluded that intraoperative infusion of octreotide did not prevent crises, but that prompt treatment of crisis was important to reduce postoperative complications.

Thus, the literature does not definitively support the notion that prophylactic octreotide LAR, a preoperative bolus of octreotide, intraoperative boluses of octreotide, and/or a continuous infusion of octreotide prevent carcinoid crises. On the other hand, there does not appear to be any harm in giving octreotide perioperatively. For example, despite the fact that octreotide decreases visceral perfusion, the rate of anastomotic leaks in patients who received continuous infusions is not higher than that generally reported in the literature. However, there may be danger in relying on octreotide to completely prevent or reduce crises, and therefore one must be prepared to treat them promptly should they arise. Surgeons and anesthesiologists alike should recognize that crises do occur at a significant rate in patients with SBNETs; they can occur in asyndromic patients and if prolonged are associated with increased rates of serious postoperative complications. Accordingly, they should be prepared to expeditiously treat hypotension with vasopressors (generally vasopressin and phenylephrine).

1b. Is Octreotide Needed for Procedures (Hepatic Arterial Embolization, Colonoscopy, Endoscopic Ultrasound Biopsies, or Percutaneous Liver Biopsies)?

Patients with SBNETs often require invasive procedures for tumor localization, staging, and/or therapy, which may include endoscopy, colonoscopy, endoscopic ultrasound, biopsy of liver tumors, hepatic arterial embolization, and ablation. There is an abundance of case reports of carcinoid crisis in patients with SBNETs and other NETs occurring during or soon after a variety of invasive procedures.[14–23] However, there are no clear data on the rate of these events in the literature. Furthermore, the role of preprocedural or periprocedural octreotide during invasive procedures to prevent carcinoid crisis is unclear as there are no relevant data to support this practice.

Recommendation: It has not been established that routine administration of octreotide either preoperatively or preprocedurally, during the procedure itself either

as an intravenous bolus or infusion, or that weaning it perioperatively prevents carcinoid crisis. Physicians should be prepared to manage carcinoid crisis events in patients with SBNETs who undergo operations or invasive procedures. Episodes of hypotension may be treated with an octreotide infusion should they occur, but vasopressors such as vasopressin and phenylephrine should also be used as needed. Many surgeons may still elect to run an octreotide infusion intraoperatively at a rate ranging from 100 to 500 µg/h in an attempt to avoid carcinoid crisis, and although this practice does not appear to be supported by the available literature, it does not appear to increase complication rates and is generally safe.

Open Versus Laparoscopic Resections

2a. Are Open Resections of SBNETs the Best Approach?

Surgical resection of SBNETs should include a complete oncologic resection of the primary tumor(s), regional lymph nodes, and mesenteric fibrosis, if feasible. Operations should be performed optimizing safety, operative time, quality of life, and cost. Regardless of the surgical approach (open vs laparoscopic/minimally invasive), adherence to these surgical principles is paramount. Intraoperative staging should be undertaken to evaluate the extent of disease. Peritoneal metastases are found in 20%of patients with SBNETs,[4] so care should be taken to search for these in the pelvis, on the sigmoid colon, mesentery, and diaphragms. The liver surface should be examined, and intraoperative ultrasound can augment preoperative imaging tests for evaluation of liver metastases, which may occur in up to 61% of patients.[4] Both ovaries should be inspected to rule out ovarian metastases, which occur in 4% of patients and can cause carcinoid syndrome.[4] The primary tumors in the jejunum or ileumare often very small,[24] so careful palpation of the small intestine from the ligament of Treitz to the ileocecal valve is essential. In 25% to 44% of patients, there are multifocal primary tumors.[4,24–26] Many of the multifocal primary tumors are subcentimeter and can be identified only by careful digital palpation.[24] Therefore, it cannot be overemphasized that careful palpation of the entire jejunum and ileum is a critical step to identify small NETs and multifocal disease.

Most patients with SBNETs (>80%) have regional lymph node metastases.[4,27] Careful review of preoperative imaging and intraoperative appraisal should be carried out to evaluate the extent of regional lymph node metastases and the characteristic mesenteric fibrosis associated with SBNET lymph node metastases. Some use lymphatic mapping to help guide the extent of intestinal and mesenteric resection,[28] but this technique has not been widely adopted. Resection of the primary tumor(s), regional lymph nodes, and mesenteric fibrosis, when possible, should be done with extreme care to maximize the length of residual viable intestine by preserving the proximal superior mesenteric artery (SMA) and vein (SMV).[29] Based on the clinical context, additional procedures, such as cholecystectomy and resection of liver or ovarian metastases, should also be considered.

The recognized standard for SBNETs is exploratory laparotomy with careful palpation of the entire jejunum and ileum to identify small and/or multifocal NETs. In fact, guidelines from North America and Europe do not consider laparoscopic surgery or minimally invasive surgery (MIS) ideal for managing SBNETs because of their small size and multifocal nature.[8,9] Consequently, the role of laparoscopic surgery/MIS in the management of patients with SBNETs is not well defined, given the risk of missing multifocal lesions, compromising nodal resection, and limiting one's ability to perform peritoneal debulking.

2b. When Is Laparoscopic Exploration Reasonable?

There are few studies in the literature describing laparoscopic resection of SBNETs. Figueiredo et al[30] reported successful laparoscopic resections in 12 patients, and Reissman et al in 20 patients.[31] Wang et al[32] described successful laparoscopic/minimally invasive resection of ileal NETs in 6 patients who presented with NETs of unknown primary. In this article, the authors emphasized the importance of palpation as part of MIS to identify the small primary tumors, which are frequently multifocal. To do this, they used a hand-assisted laparoscopic device (Gelport; Applied Medical) or a soft tissue wound retractor (Alexis Wound Retractor; Applied Medical, Rancho Santa Margarita, Calif) to exteriorize the jejunum and ileum, which facilitates complete palpation, resection of the primary tumor(s), dissection of the mesenteric lymph nodes/fibrosis, and intestinal anastomosis.[32] A larger study by Massimino et al[33] reported 63 patients with occult primaries but biopsy-proven nodal or hepatic NET metastases. They began operations laparoscopically in 46 of these patients and successfully localized the tumors in 28 (61%). Fourteen patients had conversion to an open procedure, 2 for palpation of the bowel and 12 for debulking of liver metastases. They concluded that laparoscopic exploration was superior to preoperative imaging and endoscopy for finding these primary tumors.[33]

Regardless of the surgical approach, the surgical goals should remain the same: (1) complete oncologic resection of the primary tumor(s) and mesenteric adenopathy/ fibrosis; (2) thorough staging with evaluation of the

peritoneum, liver, ovaries, primary tumor(s), and mesenteric adenopathy/fibrosis; and (3) optimization of safety, operative time, quality of life, and cost. Thorough staging and palpation for multiple primaries can be achieved by a minimally invasive approach when a hand-assisted laparoscopic device or the soft tissue wound retractor is used, which also facilitates extracorporeal anastomosis. However, extensive mesenteric adenopathy/fibrosis may preclude safe resection through a small incision, and in such cases, there should be no hesitation to convert to an open procedure to more safely achieve the proper mesenteric dissection to remove proximal nodes while maximizing viable intestine.

Recommendation: The accepted surgical approach for resection of SBNETs is an open abdominal operation, to achieve the goals of careful palpation of the entire small bowel and adequate resection of mesenteric lymph nodes while preserving vascular inflow and outflow to the remainder of the intestine. Purely laparoscopic techniques are inadequate for thorough evaluation of the small bowel for diminutive tumors, as these will not be visible through the laparoscope and not necessarily palpable with metal graspers. However, if a small incision is made, and the bowel can be run from the ligament of Treitz to the ileocecal valve and carefully palpated (with the surgeon's fingers), then this may be an acceptable alternative, as long as an appropriate bowel resection and adequate lymphadenectomy (to the origin of segmental vessels) are carried out. Cases requiring extensive nodal dissection, peritoneal debulking, and hepatic cytoreduction are better treated by an open approach. For selected patients with extensive, inoperable liver metastases, application of a laparoscopic approach may be very reasonable, depending on the surgical goals. If the goals are determining whether the patient has an SBNET primary, resecting the primary SBNET, and even adding a prophylactic cholecystectomy, these can often be accomplished laparoscopically with less morbidity for the patient.

Management of Regional and More Distant Nodes

Several factors need to be considered when determining the optimal lymph node clearance in patients with SBNETs. Should the lymph node dissection be prophylactic or therapeutic? What is the appropriate extent of lymph node dissection based on the small bowel lymphatic drainage, selective (removal of only lymph nodes adjacent to the primary SBNET) or systematic (removal of lymph nodes up to the main segmental vessels off the SMA and SMV or removal of the lymph nodes from the main SMA and SMV trunks themselves)? How should other abdominal lymph nodes be handled?

3a. What Is the Optimal Removal of Regional Lymph Nodes During Segmental Bowel Resections?

The rate of lymph node metastases in patients who have SBNETs and who have had lymph node dissection ranges from 46% to 98%.[4,27,34–36] Given this, in most patients with SBNETs with or without gross lymph node involvement, routine lymph node clearance is warranted and allows for accurate staging. Furthermore, when tumors are removed with only the adjacent mesentery, recurrence in proximal lymph nodes may occur.[8] Several retrospective studies have demonstrated increased overall survival (OS) and disease-free survival in patients with SBNETs who had lymph node dissection along with removal of the primary tumor in univariate and/or multivariate analyses.[4,27,34,36] In these studies, the numbers of lymph nodes removed were defined as at least 1, 6 or more lymph nodes, and more than 7 lymph nodes.[4,27,36] In the largest cohort studied, a retrospective analysis of the Surveillance, Epidemiology and End Results database, removal of more than 7 lymph nodes and lymph node ratio (no. of positive/no. of total nodes) of less than 0.29 were associated with higher survival rates in patients who had lymph node dissection, adjusting for age and tumor size.[27] One problem with studies using node counts in this disease is the frequent presence of large mesenteric masses, which often represent a conglomeration of lymph nodes, which cannot be accurately enumerated. Some surgeons have used isosulfan blue injection into the primary small bowel tumors to better define the lymphatic drainage of the tumor(s). This approach led to selective resection of the involved lymph node basin, changing the extent of resection in 98% of the operations and preservation of the ileocecal valve in 44% of terminal ileal tumors, with no recurrences reported in 1 to 5 years of follow-up.[35] Lymphatic mapping is not a standardly performed procedure,[9] and recommendations from Uppsala and ENETS are that regional nodes should be removed along the segmental vessels up to their junction with the main trunk of the SMV (when feasible).[4,9,37]

3b. How Should Nodes BeManaged That Are Encasing the SMV/SMA?

Mesenteric nodalmetastases from SBNETs are often considerably larger than the primary tumor(s) and associated with extensive mesenteric fibrosis and desmoplastic reaction. The nodal metastases often extend to the root of themesentery, as well as into the retroperitoneum (such as para-aortic, aortocaval, or pararenal nodes), around the pancreas and hepatic artery.[37–41] These mesenteric lymph node metastases have been stratified into 4 different groups as follows: stage 1 nodes are those close to the SBNET; stage 2 nodes involve

the distal branches of the mesenteric arteries; stage 3 nodes extend proximally without encasing the SMA; stage 4 encompasses awide spectrum of cephalad regional disease progression, including retropancreatic/retroperitoneal extension and encasement of the SMVand SMA.[37] Stage 1 to 2 nodes can be adequately treated by segmental bowel resection with removal of all nodes up to the origin of the segmental vessels coming off the SMA/SMV. Stage 3 nodes are treated by segmental resection as with stage 1 to 2 nodes, but more proximal nodes are removed from alongside the proximal vessels by incising the peritoneum overlying them and dissecting them off carefully up to the root of the mesentery. In general, patients with stage 4 nodal metastasis are commonly deemed unresectable and are often treated medically.[37–39] Ohrvall et al[37] describe transecting the mesenteric mass in these cases (while preserving the more proximal vessels) in order to remove the affected intestine.

The consequences of encasement of the mesenteric vessels vary among patients. In many individuals, the development of adequate collateral circulation may avoid the life-threatening sequela of mesenteric ischemia. Nonetheless, these patients can still suffer from chronic mesenteric ischemia and bowel obstruction, and thus, segmental resection of the primary with involved nodes may be beneficial.[37,39–41] In cases of stage 4 nodes, leaving the nodes circumferentially surrounding the SMA/SMV in place may potentially avoid the complication of catastrophic vascular compromise resulting from an overly aggressive resection, especially because these patients can still have long-term survival. However, vascular encasement can cause a variety of symptoms, including intestinal ischemia and even infarction of the small intestine. Intestinal ischemia is probably due to a combination of tumoral secretion products causing fibrosis, desmoplastic mesenteric retraction, and nodal compression, which leads to elastic vascular sclerosis, predominantly affecting the adventitia of the involved mesenteric blood vessels, leading to mesenteric luminal narrowing.[37–39] Careful dissection may allow for resection of proximal nodes in some of these patients, whereas others with encasement of the root of the mesentery by a calcified, fibrotic mass may be better served by leaving the nodal mass in place and dividing the segmental vessels at its lower edge, so as not to risk injury to the main trunks of the SMA/SMV. Patients with residual nodal disease can still have long-term survival and often adapt to SMV thrombosis by the development of collaterals over time. However, in recent years, surgeons in specialized NET centers have developed techniques to remove proximal root of the mesentery lymph node metastases in selected patients. Patients successfully treated surgically may have better quality of life because of a lower incidence of bowel obstruction, intestinal angina, and avoiding the worst consequences of mesenteric ischemia, namely, bowel perforation and/or gangrene.[37–41]

3c. How Should Nodes Beyond the Root of the Mesentery Be Managed?

Distant lymph nodes outside the typical locoregional drainage basin can be present in SBNET patients and identified on cross-sectional imaging. These include nodes in the periportal, para-aortic, aortocaval, and pararenal regions, as well as along the hepatic artery. One retrospective study identified involvement of these distant abdominal nodes in 18% of their SBNET patients and was an independent factor associated with reduced survival.[4] Management of these nodal basins should be considered when a patient is undergoing abdominal exploration and resection.

Extended lymph node dissection in the abdominal cavity has been well studied in randomized trials in both gastric and pancreatic cancers. In an effort to improve survival, these resections have included splenectomy and dissection of perihilar nodes in gastric cancer and more extensive retroperitoneal dissection in pancreatic cancer.[42,43] These experiences revealed that greater complications were observed in patients undergoing more extensive lymphadenectomy without a survival benefit. Extrapolating from these data from other tumor types suggests that in the absence of gross disease on imaging routine, prophylactic resection of these nodes is not beneficial. When gross disease in these nodes is evident by imaging, surgical resection can be considered in select circumstances, particularly if the nodes have the potential to encroach on vital structures or if resection would render the patient with no evidence of disease. Extended resections and high-risk surgical approaches should be carefully considered in the context of each patient's overall disease burden.

Recommendation: Patients with SBNETs should have regional lymph nodes removed with their segmental bowel resection. In most cases, this should include resection up to the origin of the segmental vascular branches from the SMA/SMV. Low-risk surgical patients with lymph node metastases encasing the root of the mesentery and thus the proximal SMA/SMV, whether symptomatic or not, should be considered for referral to a specialized NET center to be evaluated by experienced surgeons for possible surgical cytoreduction of the root of themesentery nodes. Symptoms of intermittent bowel obstruction, significant weight loss, intestinal angina, or signs of bowel ischemia should alert the treating

physician to more urgent referral to specialized centers. The decision to resect root of the mesentery nodes needs to be carefully considered based on the operative findings, and if compromise of the mesenteric vessels is likely with removing these nodes, then not attempting resection is advised. Distant abdominal lymph nodes outside the superior mesenteric vessels (such as para-aortic, pararenal, portocaval, aortocaval, hepatic artery) should not be routinely resected in the absence of imaging studies suggesting an imminent threat of involvement with neighboring vital structures. Resection of these nodes may be considered when they are identified on imaging, to the extent that it is feasible and will not compromise patient outcome.

The Role of Surgery in Specific Clinical Situations

4a. Should Surgical Exploration Be Considered in Patients With High-Grade Tumors?

High-grade SBNETs (grade 3, Ki-67 >20%) are typically poorly differentiated tumors, but more recently, tumors have been described with well-differentiated histology that are also high grade based on their proliferative index and/or mitotic rate. Poorly differentiated SBNETs are exceedingly rare and have an aggressive disease course, similar to their counterparts in the stomach, pancreas, and colon.[44] Metastatic disease at presentation is typical with median survival usually measured in months.[45] Well-differentiated SBNETs are rarely high grade (grade 3), but have been observed in metastases, as well as in tumors with a mixture of low- and high-grade components.[46] Often, these high-grade tumors are recognized only after resection, and the optimal treatment of patients with these SBNETs is unclear. A recent review of multiple series of high-grade gastroenteropancreatic neuroendocrine tumors/carcinomas (GEPNETs) suggests that there are 3 useful categories of grade 3 tumors, which behave differently, based on morphology and Ki-67 index: well-differentiated G3, with Ki-67 of 21% to 55% (NET G3); poorly differentiated large or small cell neuroendocrine carcinoma with Ki-67 of 21% to 55% (NEC G3); and poorly differentiated large or small cell neuroendocrine carcinoma with Ki-67 of greater than 55% (NEC G4).[47] Treatment of NET G3 tumors may be similar to that used for G2 lesions, NEC G3 tumors may benefit from treatment with oxaliplatin and/or alkylating agents, and NEC G4 tumors are commonly treated with cisplatin or carboplatin and etoposide.[47] Review of slides by an experienced pathologist is very important, and quantification of Ki-67 and/or mitotic figures is critical. Because of limited response rates of SBNETs tomedical therapy and the paucity of natural history data for NETG3 lesions,[48] resection is reasonable and should be considered, particularly for patients with localized or local-regional disease.

Recommendation: Poorly differentiated, high-grade SBNETs are very rare and should be managed primarily with systemic therapy. Well-differentiated SBNETs with high-grade features (Ki-67 >20%), if identified preoperatively, can be considered for systemic therapy, especially in the setting of widespread metastases. However, resection of limited disease may also be reasonable, given the limited options for systemic treatments and the lack of knowledge regarding their natural history.

4b. What Is the Optimal Approach for Peritoneal and Diaphragmatic Metastases Found at Exploration? Is There a Role for Hyperthermic Intraperitoneal Chemotherapy?

Small bowel neuroendocrine tumors often grow through the serosal layer of the bowel, gaining access to the peritoneal cavity. This results in peritoneal carcinomatosis, which is found in approximately 20% of patients undergoing exploration for SBNETs.[4] Areas at particular risk of peritoneal metastases are so-called “drop metastases” in the pelvis, with plaques forming on the sigmoid colon, and peritoneal lining of the pelvis. The diaphragms, lateral peritoneum, omentum, small bowel, and colonic mesentery are also frequent sites of disease. There is no good surgical or medical treatment for carcinomatosis from SBNETs, although patients treated with cytoreductive surgery can have long-term survival.[49–51] Limited areas of disease may be treated by peritoneal stripping operations that have been well described for pseudomyxoma peritonei and low-grade appendiceal tumors.[52] Other approaches are peritoneal resection limited to the areas of implants, diaphragmatic resection, sigmoid resection, or burning small lesions with electrocautery or argon beam.[53] However, because of the pattern of this spread, these procedures can never be complete, and there will always be a risk of recurrent disease. Peritoneal implants from SBNETs, like those resulting from other GI tumors, cause significant morbidity for patients. Specifically, because of the peritoneal fibrosis they cause, even small lesions can serve as a focus for bowel adhesions and obstruction. Bowel obstructions may occur at multiple locations, requiring challenging surgical procedures to relieve symptoms, and patients will be at risk of recurrence. Large plaques on the sigmoid colon may also lead to colonic obstruction. This causes morbidity for patients that is not immediately lethal, but may lead to long-term nausea and vomiting, crampy pain, and

need for diverting colostomy or parenteral nutrition. The lack of effective therapies for peritoneal disease should be considered a key argument for resection of primary SBNETs, even in the face of inoperable hepatic metastases, with the goal of preventing the development of peritoneal disease. There are multiple therapies available to treat liver metastases, but minimal effective treatments for peritoneal carcinomatosis, where the most appropriate remedy is resection of the primary tumor and nodes so that this pattern of spread does not occur.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) is a regional cancer therapy for diffuse peritoneal nodules combining surgical debulking, chemotherapy, and hyperthermia.[54] This is an intracavitary treatment in which maximal surgical debulking and resection are done, including resection of the primary lesion(s), regional nodal disease, and peritoneal stripping. Because of the diffuse pattern of spread from peritoneal implants, even if all gross disease can be removed it is highly likely that small residual nodules will grow over time. The theory behind HIPEC is that it will deliver chemotherapy to the surface of residual tumor cells in the presence of heat, which augments the kinetics of the chemotherapy drugs to kill either microscopic or small nodular disease. Hyperthermic intraperitoneal chemotherapy has been most extensively utilized for pseudomyxoma peritonei and low-grade appendiceal cancers. There are still no randomized data among the practitioners of this regional therapy to definitively prove its benefit in these diseases. It has been used for ovarian carcinoma, which commonly spreads intraperitoneally, as well as colorectal cancers and gastric cancers. There are limited data available for the use of HIPEC for SBNETs that spread intraperitoneally. Elias et al[51] treated 28 SBNET patients over a 13-year interval with cytoreductive surgery and HIPEC using oxaliplatin or oxaliplatin plus irinotecan. The recurrence rate of peritoneal metastasis was 47%, but the investigators conducting the study felt that the complications of the HIPEC did not justify utilizing this treatment, and they stopped using this for the last one-third of the patients in their surgical series and showed no difference in OS for those treated with HIPEC.[51] Randle et al[55] reported a median survival of 18.4 months in 31 patients with the more aggressive goblet cell NETs of the appendix treated by cytoreduction and HIPEC, but these tumors are not directly comparable to SBNETs.

Recommendation: The best way to prevent peritoneal implants is to operate on patients with SBNETs before they grow through the bowel wall. However, when patients present with this extent of disease, removing as much disease as possible while minimizing risks is recommended. Limited areas of seeding can be resected with the underlying peritoneum or diaphragm, and smaller lesions treated with electrocautery or argon beam. At present, there is no evidence supporting the use of HIPEC as an adjunct to these local treatments for intraperitoneal metastases from SBNETs.

4c. What Is the Role for Surgical Exploration in Patients With an Unknown Primary and Metastatic Liver Disease?

Patients with SBNETs frequently present with multiple liver lesions with no radiographic imaging identifying the primary tumor. Cross-sectional imaging identifying these liver metastases is often performed for symptoms of flushing and diarrhea, nonspecific symptoms of abdominal pain, or abnormalities of hepatic function tests. Other patients may have scans done for other reasons, such as a chest computed tomography (CT),which identifies liver lesions, or CT done for renal stones, where these unexpected liver lesions are found. A core biopsy of a liver lesion will confirm the diagnosis of metastatic NET, but in many cases, the origin of the primary tumor is undetermined. The differential diagnoses include NETs originating in the small bowel, pancreas, bronchus, thymus, colon or rectum, appendix, stomach, or duodenum. Chest CT scans should identify primary thoracic NETs, and upper endoscopy will identify the type 3 gastric carcinoids most likely to present with liver metastasis. Multiphase CT scans with intravenous contrast, magnetic resonance imaging (MRI) scans, and/or endoscopic ultrasound will usually identify a pancreatic primary as the source of liver metastasis. Colorectal primaries may be seen on CT or colonoscopy. It is very unusual to have a completely occult lesion which is not seen on radiographic and endoscopic studies to originate from sites other than the small bowel.[32,56]

Small bowel neuroendocrine tumors are frequently small and have to reach a certain size to be identified radiographically or cause obstruction leading to dilated loops of small bowel. Small bowel neuroendocrine tumor lymph node metastases are frequently evident and will more commonly identify the source of the primary.[25,56] The appearance of lymph node metastases from SBNETs is classic, usually with a spiculated mass, often containing calcifications and sometimes foreshortening of the mesentery. It is important when evaluating for occult NETs metastatic to the liver to carefully follow out the branches of the superior mesenteric vessels all the way to the bowel and look for enlarged nodes, masses, or distortion of the mesentery. Wang et al[32] reviewed their experience with 71 patients presenting with NETLMs, where 79% had primaries identified by radiology or endoscopic studies. All patients with pancreatic NETs

(PNETs) were identified by CT scan, and in the 15 patients with unknown primaries that were explored, tumors were found in the small bowel in 13 (and not found in 2 patients). They concluded that most occult primaries in patients with NETLMs will be SBNETs.[32] Massimino et al[33] described 63 patients presenting with NETLMs where the primary was not found by imaging in 52 (83%) of 63 patients. At surgical exploration, 79% had primaries identified, where 70% were SBNETs, 3% appendiceal, 3% pancreatic, 2% colonic, and 2% were ovarian. Bartlett et al[57] studied 61 patients presenting with NETLMs in which the primary was not found by imaging in 28 (46%). At laparotomy, 80% of primaries were identified (75% were SBNETs, and there was 1 duodenal primary). Keck et al[56] reported on 134 patients presenting with metastatic GEPNETs that were explored. The primary site was identified by preoperative imaging in 91%, with 10 patients not localized preoperatively. Primaries were found in 6 of these 10 patients at exploration, 5 of which were in the small bowel and 1 in the pancreas. In these studies, other investigations such as double-balloon enteroscopy and capsule endoscopy added little to the workup. Because occult primaries are usually in the midgut, even if a submucosal intestinal mass is seen by capsule endoscopy, it needs to be located by the surgeon at exploration to allow for appropriate resection. A recent study demonstrated the utility of ^{68}Ga-DOTATATE positron emission tomography (PET) scans for finding the site of unknown primary GEPNETs, which successfully localized 4 of 14 lesions.[58]

The majority of SBNET primaries are identified by palpation, and these lesions are generally easily found by carefully running the small bowel from the ligament of Treitz to the ileocecal valve between the thumb and forefinger. Up to 25% to 44% of SBNETs are multifocal,[4,24–26] and therefore it is important to run the entire bowel and not stop when 1 lesion is felt, because there may be multiple lesions. Enlarged lymph nodes in the mesentery will often be evident as well. As reported in these large series from tertiary referral centers, most NETs of unknown primary (80%) can be found at exploration, and the majority of these will be of midgut origin. Several of these studies also combined treatment of liver tumors with the intraoperative identification of the primary to maximize surgical therapy at the initial procedure. Unfortunately, the finding of NETLMs with unknown primary frequently leads to medical or embolic treatment of the liver lesions, with the assumption that unless the primary can be identified, there is no role for surgical consultation. For patients who have the option of complete or significant debulking of NETLMs, referral should be made to a center with expertise in treating NETs, and surgical exploration with palpation of the bowel should be performed. If palpation of the small and large bowel does not reveal a primary lesion, kocherization of the duodenum with digital palpation and exposure and mobilization of the pancreas with palpation and intraoperative ultrasound are additional techniques that should be used to look for the unidentified primary lesion.

Alternative strategies to determine the site of unknown primaries have used a gene expression classifier to evaluate expression profiles of metastases indicative of SBNETs versus PNETs, or immunohistochemistry, where positivity for CDX2 is consistent with SBNETs (whereas PAX6/8 and islet1 staining is consistent with PNETs).[59] Elevated serum serotonin or urinary 5′-HIAA may also point strongly to an SBNET primary. Although other primary sites can occasionally secrete serotonin and its byproducts, including pancreatic carcinoid tumors, occult lesions will most commonly be in the midgut.

Recommendation: Patients with NETLMs and unknown primaries should undergo staging with multiphase abdominal, pelvis, and chest CT scans with thin cuts to evaluate the bronchi, thymus, stomach, duodenum, colorectum, appendix, pancreas, and small bowel with its mesentery. Endoscopic ultrasound can be added to evaluate for PNETs, although most of these will be identified by CT. There may also be utility in the use of ^{68}Ga-DOTATATE scans in patients with unknown primaries.[58] However, the inability to identify the primary NET preoperatively should not inhibit exploration for the primary tumor, or potential surgical debulking of metastatic liver disease. Intraoperative identification of primary tumors is highly successful, and most will be found within the small bowel.

4d. Should Primary SBNETs Be Removed in Asymptomatic Patients With Inoperable Metastatic Liver Disease?

As discussed previously, it is relatively common for SBNET patients to have a CT scan performed for some type of abdominal sign or symptom that reveals liver metastases. A biopsy of one of these lesions revealing a NET, or elevated chromogranin A or urine 5′-HIAA, in conjunction with a mesenteric mass is highly indicative of a small bowel primary.[56] Clearly, if the patient is having symptoms of bowel obstruction, diarrhea, cramping, or intestinal ischemia, then the primary tumor should be removed to improve these symptoms. However, if the patient is asymptomatic, the benefits of removing the primary tumor are not as clearly discernable.

There are several arguments for not removing the primary SBNET in asymptomatic patients with metastatic disease. First, if the patient truly does not have symptoms, is it really possible to improve upon this with surgery? Second, the patient's ultimate survival may be dictated by the presence of distant disease, and removing the primary will not change this fact. There have been 4 randomized controlled trials showing improvement of progression free survival (PFS) in patients with metastatic SBNETs; thus, some clinicians argue that the best evidence supports treating these patients with systemic agents shown to be effective in these trials. These active agents include octreotide LAR (from the PROMID trial),[60] lanreotide (CLARINET),[61] everolimus (RADIANT4), [62] and ^{177}Lu–peptide radioreceptor therapy (NETTER-1).[63] Although most would agree that these treatments can play an important part in managing patients with metastatic SBNETs, the role of surgical resection is more controversial, principally because studies showing its advantages have all been retrospective and therefore potentially influenced by selection bias.

