Surgical Management of Pancreatic Neuroendocrine Tumors

Amareshwar Chiruvella, MD, David A. Kooby, MD*

KEYWORDS

• Carcinoid • Neuroendocrine tumor • Pancreatic neoplasm • Pancreatectomy
• Hepatectomy • Pancreatic neoplasm • Gastrinoma • Insulinoma

KEY POINTS

- Pancreatic neuroendocrine tumors (pancNETs) comprise 2% to 4% of all detected pancreatic tumors; they can be indolent, and yet their malignant potential is often underestimated.
- The management of this disease poses a challenge because of the heterogeneous clinical presentation and varying degree of aggressiveness.
- Surgical therapy remains the most efficient approach and offers the longest lasting benefits for patients with pancNETs.
- Clinical management of pancNETs involves benefits substantially from a multidisciplinary approach.

INTRODUCTION

Pancreatic neuroendocrine tumors (pancNETs) are uncommon tumors with an estimated incidence of 1 to 1.5 per 100,000 and a prevalence of 35 per 100,000 in the United States. They originate from the embryonic endodermal cells that give rise to the islets of Langerhans. These cells are specialized cells that produce, store, and secrete peptides and biogenic amines and were formerly known as the amine precursor uptake and decarboxylation cells or APUD cells.[1]

PancNETs comprise 2% to 4% of all pancreatic neoplasms, and peak incidence is found between the sixth to the eighth decades. Data from the SEER (Surveillance, Epidemiology, and End Results) registry have shown an increase in incidence from 0.17 in 1970 to 0.43 in 2007, with the lowest 5-year survival compared with other gastrointestinal neuroendocrine tumors (NETs) (**Fig. 1**).

Disclosure Statement: The authors have nothing to disclose.
Department of Surgery, Winship Cancer Institute, Emory University School of Medicine, 1365 C Clifton Road, Northeast, 2nd Floor, Atlanta, GA 30322, USA
* Corresponding author.
E-mail address: dkooby@emory.edu

Surg Oncol Clin N Am 25 (2016) 401–421
http://dx.doi.org/10.1016/j.soc.2015.12.002 **surgonc.theclinics.com**
1055-3207/16/$ – see front matter

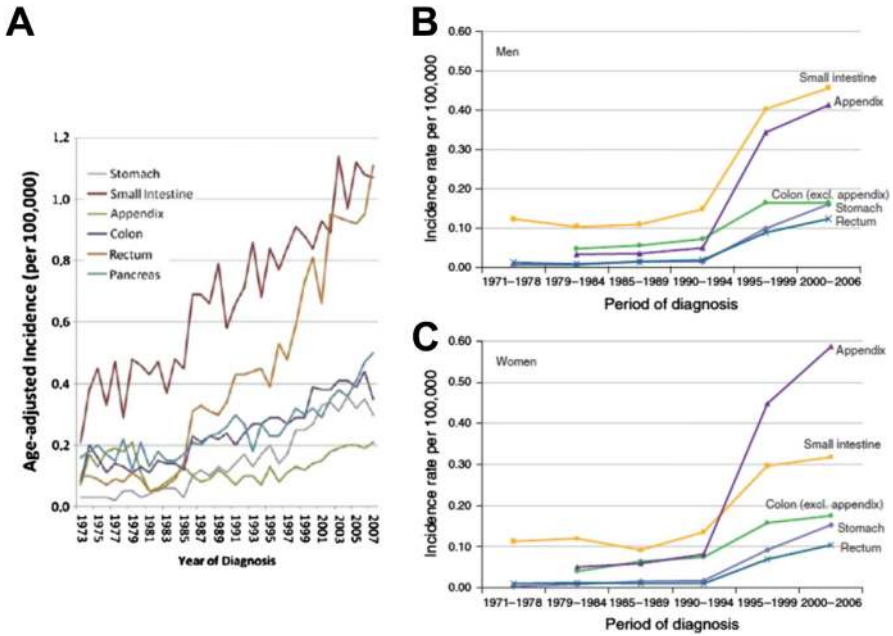

Fig. 1. Rising incidence of NETs in (*A*) all patients, (*B*) men, and (*C*) women. (*Data from* [*A*] US National Cancer Institute. SEER Database. Available at: http://seer.cancer.gov/. Accessed April, 2015; and *From* [*B*, *C*] Ellis L, Shale MJ, Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. Am J Gastroenterol 2010;105: 2566; with permission.)

PancNETs are often classified as functional (F) or nonfunctional (NF) based on the presence or absence of clinically evident hormone production. NF tumors are more common than functional tumors. Functional tumors secrete one or more biologically active peptides, which may result in systemic clinical symptoms (**Table 1**). NF is likely a misnomer because these tumors often secrete various peptides, albeit in the absence of a clinical syndrome (see **Table 1**).

Efforts have been made to create a universal classification system of these tumors from a prognostic and therapeutic standpoint. In 2000, under the auspices of the World Health Organization (WHO), a NET classification was proposed with 3 categories: well-differentiated tumors with benign or uncertain behavior; well-differentiated carcinoma with malignant characteristics; and poorly differentiated carcinoma[2,3] (**Table 2**). This classification, updated in 2010, takes into account the anatomic location, mitotic activity, and the Ki67 proliferative index. This classification was then incorporated into the seventh edition of the American Joint Committee on Cancer staging manual and into the National Comprehensive Cancer Network (NCCN) guidelines.[4,5]

GENERAL FEATURES OF PANCREATIC NEUROENDOCRINE TUMORS

There are 10 different commonly recognized pancNETs, of which 9 are associated with a clinical syndrome, including gastrinomas, insulinomas, glucagonomas, VIPomas, GRFomas, ACTHomas, somatostatinomas, pancNETs causing carcinoid syndrome, and pancNETs causing hypercalcemia. Amounts of 60% to 100% of NF pancNETs secrete various peptides such as chromogranin A, neuron-specific

