CHAPTER 65

Pancreatic neuroendocrine tumors: classification, clinical picture, diagnosis, and therapy

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INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are a group of rare, heterogeneous neoplasms that were historically referred to as islet-cell tumors (Kuo et al, 2014). Their cellular origin has been debated, but it is likely that these tumors arise from pluripotent stem cells in the pancreatic ductal/acinar system and not from the pancreatic islets themselves (Schimmack et al, 2011; Vortmeyer et al, 2004). These tumors are classified as functional, if they cause a specific hormonal syndrome, or nonfunctional. The majority of PNETs are nonfunctional. Functional tumors are named for the hormone they secrete. Gastrinomas are the most common, followed by insulinomas, and then the more rare PNETs—glucagonomas, somatostatinomas (SSomas), vasoactive intestinal peptide-secreting tumors (VIPomas), and pancreatic polypeptide-secreting tumors (PPomas) (Yao et al, 2007).

EPIDEMIOLOGY

Pancreatic neuroendocrine tumors account for approximately 7% of all neuroendocrine tumors and 1% to 2% of pancreatic tumors (Franko et al, 2010, Kuo et al, 2014; Schimmack et al, 2011). The incidence of these tumors has risen over the past 30 years from 0.17 to 0.43 cases per 100,000 people. Males and females are affected equally. Most patients are diagnosed between the ages of 60 to 80 years (Fraenkel et al, 2012). Approximately 5% of patients will have an underlying familial syndrome predisposing to PNET development, such as multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau (VHL), tuberous sclerosis (TS), or neurofibromatosis type I (NF1), and these patients tend to be diagnosed at a younger age (Schimmack et al, 2011). A family history significant for NET is the only well-established risk factor for PNET development (Hassan et al, 2008); risk factors for pancreatic adenocarcinoma, such as cigarette smoking, diabetes mellitus, chronic pancreatitis, and obesity, have not been found to be associated with the development of PNET (Ryan et al, 2014).

MOLECULAR BIOLOGY

In well-differentiated PNETs, the most commonly mutated genes are *MEN1* (44%), *DAXX/ATRX* (death domain–associated protein/alpha-thalassemia X-linked mental retardation syndrome) (43%), and *mTOR* (mammalian target of rapamycin) (15%) (Jiao et al, 2011, J. Zhang et al, 2013) (see Chapter 9B). *MEN1* is a tumor suppressor gene, and its silencing has an important role in the initiation and progression of PNETs. Mutations that disrupt the function of this gene lead to the familial syndrome MEN1, and more than 1300 different mutations in the gene have been reported in patients with this syndrome. Homozygous deletion of the gene is lethal in mouse embryos (Bertolino et al, 2003, J. Zhang et al, 2013). DAXX and ATRX are proteins that dimerize to stabilize chromatin. Loss of either of these two genes or diminished protein expression can lead to chromosomal instability and PNET development (Marinoni et al, 2014). mTOR regulates cellular proliferation, motility, and survival (J. Zhang et al, 2013). This has become an important drug target in PNETs, but blockade of this protein eventually leads to resistance and clinical relapse.

Poorly differentiated PNETs are clinically and genetically distinct from their well-differentiated counterparts. The most commonly mutated genes in this group of tumors are the tumor suppressors *p53* (95%) and *Rb* (74%) (Yachida et al, 2012, J. Zhang et al, 2013). *Bcl-2*, an important regulator of cell death, is overexpressed in the majority of high-grade PNETs and has been proposed as a potential target for treatment (Yachida et al, 2012).

PATHOLOGY AND STAGING

Pancreatic neuroendocrine tumors are generally well-circumscribed, solitary masses that can occur anywhere in the pancreas (Schimmack et al, 2011). The majority of PNETs are well-differentiated (Baudin et al, 2013). All PNETs have the potential to grow and eventually metastasize, and because of this, these tumors are considered malignant. Because the

TABLE 65.1 Grading System for Pancreatic Neuroendocrine Tumors*

Grade	Mitotic Index		Ki-67 Index
Low grade (G1)	<2 mitoses/10 HPF	AND	<3%
Intermediate grade (G2)	2-20 mitoses/10 HPF	OR	3%-20%
High grade (G3)	>20 mitoses/10 HPF	OR	>20%

HPF, High-powered field.

*This system is recommended by European Neuroendocrine Tumor Society (ENETS) and World Health Organization. It is the most widely used grading system and the method used by most surgical pathology laboratories. From Bosman FT, et al: *WHO Classification of Tumours of the Digestive System*, 4th ed. Lyon, France, WHO Press, 2010; and Rindi G, et al: Gastroenteropancreatic (neuro)endocrine neoplasms: the histology report. *Dig Liver Dis* 43:S356-S360, 2011.

TABLE 65.2 TNM Staging System for Pancreatic Neuroendocrine Tumors*

Stage	T	N	M
0	Tis	N0	M0
Ia	T1	N0	M0
Ib	T2	N0	M0
IIa	T3	N0	M0
IIb	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension		
T2	Tumor limited to the pancreas, >2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas, but without involving the celiac axis or superior mesenteric artery		
T4	Tumor involves the celiac axis or superior mesenteric artery; unresectable primary tumor		
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
MX	Distant metastases cannot be assessed		
M0	No distant metastases		
M1	Distant metastases		

*Based on the system put forth by the American Joint Committee on Cancer.

TNM, Tumor-necrosis-metastasis.

From Edge SB, et al: *American Joint Committee on Cancer Staging Manual*. New York, Springer, 2010.

likelihood of metastatic spread is so very low in subsets of patients with PNETs, the term "benign" has been used as a classification variable. Most classification schemes have considered PNET to be malignant if it invades locoregionally; has metastasized distantly or to regional lymph nodes; is greater than 2 cm in size; displays vascular, lymphatic, or perineural invasion; or has a proliferative index greater than 2% (Klöppel et al, 2004; Rindi et al, 2011).

The biologic behavior of PNETs is determined by both the grade and stage of the tumor. Grade is determined either by the mitotic index or Ki-67 index (Bosman et al, 2010). The mitotic index is expressed as the number of mitotic figures per 10 high-powered microscopic fields (HPFs), and it is recommended that 40 to 50 HPFs be examined (Klimstra et al, 2010). Ki-67 labeling tags neoplastic cells with an antibody and then reports the percentage of cells that stain positively (Jamali et al, 2008) (Table 65.1). The assay is carried out with the MIB-1 monoclonal antibody, which has shown superior efficacy to the Ki-67 antibody in paraffin-embedded tissues (Veronese et al, 1996), and thus pathology reports may refer to the test as the MIB-1 index. High-grade tumors have more than 20 mitoses/HPF or a Ki-67 index greater than 20% and are referred to as neuroendocrine carcinomas in the World Health Organization system.

The staging system most commonly used in the United States for classifying PNETs is the 2010 American Joint Committee on Cancer tumor-node-metastasis system, which is essentially the same as for pancreatic adenocarcinoma (Edge et al, 2010) (Table 65.2). Stage I indicates localized tumors, stages II and III more advanced local or regional disease, and stage IV distant metastases. The 5-year overall survival (OS) rates (nonfunctional and functional tumors combined) derived from analysis of the Surveillance Epidemiology and End Results (SEER) database are 62% for patients with localized tumors, 54% for those with regionally advanced disease, and 20% for patients with distant metastases (Halfdanarson et al, 2008).

