Surgical Management of Pancreatic Neuroendocrine Tumors

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KEYWORDS

• Pancreatic neuroendocrine tumor • PNET • Management • Surgery • Review

KEY POINTS

- Management of pancreatic neuroendocrine tumors (PNETs) is challenging because of their heterogeneous pathologic features and unpredictable clinical behaviors.
- Although most PNETs are nonfunctional, certain PNETs are functional and can present with classic endocrinopathies related to hormone excess.
- Surgery remains the cornerstone of management for localized disease, and operative approaches are customized to the clinical behavior of the particular PNET.
- Frequent evaluation of vague abdominal symptoms using axial imaging has led to an upsurge of incidentally detected, small, asymptomatic PNETs resulting in management controversies.

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are the second most common pancreatic neoplasm behind adenocarcinoma, with an overall incidence of approximately 5:1,000,000 and an estimated prevalence of 1:100,000.[1,2] PNETs are most frequently detected between the fourth and sixth decades of life. Approximately 10% to 30% of PNETs are associated with familial syndromes including multiple endocrine neoplasia type I (MEN I) and von Hippel-Lindau syndrome.[1–3] PNETs may overproduce certain hormones and present with classic endocrinopathies. Most, however, are nonfunctional incidentalomas detected on imaging obtained for unrelated reasons. With the increased use of axial imaging to evaluate vague abdominal symptoms, the rate of detection has increased fourfold to sevenfold since the year 2000, and the size of the tumors at time of diagnosis has markedly decreased.[4] PNETs have traditionally

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been thought to be biologically less aggressive than pancreatic adenocarcinomas but there has been increased recognition that the pathologic potential of PNETs is highly variable.[5,6] Many PNETs are indolent with a small proclivity to metastasize and with very favorable long-term prognoses, while others are high-grade tumors that demonstrate a relentless progression to early metastases that makes their biology seem more aggressive than typical for ductal adenocarcinomas.

Surgical resection remains the primary curative modality in the management of PNETs.[7] The current trend toward early incidental detection of the tumors combined with their heterogeneous and unpredictable pathology challenge optimal treatment decision making. In the current review, we discuss the surgical management of functional and nonfunctional PNETs with particular attention to the surgical management of small ($\leq$2 cm) asymptomatic, nonfunctional PNETs (NF-PNETs).

PATHOPHYSIOLOGY

PNETs are neuroendocrine tumors arising from the cells that make up the pancreatic islets. The underlying etiology of PNETs is believed to be acquired and/or from congenital genetic alterations in the cell of origin, but there is no genetic mutation that has been consistently and definitively associated with the development of these tumors. The most frequently mutated genes found in PNETs involve chromatin-remodeling genes, such as *MEN I* (44%) and *DAXX/ATRX* (43%), and genes of the mammalian target of Rapamycin pathway (15%).[5,8] Well-differentiated PNETs lack the alterations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* genes frequently encountered in pancreatic ductal adenocarcinomas, whereas poorly differentiated PNETs do exhibit genetic alterations found in pancreatic ductal adenocarcinomas.[9]

Functional PNETs by definition produce and secrete 1 or more active hormones. They must manifest the characteristic endocrinopathy to be considered functional. Hormones produced by PNETs include insulin, gastrin, glucagon, somatostatin, vasoactive intestinal peptide (VIP), pancreatic polypeptide, and cholecystokinin.[2,10,11] Additionally, both functional and NF-PNETs can express peptides characteristic of NETs in general, such as chromogranin A and synaptophysin. These are commonly used for purposes of diagnosis and surveillance as serologic and/or histologic markers of PNETs. Overproduction of chromogranin A and synaptophysin are not typically associated with characteristic endocrinopathies.

PNETs frequently express somatostatin receptors (SSTR1-5), which are normally present throughout the central nervous system, the gastrointestinal tract, and the endocrine and exocrine glands.[5,12] PNETs express a range of SSTRs, and synthetic somatostatin analogs, such as octreotide or lanreotide, have varying activity profiles against the range of SSTRs expressed by PNETs.

CLASSIFICATION AND STAGING

Tumors are first categorized as either functional or nonfunctional, as symptoms related to the tumor may be the primary driver for therapeutic intervention, particularly in small lesions. The vast majority of PNETs, as many as 90% in select series, are nonfunctional. Functional PNETs occur in approximately 10% of cases and are named based on their clinical endocrinopathy. They include insulinomas, gastrinomas, VIPomas, glucagonomas, and somatostatinomas (**Table 1**).[1,13] Functionality of PNETs appears to be independent of both grade and stage.

Among the various subtypes of functional tumors, insulinomas are generally less aggressive and rarely present with metastatic disease, whereas gastrinomas tend to have a higher proclivity for metastasis. In general, a loss in differentiation tends to

Table 1
Characteristics of functional pancreatic neuroendocrine tumors

Tumor Type	Frequency		Clinical Features	Diagnosis	Tumor Location	Surgical Recommendations[a]
	Sporadic	MEN I				
Insulinoma	30%–40%	10%–18%	Whipple triad, weight gain; likely benign	72-h fast; serum insulin, proinsulin, C-peptide, glucose; avoid SRS	Within pancreas	Enucleation Laparoscopic
Gastrinoma	20%–50%	30%–54%	Zollinger-Ellison syndrome; likely malignant	Secretin stimulation test	Gastrinoma triangle; often duodenum	Formal resection Intraoperative exploration Open
Glucagonoma	Rare	3%	Necrolytic migratory erythema, diabetes mellitus, anemia, weight loss, hypercoagulability	History and physical; serum glucagon	Tail of pancreas	Formal resection when possible
VIPoma	Rare	17%	Verner-Morrison syndrome; iron and vitamin B_{12} deficiency	Serum VIP	Tail of pancreas	Formal resection when possible
Somatostatinoma	Rare	<5%	Abdominal pain, weight loss, diabetes, cholelithiasis, diarrhea, steatorrhea	Serum somatostatin	Pancreas, ampulla, duodenum, jejunum	Formal resection when possible

Abbreviations: MEN I, multiple endocrine neoplasia, type 1; SRS, somatostatin receptor scintigraphy; VIP, vasoactive intestinal peptide.
[a] For sporadic cases; see text for MEN I management recommendations.

result in a loss of hormone production abilities and therefore are less likely to produce an endocrinopathy. However, the biology of these lesions is highly variable, and low-grade, localized lesions or high-grade, widely disseminated tumors may be hormonally active and cause an endocrinopathy.