Table 1
Established pancreatic neuroendocrine tumor subtypes and syndromes (most frequent)

pNET	Syndrome Name	Primary Location(s)	Incidence (No. of New/100,000/y)	Malignancy (%)	Hormone-Causing Syndrome
Functional pNETs					
Gastrinoma	ZES	Pancreas (30%), duodenum (60%–70%), other (5%–10%)	0.5–1.5	60–90 (30–560)	Gastrin
Insulinoma	Insulinoma	Pancreas (100%)	1–3	5–15	Insulin
VIPoma	Vemer-Morrison, Pancreatic cholera, WDHA	Pancreas 85%–95%, other (neural, periganglionic, adrenal) (10%)	0.05–0.2	70–90	Vasoactive intestinal peptide
Glucagonoma	Glucagonoma	Pancreas (100%)	0.01–0.1	60–75	Glucagon
Somatostastinoma	Somatostastinoma	Pancreas (50%–60%), duodenal/ jejunal (40%–50%)	<0.1%, uncommon	40–60	Somatostatin
GRFoma	GRFoma	Pancreas (30%), lung (54%), jejunal (75%), other (adrenal, foregut, retroperitoneal) (13%)	Unknown	30–50	Growth hormone–releasing factor
ACTHoma	ACTHoma	4%–25% of all ectopic Cushing syndrome	<0.1%, uncommon	95	ACTH
PET causing carcinoid syndrome	PET causing carcinoid syndrome	Pancreas (100%) (<1% of all carcinoid syndrome)	Uncommon (<50 cases)	60–90	Serotonin, tachykinins
PET causing hypercalcemia	PTHrPoma	Pancreas (100%)	<0.1%, uncommon	>85	PTHrP, other unknown
NF pNET	PPomas NF-PET	Pancreas (100%)	1–5	60–90	None secrete pancreatic polypeptide (PP) (60%–85%), chromogranin A but cause no symptoms

Abbreviations: ACTH, adrenocorticotropic hormone; GRF, growth hormone releasing factor; pNET, pancreatic neuroendocrine tumor subtypes and syndromes; PP, pancreatic polypeptide; PPoma-pNET, secreting pancreatic polypeptide; PTHrP, parathyroid hormone–related peptide; WDHA, watery diarrhea, hypokalemia, and achlorhydria.

Table 2
Evolution of World Health Organization classification of neuroendocrine tumors

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	1. Well-differentiated endocrine tumor	1. NET G1
II. Mucocarcinoid	2. Well-differentiated endocrine carcinoma	2. NET G2[a]
III. Mixed forms carcinoid-adenocarcinoma	3. Poorly differentiated endocrine carcinoma	3. NEC G3 (large cell or small cell)
IV. Pseudotumor lesions	4. Mixed exocrine-endocrine carcinoma	4. Mixed adenoneuroendocrine carcinoma
	5. Tumorlike lesions	5. Hyperplastic and preneoplastic lesions

Abbreviations: G, grade; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.
[a] G2 NET may include WDET or WDEC of the WHO 2000 classification.

enolase, pancreatic polypeptide, ghrelin, neurotensin, motilin, or subunits of human chorionic gonadotropin, all of which cause no obvious clinical syndrome.[6–9] Insulinomas, gastrinomas, and nonfunctioning pancNETs were previously reported as representing about a third of all pancNETS, respectively. More recent reports suggest pancNETs occur with increasing frequency, making up twice the above percentage of pancNETs, often discovered when still asymptomatic and without advanced disease.[10,11]

Some pancNETs are part of 1 of 4 different inherited syndromes: multiple endocrine neoplasia type-1 (MEN-1), von Hippel-Lindau disease (VHL), von Recklinghausen disease neurofibromatosis 1, and tuberous sclerosis[12] (**Table 3**). These tumors frequently differ in clinical presentation, prognosis, and management from sporadic pancNETs. Of these, MEN-1 is the most important inherited pancNET because 20% to 80% of all patients with this autosomal-dominant disorder develop a clinically relevant NET. MEN-1 is found in 20% to 25% of patients with gastrinomas, 4% with insulinomas, and less than 3% with other pancNETs. Almost all patients with MEN-1 have multifocal, asymptomatic NF-pancNETs, whereas symptomatic pancNETs occur in less than 10% of this group of patients.[12,13]

Diagnosis of pancNETs is often delayed for months to years, given their indolent nature and relatively nonspecific symptoms, even for patients with functional tumors. Around 60% to 70% of patients have metastatic disease at presentation, most commonly involving the liver and less frequently the bones.[14] With the exception of insulinomas, where fewer than 10% are considered malignant, pancNETs typically demonstrate malignant behavior in at least 50% of cases.

Preoperative imaging and localization are essential before considering surgical resection of these tumors. The imaging modalities most commonly used are triple-phase multidetector computed tomography (CT) scan and MRI with gadolinium contrast. PancNETs are usually hyperenhancing masses in the arterial phase of the scan (both primary and metastatic lesions) due to their hypervascular nature (**Fig. 2**). Contrast-enhanced ultrasound is used more frequently in Europe than in the United States and may be useful in monitoring response to treatment with peptide receptor radionuclide therapy (PRRT) and locoregional ablation of liver metastases.[15,16] As most pancNETs (excluding insulinomas) express a high density of somatostatin receptors (specifically subtypes 2 and 5), indium-111-labeled somatostatin receptor scintigraphy (SRS) is an effective localizing tool in this disease.[17,18] There is evidence that

Table 3
Association of multiple endocrine neoplasia type 1 with pancreatic neuroendocrine tumors

Syndrome	Frequency	Location/Type of Genetic Abnormality	Altered Protein Function(s)	Frequency of PETs, %	Type of PETs (%)
MEN-1 (Wermer syndrome)	Prevalence, 1–10 per 100,000	11q13; encodes 610 amino acid protein (menin)	Nuclear location; exact function unclean interacts with JunD, NF-kB, SMAD signaling pathways; effects cell cycle, growth, genomic stability, and apoptosis	80–100 (microscopic), 20–80 (clinical)	NF-PET, microscopic; > functional (20–80)
VHL	Prevalence, 2–3 per 100,000	3p25: encodes 232 amino acid protein (pVHL)	Interacts with elongins, which act as transcriptional regulators that degrade HIF, regulates cell cycle, VEGF	10–17	NF (>98)
Von Recklinghausen disease (neurofibromatosisl [NF-1])	Prevalence, 1 per 4000–5000	17q11.2: encodes 2485 amino acid protein (neurofibromin)	Ras GTPase-activating activity, binds microtubules, modulates adenylate cyclase, mTor-regulates growth, cell cytoskeleton	0–10 (uncommon)	Duodenal somatostatinomas, rare PETs
Tuberous sclerosis (Bourneville disease)	Prevalence, 1 per 10,000	9q34 (TSC1): encodes 1164 amino acid protein (hamartin); 16p13 (TSC2): encodes 1807 amino acid protein (tuberin)	Interacts with PI3K signaling pathway regulating GTPase and mTor, which play a key role in growth, energy regulation, response to hypoxia, nutrients	Uncommon	Rarely develop functional, NF-PETs

Abbreviations: HIF, hypoxia inducible factor; VEGF, vascular endothelial growth factor; VHL, von hippel lindau syndrome.