PROGNOSIS

Despite being classified as well-differentiated, the majority of PNETs will have pathologic features that increase the likelihood of future recurrence or have metastatic disease at the time of diagnosis (Schimmack et al, 2011). Low- and intermediate-grade (G1 and G2, respectively) PNETs have significantly better 5-year OS (75% and 63%, respectively) than do G3 tumors (7%) (Strosberg et al, 2011b), and functional tumors are associated with better survival than nonfunctional PNETs as they are more often identified at an earlier stage (68% vs. 60% 5-year OS) (Bilimoria et al, 2008). Approximately 60% of PNET cases will have distant metastases at presentation, which is associated with decreased survival compared with those with local or locoregional disease (Roland et al, 2012). In addition to grade and the presence of distant metastases, age at diagnosis can also help stratify patients into prognostic categories, as an older age at diagnosis correlates with impaired survival (<55 years, 67.8% 5-year OS vs. >75 years, 40.8% 5-year OS) (Bilimoria et al, 2008).

Operative resection has been associated with improved survival. Fischer and colleagues (2008) found that, in a cohort of 118 PNETs, R0 resection did not confer better survival than R1 or R2 resections in patients with well-differentiated tumors, but that patients who received any kind of resection had better survival than those who underwent an exploratory surgery without resection of the primary tumor or any debulking (median survival, ≈35 months vs. 17 months, respectively). Data on the role of surgery in poorly-differentiated PNETs are limited, in part due to the rarity of the tumor, their abbreviated survival (5-year OS, 4%) (Vinik et al, 2010), and thus conclusions cannot be drawn as to the efficacy of surgery in this group

of tumors. It is generally recommended that these patients be treated with chemotherapy, as their survival is poor, unless they have localized disease (Strosberg et al, 2010).

FAMILIAL SYNDROMES

Pancreatic neuroendocrine tumors are associated with four familial diseases: MEN1, VHL, NF1, and TS. MEN1 is the most common of these syndromes, and approximately 5% to 7% of patients with PNETs will have MEN1 (Bilimoria et al, 2008). It is inherited in an autosomal dominant fashion and characterized by the development of parathyroid adenomas that will cause hyperparathyroidism in 90% of patients, multiple functional or nonfunctional PNETs in 75%, and pituitary adenomas in 40% (Schernthaner-Reiter et al, 2016). Adrenocortical tumors (both functional and nonfunctional), thymic tumors, and bronchial NETs are also seen in some patients (Schimmack et al, 2011). Genetic testing for the disease should be performed in all first-degree relatives (including children younger than 5 years) of affected patients and those who have had a germline mutation identified in the *MEN1* gene (Thakker et al, 2012). Approximately 30% to 50% of patients will present with metastases, complications of which are the most common cause of death from MEN1 (Doherty et al, 1998, Schernthaner-Reiter et al, 2015). The surgical management of these tumors is complex and discussed in greater detail later (see Chapters 66 and 67).

VHL is an autosomal dominant syndrome caused by inactivation of the *VHL* gene, which is thought to play a role in angiogenesis (Yao et al, 2007). VHL predisposes patients to a number of cancers: renal cell carcinoma, pheochromocytoma, cerebellar and spinal hemangioblastoma, retinal angioma, endolymphatic sac neoplasms, epididymal cystadenoma, as well as cystic and solid pancreatic neoplasms (Blansfield et al, 2007). Between 10% and 15% of VHL patients will develop PNETs, although the most common pancreatic manifestation of this syndrome is simple cysts (Charlesworth et al, 2012; Schimmack et al, 2011).

PNETs may also develop in TS and NF1. The tuberous sclerosis complex 1/2 (TSC1/2) inhibits mTOR, and a defect in the *TSC2* gene leads to development of TS. *NF1*, the gene responsible for NF1, regulates the activity of *TSC2*. Loss of *NF1* leads to constitutive mTOR activation. In TS, hamartomas may develop in the brain, eyes, heart, lungs, skin, kidneys, and pancreas. In NF1, the primary manifestation is the development of benign neurofibromas in multiple locations of the peripheral nervous system. Patients are also at risk for pheochromocytomas and sarcomas. In both TS and NF1, multiple PNETs may develop in the pancreas and duodenum (Rabito et al, 2014; Yao et al, 2007).

FUNCTIONAL TUMORS: CLINICAL FEATURES

Functional PNETs are named for the hormone they hypersecrete. These PNETs tend to have better 5-year OS compared with nonfunctional PNETs (Bilimoria et al, 2008). This is likely because they are detected earlier than nonfunctional PNETs, due to the presence of symptoms.

Insulinoma

Insulinomas represent 1% to 2% of all pancreatic tumors. They are typically small (<2 cm), solitary (except in MEN1), intrapancreatic, and cause symptoms of hypoglycemia. In the rare cases where these tumors are malignant, 5-year OS is 56% (Baudin et al, 2013), and 10-year OS declines to 29% (Okabayashi et al, 2013). A critical part of the history includes establishment of the presence of Whipple's triad: plasma glucose less than 40 mg/dL, symptoms of hypoglycemia, and resolution of symptoms with a meal. The diagnosis can be confirmed by drawing plasma glucose, insulin, C-peptide, and proinsulin levels during a 72-hour fast. This panel will detect 90% of insulinomas (Ito et al, 2012). Malignant insulinomas tend to produce higher levels of insulin and proinsulin and thus more severe symptoms due to the fact that their metastases also secrete these hormones. Although most insulinomas are identified with computed tomography (CT) or ultrasound (US), when they are very small these methods may not localize the tumor, and arterial stimulation venous sampling may then be helpful. To perform this test, the right and left hepatic veins are catheterized via a femoral puncture. Calcium is injected successively into the gastroduodenal, proximal splenic, superior mesenteric, and proper hepatic arteries. After each injection, venous blood is sampled from the hepatic veins at 30, 60, and 120 seconds, and a positive localization corresponds to a twofold increase in hepatic vein insulin levels (Doppman et al, 1993). The accuracy of this method to localize the tumor to a region of the pancreas (i.e., head, body, tail) is 94% to 100% (Okabayashi et al, 2013).

Gastrinoma

In 1955, Zollinger and colleagues published their case series detailing the clinical courses of two patients with gastric acid hypersecretion, severe peptic ulceration, and pancreatic tumors. The syndrome would be named for these authors, and the tumors would eventually be known as gastrinomas. The extraordinarily high levels of gastrin secreted by these tumors are the cause of the recurrent peptic ulcers, diarrhea, and reflux esophagitis experienced by most patients and also cause the thickened mucosal folds in the stomach that are a hallmark of the disease (Anlauf et al, 2006, Kulke et al, 2010). These functional PNETs may be sporadic (67%) or familial (33%) (Anlauf et al, 2006) and tend to be solitary tumors unless seen in the context of MEN1, in which case they are small, multiple, and most likely found in the duodenum (>85%) (Kulke et al, 2010). Regardless of their etiology, they are generally found within the gastrinoma triangle (Fig. 65.1), which was described in 1984 to aid surgeons in finding these frequently diminutive tumors (Stabile et al, 1984). The majority of gastrinomas are considered malignant (60%) and have spread to regional lymph nodes by the time they are diagnosed. Liver metastases are often associated with gastrinomas that arise in the pancreas (Anlauf et al, 2006). Laboratory diagnosis of the disease requires demonstration of hypergastrinemia and abnormal gastric acid secretion. This can be done by obtaining a fasting serum gastrin and a gastric pH. If the gastrin level is 10 times normal and the gastric pH is less than 2, the diagnosis is confirmed (Ito et al, 2012). If results are equivocal, a secretin or glucacon stimulation test can be performed, as gastrinomas frequently express both of these receptors and respond by secreting abnormally large amounts of gastrin to the injected reagent (Kulke et al, 2010, Shibata et al, 2013).