Beyond functionality, PNETs are categorized by grade and pathologic stage. Recent international experience with PNETs has demonstrated that several of the pathologic features typically used to determine prognosis in cancers do not consistently predict the biologic behavior of PNETs and thus are imperfect determinants of which treatment modalities are best.[5] In these cases, lymph node involvement, large tumor size, and even presence of distant metastases do not necessarily correlate with either the length of disease-specific survival or the degree to which the functional health of the patient is compromised. Instead, the single most important determinant of prognosis is the histologic grade of the tumor. This observation has led to the development of a unique classification scheme for PNETs that differs substantially from traditional TNM staging systems used for most solid tumors. The most recent consensus classification system is the 2010 World Health Organization (WHO) classification, which has also been endorsed by the European Neuroendocrine Tumor Society (ENETS) (**Table 2**).[14,15] PNETs are generally assigned a WHO grade or class and a TNM stage. The WHO classification stratifies PNETs by the degree of differentiation and by histologic grade. The histologic grade is defined by the mitotic rate and/or Ki-67 index, with the higher of either the mitotic rate or Ki-67 index being used to determine the histologic grade of the tumor.[16,17] The pathologic staging system typically used for PNETs is outlined in the seventh edition of the American Joint Committee on Cancer (AJCC 2010) staging manual and is identical to that used for pancreatic ductal adenocarcinoma (**Table 3**).[18] Although PNETs have distinctly different tumor biology and in general have a better long-term survival than pancreatic ductal adenocarcinoma, the AJCC TNM system does provide useful stage discrimination that can aid in treatment decision making. Treating clinicians must bear in mind that histologic grade will tend to surpass stage in prognostic capability, meaning that patients with

Table 2
2010 European Neuroendocrine Tumor Society/World Health Organization nomenclature and grading system for pancreatic neuroendocrine tumors

Category	Differentiation	Grade	Mitotic Count	Ki-67 Index
Neuroendocrine tumor, Grade 1	Well differentiated	Low grade (G1)	<2 per 10 HPF	<3%
Neuroendocrine tumor, Grade 2		Intermediate grade (G2)	2–20 per 10 HPF	3%–20%
Neuroendocrine carcinoma, Grade 3, small cell	Poorly differentiated	High grade (G3)	>20 per 10 HPF	>20%
Neuroendocrine carcinoma, Grade 3, large cell				

Abbreviation: HPF, high-power microscopic fields.

Adapted from Falconi M, Bartsch DK, Eriksson B, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. Neuroendocrinology 2012;95(2):122; and Rindi G, Arnold R, Bosman F, et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: WHO classification of tumors of the digestive system, vol. 4. 2010. p. 13–4

Table 3
AJCC seventh edition TNM staging system for exocrine and endocrine tumors of the pancreas

Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ*		
T1	Tumor limited to pancreas, 2 cm or smaller in greatest dimension		
T2	Tumor limited to the pancreas, larger than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

* Includes PanIN III.
Abbreviation: AJCC, American Joint Committee on Cancer.
From American Joint Committee on Cancer. AJCC cancer staging manual. 7th edition. Chicago: American College of Surgeons; 2010; with permission.

widespread distant metastasis may be asymptomatic for years, whereas others presenting with localized high-grade disease will frequently have early recurrence and succumb to the tumor within months of diagnosis.[19]

CLINICAL PRESENTATION AND DIAGNOSIS

Nonfunctional Pancreatic Neuroendocrine Tumors

NF-PETs present as pancreatic incidentalomas on imaging obtained for unrelated reasons, with symptoms related to local mass effect, or with metastatic disease. NF-PNETs either do not produce any hormone, produce amounts of hormone insufficient to cause an endocrinopathy, or produce hormones that do not cause an endocrinopathy (eg, chromogranins, synaptophysin, neuron-specific enolase or ghrelin).[7] Because of this, NF-PNETs tend to present at a later stage than functional

tumors. Approximately 60% to 70% of patients have metastatic disease and 20% have locally advanced disease at time of diagnosis.[13] Symptoms are nonspecific and can include abdominal pain, back pain, weight loss, nausea, vomiting, anorexia, obstructive jaundice, and/or pancreatitis. NF-PNETs have male gender preponderance and most often occur in the fourth to sixth decades of life. There is no predilection for ethnicity.[2]

Biochemical Evaluation of Nonfunctional Pancreatic Neuroendocrine Tumors

The initial evaluation of NF-PNETs includes a biochemical evaluation for endocrinopathies as clinically indicated. Serum chromogranin A levels are elevated in more than 60% of patients with functional and NF-PNETs and may be used as a tumor marker in postoperative surveillance and for monitoring treatment effect.[7,17] Elevated levels have been associated with poor overall prognosis, and early decreases may be associated with favorable treatment outcomes. The specificity of chromogranin A is limited: 50% to 80%.[13,20] Falsely elevated serum chromogranin A levels can be caused by renal or hepatic failure, chronic atrophic gastritis, acute coronary syndrome, and the use of proton pump inhibitors (PPIs) or H_2 antagonists. The North American Neuroendocrine Tumor Society recommends following serum chromogranin A levels as surrogate markers of disease progression or response to therapy if abnormal at time of diagnosis.[21]