Objectively, there are 3 main lines of reasoning supporting removing the primary SBNETs in patients with metastatic disease. The first is that most patients are not truly asymptomatic. Their diagnosis of metastatic disease may have become evident while being worked up for some other condition or vague symptoms, but the fact that they had a CT scan for their evaluation suggests that they are not asymptomatic. Of 80 patients with SBNET NETLMs operated on at the University of Iowa, only 8 (10%) lacked symptoms of diarrhea, flushing, or abdominal pain.64 Surgeons from Uppsala evaluated symptoms in 121 patients with SBNETs undergoing either emergent or elective laparotomy, 93% of whom had metastases (80% mesenteric and 62% liver).[65] Half of these patients had symptoms of carcinoid syndrome (such as diarrhea and flushing, plus other manifestations), which might be ascribed to having metastatic disease. The other half had symptoms that might be related to a primary tumor, with 81% of this group having abdominal pain, 52% acute abdominal episodes, 39% nausea and distention, and 37% weight loss. The majority of patients had an operation, and of those, 82% had relief of symptoms (67% complete, 15% partial). They showed that most patients had good symptom relief for 4 to 5 years and felt their results supported removal of these primaries and nodal metastases even in "asymptomatic" patients. A follow-up study from this group with 314 patients found that in patients undergoing elective operations there was a "retrospective appreciation" of symptoms beginning at a mean of 1.25 years prior to the diagnosis.[41]

A second reason for resecting the primary is to treat or avoid those situations that lead to symptoms, that is, bowel obstruction, bleeding, mesenteric fibrosis, peritoneal dissemination, or reducing the risk of further metastasis. Clearly, if these procedures are to be performed in asymptomatic patients, they should be done with minimal morbidity and mortality, which has been shown to be achievable by several groups.[64,66] The third reason for pursuing resection of SBNETs in the setting of metastatic disease is that it may lead to a survival benefit for patients. In Hellman and colleagues'41 series of 314 patients with SBNETs (286 with mesenteric and 249 with liver metastases), 83% of patients had an operation, and the primary tumors could be resected in 95% of cases. Patients having resection of their primaries (249 patients) had a median survival of 7.4 years versus 4.0 years for those who were not resected (65 patients; $P < 0.01$). There are a few caveats to consider when interpreting the finding of improved survival in patients having resection, because retrospective studies are prone to selection bias. One is that most of the patients without liver metastases were in the resected group, and another is that it is possible that patients who were likely to do better (with less advanced disease, fewer comorbidities) had an operation, and those with worse disease or comorbidities were not operated on. Therefore, it is hard to be certain that surgical resection itself was the major factor leading to this apparent improvement in survival.

Another study of 360 patients with midgut NETs and liver metastases from 5 institutions in the United Kingdom and Ireland reported on the results of amultivariate analysis of factors contributing to patient survival.[67] Of these 360 patients, 209 (58%) had resection of their primary, 12 (3%) had surgical bypass, and 17 (5%) were explored and found to be unresectable. The median survival of those who had their primary resected was significantly longer (9.9 years) than in those who did not undergo operation (4.7 years), or for those undergoing bypass (5.6 years), or those who were explored but did not have their lesion resected (6.7 years). This reduced survival in patients who are explored and do not have their lesion resected or not bypassed suggests that removing the primary itself, rather than just selection bias for patients having an operation, was an important contributor to the survival differences observed. A wide variety of clinical, radiological, treatment, and pathologic factors were examined statistically, but the only 3 found to be significant by multivariate analysis were (1) resection of the primary tumor; (2) the age at diagnosis; and (3) Ki-67 index. The authors felt that the low mortality in the surgical group (1.4%), higher fraction of unresected patients dying of bowel obstruction, and survival advantage in resected

patients provided evidence that patients with midgut NETs and liver metastases should have their primaries resected if possible.

A recent study from Milan examined 139 patients with functional, well-differentiated NETLMs from various sites (ileal, 66; pancreas, 36; lung, 13; stomach, 5; and unknown, 19) with a median follow-up of 127 months. Resection of primary tumors was carried out in 67% of patients, and the median survival of this group was 138 versus 37 months in whom the primary tumor was not resected ($P < 0.001$ on multivariate analysis). This survival benefit of resecting the primary also held up in the 103 patients who did not have their liver metastases resected. Although this article does demonstrate a survival benefit for resecting the primary tumor when there are metastases present, it should be noted that the vast majority of patients with SBNETs in this study had their primary tumors resected (63 of 66). Likely because of this, the survival advantage for the SBNET subgroup was not specifically reported (although it was significant in those with PNETs), but it was clear that this was their preferred management of SBNET primaries.[68]

A systematic review of the literature on the question of resection of primary SBNETs in patients with unresectable liver metastases found a clear trend toward improved survival for resection.[69] One of the studies included tried to retrospectively address the issue of selection bias in carcinoid patients presenting with liver metastases that were not amenable to hepatic cytoreductive procedures.[70] There were 84 patients, of whom 60 underwent resection, and 24 were not resected. Of these, 18 were not explored (10 declined an operation, and 8 were not offered an operation by their managing physician),whereas 6 patients were explored but did not have their lesion resected. Both groups were similar in terms of Karnofsky status, chromogranin A levels, treatment with octreotide or interferon, and symptoms. Median survival of those resected was 159 months versus 47 months in those in whom the primary was not resected ($P < 0.001$). When the 6 patients explored but did not have their lesion resected were added to the resection group, survival was still improved at 108 months in the operative group versus 50 months in the nonoperative group ($P < 0.001$). The median survival of a subgroup of 28 patients with asymptomatic primary tumors that were resected was not reached and was significantly improved over nonresected patients ($P = 0.001$). The majority of patients in both groups (79%) died of liver failure, but the median time to progression of liver disease was 25 months in the nonresected group versus 56 months in the resected group. Therefore, a possible explanation for this improved survival is that resection of the primary removes the source of new liver metastases.

Recommendation: Resection of primary SBNETs in selected patients with metastatic disease should be considered when feasible to relieve existing symptoms and avoid future symptoms, and for its potential survival advantage. However, other factors need to be carefully considered, such as the patient's performance status and degree of liver replacement, with higher levels (>50%–70%) being associated with shorter survival and higher risk of significant postoperative liver dysfunction. The fact that asymptomatic patients will generally have a long survival without intervention, with or without SSAs or additional medical therapies, means that surgical procedures must be performed with minimal mortality and morbidity.

Liver-Directed Operations for Metastatic NETs

5a. What Are the Survival Advantages and Other Benefits of R0, R1, and R2 Resections for Metastatic SBNETs?

Despite the indolent nature of SBNETs, NETLMs will develop in 50% to 60% of patients.[66,71–73] These patients are at risk of developing potentially debilitating hormonal symptoms and syndromes (carcinoid syndrome and carcinoid heart disease) secondary to the hepatic tumor burden. Historically, patients with NETLMs have been reported to have a 5-year survival of approximately 30%. Although there have been recent advances in our therapeutic armamentarium in patients with advanced NETs, surgical resection remains the only potentially curative intervention for patients with NETLMs.

A study from the Mayo Clinic in 2003 evaluated the impact of surgical resection using a debulking threshold of 90% for NETLMs.[74] Of 170 patients, 90 had SBNETs, and both patients with functional and nonfunctional (ie, asymptomatic) NETLMs were included. Surgical resection was associated with a 5-year survival rate of 61% with no significant difference in survival between patients with functional or nonfunctional tumors or the site of tumor origin. Moreover, in patients with hormonal symptoms, surgical resection was associated with an improvement or complete relief of symptoms in 96% of patients.

Several subsequent studies have shown similar improvements in hormonal symptom control and survival after surgical resection of NETLMs, with 5-year survival rates between 60% and 90%.[6,64,75] One international, multi-institutional study reported on the outcome of hepatic resection in 339 patients with NETLMs, of whom 25% had SBNETs, and 72% were nonfunctional.[6] They described 5- and 10-year survival rates of 74% and 51%, respectively. Boudreaux et al[7] studied 189 patients with small bowel NETLMs that underwent hepatic cytoreduction, where they had 5- and 10-year survival rates of 87% and 77%,

respectively. The majority of these patients (86%) had carcinoid symptoms.

In comparison to other liver metastases, the more indolent nature of NETLMs and the observation that they tend to push rather than infiltrate within the liver make surgical debulking (cytoreductive surgery) an option for patients with this disease. Numerous studies have shown that when the majority of gross disease can be removed (R1 or R2 resections) the survival advantage is comparable to cases in which all disease is removed (R0 resection).[6,64,76] For example, Glazer et al[76] reported a 5-year survival of 77% for patients who underwent resection of NETLMs, and there was no survival difference in patients having R0 versus R1or R2 resections. Similarly, Graff-Baker et al[75] found no difference in disease-specific survival or liver PFS in 52 patients with NETLM who underwent an R0 versus R2 resection, with a 5-year diseases-specific survival of 90%. The international, multi-institutional study of Mayo et al[6] also found no difference in survival between those having R0 or R1 versus R2 resections of NETLMs.

Recommendation: Numerous single-institution and multi-institutional studies have shown that hepatic resection is associated not only with an improvement in control of hormonal symptoms but also with an improvement in survival, with 5-year survival rates ranging between 60% to 90%. Moreover, many of these studies have shown that regardless of whether an R0, R1, or R2 resection was achieved, there was no difference in survival. Although the optimal R2 resection threshold remains to be defined, surgical cytoreduction of NETLMs should be attempted when anatomically feasible and can be performed with low morbidity and mortality.

5b. Are Major Hepatic Resections Necessary or Are Parenchymal-Sparing Procedures Reasonable?

Recurrence of NETLMs after surgical resection is common, if not universal, and has been reported to be 90% to 95% at 5 years.[6,74] Therefore, surgical strategies have continued to evolve to allow for optimal surgical resection or cytoreduction of all or the majority of disease, while preserving and maintaining adequate functional liver parenchyma. As a result, parenchymal-sparing procedures (PSPs) of the liver, such as enucleations, nonanatomic parenchymal resections (ie, wedge resections), and intraoperative ablation (radiofrequency or microwave ablation), have all been utilized in patients with NETLMs.

In the studies by Mayo et al[6] (n = 339 [83 SBNETs]) and Saxena et al[71] (n = 74 [32 SBNETs]) in which surgical resection of NETLM was associated with 5-year survival rates of 74% and 63%, respectively, PSPs were used in 55% and 66% of cases, respectively. Intraoperative ablation in combination with surgical resection was used in up to 50% of cases in the Saxena and colleagues' study. Maxwell et al[64] recently reported their experience using PSPs in combination with a 70% debulking threshold in patients with NETLMs (n = 108), of which 74% had SBNET primaries. In this study, 93% of patients underwent wedge resections in combination with enucleations and/or ablations. Major resection was undertaken in 7% of patients, but all were done in combination with some form of PSP. The reported 5-year survival rate was 76%, which is comparable to previously reported outcomes in series using primarily major hepatic resections, with no mortality.

Recommendation: Parenchymal-sparing procedures of the liver (enucleations, wedge resections, and intraoperative ablations) have been studied in patients with NETLMs and have been associated with acceptable survival outcomes. Most patients with NETLMs ultimately die of liver failure, and even R0 resections are associated with 95% recurrence rates. Therefore, PSPs allow for preservation of functional hepatic parenchyma and should be considered a reasonable option when evaluating patients with NETLMs for hepatic resection or debulking.

5c. Should Only Patients in Whom Greater Than 90% of Metastases Can Be Debulked Undergo Hepatic Cytoreduction?

Previously, liver debulking operations had been considered applicable only for patients in whom at least 90% of the grossly visible liver metastases could be removed and for those who had no extrahepatic disease. Operations usually involved formalmajor hepatic resections, with 5-year survival rates in excess of 60%. However, it is estimated that fewer than 20% of patients with liver metastases qualify for such operations at this 90% threshold. Recently, series with expanded eligibility criteria of using a 70% debulking threshold, allowing for extrahepatic disease, and utilizing PSPs has rendered considerably more patients eligible for liver debulking surgery, while still producing excellent survival rates.[64,66,75]

The concept of a minimum debulking threshold of 90% of grossly visible liver metastases can be traced to one of the first reports of liver debulking surgery for NETLMs by McEntee et al77 from the Mayo Clinic. They operated on 37 patients, 23 of whom had SBNETs. This was in the era prior to the availability of SSAs, and the indication for operation was symptom relief in syndromic patients. Curiously, in this article that is widely quoted as the source of the 90% debulking threshold, no debulking threshold is mentioned. Rather, the term 90%is introduced in the discussion section where the authors noted that there was little relief

of symptoms unless at least 90% of the grossly visible tumors were resected. There were no survival curves, and outcomes for individual patients were listed in text form. The authors specifically commented that they could not define factors that were predictive of survival.

The next report from the Mayo Clinic by Que et al[78] included 74 NETLM patients undergoing liver debulking, 50 of whom had SBNET primaries. The indication was still for symptom relief in syndromic patients, and the debulking threshold was set at 90%, based on McEntee and colleagues'[77] series. However, the authors commented that what was noteworthy about their study was the apparent doubling of survival compared with historical controls. In fact, their published Kaplan-Meier survival curve showed a level not very far below that of the normal population. What was also a remarkable observation was that there was no significant difference in survival rates between patients who had complete and incomplete resections, so they learned that there was no oncologic survival penalty for performing only palliative versus complete resection.

The subsequent Mayo Clinic report by Sarmiento et al74 was quite different. It included 170 patients, 90 of whom had SBNETs. This was now well into the era of SSA therapy, so patients had a nonsurgical option for control of hormonal symptoms. Accordingly, their indication for operation changed. The authors stated that "surgical debulking of hepatic disease has been shown to improve survival," and the statement "a plea for resection to increase survival" was appended to the title of the article. Other major differences compared with their previous reports were that they included asyndromic patients for the first time, who comprised 37% of the population. Also, more than 50% of the operations were incomplete resections (not R0). Therefore, the indications for operation were evolving, as there could be no reason to perform incomplete resections on asyndromic patients other than to increase survival. However, patients chosen for attempted debulking were still limited to those in whom they believed they could remove at least 90%of their disease, based on their previous experience of trying to relieve symptoms. They obtained 5-year survival rates of approximately 60%, but the most important observation of this series was that there was no significant difference in survival rates between syndromic patients and asyndromic patients. It was at this point in the history of debulking surgery for NETLMs that the 90% debulking threshold, which was originally adopted for relief of hormonal symptoms, was transferred to all patients to be used as an oncologic threshold for increasing patient survival.

However, just because a 90% debulking threshold yields excellent survival rates does not prove that it is the optimal minimum oncologic debulking threshold. To this end, several series of liver debulking surgery for NETs were subsequently published from other centers showing equally good or better 5-year survival rates, in which no specific debulking threshold is mentioned.[6,7,66,79,80] More recently, Graff-Baker et al[75] reported 52 patients with SBNETs who underwent liver debulking surgery using expanded eligibility criteria. This included patients in which greater than 70% of the liver disease was deemed resectable, allowing for extrahepatic disease, and for positive margins using PSPs such as tumor enucleation to avoid major hepatic resections and reduce blood loss.[75] Neuroendocrine tumor liver metastases are expansile, pushing the liver parenchyma aside as they grow, not invasive like other types of metastases, and therefore can be enucleated. These patients had a mean of 22 tumors (range, 1–121) resected, ranging in size from a few millimeters to 16 cm. One-third of patientswith low-grade primary tumors had at least 1 intermediate-grade metastasis. There were no significant differences in liver progression rates or survival rates based on the number of tumors resected, their size, their grade, presence of extrahepatic disease, or the percentage of tumors debulked. Median time to liver progression was 72 months, but this was age dependent. Patients younger than age 50 years had a median time to liver progression of only 39 months, compared with a time not yet reached in patients older than 50 years. The series yielded a 5-year survival rate of 90%, but this was also age dependent: patients younger than 50 years had a 5-year survival rate of 73% compared with 97% in patients older than 50 years.

The 70% oncologic liver debulking threshold was confirmed by Maxwell et al, who strongly championed a parenchyma-sparing approach.64 They published a series of 108 NETLM patients undergoing liver-directed operations, 80 of whom had SBNETs. The median percent liver replacement was 10%, median number of liver lesions treated was 6, 84% of patients had concurrent resection of primary lesions, and themedian percentage of cytoreduction on preoperative versus postoperative CT scans was 80%. Median PFS of all patients was 2.2 years, and median OS was 10.5 years. For patients with SBNETs, median OS was not reached, demonstrating good results using the PSP approach. The important point of this series is that it included patients who had a wide variety of percentage of their liver tumors debulked, ranging from less than 50% through greater than 90%.

The results clearly showed that patients who had greater than 70% debulking had significantly improved survival rates compared with patients who had less than 70% (median OS not reached vs 6.5 years for all 108 patients, respectively, P = 0.009; median PFS 3.2 vs 1.3 years, P < 0.001).

Recommendation: The guidelines for liver debulking operations in patients with metastatic SBNETs may be expanded to include patients with any number or size of metastases, intermediate grade, and extrahepatic disease, provided that a 70% debulking threshold can be achieved. Furthermore, a parenchyma-sparing approach, using techniques such as tumor enucleation and ablation, may be used wherever feasible.

5d. When Is Liver Cytoreduction Not Indicated?

Although hepatic cytoreduction of NETLMs appears to benefit patients in terms of improvement of symptoms and survival, not all patients will be eligible for debulking procedures. Certainly when the threshold for obtaining 90% cytoreduction is used, 67% to 90% of patients with NETLMs will be excluded from surgical treatment.[72] When this threshold is lowered to 70%, as many as 76% of patients with NETLMs may be eligible for cytoreduction.[64] The latter study found that liver replacement of greater than 25% by NETLMs was a negative prognostic factor, as was debulking more than 5 (and >10) lesions.

Another important factor in deciding whether to perform hepatic debulking of NETLMs is the degree of liver involvement. Many patients have a large burden of disease in the liver, and resection or ablation may place the patient at high risk of liver failure. In Frilling and colleagues'[81] study of 119 patients evaluated for debulking of NETLMs, they excluded patients with greater than 70% liver replacement from consideration for cytoreduction. In addition, a study by Chamberlain et al[72] reported that patients with greater than 75% liver involvement had a poorer prognosis and that surgical resection was rarely done. Touzios et al[82] divided 60 patients with NETLMs into groups with greater than 50% and less than 50%liver involvement and found 5-year survival rates of 8% and 67%, respectively. Patients were treated "aggressively" with resection and/or ablation with or without hepatic arterial embolization or "nonaggressively" with resection of the primary but no liver-directed treatment. Of 13 patients with greater than 50% liver replacement, 7 were treated nonaggressively. These studies do not establish a clear threshold for liver replacement where an operation is absolutely contraindicated, but greater than 50% to 70% liver replacement significantly elevates the likelihood of postoperative liver dysfunction and death with surgical intervention.

Many patients present with diffuse, bilobar metastases throughout the liver, which pose significant challenges to cytoreduction. Sometimes, these are relatively small in size but 50 to 100 in number, and it is clear that no resection is possible and that even an aggressive strategy of resection, enucleations, and ablations will lead to incomplete debulking, risk significant damage to normal hepatic parenchyma, and the potential for postoperative liver failure. Frilling et al[81] divided patients referred with NETLMs (n = 119) into 3 types: (1) single metastases (19% of their patients); (2) isolated bulky metastases with smaller bilobar lesions (15% of patients); and (3) disseminated bilobar metastases with no normal liver (66%). Their approach was to perform complete resection in type 1 patients (which they did in 23 of 23 patients), whereas those with type 2 lesions were primarily treated nonsurgically (13 of 18), with only 4 having palliative cytoreduction and 1 liver transplantation. Of those with type 3 NETLMs, 16 of 78 had liver transplantation (with 4 operative mortalities), and 57 had embolization and/or peptide receptor radionuclide therapy (PRRT). The strategy used by this group appears to be more conservative than that used by others in recent series,[64,75] but it is difficult to extrapolate these definitions of types 2 and 3 metastases to other studies. Clearly, patients with diffuse metastases (some type 2 and all type 3 patients) are the most challenging and may be better served by embolization, PRRT, systemic therapy, or liver transplantation.

The Working Group on Neuroendocrine Tumor Liver Metastases reviewed the available evidence related to multiple aspects of NETLMs and came up with recommendations for when resection should be done, but did not specifically address supplementing resection with enucleation and/or ablative techniques.[83] To be a candidate for resection of NETLMs, they specified 5 criteria: (1) World Health Organization grade 1 or 2 tumors; (2) the absence of unresectable extrahepatic disease; (3) type 1 or 2 tumors where R0 or R1 resection is possiblewith at least a 30%liver remnant; (4) the absence of advanced carcinoid heart disease; and (5) when procedures can be done in tertiary referral centers. They also suggested that grade 3 tumors were generally not resectable because of their diffuse, bilobar nature and high rate of recurrence. They concluded that quality data addressing when to perform less than complete cytoreduction were lacking in the literature and that available studies were likely affected by selection bias. As such, they did not make a recommendation.

Unquestionably, other patient-related factors need to be taken into account when considering resection or cytoreductive procedures. As mentioned, significant carcinoid heart disease is a contraindication and leads to increased right-sided pressure and increased risk of liver surgery. Cirrhosis predicts for poor postoperative liver function and preexisting liver injury, such as that resulting from previous embolization, radioembolization, or PRRT should be carefully assessed before considering surgery. As with liver surgery for any other disease process, comorbidities such as atherosclerotic cardiovascular disease, impaired pulmonary function, and poor performance status should all be considered as potential contraindications to major operative intervention. As in hepatocellular carcinoma, other factors, such as good performance status and preserved liver function (as measured by serum bilirubin within normal limits), Child-Pugh class A or Model for Endstage Liver Disease scores of less than 9, and lack of portal hypertension, are desirable in resection candidates.[84]

Another option for SBNET patients with NETLMs who might not be candidates for hepatic cytoreduction is liver transplantation. The Milan criteria and ENETS guidelines require that tumors be low grade (Ki-67 <10% per ENETS), the primary tumor has been removed, there is no extrahepatic disease (by ^{68}Ga PET/CT), stable disease has been demonstrated in the prior 6months, age is younger than 55 years, and there is less than 50% liver involvement (or <75% with refractory symptoms per ENETS).[85,86] Exclusion criteria are small cell or high-grade tumors, medical or surgical conditions including comorbidities, non-GI carcinoids, and tumor not drained by the portal system.[86] In a literature review of 706 patients undergoing hepatic transplantation of NETLMs, Fan et al[87] reported 5-year survival rates of 50% and 5-year disease-free survival rates of 30% in the 3 largest series (514 patients). Therefore, liver transplantation may be an option with good results for some patients, but the scarcity of organs and the requirement that patients generally have favorable tumor biology[86] (and thus may also be candidates for cytoreduction) have limited its use. This pattern of practice was confirmed in a study from Uppsala evaluating 33 SBNET patients with NETLMs meeting the Milan criteria where none were referred for transplant. They had excellent survival with standard multimodality treatment (5-year survival of 97%) which they felt were better than results from the literature for liver transplantation (76% 5-year survival).[88]

Recommendation: Patients with poor performance status, substantial comorbidities, or evidence of significant hepatic dysfunction should not be offered hepatic cytoreduction. Patients with grade 3 SBNET NETLMs are rare, but those who are found to have high-grade lesions on liver biopsy are at significant risk of rapid progression, are less likely to benefit from an operation, and should be referred for systemic medical therapy. Patients with significant liver replacement with tumor (such as that exceeding 50%–70%) are at high risk of having a compromised liver remnant and for postoperative liver failure, and therefore other strategies, such as embolization, PRRT, or medical therapy, are preferable. Those with diffuse liver metastases that are not amenable to a resection, enucleation, and ablation strategy that can effectively achieve at least 70% cytoreduction should also not be considered for an operation. The presence of extrahepatic disease itself is not an absolute contraindication to cytoreductive strategies64,75 but needs to be carefully considered in the decision to offer these procedures with potential for patient morbidity. Liver transplantation is controversial, but may be an option for some patients if the Milan and ENETS criteria are met.[85,86]

Prophylactic Cholecystectomy in SBNET Patients

6a. Should Cholecystectomy Be Routinely Performed in SBNET Patients During Exploration? When Is Cholecystectomy Indicated in Patients Receiving SSAs (Who Still Have Their Gallbladders)?

Gallbladder disease is commonly seen as a result of longterm SSA therapy. It is well known that SSAs decrease gallbladder function and can cause gallstones in patients on chronic therapy.[89,90] In the general population, gallstone disease occurs in 10% to 20%,[91] but the majority are asymptomatic.[92] However, the prevalence of gallstones in patients on SSAs is much higher, between 52% and 63%.[93] Up to 77% of patients with SBNETs will require treatment with SSAs; therefore, the risk of developing gallbladder pathology is significantly increased.[94] Norlén et al reviewed their cases of SBNETs in which the tumor was resected and patients received SSAs and found that 63% of evaluable patients had gallstones. They reported that 22% of patients receiving SSAs required cholecystectomy or a drainage procedure, and the 5-year cumulative risk of having cholecystectomy or drainage was 19%. In 23 patients undergoing hepatic arterial embolization procedures with gallbladders left in place, 3 developed gallbladder complications (septicemia, cholecystitis, cholangitis). They concluded that cholecystectomy should be performed in patients having resection of SBNETs who are likely to receive SSAs, especially if they have liver metastases.[94] Trendle et al[93] found that 18% of patients receiving subcutaneous SSAs eventually

had cholecystectomy performed, but did not feel that prophylactic cholecystectomy was indicated in all patients receiving SSAs, although it should be considered in conjunction with resection of the SBNET or cytoreductive operations.

The timing of when to perform cholecystectomy is highly dependent on the patient situation. The major influences are (1) the probability of requiring SSA therapy and (2) the risk associated with future laparoscopic cholecystectomy. For the minority group of patients with limited early-stage disease, tumor resection may be performed laparoscopically with a minilaparotomy to palpate the bowel, with minimal risks of major adhesions. However, if the patient requires major liver debulking or extended lymphadenectomy that may result in significant adhesions in the right upper quadrant, then future laparoscopic cholecystectomy may be compromised.

Recommendation: If there is a high likelihood that the patient will require long-term SSA therapy (such as those with liver metastases, peritoneal disease, or significant nodal involvement), prophylactic cholecystectomy should be performed at the time of the original operation. Patients receiving prolonged treatment with SSAs are at high risk of gallstone formation, and previous cytoreductive procedures may complicate future laparoscopic cholecystectomy. If a patient has already had their primary tumor removed, and cholecystectomy was not performed, then a prophylactic cholecystectomy is not recommended for those who are receiving SSAs and are asymptomatic.[85] Cholecystectomy can be delayed until a future abdominal procedure is planned (like hepatic cytoreduction), or until such time that the patient develops symptoms of biliary colic or complications from embolization.

Imaging: What Are the Optimal Imaging Modalities for Diagnosis, Staging, and Follow-up of SBNETs?

7a. What Is the Role of Cross-sectional Imaging Modalities for Localizing SBNETs and Following for Progression?

Imaging for NETs can be divided into anatomic and functional categories. The former includes examinations such as CT and MRI scans, which generally demonstrate masses and their relationships to other structures. Functional imaging tests take advantage of the fact that NETs take up radiolabeled somatostatin (or glucose) and help define that masses seen are NETs and are particularly useful in helping to define the extent of disease. In surgical series of patients presenting with NET metastases ultimately shown to have SBNETs on exploration, Keck et al[56] reported that 74 (82%) of 90 primary tumors were found by preoperative CT. It is important to emphasize that this study used not only the typical CT findings of a small bowel mass or thickening, but also the presence of mesenteric lymphadenopathy for CT localization to be considered positive for localization of SBNETs. Other similar studies found lower levels of sensitivity for CT detection of SBNET primaries, which did not include mesenteric lymphadenopathy, with rates of 35% (n = 79),[32] 7% (n = 63),[33] and 38% (n = 61).[57]

These studies used a variety of CT techniques, including the frequent use of positive oral contrast agents, which makes the small bowel contents appear white, obscuring identification of small, enhancing lesions within the bowelwall. The use of negative contrast agents, such as water, milk, or polyethylene glycol improves the ability to identify small bowel lesions.[95] Computed tomography optimized to evaluate the small bowel will utilize a negative oral contrast agent along with high-spatial-resolution, multiplanar imaging. Different options include enteroclysis, where contrast is administered through a tube placed at the junction of duodenum and jejunum under fluoroscopy,[96–98] or enterography, where the patients drinks 1.5 to 2 L over 45 to 60 minutes.[95,99] A metaanalysis of CT enteroclysis for small bowel tumors reported a pooled sensitivity of 92.8% and a pooled specificity of 99.2%.[96] Computed tomography enterography can provide comparable accuracy to CT enteroclysis and has the advantage of not requiring placement of a nasojejunal tube, but does require that large volumes be consumed orally over a short period.[100,101] Computed tomography enterography may result in suboptimal bowel distension without adequate patient compliance with oral contrast consumption. Magnetic resonance imaging optimized to evaluate the small bowel has also shown good sensitivity for the detection of Crohn disease[102] and small bowel tumors.[103] One recent series of 150 patients comparing the results of CT and MRI enterography for detecting small bowel tumors found that the sensitivity of MRI (93%) was actually higher than CT (76%; P = 0.04).[104] The choice of modality (CT vsMRI) will vary based on local practice pattern and expertise, but as long as the correct technique is utilized (multiphase with thin cuts), the results for detection of SBNETs should be good with either method.

Cross-sectional imaging for initial staging of NETs should include a CT scan of the abdomen and pelvis with multiphase imaging of the abdomen. Although ^{68}Ga-labeled DOTA–conjugated peptide PET/CT should accurately identify the primary tumor and sites of metastatic disease, initial cross-sectional imaging is useful for planning therapy (operation or liver-directed therapy) and as a baseline for follow-up imaging.