Glucagonoma

Only about 400 cases of glucagonomas have been reported in the literature (Sahoo et al, 2014). These tend to be large

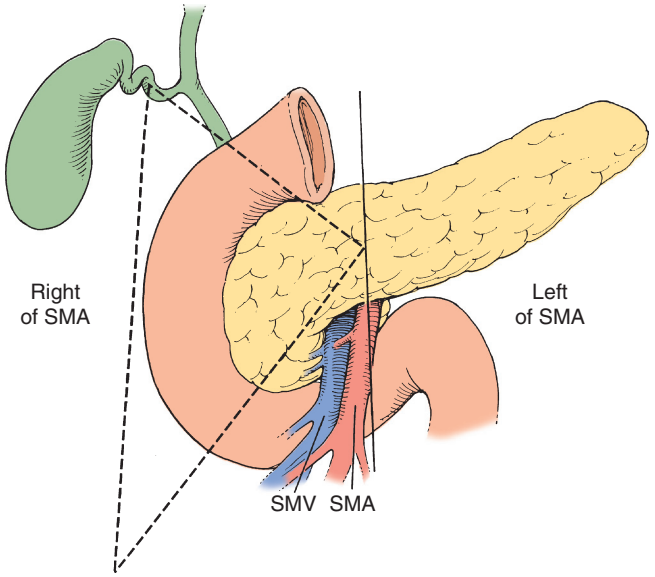

FIGURE 65.1. Gastrinoma triangle. Approximately 90% of gastrinomas are thought to arise in this anatomic location. The apex is at the junction of the cystic duct and common bile duct, the inferior aspect lies at the junction of the second and third parts of the duodenum, and the medial extent lies at the junction of the head and body of the pancreas. *SMA,* Superior mesenteric artery; *SMV,* superior mesenteric vein. *(From Howard TJ, et al: Anatomic distribution of pancreatic endocrine tumors.* Am J Surg *159:258-264, 1990.)*

(>6 cm) and solitary pancreatic tumors. The most common symptoms of the disease are glucose intolerance, migratory necrolytic erythema, and weight loss (Kulke et al, 2010). The migratory rash is often the first manifestation (Fang et al, 2014). It tends to start in the perineum and then spreads to the trunk and extremities. The diagnosis is achieved when an elevated plasma glucagon level is found in the context of an enhancing pancreatic mass on CT. Approximately 60% will have liver metastases at diagnosis (Kulke et al, 2010). In a case report of 23 glucagonomas, the 5-year OS (regardless of treatment) was nearly 75% (Kindmark et al, 2007).

Vasoactive Intestinal Peptide-Secreting Neuroendocrine Tumor

VIPomas tend to be solitary, intrapancreatic tumors, greater than 50% of which are metastatic at presentation (Kulke et al, 2010). The hypersecretion of VIP, a neurotransmitter and intestinal secretagogue, leads to the development of "pancreatic cholera" (Kane et al, 1983), also known as Verner-Morrison syndrome (Verner et al, 1958), which is characterized by large-volume (average, 4.5 L) watery diarrhea that leads to metabolic acidosis, achlorhydria, and hypokalemia. If not properly identified and treated, patients will eventually succumb to renal failure secondary to hypovolemia (Fabian et al, 2012). As with the other functional PNETs, the diagnosis is made by radiographic evidence of a pancreatic tumor and a history consistent with the syndrome associated with hypersecretion of VIP. Further confirmation is made by demonstration of an elevated plasma VIP level.

Somatostatinoma

SSomas have a less-defined clinical syndrome than do the other functional PNETs, and not all tumors that hypersecrete somatostatin will cause symptoms. The syndrome may include glucose intolerance, cholelithiasis, weight loss, diarrhea, steatorrhea, or anemia. These tumors may arise either in the pancreas (56%) or duodenum and may be more aggressive if intrapancreatic (Nesi et al, 2008). Duodenal SSomas are associated with NF1 in approximately 50% of cases. If discovered in this context, they are less likely to be malignant (Williamson et al, 2011).

Pancreatic Polypeptide-Secreting Neuroendocrine Tumors

PNETs that predominantly secrete pancreatic polypeptide (PP) are extremely rare, and whether they should be classified as functional is a matter of debate, as no specific syndrome has been defined. Patients may present with intermittent abdominal pain, pancreatitis (Kuo et al, 2008), and some patients may develop glucose intolerance (Maxwell et al, 2014). If these tumors occur in the context of MEN1, they tend to be multifocal and malignant (Kuo et al, 2008). PP can be used as a marker for PNETs in MEN1 patients, as fasting PP levels greater than three times normal have been shown to correlate with the presence of a PNET that will likely be large enough to detect by standard imaging (Mutch et al, 1997).

NONFUNCTIONAL TUMORS: CLINICAL FEATURES

Nonfunctional PNETs are characterized by their lack of hormone production and hormone-associated syndromes. It is difficult to know what proportion of PNETs are truly nonfunctional, as reports vary widely, ranging from 10% to 91% (Halfdanarson et al, 2008; Hill et al, 2009; Franko et al, 2010; Phan et al, 1998; Vagefi et al, 2007). This wide range is due to two main factors. Rates calculated from single institutions may be lower due to a referral bias for functional tumors at academic medical centers. If rates are calculated using large, public databases such as SEER or the National Cancer Database (NCDB), they often will identify higher numbers of nonfunctional tumors, as these repositories do not collect data on hormone levels. Thus the default in these databases is categorization of a PNET as nonfunctional unless a specific functional histology code is recorded, such as insulinoma, glucagonoma, VIPoma, or gastrinoma. Given all of this, a reasonable estimate of the proportion of nonfunctional PNETs is approximately 75% (Choti et al, 2012).

In one report, 39% of these tumors were discovered because of symptoms related to the tumor's mass effect—abdominal pain, jaundice, weight loss, abdominal mass, nausea, vomiting, back pain, or pancreatitis (Birnbaum et al, 2014). Nonfunctional PNETs causing symptoms tend to be larger than those PNETs found incidentally (2.5 vs. 1.8 cm) and are more likely to have involved nodes at diagnosis (Birnbaum et al, 2014).

Approximately 35% of PNETs are discovered incidentally, and this is occurring with greater frequency as the use of high-quality axial imaging is increasing (Crippa et al, 2014) (see Chapters 18 and 19). In one series of incidentally discovered PNET, 19% were classified as having benign histopathologic findings, 52% had uncertain histology, and 28% were considered to have malignant pathologic features. The benign tumors and those with uncertain histology were associated with a 5-year OS of 89% and 93%, respectively, whereas malignant tumors had 50% 5-year OS (Haynes et al, 2011).

Whether discovered incidentally or due to symptoms, chromogranin A (CgA), PP, pancreastatin (PST), neurokinin A (NKA), and serotonin are blood tests that should be considered. Chromogranin A levels have been shown to correlate with tumor burden, and posttreatment decreases correlate with favorable outcomes, whereas rising levels may suggest recurrent or progressive disease (Kanakis et al, 2012). Pancreatic polypeptide is often obtained to identify NETs in the cases where CgA is negative (Kuo et al, 2014). PST, a posttranslational product of CgA has been found to be an even more powerful prognostic test than CgA in surgically managed PNET patients, as patients with elevated PST preoperatively that remains elevated postoperatively have at least a 90% chance of progression and an almost 40% risk of death within 5 years. Patients that had their PST normalize postoperatively have a low risk of death (Sherman et al, 2014). NKA can be used as a diagnostic marker for NETs but has less prognostic utility than PST. Serotonin is elevated in 43% of foregut NETs (Kema et al, 1994), but its moderate sensitivity and specificity limit its diagnostic usefulness.

