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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.

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