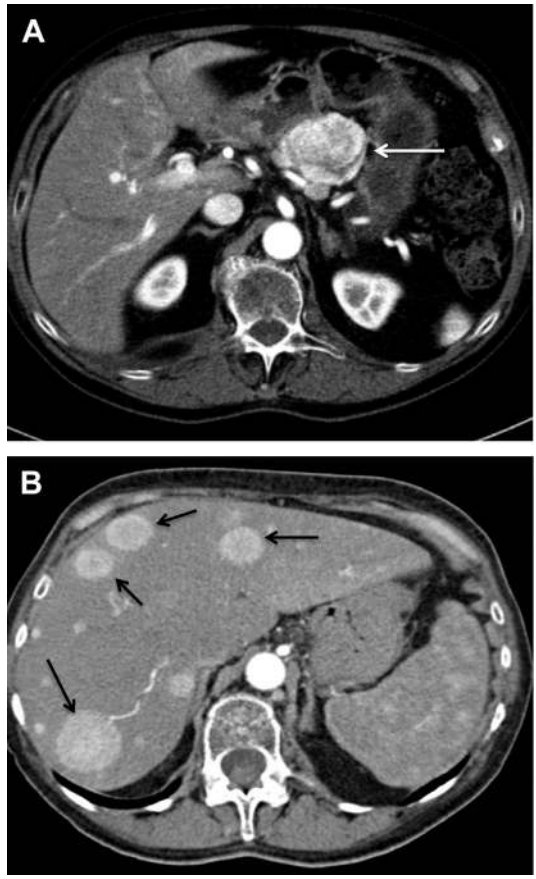

Fig. 2. CT imaging of pancreatic neuroendocrine primary tumor (*A*, *arrow*) and metastatic disease (*B*, *arrows*).

SRS informs us of tumor receptor status, and that this may be useful for guiding therapeutic use of somatostatin analogues. Recent development of PET scanning with gallium-68-labeled somatostatin analogues (DOTATOC, DOTANOC, and DOTATATE) may be more sensitive than CT, MRI, and octreoscan in detecting NETs (100% vs 75%).[19,20]

Management steps for pancNETs include establishing diagnosis, localizing tumor, assessing for underlying inherited disorder, controlling hormonal excess when present, removing and/or ablating tumor if possible and appropriate, and considering alternative forms of therapy (regional and/or medical). Depending on the situation, pancNETs can either be enucleated or removed with formal organ resection. The former approach is considered in cases of smaller tumors with presumed indolent behavior, assuming pancreatic duct disruption can be avoided. Intraoperative ultrasound (IOUS) is an integral part of resection of these tumors. If the above criteria are not met, formal resection, such as pancreaticoduodenectomy, distal pancreatectomy, and the less commonly performed central pancreatectomy, is considered.

SURGICAL MANAGEMENT OF LOCALIZED PANCREATIC NEUROENDOCRINE TUMORS

Insulinoma

Insulinoma is the most common form of F-pancNET encountered. It can be sporadic or associated with MEN-1. It is more commonly found in women (F:M = 2:1) in the fifth or sixth decade and can present in the third decade of life in patients with MEN-1. Sporadic insulinomas are usually unifocal, but those associated with MEN-1 may present with multifocal disease. Clinical presentation is characterized by the Whipple triad constituted by hypoglycemia after a fast or exercise, neuroglycopenic symptoms, and immediate relief with oral or intravenous glucose administration.[21] Most patients also present with hyperphagia and new-onset weight gain.

The diagnostic criteria for insulinoma are established during a 72-hour fast or until symptoms develop with a blood glucose less than 50 mg/dL, elevated insulin, C-peptide, and proinsulin, in the absence of urine or plasma sulfonylureas, and relief of symptoms after an oral glucose load (**Box 1**); 99% of insulinomas can be detected in this manner. Approximately 80% to 90% of insulinomas are small (<2 cm), solitary, benign tumors that are equally distributed among the head, body, and tail of the pancreas. The remaining 10% occur as multiple tumors in the setting of MEN-1.[22,23] Most insulinomas are less than 2 cm in diameter and are benign, with a brick-red appearance due to increased vascularity. Given their small size, preoperative localization remains a challenge. CT scanning can detect approximately two-thirds of all lesions on arterial phase imaging. MRI is typically performed as a second-line imaging modality after CT, although the sensitivity for detecting these tumors may be higher than that of a CT scan. The sensitivity of endoscopic ultrasound (EUS) varies with tumor location (92.6%, 78.9%, and 40.0% for the head, body, and tail of the pancreas, respectively) and with user experience.[24] SRS for this type of tumor is limited because only 30% possess somatostatin type 2 receptors.[25] Intra-arterial calcium stimulation (selective infusion of calcium into branches of the celiac axis and superior mesenteric artery) with hepatic venous sampling for insulin can be a sensitive localizing modality, but carries some risk of complications,[26] and is typically used when the tumor or tumors are not localized with other forms of imaging (**Fig. 3**).

Despite this, 20% to 50% of insulinomas remain undetected at the time of surgery. Some evidence suggests that preoperative localizing studies for the primary tumor may not be necessary.[27,28] This finding is based on the observation that a combination of surgical exploration and IOUS can detect more than 90% of insulinomas.