IMAGING

Imaging and endoscopy are used for primary tumor detection, staging, surgical planning, and evaluation of somatostatin receptor expression. The modalities used most often are CT (see Chapter 18), magnetic resonance imaging (MRI) (see Chapter 19), endoscopic US (EUS) (see Chapter 16), standard US (see Chapter 15), somatostatin receptor scintigraphy (SRS), and positron-emission tomography (PET) (see Chapter 17).

CT is often the first modality used to image PNETs, as it is valuable for detection of the primary, regional, and metastatic disease (Fig. 65.2). Its sensitivity for tumors greater than 2 cm is 80% to 100% (Kuo et al, 2014), although it is more sensitive for hepatic metastases than it is for primary tumors (Chiti et al, 1998; Sundin et al, 2009). This modality is able to detect some PNETs smaller than 0.5 cm (Alsohaibani et al, 2008), although it is more likely to miss these small lesions when compared with EUS (Khashab et al, 2011). CT imaging should be obtained with oral and intravenous (IV) contrast. IV contrast is important for the detection of the primary tumor and metastases, as PNETs and their metastases tend to be hypervascular and best seen in the arterial phase. These lesions will wash out in the venous and delayed phases (Bushnell et al, 2011). Oral contrast is helpful for visualizing the duodenum (Kuo et al, 2014).

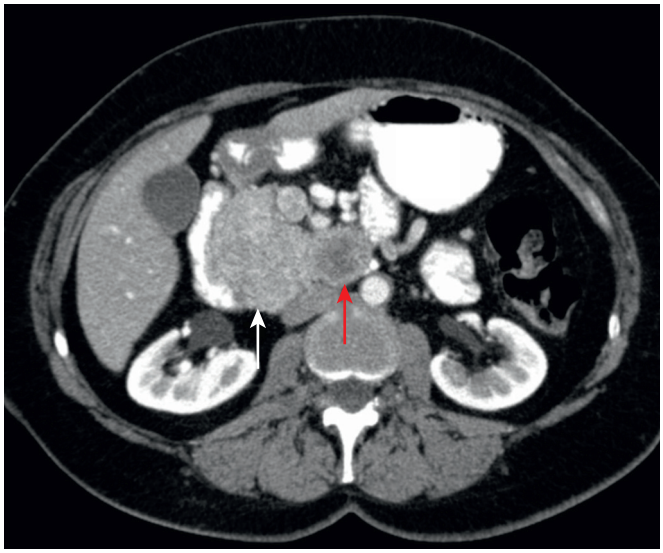

FIGURE 65.2. Arterial phase of a contrast-enhanced computed tomography of the abdomen showing an early enhancing pancreatic neuroendocrine tumor in the head and uncinate process of the pancreas *(white arrow),* with a necrotic node medially *(red arrow).*

MRI should be considered a second-line test for detection of primary PNETs and used when superior delineation of hepatic metastases is required (Dromain et al, 2005), when patients have an iodinated contrast allergy, or in cases of renal failure (Sundin, 2012). This study should also be obtained with IV contrast. The tumors will be hypointense on T1 and hyperintense on T2 images. As with CT, lesions less than 1 cm may be missed, regardless of contrast administration (Kuo et al, 2014).

US is most commonly combined with endoscopy or used intraoperatively in the localization of PNETs. EUS may be used to identify the primary tumor, local nodal involvement, and when combined with fine needle biopsy, to obtain tissue diagnosis with a diagnostic accuracy of 90% (Atiq et al, 2012; Bernstein et al, 2013). It has a sensitivity of 79% to 82% (Rosch et al, 1992) and can detect tumors as small as 2 to 3 mm (Kuo et al, 2014). US is commonly used intraoperatively to localize small tumors such as insulinomas. In this role, it has a sensitivity of 80% to 100% (Okabayashi et al, 2013), although like EUS, is highly operator dependent.

SRS is used in the diagnosis and surveillance of patients with PNETs and is also used to determine whether patients may benefit from peptide receptor radionuclide therapy (PRRT) (Lu et al, 2013). There are five types of somatostatin receptors (SSTR1 to SSTR5), and SSTR2 is frequently expressed on well-differentiated NETs and serves as the primary receptor for somatostatin analogue imaging and treatment (Reubi et al, 1990).

The original, and most common, somatostatin analogue–based imaging modality is the OctreoScan, which uses the radiotracer indium-111–DPTA-octreotide (Krenning et al, 1993). In its most basic form, this study produces a whole-body planar image with dark spots indicating where radiotracer has bound to SSTR2 (and to a lesser extent, SSTR5 and SSTR3) (Theodoropoulou et al, 2013). In most centers, these planar images are enhanced by combining the OctreoScan with single-photon emission computed tomography (SPECT), which adds axial three-dimensional imaging to the functional scintigraphic image, greatly improving the diagnostic accuracy (Lu et al, 2013). In one study, the addition of SPECT to OctreoScan improved lesion detection by 52% (Krausz et al, 2003).

The most modern iteration of somatostatin receptor–based imaging combines PET with CT, and uses the positron emitter gallium-68 to label various somatostatin analogues—most commonly ^{68}Ga-DOTA-Tyr(3)-octreotide (DOTATOC), ^{68}Ga-DOTA-1-Nal(3)-octreotide (DOTANOC), and ^{68}Ga-DOTA-Tyr(3)-octreotate (DOTATATE)—which then bind to their respective SSTR subtypes. Each ligand varies in its affinity for the various SSTR subtypes, but these differences are not clinically significant (Sundin, 2012). ^{68}Ga-PET/CT will detect both functional and nonfunctional PNETs (Naswa et al, 2013; Sahoo et al, 2014; Treglia et al, 2013). Studies comparing ^{68}Ga-PET/CT and conventional imaging modalities (CT, MRI, OctreoScan) consistently demonstrate the superiority of

^{68}Ga-PET/CT in the detection of NET primary tumors and metastases (Buchmann et al, 2007; Gabriel et al, 2007; Naswa et al, 2011). However, care must be taken to differentiate NETs from physiologic uptake of ^{68}Ga, as is seen in the uncinate process of the pancreas (Krausz et al, 2012), pituitary, spleen (or accessory spleen), and kidneys (Kroiss et al, 2013). Despite its demonstrated utility in NET imaging, ^{68}Ga-PET/CT has not yet been approved for general use in the United States, although trials at select centers are ongoing.

18-Fluoro-deoxy-glucose PET (^{18}FDG PET) is most often used in PNETs when other conventional imaging methodologies have failed to detect the primary tumor, or in cases when the tumor is high grade (Bhate et al, 2010). Patients found to have PNETs with uptake on ^{18}FDG PET are more likely to have early disease progression than those who are ^{18}FDG PET negative (Garin et al, 2009).

SURGICAL MANAGEMENT

Resection of the Primary Tumor: Surgical Considerations

Surgical excision of the primary PNET, regional nodal disease, and distant metastases are required to achieve cure of the disease, although this is often unlikely as the majority of patients will present with advanced disease. Despite this, patients may derive benefit from surgical resection and should therefore be evaluated and treated by a surgeon familiar with the nuances of NET-directed operations (see Chapters 66 and 67). In general, resection is indicated for (1) functional, symptomatic PNETs; (2) isolated, G1 or G2 PNETs greater than 2 cm; and (3) patients with metastatic disease in which all visible metastases can be resected (Kuo et al, 2014). Palliative resection of the primary PNET and hepatic debulking may be considered for those patients with symptomatic, advanced disease when the liver is the only focus of distant metastases and approximately 80% of the hepatic disease can be resected (Bertani et al, 2014).