Imaging of Nonfunctional Pancreatic Neuroendocrine Tumors

Dedicated pancreas multiphasic computed tomography (CT) or MRI remains the first step in assessing the primary tumor site and extent of disease.[5,10] On triple-phase CT, NF-PNETs are well-circumscribed hypervascular lesions and best visualized in the late arterial or portal-venous inflow phase (**Fig. 1**).[12,22] Calcifications also may be present. Local invasion of vascular structures also can be assessed to determine resectability. CT has a sensitivity and specificity of 63% to 82% and 83% to 100%, respectively,

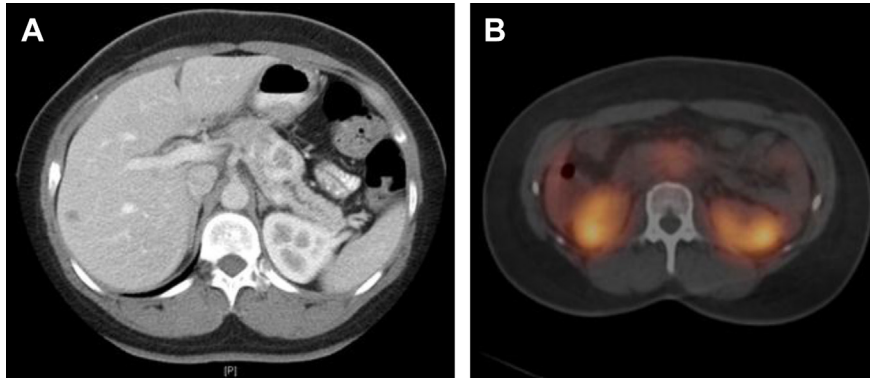

Fig. 1. Representative image (*A*) from contrast-enhanced CT for a 36-year-old woman presenting with vague abdominal pain demonstrating characteristic hyperenhancement on arterial phase typical of PNETs. The hypointense lesion in the right lobe of the liver was not visualized on octreotide scan, evaluated by MRI, and found to be a cyst. The pancreatic mass was managed by laparoscopic distal pancreatectomy with splenectomy. The patient is now 2 years post resection with no evidence of recurrence. Representative image (*B*) from octreotide scan for the same patient preoperatively. The image demonstrates mild octreotide binding typical of an NF-PNET.

varying with the size of the lesion. For liver metastases, the mean sensitivity and specificity are 82% and 92%, respectively. Approximately 10% of NF-PNETs appear as cystic lesions within the pancreas and can have a misdiagnosis rate of 43% from other cystic pancreatic lesions.[22,23] MRI has improved tissue contrast in evaluating the pancreas and the liver (**Fig. 2**). NF-PNETs are typically dark on T1-weighted images and bright on T2-weighted images. Sensitivity and specificity for MRI varies between 85% to 100% and 75% to 100%, respectively.[22] Mean detection rate is 73% for NF-PNETs and 82% for NET liver metastasis.[12] Magnetic resonance cholangiopancreatography (MRCP) can also be included during MRI for preoperative planning. MRI is most useful when monitoring developing or persistent hepatic lesions.

In addition to traditional axial imaging, 2 nuclear medicine modalities are available for evaluation of NF-PNETs: somatostatin receptor scintigraphy (SRS) and PET. Many PNETs express high levels of a number of SSTRs, particularly SSTR-2, and can therefore be imaged with radiolabeled somatostatin analogs (see **Fig. 1**), such as ^{111}In-pentetreotide (Octreoscan). SRS is more commonly available and often used for localizing NF-PNETs, staging these tumors, identifying sites of metastatic disease, surveying for recurrence, and assessing the effect of systemic therapy. There are few data, however, to support the contention that these tests provide information above that gained by high-quality CT or MR axial imaging. SRS is costly and can present a significant logistical burden for the patient.

Imaging using PET involves 2 types of radiotracers: those that bind to SSTRs and those that characterize tumor metabolism. Traditional fludeoxyglucose (FDG)-PET scanning may not visualize NF-PNETs well due to their low metabolic rate, but has been used to characterize highly metabolically active poorly differentiated PNETs. Compared with SRS, PET involving SSTRs allows improved contrast and can detect

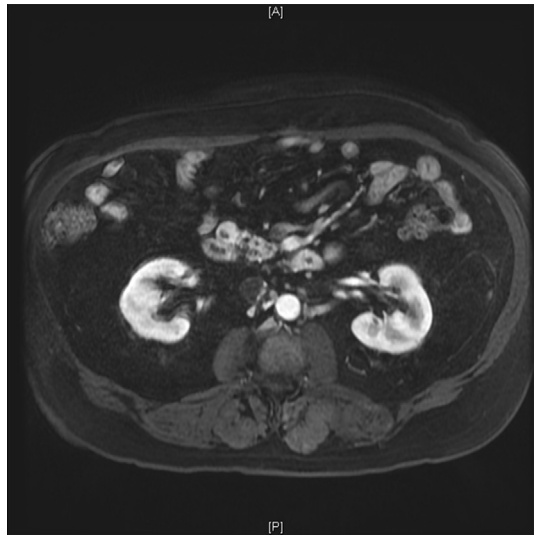

Fig. 2. Select images from contrast-enhanced axial MR imaging demonstrating a hyperenhancing mass in the pancreatic head. Endoscopic ultrasound with aspiration was consistent with a pancreatic neuroendocrine tumor. Biochemical workup was negative. This PNET was managed with enucleation. Margins were negative. The patient recovered without complication and is 2 years post resection with no evidence of disease recurrence on follow-up axial imaging.

tumors approximately 0.5 cm in size. Combined with CT, PET/CT has shown improvement in localization of both functional and NF-PNETs.[22] In one study, use of PET/CT changed treatment decisions in 59.6% of patients compared with CT or MRI alone.[24] Most patients in this study were characterized as well-differentiated, but functionality was not reported.