Definitive treatment of insulinomas is surgical resection; however, presurgical medical therapy is provided to alleviate symptoms, including eating small, frequent meals

Box 1
Diagnostic criteria for insulinoma

- Monitored fast for less than 48 hours with documented blood glucose less than 50 mg/dL with hypoglycemic symptoms
- Relief of symptoms after oral glucose load
- Elevated insulin level (>5–10 μU/mL)
- Increased serum proinsulin level (>22 pmol)
- Absence of urinary or plasma sulfonylureas
- Elevated C-peptide levels

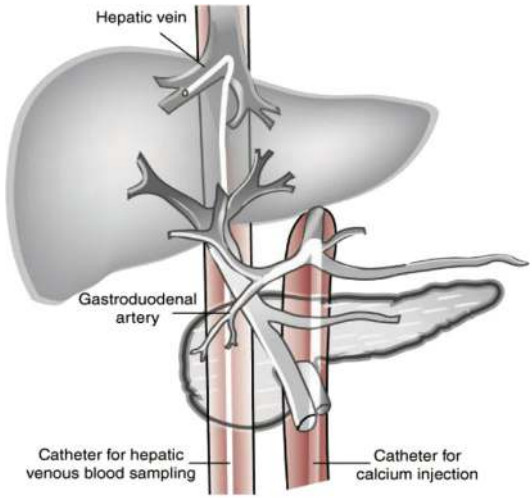

Fig. 3. Schematic of calcium stimulation testing for localization of insulinomas. Catheters are placed in the arterial system for calcium injection and in the venous system for sampling. (*From* Vanderveen K, Grant C. Insulinoma. In: Morita SY, Dackiw APB, Zeiger MA, editors. Endocrine surgery. Chapter 17. McGraw-Hill Manual; 2010; with permission.)

and using insulin antisecretagogues, such as diazoxide or octreotide, both of which work only 40% to 60% of the time.[29,30] Before proceeding to surgery, the presence of MEN-1 must be excluded by testing for other components such as hyperparathyroidism and pituitary tumors. Intraoperative glucose monitoring is essential to avoid hypoglycemia, and dextrose infusion must be stopped before surgical resection to permit intraoperative glucose measurements as an indicator of biochemical cure. Many sporadic adenomas are amenable to enucleation. Surgical exploration commences by gaining access to the pancreas in the lesser sac and traversing the gastrocolic omentum. A wide kocherization of the duodenum is essential for tumor involving the pancreatic head. This wide kocherization enables palpation to be combined with IOUS, which in experienced hands can detect up to 98% of insulinomas.[31] It also helps to detect the location of the pancreatic duct to ascertain safety during enucleation and prevent a pancreatic fistula. Once the insulinoma is enucleated, a thorough examination must be performed to evaluate for a ductal leak, in the presence of which a suture repair can be attempted along with surgical drainage (**Fig. 4**). Rates of pancreatic fistula reported after enucleation are higher than those after a formal resection, in the range of 18% to 38%.[32]

In MEN-1 patients, these tumors are multiple and subcentimeter and usually coalesce. If multiple tumors are found throughout the pancreas, judicious use of surgical resection must be considered because total pancreatectomy should be avoided for insulinomas in most cases. If the lesion is not found, a pancreatic biopsy specimen should be obtained to rule out nesidioblastosis (a condition characterized by diffuse β-cell proliferation), in which case a subtotal pancreatectomy can improve symptoms.

No follow-up is necessary in the case of benign insulinomas unless symptoms recur. For malignant insulinomas and those associated with MEN-1, follow-up is every 3 to 12 months with biomarkers, CT/MRI, and octeroscan/PET.

The treatment of malignant/metastatic pancNETs is discussed in a separate section.

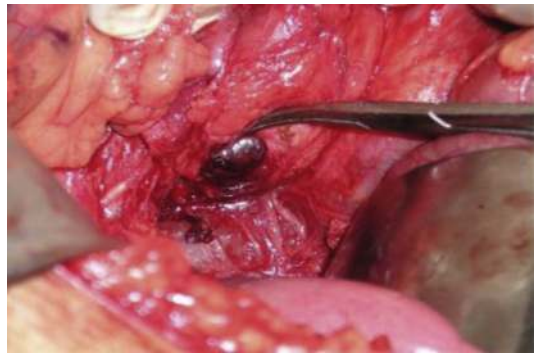

Fig. 4. Enucleation of insulinoma: a salmon-colored tumor being dissected out from the pancreatic parenchyma. (*From* Shah S, Patel A, Prajapati J, et al. Insulinoma: a commonly misdiagnosed pancreatic tumour. Internet J Gastroenterol 2009;9(1):2; with permission.)

Gastrinoma

Gastrinomas are the second most common functional islet cell tumor of the pancreas. Mean age at diagnosis is 50 years with a slight male predominance. Although slow growing in nature, more than 60% demonstrate malignant behavior. Because of their indolent growth pattern, 10-year patient survival approaches 90% even in the presence of metastatic disease. Two-thirds of all gastrinomas are sporadic, with the remainder associated with MEN-1. Individuals with gastrinomas associated with MEN-1 may have a better 20-year survival rate than individuals with sporadic gastrinomas.[33] As with other pancNETs, gastrinomas in the setting of MEN-1 tend to be multifocal, and as many as 50% of patients have distant metastases at the time of presentation.[34]

The clinical syndrome associated with gastrinoma (Zollinger-Ellison syndrome [ZES]) arises principally from dysregulated hypergastrinemia and subsequent luminal hyperacidity resulting in development of intractable gastrointestinal ulcers. Diarrhea, heartburn, nausea, and weight loss are the typical constellation of symptoms at presentation. With the advent and widespread use of antisecretory medications, patients may or may not present with intractable ulcer disease at the time of diagnosis. Given the nonspecificity of symptoms and relative rarity of this disorder, the mean time to diagnosis is around 5.9 years.[35,36] The diagnostic criteria (**Table 4**) include an increased basal acid output in the presence of a fasting gastrin level (FSG) >100 pg/mL or >10-fold the upper limit of normal. Proton pump inhibitors (PPIs) are stopped at least a week prior and H2 antagonists 2 days before testing. Because almost two-thirds of patients with ZES have equivocal FSG levels, secretin stimulation testing or

Table 4
Diagnostic criteria for gastrinoma

Fasting gastrin level	>100 pg/mL or >10 times higher than upper limit of normal
Basic acid output level	>15 mEq/h
Secretin stimulation testing	Increase of >200 pg/mL
Calcium infusion provocative testing	Rise >395 pg/mL

Patients should not take antisecretory agents a minimum of 3 to 7 days.

calcium provocative testing can be useful in establishing the diagnosis. An increase of 200 pg/mL in the serum gastrin level following secretin administration is consistent with ZES. Higher serum gastrin levels are seen with pancreatic rather than duodenal primaries and in patients with tumors larger than 3 cm and/or those with liver metastases.[35]

Modalities for localizing gastrinomas are similar to those used for insulinomas and include CT, MRI, EUS, SRS, and angiography with selective hepatic venous sampling after intra-arterial secretin injection. SRS is considered the imaging modality of choice for both primary and metastatic gastrinomas with a sensitivity and specificity of more than 90% compared with 30% to 50% with CT or MRI.[37,38]