It is generally accepted that nonfunctional PNETs greater than 2 cm should be resected, given their metastatic potential. However, much debate exists around what to do about smaller PNETs. In many centers, these small tumors are observed with serial imaging and resected if they show signs of progression. Evidence for this approach is conflicting. Lee and colleagues (2012) compared patients with nonfunctional PNETs less than 4 cm who were managed nonoperatively ($n = 77$; median tumor size, 1 cm) with patients who underwent resection ($n = 56$; median tumor size, 1.8 cm). Nine percent of the operative group had positive nodes and a median tumor size of 2.4 cm. The study had a mean follow-up of 3.75 years (maximum, 12.75 years). The median primary tumor size in the nonoperative group did not change during follow-up, nor was there disease progression or disease-specific mortality in this group, suggesting that small PNETs can be safely managed nonoperatively. Kuo and colleagues' (2013) review of the SEER database demonstrated that PNETs less than 2 cm were associated with a 27.3% rate of nodal metastasis and 9.1% rate of distant metastasis. Thus a reasonable number of these small tumors may progress beyond the point of being able to offer a patient curative surgery. More recently, a study examining the survival of patients in the NCDB with localized, nonfunctioning PNETs less than 2 cm ($n = 380$) showed that OS was significantly improved in those patients who underwent resection of their primary (median survival > 5 years, compared with 2.3 years in observation group) (Sharpe et al, 2015). However, because inclusion in NCDB requires a tissue diagnosis, this study would not have included many patients with incidentally found tumors that were being followed by imaging. Therefore the optimal management of nonfunctional tumors less than 2 cm is unclear. In patients with significant comorbidities, tumors less than 1 cm without imaging findings suspicious for invasion or nodal metastases, or evidence of an increase in size over time, it seems reasonable to observe these tumors. Furthermore, pancreas-directed operations are not without risk. In the series from Lee and colleagues (2012), 46% of the surgically treated patients had some sort of perioperative complication, the most common of which was development of a pancreatic fistula.

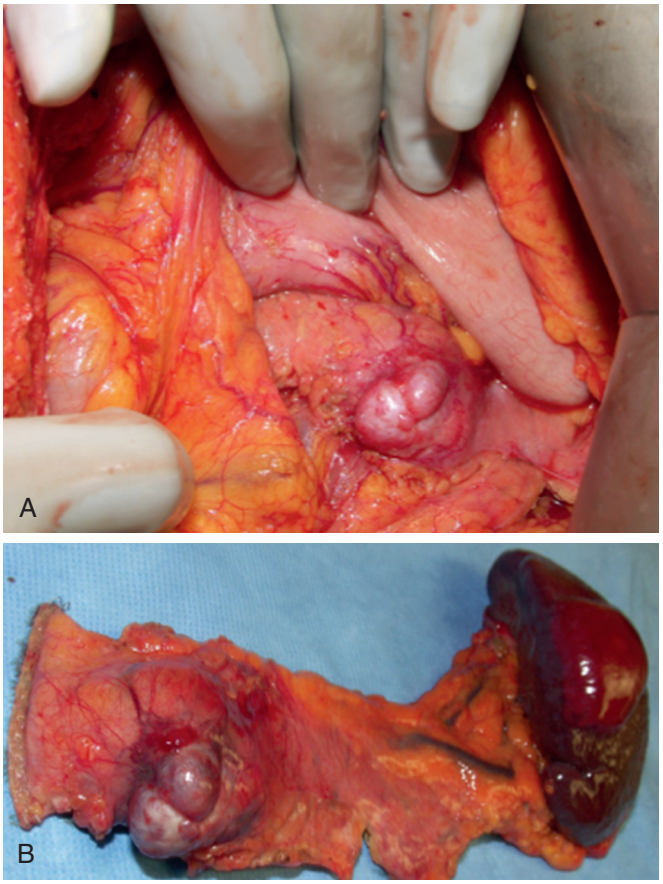

FIGURE 65.3. **A,** Intraoperative view of a pancreatic neuroendocrine tumor located in the body of the pancreas. **B,** Specimen resulting from distal pancreatectomy and splenectomy.

Lesions in the body and tail are generally treated with distal pancreatectomy (Fig. 65.3). As larger tumors commonly invade the splenic vein, splenectomy is often performed, although in cases where the tumors are small and do not invade the vein, splenic preservation should be considered. Warshaw (1988) showed this could be performed safely in 22 patients by retaining the short gastric vessels, even if the splenic artery and vein have been divided (Fig. 65.4). This may allow for preservation of the immunologic and hematologic function of the spleen. In the 2011 retrospective follow-up study at Massachusetts General Hospital of 158 patients who received the Warshaw procedure between 1986 and 2009, only 1.9% of patients required reoperation due to splenic failure (Ferrone et al, 2011). Tumors in the head, especially if large, will require

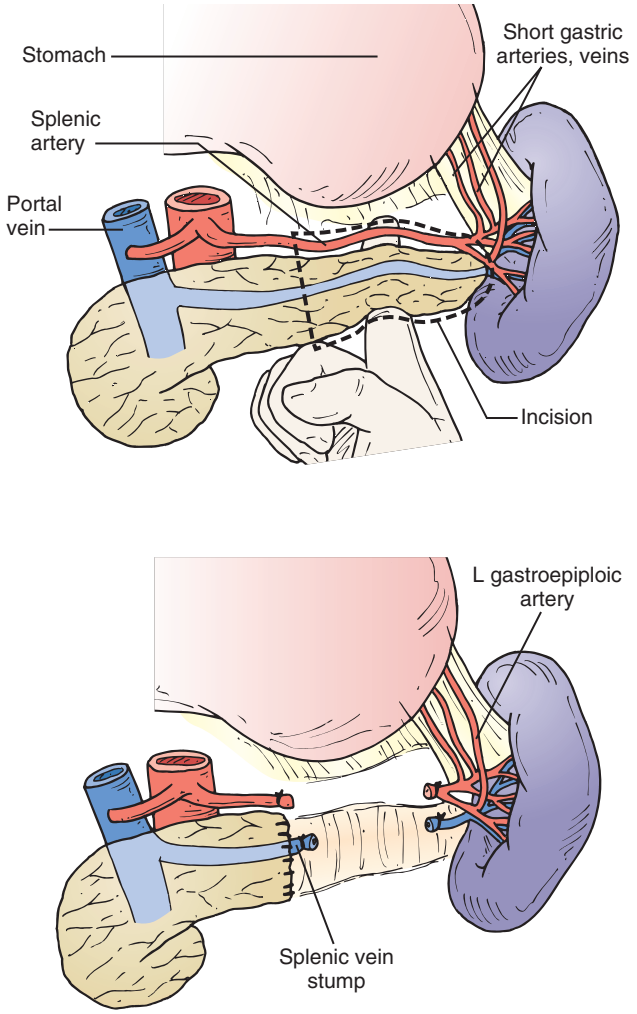

FIGURE 65.4. Diagram of key concepts in spleen-preserving distal pancreatectomy (Warshaw procedure). *Top,* the pancreas is mobilized by incising the retroperitoneum along the left inferior margin and opening the avascular plane behind it. Dissection is carried to the left, past the tip of the pancreas to isolate the splenic vascular pedicle. *Bottom,* the splenic artery and vein can be ligated and divided individually (as shown) or together, then body and tail of pancreas removed. The gastroepiploic arcade and short gastric vessels should be left undisturbed. *(Redrawn from Warshaw AL: Conservation of the spleen with distal pancreatectomy.* Arch Surg *123:550-553, 1988.)*

pancreaticoduodenectomy (PD). Small tumors in the head can be considered for enucleation.