Neuroendocrine tumormetastases to the liver can have a very heterogeneous appearance, and multiphase imaging provides the best chance to detect and characterize these lesions.[105] In addition, a small proportion of NET metastases may be seen only on arterial-phase imaging, which essentially mandates multiphase imaging for accurate initial staging.[106] In cases of known SBNET, the use of enterography technique depends on the clinical scenario. Computed tomography or MRI enterography will provide the best chance of identifying all sites of small bowel tumor, but if an operation is planned, this may not be necessary because small bowel palpation to detect all tumor sites is routine practice. Computed tomography is considered the first-line imaging modality based on availability, speed, cost, and ease of use relative to MRI. However, MRI of the abdomen and pelvis is also acceptable and would be preferred in some scenarios (ie, prior adverse reaction to CT contrast, renal insufficiency, and radiation exposure) and may give more information on the tumor burden within the liver.[107] The Working Group on NETLMs suggests that MRI is the best method of imaging for NETLMs, whereas 3-dimensional CT is useful for determining the size of future liver remnant prior to resection.[83]

After resection of the primary tumor or in cases of advanced disease, earlier NANETS guidelines recommended follow-up surveillance imaging of the abdomen and pelvis with multiphase CT or MRI every 3 to 6 months, which could be extended to 6 to 12 months in those with stable disease.[107] Recent evidence suggests that an annual follow-up interval is reasonable in those having complete resection of SBNETs, then being extended to every 24 months after a few years.[108] In general, CT will be the modality of choice given its availability, speed, and lower cost relative to MRI. Computed tomography is also probably more sensitive for recurrent nodal or mesenteric disease, whereas MRI will image the liver better without ionizing radiation. Either multiphase CT or MRI is important to accurately detect all hepatic metastases and evaluate changes in enhancement, which may indicate response to therapy. For example, hepatic metastases treated with liver-directed therapy or antiangiogenic drugs may result in decreased enhancement without much change in size.[109]

Recommendation: Anatomic imaging using CT or MRI is recommended for diagnosis, staging, and follow-up of patients with SBNETs. Computed tomography scans are more readily available and less expensive, but deliver ionizing radiation, and require intravenous contrast, to which some patients have allergies and can be an issue for those with borderline renal function. Multiphase CT is very good for imaging primary tumors (which is improved further by use of negative GI contrast), the locations and extent of nodal disease, identifying peritoneal disease, and the distribution of liver metastases. Magnetic resonance imaging is excellent for imaging liver lesions and may provide improved information over multiphase CT, but this may come at the expense of reduced definition of nodal disease.

7b.What Is the Role of Nuclear Imaging for Localizing SBNETs and Following for Progression?

The previous NANETS recommendation was to perform ^{111}In-octreotide single-photon emission CT (SPECT) for nuclear imaging of SBNETs as part of the initial workup.[107] The main value of functional SSA-based imaging studies such as ^{111}Inoctreotide SPECT is to confirm that the lesions that are seen on anatomic imaging have uptake and therefore are NETs, to screen for metastatic disease throughout the body (such as the bones), and gauge the potential for response to PRRT and SSAs.[25] Some also use these scans and ^{111}In-octreotide for probe-directed exploration for challenging sites of disease.[110,111] The sensitivity of ^{111}Inoctreotide SPECT in surgical series looking for occult SBNETs in patients presenting with NETLMs was low, calling this into question, unless initial anatomic imaging is negative.[25,112] The range of ^{111}In-octreotide SPECT sensitivity for identifying SBNET primaries has been reported to be as low as 2%,[33] with other studies reporting higher rates of 22%,[54] 26%,[32] and 56%.[56] The image quality is generally poor unless coregistered with CT and may not significantly affect surgical decision making.[25]

More recently, ^{68}Ga-labeled DOTA–conjugated peptides have been developed for somatostatin receptor PET imaging. The 3 most commonly used ^{68}Ga-labeled somatostatin receptor PET imaging agents are ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, and ^{68}Ga-DOTANOC. Despite the slight variation of the somatostatin receptor affinity of these agents, all of them have shown excellent sensitivity in detection of NETs. At this time, there is no evidence of significant diagnostic superiority of one agent over the others.[113–116] ^{68}Ga-DOTATATEwas recently approved by the US Food and Drug Administration (FDA) in June 2016, whereas ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC are considered investigational. These agents provide significant advantages over ^{111}In-octreotide because of the higher resolution achieved with PET compared with SPECT and higher affinity of ^{68}Ga-DOTATATE for target somatostatin receptors (subtype 2; sstr2).[117,118] The radiation dose to the patient is significantly lower with ^{68}Ga-DOTAagents compared with ^{111}Inoctreotide, and imaging with ^{68}Ga-DOTAagents is typically completed in 90 minutes,

compared with multiple imaging sessions obtained over 24 hours with ^{111}In-octreotide.[119] A meta-analysis of 17 eligible studies with 971 patients found a high accuracy of ^{68}Ga-DOTATATE in diagnosing NETs, with a sensitivity of 90.9% (confidence interval, 81.4%–96.4%) and specificity of 90.6% (confidence interval, 77.8%–96.1%).[120] Sadowski et al[58] recently compared ^{68}Ga-DOTATATE with ^{111}In-octreotide and CT imaging in 131 patients with NETs. They found that ^{68}Ga-DOTATATE PET/CT was significantly more sensitive for detection of NET lesions, with a sensitivity of 95% compared with 31% for ^{111}Inoctreotide and 45% for CT imaging.

Initial staging of SBNETs should potentially include the use of ^{68}Ga-DOTA somatostatin receptor PET/CT imaging because numerous series have shown ^{68}Ga-DOTAagents can lead to a change in management.[58,121–124] Improved accessibility is expected now that ^{68}Ga-DOTATATE imaging is FDA approved, and thiswill become the specific agent of choice in the United States. Newgeneration PET/CT scanners also allow for simultaneous diagnostic quality multiphase liver CT imaging with intravenous contrast to improve detection of hepatic disease. This provides initial whole-body imaging with sensitivity and accuracy rivaling cross-sectional imaging, with the exception that PET/MRI with gadoxetate disodium may potentially provide higher sensitivity for hepatic metastases.125 If ^{68}Ga-DOTA PET/CT is not available, then ^{111}In-octreotide SPECT could be substituted. However, as ^{68}Ga-DOTA PET/CT becomes more widely available over the next few years, ^{111}Inoctreotide SPECT will no longer be considered standard-of-care imaging for SBNET staging. Nuclear imaging may also be useful for follow-up of NETs when cross-sectional imaging is equivocal or when there is high clinical suspicion for active disease, but cross-sectional imaging is negative. Somatostatin receptor nuclear imaging is also valuable in restaging of recurrent NETs for planning therapy and is essential to determine if the patient will qualify for PRRT.

The value of fluorodeoxyglucose (^{18}F-FDG) PET/CT for NETs appears to be in patients with higher-grade tumors (Ki-67 >15%)[126] and uptake predicts for early disease progression and poorer prognosis.[127–129] In 1 study, ^{18}F-FDG uptake was seen in 60% of well-differentiated tumors and in 100% of poorly differentiated NETs, as compared with 80% and 57% for ^{111}In-octreotide SPECT, respectively. Therefore, ^{18}F-FDG PET/CT may have value for staging, prognosis, and selecting NET patients who might benefit from medical versus surgical therapy, but the utility of these scans appears to be limited to patients with higher-grade tumors.[130]

Recommendation: Functional imaging studies such as ^{111}Inoctreotide SPECT and ^{68}Ga-DOTA PET/CT have utility in identification of NET primary tumors and their metastases. ^{111}Inoctreotide SPECT may not add much to surgical decision making, other than confirming that suspicious lesions seen on anatomic imaging are NETs, assessing the potential for PRRT, and identifying occult sites of metastatic disease. ^{68}Ga-DOTA PET/CT imaging has several advantages over ^{111}In-octreotide SPECT in terms of resolution, sensitivity, radiation exposure, and convenience and is expected to replace ^{111}In-octreotide SPECT now that ^{68}Ga-DOTATATE has been FDA approved in the United States. ^{18}F-FDG PET/CT is not useful in the routine staging of well-differentiated NETs, but may have utility in staging of higher-grade tumors.

Should Capsule Endoscopy Play a Role in the Identification of Primary SBNETs?

In the workup of patients with NETs, physicians often attempt to elucidate the primary site, allowing clinicians to optimize the management and understanding of the clinical course and disease outcome. Small bowel neuroendocrine tumors are notoriously difficult to confirm. Despite the presence of bulky metastatic disease, the primary site may be subcentimeter, multifocal, and submucosal—all features that may present challenges in localization of the small bowel primary.

Video capsule endoscopy (VCE), double-balloon enteroscopy, and colonoscopy may all be used to endoscopically localize small bowel primaries. Video capsule endoscopy is the most frequently considered as it is noninvasive and relatively easier to perform. van Tuyl and colleagues[131] assessed the utility of VCE in the evaluation of patients with NETs of unknown primary and demonstrated a sensitivity of 60% (12 of 20 patients). The limitation of this study was the lack of histological confirmation in all patients. In an English study, VCE was performed in 10 patients with metastatic NETs of unknown primary and localized the primary in 8, the majority of which were later confirmed histopathologically.[132] Although these findings presented an impressive sensitivity of 80% for VCE, this represents the experience of a small number of patients, and the total number of patients who underwent VCE in an attempt to localize primary tumors was not reported.

In 2 surgical studies assessing the performance of presurgical imaging modalities in localizing metastatic disease of unknown primary, VCE was infrequently performed, but contributed minimally to localizing the primary site (2 of 4 in Bartlett et al,[57] 0 of 2 in Massimino

et al[33]). For patients undergoing surgical resection or debulking, close inspection of the small bowel with palpation was by far the best test for localization of small bowel primaries, with a sensitivity of 75%when considering laparotomy alone and 79% to 93% when considering laparotomy with all other presurgical imaging modalities.[33,57] The strength of these studies was that all small bowel primaries were confirmed histopathologically. Limitations of capsule endoscopy include an inability to biopsy and the possibility of capsule retention. For this reason, capsule endoscopy is contraindicated in those with obstructive symptoms and in patients (particularly the elderly) with swallowing dysfunction. Other limitations of VCE include the potential nonvisualization of small submucosal tumors, incomplete detection of multifocal disease, and the possibility of false-positive results. This means that physicians need to carefully select which patients would benefit from capsule endoscopy.

Colonoscopy and double-balloon enteroscopy have other limitations related to identifying primary SBNETs. Colonoscopy with terminal ileal intubation may yield a limited view of the terminal ileum, but this is typically not sufficient to visualize enough small bowel to localize the primary site in a majority of patients. Although balloon enteroscopy allows more extensive examination of the small bowel and potentially enables histopathologic confirmation, balloon enteroscopy is a prolonged, advanced endoscopic procedure that is not widely available outside tertiary centers and is extremely operator dependent.

Recommendation: Video capsule endoscopy and double balloon enteroscopy have limited roles in the diagnosis of SBNETs, although there may be some utility in patients with unknown primary lesions where the preoperative diagnosis is essential for referral for surgical management. Because most patients with metastatic GEPNETs and undiagnosed primaries after imaging will have SBNETs, surgical exploration is a higher-yield procedure with therapeutic benefits as well.

Discussion

The incidence of SBNETs is on the rise, and surgeons will be seeing increasing numbers of these patients with these tumors in their clinical practice. The management of patients with SBNETs can be very challenging because physicians may manage only a few cases in their careers, and patients may live for a long time, despite often presenting with metastatic disease. Aggressive surgical management of SBNETs appears to be very useful in well-selected patients and may improve patient survival, but randomized clinical trials demonstrating this are lacking. Such trials will likely never be performed given the challenges of randomization in patients who are candidates for resection.

There are a variety of clinical situations in which questions frequently arise in the management of patients with SBNETs, where the answers are not clear from the literature, but physicians specializing in the care of these patients generally agree on. We assembled a group of experts in the management of patients with SBNETs, reviewed the relevant data addressing these questions, and have put forth consensus recommendations in this article. The objective of this conference was to improve the care of NET patients by increasing awareness of treatment options and providing expert recommendations based on clinical experience and careful review of the literature. Although the lack of randomized trials makes it difficult to prove the validity of these clinical recommendations, consensus or near consensus of our expert panel was reached for all of these questions. Our hope is that this article will offer guidance for physicians struggling to decide on how to deliver optimal care to their patients with SBNETs.

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REFERENCES

References

1. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26:3063–3072.
2. Howe JR, Karnell LH, Menck HR, et al. The American College of Surgeons Commission on Cancer and the American Cancer Society. Adenocarcinoma of the small bowel: review of the National Cancer Data Base, 1985–1995. *Cancer.* 1999;86:2693–2706.
3. Bilimoria KY, Bentrem DJ, Wayne JD, et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. *Ann Surg.* 2009;249:63–71.
4. Norlén O, Stålberg P, Öberg K, et al. Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. *World J Surg.* 2012;36:1419–1431.
5. Dahdaleh FS, Calva-Cerqueira D, Carr JC, et al. Comparison of clinicopathologic factors in 122 patients with resected pancreatic and ileal neuroendocrine tumors from a single institution. *Ann Surg Oncol.* 2012;19:966–972.
6. Mayo SC, de JongMC, Pulitano C, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol.* 2010;17:3129–3136.
7. Boudreaux JP, Wang YZ, Diebold AE, et al. A single institution's experience with surgical cytoreduction of stage IV, well-differentiated, small bowel neuroendocrine tumors. *J AmColl Surg.* 2014;218:837–844.
8. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas.* 2010;39:753–766.
9. Niederle B, Pape UF, Costa F, et al. ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. *Neuroendocrinology*. 2016;103:125–138.
10. Kinney MA, Warner ME, Nagorney DM, et al. Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. *Br J Anaesth.* 2001;87:447–452.
11. Massimino K, Harrskog O, Pommier S, et al. Octreotide LAR and bolus octreotide are insufficient for preventing intraoperative complications in carcinoid patients. *J Surg Oncol.* 2013;107:842–846.
12. Woltering EA, Wright AE, Stevens MA, et al. Development of effective prophylaxis against intraoperative carcinoid crisis. *J Clin Anesth.* 2016;32:189–193.
13. Condron ME, Pommier SJ, Pommier RF. Continuous infusion of octreotide combined with perioperative octreotide bolus does not prevent intraoperative carcinoid crisis. *Surgery.* 2016;159:358–365.
14. Bissonnette RT, Gibney RG, Berry BR, et al. Fatal carcinoid crisis after percutaneous fine-needle biopsy of hepatic metastasis: case report and literature review. *Radiology.* 1990;174:751–752.
15. Mehta AC, Rafanan AL, Bulkley R, et al. Coronary spasm and cardiac arrest from carcinoid crisis during laser bronchoscopy. *Chest.* 1999;115:598–600.
16. Janssen M, Salm EF, Breburda CS, et al. Carcinoid crisis during transesophageal echocardiography. *Intensive Care Med.* 2000;26:254.
17. Ozgen A, Demirkazik FB, Arat A, et al. Carcinoid crisis provoked by mammographic compression of metastatic carcinoid tumour of the breast. *Clin Radiol.* 2001;56:250–251.
18. Kharrat HA, Taubin H. Carcinoid crisis induced by external manipulation of liver metastasis. *J Clin Gastroenterol.* 2003;36:87–88.
19. Sinha V, Dyer P, Shuvro RC, et al. Case of carcinoid crisis following a fine-needle biopsy of hepatic metastasis. *Eur J Gastroenterol Hepatol.* 2009;21:101–103.
20. Morrisroe K, Sim IW, McLachlan K, et al. Carcinoid crisis induced by repeated abdominal examination. *Intern Med J.* 2012;42:342–344.
21. Jacobs RE, Bai S, Hindman N, et al. Carcinoid abdominal crisis: a case report. *J Surg Oncol.* 2014;110:348–351.
22. Magabe PC, Bloom AL. Sudden death from carcinoid crisis during image-guided biopsy of a lung mass. *J Vasc Interv Radiol.* 2014;25: 484–487.

23. Majeed F, Porter TR, Tarantolo S, et al. Carcinoid crisis and reversible right ventricular dysfunction after embolization in untreated carcinoid syndrome. *Eur J Echocardiogr.* 2007;8:386–389.
24. Moertel CG. Karnofsky memorial lecture. An odyssey in the land of small tumors. *J Clin Oncol.* 1987;5:1502–1522.
25. Dahdaleh FS, Lorenzen A, Rajput M, et al. The value of preoperative imaging in small bowel neuroendocrine tumors. *Ann Surg Oncol.* 2013;20:1912–1917.
26. Maxwell JE, Sherman SK, O'Dorisio TM, et al. Is multifocality an indicator of aggressive behavior in small bowel neuroendocrine tumors? *J Am Coll Surg.* 2015;221(Suppl 1):S60.abstract.
27. Landry CS, Lin HY, Phan A, et al. Resection of at-risk mesenteric lymph nodes is associated with improved survival in patients with small bowel neuroendocrine tumors. *World J Surg.* 2013;37:1695–1700.
28. Wang YZ, Joseph S, Lindholm E, et al. Lymphatic mapping helps to define resection margins for midgut carcinoids. *Surgery.* 2009;146:993–997.
29. Kerstrom G, Hellman P, Hessman O. Midgut carcinoid tumours: surgical treatment and prognosis. *Best Pract Res Clin Gastroenterol.* 2005;19:717–728.
30. Figueiredo MN, Maggiori L, Gaujoux S, et al. Surgery for small-bowel neuroendocrine tumors: is there any benefit of the laparoscopic approach? *Surg Endosc.* 2014;28:1720–1726.
31. Reissman P, Shmailov S, Grozinsky-Glasberg S, et al. Laparoscopic resection of primary midgut carcinoid tumors. *Surg Endosc.* 2013;27:3678–3682.
32. Wang SC, Parekh JR, Zuraek MB, et al. Identification of unknown primary tumors in patients with neuroendocrine liver metastases. *Arch Surg.* 2010;145:276–280.
33. Massimino KP, Han E, Pommier SJ, et al. Laparoscopic surgical exploration is an effective strategy for locating occult primary neuroendocrine tumors. *Am J Surg.* 2012;203:628–631.
34. Landerholm K, Zar N, Andersson RE, et al. Survival and prognostic factors in patients with small bowel carcinoid tumour. *Br J Surg.* 2011;98:1617–1624.
35. Wang YZ, Carrasquillo JP, McCord E, et al. Reappraisal of lymphatic mapping for midgut neuroendocrine patients undergoing cytoreductive surgery. *Surgery.* 2014;156:1498–1502; discussion 1502–1503.
36. Watzka FM, Fottner C, Miederer M, et al. Surgical treatment of NEN of small bowel: a retrospective analysis. *World J Surg.* 2016;40:749–758.
37. Ohrvall U, Eriksson B, Juhlin C, et al.Method for dissection of mesenteric metastases in mid-gut carcinoid tumors. *World J Surg.* 2000;24:1402–1408.
38. Strobbe L, D'Hondt E, Ramboer C, et al. Ileal carcinoid tumors and intestinal ischemia. *Hepatogastroenterology.* 1994;41:499–502.
39. Akerström G, Hellman P, Hessman O, et al. Management of midgut carcinoids. *J Surg Oncol.* 2005;89:161–169.
40. Sutton R, Doran HE, Williams EM, et al. Surgery for midgut carcinoid. Endocr Relat Cancer. 2003;10:469–481.
41. Hellman P, Lundstrom T, Ohrvall U, et al. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. *World J Surg.* 2002;26:991–997.
42. Farnell MB, Aranha GV, Nimura Y, et al. The role of extended lymphadenectomy for adenocarcinoma of the head of the pancreas: strength of the evidence. *J Gastrointest Surg*. 2008;12:651–656.
43. McCulloch P, Niita ME, Kazi H, et al. Gastrectomy with extended lymphadenectomy for primary treatment of gastric cancer. *Br J Surg.* 2005;92:5–13.
44. Smith JD, Reidy DL, Goodman KA, et al. A retrospective review of 126 high-grade neuroendocrine carcinomas of the colon and rectum. *Ann Surg Oncol.* 2014;21:2956–2962.
45. Smith J, Reidy-Lagunes D. The management of extrapulmonary poorly differentiated (high-grade) neuroendocrine carcinomas. *Semin Oncol.* 2013;40:100–108.
46. Tang LH, Untch BR, Reidy DL, et al.Well-differentiated neuroendocrine tumors with a morphologically apparent high-grade component: a pathway distinct from poorly differentiated neuroendocrine carcinomas. *Clin Cancer Res.* 2016;22:1011–1017.
47. Fazio N, Milione M. Heterogeneity of grade 3 gastroenteropancreatic neuroendocrine carcinomas: new insights and treatment implications. *Cancer Treat Rev.* 2016;50:61–67.
48. Ramirez RA, Beyer DT, Chauhan A, et al. The role of capecitabine/temozolomide in metastatic neuroendocrine tumors. *Oncologist*. 2016;21:671–675.

49. Boudreaux JP, Putty B, Frey DJ, et al. Surgical treatment of advanced-stage carcinoid tumors: lessons learned. *Ann Surg.* 2005;241: 839–845; discussion 845–846.
50. Norlén O, Edfeldt K, Akerstrom G, et al. Peritoneal carcinomatosis from small intestinal neuroendocrine tumors: clinical course and genetic profiling. *Surgery.* 2014;156:1512–1521; discussion 1521–1522.
51. Elias D, David A, Sourrouille I, et al. Neuroendocrine carcinomas: optimal surgery of peritoneal metastases (and associated intra-abdominal metastases). *Surgery.* 2014;155:5–12.
52. Glehen O, Gilly FN, Boutitie F, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer.* 2010;116: 5608–5618.
53. Kianmanesh R, Ruszniewski P, Rindi G, et al. ENETS consensus guidelines for the management of peritoneal carcinomatosis from neuroendocrine tumors. *Neuroendocrinology.* 2010;91:333–340.
54. Bartlett EK, Meise C, Roses RE, et al. Morbidity and mortality of cytoreductionwith intraperitoneal chemotherapy: outcomes from the ACS NSQIP database. *Ann Surg Oncol*. 2014;21:1494–1500.
55. Randle RW, Griffith KF, Fino NF, et al. Appendiceal goblet cell carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Surg Res*. 2015;196:229–234.
56. Keck KJ, Maxwell JE, Menda Y, et al. Identification of primary tumors in patients presenting with metastatic gastroenteropancreatic neuroendocrine tumors. *Surgery.* 2017;16:272–279.
57. Bartlett EK, Roses RE, Gupta M, et al. Surgery for metastatic neuroendocrine tumors with occult primaries. *J Surg Res.* 2013;184: 221–227.
58. Sadowski SM, Neychev V, Millo C, et al. Prospective study of ^{68}Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. *J Clin Oncol.* 2016;34:588–596.
59. Maxwell JE, Sherman SK, Stashek KM, et al. A practical method to determine the site of unknown primary in metastatic neuroendocrine tumors. *Surgery.* 2014;156:1359–1365; discussion 1365–1366.
60. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol.* 2009;27:4656–4663.
61. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl JMed.* 2014;371: 224–233.
62. Yao JC, FazioN, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet.* 2016;387:968–977.
63. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-DOTATATE for midgut neuroendocrine tumors. *N Engl J Med.* 2017;376:125–135.
64. Maxwell JE, Sherman SK, O'Dorisio TM, et al. Liver-directed surgery of neuroendocrine metastases: what is the optimal strategy? *Surgery.* 2016; 159:320–333.
65. Makridis C, Rastad J, Oberg K, et al. Progression of metastases and symptom improvement from laparotomy in midgut carcinoid tumors. *World J Surg*. 1996;20:900–906; discussion 907.
66. Chambers AJ, Pasieka JL, Dixon E, et al. The palliative benefit of aggressive surgical intervention for both hepatic and mesenteric metastases from neuroendocrine tumors. *Surgery.* 2008;144:645–651; discussion 651–653.
67. Ahmed A, Turner G, King B, et al. Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. *Endocr Relat Cancer.* 2009;16:885–894.
68. Citterio D, Pusceddu S, Facciorusso A, et al. Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver. *Eur J Surg Oncol.* 2017;43:380–387.
69. Capurso G, Rinzivillo M, Bettini R, et al. Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases. *Br J Surg.* 2012;99:1480–1486.
70. Givi B, Pommier SJ, Thompson AK, et al. Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival. *Surgery.* 2006;140:891–897; discussion 897–898.
71. Saxena A, Chua TC, Perera M, et al. Surgical resection of hepatic metastases from neuroendocrine neoplasms: a systematic review. *Surg Oncol*. 2012;21:e131–e141.

72. Chamberlain RS, Canes D, Brown KT, et al. Hepatic neuroendocrine metastases: does intervention alter outcomes? *J Am Coll Surg.* 2000;190: 432–445.
73. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer.* 2003;97:934–959.
74. Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg.* 2003;197:29–37.
75. Graff-Baker AN, Sauer DA, Pommier SJ, et al. Expanded criteria for carcinoid liver debulking: maintaining survival and increasing the number of eligible patients. *Surgery.* 2014;156:1369–1376; discussion 1376–1377.
76. Glazer ES, Tseng JF, Al-RefaieW, et al. Long-term survival after surgical management of neuroendocrine hepatic metastases. *HPB (Oxford).* 2010; 12:427–433.
77. McEntee GP, Nagorney DM, Kvols LK, et al. Cytoreductive hepatic surgery for neuroendocrine tumors. *Surgery.* 1990;108:1091–1096.
78. Que FG, Nagorney DM, Batts KP, et al. Hepatic resection for metastatic neuroendocrine carcinomas. *Am J Surg.* 1995;169:36–42; discussion 42–43.
79. Landry CS, Scoggins CR, McMasters KM, et al. Management of hepatic metastasis of gastrointestinal carcinoid tumors. *J Surg Oncol.* 2008;97: 253–258.
80. Norlén O, Stålberg P, Zedenius J, et al. Outcome after resection and radiofrequency ablation of liver metastases from small intestinal neuroendocrine tumours. *Br J Surg.* 2013;100:1505–1514.
81. Frilling A, Li J,Malamutmann E, et al. Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. *Br J Surg.* 2009;96:175–184.
82. Touzios JG, Kiely JM, Pitt SC, et al. Neuroendocrine hepatic metastases: does aggressive management improve survival? *Ann Surg.* 2005;241: 776–783; discussion 783–785.
83. Frilling A,Modlin IM, Kidd M, et al. Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol.* 2014;15: e8–e21.
84. Ribero D, Curley SA, Imamura H, et al. Selection for resection of hepatocellular carcinoma and surgical strategy: indications for resection, evaluation of liver function, portal vein embolization, and resection. *Ann Surg Oncol.* 2008;15:986–992.
85. 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;95:157–176.
86. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J Hepatol.* 2007;47:460–466.
87. Fan ST, Le Treut YP, Mazzaferro V, et al. Liver transplantation for neuroendocrine tumour liver metastases. *HPB (Oxford)*. 2015;17:23–28.
88. Norlén O,DaskalakisK,Oberg K, et al. Indication for liver transplantation in young patients with small intestinal NETs is rare? *World J Surg.* 2014; 38:742–747.
89. Ahrendt SA, McGuire GE, Pitt HA, et al. Why does somatostatin cause gallstones? *Am J Surg.* 1991;161:177–182; discussion 182–183.
90. Ewins DL, Javaid A, Coskeran PB, et al. Assessment of gall bladder dynamics, cholecystokinin release and the development of gallstones during octreotide therapy for acromegaly. *Q JMed*. 1992;83:295–306.
91. Shaffer EA. Gallstone disease: epidemiology of gallbladder stone disease. *Best Pract Res Clin Gastroenterol.* 2006;20:981–996.
92. Sakorafas GH, Milingos D, Peros G. Asymptomatic cholelithiasis: is cholecystectomy really needed? A critical reappraisal 15 years after the introduction of laparoscopic cholecystectomy. *Dig Dis Sci*. 2007;52: 1313–1325.
93. Trendle MC, Moertel CG, Kvols LK. Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. *Cancer.* 1997;79:830–834.
94. Norlén O, Hessman O, Stålberg P, et al. Prophylactic cholecystectomy in midgut carcinoid patients. *World J Surg.* 2010;34:1361–1367.
95. Ilangovan R, Burling D, George A, et al. CTenterography: review of technique and practical tips. *Br J Radiol.* 2012;85:876–886.
96. Soyer P, Aout M, Hoeffel C, et al. Helical CT-enteroclysis in the detection of small-bowel tumours: a meta-analysis. *Eur Radiol.* 2013;23:388–399.