Functional Pancreatic Neuroendocrine Tumors

Functional PNETs are hormonally active tumors. Patients present with symptoms driven by the hormones the tumors produce: an endocrinopathy. Functional PNETs are typically detected at an earlier stage than nonfunctional tumors, although their detection can be delayed due to the rarity of the tumors, and the symptoms may be attributed to other potential etiologies. When suspicions are raised early, the tumors may be small and difficult to localize. Multiple radiologic modalities are used in the evaluation of these patients to localize the tumors before operative exploration. However, it is not uncommon for patients to be operatively explored before definitive radiographic localization given the certainty of the diagnosis.

Insulinoma

Insulinomas comprise approximately 35% to 40% of functional PNETs.[6] These are hormonally active tumors, produce symptoms early, are typically small (<2 cm in size), and are solitary lesions at the time of presentation. They may develop in any location within the pancreatic parenchyma but are found only within the pancreas. These are typically not metastatic at presentation, but invasive transformation has been reported.[25,26]

Insulinomas present with neuroglycopenic symptoms of palpations, tremors, diaphoresis, weakness, confusion, agitation, loss of consciousness, and/or seizures that are associated with hypoglycemia and relieved with oral intake or intravenous glucose infusion. The constellation of documented hypoglycemia, neuroglycopenic symptoms, and resolution of those symptoms with glucose intake is identified as the Whipple Triad. Combined with the anabolic effects of insulin, patients with insulinoma often will eat to manage their glycopenic symptoms and gain weight.[7]

Diagnosis is confirmed biochemically with the evaluation of serum insulin, proinsulin, C-peptide, and glucose levels to establish endogenous paradoxic hyperinsulinism occurring at times of hypoglycemia. Ninety percent to 95% of patients will develop hypoglycemia during a 48-hour observed fast, although a 72-hour observed fast is the gold standard.[7,27] Sulfonylurea metabolites also should be evaluated to exclude factitious hyperinsulinism. Patients have also been reported to demonstrate islet cell hyperplasia (nesidioblastosis) and, rarely, multifocal insulinomas months to years following Roux-en-Y gastric bypass.[28]

Once biochemically confirmed, most insulinomas can be localized with contrast-enhanced CT or MRI. These tumors are typically well-circumscribed. Endoscopic ultrasound (EUS) can aid in the diagnosis and localization of these tumors with identification of lesions as small as 2 to 5 mm. Compared with normal pancreatic parenchyma, insulinomas appear hypodense on ultrasound. Intraoperative ultrasound is also frequently used if these tumors cannot be localized preoperatively.

SRS is not helpful given the tumor's low expression of SSTR-2.[22,29] Interestingly, insulinomas overexpress glucagonlike peptide 1 (GLP-1) receptor, and radiolabeled GLP-1 analogs, such as exendin-3 and exendin-4, have been developed with promising results.[30] SRS is, however, useful to evaluate the burden of disease and to test the appropriateness of peptide receptor radiotherapy (PRRT).

Gastrinoma

Gastrinomas arise predominantly within the duodenum followed by the pancreas. Passaro[31] identified an anatomic triangle called the gastrinoma triangle, where most gastrinomas originate. This triangle is outlined by the junction of the cystic duct and common bile duct, the junction of the neck and body of the pancreas, and the lateral wall of the duodenum between the second and third portions. Up to 90% of these lesions are malignant with pancreatic gastrinomas often more aggressive than those found within the wall of the duodenum.[7] Patients present with the Zollinger-Ellison syndrome: severe refractory peptic ulcer disease, gastric acid hypersecretion, and diarrhea.[32] Metastatic disease is present in approximately 30% of patients with gastrinomas, and therefore symptoms associated with hepatic metastases may also be the presenting symptoms. Gastrinomas are the most common PNET in patients with MEN I occurring in up to 50% of cases.[3,33]

Gastrinomas that produce the Zollinger-Ellison syndrome can be biochemically diagnosed by measuring fasting serum gastrin concentration and/or performing a secretin stimulation test. Diagnosis, however, remains quite difficult due to the many conditions that can lead to hypergastrinemia, such as gastroesophageal reflux disease, gastric outlet obstruction, antral G-cell hyperplasia, and retained gastric antrum. In the presence of gastric acid production (ie, not due to secondary hypergastrinemia), a serum gastrin value of more than 1000 pg/mL is diagnostic, but this occurs in only 5% to 9% of patients. Two-thirds of patients have a fasting serum gastrin value that is less than 10 times the upper limit of normal, a nondiagnostic range.[34] Higher levels of gastrin are associated with pancreatic tumors, larger tumors, and metastatic disease.

A secretin stimulation test is used in instances in which a fasting serum gastrin is nondiagnostic and there is no mass lesion apparent on axial imaging. Patients taking PPIs can produce false-positive results. In these instances in which provocative testing is needed to secure a diagnosis, PPIs should be discontinued by tapering over 1 week before the test and switched to H_2 antagonists. Once this is done, baseline serum gastrin is measured, an ampule of secretin is given intravenously, and serum gastrin levels repeated sequentially over time. A change in fasting serum gastrin levels of 120 pg/mL or more is associated with a sensitivity and specificity of 94% and 100%, respectively.[35] This is biochemical proof of a gastrinoma. Selective venous sampling for gastrin of the drainage of the pancreas can be performed to localize the tumor preoperatively. Gastrinomas typically express SSRT-2, and SRS is another useful modality to localize gastrinomas before surgical exploration. Rarely, all efforts to localize the tumor preoperatively will fail, and operative exploration with intraoperative ultrasound and manual palpation of the wall of the duodenum will be indicated.

Other Functional Pancreatic Neuroendocrine Tumors

Other functional PNETs are exceptionally rare and include glucagonomas, VIPomas, and somatostatinomas. Glucagonomas classically present with weight loss, venous thrombosis, and necrolytic migratory erythema. VIPomas cause Verner-Morrison syndrome, also referred to as the WDHA (watery diarrhea, hypokalemia, achlorhydria) syndrome or pancreatic cholera. Patients with somatostatinomas can present with diabetes mellitus, cholelithiasis, diarrhea, and steatorrhea. Most of these functional PNETs are metastatic at presentation, and surgical management is limited.