More limited procedures, such as enucleation, are acceptable for the resection of small, isolated PNETs and are associated with relatively low rates of complications (Fig. 65.5). Three recent studies reported on the safety and efficacy of enucleation as a means to treat small (1 to 3 cm) PNETs. Compared with patients who underwent PD or distal pancreatectomy for their tumors, patients having enucleation experienced less blood loss, shorter operative times, fewer postoperative complications, and less pancreatic insufficiency (Cauley et al, 2012; Hackert et al, 2011; T. Zhang et al, 2013). Enucleation can be approached safely either via laparotomy or laparoscopy (Fendrich et al, 2011; Karaliotas et al, 2009) but should be reserved for those PNETs most likely to be benign. Given that condition, this procedure is generally performed on insulinomas and small, isolated gastrinomas or nonfunctional PNETs (Kulke et al, 2010). From a technical standpoint, enucleation should only be considered for PNETs that are 2 to 3 mm away from the main pancreatic duct, less than 2 cm in size, and located relatively near the surface of the pancreatic parenchyma. In addition, intraoperative US should be used to help visualize the location of the pancreatic duct during the procedure (Cauley et al, 2012; Hackert et al, 2011; T. Zhang et al, 2013).

To improve patient recovery, distal pancreatectomy may be performed laparoscopically. A recent meta-analysis examined 18 studies that included 1814 patients with pancreatic tumors amenable to resection via distal pancreatectomy. Forty-three percent of patients underwent laparoscopic resection, and the rest were approached with laparotomy. The laparoscopic group had a shorter length of stay, less blood loss, and fewer postoperative complications. Encouragingly, there was no difference in margin positivity, postoperative pancreatic fistula development, or mortality, although there did seem to be a trend toward fewer lymph nodes being sampled with the laparoscopic approach (Venkat et al, 2012). Some surgeons have begun performing robotic distal pancreatectomy, and although they anecdotally report good outcomes, insufficient evidence has been gathered to support the routine use of this modality in oncologic cases (Cirocchi et al, 2013).

A common debate in the management of NETs is whether or not to resect the primary tumor in the presence of advanced disease. One argument against resection is that the patient is unlikely to obtain a curative (R0) resection and thus bears the risk of a large operation without the reward of improved survival. Vascular invasion by the primary tumor is often treated as a contraindication for resection, but recently, Norton and colleagues (2011) reported that not only did most conventional imaging studies overestimate the degree to which vascular structures are encased or invaded, but that PNETs could be dissected off these vessels in greater than 90% of cases, and fewer than 20% of cases required vascular reconstruction. Vascular invasion or encasement on preoperative imaging should therefore not be considered as contraindicating resection. Hill and colleagues (2009) compared patients with all stages of disease who underwent surgical resection with those who did not. They found that those who had surgery had significantly better OS (median, 114 months) compared with those who were medically managed (median, 35 months). This trend even persisted in the subgroup of patients with M1 disease, with those who underwent surgery having a significant survival advantage over those who did not (Fig. 65.6). Bertani and colleagues (2014) recently analyzed the outcome of a cohort of 43 PNET patients with hepatic metastases who were either treated with palliative surgery or managed medically. Ultimately, 37% had their primary tumor resected. Even in this small group of patients, a difference in OS was seen. Those who had their primary tumor resected had a 5-year OS of 82%, compared with an OS of 52% in the patients who were not resected ($P = .05$). One must keep in mind that there is significant selection bias in each of these studies, and thus the benefit of resection cannot be assumed; however, the results are encouraging for operative resection, and it is unlikely that randomized trials will address these questions.

Surgical Considerations With Familial Syndromes

Resection of the primary tumor in the context of MEN1 is more difficult and more controversial than when a patient has

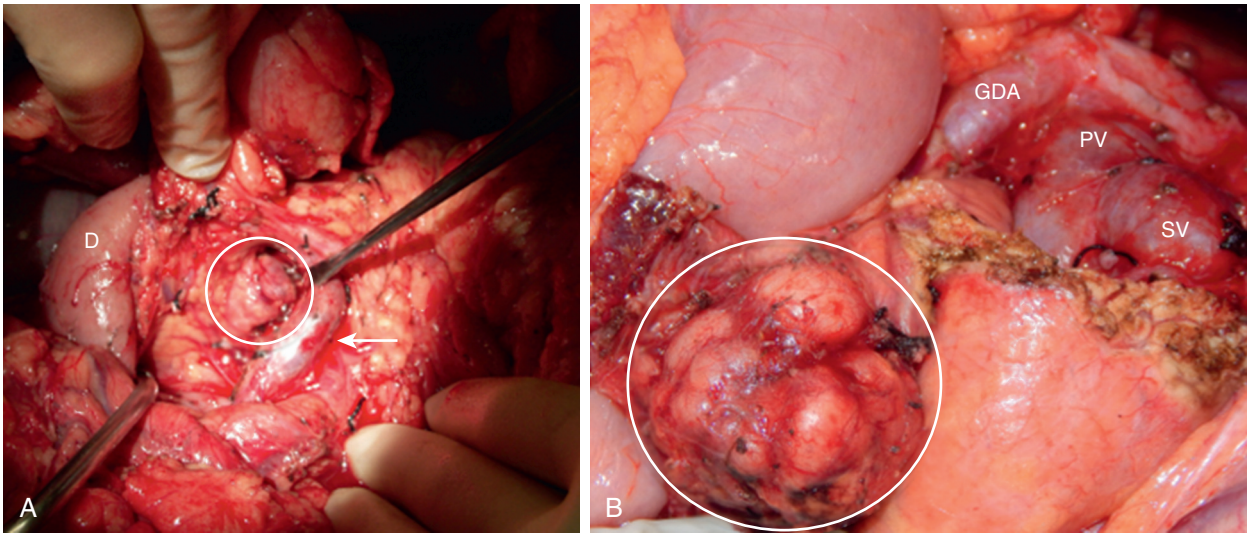

FIGURE 65.5. **A,** Enucleation of an insulinoma in the uncinate process. The tumor is indicated by the *circle,* with the duodenum laterally *(D).* The superior mesenteric vein is pulled medially for exposure *(arrow).* **B,** Enucleation of a pancreatic neuroendocrine tumor located at the superior aspect of the neck of the pancreas. The tumor *(circle)* is mostly detached at this point and rolled inferiorly over the pancreas. *GDA,* Gastroduodenal artery; *PV,* portal vein; *SV,* splenic vein.