97. Soyer P, Dohan A, Eveno C, et al. Carcinoid tumors of the small-bowel: evaluation with 64-section CT-enteroclysis. *Eur J Radiol.* 2013;82: 943–950.
98. Kamaoui I, De-Luca V, Ficarelli S, et al. Value of CTenteroclysis in suspected small-bowel carcinoid tumors. *AJR Am J Roentgenol*. 2010; 194:629–633.
99. Baker ME, Hara AK, Platt JF, et al. CTenterography for Crohn's disease: optimal technique and imaging issues. *Abdom Imaging.* 2015;40: 938–952.
100. Minordi LM, Vecchioli A, Mirk P, et al. CTenterography with polyethylene glycol solution vs CTenteroclysis in small bowel disease. *Br J Radiol.* 2011;84:112–119.
101. Paparo F, Garlaschi A, Biscaldi E, et al. Computed tomography of the bowel: a prospective comparison study between four techniques. *Eur J Radiol.* 2013;82:e1–e10.
102. Grand DJ, Guglielmo FF, Al-Hawary MM. MR enterography in Crohn's disease: current consensus on optimal imaging technique and future advances from the SAR Crohn's disease-focused panel. *Abdom Imaging.* 2015;40:953–964.
103. Amzallag-Bellenger E, Soyer P, Barbe C, et al. Prospective evaluation of magnetic resonance enterography for the detection of mesenteric small bowel tumours. *Eur Radiol.* 2013;23:1901–1910.
104. Masselli G, Di Tola M, Casciani E, et al. Diagnosis of small-bowel diseases: prospective comparison of multi-detector row CT enterography with MR enterography. *Radiology.* 2016;279:420–431.
105. Milin S, Brunaud L, Orry X, et al. Prevalence of hepatic lesion types defined by T2-weighted and dynamic gadolinium-enhancedMR imaging in patients with metastasized neuroendocrine tumors. *Abdom Radiol (NY)*. 2016;41:2132–2141.
106. Dromain C, de Baere T, Baudin E, et al. MR imaging of hepatic metastases caused by neuroendocrine tumors: comparing four techniques. *Am J Roentgenol.* 2003;180:121–128.
107. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas.* 2013;42:557–577.
108. Singh S, Chan DL, Moody L, et al. Development of follow up recommendations for completely resected gastroenteropancreatic neuroendocrine tumours (GEP-NETS): practice survey of Commonwealth Neuroendocrine Tumour Collaboration (CommNETS) in conjunction with North American Neuroendocrine Tumour Society (NANETS). *J Clin Oncol.* 2017; (Suppl 4S):abstract 224.
109. Kim KW, Krajewski KM, NishinoM, et al. Update on the management of gastroenteropancreatic neuroendocrine tumors with emphasis on the role of imaging. *Am J Roentgenol.* 2013;201:811–824.
110. Wang YZ, Diebold A, Woltering E, et al. Radioguided exploration facilitates surgical cytoreduction of neuroendocrine tumors. *J Gastrointest Surg.* 2012;16:635–640.
111. Wang YZ,Mayhall G, Anthony LB, et al. Cervical and upper mediastinal lymph node metastasis from gastrointestinal and pancreatic neuroendocrine tumors: true incidence and management. *J Am Coll Surg.* 2012;214:1017–1022.
112. Maxwell JE, O'Dorisio TM, Howe JR. Biochemical diagnosis and preoperative imaging of gastroenteropancreatic neuroendocrine tumors. *Surg Oncol Clin N Am.* 2016;25:171–194.
113. Poeppel TD, Binse I, Petersenn S, et al. ^{68}Ga-DOTATOC versus ^{68}Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. *J NuclMed.* 2011;52:1864–1870.
114. Kabasakal L, Demirci E, Ocak M, et al. Comparison of ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC PET/CT imaging in the same patient group with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2012;39: 1271–1277.
115. Treglia G, Castaldi P, Rindi G, et al. Diagnostic performance of gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. *Endocrine.* 2012;42:80–87.
116. Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging*. 2013;40:1770–1780.
117. Reubi JC, Schar JC, Waser B, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. *Eur J NuclMed.* 2000; 27:273–282.
118. Antunes P, Ginj M, Zhang H, et al. Are radiogallium-labelled DOTA–conjugated somatostatin analogues superior to those labelled with other radiometals? *Eur J Nucl Med Mol Imaging.* 2007;34: 982–993.
119. Walker RC, Smith GT, Liu E, et al. Measured human dosimetry of ^{68}Ga-DOTATATE. *J NuclMed.* 2013;54:855–860.
120. Deppen SA, Blume J, Bobbey AJ, et al. ^{68}Ga-DOTATATE compared with ^{111}In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. *J NuclMed.* 2016;57:872–878.

121. Ilhan H, Fendler WP, Cyran CC, et al. Impact of (68)Ga-DOTATATE PET/CT on the surgical management of primary neuroendocrine tumors of the pancreas or ileum. *Ann Surg Oncol.* 2015;22: 164–171.
122. Deppen SA, Liu E, Blume JD, et al. Safety and efficacy of ^{68}Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. *J NuclMed.* 2016;57:708–714.
123. Pruthi A, Pankaj P, Verma R, et al. Ga-68 DOTANOC PET/CTimaging in detection of primary site in patients with metastatic neuroendocrine tumours of unknown origin and its impact on clinical decision making: experience from a tertiary care centre in India. *J Gastrointest Oncol.* 2016;7:449–461.
124. Skoura E, Michopoulou S, Mohmaduvesh M, et al. The impact of ^{68}Ga-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;57:34–40.
125. Hope TA, Pampaloni MH, Nakakura E, et al. Simultaneous (68)Ga-DOTA-TOC PET/MRI with gadoxetate disodium in patients with neuroendocrine tumor. *Abdom Imaging.* 2015;40:1432–1440.
126. Binderup T, Knigge U, Loft A, et al. Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. *J Nucl Med.* 2010;51:704–712.
127. Garin E, Le Jeune F, Devillers A, et al. Predictive value of 18F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. *J NuclMed.* 2009;50:858–864.
128. Binderup T, Knigge U, Loft A, et al. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res.* 2010;16:978–985.
129. SquiresMH, Adsay NV, SchusterDM, et al. Octreoscan versus FDG-PET for neuroendocrine tumor staging: a biological approach. *Ann SurgOncol.* 2015;22:2295–2301.
130. Howe JR. The supporting role of (18)FDG-PET in patients with neuroendocrine tumors. *Ann Surg Oncol.* 2015;22:2107–2109.
131. van Tuyl SA, van Noorden JT, Timmer R, et al. Detection of small-bowel neuroendocrine tumors by video capsule endoscopy. *Gastrointest Endosc.* 2006;64:66–72.
132. Frilling A, Smith G, Clift AK, et al. Capsule endoscopy to detect primary tumour site in metastatic neuroendocrine tumours. *Dig Liver Dis.* 2014;46:1038–1042.

NANETS
NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors

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Abstract

There have been significant developments in diagnostic and therapeutic options for patients with neuroendocrine tumors (NETs). Key phase 3 studies include the CLARINET trial, which evaluated lanreotide in patients with nonfunctioning enteropancreatic NETs; the RADIANT-2 and RADIANT-4 studies, which evaluated everolimus in functioning and nonfunctioning NETs of the gastrointestinal tract and lungs; the TELESTAR study, which evaluated telotristat ethyl in patientswith refractory carcinoid syndrome; and the NETTER-1 trial, which evaluated ^{177}Lu-DOTATATE in NETs of the small intestine and proximal colon (midgut). Based on these and other advances, the North American Neuroendocrine Tumor Society convened a multidisciplinary panel of experts with the goal of updating consensus-based guidelines for evaluation and treatment of midgut NETs. The medical aspects of these guidelines (focusing on systemic treatment, nonsurgical liver-directed therapy, and postoperative surveillance) are summarized in this article. Surgical guidelines are described in a companion article.

Key Words

NANETS, medical management, neuroendocrine tumor, midgut NETs

During the past several years, we have witnessed significant advances in diagnostic and therapeutic options for patients with advanced neuroendocrine tumors (NETs). Two studies established the role of somatostatin analogs (SSAs) as antiproliferative agents in patients with well-differentiated NETs. In the early-line treatment setting, the phase 3 PROMID study randomized patients with metastatic midgut NETs to receive octreotide long-acting repeatable (LAR) 30 mg versus placebo. Time to progression was significantly improved with treatment.[1] The phase 3 CLARINET study compared lanreotide to placebo in a more heterogeneous population of patients with gastroenteropancreatic NETs, also demonstrating a clinically and statistically significant improvement in progression-free survival (PFS).[2]

Other recent phase 3 studies have investigated new drugs in patients with progressive disease. In the RADIANT-4 study, everolimus was compared with placebo in nonfunctional NETs of the gastrointestinal tract and lung, demonstrating a significant improvement in PFS.[3] More recently, patients with progressive midgut NETs were randomized to receive the radiolabeled SSA ^{177}Lu-DOTATATE (investigational arm) or high-dose octreotide LAR at 60mgmonthly (control arm) in the NETTER-1 trial.[4] Asubstantial improvement in PFSwas documented with the investigational agent. For symptom control, the phase 3 TELESTAR study compared 2 doses of an oral serotonin synthesis inhibitor, telotristat ethyl, to placebo in carcinoid syndrome patients with refractory diarrhea. Telotristat ethyl treatment was associated with a significant reduction in daily bowel movements corresponding to decline in urine 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin.[5]

Although these agents were tested in various populations of NETs, all have had an important and specific impact on the management of midgut NETs, defined as NETs originating in the jejunum, ileum, and proximal colon. Midgut NETs are typically slow-growing tumors and are often associated with the carcinoid syndromewhenmetastatic. Until recently, they were characterized by resistance to systemic treatments other than SSAs and interferon-α (IFN-α). The introduction of new treatment options for tumor and symptom control offers the potential to improve patient outcomes and quality of life, but also raises many questions. How should new treatments be integrated into the therapeutic algorithm? How should they be sequenced? Do they have activity in settings beyond their labeled indications? To address these and other aspects of the management of midgut NETs, a panel of experts was convened by the North American Neuroendocrine Tumor Society, with the goal of developing updated consensus-based guidelines for the treatment of midgut NETs. During this meeting, issues regarding surgical and medical treatment of midgut NETs were discussed separately.

Materials and methods

The Medical Management of Midgut NETs panel consisted of 15 participants, including 7 medical oncologists, 3 endocrinologists, 2 pathologists, an interventional radiologist, a cardiologist, and a cardiac surgeon, all with expertise in various aspects of midgut NET management. Institutions represented on the panel included Stanford University, the University of California San Francisco, MD Anderson Cancer Center, Mayo Clinic, Memorial Sloan Kettering Cancer Center, Moffitt Cancer Center, the University of Iowa, the University of California Los Angeles, Sunnybrook Research Institute (Toronto, Canada), St

Vincent's Hospital (Sydney, Australia), the University of Pennsylvania, Mount Sinai Hospital, and the Dana-Farber Cancer Institute.

Participants in the medical panel debated various topics through a series of short presentations. Presentations were limited to 5 to 10 minutes and included key literature references, with an emphasis on recent advances in the diagnosis and management of patients with NETs. Topics included postoperative surveillance, management of patients with asymptomatic disease, appropriate use of SSAs, appropriate use of novel treatments including everolimus, ^{177}Lu-DOTATATE and telotristat ethyl, the role of liver directed embolization therapies, and the management of carcinoid syndrome, including carcinoid heart disease (CaHD). Discussions took place after associated presentations. Subsequently, participants voted on multiple-choice questions designed to address areas of controversy using an electronic audience response system (ARS). Although questions were occasionally rephrased for clarity, there was no attempt to alter questions for the purpose of generating a consensus. Following separate medical and surgical panel meetings, all participants in the guidelines committee met in a joint session to summarize discussions and review ARS polling results.

Guidelines were categorized into a series of topics based on the outcomes of the discussions and ARS polling results. For these guidelines, we defined "consensus" as no more than 1 oppositional vote and "significant majority" as 75% agreement or greater. We identified many areas with lack of consensus, which suggests potential opportunities for clinical research. This article summarizes the medical guidelines pertaining to management of advanced, unresectable, midgut NETs and postoperative surveillance of stages I–III NETs. Operative guidelines pertaining to surgical management of local, locoregional, and advanced NETs are reported in a separate manuscript.

Results

The following topics concerning medical management and surveillance of midgut NETs were discussed:

Surveillance After Resection of Stages I–III Midgut NET: Duration and Frequency of Visits

Patients with localized or locally advanced midgut NETs typically undergo surgical resection consisting either of right hemicolectomy or partial small bowel resection. The majority of resected tumors involve locoregional lymph nodes (stage III). The results of studies assessing outcomes in several databases suggest that long-term recurrence rates are approximately 50%.[6,7] Because of the slow-growing nature of most midgut NETs, metastatic recurrences can occur many years after surgical resection; prospective studies evaluating surveillance strategies have not been performed. There was consensus among panel members that surveillance should continue beyond 5 years. However, there was lack of consensus over whether surveillance should continue beyond 10 years. We therefore recommend that duration of surveillance be approximately 10 years, with the option of continuing surveillance beyond that interval, especially among younger patients or those considered to be at particularly high risk of recurrence (eg, numerous involved lymph nodes).

Frequent surveillance visits are generally not required. A significant majority of the expert panel members recommended initiating radiographic surveillance at 6-month intervals and transitioning to less frequent intervals (eg, annual surveillance) after 1 year in the absence of recurrence. There was no consensus on whether proliferative activity of the tumor would impact surveillance recommendations. There are limited data on recurrence risk of stage I tumors, but a significant majority of participants stated that they would perform surveillance even on patients with very early-stage tumors.

In summary, long-term (approximately 10 years) but infrequent (annual) radiographic surveillance is appropriate for most patients with completely resected stages I–III midgut NETs.

Surveillance After Resection of Stages I–III Midgut NET: Imaging Studies and Tumor Markers

Midgut NETs typically metastasize to the liver. Other common sites of metastases include mesenteric and retroperitoneal lymph nodes, peritoneum, and bone. Cross-sectional imaging studies (multiphasic computed tomography scans or magnetic resonance imaging scans focusing on the abdomen/pelvis) are recommended for routine surveillance of patients with resected midgut NETs. A consensus was achieved that somatostatin-receptor nuclear imaging (eg,OctreoScan or ^{68}Ga-DOTATATE scan [Netspot]) should be performed as a baseline preoperative test, but that further somatostatin-receptor imaging is not indicated for routine surveillance unless needed to evaluate symptoms or abnormalities on conventional scans.[8]

Tumor markers including chromogranin A (CgA), pancreastatin, and neuron-specific enolase, among others, can be obtained as part of a surveillance regimen; however, their value in early detection of recurrence is

unknown. Chromogranin A is a protein associated with secretory endocrine vesicles and correlates with tumor burden. Elevated CgA levels may be observed months to years before radiographic evidence of recurrence is seen, but the low sensitivity and specificity of CgA limit its use in surveillance. Pancreastatin is a breakdown product of CgA, which may be characterized by improved specificity, particularly among patients using proton pump inhibitors. Neuron-specific enolase is characterized by relatively low sensitivity, particularly in well-differentiated tumors. There was lack of consensus regarding the appropriateness of measuring these tumor markers among patients undergoing radiographic surveillance. Roughly half of panel members indicated that high false-positive and false-negative rates limit their utility.

Management of Patients With Incidentally Detected, Asymptomatic Low-Volume Metastatic Tumors

Increasingly, patients are diagnosed incidentally as having metastatic NETs as they undergo scans and endoscopic evaluations for unrelated conditions. There is significant disagreement among experts over initial management of asymptomatic patients with low-volume, surgically unresectable disease: whether to initiate SSA therapy or to monitor closely until evidence of progression. Two phase 3 studies compared SSAs versus placebo in patients with relatively low-volume, indolent metastatic disease. The PROMID study compared octreotide LAR versus placebo in patients with midgut NETs and absent or mild carcinoid syndrome, whereas the CLARINET study compared depot-lanreotide with placebo in a population of nonfunctional gastroenteropancreatic NETs with predominantly stable disease at baseline.[1,2] Both studies demonstrated conclusively that SSAs can inhibit tumor growth and delay time to progression. However, neither study showed any evidence of prolongation in overall survival with treatment, likely owing to crossover to the active drug at the time of progression. In the CLARINET study, median PFS on the placebo arm was 18 months, raising multiple questions. Does early versus late use of SSAs in asymptomatic patients impact survival? Should asymptomatic patients be monitored without treatment until progression?

When we presented a clinical vignette describing a newly diagnosed asymptomatic midgut NET patient with low-volume disease, there was no consensus among the expert panel on whether to treat with SSAs or observe the patient, with roughly half respondents selecting “SSA treatment” and half selecting “observation.” We therefore conclude that either observation or initiation of SSA therapy is acceptable in an asymptomatic patient with low-volume disease. In patients in whom observation is selected, a strategy of close observation (eg, scans roughly every 3–4months initially) should be adopted. Patients with stable disease can subsequently be monitored less frequently (eg, every 6 months). The role of tumor markers in patients with asymptomatic low-volume disease remains unknown.

Pathological Diagnosis of Metastatic Disease: Minimal Requirements and Optional Tests

The pathological diagnosis of metastatic NET is often obtained via needle biopsy and aided by use of immunostaining for synaptophysin and chromogranin. Evaluation of tumor differentiation and grade is critically important for predictive and prognostic purposes. Tumor grade is measured using mitotic rate and/ or Ki-67 proliferative index.[9] There was consensus that both differentiation and grade should be reported. A significant majority of the expert panel indicated that both mitotic rate and Ki-67 index should be measured. Although surgical specimens or core needle biopsies are optimal for accurate assessment of differentiation and grade, a consensus was achieved that fine-needle aspiration can provide adequate information in most cases.

In metastatic NETs where the primary site is uncertain, positive immunostains for CDX2 can point to a midgut primary and should be performed, along with other stains such as TTF1 (suggests lung primary) and ISL-1 (islet-1), which is suggestive of pancreatic primary.

First-Line Management of Symptomatic Patients With Tumor-Related Symptoms or Carcinoid Syndrome

Somatostatin analogs (octreotide LAR and lanreotide) are appropriate initial therapy in most patients with unresectable metastatic midgut NETs for control of carcinoid syndrome and inhibition of tumor growth. The antiproliferative effects of SSAs were established in the PROMID and CLARINET trials, and their antisecretory effects have been described in numerous single-arm studies, retrospective series, and a randomized study.[1,2,10–14] In general, SSAs are associated with major improvements in flushing and diarrhea in roughly 75% of patients with carcinoid syndrome. Because of their relatively benign side effect profile, SSAs are typically selected as first-line systemic therapy.

Selection of Octreotide LAR Versus Lanreotide

Currently, 2 long-acting SSAs are commercially available: octreotide LAR and lanreotide. Octreotide LAR is administered every 4 weeks as an intramuscular injection, whereas lanreotide is administered in the same schedule as a deep subcutaneous injection. Both drugs have similar somatostatin receptor subtype– binding

profiles, with particular affinity for somatostatin receptor subtype 2. Both have shown evidence of antisecretory and antiproliferative effects in clinical trials. Indeed, the hazard ratio for time to progression on the PROMID study (0.35) was similar to the hazard ratio for PFS in the CLARINET study midgut NET subgroup.[1,2] However, in the United States, octreotide is approved by the Food and Drug Administration (FDA) for palliation of carcinoid syndrome, whereas lanreotide is approved for control of tumor growth. When asked whether the 2 drugs can be used interchangeably or whether they should be prescribed according to label (octreotide for control of syndrome and lanreotide for control of tumor growth), roughly half of the experts selected the former, and half selected the latter. We therefore conclude that no definitive statements can be made regarding selection between octreotide LAR and lanreotide in patients with midgut NETs regardless of the presence of carcinoid syndrome.

Management of Patients With Negative Somatostatin-Receptor Imaging

The large majority of midgut NETs express high levels of somatostatin receptors that are targeted by SSAs and can be visualized by somatostatin-receptor imaging. Traditionally, somatostatinreceptor scintigraphy (OctreoScan) has been used to assess somatostatin-receptor expression. More recently, a variety of novel radiopeptides for positron emission photography (PET) imaging of the somatostatin receptor have been developed (eg, ^{68}Ga-DOTA-Tyr^{3}-octreotide, ^{68}Ga-DOTATOC and ^{68}Ga-DOTATyr^{3}- octreotate, ^{68}Ga-DOTATATE).[15] These radiopeptides vary in their affinity for the different somatostatin receptor subtypes 1 to 5, but the resultant PET imaging has been shown to have higher sensitivity for NETs, particularly for imaging small lesions. [8,15] Historically available in the United States only as a research tool, the ^{68}Ga-DOTATATE PET scan recently received FDA approval. As such, use of somatostatin-receptor PET imaging is becoming routine in the clinical setting and should be considered instead of traditional somatostatin-receptor scintigraphy and/or when a patient with advanced disease has a negative OctreoScan.When asked whether SSAs should be used in patients with carcinoid syndrome who lack evidence of somatostatinreceptor expression based on somatostatin imaging, there was a consensus that SSAs should be tried regardless of somatostatin receptor imaging results.

Treatment After Radiographic Progression on First-Line SSA

There are several new and emerging systemic treatment options for patients with midgut NETs progressing radiographically on SSA therapy. Everolimus was recently approved by the FDA for treatment of nonfunctional NETs based on the RADIANT-4 study, a randomized, placebo-controlled study of patients with progressive, nonfunctional NETs of the gastrointestinal tract and lung.[3] Median PFS improved from 3.9 to 11 months ($P < 0.00001$). An earlier study, the RADIANT-2 trial, randomized patients with progressive NETs and a history of carcinoid syndrome to receive everolimus plus octreotide LAR versus placebo plus octreotide LAR.[16] This study, in which a majority of patients had NETs of midgut origin, fell narrowly short of statistical significance for its primary end point of PFS improvement.

In the NETTER-1 trial, patients with progressive midgut NETs were randomized to receive ^{177}Lu-DOTATATE versus high dose octreotide (60 mg every 4 weeks).[4] ^{177}Lu-DOTATATE is a radiolabeled SSA, a form of treatment also known as peptide receptor radiotherapy (PRRT). The primary end point was PFS by central, blinded radiology review. In this study, median PFS was 8 months on the high-dose octreotide arm and was not yet reached on the ^{177}Lu-DOTATATE arm, translating to a 79% improvement in PFS ($P < 0.00001$).

Other treatment options that have been traditionally available for progressive midgut NETs include IFN-α (typically in combination with SSA) and hepatic arterial embolization for patients with liver-dominant disease. Interferon-α has been studied in multiple single-armstudies and several randomized but underpowered clinical studies.[17–19] It has not been approved by the FDA for this indication, but may have cytostatic activity. Hepatic arterial embolization therapies have been predominantly studied in retrospective institutional series. Several strategies are routinely used in clinical practice, including bland embolization, chemoembolization, and selective internal radiation therapy. Treatment is associated with tumor shrinkage and a reduction in hormone-mediated symptoms in more than 50% of patients; however, there are no randomized data regarding the superiority of one modality over another.[20–22]

When asked about appropriate choice of second-line treatment in patients with somatostatin receptor–positive midgut NETs, a significant majority of the expert panel selected ^{177}Lu-DOTATATE as the most appropriate option based on the results of the NETTER-1 study. It was noted that the evidence of everolimus efficacy appears stronger in nonmidgut NETs (which represented the majority of patients on the RADIANT-4 study) compared with midgut NETs (which represented the majority of patients on the RADIANT-2 study). Interferon-α was not selected as an option by any members of the panel based on the relatively weak level of evidence supporting its use and

its side effect profile, which includes significant fatigue. While liver embolization therapies appear to result in high radiographic response rates, most experts indicated that there was insufficient high-quality evidence to favor embolization as a second-line option for patients with progressive midgut NETs. Most panelists supported its use as a later line of treatment for patients with liver-dominant disease. There was debate about the role of liver-directed therapy in patients with a high burden of liver disease (in part because of the relatively low response rate associated with ^{177}Lu-DOTATATE therapy).[4] There was a consensus that randomized prospective clinical trials of liver embolization are needed to test the benefit of embolization in patients with progressive midgut NETs. The risks associated with sequence of therapy also warrant further investigation (ie, PRRT then liver-directed therapy vs liver-directed therapy then PRRT). For patients with liver-predominant disease and suboptimal control of carcinoid syndrome, liver embolization was considered an appropriate second-line treatment option (see "Should Liver Embolization Be Considered as an Early Line of Treatment for Patients With Suboptimal Control of Carcinoid Syndrome?) based on high rates of symptomatic response associated with this therapy.

Management of Patients With Progressive Midgut NET and Negative Somatostatin-Receptor Imaging

In patients who are not candidates for radiolabeled SSAs (because of weak or absent somatostatin-receptor expression) and have liver-dominant metastases, an equal number of panelists chose everolimus versus liver embolization as treatment options. In patients with extensive extrahepatic metastases and weak/absent somatostatin-receptor expression, everolimus is the appropriate choice of therapy.

Does Tumor Functionality (History of Carcinoid Syndrome) Influence Selection of Everolimus as a Treatment Option?

The labeled indication for everolimus is for treatment of progressive nonfunctional NETs, based on eligibility criteria for the RADIANT-4 study.[23] A large number of metastatic midgut NETs (>50% in some studies) secrete serotonin and are associated with the carcinoid syndrome.[24] A trend toward improved PFS with everolimus was demonstrated in the patients with carcinoid syndrome in the RADIANT-2 study; however, the result did not meet the prespecified threshold for statistical significance.[16] When asked whether tumor functionality influences choice of everolimus, half of the respondents indicated that they were less likely to recommend everolimus in a functional tumor, and half indicated that tumor functionality had no impact on their choice. No panelist stated that they would refrain from use of everolimus in functional NETs. Therefore, we recommend that everolimus should be considered an option for patients with progressive midgut NETs, even if there is a history of carcinoid syndrome.

Role of Interferon-α

Several small randomized clinical trials have investigated use of IFN-α in patients with progressive carcinoid tumors.[17–19] More recently, a randomized phase 3 clinical trial of bevacizumab versus IFN-α showed no evidence of improved PFS with either arm of the study; however, the bevacizumab arm was associated with a higher response rate, longer time on treatment, and fewer clinically significant toxicities.[25] When asked about their use of IFN-α, a significant majority of panelists indicated that they never use IFN-α, and the remainder stated that they rarely prescribe the drug. We therefore conclude that in the current treatment landscape IFN-α should generally be considered only if no other option is available for the patient.

Choice of Embolization Therapy

Current transarterial embolic options can be broadly classified into 3 types: bland embolization, chemoembolization, and radioembolization (also known as selective intrahepatic radiotherapy).[22] All 3 have been primarily evaluated in institutional series rather than prospective clinical trials. There is currently no standard-of-care embolization modality, and choice of therapy is often based on institutional preferences. There have been no completed randomized clinical trials comparing embolization modalities. One prospective trial comparing bland to chemoembolization in midgut NETs was terminated early because of poor accrual.[26] On analysis of 26 patients enrolled, there was no evidence of improvement in PFS with bland versus chemoembolization, nor were there any significant differences in toxicities, although the results were underpowered because of underenrollment.

Although radioembolization is generally associated with fewer short-term toxicities than bland or chemoembolization, there has been increased recognition that some patients may develop chronic radioembolization-induced liver disease that mimics cirrhosis in its radiographic appearance and results in hyperbilirubinemia and portal hypertension.[27,28] After discussion of risks/benefits associated with different embolization modalities, the panel members were unable to reach consensus on a preferred type of embolization. We therefore conclude that any of the embolizationmodalities can be considered appropriate and that patients should be informed of the risks and benefits of each approach. There was consensus that prospective randomized clinical trials

with long-term follow-up, such as the ongoing Randomized Embolization Trial in Neuroendocrine Tumors (RETNET, ClinicalTrials.gov NCT02724540), are needed to compare embolization modalities for evidence of both benefit and toxicity.

Does Potential Availability of PRRT Affect Use of Radioembolization?

There are few data indicating whether the addition of systemic radiotherapy (via PRRT) to patients who have undergone intrahepatic radiation (through radioembolization) increases the risk of radiation-induced liver damage. However, based on this theoretical concern, there was consensus among panel members that availability of PRRTwould reduce their propensity to recommend radioembolization treatments. There was consensus that the question of cumulative liver radiation needs to be studied more closely. The lack of data regarding optimal sequence and longterm toxicity for current treatment options (eg, liver-directed therapy of all types and ^{177}Lu-DOTATATE) presents a significant challenge. As outcomes improve in this patient population, the significance of long-term toxicities could become more profound.[28]

Should Liver Embolization Be Considered as an Early Line of Treatment for Patients With Suboptimal Control of Carcinoid Syndrome?

In most series, hepatic arterial embolization treatments are associated with high rates of symptom improvement, particularly in patients with hormonal syndromes.[22] When presented with a clinical vignette of a patient with inoperable liver metastases and suboptimal control of carcinoid syndrome on SSA therapy, there was consensus that liver embolization was an appropriate palliative treatment modality. However, some panel members indicated that systemic treatment options such as everolimus or PRRT could also be added to SSAs to achieve improved symptom control. Higher-quality data are needed to compare symptom control using various treatment modalities.

Should SSAs Be Continued Beyond Progression?

In patients with carcinoid syndrome, SSAs are generally continued across multiple lines of therapy to palliate symptoms. However, in patients with nonfunctioning tumors, it is unclear whether SSAs should be continued across lines of treatment. When presented with a clinical vignette describing a nonfunctional midgut NET with slow progression of disease on SSA treatment (10% growth over 1 year), roughly half the panelists recommended continuation of SSA together with next line of therapy versus discontinuation of the drug. When presented with a similar scenario but rapid disease progression, a significant majority advocated stopping SSA treatment. Our findings suggest a need for a clinical trial to address the question of continuation of SSA treatment beyond progression.

Can Liver Embolization Therapies Be Repeated in Patients Who Have Progressed After Earlier Embolizations?

There was consensus agreement that embolizations can be repeated among patients who responded to prior hepatic arterial embolizations. However, there was also agreement that multiple liver-directed therapies can eventually result in cumulative liver toxicity. Furthermore, the risks and benefits of repeat embolizations must be considered carefully in the context of other approved and emerging therapies for midgut NETs (eg, PRRT).

Management of Refractory Carcinoid Syndrome and Role of Telotristat Ethyl

Carcinoid syndrome frequently develops in patients with metastatic midgut NETs. Serotonin is the primary hormone associated with carcinoid syndrome, and particularly with diarrhea, whereas flushing appears to be multifactorial. Somatostatin analogs are highly effective at palliating the carcinoid syndrome; however, many patients have suboptimal control or become somewhat refractory to SSAs over time.[29,30] Strategies for management of refractory carcinoid syndrome have included increasing dose or frequency of SSAs, addition of short acting octreotide for breakthrough symptoms, and initiation of antidiarrheal therapies with loperamide, diphenoxylate-atropine, or other nonspecific medications.[31] It is also important to rule out competing causes of diarrhea such as pancreatic insufficiency from SSA use, short gut syndrome, or biliary salt malabsorption related to intestinal surgery. Pancreatic enzymes can be prescribed empirically if fat malabsorption is suspected. Bile acid sequestrants (such as cholestyramine and colestipol) are recommended to treat bile acid malabsorption.

Recently, the oral serotonin inhibitor telotristat ethyl has been developed for management of refractory diarrhea in the setting of carcinoid syndrome.[32] Telotristat inhibits the enzyme tryptophan hydroxylase, which mediates the rate-limiting step in the serotonin biosynthesis. With minimal activity in the central nervous system, it appears to have little effect on the role of serotonin as a neurotransmitter.