SURGICAL MANAGEMENT

Principles of Surgical Management

Surgical resection remains the only potentially curative treatment for patients with PNETs.[36,37] Indeed, the goals are to prevent metastases and improve long-term survival. Surgery also may alleviate symptoms from hypersecretion of hormones by functional tumors or symptoms that may be due to nonfunctional tumors. According to the National Comprehensive Cancer Network guidelines, patients with localized PNETs should undergo resection except in those cases in which patients are unfit for surgery or have widely metastatic disease.[38] Several controversies remain, however, regarding the implementation of surgery in the management of PNETs. First, recent success with watchful waiting in elderly patients and patients with high perioperative risk that present with small NF-PNETs has led to the hypothesis that certain small PNETs are very indolent and exceedingly unlikely to represent a substantial threat to the patient during his or her lifetime. Yet, all pancreatic surgeons will have patients with high-grade localized tumors with early and aggressive recurrences after resection. These phenomena have driven recent recognition that there are tumors that present as localized disease but that should not be resected, either because they are not a threat to the patient or they are so aggressive that resection will provide no benefit. The second controversy in the field is with regard to the application of minimally invasive and pancreas-sparing operations (ie, enucleations and central pancreatectomies) to the treatment of PNETs. Last, there remains debate about the role and extent of surgery in patients with MEN I presenting with PNETs.[20,21]

Asymptomatic Small Pancreatic Neuroendocrine Tumors

The increased utilization of high-resolution axial imaging to evaluate vague abdominal symptoms has resulted in a significant increase in the diagnosis of asymptomatic NF-PNETs.[4] The surgical management of pancreatic neuroendocrine incidentalomas is a topic of active debate. There are no clear radiologic or histologic features that are in isolation definitively predictive of malignancy.[19,39,40] Tumor size has traditionally been thought to be directly related to malignant potential, with larger tumors thought to be more likely to behave aggressively and carry more risk of death from disease. Previous investigators, considering the substantial risk of perioperative morbidity and the potential for exocrine and endocrine pancreatic insufficiency after pancreatectomy, have proposed an "observation first" approach for small, incidentally detected tumors.[41,42] There is, however, increasing recognition that there exist small high-grade tumors with aggressive behavior.

The data in the literature currently are mixed on the appropriate management strategy for small, asymptomatic PNETs. In a recent study using data between 1993 and 2013 from Memorial Sloan Kettering Cancer Center's institutional cancer database, Sadot and colleagues[4] constructed a matched case-control study of patients with PNETs of 3 cm or smaller who were observed with those who underwent upfront resection. They found that of those tumors that were observed, 51% increased in size, 18% experienced no change in size, and 31% experienced a decrease in size with no difference in overall survival ($P = .3$) between groups. Within the limitations of their study, they concluded that a watchful waiting approach is justified in the management of small, asymptomatic NF-PNETs. Other studies have demonstrated similar results stating that observation is acceptable for patients with PNETs smaller than 2 cm. In a single-center retrospective study, Zhang and colleagues[43] found that the overall survival of patients with NF-PNETs was improved

when managed surgically. The effect of surgery was particularly pronounced when tumors were larger than 1.5 cm in diameter, and observation was recommended for those tumors that were smaller. Similarly, Kishi and colleagues[44] found that NF-PNETs of 1.5 cm or smaller can be safely observed with imaging studies at 6-month intervals. Regenet and colleagues[45] examined the natural course of 66 patients with NF-PNETs of 2 cm or smaller managed operatively and 14 patients managed non-operatively. They found that a tumor size cutoff of 1.7 cm was 92% sensitive and 75% specific for predicting malignancy, and therefore recommended surgical resection for tumors larger than 1.7 cm. Because even small NF-PNETs can develop metastases in 7.7% to 29% of patients, size alone may not be an appropriate criterion in predicting their behavior. Scarpa and colleagues[46] suggested a Ki-67 cutoff of 5%, but this was not predictive in the study by Regenet and colleagues.[45] Contrary to the findings of these studies, in a large population study using the National Cancer Data Base, Sharpe and colleagues[47] examined 380 patients with NF-PNETs of 2 cm or smaller between 1998 and 2006. Eighty-one percent of the cohort underwent resection and 19% were observed. The 5-year overall survival was 73.6%, with a median follow-up of 5 years. Of those who underwent resection, their 5-year overall survival was 82.2% compared with a 5-year overall survival of 34.3% in those who underwent observation ($P<.0001$, **Fig. 3**). Surgical management continued to be strongly associated with survival even after accounting for tumor size, location, and lymph node status. Tumor grade was also strongly associated with overall survival, as surgical management continued to provide a benefit independent of tumor grade (**Fig. 4**).

