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

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Pancreatic neuroendocrine tumors (pNETs) are heterogeneous neoplasms thought to arise from islet cells of the pancreas.\textsuperscript{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.\textsuperscript{3,4} Much of this rise can be explained by localized disease identified incidentally through the increased use of imaging and endoscopy,\textsuperscript{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.\textsuperscript{4}

Along with an increase in incidence of pNETs, there has been an increase in the overall survival (OS) of patients.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{9}

Immunohistochemistry (IHC) for the general neuroendocrine markers, synaptophysin and chromogranin A (CgA), is generally considered mandatory.\textsuperscript{10,11} Nearly all pNETs demonstrate diffuse,
strong synaptophysin expression, whereas 80% to 90% express CgA.\textsuperscript{12,13} Synaptophysin is less specific for pNENs than CgA, and when faced with a synaptophysin+/CgA− tumor, solid pseudopapillary tumor (β-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 neuroendocrinemark, particularly useful in the diagnosis of NECs.\textsuperscript{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 pNEN from lymphoma.\textsuperscript{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).\textsuperscript{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.”\textsuperscript{7,8} 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\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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%).

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. 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. 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. Features of VHL include hemangioblastomas of the central nervous system, endolymphatic sac tumors, epididymal cystadenomas, pheochromocytomas, renal cell carcinomas, pancreatic cysts, and pNETs. 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. 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. 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. In addition, the American College of Medical Genetics and Genomics recommends MEN1 testing for all gastrinoma patients and all patients with multifocal pNETs.

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, 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, but these recommendations are not borne out by available original data or recent reviews 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).

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

Because 111In-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. The greatest source of discordance are IHC-negative patients (≥50% of patients with negative positron emission tomography), although this fraction is shrinking in the SSTR-PET era.

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. In the recent European Neuroendocrine Tumor Society Pathology Guideline, SSTR2A IHC is included as an optional element, indicated when functional imaging is not available. SSTR2A IHC may also be useful as part of a panel of immunostains to distinguish NET G3 (typically strongly positive) from NEC (usually negative). 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. Chromogranin A is often significantly elevated in patients on proton pump inhibitors (PPIs) or with coexisting medical conditions including atrophic gastritis and renal insufficiency. Multiple studies have shown that higher CgA levels correlate with shorter survival and more advanced disease, but the value of CgA when added to imaging studies is likely low. Preoperatively elevated CgA seems to predict higher recurrence risk after resection, 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. 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. 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. 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 ¹⁷⁷Lu-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.

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. 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. 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 aphthous 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. 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. A retrospective study of streptozocin, doxorubicin, and 5-fluorouracil (5-FU) demonstrated a response rate of 39% and median PFS of 18 months. Several other retrospective studies support the activity of streptozocin based therapy, in combination with either 5-FU or doxorubicin, but other studies have not confirmed significant the efficacy of streptozocin with doxorubicin.

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.\(^9\)

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.\(^30\) 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.\(^93\) 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 approximately 75% of planned treatment. Adverse effects included cytopneas, 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 myelodysplastic 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,\(^93,94,105\) 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).\(^109,110\) For example, Binnebeek et al\(^111\) 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 tomography (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. As such, use of lanreotide in SRS-negative patients has not been well studied. Because we know that a significant proportion 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.91,92,93

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 lesions115-118 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 intraarterial 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.95 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.79 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. \textsuperscript{77,78} Similarly, tumor bulk was not evaluated in a retrospective analysis of predictors of response to capecitabine/temozolomide in pNETs. \textsuperscript{89} In contrast, Kouvaraki et al\textsuperscript{89} 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 \(\leq 75\%\) 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. \textsuperscript{90} The value of PRRT is also uncertain in bulky disease. Brabander et al\textsuperscript{99} 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. \textsuperscript{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, \textsuperscript{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. \textsuperscript{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, \textsuperscript{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 \textsuperscript{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). \textsuperscript{124} Similarly, use of PRRT and/or alkylator-containing chemotherapy regimens may increase the risk of bone marrow toxicity. \textsuperscript{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. 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. Given the considerable symptomatic burden hormonal secretion can have on NET patients, 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 (NECs). As a result, there is little if any evidence supporting the continuation of SSAs beyond progression of disease in non-functional NECs. There was no consensus among panel members regarding the continuation of SSAs beyond progression.