Telotristat was studied in the phase 3, placebo-controlled TELESTAR trial at 2 doses, 250 and 500 mg, 3 times daily.[5] Eligible patients had carcinoid syndrome and at least 4 bowel movements per day. The primary end point of the study was reduction in the number of daily bowel movements, averaged over a 12-week period.

A key secondary end point was reduction in levels of urine 5-HIAA. The trial showed a statistically significant 35%improvement in mean daily bowel movements associated with the 500-mg thrice-daily dose at week 12 compared with baseline. Moreover, levels of urine 5-HIAA improved significantly in both treatment groups versus the placebo group: at week 12, mean urine 5-HIAA decreased by 58 mg/24 hours in patients receiving the 500-mg dose and 40 mg/24 hours with the 250-mg dose; mean urinary 5-HIAA levels increased in the placebo group by 11 mg/24 hours at week 12. Adverse effects were generally mild.

A consensus was reached that in a patient with stable radiographic disease and refractory carcinoid syndrome characterized by suboptimal control of diarrhea, telotristat ethyl was the appropriate drug of choice. Under these circumstances, telotristat was considered a more appropriate choice than an increase in SSA dose, use of short-acting octreotide, or use of nonspecific antidiarrheal or antitumor therapy. However, in a circumstance where increase in flushing and/or diarrhea occurs only toward the end of a 4-week SSA cycle, the majority of participants advocated increase in frequency of SSA (to every 3 weeks) as the preferred intervention. In the setting of refractory carcinoid syndrome stemming from tumor progression, antitumor therapy should be considered.

Use of Telotristat Ethyl in a Patient With Normal Urine 5-HIAA

In the TELESTAR study, patients with normal urine 5-HIAA, a serotonin metabolite, represented roughly 25% of the enrolled population and appeared to derive similar benefit from the drug.[5] However, the mechanism of benefit is uncertain. When asked whether they would consider use of telotristat in a patient with normal levels of urine 5-HIAA but suboptimal control of diarrhea, roughly half the respondents stated that they would consider use of telotristat.

Carcinoid Heart Disease: Screening and Surveillance

Carcinoid heart disease is characterized by fibrosis of right-sided cardiac valves (tricuspid/pulmonic) and endocardium and eventually leads to right heart failure.[33] It is usually associated with highly elevated levels of circulating serotonin. Indeed, serotonin is generally considered to be the primary etiologic factor. Estimates of the incidence of CaHD among patients with metastatic midgut carcinoid tumors vary widely; past reports indicated an occurrence rate of approximately 50%; however,more recent reports point to a decline in the condition, possibly associated with use of SSAs.[34]

Definitive treatment for CaHD consists of valve replacement, typically involving both the tricuspid and pulmonary valves. Identification of CaHD prior to onset of right heart failure is important to optimize postoperative outcomes. Another possible advantage of early detection is the ability to institute more aggressive medical therapy to reduce serotonin output, thereby potentially impacting the progression of CaHD.

Echocardiographic imaging is the most common and accurate evaluation method for CaHD.[33] Serum N-terminal pro–brain natriuretic peptide (BNP) is another method of assessing for evidence of heart failure, with a high negative predictive value.[33]

There are limited data to guide selection of patients who are most appropriate for CaHD surveillance. Among the expert panel, some advocated baseline echocardiogram in all midgut NET patients with advanced disease, whereas others recommended baseline echocardiogram only in patients with significant elevations in levels of serotonin, or its metabolite 5-HIAA. Regular echocardiographic evaluation was recommended for all patients at risk, but there was no consensus on how this population should be defined and/or how often echocardiograms should be performed. There was agreement that in patients with evidence of mild CaHD echocardiographic evaluation should be performed at least once a year. There was no consensus as to whether serum BNP, or its profactor, N-terminal pro-BNP, is of any additional diagnostic benefit among patients undergoing echocardiographic surveillance.

As a result of these discussions,we recommend that at a minimum all patients with significant elevations in serotonin or 5-HIAA levels (eg, >5 upper limit of normal) undergo annual echocardiography. Screening of patients with less prominent elevations of serotonin levels can be likewise considered. Patients with evidence of early CaHD should be monitored more closely. Health care providers should have a low threshold to obtain an echocardiogram in any patient with midgut NET exhibiting signs or symptoms of CaHD.

Use of Telotristat Ethyl for Prevention of CaHD

Because CaHD is associated with significant elevations in serum serotonin, reductions in levels of circulating serotonin should, in theory, reduce the risk of development or progression of CaHD. However, to date, there are no data to suggest that telotristat ethyl, a serotonin inhibitor, can inhibit development or progression of CaHD. Studies to test the potential effects of telotristat on CaHD are

anticipated to be logistically challenging because of the rarity of the condition and difficulty in establishing validated end points.

When presented with a vignette describing a patient with symptomatically controlled carcinoid syndrome, highly elevated levels of urine 5-HIAA (>5 upper limit of normal) but no evidence of CaHD on echocardiogram, a small minority of the expert panel recommended initiation of telotristat for CaHD prevention. When presented with a vignette describing a similar patient with early evidence of CaHD, a nonsignificant majority recommended that telotristat therapy should be initiated. We therefore suggest that telotristat can be considered in patients with significantly elevated urine 5-HIAA (or other measures of circulating serotonin) and echocardiographic signs of valvular damage associated with CaHD. However, more evidence is needed before telotristat can be definitively recommended for prevention or management of CaHD. At this time, we do not recommend initiation of telotristat simply for the purpose of reducing serotonin levels in patients lacking evidence of valvular damage.

Valve Replacement for CaHD

Surgical valve replacement is generally the recommended treatment for patients with moderate to severe CaHD who otherwise have a life expectancy exceeding 1 year.[33] There was a consensus among the expert panel that both tricuspid and pulmonary valves should be evaluated carefully for evidence of thickening and insufficiency preoperatively as well as operatively. In most cases, replacement of both valves is performed during the same operation.

There is an increasing tendency for placement of bioprosthetic valves for avoidance of anticoagulation and evidence of improved outcomes and survival. However, the literature also indicates a role for mechanical valves when anticoagulation can be tolerated to avoid early valve degeneration. As evidence matures further, a role for percutaneous valve-in-valve therapy and the protective effects of telotristat on bioprosthetic valves might shift the paradigm further toward bioprosthetic valves. In the meantime, the choice of valve prosthesis should be individualized to each patient.When debating the optimal prosthetic valve type, a significant majority of the panel selected bioprosthetic valves.

Monitoring of Serotonin Levels in Patients With Advanced Midgut NETs

A significant majority of the expert panel indicated that they routinely monitor serotonin output in patients with advanced midgut NETs, typically at the time of radiographic staging. There are multiple methods for measuring serotonin output, including blood serotonin levels, 24-hour urine 5-HIAA measurements, and plasma 5-HIAA measurements.[35] There was no consensus regarding the optimal method for measurement of serotonin output. Half of respondents indicated that plasma 5-HIAA measurements were sufficiently validated for routine use as an alternative to 24-hour urine 5-HIAA collections.

Monitoring of Nonhormonal Tumor Markers in Patients With Advanced Midgut NETs

Chromogranin A is the most commonly measured nonspecific tumor marker in patients with midgut NETs; however, there was consensus that high rates of false-positive and false-negative results as well as unexplained fluctuations limit its utility.[36,37] Chromogranin A has been validated as a prognostic marker in midgut NET in randomized clinical trials.[38] Pancreastatin, a breakdown product of CgA, may be more specific in certain contexts, such as patients using proton pump inhibitors (which raise CgA levels).[39,40]

A significant majority of the expert panel reported that they measure tumor markers such as CgA and/or pancreastatin in routine practice, but a significantmajority also indicated that these tumor markers assist in patient management only occasionally or rarely. As a result, no consensus was achieved on whether tumor markers should be routinely measured in patients with advanced midgut NETs. Studies of the relatively novel 51-gene, polymerase chain reaction–based NETest report higher rates of sensitivity, specificity, and accuracy compared with conventional monoanalyte tumor markers.[41] Validation studies are ongoing.

Discussion

In the past 8 years, the treatment landscape for midgut NETs has changed significantly. Five positive phase 3 clinical trials have transformed a field that was previously characterized by absence of high-quality, randomized prospective trials. The updated North American Neuroendocrine Tumor Society guidelines for medical management of midgut NETs discuss the appropriate

use of new diagnostic and therapeutic agents. These include ^{177}Lu-DOTATATE and everolimus in patients with radiographically progressive tumors, telotristat ethyl in patients with suboptimal control of diarrhea in the context of carcinoid syndrome, and ^{68}Ga-DOTATATE (Netspot) for identification of somatostatin receptor–expressing tumors.

However, it is important to acknowledge that many questions remain unanswered. Further clinical research will be needed to address key issues pertaining to the management of midgut NETs. We have identified the following high-priority areas for study: randomized trials comparing liver-directed treatments to systemic treatments (including PRRT) in patients with progressive, liverdominant, midgut NETs; randomized trials comparing radiolabeled SSAs to everolimus in progressive somatostatin receptor–expressive midgut NETs; randomized trials comparing risks/benefits of various transarterial liver embolization modalities; trials evaluating effects of telotristat ethyl on clinical and echocardiographic progression of CaHD; biomarker validation studies comparing sensitivity and specificity of monoanalyte and multianalyte circulating tumor makers; studies testing whether early changes in biomarkers accurately predict subsequent clinical and radiographic changes; and prospective longitudinal studies evaluating risk of recurrence and optimal monitoring after resection of early-stage midgut NETs. Future guidelines will hopefully be able to rely on high-level data to answer key questions pertaining to selection and sequencing of treatments and ensure that diagnostic tests are judiciously performed.

REFERENCES

References

1. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27: 4656–4663.
2. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371: 224–233.
3. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968–977.
4. Strosberg J, El-Haddad G,Wolin E, et al. Phase 3 trial of 177Lu-DOTATATE for midgut neuroendocrine tumors. N Engl J Med. 2017;376:125–135.
5. Kulke MH, Hörsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. J Clin Oncol. 2017;35:14–23.
6. Le Roux C, Lombard-Bohas C, Delmas C, et al. Relapse factors for ileal neuroendocrine tumours after curative surgery: a retrospective French multicentre study. Dig Liver Dis. 2011;43: 828–833.
7. Dieckhoff P, Runkel H, Daniel H, et al.Well-differentiated neuroendocrine neoplasia: relapse-free survival and predictors of recurrence after curative intended resections. Digestion. 2014;90:89–97.
8. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J NuclMed. 2007;48:508–518.
9. Klimstra DS,Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010;39:707–712.
10. Kvols LK, Moertel CG, O'Connell MJ, et al. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. N Engl JMed. 1986;315:663–666.
11. Vinik AI, Wolin EM, Liyanage N, et al. Evaluation of lanreotide depot/autogel efficacy and safety as a carcinoid syndrome treatment (ELECT): a randomized, double-blind, placebo-controlled trial. Endocr Pract. 2016;22:1068–1080.
12. Rubin J, Ajani J, Schirmer W, et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate inmalignant carcinoid syndrome. J Clin Oncol. 1999;17:600–606.
13. O'Toole D, Ducreux M, Bommelaer G, et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. Cancer. 2000;88:770–776.
14. Ruszniewski P, DucreuxM, Chayvialle JA, et al. Treatment of the carcinoid syndrome with the longacting somatostatin analogue lanreotide: a prospective study in 39 patients. Gut. 1996;39:279–283.
15. Johnbeck CB, Knigge U, Kjær A. PET tracers for somatostatin receptor imaging of neuroendocrine tumors: current status and review of the literature. Future Oncol. 2014;10:2259–2277.
16. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378:2005–2012.
17. Faiss S, Pape UF, Böhmig 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 ClinOncol. 2003;21: 2689–2696.
18. Kölby L, Persson G, Franzén S, et al. Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. Br J Surg. 2003;90:687–693.
19. Arnold R, Rinke A, Klose KJ, et al. Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. Clin Gastroenterol Hepatol. 2005;3:761–771.
20. Pitt SC, Knuth J, Keily JM, et al. Hepatic neuroendocrine metastases: chemo- or bland embolization? J Gastrointest Surg. 2008;12: 1951–1960.

21. Devcic Z, Rosenberg J, Braat A, et al. The efficacy of hepatic 90Y resin radioembolization for metastatic neuroendocrine tumors: a meta-analysis. J Nucl Med. 2014;55:1404–1410.
22. Kennedy AS. Hepatic-directed therapies in patients with neuroendocrine tumors. Hematol Oncol Clin North Am. 2016;30:193–207.
23. Yao J, Fazio N, Singh S, et al. Everolimus in advanced, nonfunctional neuroendocrine tumors of lung or gastrointestinal origin: efficacy and safety results from the placebo-controlled, double-blind, multicenter, phase 3 RADIANT-4 study. Eur J Cancer. 2015;51(suppl 3): S709–S710.
24. Strosberg JR, Weber JM, Feldman M, et al. Prognostic validity of the American Joint Committee on Cancer staging classification for midgut neuroendocrine tumors. J Clin Oncol. 2013;31:420–425.
25. Yao JC, Guthrie K, Moran C, et al. SWOG S0518: phase III prospective randomized comparison of depot octreotide plus interferon 2b versus depot octreotide plus bevacizumab (NSC #704865) in advanced, poor prognosis carcinoid patients (NCT00569127). J Clin Oncol. 2015;33: abstr 4004.
26. Maire F, Lombard-Bohas C, O'Toole D, et al. Hepatic arterial embolization versus chemoembolization in the treatment of liver metastases from well-differentiated midgut endocrine tumors: a prospective randomized study. Neuroendocrinology. 2012;96:294–300.
27. Gil-Alzugaray B, Chopitea A, Iñarrairaegui M, et al. Prognostic factors and prevention of radioembolization-induced liver disease. Hepatology. 2013;57:1078–1087.
28. Bennink RJ, Cieslak KP, van Delden OM, et al. Monitoring of total and regional liver function after SIRT. Front Oncol. 2014;4:152.
29. Toumpanakis C, Garland J, Marelli L, et al. Long-term results of patients with malignant carcinoid syndrome receiving octreotide LAR. Aliment Pharmacol Ther. 2009;30:733–740.
30. Ruszniewski P, Ish-Shalom S, Wymenga M, et al. Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. Neuroendocrinology. 2004;80:244–251.
31. Strosberg J, Weber J, Feldman M, et al. Above-label doses of octreotide-LAR in patients with metastatic small intestinal carcinoid tumors. Gastrointest Cancer Res. 2013;6:81–85.
32. Pavel M, Hörsch D, Caplin M, et al. Telotristat etiprate for carcinoid syndrome: a single-arm, multicenter trial. J Clin EndocrinolMetab. 2015;100:1511–1519.
33. Luis SA, Pellikka PA. Carcinoid heart disease: diagnosis and management. Best Pract Res Clin Endocrinol Metab. 2016;30:149–158.
34. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. Neuroendocrinology. 2009;89:471–476.
35. Tellez MR, Mamikunian G, O'Dorisio TM, et al. A single fasting plasma 5-HIAAvalue correlates with 24-hour urinary 5-HIAAvalues and other biomarkers in midgut neuroendocrine tumors (NETs). Pancreas. 2013;42:405–410.
36. Massironi S, Rossi RE, Casazza G, et al. Chromogranin A in diagnosing and monitoring patients with gastroenteropancreatic neuroendocrine neoplasms: a large series from a single institution. Neuroendocrinology. 2014;100:240–249.
37. YangX,Yang Y, Li Z, et al. Diagnostic value of circulating chromograninA for neuroendocrine tumors: a systematic review and meta-analysis. PLoS One. 2015;10:e0124884.
38. Yao JC, Hainsworth JD, Wolin EM, et al. Multivariate analysis including biomarkers in the phase III RADIANT-2 study of octreotide LAR plus everolimus (E + O) or placebo (P + O) among patients with advanced neuroendocrine tumors (NET). J Clin Oncol. 2012;30: abstr 4014.
39. 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;45:560–566.
40. Woltering EA, Beyer DT, Thiagarajan R, et al. Elevated plasma pancreastatin, but not chromogranin A, predicts survival in neuroendocrine tumors of the duodenum. J Am Coll Surg. 2016;222:534–542.
41. Modlin IM, Aslanian H, Bodei L, et al. A PCR blood test outperforms chromogranin A in carcinoid detection and is unaffected by proton pump inhibitors. Endocr Connect. 2014;3:215–223.

Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors

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Executive Summary

Somatostatin receptor positron emission tomography (SSTR-PET) is an imaging modality for patients with neuroendocrine tumors (NETs) that has demonstrated a significant improvement over conventional imaging (CI). SSTR-PET should replace In-111 pentetreotide scintigraphy (OctreoScan) in all indications in which SSTR scintigraphy is currently being used. These appropriate use criteria (AUC) are intended to aid referring medical practitioners in the appropriate use of SSTR-PET for imaging of patients with NETs, and the indications were evaluated in well-differentiated NETs. Of the 12 clinical scenarios evaluated, nine were graded as appropriate: initial staging after the histologic diagnosis of NET, evaluation of an unknown primary, evaluation of a mass suggestive of NET not amenable to endoscopic or percutaneous biopsy, staging of NET prior to planned surgery, monitoring of NET seen predominantly on SSTR-PET, evaluation of patients with biochemical evidence and symptoms of a NET, evaluation of patients with biochemical evidence of a NET without evidence on CI or a prior histologic diagnosis, restaging at time of clinical or laboratory progression without progression on CI, and new indeterminate lesion on CI with unclear progression. Representatives from the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the American College of Radiology (ACR), the American Society of Clinical Oncology (ASCO), the North American Neuroendocrine Tumor Society (NANETS), the European Association of Nuclear Medicine (EANM), the Endocrine Society, the Society of Surgical Oncology, the National Comprehensive Cancer Network (NCCN), the American College of Physicians (ACP), the American Gastroenterological Association (AGA), and the World Conference on Interventional Oncology (WCIO) assembled under the auspices of an autonomous workgroup to develop the following AUC.

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1. Society of Nuclear Medicine and Molecular Imaging
2. American College of Radiology
3. American Society of Clinical Oncology
4. North American Neuroendocrine Tumor Society
5. European Association of Nuclear Medicine
6. Endocrine Society
7. Society of Surgical Oncology
8. National Comprehensive Cancer Network
9. American College of Physicians
10. 1American Gastroenterological Association
11. World Conference on Interventional Oncology

Introduction

Neuroendocrine Tumors (NETs)

NETs are relatively rare and encompass a heterogeneous group of tumors with an incidence of approximately 7.0 in 100,000 (*1,2*), although it is increasing. The most common type are gastroenteropancreatic (GEP)-NETs, which are broken down by sites of origin into gastric, pancreatic, small bowel, colorectal, and those of unknown origin. In addition to GEP-NETs, there are a large number of subtypes of NETs, including pheochromocytomas, paragangliomas, medullary thyroid cancer, merkel cell cancer, and bronchial carcinoids. Given the lack of evidence in other disease subtypes, these AUC will focus on the role of SSTR-PET in well-differentiated GEP-NETs. Although not covered in the clinical scenarios in this document, the belief is that SSTR-PET will be valuable in many SSTR-positive diseases beyond GEP-NETs.

Somatostatin Receptor (SSTR)

Somatostatin is a naturally occurring hormone that acts by binding to SSTR, a receptor that is overexpressed on most NETs. There are 5 predominant subtypes of SSTR, type 2 being the most commonly expressed in NETs (*3*). Somatostatin analogs (SSAs) such as octreotide and lanreotide exert their therapeutic effects by activating SSTRs, which slows tumor growth and inhibits tumor-associated hormone secretion. The presence of SSTRs can be imaged by labeling SSAs with a radionuclide, which was originally performed with octreotide, an octapeptide SSA (*4–6*). In-111 pentetreotide (OctreoScan) was the standard imaging modality for staging and characterizing NETs prior to SSTR-PET.

SSTR-PET

Newer imaging agents targeting SSTR labeled with gallium-68 have subsequently been developed, namely, DOTATATE and DOTATOC (*7*). ^{68}Ga-DOTATATE (NETSPOT, Advanced Accelerator Applications) is currently approved by the Food and Drug Administration. A New Drug Application for ^{68}Ga-DOTATOC is being developed by the University of Iowa. These agents have a number of benefits over In-111 pentetreotide, including improved detection sensitivity, improved patient convenience due to the 2-hour length of study, decreased radiation dose, decreased biliary excretion due to earlier imaging after radiotracer administration, and the ability to quantify uptake. This AUC document focuses on ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC, which are collectively referred to as SSTR-PET. Little head-to-head data are available that compare different SSTR-PET agents, but no relevant differences have been demonstrated between the 2 agents when used for imaging (*8,9*). In general, the workgroup agreed that for all indications for which In-111 pentetreotide is used, it should be replaced with SSTR-PET.

Safety and Dosimetry of SSTR-PET

Human dosimetry data for ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC have been reported (*10,11*), and the estimated total body radiation dose is 4.8 mSv for ^{68}Ga-DOTATATE and 4.3 mSv for ^{68}Ga-DOTATOC for a 185 MBq (5 mCi) administration (Table 1). No adverse events have been reported in association with the administration of SSTR-PET agents (*12*).

Use of Intravenous (IV) Contrast With SSTR-PET

Standard PET/CTs have frequently been performed without the administration of IV contrast. The use of IV contrast has been shown to increase the detection rate of liver metastases for ^{18}F-FDG PET as well as for SSTRPET (*13,14*). Contrast can also help with the detection of small bowel primaries (*15*). Given the importance of contrast- enhanced imaging studies, we strongly recommend that all SSTR-PET studies be performed with IV contrast whenever possible. Not only does this improve the diagnostic accuracy of the imaging study, but it also prevents the need for additional contrast-enhanced studies in the same patient.

Role of PET/MRI Versus PET/CT

PET/MRI is a simultaneous modality that allows for PET and MRI to be acquired together. In patients with liver-predominant NETs, this allows improved liver imaging with MRI in conjunction with SSTR-PET. Studies have shown that PET/MRI provides improved staging of liver metastases (*16,17*), but, more important, it allows for the acquisition of liver imaging with the same CI modality as used for monitoring at other times. This is important, as the imaging technique can change the appearance of liver metastases independent of their progression, and therefore a consistent imaging technique needs to be maintained across time. PET/CT, on the other hand, is superior for patients with mesenteric, osseous, and pulmonary disease. In both PET/MRI and PET/CT, incorporation of contrast-enhanced cross-sectional imaging is encouraged.

Role of SSTR-PET in Pediatric Populations

SSTR-PET is safe in infants, children, and young adults. The dose should be adjusted to the patient's weight, the recommended dose being 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4 mCi) (*18*). SSTR-PET is the recommended functional imaging modality for pediatric NETs and is also recommended for as sessing neuroblastoma, paraganglioma, and pheochromocytoma, especially in the setting of MIBG-negative disease (*19,20*).

Meningiomas occurring in children and adolescents with neurofibromatosis type 2 express SSTRs and are visualized on SSTR-PET. Although medulloblastoma and supratentorial primitive neuroectodermal tumors highly express SSTR type 2, the ability of SSTR-PET agents to pass the blood-brain barrier has not been formally tested.

Considerations of Tumor Grade and Imaging Modality

NETs vary in tumor aggressiveness, and tumors are categorized by histologic evaluation. Precise rules for classification vary by tumor site or origin. GEP-NETs are typically classified on the basis of the Ki67 proliferation index and/or the mitotic count (*21*) (Table 2). Well-differentiated (G1 and G2) NETs are relatively indolent, with a prognosis measured in years even in the face of metastatic disease. High-grade (G3) poorly differentiated neuroendocrine carcinomas (NECs) are typically much more aggressive and nearly always metastatic at diagnosis. Tumors in the recently identified category of well-differentiated G3 NETs are thought to harbor an intermediate prognosis (closer to traditional well-differentiated NETs) (*22*).

Unresectable well-differentiated NETs of all sites are often treated with liver-directed therapy (e.g., ablation, bland embolization, chemotherapy, or radioembolization), SSAs, or everolimus (*23,24*). Sunitinib is reserved for patients with advanced pancreatic NETs; temozolomide- or streptozocin-based chemotherapy is also typically reserved for this population (*23*). Poorly differentiated NECs (e.g., large and small cell subtypes) are typically treated with first-line platinum-based chemotherapy or with salvage therapy consisting of several other chemotherapy regimens (i.e., selected from the small cell lung carcinoma armamentarium and/or regimens commonly used for colorectal cancer if arising in the GI tract). An important consideration is that, although data from a randomized trial recently confirmed the value of peptide receptor radionuclide therapy (PRRT) in well-differentiated NETs arising in the midgut, the use of SSTR-PET is less clear in high-grade NECs.

The indications and their appropriateness reviewed in this manuscript bundle Grade 1 and Grade 2 NETs into 1 group. The exception to this may be well-differentiated Grade 3 NETs, for which optimal treatment is unclear. Patients with these tumors may be candidates for PRRT if they have high expression on SSTR-PET; SSTR-PET may therefore be helpful in selecting patients for this therapy. Typically, high-grade NECs have lower SSTR expression, as evidenced by less tracer uptake on SSTR-PET, and are better imaged with ^{18}F-FDG-PET (*25*). Furthermore, significant tumor heterogeneity can occur in patients, with the coexistence of both well-differentiated and poorly differentiated tumors; in this case, a combination of ^{18}F-FDG and SSTR-PET can be helpful in characterizing disease (*26,27*).

Understanding Stage Migration When Using SSTR-PET

Several studies indicate that SSTR-PET imaging is superior to SSTR scintigraphy or conventional anatomic imaging (CI: e.g., CT or MRI). For example, SSTR-PET can locate the primary tumor site and often demonstrates additional lesions not captured by CI, resulting in better staging that results in clinically relevant changes in management in about one-third of patients (*28*). However, it is important to recognize that identification of more extensive disease may not always have an impact on clinical management and may increase patient and provider anxiety by demonstrating more disease burden than previously visualized with conventional testing. As with any other novel imaging modality, it is important for physicians and patients to realize that direct comparisons between SSTR-PET and other imaging tests are not equivalent, and what appears to be disease progression on the first SSTR-PET study may simply represent more accurate staging, disease progression being confirmed only by comparing like scans over time.

Methodology

Workgroup Selection

The experts of the AUC workgroup were convened by SNMMI to represent a multidisciplinary panel of health care providers with substantive knowledge of NETs. In addition to SNMMI member representation, international representatives from ASCO, NANETS, and EANM were included in the workgroup. Nine physician members and 1 patient advocate were ultimately selected to participate and contribute to the resulting AUC. A complete list of workgroup participants can be found in Appendix A. Appendix B is a summary of definitions of terms and acronyms, and Appendix C provides the disclosures and conflicts of interest statement.

AUC Development

The process for AUC development was modeled after the RAND/UCLA Appropriateness Method (*29,30*) and included the development of a list of common scenarios encountered in the management of patients with NETs, a systematic review of evidence related to these scenarios, and the development of an appropriateness score for each scenario by using a modified Delphi process. This process strove to adhere to the standards of the Institute of Medicine of the National Academies for developing trustworthy clinical guidance (*31*). The process included a

systematic synthesis of available evidence, individual and group ratings of the scenarios by using a formal consensus process, and AUC recommendations based on final group ratings and discussions. Development of these AUC based on traditional outcome measures would have been optimal, but the literature review did not return significant numbers of articles with this information.

Scope and Development of Clinical Scenarios (or Indications)

To begin this process, the workgroup discussed various potential clinical scenarios for which the use of SSTR-PET might be considered. The scope of this workgroup was to focus on the appropriate use of SSTR-PET specifically for the diagnosis and management of NETs. For all scenarios, the relevant populations were men and women with NETs of any age, of any race, or of any geographic location (rural, urban, etc.).

The workgroup identified 12 scenarios for patients with NETs. The scenarios are intended to be as representative of the relevant patient population as possible for development of AUC. The resulting AUC are based on evidence and expert opinion regarding diagnostic accuracy and effects on clinical outcomes and clinical decision making as applied to each scenario. Other factors affecting the AUC recommendations were potential harm—including long-term harm that may be difficult to capture— costs, availability, and patient preferences.

Systematic Review

To inform the workgroup, a systematic review of the relevant evidence was commissioned by an independent group, the Pacific Northwest Evidence-Based Practice Center of Oregon Health and Science University *(57*). The primary purpose of the systematic review was to assess the diagnostic accuracy and comparative effectiveness of SSTR-PET in patients with NETs. Two additional meta-analyses were also included in the process (*12,32*).

The key research questions used to guide the systematic review were as follows: What is the diagnostic accuracy of SSTR-PET compared with In-111 pentetreotide, ^{18}F-FDG-PET, and/or CT/MRI for identification of primary NETs, NET metastases, or tumor staging? How does diagnostic accuracy vary according to patient or tumor characteristics (e.g., Ki-67, grade and differentiation, or site of origin)? What is the predictive utility of SSTR-PET compared with OctreoScan, ^{18}F-FDG-PET, and/or CT/MRI for predicting response to PRRT or SSA therapy? How does predictive utility vary according to patient or tumor characteristics? What are the effects of SSTR-PET imaging compared with In-111 pentetreotide, ^{18}FFDG-PET, and/or CT/MRI on clinical decision making? How do effects on clinical decision making vary according to patient or tumor characteristics?

The inclusion and exclusion criteria for papers for this review were based on the study parameters established by the workgroup, using the PICOTS (population, intervention, comparisons, outcomes, timing, and setting) approach. Searches were conducted on the following databases: the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and OVID MEDLINE (from 2000 through November 2016). These searches were supplemented by reviewing the reference lists of relevant publications.

Two reviewers independently assessed abstracts and full-text articles for inclusion and rated study quality as defined by the established PICOTS parameters. The quality (based on the risk of bias) of each study was categorized as "good," "fair," or "poor" by using U.S. Preventive Services Task Force criteria for randomized trials and cohort studies (*33*), Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic accuracy studies (*34*), and Assessment of Multiple Systematic Reviews (AMSTAR) for systematic reviews (*35*). The strength of overall evidence was graded as high, moderate, low, or very low by using methods based on quality of evidence, consistency, directness, precision, and reporting bias.