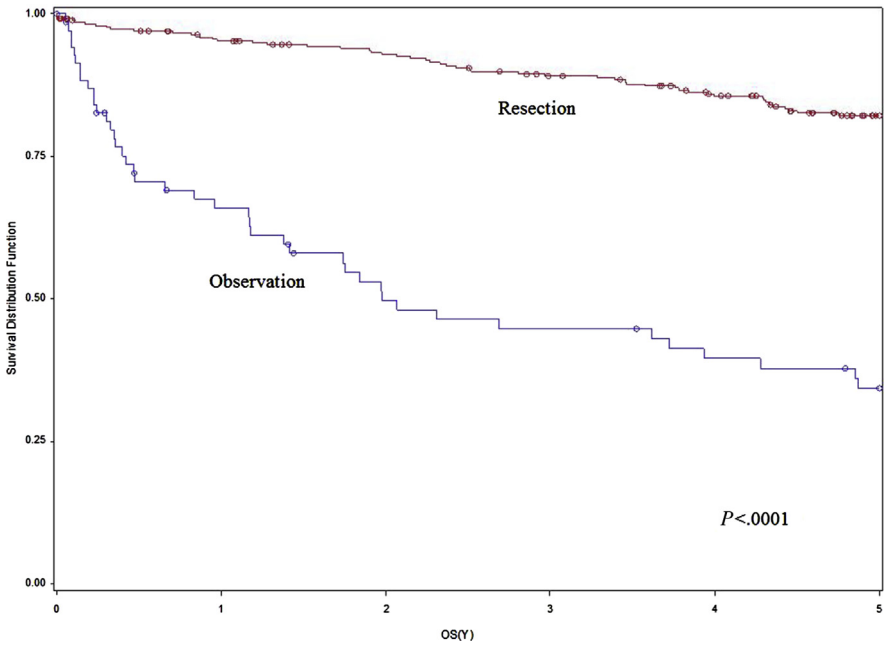

Fig. 3. Kaplan-Meier survival estimates comparing patients with PNETs $\leq$2 cm who underwent surgical resection or observation. (*From* Sharpe SM, In H, Winchester DJ, et al. Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. J Gastrointest Surg 2015;19(1):120. [discussion: 123]; with permission.)

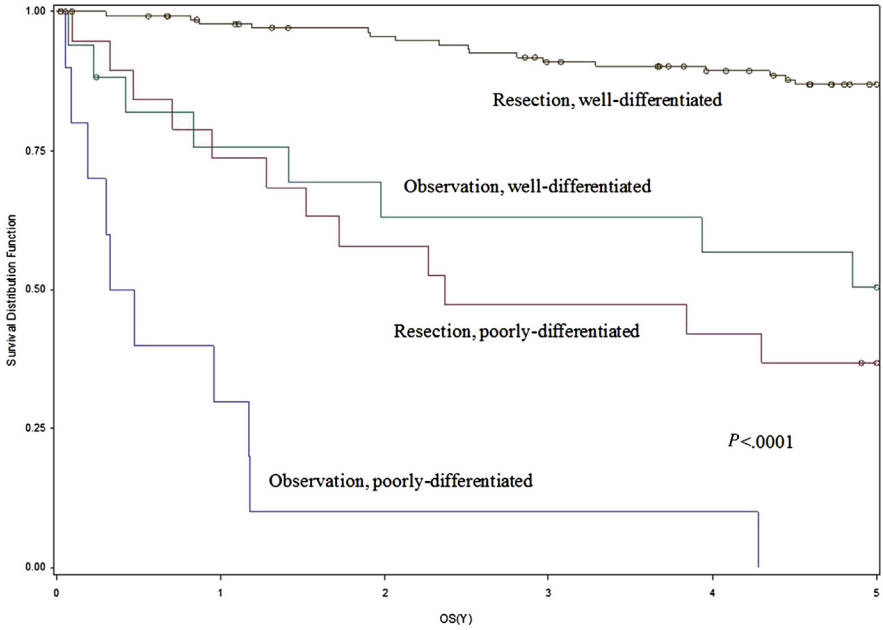

Fig. 4. Kaplan-Meier survival estimates comparing patients with PNETs $\leq$2 cm who underwent surgical resection or observation, by histologic grade. (*From* Sharpe SM, In H, Winchester DJ, et al. Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. J Gastrointest Surg 2015;19(1):122. [discussion: 123]; with permission.)

A novel strategy to the management of these small, incidentally discovered NF-PNETs is to obtain a tissue diagnosis with EUS and fine-needle aspiration (FNA), thereby aiding decision making based on cytopathology. Reliability between EUS-FNA cytopathology and surgical specimen histology is reportedly 70% to 80%.[48,49] Studies have previously demonstrated the additional benefit of EUS in localizing lesions not seen on CT but clinically suspected (eg, insulinoma), particularly for PNETs smaller than 2 cm.[50] The tissue sampling capabilities of EUS with FNA may be able to stratify patients with incidentally discovered small, asymptomatic NF-PNETs to surgery versus observation although specific studies in this population are lacking. Studies have argued that small (<2 cm) NF-PNETs with a WHO Grade 3 should be treated surgically, but cautioned the decision-making ability of those with WHO Grade 2.[51,52]

Our current approach to incidentally found NF-PNETs has been to pursue resection for tumors that are 2 cm in size or larger, unless there is evidence of significant metastatic disease or major comorbidity that would make resection untenable. For tumors that are smaller than 1 cm, we generally pursue observation with close interval surveillance. Our regimen involves repeat axial imaging 3 months following diagnosis and then at 6-month intervals for 1 year and yearly thereafter. We reconsider surgical resection if the tumor size changes substantially on surveillance imaging. For tumors between 1 and 2 cm, we tend to individualize treatment based on the age of the patient and location of the tumor. We will have a discussion with the patient regarding the risks and benefits in light of the location of the lesion and undergo a process of shared decision making with the understanding that either resection or close interval surveillance are reasonable.

The Role of Enucleation

There has been very little evidence that lymph node clearance provides any survival advantage in the management of PNETs. For this reason and because anatomic resections (pancreaticoduodenectomy and left pancreatectomy) carry significant risk of major perioperative morbidity, many prior investigators have suggested that PNETs might simply and effectively be managed by enucleation.[53–55] Patient selection is of the utmost importance when considering enucleation. Tumors that are likely to be benign, solitary, and are not abutting the pancreatic or biliary ducts are appropriate for enucleation.[7] Cauley and colleagues[56] compared the surgical outcomes of 45 patients undergoing enucleation with 90 patients undergoing pancreatectomy and found that enucleation was significantly associated with shorter operative times, lower blood loss, and lower rates of pancreatic insufficiency compared with patients undergoing pancreatectomy. Pitt and colleagues[53] compared patients undergoing enucleation versus pancreatectomy for localized PNETs, and found similar overall morbidity and 5-year survival rates between groups. Enucleation was associated with decreased blood loss, operative time, and hospital length of stay. Despite these positive results, pancreatic fistula was significantly greater in the enucleation group (38% vs 15%, $P<.01$). However, most pancreatic fistulas in the enucleation group were ISGPF (International Study Group on Pancreatic Fistula) grade A, whereas those in the resection group were ISGPF grade B. After appropriate patient selection, the data on this subject would suggest that enucleation is a safe and effective strategy for small PNETs, both functional and nonfunctional.