The role of SSAs maintenance therapy after PRRT treatment remains controversial, especially in pNET patients. The approval for radiolabeled DOTATATE recommends continuing SSAs until disease progression or up to 18 months after treatment initiation. 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. 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. 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. 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. 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. 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. 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. 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. Other retrospective studies have also suggested that temozolomide-based therapy is effective for G3 pNETs.

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.

Peptide Receptor Radionuclide Therapy
There is limited literature to suggest that $^{177}$Lu-DOTATATE PRRT is an effective treatment in G3 pNETs. 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-PET who 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. There was a consensus that platinum and etoposide chemotherapy was an acceptable first-line option. Irinotecan as an alternative to etoposide is also acceptable. 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. 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. 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. 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
Immunotherapy is being investigated in NECs. Single-agent PD-1/PD-L1 immune checkpoint inhibitor therapy does not seem to provide meaningful treatment benefit, and alternative regimens assessing the combination with cytotoxic chemotherapy or dual immune checkpoint blockade remain under investigation. Despite recent advances in small cell lung cancer, in which checkpoint inhibition in combination with cytotoxic chemotherapy has shown some benefit, 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. 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). Peptide receptor radionuclide therapy with agents like Lu-DOTATATE is associated with major shrinkage in a subset of cases. Although shrinkage is by no means guaranteed, there are reports of symptomatic improvement in hypoglycemic patients with insulinoma after 1 cycle of therapy.

Acutely, however, patients should be counseled regarding the symptoms of hypoglycemia and potential precipitating factors (such as exercise and/or prolonged periods between meals). 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. 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. 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. 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. 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. 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. Everolimus combined with 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). Traditionally, PPIs were started using upward dose titration to acutely control acid output, but this is not routinely done. 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. However, acute loss of control of acid output can be devastating, and twice-daily therapy is recommended to protect against acute absorption problems. Zollinger-Ellison syndrome (ZES) patients who also have MEN-1, gastroesophageal reflux disorder, or prior partial gastric resection are often difficult to control and also require higher doses of PPI twice daily for acid suppression. A medic alert bracelet is recommended. Intravenous control of acid output during periods when patients are fasting is possible with H2 receptor antagonists and PPIs, but PPIs are superior. Acid hypersecretion may not completely normalize after
successful tumor resection, and maintenance low-dose acid suppression is often required long term. Before starting maintenance PPI for any indication, physicians should consider the possibility of ZES, as PPI therapy confounds the workup of this condition.\textsuperscript{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-secreting 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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{177}Lu-DOTATATE group versus 10.8% in the control group.\textsuperscript{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.\textsuperscript{91}

In a prospective phase II trial by Sansovini et al,\textsuperscript{201} 60 patients with progressive pNETs were treated with 18.5 to 25.9 GBq of \textsuperscript{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\textsuperscript{185} 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%. \textsuperscript{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 \textsuperscript{177}LuDOTATATE is very rare (<1%) with coinfusion of cationic amino acids for renal protection and is significantly less common than previously reported with \textsuperscript{90}Y-DOTATOC.\textsuperscript{92,121,202}

In summary, multiple single-arm studies suggest PRRT with \textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\(^\text{206}\) 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.\(^\text{207}\) 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.\(^\text{208}\) Similarly, a Dutch group demonstrated in 2018 that the combination was feasible and safe.\(^\text{209}\) 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.\(^\text{210,211}\) 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.\(^\text{212,213}\) Valle et al\(^\text{214}\) 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.\(^\text{215,216}\) 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. 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.
Table 1: 2019 WHO Classification of GEP Neuroendocrine Epithelial Neoplasms

<table>
<thead>
<tr>
<th>Classification/Grade</th>
<th>Ki-67 Proliferation Index, %</th>
<th>Mitotic Count, Per 2 mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated NET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>&lt;3</td>
<td>&lt;2</td>
</tr>
<tr>
<td>G2</td>
<td>3–20</td>
<td>2–20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>PD-NEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3 (small cell or large cell type)</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>
**Table 2: Required and Recommended Reporting Elements for Biopsies and Resections of Pancreatic Neuroendocrine Epithelial Neoplasms**