The goals of surgery are 2-fold: resection of primary tumor for potential cure and prevention of malignant progression. Most gastrinomas (80%) are found in the gastrinoma triangle, as described by Stabile and colleagues[39] (**Fig. 5**). The gastrinoma triangle is defined by a line that joins the confluence of the cystic and common bile ducts superiorly, the junction of the second and third portions of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially. Historically, ZES patients were offered total gastrectomy to control acid production; however, with the advent of PPIs, this is no longer performed. A complete exploration of the gastrinoma triangle is performed intraoperatively and starts with an extended Kocher maneuver to mobilize the duodenum and gain exposure of the pancreas in the lesser sac. Bimanual palpation and use of IOUS is a key step in identifying small lesions and multifocal tumors. Irrespective of the presence of pancreatic tumors, a routine duodenotomy is advocated by some experts in all patients undergoing operative exploration for ZES.[40,41] Several studies have shown that a routine duodenotomy doubles the cure rate from 30% to 60%.[40,41] Pancreatic tumors that are small and away from the pancreatic duct can be enucleated; however, large, unencapsulated tumors, deep within the pancreas and close to the pancreatic duct, require formal resection. Duodenal tumors less than 0.5 cm can be enucleated but larger tumors require a full-thickness excision of the duodenal wall. In about 5% of cases, the surgeon is unable to localize these tumors, in which case, a highly selective vagotomy may be considered to decrease postoperative requirement of antisecretory medications.

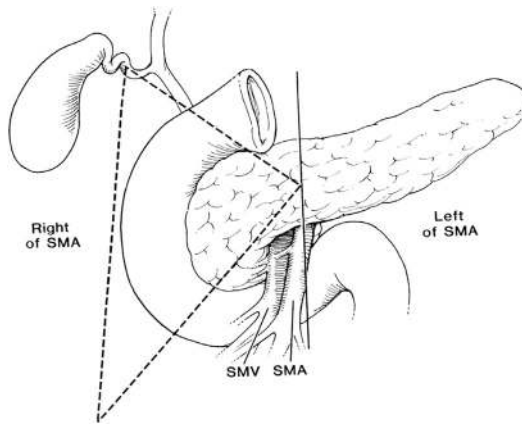

Fig. 5. Gastrinoma triangle. This region is bound by the junction of cystic/common bile ducts, junction of the second and third parts of the duodenum, and the junction of the neck and body of the pancreas. SMA, superior mesenteric artery; SMV, superior mesenteric vein. (*From* Howard TJ, Sawicki M, Lewin KJ, et al. Pancreatic polypeptide immunoreactivity in sporadic gastrinoma: relationship to intra-abdominal location. Pancreas 1993;11:351; with permission.)

There exists some controversy regarding the management of MEN-1-associated gastrinomas. Because more than 50% of these patients have metastatic and multifocal disease at presentation, MEN-1 patients are rarely cured by surgery (**Fig. 6**). Hence, the goal of surgery in this group of patients is to reduce the risk of metastases and improve survival. Bartsch and colleagues[42] showed that patients with tumors less than 1 cm have only a 4% likelihood of having liver metastases compared with 60% of those with a tumor size greater than 3 cm. Most centers now observe patients with tumors smaller than 2 cm, and recommendations are to resect the primary tumor if size is greater than 2 cm. Controversy still exists about the use of a Whipple procedure in management of pancreatic head tumors in MEN-1 patients. For now, this approach is recommended for young patients and those who have large isolated pancreatic head tumors.[40,43] In the case of MEN-1 with primary hyperparathyroidism and ZES,

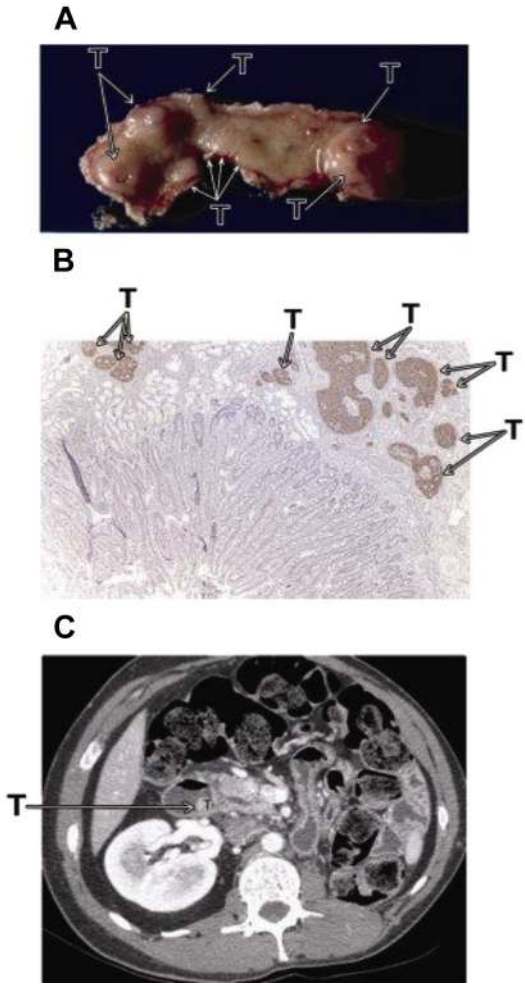

Fig. 6. Multifocality of MEN-1 gastrinomas. (*A*) Multifocal tumor (T) in a pancreatic resection gross specimen. (*B*) Multifocal tumor deposits (T) in a low-power photomicrograph. (*C*) Duodenal primary tumor (T). (*From* Huang LC, Poultsides GA, Norton JA. Surgical management of neuroendocrine tumors of the gastrointestinal tract. Oncology 2011;25(9):794–803.)

studies have shown that successful neck exploration for resection of parathyroid hyperplasia can reduce end organ effects of hypergastrinemia.[44] In these patients, parathyroidectomy must be performed before attempting a resection for the gastrinoma.[45]

Surgical treatment of sporadic gastrinomas has a high cure rate with a 20-year disease-free survival of 98% compared with 74% in nonoperated cases. Patients are followed yearly with fasting serum gastrin and chromogranin levels. A secretin provocation test is used if the patient is on PPIs. Imaging studies are less indicated if the above biochemical studies remain normal.