Literature searches resulted in 635 potentially relevant articles. After a dual review of the abstracts and titles, 237 articles were selected for full-text review and 17 publications were determined to meet the criteria for inclusion in this review.

Rating and Scoring Process

In developing these AUC for SSTR-PET, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: "The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics" (*36*).

At the beginning of the process, workgroup members convened at an in-person forum to develop the initial scenarios. On evaluating the evidence summary of the systematic literature review, the workgroup further refined its draft clinical scenarios to ensure their accuracy and facilitate consistent interpretation when scoring each scenario for appropriateness. Using the evidence summary, workgroup members were first asked

individually to assess the benefits and risks of SSTR-PET for each of the identified scenarios and provide an appropriateness score for each scenario. After deliberate discussion, each member independently provided a second round of scores for each scenario. For each scenario, the mode numeric score was determined and then assigned to the associated appropriate use category. The results of second-round scoring continued to indicate some difference in opinion among members about the appropriateness of certain scenarios. Therefore, the workgroup continued its deliberations and further clarified the criteria for assigning the different scores before conducting a third round of scoring, which reflected a group-level consensus of scores. For this final scoring round, the members were asked to include their expert opinion. All members contributed to the final discussion, and no one was forced into consensus. After the rating process was completed, the final appropriate use ratings were summarized in a format similar to that outlined by the RAND/UCLA Appropriateness Method.

The workgroup scored each scenario as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9. Scores 7–9 indicate that the use of the procedure is appropriate for the specific scenario and is generally considered acceptable. Scores 4–6 indicate that the use of the procedure may be appropriate for the specific scenario. This implies that more research is needed to classify the scenario definitively. Scores 1–3 indicate that the use of the procedure is rarely appropriate for the specific scenario and generally is not considered acceptable.

As stated by other societies that develop AUC, the division of these scores into 3 general levels of appropriateness is partially arbitrary, and the numeric designations should be viewed as a continuum. In addition, if there was a difference in clinical opinion for a particular scenario such that workgroup members could not agree on a common score, that scenario was given a score of 5 to indicate a lack of agreement on appropriateness based on the available literature and the members' collective clinical opinion, indicating the need for additional research.

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of SSTR-PET and final AUC scores in patients with NETs are presented in Table 3. In grading clinical indications, we focused on well-differentiated NETs.

Scenario 1: Initial staging after the histologic diagnosis of NETs (Score 9 –appropriate). There was consensus that SSTR-PET should be used for the staging of patients with NETs. The systematic review clearly demonstrated the superiority of SSTR-PET over both CI and SSTR scintigraphy (*57*). It is important to take into account the type and size of NETs. For example, patients with subcentimeter rectal NETs likely do not require SSTR-PET at initial staging, given the extremely low incidence of metastatic disease in these patients.

Scenario 2: Localization of a primary tumor in patients with known metastatic disease, but an unknown primary (Score 9 – appropriate). Up to 20% of patients with NETs have unknown primaries after initial workup, and localization of the primary tumor is important, as treatment options vary depending on the origin of the tumor (*37*). In one prospective study, the primary tumor was found in 38% of patients who were imaged with SSTR-PET (*38*). In another paper, the primary tumors of 4 of 14 patients with unknown primaries were detected by using SSTR-PET (*39*). This was uniformly agreed to be an appropriate indication for SSTR-PET.

Scenario 3: Selection of patients for SSTR-targeted PRRT (Score 9 – appropriate). PRRT is increasingly becoming an important component of the treatment algorithm for patients with NETs. PRRT localizes radiation delivered by radionuclides, typically lutetium-177 (^{177}Lu) or yttrium-90 (^{90}Y), to NET cells by internalization after binding to SSTR. The pivotal prospective randomized phase 3 NETTER-1 trial demonstrated significant prolongation of progression-free survival in patients with midgut NETs after treatment with ^{177}Lu-DOTATATE compared with high-dose octreotide (*40*). For enrollment, the NETTER-1 trial did not use SSTR-PET but required patients to have evidence of SSTR expression on In-111 pentetreotide on the basis of the Krenning scale (*41*). Virtually all other single-arm PRRT studies have required uptake on SSTR imaging as an eligibility criterion. The workgroup agreed that SSTR-PET can be used in place of In-111 pentetreotide for patient selection for PRRT. Uptake on SSTR-PET can be predictive of therapeutic response to PRRT (*42*), and it is likely that SSTR-PET will prove to be a more accurate selection tool than In-111 pentetreotide for PRRT, although criteria for positive disease have yet to be developed for SSTR-PET.

Scenario 4: Staging NETs prior to planned surgery (Score 8 – appropriate). Published series reporting on surgical cytoreduction of NET liver metastases have demonstrated that, although it is not curative, it improved survival compared with historic controls (e.g., all patients with NET metastases from large national databases) (*43–47*). The conventional wisdom is that surgical debulking "sets the clock back" but does not cure patients; thus, the presence of extrahepatic disease is not necessarily an absolute contraindication. With the development of SSTR-PET, more extensive metastatic disease is being detected, and there is no consensus on how to manage patients surgically if extensive nonresectable disease is seen on SSTR-PET. If the bulk of metastatic disease is in the liver or abdominal lymph nodes, then surgical intervention may be warranted. In cases with extensive bone, mediastinal, and/or neck metastases, the benefits of hepatic cytoreduction are less clear, especially in those patients with impaired performance status and higher grade tumors. Nonetheless, the workgroup agreed that SSTR-PET should be used to guide surgical planning and to rule out extensive extraabdominal disease in patients prior to undergoing hepatic cytoreductive procedures.

Scenario 5: Evaluation of a mass suggestive of a NET not amenable to endoscopic or percutaneous biopsy (e.g., ileal lesion, hypervascular pancreatic mass, mesenteric mass) (Score 8 – appropriate). A major role for SSTR-PET is to demonstrate the presence of SSTRs noninvasively. This can help narrow the differential diagnosis of a lesion and therefore help determine the correct treatment algorithm. In the setting in which a biopsy is not easily obtained, either because of technical limitations such as the lack of access to enteroscopy or because of increased risk of invasive biopsy such as a hypervascular lesion or one too close to large vessels, SSTR-PET can demonstrate noninvasively that an uncharacterized mass is SSTR positive and therefore most likely a NET. In addition, other SSTR-positive disease may be revealed that is more amenable to biopsy.

Scenario 6: Monitoring of NETs seen predominantly on SSTR-PET (Score 8 – appropriate). With the use of SSTR-PET, we are seeing more disease that is not appreciable on CI. In particular, osseous metastatic disease is frequently underestimated by CI (*39,48*), and the only way to visualize the extent of disease is by using SSTR-PET. In these cases, when the extent of disease cannot be reliably visualized on CI, SSTR-PET is indicated for routine imaging and follow-up.

Scenario 7: Evaluation of patients with biochemical evidence and symptoms of a NET without evidence of it on CI and without prior histologic diagnosis of a NET (Score 7 – appropriate). This indication resulted in significant disagreement within the workgroup. On the one hand, the overall yield of finding a NET in this patient population is low, and SSTR-PET may also result in false positives that could lead to unnecessary additional tests or procedures (*12*). However, in such a situation, a negative SSTR-PET result may play an important role, as it could end the diagnostic workup, resulting in a more cost-effective evaluation. Furthermore, on the rare occasion when a study result is positive, further investigation of the lesion may be useful in identifying the tumors that are present.

Scenario 8: Restaging at time of clinical or laboratory progression without progression on CI (Score 7 – appropriate). There was a concern that in comparison to CI, SSTR-PET may demonstrate apparent progression that would be misinterpreted and lead to inappropriate changes in management. Baseline imaging with SSTR-PET is essential, since comparison with CI would likely show more disease. Nonetheless, SSTR-PET allows better evaluation of disease than does CI, and therefore in the setting of clinical and/or biochemical progression, it can be important for selecting the appropriate therapy.

Scenario 9: New indeterminate lesion on CI, with unclear progression (Score 7 – appropriate). SSTR positivity is an important finding for demonstrating that a lesion is in fact a NET; therefore, to characterize a finding on CI, SSTR-PET can be used to clarify whether a suspicious lesion is a NET and represents true progression and/or recurrence. In addition, it is possible for NETs to dedifferentiate, changing from well-differentiated to poorly differentiated NETs over time (*49*). SSTR-PET can be an indirect indicator of grade, and therefore reimaging at the time of progression can provide insight into possible underlying dedifferentiation of a tumor.

Scenario 10: Restaging of patients with NETs at initial follow-up after resection with curative intent (Score 6 – may be appropriate). There was a lack of consensus among the committee for this indication. One concern was that it would lead to overuse of SSTR-PET in patients without evidence of disease. Many suggested that a single SSTR-PET may be indicated after resection, but the main issue with the indication was the lack of impact on patient management. Visualizing small-volume residual disease after surgical resection is unlikely to change patient management; thus, some felt that it would be more appropriate to wait for biochemical evidence for

recurrence or radiologic evidence on CI before performing SSTR-PET. If a patient did not undergo SSTR-PET prior to surgical resection, a single SSTR-PET should be considered to complete staging postoperatively.

Scenario 11: Selection of patients with nonfunctional NETs for SSA treatment (Score 6 – may be appropriate). Although it is very likely that SSTR expression correlates with benefit from SSA treatment, this has not been proven definitively in clinical trials. The CLARINET trial, which demonstrated the antiproliferative activity of lanreotide in GEP-NETs, required evidence of SSTR expression with In-111 pentetreotide for enrollment (*50*). The PROMID study, which evaluated octreotide in midgut NETs, did not require evidence of SSTR expression; however, only 12% of patients had negative imaging results with In-111 pentetreotide (*51*). Only one study has reported that higher uptake on SSTR-PET predicts improved response to SSA therapy (*52*). Because of the benign side effect profile of SSAs, the workgroup did not reach a consensus that confirmation of SSTR expression is necessary for initiation of treatment with octreotide or lanreotide. The workgroup also noted that in syndromic patients, SSTR analogs should be initiated independent of findings on SSTR-PET.

Scenario 12: Monitoring in patients with NETs seen on both CI and SSTR-PET with active disease and no clinical evidence of progression (Score 5 – may be appropriate). The consensus was that if CI can detect metastatic disease, then SSTR-PET should not be used for routine imaging. There was a belief that intermittent SSTR-PET (once every 2 to 3 years) may be helpful in evaluating for progression if CI results are stable, although it should not be used in place of CI for routine monitoring of patients.

Summary of Recommendations

SSTR-PET should replace In-111 pentetreotide in all indications in which In-111 pentetreotide is currently being used. SSTR-PET has demonstrated better sensitivity and specificity than CI and In-111 pentetreotide. There are specific instances in which SSTR-PET is clearly preferred: at initial diagnosis, when selecting patients for PRRT, and for localization of unknown primaries. For patients in which the tumor is readily seen on CI, SSTR-PET is not needed for routine monitoring.

Benefits and Harms of Implementing the AUC Guidance

Some providers have raised the concern that AUC for medical imaging might inappropriately limit access to health care services (*53*). For example, several authors of papers included in our meta-analysis suggested that the AUC might lead to denial of reimbursement for needed imaging services because of incomplete AUC or lack of strong evidence for a particular procedure (*54*). It is hoped that besides providing recommendations for the appropriate use of SSTR-PET, this document will demonstrate gaps in the literature and subsequently encourage new investigations to address these gaps.

Integration of AUC into clinical decision support tools can assist health care providers and offer a way to track comparisons between the AUC model and the payer's reimbursement policy (*54,55*). Ultimately, this may lead to a more efficient approval process for advanced diagnostic imaging procedures, including radiology and nuclear medicine procedures, saving time and effort for the referring provider and the imaging facility. However, the difficult task of writing AUC for all scenarios and keeping the AUC current remains a large obstacle to the effective use of the clinical decision support model.

Qualifying Statements

Study/Evidence Limitations

Although a large literature focuses on SSTR-PET, the workgroup found the body of medical literature regarding the use of SSTR-PET to be limited when rigorous inclusion criteria were applied to the systematic literature review. Most articles did not use pathology as a correlate to imaging and so sensitivity and specificity measurements were often limited. Information was also scarce on the role of SSTR-PET in high-grade NECs and other less common subtypes of NETs (e.g., well-differentiated G3 NETs, paraganglioma/pheochromocytoma). In addition, little data were available on the use of SSTR-PET in pediatric populations or on how SSTR-PET can be used to predict and evaluate the response to PRRT.

Implementation of this AUC Guidance

SNMMI has been working with several other medical specialty societies to develop broad-based multidisciplinary clinical guidance documents. This collaboration should foster the acceptance and adoption of this guidance by other specialties.

SNMMI has developed a multipronged approach to disseminate the AUC for SSTR-PET in NETs to all relevant stakeholders—referring physicians, nuclear medicine physicians, and patients. The dissemination and implementation tactics will be a mix of outreach and educational activities and will be targeted to each of these audiences.

SNMMI will create detailed case studies for its members and for referring physicians and make them available via online modules and webinars. These cases will cover the appropriate clinical scenarios for the use of SSRT-PET, as well as some cases in which the results of SSRT-PET are equivocal.

Related resources such as the systematic review supporting the development of these AUC, a list of upcoming education events on the AUC, factsheets, and other didactic materials will be made available on the SNMMI webpage dedicated to the SSRT-PET AUC. Live sessions will be held at the SNMMI annual and midwinter meetings, as well as at the relevant societal meetings of referring physicians, to highlight the importance of these AUC.

SNMMI also aims to create a mobile application for the SSTR-PET AUC for both Apple and Android platforms. Mobile applications are becoming increasingly popular in the health-care industry and can be used to push updates to all users.

In addition to these activities, SNMMI will undertake patient-focused outreach to provide education on how AUC can play an invaluable role in achieving a more accurate diagnosis.

Appendix A: Workgroup Members and Literature Reviewers

Workgroup

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Appendix B: Definition of Terms and Acronyms

ACP: American College of Physicians

ACR: American College of Radiology

AGA: American Gastroenterological Association

ASCO: American Society of Clinical Oncology

AUC: appropriate use criteria

CI: conventional imaging (CT, MRI, ultrasound, plain film radiography)

CT: A computed tomography (CT) scan is an imaging method that uses x-rays to create pictures of cross-sections of the body.

EANM: European Association of Nuclear Medicine

ED: effective dose

GEP: gastroenteropancreatic

IA: injected activity

IV: intravenous

Ki-67:

MRI: magnetic resonance imaging

NANETS: North American Neuroendocrine Tumor Society

NCCN: National Comprehensive Cancer Network

NEC: neuroendocrine carcinoma

NET: neuroendocrine tumor

OctreoScan: ^{111}In-pentetreotide scintigraphy

PET: positron emission tomography

PET/CT: A combination device that provides detail on both function and anatomy by superimposing the

precise location of abnormal metabolic activity (from PET) on a detailed anatomic image (from CT).

PRRT: peptide receptor radionuclide therapy

SNMMI: Society of Nuclear Medicine and Molecular Imaging

SSA: somatostatin analog

SSTR: somatostatin receptor

SSTR-PET: somatostatin receptor positron emission tomography

WCIO: World Conference on Interventional Oncology

Appendix C: Disclosures and Conflicts of Interests (COIS)

SNMMI rigorously attempted to avoid any actual, perceived, or potential COIs that might have arisen as a result of an outside relationship or personal interest on the part of the workgroup members or external reviewers. Workgroup members were required to provide disclosure statements of all relationships that might be perceived as real or potential COIs. These statements were reviewed and discussed by the workgroup chair and SNMMI staff and were updated and reviewed by an objective third party at the beginning of every workgroup meeting or teleconference. The disclosures of the workgroup members can be found in Table 1C. A COI was defined as a relationship with industry—including consulting, speaking, research, and nonresearch activities— that exceeds $5,000 in funding over the previous or upcoming 12-month period. In addition, if an external reviewer was either the principal investigator of a study or another key member of the study personnel, that person's participation in the review was considered likely to present a COI. All reviewers were asked about any potential COI. A COI was also considered likely if an external reviewer or workgroup member was either the principal investigator or a key member of a study directly related to the content of this AUC document. All external reviewers were asked about any potential COI.

TABLES

Table 1: Dosimetry for ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC

	^{68}Ga-DOTATATE (10)	^{68}Ga-DOTATOC (11)	^{18}F-FDG (56)
Organ			
Kidneys (mSv/MBq)	9.2E-02	2.2E-01	1.7E-02
Liver (mSv/MBq)	4.5E-02	7.4E-02	2.1E-02
Spleen (mSv/MBq)	2.8E-01	2.4E-01	1.1E-02
Bladder wall (mSv/MBq)	1.3E-01	7.0E-02	1.3E-01
Dose			
ED (mSv/MBq)	2.6E-02	2.3E-02	1.9E-02
Typical IA			
MBq	185	185	370
mCi	5	5	10
Estimated ED per scan (mSv)	4.8	4.3	70

ED = effective dose; IA = injected activity.

Table 2: Classification of GEP-NETs (21)

Differentiation	Grade	Ki67 index	Proliferative rate	SSTR-PET positivity
Well differentiated	Low grade (G1)	< 3%	< 2 mitoses/10 hpf	+++
	Intermediate grade (G2)	3%–20%	2–20 mitoses/10 hpf	++
Poorly differentiated	High grade (G3)	>20%	>20 mitoses/20 hpf	Variable*

GEP-NETs = gastroenteropancreatic-neuroendocrine tumors; SSTR-PET = somatostatin receptor positron emission tomography.

*In high-grade NETs, SSTR positivity is variable, and frequently 18F-FDG-PET performs better as an imaging study in patients with these NETs. SSTR-PET results may be positive for well-differentiated G3 tumors, and imaging may be helpful in finding patients who are candidates for peptide receptor radionuclide therapy.

Table 3: Clinical Scenarios for SSTR-PET

Scenario no.	Description	Appropriateness	Score
1	Initial staging after the histologic diagnosis of NET	Appropriate	9
2	Localization of a primary tumor in patients with known metastatic disease but an unknown primary	Appropriate	9
3	Selection of patients for SSTR-targeted PRRT	Appropriate	9
4	Staging NETs prior to planned surgery	Appropriate	8
5	Evaluation of a mass suggestive of a NET not amenable to endoscopic or percutaneous biopsy (e.g., ileal lesion, hypervascular pancreatic mass, mesenteric mass)	Appropriate	8
6	Monitoring of NETs seen predominantly on SSTR-PET	Appropriate	8
7	Evaluation of patients with biochemical evidence and symptoms of a NET without evidence of it on CI and without prior histologic diagnosis of a NET	Appropriate	7
8	Restaging at time of clinical or laboratory progression without progression on CI	Appropriate	7
9	New indeterminate lesion on CI with unclear progression	Appropriate	7
10	Restaging of patients with NETs at initial follow-up after resection with curative intent	May be appropriate	6
11	Selection of patients with nonfunctional NETs for SSA treatment	May be appropriate	6
12	Monitoring in patients with NET seen on both CI and SSTR-PET with active disease and no clinical evidence of progression	May be appropriate	5

SSTR-PET = somatostatin receptor positron emission tomography; NET = neuroendocrine tumor; PRRT = peptide receptor radionuclide therapy; CI = conventional imaging; SSA = somatostatin analog.

REFERENCES

References

1. Hallet J, Law CHL, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015;121:589–597.
2. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017.
3. John M, Meyerhof W, Richter D, et al. Positive somatostatin receptor scintigraphy correlates with the presence of somatostatin receptor subtype 2. Gut. BMJ Publishing Group. 1996;38:33–39.
4. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med. 1993;20:716–731.
5. Bombardieri E, Ambrosini V, Aktolun C, et al. 111In-pentetreotide scintigraphy: procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging. Springer-Verlag. 2010;37:1441–1448.
6. Lamberts SW, Bakker WH, Reubi JC, Krenning EP. Somatostatin-receptor imaging in the localization of endocrine tumors. N Engl J Med. 1990;323:1246–1249.
7. Antunes P, Ginj M, Zhang H, et al. Are radiogallium-labelled DOTAconjugated somatostatin analogues superior to those labelled with other radiometals? Eur J Nucl Med Mol Imaging. 2007;34:982–993.
8. Poeppel TD, Binse I, Petersenn S, et al. 68Ga-DOTATOC versus 68Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. J Nucl Med. 2011;52:1864–1870.
9. Velikyan I, Sundin A, Sörensen J, et al. Quantitative and qualitative intrapatient comparison of 68Ga-DOTATOC and 68Ga-DOTATATE: net uptake rate for accurate quantification. J Nucl Med. 2014;55:204–210.
10. Walker RC, Smith GT, Liu E, Moore B, Clanton J, Stabin M. Measured human dosimetry of 68Ga-DOTATATE. J Nucl Med. 2013;54:855–860.
11. Hartmann H, Zöphel K, Freudenberg R, et al. [Radiation exposure of patients during 68Ga-DOTATOC PET/CT examinations]. Nuklearmedizin. 2009;48:201–207.
12. Graham MM, Gu X, Ginader T, Breheny P, Sunderland J. (68)Ga-DOTATOC Imaging of Neuroendocrine Tumors: A Systematic Review and Meta-Analysis. J Nucl Med. 2017.
13. Badiee S, Franc BL, Webb EM, et al. Role of IV iodinated contrast material in 18F-FDG PET/CT of liver metastases. American Journal of Roentgenology. 2008;191:1436–1439.
14. Ruf J, Heuck F, Schiefer J, et al. Impact of Multiphase 68Ga-DOTATOC-PET/CT on therapy management in patients with neuroendocrine tumors. Neuroendocrinology. 2010;91:101–109.
15. Schreiter NF, Maurer M, Pape U-F, Hamm B, Brenner W, Froeling V. Detection of neuroendocrine tumours in the small intestines using contrast-enhanced multiphase Ga-68 DOTATOC PET/CT: the potential role of arterial hyperperfusion. Radiol Oncol. 2014;48:120–126.
16. Hope TA, Pampaloni MH, Nakakura E, et al. Simultaneous (68)Ga-DOTA-TOC PET/MRI with gadoxetate disodium in patients with neuroendocrine tumor. Abdom Imaging. Springer US. 2015;40:1432–1440.
17. Sawicki LM, Deuschl C, Beiderwellen K, et al. Evaluation of (68)Ga-DOTATOC PET/MRI for whole-body staging of neuroendocrine tumours in comparison with (68)Ga-DOTATOC PET/CT. European radiology. Springer Berlin Heidelberg. 2017;26:3063–3069.
18. NETSPOT Prescribing Information. www.accessdata.fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208547s000lbl.pdf. Accessed April 8, 2017.
19. Kong G, Hofman MS, Murray WK, et al. Initial Experience With Gallium-68 DOTA-Octreotate PET/CT and Peptide Receptor Radionuclide Therapy for Pediatric Patients With Refractory Metastatic Neuroblastoma. J Pediatr Hematol Oncol. 2016;38:87–96.
20. Kroiss A, Putzer D, Uprimny C, et al. Functional imaging in phaeochromocytoma and neuroblastoma with 68Ga-DOTA-Tyr 3-octreotide positron emission tomography and 123I-metaiodobenzylguanidine. Eur J Nucl Med Mol Imaging. 2011;38:865–873.

21. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010;39:707–712.
22. Raj N, Valentino E, Capanu M, et al. Treatment Response and Outcomes of Grade 3 Pancreatic Neuroendocrine Neoplasms Based on Morphology: Well Differentiated Versus Poorly Differentiated. Pancreas. 2017;46:296–301.
23. Raymond E, Dahan L, Raoul J-L, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:501–513.
24. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968–977.
25. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and 18F-FDG. Cancer. 2008;112:2447–2455.
26. Hofman MS, Hicks RJ. Changing paradigms with molecular imaging of neuroendocrine tumors. Discov Med. 2012;14:71–81.
27. Chan DL, Pavlakis N, Schembri GP, et al. Dual Somatostatin Receptor/FDG PET/CT Imaging in Metastatic Neuroendocrine Tumours: Proposal for a Novel Grading Scheme with Prognostic Significance. Theranostics. 2017;7:1149–1158.
28. Barrio M, Czernin J, Fanti S, et al. The Impact of Somatostatin Receptor- Directed PET/CT on the Management of Patients with Neuroendocrine Tumor: A Systematic Review and Meta-Analysis. J Nucl Med. 2017;58:756–761.
29. Hendel RC, Patel MR, Allen JM, et al. Appropriate use of cardiovascular technology: 2013 ACCF appropriate use criteria methodology update: a report of the American College of Cardiology Foundation appropriate use criteria task force. J Am Coll Cardiol. 2013;61:1305–1317.
30. Fitch K, Bernstein SJ, Aguilar MD, Burnand B. The RAND/UCLA appropriateness method user's manual. 2001.
31. Institute of Medicine of the National Academy. Clinical Practice Guidelines We Can Trust. National Academies Press. 2011.
32. 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;57:872–878.
33. US Preventive Services Task Force. US Preventive Services Task Force Procedure Manual. Rockville, MD: Agency for Healthcare Research and Quality. 2008.
34. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155:529–536.
35. Shea BJ, Bouter LM, Peterson J, et al. External Validation of a Measurement Tool to Assess Systematic Reviews (AMSTAR). Gagnier J, editor. PLoS ONE. 2007;2:e1350–e1355.
36. Appropriate Use Criteria (AUC) Development Process. snmmi.org. http://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=15665. Accessed August 5, 2017.
37. Bellizzi AM. Assigning site of origin in metastatic neuroendocrine neoplasms: a clinically significant application of diagnostic immunohistochemistry. Adv Anat Pathol. 2013;20:285–314.
38. 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;58:1054–1057.
39. 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;34:588–596.
40. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017;376:125–135.
41. Krenning EP, Valkema R, Kooij PP, et al. Scintigraphy and radionuclide therapy with [indium-111-labelled-diethyl triamine penta-acetic acid-D-Phe1]-octreotide. Ital J Gastroenterol Hepatol. 1999;31 Suppl 2:S219–S223.
42. Kratochwil C, Stefanova M, Mavriopoulou E, et al. SUV of [(68)Ga]DOTATOC-PET/CT Predicts Response Probability of PRRT in Neuroendocrine Tumors. Mol Imaging Biol. 2014.
43. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg. 2003;197:29–37.
44. Glazer ES, Tseng JF, Al-Refaie W, et al. Long-term survival after surgical management of neuroendocrine hepatic metastases. HPB (Oxford). 2010;12:427–433.

45. Mayo SC, de Jong MC, Pulitano C, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. Annals of surgical oncology. 2010;17:3129–3136.
46. Graff-Baker AN, Sauer DA, Pommier SJ, Pommier RF. Expanded criteria for carcinoid liver debulking: Maintaining survival and increasing the number of eligible patients. Surgery. 2014;156:1369–76–discussion1376–7.
47. Maxwell JE, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy? Surgery. 2016;159:320–333.
48. Putzer D, Gabriel M, Henninger B, et al. Bone metastases in patients with neuroendocrine tumor: 68Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. Journal of Nuclear Medicine. 2009;50:1214–1221.
49. Tang LH, Untch BR, Reidy DL, et al. Well-Differentiated Neuroendocrine Tumors with a Morphologically Apparent High-Grade Component: A Pathway Distinct from Poorly Differentiated Neuroendocrine Carcinomas. Clin Cancer Res. American Association for Cancer Research. 2016;22:1011–1017.
50. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371:224–233.
51. Rinke A, Müller H-H, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27:4656–4663.
52. Koch W, Auernhammer CJ, Geisler J, et al. Treatment with octreotide in patients with well-differentiated neuroendocrine tumors of the ileum: prognostic stratification with Ga-68-DOTA-TATE positron emission tomography. Mol Imaging. 2014;13:1–10.
53. Bettmann MA. The ACR Appropriateness Criteria: view from the committee chair. J Am Coll Radiol. 2006;3:510–512.
54. Thrall JH. Appropriateness and imaging utilization: "computerized provider order entry and decision support". Acad Radiol. 2014;21:1083–1087.
55. Sistrom CL. In support of the ACR Appropriateness Criteria. J Am Coll Radiol. 2008. pp. 630–5–discussion636–7.
56. Brix G, Lechel U, Glatting G, et al. Radiation exposure of patients undergoing whole-body dual-modality 18F-FDG PET/CT examinations. J Nucl Med. 2005;46:608–613.
57. Pacific Northwest Evidence-Based Practice Center. *Systematic Review: Somatostatin Imaging for Neuroendocrine Tumors.* Portland, Oregon: Oregon Health and Science University; May 2017.

NANETS
NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

Consensus Guidelines for the Management and Treatment of Neuroendocrine Tumors

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Abstract

Neuroendocrine tumors are a heterogeneous group of tumors originating in various anatomic locations. The management of this disease poses a significant challenge because of the heterogeneous clinical presentations and varying degrees of aggressiveness. The recent completion of several phase 3 trials, including those evaluating octreotide, sunitinib, and everolimus, demonstrate that rigorous evaluation of novel agents in this disease is possible and can lead to practice-changing outcomes. Nevertheless, there are many aspects to the treatment of neuroendocrine tumors that remain unclear and controversial. The North American Neuroendocrine Tumor Society published a set of consensus guidelines in 2010, which provided an overview for the treatment of patients with these malignancies. Here, we present a set of consensus tables intended to complement these guidelines and serve as a quick, accessible reference for the practicing physician.

Key Words

neuroendocrine tumors, carcinoid, neuroendocrine/diagnosis, neuroendocrine/treatment, neuroendocrine/pathology, pheochromocytoma

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors originating in various locations, including gastrointestinal tract, lung, and pancreas. The disease management poses a significant challenge because of the heterogeneous clinical presentations and varying degree of aggressiveness. The recent completion of several phase 3 trials, including those evaluating octreotide, sunitinib, and everolimus, demonstrate that rigorous evaluation of novel agents in this disease is possible and can lead to practice-changing outcomes. Nevertheless, there are many aspects to the treatment of NETs that remain unclear and controversial.