<table>
<thead>
<tr>
<th>Data Element</th>
<th>Associated Required or Recommended IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Required data element</strong></td>
<td></td>
</tr>
<tr>
<td>Diagnosis: well-differentiated NET or PD-NEC (specify small cell or large cell variant if possible)</td>
<td>• Synaptophysin and CgA to establish neuroendocrine nature (required)</td>
</tr>
<tr>
<td></td>
<td>• Broad-spectrum keratin to confirm epithelial nature (highly recommended in primary and regional disease and required in distant metastasis)</td>
</tr>
<tr>
<td></td>
<td>• p53, Rb, ATRX, and DAXX are recommended in the distinction of well-differentiated NET G3 from PD-NEC</td>
</tr>
<tr>
<td>Ki-67 proliferation index (proliferation index &gt;20% is implied for high grade NEN either well-differentiated NET G3 or a PD-NEC; for known PD-NEC performance is not mandatory)</td>
<td>• Ki-67 on at least one block of tumor (required)</td>
</tr>
<tr>
<td></td>
<td>• Ki-67 on at least one block of tumor and matched distant metastasis (recommended)</td>
</tr>
<tr>
<td>Mitotic count per 10 HPF (in biopsies with &lt;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)</td>
<td></td>
</tr>
<tr>
<td>Grade: G1, G2, or G3 for well-differentiated NET (grade for PD-NEC need not be explicitly stated)</td>
<td></td>
</tr>
<tr>
<td>Data elements in CAP Cancer Protocol: for resection specimens</td>
<td></td>
</tr>
<tr>
<td><strong>Recommend data element</strong></td>
<td></td>
</tr>
<tr>
<td>Comment on site of origin (for metastasis of occult origin)</td>
<td>• IHC panel in a well-differentiated NET may 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</td>
</tr>
<tr>
<td></td>
<td>• 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</td>
</tr>
</tbody>
</table>
Table 3: Types of F-pNETs

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Hormone</th>
<th>Clinical Syndrome</th>
<th>Laboratories to Evaluate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>Insulin or proinsulin</td>
<td>Hypoglycemia symptoms (especially at night and when fasting and including sweating, shaking, confusion)</td>
<td>Glucose, insulin, proinsulin, C-peptide</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Gastrin</td>
<td>ZES (severe gastrointestinal reflux; pain, diarrhea, esophageal symptoms)</td>
<td>Gastrin and gastric pH by endoscopy</td>
</tr>
<tr>
<td>VIPoma</td>
<td>VIP</td>
<td>Profuse watery diarrhea with hypokalemia</td>
<td>VIP and BMP</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucagon</td>
<td>Glucose intolerance (diabetes mellitus, hyperglycemia), rash, weight loss</td>
<td>Glucagon, HbA₁c</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Somatostatin</td>
<td>Diabetes mellitus, hyperglycemia, cholelithiasis, diarrhea</td>
<td>Somatostatin, HbA₁c</td>
</tr>
<tr>
<td>ACTHoma</td>
<td>ACTH (or rarely CRH)</td>
<td>Cushing syndrome</td>
<td>ACTH, cortisol, 1 mg dexamethasone suppression test, 24-h urinary free cortisol, midnight salivary cortisol</td>
</tr>
<tr>
<td>GRHoma</td>
<td>Growth hormone–releasing hormone</td>
<td>Acromegaly</td>
<td>IGF1</td>
</tr>
<tr>
<td>PTHrPoma</td>
<td>PTHrP</td>
<td>Hypercalcemia</td>
<td>PTHrP, PTH, calcium, albumin, 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D</td>
</tr>
<tr>
<td>Other</td>
<td>Serotonin, calcitonin</td>
<td>Any hormone</td>
<td>Diarrhea, flushing Symptoms related to hormone production</td>
</tr>
</tbody>
</table>

BMP, basic metabolic profile; CRH, corticotrophin-releasing hormone; HbA₁c, glycated hemoglobin; IGF1, insulin-like growth factor 1.


91. Ramage J, Naraev BG, Halfdanarson TR. Peptide receptor radionuclide therapy for patients with advanced pancreatic...