Nonfunctional Pancreatic Neuroendocrine Tumors

More than 75% of pancreatic endocrine tumors are NF-pancNETs.[46] They are so named because they lack a clinical syndrome of hormonal overproduction. Because the symptoms of NF-pancNETs are nonspecific, they are usually diagnosed late in the course of their disease, when noted to be large tumors with a high rate (60%) of metastatic disease at the time of diagnosis. About 8% of pancNETs occur in association with MEN-1, and in patients with MEN-1, 55% of tumors are NF-pancNETs.[47]

These tumors are usually discovered on routine radiographic imaging for nonspecific abdominal complaints. With compression of surrounding structures, many patients complain of pain or obstruction. Presence of these tumors is ascertained by measuring inert tumor markers such as chromogranin, pancreatic polypeptide, neuron-specific enolase, protein S, and neurotensin. Given their larger size, they are easily detected by CT/MRI, and EUS-guided biopsy can be considered. SRS is recommended to determine receptor expression status for postsurgical treatment with somatostatin analogues. The natural history of NF-pancNETs in MEN-1 is not well established. Malignant pancNETs are the most common cause of death in patients with MEN-1. They are the most common enteropancreatic NET associated with MEN-1 and confer a worse prognosis than functioning tumors such as insulinoma and gastrinoma.

Treatment of sporadic NF-pancNETs is surgical resection that is geared toward cure. The approach to surgery in MEN-1 patients, however, remains controversial. The goal of treatment here is to reduce morbidity and mortality because of metastatic disease while preserving as much pancreatic tissue as possible. MEN-1 patients tend to have a field defect that makes the entire pancreas at risk for neoplastic disease; therefore, resection of a primary lesion does not necessarily prevent recurrence in the remaining gland. Triponez and colleagues[48] showed in their analysis of the French "Groupe d' Etude des Tuneurs Endocrines" database that the risk of lymph node or distant metastases correlates directly with primary tumor size. In this study, only 3% of patients with tumors less than 2 cm had synchronous lymph nodes or distant metastases, and their survival was similar to patients with MEN-1 who had no pancreaticoduodenal involvement. Another study by the same group reported the presence of synchronous metastases in 43% of patients with NF-pancNETs of more than 3 cm, in 18% of patients with tumors between 2.1 and 3.0 cm, and in only 4% of patients with tumors less than 1 cm.[49]

Currently, several different recommendations exist for the management of MEN-1 patients with small NF-pancNETs. The clinical practice guidelines for MEN-1 by Thakker and colleagues[50] suggest considering surgical resection for tumors larger than 1 cm in size. The NCCN guidelines in the United States suggest a more conservative approach for tumors 1 to 2 cm in size in the absence of rapid progression on serial imaging. There seems to be consensus for a conservative stance toward tumors less than 1 cm and for resection for tumors greater than 2 cm. The management of tumors between 1 and 2 cm remains a matter of debate. Surgical resection is also

recommended for lesions that have significant growth, such as doubling of tumor size over a 3- to 6-month interval for tumors of any size.

Other Functional Pancreatic Neuroendocrine Tumors

Glucagonomas are rare tumors that present in the fifth or sixth decade of life. They are frequently large (usually greater than 4 cm) at diagnosis, and 60% to 70% are malignant. Association with MEN-1 is rare. Clinical manifestations encompass what is commonly known as the "4 D syndrome," which includes diabetes mellitus type 2, dermatitis (necrolytic migratory erythema), deep vein thrombosis, and depression.[51] Other symptoms include weight loss, anemia, painful glossitis, and pulmonary emboli.

Biochemical diagnosis is made by measuring elevated plasma levels of glucagon to greater than 500 pg/mL and decreased levels of amino acids. Because most patients present with large tumors, CT scan with contrast is sufficient to detect 86% of tumors. SRS has also been shown to be useful in locating tumors and for long-term follow-up of patients.[52] These tumors cluster in the pancreatic tail and often present with synchronous liver metastases that may be amenable to distal pancreatectomy with or without partial hepatectomy in a staged or simultaneous fashion. A complete, margin-negative resection is typically achieved in only 30% of cases.[53] Somatostatin analogues should be considered preoperatively because their use can markedly diminish circulating levels of glucagon controlling its catabolic effects. Like other metastatic pancNETs, liver metastases have been treated with resection, ablation, hepatic artery embolization, and liver transplantation.

Somatostatinomas represent only 1% of all pancNETs and present clinically with steatorrhea, cholelithiasis, diabetes mellitus type 2, and hypochlorhydria that together comprise the somatostatinoma syndrome.[54] Most patients present with solitary lesions that are around 5 to 6 cm in size, and these clinical manifestations are rarely observed with lesions arising in the duodenum. Most somatostatinomas are malignant at presentation, and more than 75% have evidence of metastases at the time of surgical exploration particularly in tumors greater than 2 cm in size.[55]

Most are located in the head of the pancreas, and resection usually involves pancreaticoduodenectomy. Some surgeons perform a cholecystectomy at the same time because of the high incidence of symptomatic cholelithiasis in these patients. In patients without metastatic disease, the median 5-year survival can be 100% versus 60% in patients who undergo pancreatectomy and debulking of metastatic disease.[53]

MANAGEMENT OF NEUROENDOCRINE LIVER METASTASES

Hepatic metastases occur in more than 50% of patients with NETs. In contrast to exocrine pancreatic cancers, patients with endocrine tumors may warrant aggressive treatment and may benefit from reoperation for resectable recurrences or metastatic disease due to their indolent nature. Debulking of metastatic disease, even in situations wherein not all of the tumor can be removed, may still hold value in cases wherein patients are symptomatic from hormonal activity relating to the disease burden. Neuroendocrine liver metastases (NELMs) can progress without raising suspicion, until symptoms associated with pain, mass effect, or hormone overproduction occur. The rationale for cytoreductive surgery is (1) to improve quality of life in patients with bulky, symptomatic tumors; (2) to reduce volume to prevent further metastases; (3) to improve symptom-free survival.[56] The estimated 5-year survival in patients treated medically ranges from 0% to 40%. Studies have shown extended survival and symptom control with aggressive cytoreduction.[14,57]