The Role of Central Pancreatectomy

Central pancreatectomy is an acceptable alternative to the management of PNETs when the lesion is not amenable to enucleation.[57] As a parenchyma-sparing operation, central pancreatectomy has the benefit of minimizing postoperative endocrine and exocrine insufficiency, and can be approached laparoscopically.[58] However, central pancreatectomy has been associated with longer operative times and higher rates of pancreatic fistula (~30%), despite having endocrine and exocrine preservation rates equivalent to traditional pancreatectomies.[59,60] Given the rarity of this operation, few studies have examined the impact of central pancreatectomy on outcomes specifically for PNETs. In a large single-center experience involving 100 total patients, 35 patients underwent central pancreatectomy for PNET (25 patients were WHO grade 1, 9 WHO grade 2, and 1 WHO grade 3).[61] Overall morbidity was 72%, and 63% of patients had pancreatic fistula. With a median follow-up of 36 months, one of the patients with PNET (3-cm lesion, WHO grade 2) developed recurrence. As with enucleation, appropriate patient selection is warranted when pursuing central pancreatectomy in light of the paucity of evidence.

Minimally Invasive Techniques

Minimally invasive approaches (ie, laparoscopy, robotics) have recently been more frequently applied to the management of both functional and NF-PNETs.[62,63] No consensus has been established regarding the indications of minimally invasive surgery, but laparoscopic surgery has been shown to be feasible and safe for appropriately selected PNETs.[64–66]

Laparoscopic enucleation can be accomplished successfully for well-circumscribed, small (<3 cm) PNETs with noninvasive features and without involvement of the main pancreatic duct or ampulla.[54,62] As such, laparoscopic enucleation is not limited to the location of the lesion, but rather by proximity to vessels and the pancreatic

duct.[55] Intraoperative ultrasonography is often used to confirm tumor location and its relation to critical vasculature (eg, superior mesenteric artery and vein) and the main pancreatic duct (>2–3 mm) before proceeding with enucleation. Formal pancreatic resection is recommended when enucleation cannot be accomplished and is based on tumor location (ie, head, body, tail).

Laparoscopic distal pancreatectomy has been shown to be safe, and short-term outcomes may be favorable with this approach over an open approach.[63–65,67,68] Several techniques have been described including spleen-preserving (eg, Warshaw technique) and spleen-sacrificing methods of laparoscopic distal pancreatectomy.[69] Our approach is to pursue splenectomy for patients with ductal adenocarcinoma to produce an adequate lymphadenectomy.[66] For PNETs, the main factors that dictate the procedure chosen are the location of the tumor within the pancreatic body or tail and its relation to the splenic vessels and splenic hilum. Again, there has been little indication that lymph node clearance provides a survival advantage in PNET, and a strong argument can be made for splenic preservation in most cases in which the tumor is remote from the splenic hilum. Our approach in these patients is to be selective regarding splenectomy. In patients for whom there is evidence of lymphadenopathy on preoperative studies, we will pursue distal pancreatectomy with splenectomy. In patients for whom there is no evidence of significant lymphadenopathy on preoperative imaging and for whom spleen preservation is technically possible (tumor remote from the splenic hilum), we will perform laparoscopic distal pancreatectomy by means of the Warshaw spleen-preserving technique: saving the short gastric blood supply to the spleen while ligating the splenic artery and vein. Frozen sections are routinely sent to confirm adequate margin and to evaluate the grade of the tumor. If margins are involved or the tumor is high grade on frozen section, we continue with splenectomy to obtain an adequate lymphadenectomy.

Laparoscopic pancreaticoduodenectomy has been slow to gain popularity because of technical demands, long operative times, and increased cost.[70–73] Moreover, many surgeons have been reluctant to use the technique in the setting of malignancy, particularly pancreatic adenocarcinoma, because there are limited data regarding short-term and long-term oncologic outcomes. In patients with PNETs, there is additional potential complexity with regard to the reconstruction laparoscopically, as most patients with PNET will have normal-sized, small-caliber pancreatic ducts and soft glands. Both of these features contribute substantial difficulty to the pancreaticojejunostomy and garner increased risk of postoperative pancreatic fistula even under the best possible circumstances.

Robotic surgery has quickly evolved over the past decade, particularly fueled by patient preference. The robotic technique has been shown to be feasible for both distal pancreatectomy and pancreaticoduodenectomy, and short-term outcomes are encouraging.[74] Further studies are needed to assess the applicability of robotic surgery to PNETs.

Functional Pancreatic Neuroendocrine Tumors

Surgical management of functional PNETs varies depending on the tumor type, the tumor extent, and the underlying genetic etiology. Patients presenting with functional PNETs in the context of MEN I present several unique management problems and are discussed further in the next section. Insulinomas, either as part of MEN I or sporadic findings, are indolent tumors and rarely metastasize to regional lymph nodes. For these reasons, enucleation is often all that is needed for appropriate management.[75]

Sporadic gastrinomas have a greater potential for malignant behavior and can occur anywhere within the gastrinoma triangle, making localization challenging. Localization may need to be performed at the time of the operation using manual palpation and

intraoperative ultrasonography, endoscopic duodenal transillumination, or duodenotomy.[7] The use of minimally invasive resection is thus controversial for these tumors. Because gastrinomas are more likely to be malignant, surgical management warrants formal pancreatic resection with regional lymphadenectomy. Norton and colleagues[33] reported the results of 151 patients with Zollinger-Ellison syndrome treated operatively as part of a prospective study of the National Institutes of Health. Twenty-eight patients had MEN I. Twenty-three patients had 2 operations, whereas 2 patients had 3 or more operations. The duodenum was the most common location of gastrinomas independent of MEN I status (74 patients, 49%). Five-year disease-free survival among patients with sporadic gastrinomas was 40% compared with 4% for patients with MEN I; however, the 5-year disease-specific survival for sporadic gastrinomas and MEN I were both 100%. Lymph nodes in the region of the head of the pancreas and duodenum should be routinely removed at surgery even if they appear normal because they may contain microscopic gastrinoma.