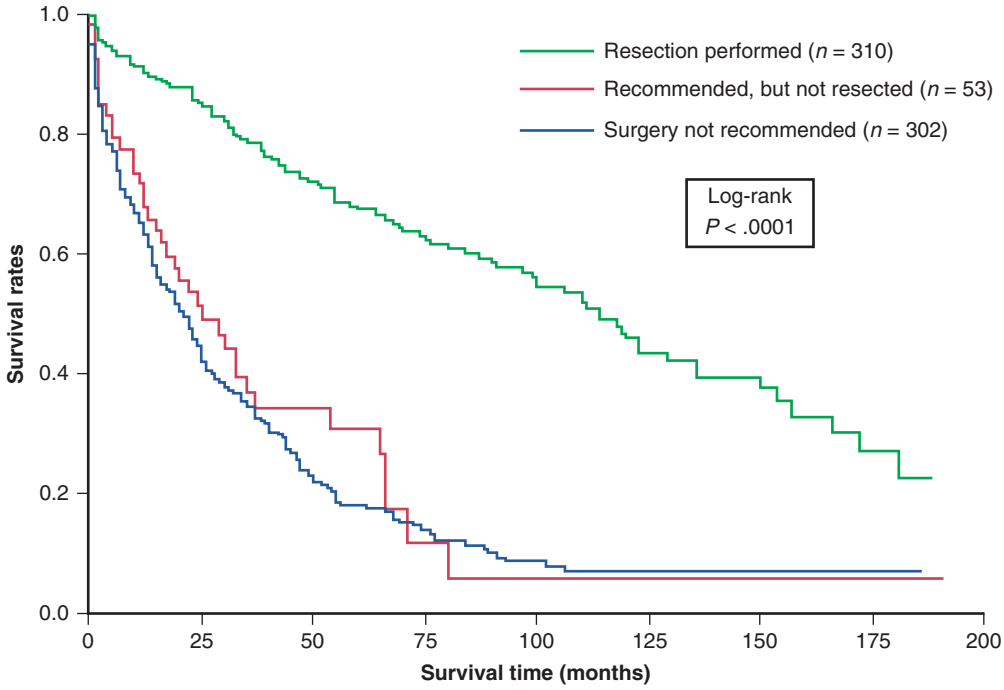

FIGURE 65.6. In a retrospective analysis of the Surveillance Epidemiology and End Results database, Hill and colleagues (2009) demonstrated that overall survival of pancreatic neuroendocrine tumor patients can be improved if surgical resection of the primary tumor can be performed. Patients in whom surgery was recommended, but not performed (including palliative procedures), had median survival on par with patients in whom surgery was not offered. This observation held across all disease stages. *(Modified from Hill JS, et al: Pancreatic neuroendocrine tumors: the impact of surgical resection on survival.* Cancer *115:741-751, 2009).*

a sporadic PNET. The three types of PNETs most frequently encountered in MEN1 are insulinomas, gastrinomas, and nonfunctional tumors. Imaging will frequently show multiple small tumors, and in many cases, both functional and nonfunctional PNETs will be present (Fendrich et al, 2011). Insulinomas will typically arise in the tail of the pancreas, and when many PNETs are seen at the time of surgery, it is suggested that a distal pancreatectomy (to the level of the superior mesenteric vein) be performed. PNETs in the head of the pancreas should be enucleated, if possible. Cure rates of 90% have been achieved with this method (Giudici et al, 2012).

Gastrinomas in MEN1 are more difficult to treat than are insulinomas. Much debate exists as to how to treat these tumors surgically, as biochemical cure is rare and recurrence is frequent. In MEN1, these tumors tend to occur in the duodenum, and so in addition to careful US examination of the pancreas, transillumination of the duodenum and duodenotomy should be performed for palpation of the wall, to ensure excision of all

gastrinomas (Sugg et al, 1993). If the number of gastrinomas present in the duodenum precludes simple excision, pancreas-preserving total duodenectomy should be considered, along with enucleation of as many PNETs greater than 1 cm as possible (Imamura et al, 2011). More extensive surgery is recommended in those patients with primary gastrinomas greater than 2 cm, as patients who undergo aggressive surgical treatment are more likely to see resolution of their Zollinger-Ellison syndrome and are at less risk of developing hepatic metastases than those with similarly sized PNETs who are not resected. Thus, if the gastrinoma primary is located in the head of the pancreas, especially if greater than 2 cm in size, a pylorus-preserving PD is indicated (Fendrich et al, 2011; Lee et al, 2012).

Pancreatic NETs are found in 12% to 17% of patients with VHL, and approximately 17% of those tumors will eventually metastasize. Libutti and colleagues (1998) suggested that PNETs greater than 3 cm should be resected because in their cohort, the median size of PNETs in patients with metastatic disease was 5 cm versus only 2 cm in those with localized disease. Their surgical strategy was validated by a prospective study in which 44 patients with VHL and PNETs were either observed or resected, based on the size of their tumors. Patients were followed for a median of 32 months (range, 4 to 110 months), and none that had undergone resection developed metastatic disease (Libutti et al, 2000). Blansfield and colleagues (2007) built upon these recommendations by suggesting that a germline mutation in exon 3 and a doubling time less than 500 days should also be taken into account, as these features correlate with PNETs that are likely to metastasize. The Libutti study (2000) confirmed that the majority of patients with metastatic PNETs in VHL have a mutation in exon 3, but no study has been performed to validate the inclusion of the Blansfield guidelines along with these size criteria.

Management of Metastatic Disease

At least 20% of PNET patients will have spread to regional lymph nodes at the time of diagnosis (Tsutsumi et al, 2012). There is no guideline on the number of lymph nodes that should be sampled or requirement that formal lymphadenectomy be performed in PNET patients, but lymph node metastases are associated with an increase risk of recurrence in these patients (Hashim et al, 2014), and recent studies suggest that more a more aggressive approach may be of benefit. In 2012, Bartsch and colleagues analyzed 48 cases of sporadic gastrinoma with N1 disease. These patients had their primary tumor resected (via a variety of procedures) and a systematic lymphadenectomy performed, which included clearance of the peripancreatic and pancreaticoduodenal lymph nodes, the lymph nodes in the hepatoduodenal ligament along the hepatic artery, and the lymph nodes in between the aorta and inferior vena cava. To be classified as a formal lymphadenectomy, more than 10 lymph nodes were required to have been pathologically assessed. In this set of patients, a formal lymphadenectomy resulted in a significantly higher postoperative biologic cure rate (fasting gastrin <125 pg/mL and negative secretin stimulation test) and a trend toward improved disease-free survival (Bartsch et al, 2012). In a set of patients with sporadic gastrinomas who were treated by enucleation only versus a more extensive pancreatic procedure and formal lymphadenectomy, a significant improvement in time-to-recurrence was seen in those who had lymphadenectomy (Giovinazzo et al, 2013).

A major consideration in the surgical management of PNETs is how to treat hepatic metastases, which are seen in approximately 50% of patients (Bertani et al, 2014). Although curative resection is rarely achieved, surgical reduction of hepatic tumor burden may diminish symptoms related to functional tumor syndromes and also delay liver failure secondary to hepatic replacement (Niederhuber et al, 2006). Thus it is generally accepted that surgical debulking of hepatic disease is prudent for patients in whom it is estimated that an 80% to 90% reduction of metastatic burden can be made. The gold-standard cytoreductive technique is formal segmental resection (Mayo et al, 2010; Norton et al, 2003; Sarmiento et al, 2003), although wedge resection, enucleation, and ablation (radiofrequency or microwave ablation, hepatic artery embolization) (see Chapter 30) are also valuable techniques and have the advantages of preserving a maximal amount of normal liver parenchyma, with lower complication rates. Ablative techniques are best used for small metastases (<5 cm) and can be used to treat many lesions in one setting (Elias et al, 2009; Eriksson et al, 2008; Zappa et al, 2012). Because most patients with liver metastases have large, multiple tumors, hepatic artery embolic therapy is often the most rational approach. A standard set of criteria guide patient selection in patients with NETs (Mazzaferro et al, 2007), and preoperative factors that may predict poor outcome are location of the primary in the pancreas or duodenum, need for upper abdominal exenteration, and hepatomegaly. A patient presenting for transplant with a PNET and hepatomegaly has an estimated 5-year survival of 12%, which improves to 68% if the patient has only one or neither of those factors (Le Treut et al, 2008).

NONSURGICAL MANAGEMENT

Medical management for PNETs is indicated for patients with symptomatic functional tumors, metastatic disease, those with high-grade disease that are not candidates for surgical resection, and for patients that have progressed despite maximal surgical management. The goal should be to improve quality of life and extend survival (Kuo et al, 2014; Vinik et al, 2010).