A retrospective study by Chamberlain and colleagues[14] in 2000 at Memorial Sloan-Kettering Cancer Center reviewed records of 85 patients with hepatic NET metastases between 1992 and 1998. In this study, 41 patients had carcinoids, 26 were NF-pancNETs, and 18 were F-pancNETs. Eighty-four percent of patients had bilobar metastases. Thirty-three patients underwent hepatic artery embolization (HAE), and 34 underwent hepatic resection. Eighteen patients were treated with best medical treatment (BMT). The 1-, 3-, and 5-year survival rates for patients treated by HAE are 94%, 83%, and 51%, respectively, and the 1-, 3-, and 5-year survivals for patients treated operatively were 94%, 83%, and 76%, which was far superior to the 0% to 40% 5-year survival rate on BMT alone. The authors of this report concluded that hepatic metastases from NETs are best managed through a multidisciplinary approach, and that although surgical resection of NELMs may prolong survival, it is rarely curative. In 2003, Sarmiento and colleagues,[58] using data from the Mayo Clinic, published a retrospective review of 170 patients with NELMs who were identified between 1977 and 1998. Primary sites were carcinoid of the small bowel and pancNETs. Resection was classified as complete (75 patients) or incomplete (palliative intent, 95 patients). When done for palliation, all patients had at least 90% of their disease resected. Overall survival was 61% at 5 years with a median survival of 81 months, and recurrence rate was 84% at 5 years. No difference was found in recurrence rates between carcinoids and islet cell tumors (82% vs 88%). No difference was found in overall survival either. Recurrence rates were lower for patients with a complete resection compared with those who underwent an incomplete resection (76% vs 91% at 5 years with median time to recurrence being 30 months vs 16 months). The conclusion drawn from this study was that, in the case of resectable lesions and good operative candidacy, aggressive resection for NET metastases definitely improved survival. Recurrence was high within 5 years of resection.

More recently, Mayo and colleagues[59] reported 339 patients who underwent surgical management of NELMs at 8 major hepatobiliary centers. Most had a pancreatic (40%) or a small bowel (25%) primary tumor. Seventy-eight percent of patients underwent hepatic resection; 3% underwent ablation alone, and 19% underwent both ablation and resection. Forty-six patients underwent a second liver-directed procedure. Median survival after surgery in this study was 125 months, with overall 5-year and 10-year survival rates of 74% and 51%, respectively (**Fig. 7**). Patients whose metastatic burden was confined to the liver had a median survival of 148 months following surgery compared with 85 months in patients with extrahepatic disease also. Looking at patients who underwent a repeat resection, median survival in this subset also was significant at 82.9 months. As with the Mayo Clinic study, the recurrence rate was still 94% at 5 years with a median time to recurrence of 15.2 months. On performing a multivariate analysis, 2 other factors that impacted survival aside from presence of extrahepatic disease were nonfunctional NET and synchronous disease, with increased recurrence found in these subsets of patients. Using this information, the investigators plotted Kaplan-Meier survival curves stratified by margin status and functionality of the tumor. They found that patients with functional tumors who had an R0/R1 resection had greater survival than the nonfunctional tumors (see **Fig. 7**). Thus, this study, like the others before it, showed that although cytoreduction definitely improves survival despite a high recurrence rate, it serves a better purpose in patients with functional NELMs who undergo R0/R1 resections than the nonfunctional tumors, in which case other liver-directed therapies may have to be considered.

Although patients with symptomatic disease are often offered cytoreduction to help palliate symptoms, the role of surgery for asymptomatic and nonfunctional NELMs is more controversial and needs to be highly individualized. Most patients with NELMs

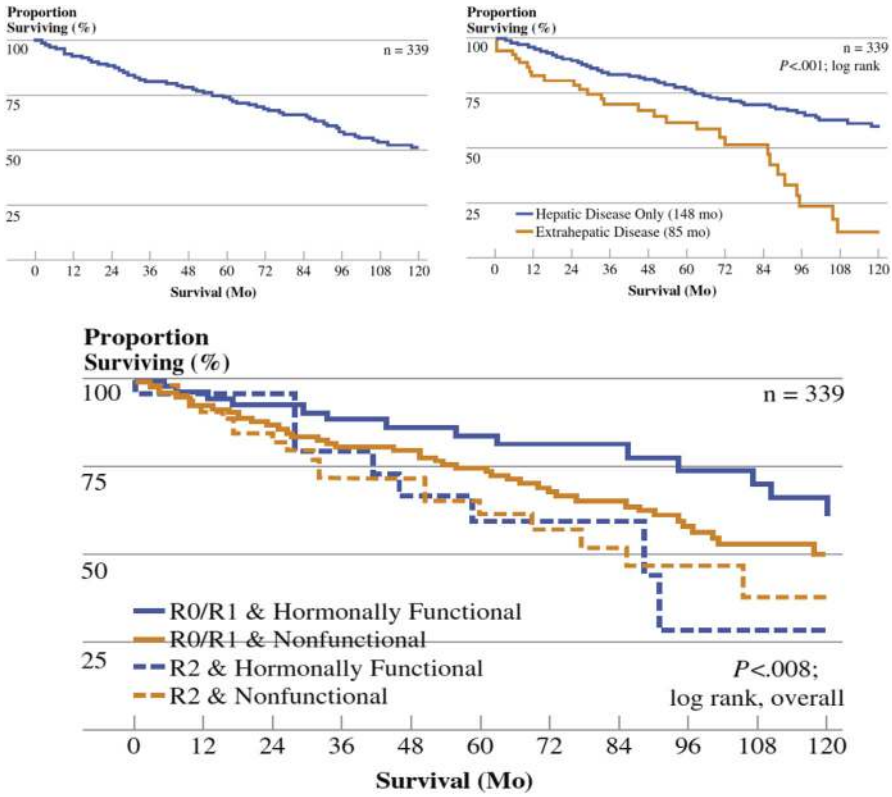

Fig. 7. Kaplan-Meier survival curves after surgical resection of NELMs. (*Data from* Mayo SC, Herman JM, Cosgrove D, et al. Emerging approaches in the management of patients with neuroendocrine liver metastasis: role of liver-directed and systemic therapies. J Am Coll Surg 2013;216(1):123–34.)

will present with bilobar disease, and achieving an R0 resection appears to be significantly lower compared with resections performed for colorectal metastases.[60–62] The literature supports the notion that patients in whom more than 75% of the liver is involved have a poor prognosis, and surgery alone should be avoided[14]; this is the reason in most centers, that NELM resection is usually combined with ablation to treat the hepatic tumor burden. Also, less than 20% of recurrences are amenable to reoperative surgery, and hence, other liver-directed therapies must be considered.