The North American Neuroendocrine Tumor Society (NANETS) was founded in 2006; and at that time, its board members convened a consensus guidelines committee in an effort to develop an expert consensus opinion on the treatment of these uncommon diseases. Although other comprehensive guidelines exist (ie, National Comprehensive Cancer Network Neuroendocrine Tumor guidelines, European Neuroendocrine Tumor Society (ENETs) guidelines), it was felt that the NANETS guidelines could enhance and complement these existing guidelines through the use of expert opinion added to evidenced-based recommendations. The first set of consensus guidelines[1–7] was published in 2010 and were intentionally comprehensive in scope. Here, we present a set of consensus tables intended to complement these guidelines and serve as a quick, accessible reference for the practicing physician. Consensus tables were developed and revised during a series of meetings between October 2011 and October 2012. Eight tables were created to define treatment and workup recommendations. These tables include the following: (1) Pathology; (2) NETs of the thorax; (3) Gastric NETs; (4) Pancreatic NETs; (5) NETs of the small bowel and cecum (‘‘midgut’’); (6) NETs of the colon and rectum (‘‘hindgut’’); (7) Pheochromocytoma, paraganglioma, and medullary thyroid cancer; and (8) High-grade neuroendocrine carcinoma. The tables include 2 categories of recommendations as either *Consider* or *Recommend*. Emphasis was placed on the development of sound guidelines based on the data when available and consensus expert opinion; controversial topics were also addressed. Each table includes guidelines for workup, treatment, and follow-up. When the disease-specific full consensus guidelines documents are next updated these consensus tables will be incorporated.

It should be noted that there was unanimous decision that all patients should be considered for clinical trials when possible. In addition, all members believe that the approach to patient management should include a team of experts that include, but are not limited to, medical and surgical oncologists, radiologists, gastroenterologists, interventional radiologists, and pathologists. Additionally, some of the controversial topics included in the tables were brought back to NANETS members and further refined during subsequent meetings and teleconferences. This introduction has been structured to further address some of these key issues.

Key Updates Since Publication of 2010 NANETS Consensus Guidelines

Since the 2010 publication of the NANETS Consensus Guidelines in Pancreas, a number of practice-changing studies have been published.

The RAD001 in Advanced Neuroendocrine Tumors-3 (RADIANT-3) study,[8] published in 2011, is a randomized phase 3 study evaluating the efficacy of everolimus in advanced pancreatic NETs. In this international multisite

study, 410 patients with low- or intermediate-grade, progressive, advanced pancreatic NETs were randomized to receive everolimus, 10 mg oral daily, or placebo. The median progression-free survival (PFS) was 11.0 months with everolimus compared with 4.6 months with placebo (hazard ratio, 0.35; 95% confidence interval, 0.27—0.45; P G 0.001). The response rate was 5% in the everolimus arm compared with 2% in the placebo arm. The median overall survival has not been reached.

In another phase 3 study published in 2011, 171 patients with advanced, well-differentiated, progressive pancreatic NETs were randomized to receive sunitinib, 37.5 mg orally daily, or placebo.[9] The study was discontinued prematurely after an independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo arm and a difference in PFS that favored the sunitinib arm during an unplanned interim analysis. The median PFS was 11.4 months in the sunitinib arm compared with 5.5 months in the placebo arm (hazard ratio, 0.42; 95% confidence interval, 0.26—0.66; P G0.001). Response rates in the sunitinib and placebo arms were 9.3% and 0%, respectively. The median overall survival could not be estimated given the high number of censored events in both groups.

In addition to the aforementioned treatment advances, there were 2 key publications on NET pathology reporting.[4,10] A formal assessment of grade and differentiation using the minimum pathology data set described below in the pathology consensus table should be required for all patients before initiating therapy given the implications on treatment. There are different treatment algorithms for well-differentiated versus poorly differentiated NETs.

Key Controversial Topics

Several controversial topics were identified during the course of guidelines development (Table 1). A few of these topics are highlighted here.

Indications for Targeted Therapies

Based on the aforementioned phase 3 clinical trials, sunitinib and everolimus are Food and Drug Administration approved and recommended for patients with progressive metastatic pancreatic NETs. Everolimus was also studied in metastatic functional (ie, hormone secreting) carcinoid tumors in a large phase 3 clinical trial. Although this study did not meet its primary endpoint of PFS, there was a trend toward longer PFS in the treatment arm.[11] At the current time, we do not have sufficient evidence to recommend routine use of everolimus in carcinoid tumors; the level of recommendation for everolimus in the treatment of advanced carcinoid is listed as ‘‘consider’’.

Indications for Cytotoxic Therapies

Cytotoxic therapies such as streptozocin, 5-fluorouracil, or temozolomide should be considered in the palliation of patients with advanced pancreatic NET and symptoms related to tumor bulk. There are no prospective randomized data for a temozolomidebased regimen; however, a single-institution series showed promising activity,[12] and randomized clinical trials using temozolomide are planned. Cytotoxic therapies are currently listed as ‘‘consider’’ for pancreaticNET. There is currently no known role for cytotoxic therapies in advanced carcinoid.

Indication and Dosing of Somatostatin Analogs Refractory carcinoid syndrome is an unmet medical need. Carcinoid syndrome is caused by the secretion of serotonin and other bioactive amines into the systemic circulation and is manifested by flushing and diarrhea, fibrosis of the right-sided heart valves, and intestinal mesentery. Currently available somatostatin analogs include octreotide and lanreotide and can ameliorate the symptoms of carcinoid syndrome. Over time, however, patients with the carcinoid syndrome may become refractory to somatostatin analogs. For this reason, NET physicians often increase the dose and/or frequency of somatostatin analogs in an attempt to control refractory carcinoid syndrome. Such an approach has anecdotally improved symptoms although has never been tested in a rigorous and/or randomized fashion. The committee ‘‘recommends’’ that somatostatin analog doses could be escalated or interval shortened in an attempt to control these symptoms, but note that no prospective data exist.

The placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors PROMID trial also demonstrated antitumor efficacy of octreotide in advanced midgut carcinoid tumors.[13] Despite this evidence in midgut tumors, there are no prospective data for the use of somatostatin analogs as antiproliferative agents in pancreatic NETs, although ongoing clinical trials are poised to answer this question.

Serum Biomarkers in Diagnosis and Surveillance

Plasma chromogranin A (CgA) and 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) levels can be elevated as surrogate markers of possible progression or response. 5- Hydroxyindoleacetic acid is not as useful in patients

with foregut (bronchial or gastric) or hindgut (rectal) NETs or in most patients with pancreatic NETs that do not secrete serotonin. Chromogranin A is a 49-kd protein that is contained in the neurosecretory vesicles of the NET cells and is commonly detected in the plasma of patients with endocrine neoplasms. Elevated plasma CgA levels have been associated with poor overall prognosis in patients with NETs.[14] Additionally, early decreases may be associated with favorable treatment outcomes in some studies. The committee ''recommends'' following CgA levels in patients with advanced disease in patients who have elevated CgA levels at diagnosis and ''considers'' following CgA in resected disease.

Role of Surgical Debulking

Progression of liver metastases is the predominant cause of mortality in many NET patients. The median survivals of 24 to 128 months are reported with treatment.[15–17] For this reason, hepatic resection, radiofrequency ablation, and hepatic arterial embolization have been used to control tumor burden. In patients in whom all hepatic metastases seem to be resectable, and in whom no (or mild nonclinically significant) extrahepatic disease is observed, resection should be ''considered''.[18–21] The lack of randomized data and selection bias may confound quantitative interpretation of reported results. Nevertheless, resection should be considered in carefully selected patients, particularly with functional tumors, where the tumors can be removed safely. Asymptomatic patients, in the setting of resectable disease, should also be ''considered'' as candidates for surgical debulking.

In recent years, we have witnessed many advances in NET trial design, conduct, and accrual—culminating in the FDA approval of 2 new biologic agents in this disease. There is ongoing research in biomarkers, imaging, and novel agents. Below we present 8 consensus tables summarizing available data and expert consensus in the field of NETs (Tables 2—9).

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TABLES

Table 1: Controversial Topics

Pancreas
Use of octreotide for tumor control in patients with advanced pancreatic NETs
Indications for initiating targeted therapies or cytotoxic chemotherapy in patients with advanced pancreatic NETs
Midgut
Specific recommendations for dosing of octreotide LAR in refractory carcinoid syndrome
Indications for initiating octreotide for tumor control in patients with advanced carcinoid tumors
Dose escalation of octreotide for tumor control in patients with advanced carcinoid tumors
Indications for right hemicolectomy in patients with appendiceal carcinoids with high-risk features, which could be defined by size, infiltration into mesentery, located at base, and higher grade of tumor
Frequency of echocardiograms in functional midgut tumors
Pheochromocytoma
Indications for systemic chemotherapy in patients with advanced pheochromocytoma/paraganglioma
Surgery
Role of surgical debulking in asymptomatic patients with metastatic liver predominant NET
Role of surgical debulking in patients where an R0 resection cannot be achieved
Embolization
Role of bland embolization, radioembolization and chemoembolization
All
Use and frequency of chromogranin A in following patients on or off treatment
Use of everolimus and sunitinib in patients without pN
Use of somatostatin scintigraphy imaging to follow disease

Table 2: Neuroendocrine Tumor Pathology

Thoracic NET Pathology		
Mitotic rate should be obtained. Use of the World Health Organization (WHO) and International Association for the Study of Lung Cancer grading system is recommended. If specimen is inadequate, a second biopsy is recommended.		
Test or Procedure	Recommendation	Comment
Grading (proliferative rate)		
Mitotic rate	Recommend	Mitoses/10 HPF*
Ki67	Consider	
Typical carcinoid	Recommend	< 2 mitoses/10 HPF
Atypical carcinoid	Recommend	≥ 10 mitoses/10 HPF
High grade (small cell or large cell neuroendocrine carcinoma)	Recommend	> 10 mitoses/10 HPF
Presence of necrosis	Recommend	Absent: typical carcinoid; present: atypical carcinoid
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	May be appropriate
Biopsy or resection of primary tumor		
Anatomic site of tumor	Recommend	
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	Lung primary: invasion into pleura, main stem bronchus, pericardium, chest wall, or diaphragm. Thymic primary: invasion through tumor capsule, invasion into pleura, lung, pericardium, or adjacent structures
Nodal metastases	Recommend	
Resection margins	Recommend	Positive/negative
Vascular or perineural invasion	Recommend	Present/absent
Presence of nonneuroendocrine components	Recommend	Present/absent

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Table 2: Neuroendocrine Tumor Pathology (Continued)

Gastric NET Pathology		
Mitotic rate or Ki67 should be obtained. When both mitotic rate and Ki67 are obtained, the higher grade is assigned. If specimen is inadequate, a second biopsy is recommended.		
Test or Procedure	Recommendation	Comment
Grading (proliferative rate)		
Mitotic rate	Recommend	
G1		< 2 mitoses/10 HPF*
G2		2–20 mitoses/10 HPF
G3		> 20 mitoses/10 HPF
Ki 67	Recommend	
G1		< 3%
G2		3%–20%
G3		> 20%
Histology differentiation	Recommend	Poorly differentiated NECs (G3) are highly aggressive and need distinguishing from other NE
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
Cytokeratin	Consider	Marker for carcinoma
CDX2	Consider	Marker for bowel origin
CD56	Consider	Less specific marker for neuroendocrine phenotype
Biopsy or resection of primary tumor		
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	Present/absent
Nodal metastases	Recommend	
Distant metastases	Recommend	Pathologic metastasis (pM) denotes metastases location
Presence of nonneuroendocrine components	Recommend	Present/absent
Biopsies of nontumoral gastric mucosa	Recommend	Helps differentiate types of gastric NETs
Histology/immunohistochemistry		
Atrophic gastritis present		
Enterochromaffin-like (ECL) hyperplasia present		
Parietal cell hypertrophy present		

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Table 2: Neuroendocrine Tumor Pathology (Continued)

Pancreatic NET Pathology		
Mitotic rate or Ki67 should be obtained. When both mitotic rate and Ki67 are obtained, the higher grade is assigned. If specimen is inadequate, repeat biopsy is recommended.		
Test or Procedure	Recommendation	Comment
Subtype		
Small cell, non–small cell (ie, large cell)	Recommend	
Grading (proliferative rate)	Recommend	
Mitotic rate		
G1		< 2 mitoses/10 HPF*
G2		2–20 mitoses/10 HPF
G3		> 20 mitoses/10 HPF
Ki 67		
G1		< 3%
G2		3%–20%
G3		> 20%
Histology differentiation	Recommend	Poorly differentiated NECs (G3) are highly aggressive and need to be distinguished from other NETs
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
Cytokeratin	Consider	Marker for carcinoma
CDX2	Consider	Marker for bowel origin
CD56	Consider	Less specific marker for neuroendocrine phenotype
Biopsy or resection of primary tumor		
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	
Nodal metastases	Recommend	
Distant metastases	Recommend	pM denotes metastases location
Presence of nonneuroendocrine components	Recommend	Present/absent

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Table 2: Neuroendocrine Tumor Pathology (Continued)

Midgut NET Pathology		
Mitotic rate or Ki67 should be obtained. When both mitotic rate and Ki67 are obtained, overall grade is defined by the higher of the two. If specimen is inadequate, a second biopsy is recommended.		
Test or Procedure	Recommendation	Comment
Grading (proliferative rate)	Recommend	
Mitotic rate		
G1		< 2 mitoses/10 HPF*
G2		2–20 mitoses/10 HPF
G3		> 20 mitoses/10 HPF
Ki 67		
G1		< 3%
G2		3%–20%
G3		> 20%
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
Cytokeratin	Consider	Marker for carcinoma
CDX2	Consider	Marker for bowel origin
CD56	Consider	Less specific marker for neuroendocrine phenotype
Resection of primary tumor		
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	
Nodal metastases	Recommend	
Distant metastases	Recommend	pM should be used to denote metastases location
Presence of nonneuroendocrine components	Recommend	Present/absent

Continued on next page

Table 2: Neuroendocrine Tumor Pathology (Continued)

Hindgut NET Pathology		
Mitotic rate or Ki67 should be obtained. When both mitotic rate and Ki67 are obtained grade is the higher of grade determined by mitotic rate or Ki67. If specimen is inadequate, a second biopsy is recommended.		
Test or Procedure	Recommendation	Comment
Grading (proliferative rate)	Recommend	
Mitotic rate		
G1		< 2 mitoses/10 HPF*
G2		2–20 mitoses/10 HPF
G3		> 20 mitoses/10 HPF
Ki 67		
G1		< 3%
G2		3%–20%
G3		> 20%
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
CDX2	Consider	Marker for bowel origin
CD56	Consider	Less specific marker for neuroendocrine phenotype
Resection of primary tumor		
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	
Nodal metastases	Recommend	
Distant metastases	Recommend	pM denotes metastases location
Presence of nonneuroendocrine components	Recommend	Present/absent

Continued on next page

Table 2: Neuroendocrine Tumor Pathology (Continued)

Pheochromocytoma/Paraganglioma Pathology		
Distinction between benign and malignant disease is difficult to ascertain pathologically.		
Test or Procedure	Recommendation	Comment
Patient and tumor characteristics		
Age	Recommend	Younger age increases suspicion of genetic disease
Extra-adrenal location	Recommend	Extra-adrenal location increases the risk of malignancy
Pathology reporting		
Multicentricity	Recommend	Can increase suspicion of genetic disease
Accompanying medullary hyperplasia	Recommend	Can increase suspicion of genetic disease
Ki67	Consider	Rates >2%–3% can be associated with malignancy
Periadrenal adipose tissue	Consider	
Large nests/diffuse growth	Consider	
Focal or confluent necrosis	Consider	Can be associated with malignancy
Cellularity	Consider	
Tumor cell spindling	Consider	
Cellular monotony	Consider	
Mitotic rate	Consider	>3/10 HPF* can be associated with more aggressive behavior
Atypical mitosis	Consider	
Hyperchromasia	Consider	
Profound nuclear pleomorphism	Consider	
Immunohistochemistry		
CgA	Recommend	Marker of neuroendocrine phenotype
Synaptophysin	Consider	Marker of neuroendocrine phenotype
S-100	Consider	Marker for sustentacular supporting framework
Cytokeratin	Consider	Negative staining supports pheochromocytoma/paraganglioma over carcinoid tumor or NET

Continued on next page

Table 2: Neuroendocrine Tumor Pathology (Continued)

Poorly Differentiated NET Pathology		
Test or Procedure	Recommendation	Comment
Subtype		
Small cell, non–small cell (ie, large cell)	Recommend	
Grading (proliferative rate)		
Mitotic rate (G3)	Recommend	> 10 mitoses/10 HPF* for lung
		> 20 mitoses/10 HPF for Gastroenteropancreatic-NET
Ki 67	Recommend	> 20%
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
Cytokeratin	Consider	Marker for epithelial carcinoma
CDX2	Consider	Marker for bowel origin
CD56	Consider	Less specific marker for neuroendocrine phenotype
Resection of primary tumor		
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	
Nodal metastases	Recommend	
Distant metastases	Recommend	pM should be used to denote metastases location
Presence of nonneuroendocrine components	Recommend	Present/Absent

*Based on a 0.5-mm field diameter at high power, which yields a total area of 2 mm2 for 10 high power fields. ECL indicates enterochromaffin-like; GEP, gastroenteropancreatic.

Table 3: Neuroendocrine Tumors of the Thora

Initial workup		
Test or Procedure	Recommendation	Comment
Blood and urine markers (Baseline)		
Adrenocorticotropic hormone	Consider	As clinically indicated
CgA	Consider	Investigational in thoracic NET, check at baseline
Urine 5-hydroxyindoleacetic acid (5-HIAA)	Consider	As clinically indicated
Imaging (baseline)		
Anatomic imaging		
Chest and abdomen (multiphasic computed tomography [CT])	Recommend	
Magnetic resonance imaging (MRI) with gadoxetate (Eovist)	Consider	In patients where surgery is being considered to get a better sense of liver disease burden, particularly, when CT shows indeterminate lesions in the liver that need characterizing
MRI of the chest	Consider	To determine resectability in thymic tumors
[^{18}F]-fluorodeoxyglucose positron emission tomography (PET)	Consider	May be considered in undifferentiated tumors and/or to further characterize negative/equivocal octreotide scans
Luminal imaging		
Bronchoscopy	Consider	
Endobronchial ultrasound	Consider	
Nuclear imaging	Recommend	Planar and SPECT imaging. Imaging at 4–6 hours and 24–48 hours
[^{111}In-DTPA0] octreotide scintigraphy		

Treatment of Thymic NET		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely.		
Disease Stage	Intervention	Recommendation
Locoregional disease	Surgical resection including mediastinal lymphadenectomy	Recommend
Recurrent localized disease	Surgical resection of localized disease	Recommend
Metastatic/unresectable disease	Everolimus	Consider
	Interferon α	Consider
	Radiation for unresectable disease	Consider
	Temozolomide	Consider

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Table 3: Neuroendocrine Tumors of the Thora (Continued)

Treatment of Lung/Bronchial NET		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Disease Stage	Intervention	Recommendation
Locoregional disease	Surgical resection with hilar/mediastinal lymph node sampling is recommended	Recommend
Recurrent disease, resectable	Surgical resection	Recommend
Metastatic/unresectable disease	Everolimus	
	Interferon α	Consider
	Radiation for unresectable disease	Consider
	Temozolomide	Consider
Follow-Up		
Follow-up for resected disease is recommended 3 to 6 months after curative resection and then every 6 to 12 months for at least 7 years. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patient with long duration (912 month) of stable disease.		
Test or Procedure	Recommendation	Comment
Blood and urine markers		
Adrenocorticotropic hormone	Consider	Consider following if abnormal at baseline
CgA	Consider	Consider following if abnormal at baseline
Urine 5-HIAA	Consider	Consider following if abnormal at baseline
Imaging		
Anatomic imaging (CT or MRI)	Recommend	See initial imaging for details
Nuclear imaging	Consider	As clinically indicated for suspected recurrence
[^{111}In-DTPA0]octreotide scintigraphy		(see initial imaging for details)

Table 4: Gastric NETs

Initial workup		
Test or Procedure	Recommendation	Comment
Blood and urine markers (Baseline)		
Gastric pH	Recommend	Gastric pH helps differentiate type I (gastric pH >4) from type II (gastric pH <2). Type II requires workup for Multiple Endocrine Neoplasia (MEN) 1 syndrome. Type III gastric pH <4
Gastrin	Recommend	Should be fasting and off PPI when feasible (types I and II will have elevated gastrin levels; type III will have normal gastrin level)
5-HIAA	Consider	As indicated for atypical type III foregut tumors or if symptoms suggestive of carcinoid syndrome. Need to follow diet during collection.
Anti-intrinsic factor and antiparietal cell antibodies	Consider	Only in type I. Consider workup for polyglandular syndrome
CgA	Consider	Recommended for type III (normogastrinemic) gastric carcinoids; false positive with proton pump inhibitor use and renal insufficiency
Imaging (baseline)		
Anatomic imaging		
Abdomen and pelvis (multiphasic CT or MRI)	Recommend	For types II and III only
MRI with gadoxetate (Eovist)	Consider	In patients where surgery is being considered to get a better sense of liver disease burden, particularly, when CT shows indeterminate lesions in the liver that need characterizing
Luminal imaging		
Esophagogastroduodenoscopy (EGD)	Recommend	Permits sampling of gastric mucosa and determination of disease extent
Endoscopic ultrasound (EUS)	Consider	Best procedure to determine tumor size/infiltration and to identify possible lymph node metastases
Nuclear imaging		
[^{111}In-DTPA0] octreotide scintigraphy	Consider	

Table 4: Gastric NETs (Continued)

Surgery of Primary Tumors		
In general, resection is recommended for local regional disease and in setting of impending obstruction and should still be considered for patients with advanced disease. Ability to resect primary tumors depends on the number, size, depth of invasion, and institutional expertise. In patients with suspected carcinoid syndrome who undergo major procedures, a preoperative bolus of octreotide, 250 to 500 Hg intravenous, is recommended with additional bolus doses available throughout the procedure.		
Tumor Type	Intervention	Recommendation
Type I		
<1 cm	Surveillance or endoscopic removal	Recommend
1–2* cm (up to 6 polyps)	Surveillance with repeat endoscopy approximately every 3 years or endoscopic resection. Endoscopic US could be used to assess depth of invasion but should be individualized. If submucosal invasion, endoscopic mucosal resection is increasingly used.	Recommend
>2* cm (up to 6 polyps)	Endoscopic resection (if possible) or surgical resection	Recommend
>2* cm (>6 polyps)	Must be individualized and could include surveillance, endoscopic resection or surgical resection	Recommend
Type II		
<1 cm	Surveillance or endoscopic removal	Recommend
1–2 cm	Endoscopic resection. EUS should be used to assess depth of invasion. If submucosal invasion, endoscopic mucosal resection is increasingly used.	Recommend
>2 cm	Surgical resection or endoscopic resection (if possible)	Recommend
Type III	Partial gastrectomy and lymph node dissection	Recommend

Table 4: Gastric NETs (Continued)

Advanced Disease—Oncologic Control of Gastric NETs		
Advanced disease is typically limited to type III only. Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Indication	Intervention	Recommendation
Newly diagnosed with low or intermediate tumor volume	Observation if no hormonal symptoms present	Recommend
	Octreotide LAR	Consider
Newly diagnosed with high-volume disease	Everolimus	Consider
	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider
Stable disease	Observation if no hormonal symptoms	Consider
Progressive disease	Everolimus	Consider
	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider
	Refer to specialty center	Consider
Hormonal Syndrome Control		
Carcinoid syndrome is rarely found in gastric NETs (type III only).		
Carcinoid syndrome		
Initial or nonrefractory	Long-acting somatostatin analogs; octreotide LAR, 20–30 mg IM is available in the United States. Immediate release octreotide can be used for breakthrough symptoms.	Recommend
Refractory syndrome with stable tumor volume	Antidiarrheal agents	Recommend
	Debulk tumor with liver-directed therapy if possible	Recommend
	Escalate dose or shorten dosing interval of long-acting somatostatin analog. No prospective data exist.	Recommend
	Add low-dose interferon α (short-acting or pegylated form)	Consider
	Referral to specialty center	Consider
	Rotate somatostatin analog as available	Consider

Table 4: Gastric NETs (Continued)

Indication	Intervention	Recommendation
Refractory syndrome with increasing tumor volume	Measures for refractory syndrome	Recommend
	Measures for oncologic control See Oncologic control section.	Recommend
	Refer to specialty center	Consider
Follow-Up		
Follow-up for resected gastric NET disease is recommended 3 to 6 months after curative resection and then every 6 to 12 months for at least 7 years. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patient with long duration (>12 months) of stable disease.		
Test or Procedure	**Recommendation**	**Comment**
Blood and urine markers		
CgA	Consider	Consider following if abnormal at baseline
Specific hormone marker	Consider	Consider following if abnormal at baseline
Imaging		
Anatomic imaging (multiphasic CT or MRI)	Recommend	See initial imaging for details
Luminal Imaging		
EGD		
Gastric pH		
Nuclear imaging	Consider	As clinically indicated for suspected recurrence (see initial imaging for details)
[^{111}In-DTPA0]octreotide scintigraphy		

*Multiple lesions that are larger than 1 to 2 cm should be individually decided and could include local resection, surgical resection, or watchful waiting. EGD indicates esophagogastroduodenoscopy; MEN, multiple endocrine neoplasia.

Table 5: Pancreatic NETs

Initial workup		
Test or Procedure	Recommendation	Comment
Blood and urine markers (Baseline)		
CgA	Recommend	Especially useful if nonfunctional pancreatic NET suspected. False positive with proton pump inhibitor use and renal insufficiency
5-HIAA	Recommend	As clinically indicated
Gastrin	Recommend	As clinically indicated; need to follow diet during collection
Glucagon	Recommend	As clinically indicated; should be fasting
Insulin/proinsulin	Recommend	As clinically indicated; should be fasting with concurrent glucose
Pancreatic polypeptide	Recommend	As clinically indicated
VIP	Recommend	As clinically indicated
Other [Parathyroid hormone-related peptide, growth hormone releasing factor, etc]	Recommend	As clinically indicated
Genetic testing		
Inherited syndromes (Von-Hippel Lindau, tuberous sclerosis, neurofibromatosis-1)	Recommend	Genetic testing needs to be considered if clinical or family history is suggestive of these syndromes (see text for details of syndromes)
(Von-Hippel Lindau, tuberous sclerosis, neurofibromatosis-1)		
Multiple Endocrine Neoplasia Type 1 (MEN1)	Consider	Genetic testing for MEN 1 is recommended in all young patients with gastrinomas or insulinomas, any patient with a family or personal history of other endocrinopathies (especially hyperparathyroidism) or multiple pancreatic NETs.

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Table 5: Pancreatic NETs (Continued)

Imaging (baseline)		
Anatomic imaging		
Abdomen and pelvis (multiphasic CT or MRI)	Recommend	Thin sections
MRI with gadoxetate (Eovist)	Consider	In patients where surgery is being considered to get a better sense of liver disease burden, particularly, when CT shows indeterminate lesions in the liver that need characterizing
Additional sites	Consider	As clinically indicated
Luminal imaging		
EGD	Consider	In patients suspected of gastrinoma to visualize prominent gastric folds in Zollinger Ellison Syndrome; also with duodenal NETs (often nonfunctional) and in MEN 1 who have submucosal duodenal lesions
EUS	Consider	Should be performed for diagnostic purposes if pancreatic NET is suspected and no primary identified on cross-sectional imaging; helps identify small pancreatic NET lesions
Nuclear imaging		
[^{111}In-DTPA0] octreotide scintigraphy	Recommend	Planar and SPECT imaging. Imaging at 4–6 hours and 24–48 hours
Surgery of Primary Tumors		
In general, resection is recommended for local regional disease and should still be considered for patients with advanced disease. Optimize nutritional status and control of hormone excess state medically preoperatively as outlined in the functional pancreatic NET section.		
Functional Status	Intervention	Recommendation
Functional pancreatic NET		
Gastrinoma		
Sporadic	Surgical removal with enucleation, resection, or occasionally a pancreaticoduodenectomy. Routine duodenotomy and periduodenal/ tumoral nodal dissection required	Recommend
With MEN1	If imaged tumor is <2–2.5 cm, most observe, although some recommend enucleation or resection. Pancreaticoduodenectomy rarely indicated	Recommend
Other functional tumor (sporadic or with MEN1)	Enucleation or surgical resection/ enucleation	Recommend

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Table 5: Pancreatic NETs (Continued)

Functional Status	Intervention	Recommendation
Nonfunctional pancreatic NET		
Sporadic	Enucleation or surgical resection with lymph node dissection. Observation in elderly or comorbid conditions	Recommend
With MEN1	If imaged tumor is <2–2.5 cm, most observe, although some recommend enucleation or resection. Pancreaticoduodenectomy rarely indicated. If >2–2.5 cm, enucleation or surgical resection with adjacent lymph node dissection.	Recommend
With VHL	If imaged tumor is >3 cm, surgical resection is recommended.	Recommend
Advanced Disease—Oncologic Control of Pancreatic NETs		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Indication	Intervention	Recommendation
Newly diagnosed with low or intermediate tumor volume	Observation if no hormonal syndrome	Recommend
Newly diagnosed with high-volume disease	Observation for a brief 3-month period if no hormonal syndrome	Recommend
	Everolimus	Consider
	Hepatic artery embolization when liver dominant disease (bland embolization, chemoembolization, or radioembolization per institutional practice)	Consider
	Sunitinib	Consider
Stable disease	Observation if no hormonal syndrome	Recommend
Progressive disease	Sunitinib	Recommend
	Everolimus	Recommend
	Cytotoxic chemotherapy	Consider
	Hepatic artery embolization when liver dominant disease (bland embolization, chemoembolization, or radioembolization per institutional practice)	Consider
	Octreotide LAR	Consider

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Table 5: Pancreatic NETs (Continued)

Hormonal Syndrome Control		
Please also see the section entitled, ''Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Colon'' for control of hormonal syndromes in the carcinoid syndrome.		
Indication	Intervention	Recommendation
Insulinoma		
Initial or nonrefractory	Dietary modification	Recommend
	Diazoxide 200–600 mg/d	Recommend
	Everolimus	Recommend
	Medicalert bracelet	Recommend
	Glucagon pen	Consider
	Somatostatin analogs. May worsen hypoglycemia in some cases; therefore, consider short-acting octreotide trial before initiation of octreotide LAR).	Consider
	Steroids (ie, decadron)	Consider
Gastrinoma	Oral proton pump inhibitors	Recommend
Initial and long-term	BID or TID dosing of Proton Pump Inhibitor	Recommend
	Medicalert bracelet	Consider
	Octreotide LAR	Consider
Other functioning PETs	Octreotide LAR	Recommend
Refractory syndrome with stable tumor volume	Nonspecific antidiarrheal agents as clinically indicated	Recommend
	Escalate dose or shorten dosing interval of octreotide LAR	Consider
	Liver-directed therapy if possible	Consider
	Surgical debulking	Consider
Refractory syndrome with increasing tumor volume	Measures for refractory syndrome	Recommend
	Measures for oncologic control (see Oncologic control section).	Recommend
	Referral to specialty center	Recommend

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Table 5: Pancreatic NETs (Continued)

Follow-Up		
Follow-up for resected pancreatic is recommended 3 to 6 months after curative resection and then every 6 to 12 months for at least 7 years. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patient with long duration (>12 months) of stable disease.		
Test or Procedure	Recommendation	Comment
Blood and urine markers		
CgA	Consider	Consider following if abnormal at baseline
Specific hormone marker	Consider	Consider following if abnormal at baseline
Imaging		
Anatomic imaging (multiphasic CT or MRI)	Recommend	See initial imaging for details
Nuclear imaging	Consider	As clinically indicated for suspected recurrence (see initial imaging for details)
[^{111}In-DTPA0]octreotide scintigraphy		

GRF indicates growth hormone releasing factor; PPI, proton pump inhibitor; PTH, parathyroid hormone; VHL, Von-Hippel Lindau; ZES, Zollinger Ellison syndrome.