The symptoms of insulinomas and gastrinomas can be treated with medications. The hypoglycemia seen with insulinomas can be treated with diazoxide (200 to 600 mg/day). This is a fast-acting drug but may only work in approximately 50% of patients. Nearly 50% of patients taking the drug will experience side effects, which include fluid retention, nausea, hirsuitism, palpitations, and anorexia (Baudin et al, 2013; Oberg, 2010). Symptoms secondary to Zollinger-Ellison syndrome are best treated with proton-pump inhibitors (PPI), and the dose should be titrated to effect. If patients are not candidates for surgery, they can be sustained on PPI over the long term, as studies show patients treated for more than 10 years do not develop tachyphylaxis, although they may develop achlorhydria, which can lead to nutritional deficiencies (Kulke et al, 2010).

Somatostatin Analogue–Based Treatments

Somatostatin analogues are the first-line treatment for nonfunctional metastatic PNETs and can also be used to moderate symptoms in a number of functional PNETs (Baudin et al, 2013; Eldor et al, 2011; Jawiarczyk et al, 2012; Kindmark et al, 2007; Shojamanesh et al, 2002). These drugs mediate their antiproliferative activity by binding primarily to SSTR2, SSTR5, and SSTR3, which eventually stimulate cell-cycle arrest and inhibition of mitosis (Toumpanakis et al, 2013). This

class of drugs tends to be well tolerated, with the most common side effects being flatulence, diarrhea or steatorrhea, nausea, cholelithiasis, and glucose intolerance (Panzuto et al, 2006, Kulke et al, 2010). These drugs display a modicum of antitumor activity. A retrospective study in 2013 demonstrated partial response in 7% of patients, stable disease in 58%, and progressive disease in 35%. There were no complete responses, and only two of three partial responses persisted beyond 12 months of treatment (Jann et al, 2013). The recent CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) trial randomized patients to lanreotide (a long-acting somatostatin analogue) or placebo in patients with advanced gastrointestinal and pancreatic (45% of patients) NETs. Patients given lanreotide had significantly longer progression-free survival (PFS), although no difference in their quality of life or OS (Caplin et al, 2014).

PRRT targets SSTR-expressing tumor cells by coupling somatostatin analogues to radioactive elements, which emit β-particles (yttrium-90–DOTA-Tyr[3]-octreotide [^{90}Y-DOTATOC]) or a combination of β- and γ-particles (lutetium-177–DOTA-Tyr[3]-octreotate [^{177}Lu-DOTATOC]) (Theodoropoulou et al, 2013). This is a relatively new treatment that is used in patients with progressive, advanced neuroendocrine disease. It is approved for use in Europe but is still being trialed in the United States. The first preliminary report from the U.S. group performing the Phase II study indicated that a radiologic response was seen in 31% of patients. Most patients demonstrated stable disease (41%). The median PFS for those who completed at least four cycles of treatment was 16.5 months. The study also showed that patients with smaller hepatic tumor burdens were more likely to respond to PRRT, which provides further support for aggressive surgical debulking of hepatic metastases prior to PRRT (Delpassand et al, 2014).

Systemic Chemotherapy

Systemic chemotherapy has been generally disappointing in PNETs. Early studies combined 5-fluorouracil (5-FU), doxorubicin, streptozocin (STZ), interferon-α, and cisplatin in a variety of combinations with modest to poor responses (Fjallskog et al, 2002; Kouvaraki et al, 2004; Moertel et al, 1980; Pavel et al, 2005; Turner et al, 2010). The most promising recent regimen combines capecitabine and temozolomide (CAPTEM). Only one study has reported a complete response on this regimen, but many patients have achieved partial responses, and the minority in each study progressed. The median duration of response is approximately 1 year in most studies, which is an improvement over many of the previous chemotherapy regimens (Fine et al, 2013; Peixoto et al, 2014; Saif et al, 2013; Strosberg et al, 2011a). For CAPTEM to be established as the standard of care, randomized trials will need to be performed comparing STZ-based regimens to CAPTEM.

Poorly differentiated PNETs are most commonly treated with cisplatin and etoposide, as these tumors are histologically similar to small-cell lung cancers. Response rates vary from 42% to 67%, and median survival hovers just at more than 1 year (Mitry et al, 1999; Moertel et al, 1991). Newer drug combinations have been suggested, but response rates do not exceed those obtained with cisplatin and etoposide (Bajetta et al, 2014).

Biologic Therapies

The most effective systemic biologic therapies in PNETs are the mTOR inhibitors, of which everolimus is the best known. The mTOR pathway regulates cell survival, proliferation, and metabolism; several genes in the pathway are important in the development of familial syndromes (NF1, TS) (Chan et al, 2014). The RAD001 in Advanced Neuroendocrine Tumors 3 (RADIANT-3) trial tested the effects of everolimus versus placebo in advanced PNETs. In this study, 64% of patients demonstrated some tumor shrinkage while on the drug, compared with 21% who were treated with the placebo. Median PFS was significantly better with everolimus (11.0 months), compared with the placebo (4.6 months). Most adverse events were grade 1 or 2 and included stomatitis, rash, diarrhea, fatigue, and upper respiratory infections (Yao et al, 2011). Everolimus can be used in insulinomas because one of the drug's known side effects is induction of glucose intolerance, which may eliminate the symptoms of hypoglycemia in some patients (Asayama et al, 2014; Baudin et al, 2013). A recent Phase II study investigated the synergistic effects of everolimus and octreotide in a group of 50 NET patients, 14 of whom had PNETs. Of the PNETs, 14% had a partial response, and none had a complete response. Although these results are mediocre, the clinical benefit rate for this regimen was 92%, which is better than many other drug combinations (Bajetta et al, 2014). This drug has been approved by the U.S. Food and Drug Administration to treat advanced PNETs.

Another biologic agent used to treat advanced PNETs is sunitinib. This is a protein kinase inhibitor that blocks the actions of vascular endothelial growth factor, platelet-derived growth factor, and c-KIT. In 2011, 171 patients with advanced PNETs were randomized to receive oral sunitinib or placebo. The treatment group enjoyed a significantly better PFS (11.4 months vs. 5.5 months, $P < .001$), fewer deaths (10% vs. 25%, $P = .02$), and a greater number of confirmed objective tumor responses (8/74 vs. 0/74, $P = .007$). The improvements seen in the treatment group were so great that the trial was stopped early and all patients receiving the placebo were offered sunitinib (Raymond et al, 2011). This is the second drug in the past 30 years that has been approved for use in advanced PNETs.

SURVEILLANCE AND FOLLOW-UP

The National Comprehensive Cancer Network has put out a set of guidelines for the surveillance and follow-up of PNETs. If a patient has been resected, biochemical markers and a contrast-enhanced CT or MRI should be obtained at least once in the 3 to 12 months after surgery. Thereafter, if the patient does not recur, they should be followed every 6 to 12 months for 10 years with an examination, appropriate NET laboratory tests (CgA, PST), and consideration of either CT or MRI (Kulke et al, 2015). The exception to this would be in the case of a benign insulinoma, which may only need to be followed for 1 to 2 years unless the patient had multiple lesions or has MEN1.

If the patient experiences a recurrence, has G3 disease, or has locoregional or distant unresectable disease, follow-up will be determined by the patient's clinical condition and the behavior of the tumor. An asymptomatic patient with a low tumor burden can be followed every 3 to 12 months with biomarkers and imaging. Onset of new symptoms or evidence of disease progression should prompt more frequent follow-up.

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