Surgical resection whenever possible is recommended for other functional PNETs, particularly for symptom control and chance of cure. Glucagonomas are typically large and advanced at the time of presentation.[76,77] As such, enucleation and minimally invasive approaches are not recommended. Similarly, up to 80% of patients with VIPomas and up to 75% of patients with somatostatinomas have metastatic disease at the time of diagnosis.[78–80] Cytoreductive surgery may have a role to play to improve hormonal control.[81,82]

Multiple Endocrine Neoplasia Type I

MEN I is an autosomal dominant disorder attributed to a mutation in the *MEN I* tumor suppressor gene located at chromosome 11q13. Patients with MEN I usually develop primary hyperparathyroidism (90%–100%), followed by PNETs that can be functional (20%–70%), of which gastrinoma is the most common, or nonfunctional (80%–100%), and pituitary adenomas (20%–65%).[3] Surgical management of MEN I primarily involves subtotal parathyroidectomy for the primary hyperparathyroidism.

The surgical management of PNETs in patients with MEN I is challenging, as tumors in MEN I are almost always diffuse and multifocal.[83] Most agree that surgical resection should be undertaken for patients with MEN I who develop insulinomas or other rare functional PNETs.[84] These tend to be indolent tumors and patients will typically have prolonged symptomatic improvement with resection of detectable pathology. Patients presenting with gastrinoma in the context of MEN I present a unique management problem. The lesions tend to be multiple, recurrence is common, and there is little survival benefit afforded by resection.[3,85] Patients with MEN I and gastrinoma will rarely be cleared of the disease by local resection. Symptoms associated with Zollinger-Ellison syndrome are now effectively managed with PPIs or H_2-antagonists. Incomplete resection is not beneficial, and surgery is not indicated when there are extensive metastases. Studies have shown that patients with MEN I with gastrinoma are more likely to die of other causes than their gastrinomas.[3]

Up to 60% of patients with MEN I will have NF-PNETs. These lesion can grow to sizes that cause symptoms in up to 12%.[3] Similar to the debate in sporadic cases, there is no consensus to the management of small NF-PNETs in those with MEN I. Several studies have shown that patients with NF-PNETs smaller than 2 cm have no difference in long-term survival compared with those with MEN I and no PNETs.[7,83,85,86] Others recommend surgery for those that are 1 cm.[87] Unfortunately, the rarity of the disease prevents adequate evidence-based conclusions. Nevertheless, surgical management is warranted when NF-PNETs are large (>2 cm) or symptomatic when they occur in patients with MEN I akin to recommendations for sporadic cases.[87]

Metastatic Disease

PNETs present with distant metastases in approximately 40% to 45% of cases. The liver is the most common site of metastasis.[88] Resection of metastatic disease undoubtedly has a role to play in select patients with metastatic PNETs.[7,89] There is little to no level-I evidence to aid decision making in these cases. The treatment decisions should be individualized based on the underlying general health of the patient, the tumor's underlying biology, and the pattern of metastasis. ENETS has developed a consensus opinion regarding the minimum requirements for hepatectomy for curative intent of metastatic disease: technically feasible, well-differentiated disease with an acceptable morbidity and less than 5% mortality, absence of right heart insufficiency, absence of extra-abdominal metastases, and absence of diffuse peritoneal carcinomatosis.[14] Multiple prior studies have shown increased survival when an R0 resection is achieved compared with an R1 resection. Significant controversy exists regarding the role of cytoreductive surgery.[89,90] Most consensus guidelines recommend considering cytoreductive surgery if more than 90% of the tumor burden can be removed, the patient is symptomatic from disease, and the tumor is indolent. Tumor debulking has been argued to prevent the development of symptoms or provide symptom control (eg, from mass effect), to facilitate liver-directed therapies, and to increase survival.[90–92]

Treatment methods used for colorectal liver metastases are also used for liver metastases in PNETs. Liver-directed therapies, such as radiofrequency ablation and transcatheter embolization/transcatheter chemoembolization, have been used when resection is not feasible with reasonable results.[7,81,89,93] Liver transplantation has also been applied to some patients with PNET and isolated diffuse liver metastasis.[94] Mazzaferro and colleagues[95] reported a 96% 5-year survival and an approximately 80% 5-year recurrence-free survival for 30 patients who underwent liver transplantation following stringent patient selection criteria (**Box 1**).

Box 1
Milan criteria for liver transplantation in patients with hepatic metastases from neuroendocrine tumors

Inclusion Criteria

1. Confirmed histology of carcinoid tumor (low-grade neuroendocrine tumors) with or without syndrome
2. Primary tumor drained by the portal system (pancreas and intermediate gut: from distal stomach to sigmoid colon) removed with a curative resection (pretransplant removal of all extrahepatic tumor deposits) through surgical procedures different and separate from transplantation
3. Metastatic diffusion to liver parenchyma $\leq$50%
4. Good response or stable disease for at least 6 months during the pretransplantation period
5. Age $\leq$55 years

Exclusion Criteria

1. Small-cell carcinoma and high-grade neuroendocrine carcinomas (noncarcinoid tumors)
2. Other medical/surgical conditions contraindicating liver transplantation, including previous tumors
3. Nongastrointestinal carcinoids or tumors not drained by the portal system

From Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? J Hepatol 2007;47(4):462; with permission.

SUMMARY

PNETs are a heterogeneous group of tumors within a spectrum of neuroendocrine disease. Endocrinopathies produced by roughly 10% of these tumors have been their historical allure. However, with the increasing use of high-resolution imaging, PNETs are more frequently found when smaller, and we do not yet understand their optimal management. Nevertheless, because of their potential for malignancy, surgical resection remains a foundation in their management.

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