Table 6: Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Cecum

Initial workup		
Test or Procedure	Recommendation	Comment
Blood and urine markers (Baseline)		
CgA	Recommend	Often negative in those with localized tumors. False positive with proton pump inhibitor use and renal insufficiency
Urine 5-HIAA	Recommend	Need to follow diet during collection
Imaging (baseline)		
Anatomic imaging		
Abdomen and pelvis (multiphasic CT or MRI)	Recommend	Thin section with negative bowel contrast if attempting to identify primary tumor. Consider MRI if unable to give iodine-based contrast. Consider specific enterography protocols if available.
MRI with gadoxetate (Eovist)	Recommend	In patients where surgery is being considered to get a better sense of liver disease burden, particularly when CT shows indeterminate lesions in the liver that need characterizing
Additional sites	Recommend	As clinically indicated

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Table 6: Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Cecum (Continued)

Test or Procedure	Recommendation	Comment
Luminal Imaging		
Colonoscopy	Recommend	Terminal ileal intubation
Deep enteroscopy	Consider	Best approached bidirectionally; tattoo location if identified
Nuclear imaging		
[111In-DTPA0]octreotide scintigraphy	Recommend	Planar and SPECT imaging. Imaging at 4–6 hours and 24–48 hours
Cardiac imaging		
Echocardiogram	Consider	If symptoms of carcinoid heart are suspected or as clinically indicated

Surgery of Primary Tumors
In general, resection is recommended for local regional disease and in setting of impending obstruction and should still be considered for patients with advanced disease. Ability to resect primary depends on size, depth of invasion, and institutional expertise. In patients with suspected carcinoid syndrome who undergo major procedures, a preoperative bolus of octreotide 250 to 500 µg IV is recommended with additional bolus doses available throughout procedure.

Primary Site/Size	Intervention	Recommendation
Appendix, cm		
<1	Excision	Recommend
1–2	Excision	Recommend
	Right hemicolectomy with node dissection if high risk features present	Consider
>2	Right hemicolectomy with node dissection	Recommend
Cecum	Right hemicolectomy with node dissection	Recommend
Ileum	Resection with node dissection. Ileocecal valve and right colon can be preserved for more proximal tumors. Full bowel examination required at time of surgery in case of lateral metastases.	Recommend
Jejunum	Resection with node dissection. Full bowel examination required at time of surgery in case of lateral metastases.	Recommend
Root of mesentery disease	Refer to expert center for assessment when nodal disease approaches branches of Superior Mesenteric Vein or Superior Mesenteric Artery.	Recommend

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Table 6: Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Cecum (Continued)

Advanced Disease—Oncologic Control		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Indication	Intervention	Recommendation
Newly diagnosed with low or intermediate tumor volume	Observation if no hormonal symptoms present	Recommend
	Octreotide LAR	Consider
Newly diagnosed with high-volume disease	Everolimus	Consider
	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider
Stable disease	Observation if no hormonal symptoms	Consider
Progressive disease	Refer to specialty center	Recommend
	Everolimus	Consider
	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider
Hormonal Syndrome Control		
Carcinoid syndrome		
Initial or nonrefractory	Long-acting somatostatin analogs; octreotide LAR 20–30 mg IM is available in the United States. Immediate release octreotide can be used for breakthrough symptoms.	Recommend
Refractory syndrome		
Stable tumor volume	Antidiarrheal agents	Recommend
	Debulk tumor with liver-directed therapy if possible	Recommend
	Escalate dose or shorten dosing interval of long-acting somatostatin analog. No prospective data exist.	Recommend
	Add low-dose interferon α (short-acting or pegylated form)	Consider
	Referral to specialty center	Consider
	Rotate somatostatin analog as available	Consider

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Table 6: Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Cecum (Continued)

Increasing tumor volume	Measures for refractory syndrome	Recommend
	Measures for oncologic control (see Oncologic control section)	Recommend
	Refer to specialty center	Consider
Follow-Up		
Follow-up for resected disease is recommended 3 to 6 months after resection with curative intent and then every 6 to 12 months for at least 7 years. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patient with long duration (>12 months) of stable disease.		
Test or Procedure	**Recommendation**	**Comment**
Blood and urine markers		
CgA	Consider	Consider following if abnormal at baseline
Urine 5-HIAA	Consider	Consider following if abnormal at baseline
Imaging		
Anatomic imaging (multiphasic CT or MRI)	Recommend	See initial imaging for details
Nuclear imaging	Consider	As clinically indicated for suspected recurrence (see initial imaging for details)
[^{111}In-DTPA0]octreotide scintigraphy		

SMA indicates superior mesenteric artery; SMV, superior mesenteric vein.

Table 7: Neuroendocrine Tumors of the Distal Colon and Rectum

Initial workup		
Test or Procedure	**Recommendation**	**Comment**
Blood and urine markers (Baseline)		
CgA	Recommend	Often negative in those with localized tumors. False positive with proton pump inhibitor use and renal insufficiency
Urine 5-HIAA	Consider	Need to follow diet during collection
Imaging (baseline)		
Anatomic imaging		
Abdomen and pelvis (multiphasic CT or MRI)	Recommend	Recommended for patients with tumors 92 cm, invasion beyond submucosa, or lymph node involvement. Could also consider for tumors with elevated mitotic rate or poor differentiation.

Table 7: Neuroendocrine Tumors of the Distal Colon and Rectum (Continued)

MRI with gadoxetate (Eovist)	Consider	In patients where surgery is being considered to get a better sense of liver disease burden, particularly when CT shows indeterminate lesions in the liver that need characterizing.
Additional sites	Consider	As clinically indicated
Luminal imaging		
Colonoscopy	Recommend	Often detected incidentally on colonoscopy; consider tattoo for localization.
EUS		
Nuclear imaging		
[^{111}In-DTPA0]octreotide scintigraphy	Recommend	Planar and SPECT imaging. Imaging at 4–6 hours and 24–48 hours

Surgery of Primary Tumors		
In general, resection is recommended for local regional disease and in setting of impending obstruction and should still be considered for patients with advanced disease. Ability to resect primary depends on size, depth of invasion, and institutional expertise.		
Primary Site/Size	Intervention	Recommendation
<1	Endoscopic resection (polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection) for those with mucosal or submucosal tumors	Recommend
1–2	Transanal excision via rigid or flexible dissection. Could also consider after endoscopic resection with positive margins	Recommend
>2	Surgical resection (low anterior resection or abdominoperineal resection) for larger tumors, tumors invading muscularis propria, or those with lymphadenopathy	Recommend
Incidentally discovered	Tattoo location if polyp has unusual features suggestive of carcinoid at screening colonoscopy.	Consider

Advanced Disease—Oncologic Control		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Indication	Intervention	Recommendation
Newly diagnosed with low or intermediate tumor volume	Observation if no hormonal syndrome	Recommend
	Octreotide LAR	Consider

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Table 7: Neuroendocrine Tumors of the Distal Colon and Rectum (Continued)

Newly diagnosed with high-volume disease	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider
Stable disease	Observation if no hormonal syndrome	Consider
Progressive disease	Refer to specialty center	Recommend
	Everolimus	Consider
	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider

Follow-Up
Intensity and duration of surveillance depends on stage of disease. Stage I tumors require no surveillance. Stage II or III should be followed 3 to 6 months after curative resection and then every 6 to 12 months for at least 7 years. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patients with long duration (>12 months) of stable disease.

Test or Procedure	Recommendation	Comment
Blood and urine markers		
CgA	Consider	Consider following if abnormal at baseline
Urine 5-HIAA	Consider	Consider following if abnormal at baseline
Imaging		
Anatomic imaging (multiphasic CT or MRI)	Recommend	See initial imaging for details
Nuclear imaging	Consider	As clinically indicated for suspected recurrence (see initial imaging for details)
[^{111}In-DTPA0]octreotide scintigraphy		

Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer

Initial workup (Pheochromocytoma/Paraganglioma)		
Test or Procedure	Recommendation	Comment
Blood and urine markers (Baseline)		
Hormonal markers		
Fractionated or free metanephrines (ie, normetanephrine and metanephrines) in urine or plasma, respectively, or both	Recommend	It is preferred to measure fractionated or free metanephrines versus the parent catecholamines. Blood sampling should be done in the supine position after a 20-minute rest.
>4 upper reference range		Diagnostic of pheochromocytoma
1–4 upper reference range		Needs further evaluation. First, exclude drug effect, and then use clonidine suppression test coupled with the measurement of plasma normetanephrine (does not work if coupled with the measurement of plasma metanephrine).
Genetic counseling/genetic testing when appropriate	Recommend	To choose the proper genetic testing sequence, consider the biochemical profile of catecholamine secretion, age of the patient, localization of the primary tumor, and previous family history.
Methoxytyramine	Consider	Marker of dopamine secreting tumors, associated with malignancy and mutations in the succinate dehydrogenase complexYrelated tumors
Imaging (baseline)		
Anatomic imaging		
Abdomen and pelvis (multiphasic CT or MRI)	Recommend	Both modalities are effective for localizing and characterizing adrenal masses.
MRI with gadoxetate (Eovist)	Consider	In patients where surgery is being considered to get a better sense of liver disease burden, particularly, when CT shows indeterminate lesions in the liver that need characterizing
Additional sites	Consider	As clinically indicated, if no lesion is seen on abdomen and pelvis imaging
Nuclear imaging		Planar and SPECT imaging. Imaging at 4–6 hours and 24–48 hours
Iodine 123		
[^{123}I]-metaiodobenzylguanide (MIBG) ([^{123}]I-MIBG) scintigraphy	Consider	Should be used on all functional tumors except adrenal pheochromocytomas G5 cm that are associated with elevations of plasma and urine metanephrine (rarely metastatic). Also to be used when treatment with 131I-MIBG is considered (metastatic disease already proven by anatomic imaging)

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Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer (Continued)

[^{18}F]-fluorodeoxyglucose PET	Consider	Obtain if [^{123}]I-MIBG scan is negative and there is concern for metastatic disease.
[^{111}In-DTPA0]octreotide scintigraphy (octreotide scan)	Consider	Obtain if [^{123}]-MIBG scan is negative and there is concern for metastatic disease as well as when treatment with octreotide is considered (metastatic disease already proven by anatomic imaging).
Surgery of Primary Tumors (Pheochromocytoma/Paraganglioma)		
For major procedures, start phenoxybenzamine at 10 mg oral 2 times a day and titrate to control hypertension. May also use α-1 adrenoceptor blockers. Also consider calcium channel blocker or angiotensin receptor blockers, especially in patients with mild hypertension, and treatment should be for at least 10 to 14 days before surgery. Use volume expansion through hydration before surgery. If tachycardia is present, add β-adrenoceptor blocker (atenolol preferred). Only start after appropriate α-blockade has started.		
Surgical Approach	Intervention	Recommendation
Laparoscopic resection	Procedure of choice if no evidence of local invasion or malignancy. Consider cortical sparing adrenalectomy if familial or bilateral disease.	Recommend
Test or Procedure	Recommendation	Comment
Open resection	Procedure of choice if evidence of local invasion or malignancy or recurrent disease.	Recommend
Cytoreductive resection when locally unresectable or distant metastases present	Cytoreductive surgery should be considered in all patients to help aid in symptom control.	Consider
Advanced Disease–Oncologic Control (Pheochromocytoma/Paraganglioma)		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Indication	Intervention	Recommend
Locally unresectable	Cytoreductive surgery, if feasible	Recommend
	External beam radiation therapy	Consider
Distant Disease	Cytoreductive surgery, if feasible	Recommend
	[^{131}I]-MIBG treatment if [^{123}I]-MIBG–positive disease	Consider
	Radiofrequency ablation	Consider
	Systemic chemotherapy (cyclophosphamide, vincristine, and dacarbazine,) if [^{123}I]-MIBG–negative disease or rapidly progressing	Consider

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Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer (Continued)

Hormonal Syndrome Control (Pheochromocytoma/Paraganglioma)		
Indication	Intervention	Recommendation
Treatment of catecholamine overproduction	Alpha-blockade for symptom control. May change to selective α-1 blockers for long-term treatment	Recommend
	Beta-blockade if necessary after adequate α-blockade in patients with tachycardia	Recommend
Treatment of catecholamine crisis	Alpha-methyl-para-tyrosine	
	Phentolamine IV bolus 2.5–5 mg at 1 mg/min, may repeat every 5 minutes or run as an infusion (100 mg in 500 mL of Dextrose 5% water). Alternative is nitroprusside infusion at 0.5–5.0 µg/kg per minute. (do not exceed 3.0 µg/kg per minute for long-term use)	Recommend

Follow-up (Pheochromocytoma/Paraganglioma)		
Follow-up for resected disease is recommended 6 and 12 months after curative resection and then annually. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patient with long duration (>12 months) of stable disease.		
Test or Procedure	Recommendation	Comment
Blood and urine markers		
Fractionated or free metanephrines	Recommend	
CgA	Consider	May be used if tumor does not produce significant levels of plasma metanephrines, especially those with succinate dehydrogenase complex gene mutations
Imaging		
Anatomic imaging (multiphasic CT or MRI)	Recommend	As clinically indicated for suspected recurrence.
PET scan, octreotide scan, MIBG scan	Consider	As clinically indicated for suspected recurrence.
Initial workup (Medullary Thyroid Cancer)		
Blood and urine markers (baseline)		
Tumor markers		
Calcitonin	Recommend	Correlates with tumor burden
Carcinoembryonic antigen (CEA)	Consider	Preferentially expressed in less differentiated tumors
Refer for genetic counseling/testing	Recommend	

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Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer (Continued)

Test or Procedure	Recommendation	Comment
Test for associated tumors (pheochromocytoma and hyperparathyroidism)		
Fractionated or free metanephrines (ie, normetanephrine and metanephrines) in urine or plasma, respectively, or both	Recommend	Fractionated or free metanephrines preferred over the parent catecholamines. Blood sampling should be done in the supine position after a 20-minute rest.
Calcium	Recommend	If abnormal, obtain a PTH level.
Imaging (baseline)		
Anatomic imaging		
CT of chest, mediastinum, and abdomen	Recommend	Evaluate for metastatic disease, especially if evidence of nodal disease on neck ultrasound or calcitonin is significantly elevated.
Neck ultrasound	Recommend	To assess for additional thyroid masses and neck lymphadenopathy
Laparoscopy of liver	Consider	As clinically indicated if concerned about micrometastatic disease in the liv
Surgery of Primary Tumors (Medullary Thyroid Cancer)		
Intervention	Recommendation	Comment
Primary tumor resection		
Locoregional disease	Recommend	
Advanced disease	Consider	
Nodal disease		
Bilateral central neck dissection	Recommend	For locoregional disease
	Consider	For advanced disease
Ipsilateral lateral neck dissection	Recommend	If evidence of nodal disease on preoperative imaging
	Consider	If tumor is >1 cm or there is evidence of positive nodes in the central neck
Contralateral lateral neck dissection	Recommend	If evidence of nodal disease on preoperative imaging
	Consider	If bilateral tumors, or extensive lateral adenopathy on the side of the tumor
Prophylactic surgery (medullary thyroid cancer)		
Preoperative		
Test for pheochromocytoma, hyperparathyroidism	Recommend	All patients should be tested for a pheochromocytoma (fractionated metanephrines in plasma or urine) and hyperparathyroidism (serum calcium) preoperatively.
Baseline tumor markers (calcitonin and CEA)	Recommend	
Neck ultrasound	Recommend	Evaluate for tumors and/or lymphadenopathy

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Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer (Continued)

Intervention	Recommendation	Comment
Surgical treatment		
Total thyroidectomy	Recommend	Should be performed by age 1 in MEN 2B and by age 5 in MEN 2 and Familial Medullary Thyroid Carcinoma.
Bilateral central neck dissection	Consider	If elevated preoperative calcitonin or evidence of tumor on neck ultrasound

Advanced Disease–Oncologic Control (Medullary Thyroid Cancer)		
Generally for NETs, lines of therapy have not been established when multiple options are listed. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Disease Stage	Intervention	Recommendation
Locally unresectable	Cytoreductive surgery, if feasible	Recommend
	Vandetanib	Recommend
	External beam radiation therapy should be used only if surgical resection is not feasible or surgical resection is incomplete	Consider
Distant disease	Cytoreductive surgery, if patient is symptomatic and resection is feasible	Recommend
	Vandetanib	Recommend
	Palliative regional therapy (RFA, embolization, etc.)e	Consider

Hormonal Syndrome Control (Medullary Thyroid Cancer)		
Indication	Intervention	Recommendation
Refractory symptoms due to hypercalcitonemia	Long-acting somatostatin analogs	Recommend
	Cytoreductive surgery of unresectable disease	Consider

Follow-up (Medullary Thyroid Cancer)		
Follow-up for resected disease is recommended 3 to 6 months after curative resection and then annually; maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 to 12 months for patient with long duration (>12 months) of stable disease. Follow-up after prophylactic thyroidectomy if no tumor present or only c-cell hyperplasia found is recommended every 1 to 2 years.		
Test or Procedure	Recommendation	Comment
Biomarkers (calcitonin and CEA)	Recommend	
Fractionated plasma and/or urinary metanephrines	Recommend	Annually, if at risk for MEN 2A or 2B
Serum calcium	Recommend	Annually, if at risk for MEN2A

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Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer (Continued)

Imaging		
Neck ultrasound	Recommend	May discontinue if calcitonin and CEA are stable and previous ultrasound was negative. Consider in advanced disease.
Anatomic imaging		
CT or MRI	Consider	As clinically indicated for suspected recurrence
Additional imaging	Consider	As clinically indicated for rising calcitonin and/or CEA

CEA indicates carcinoembryonic antigen; D5W, dextrose 5% water; FMTC, familial medullary thyroid carcinoma; PTH, parathyroid hormone.

Table 9: Poorly Differentiated NECs

Generally, blood and urine markers are not helpful in poorly differentiated NECs.		
Initial workup (Medullary Thyroid Cancer)		
Test or Procedure	Recommendation	Comment
Imaging (baseline)		
Anatomic imaging		
CT chest, abdomen, and pelvis	Recommend	Used for baseline imaging and to monitor for response to treatment
Brain MRI	Consider	MRI of brain is recommended for poorly differentiated NEC of lung origin. Risk of brain metastases for extrapulmonary NEC is rare. Should be considered as clinically indicated.
Nuclear imaging		
Bone scan	Consider	
[^{18}F]-fluorodeoxyglucose PET	Consider	If clinically appropriate. Poorly differentiated NEC can be strongly hypermetabolic on FDG-PET CT scan, which may be helpful to stage disease and monitor response to treatment.
[^{111}In-DTPA0]octreotide scintigraphy	Consider	Consider only if disease is not avid on FDG-PET scan.

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Table 9: Poorly Differentiated NECs (Continued)

Treatment of Poorly Differentiated NEC		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy.		
Disease Stage	Intervention	Recommendation
Locoregional disease, resectable		
Clinical stage T1-2, NO	Surgical resection, including removal of tumor with negative margins. Risk of recurrence is high, however.	Recommend
	Postoperative therapy with 4Y6 cycles of cisplatin or carboplatin and etoposide. Radiation should only be considered in cases where risk of local recurrence is considered high and morbidity is low.	Recommend
Clinical stage in excess of T1-2, N0	Chemotherapy with or without concurrent radiotherapy	Recommend
	Surgery where morbidity is low, particularly where risk of obstruction is high. Risk of recurrence is high, however. Consider postoperative therapy with 4–6 cycles of cisplatin or carboplatin and etoposide. Radiation should only be considered in cases where risk of local recurrence is considered high and morbidity is low.	Consider
Locoregional disease, unresectable	Platinum-based chemotherapy regimen (cisplatin or carboplatin and etoposide) for 4–6 cycles with concurrent or sequential radiation	Recommend
Metastatic: initial therapy	Platinum-based chemotherapy*	Recommend
Metastatic: progressive or relapsed disease	For relapse >6 months after termination of first-line therapy: original chemotherapy regimen	Recommend
	For relapse <3–6 months: irinotecan or topotecan, paclitaxel, docetaxel, vinorelbine, gemcitabine, temozolomide may be considered.	Consider

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Table 9: Poorly Differentiated NECs (Continued)

Follow-Up		
Follow-up for resected disease is recommended every 3 months for 1 year, followed by every 6 months. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 6 to 12 weeks.		
Test or Procedure	Recommendation	Comment
Imaging		
Anatomic imaging (CT or MRI)	Recommend	See initial imaging for details
Nuclear imaging	Consider	As clinically indicated. Poorly differentiated NEC can be strongly hypermetabolic on FDG-PET CT scan, which may be helpful to stage disease and monitor response to treatment.
[^{18}F]-fluorodeoxyglucose PET		

*Chemotherapy regimens active against small-cell lung cancer are recommended. Cisplatin and etoposide have demonstrated activity in the treatment of poorly differentiated NEC. Substitution of carboplatin for cisplatin and irinotecan for etoposide can be considered. Four to 6 cycles of chemotherapy typically administered. Optimal duration of therapy is not clearly defined.

REFERENCES

References

1. Anthony LB, Strosberg JR, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (nets): well-differentiated nets of the distal colon and rectum. *Pancreas*. 2010;39(6):767–774.
2. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas.* 2010;39(6):753–766.
3. Chen H, Sippel RS, O'Dorisio MS, et al. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. *Pancreas*. 2010;39(6):775–783.
4. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas.* 2010;39(6):707–712.
5. 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.
6. Phan AT, Oberg K, Choi J, et al. NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the thorax (includes lung and thymus). *Pancreas.* 2010;39(6):784–798.
7. Strosberg JR, Coppola D, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. *Pancreas.* 2010;39(6):799–800.
8. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):514–523.
9. 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.
10. 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.
11. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet.* 2011;378(9808):2005–2012.
12. 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.
13. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656–4663.
14. 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.
15. 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.
16. Madoff DC, Gupta S, Ahrar K, et al. Update on the management of neuroendocrine hepatic metastases. *J Vasc Interv Radiol.* 2006;17(8):1235–1249; quiz 1250.
17. Reidy DL, Tang LH, Saltz LB. Treatment of advanced disease in patients with well-differentiated neuroendocrine tumors. *Nat Clin Pract Oncol.* 2009;6(3):143–152.
18. Schurr P, Strate T, Rese K, et al. Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. *Ann Surg.* 2007;245(2):273–281.

19. Touzios J, Kiely J, Pitt S, et al. Neuroendocrine hepatic metastases: does aggressive management improve survival? *Ann Surg.* 2005;241(5):776–783.
20. Sarmiento J, Heywood G, Rubin J. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg.* 2003;197:29–37.
21. Chamberlain R, Canes D, Brown K, et al. Hepatic neuroendocrine metastases: does intervention affect outcome? J *Am Coll Surg*. 2000;190:432–445.

NANETS
NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

The North American Neuroendocrine Tumor Society (NANETS) Guidelines

Mission, Goals, and Process

Larry K. Kvols, MD[*] and Kari L. Brendtro[†]

The North American Neuroendocrine Tumor Society (NANETS) had its initial organizational meeting in Portland, Oregon on September 28, 2006 to establish a professional society with the primary purpose to improve neuroendocrine tumor disease management through increased research and educational opportunities. This founding group was comprised of scientists, physicians, and surgeons representing a variety of specialties, all with a particular interest in neuroendocrine tumors (NETs).

During this initial assembly, by-laws were adopted, officers were elected, and specific objectives were prioritized. The NANETS was registered and granted nonprofit 501(c)(3) status by the Internal Revenue Service on February 21, 2007. The first project decided by the organization was to develop an authoritative consensus guideline containing appropriate NET disease management to serve as a practical resource for health care providers. These guidelines would incorporate early detection procedures for a definitive diagnosis, various aspects of imaging, histopathology, biochemical evaluation, surgical interventions, and evidence-based treatments with emphasis on a multidisciplinary team-based approach to patient care.

To begin the development of the guidelines, we reviewed all the evidence-based literature published on the management of NETs and evaluated the practice guidelines developed by other academic societies such as the European Neuroendocrine Tumor Society, World Health Organization, and National Comprehensive Cancer Network. In addition, we determined the best working format and procedures to develop the NANETS standards.

The next and most important step in the writing process was to assemble various recognized authorities representing a wide range of disciplines from the United States, Canada, and Europe specializing in these challenging diseases (Table 1). This was done at a separate assembly in Bermuda on October 2, 2008 before the beginning of the NANETS first annual symposium.

This entire group was challenged to not merely summarize other consensus papers but to enhance the already published data and assure the NANETS standards are “distinctive” and applicable to available and approved treatments in North America. Therefore, the main objective for each of the specialty panels was to assess

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and compare supporting publications and formulate draft position papers for their working subgroup. Each writing chair was given the responsibility for the coordination of communication and exchanging of information within their subgroup.

After the Bermuda meeting, it was determined that the manuscripts would address key aspects of neuroendocrine tumor diagnosis and treatment by organ site. The position papers from all subgroups were then completed and the contributions compiled and distributed to all participants for additional input. Two lead authors volunteered to assimilate the submitted data, edit, and complete one of each of the following manuscripts. These primary authors reviewed the material to determine what information was still needed and obtained additional contributions regarding their topics from each of the writing group chairs.

The manuscripts and lead authors are as follows:

1. The NANETS Consensus Guideline for the Pathologic Classification of Neuroendocrine Tumors: A Review of Nomenclature, Grading and Staging Systems—Klimstra/Suster
2. The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Well-Differentiated NETs of the Stomach and Pancreas—Kulke/Jensen
3. The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Well-Differentiated NETs of the Jejunum, Ileum, Appendix, and Cecum—Yao/ Boudreaux
4. The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Well-Differentiated NETs of the Distal Colon and Rectum—Pommier/Anthony
5. The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Well-Differentiated NETs of the Thorax (Includes Lung and Thymus)—Phan/ Maples
6. The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Pheochromocytoma, Paraganglioma, and Medullary Thyroid Cancer—Chen/Pacak
7. The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Poorly Differentiated (High Grade) Extrapulmonary Neuroendocrine Carcinomas—Strosberg/Kvols
8. The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Diagnostic Approach to NETs—Woltering/Vinik

Once the draft copies of each paper were complete, they were posted on a secure page on the NANETS website for all writing group members to review and make comments. All input was then collected and forwarded to the appropriate lead authors for evaluation and inclusion of applicable remarks. The revised manuscripts were then reviewed by select NANETS officers to assure the content was in the required format and complete for all sections. Finally, the last draft of each guideline was circulated to the NANETS Board of Directors, Executive Committee, Advisory Board, and Writing Group chairs for consensus and approval for publication. The final review was completed in May 2010.

In closing, the following 8 manuscripts are the result of a cooperative project beginning in 2008 and involving numerous experts who have committed an enormous amount of time and energy with enthusiasm, dedication, and patience. Each individual's contributions have been valuable in creating the final product. Our hope is that these guidelines will provide the practical information necessary for professionals from a variety of specialties to reach a proper diagnosis and develop a treatment plan for their NET patients. In particular, we anticipate that these will be useful resources for busy clinicians who may only encounter these tumors infrequently. The NANETS anticipates continued interactions with professionals from all areas of medicine to update and enhance the guidelines throughout the upcoming years when new evidence-based studies are available. The NANETS also looks forward to and encourages collaboration with all providers managing NET patients to develop the most effective management strategies by using a multidisciplinary approach that will improve patients' quality of life, optimize survival, and lead to the most positive outcomes.

Finally, we want to acknowledge our European colleagues, European Neuroendocrine Tumor Society officers, and consensus guideline committees for their time and expertise during this collaborative endeavor. The experiences they shared about development and execution of the guideline process were invaluable.

We look forward to further input from the membership of NANETS and other professional groups and health care providers for updating the NANETS Guidelines in the near future.

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