Ablation has thus been used (1) for deeper lesions that are less than 4 cm and less than 8 to 10 in number to minimize volume of resection; (2) in patients with recurrence following a prior resection; (3) as an adjunct to resection in patients with bilobar disease; (4) to palliate symptoms in patients with inoperable tumors. Several modalities are available, such as radiofrequency ablation (RFA, most common), microwave, laser, and cryotherapy. RFA is the dominant ablative modality used and is done in a percutaneous, open, or laparoscopic fashion. Several studies have shown a reduction in local and hormonal symptoms in 70% to 80% of patients for 1 year with a 50% reduction of tumor markers in a similar number of patients. Mazzaglia and colleagues[63] reported on the largest series of laparoscopic RFA, involving 63 patients with NELMs. All had resectable disease on imaging. Sixty-three patients were treated

for 452 liver metastases without resection. Twenty-two percent of them had repeat ablations for progression of disease.

Fifty-seven percent of patients in this study were symptomatic, and 94% of them achieved symptom relief after the procedure. Median duration of symptom control was 11 months. The 5-year survival after RFA was 48% with a median survival of 3.9 years, which was higher than their medically treated counterparts. Breaking up survival based on number of ablations, patients who underwent single ablations had a survival of 5.2 years compared with 2.9 years for patients who underwent multiple ablations. Unfortunately, progressive liver disease was demonstrated on surveillance imaging in 80% of patients. Given this high rate of recurrence with surgery and ablation, many investigators suggested that the use of intra-arterial therapy (IAT) might be better suited for treating NELMs.

The concept of IAT stems from the fact that NELMs, unlike most hepatic metastases, derive their blood supply from the hepatic artery. Embolization of the feeding vessels to the tumor thus deprives them of their blood supply and helps retard tumor progression and palliate symptoms. IAT consists of (1) transarterial chemoembolization (TACE); (2) transarterial bland embolization (TAE); (3) chemoembolization with drug-eluting beads; and (4) radioembolization using Y90 spheres. Detailed discussion on IAT is beyond the scope of this topic; however, the authors will present one of the largest studies to date comparing surgery versus IAT for treatment of NELMs by Mayo and colleagues.[59] They compared 753 patients who underwent either surgery (339) or IAT/TACE (414) from 1985 to 2010. However, there were statistically significant differences in the baseline characteristics of the patient populations. For example, IAT patients were more likely to have an unknown primary, extrahepatic disease, bilobar disease, and higher disease burden (>25% liver involvement)—all of which were independent predictors of decreased survival in univariate analyses. Median survival with surgery was 123 months with a 5-year survival of 74% versus 33.5 months and 30% for IAT. An issue here was patient selection, because there was higher disease burden and worse biology for patients in the IAT arm. Using propensity score methodology, a subgroup of 118 patients (66 surgery and 52 IAT) were identified who were matched on similar clinicopathologic features. Analyzing this subgroup, the median survival was 84 months versus 38.9 months for surgery versus IAT. Additional analysis of this cohort, based on symptoms and tumor burden, revealed that high-volume, symptomatic patients benefited most from surgical management. Asymptomatic patients, on the other hand, fared better with IAT, although this difference did not reach statistical significance (16.7 months with surgery vs 18 months with IAT). Hence, this study concluded that surgery should be reserved for low-volume disease or high-volume functional disease, without compromising the functional liver remnant. In contrast, patients with a high burden of hepatic disease, especially those with asymptomatic disease, are probably best served with locoregional IAT than a surgical resection.

ROLE OF LIVER TRANSPLANTATION IN TREATMENT OF NEUROENDOCRINE LIVER METASTASES

Orthotopic liver transplantation (OLT) for patients with NELMs who have unresectable disease remains controversial and is performed only at a few centers. Reasons cited by advocates for OLT are (1) relative indolent nature of NETs; (2) propensity for liver-only metastases; and (3) high risk of intrahepatic recurrence after resection.[59] In Europe, NELMs account for only 0.4% of liver transplants. There have been no meaningful published data that show an improvement in life expectancy after transplant compared

with spontaneous survival, that is, 20% to 30% at 5 years. To date, the largest series examining the role of OLT for NELMs was a multicenter French study by Le Treut and colleagues.[64] This study included 85 patients who underwent liver transplantation for NELMs from 1989 to 2005. In 40 cases, the primary tumor was located in the pancreas or the duodenum, digestive tract in 26 cases, and the bronchial tree in 5 cases. In the remaining 14 cases, the primary was undetermined. The investigators reported an in-hospital mortality of 14% and an overall survival rate of 47%. Factors associated with a poor prognosis were hepatomegaly and a primary NET arising from the duodenum or pancreas. Twenty-three patients who had both unfavorable prognostic factors had a 5-year survival rate of 12% versus 68% for the 55 patients presenting with one or neither factor. The study concluded that liver transplant can benefit selected patients with nonresectable NELMs. However, patients presenting with pancreaticoduodenal primaries in association with hepatomegaly are poor indications for liver transplantation. Mazzaferro and colleagues[65] developed criteria analogous to the Milan criteria for HCC. The inclusion criteria include low-grade NET histology, primary tumor drained by the portal system removed with a curative resection pretransplantation, less than 50% hepatic involvement by tumor, stable disease for at least 6 months during the pretransplantation period, and age 55 years or younger.

As of 2012, the NCCN practice guidelines consider transplantation for NELM to be investigational and not part of routine care at this time.[59]

SUMMARY

With the advent of various medical treatment options for these tumors, including somatostatin analogues, cytotoxic agents, mTOR inhibitors, and PRRT, the management of pancNETs and NELMs has truly become multimodal. Although the discussion regarding medical management of pancNETs using these modalities can be found in the article by Jennifer A. Chan and Matthew H. Kulke: Medical Management of Pancreatic Neuroendocrine Tumors: Current and Future Therapy, in this issue, surgical resection still plays a significant role with regards to improved survival and symptom control. Although liver-directed therapy such as ablation and IAT has been studied in tandem, and in comparison with surgery, further research is required to analyze the use of medical treatment options in concert with surgical resection in both the adjuvant and neoadjuvant settings to improve patient outcomes.

REFERENCES

1. Kloppel G, Heitz PU. Classification of normal and neoplastic neuroendocrine cells. Ann N Y Acad Sci 1994;733:19–23.
2. Rindi G, Capella C, Solcia E. Introduction to a revised clinicopathological classification of neuroendocrine tumors of the gastroenteropancreatic tract. Q J Nucl Med 2000;44(1):13–21.
3. Rindi G, Klöppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006; 449(4):395–401.
4. American Joint Commission on Cancer, American Cancer Society. AJCC cancer staging manual. 7th edition. New York: Springer; 2010.
5. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Neuroendocrine tumors. 2012.
6. Ito T, Igarashi H, Jensen RT. Therapy of metastatic pancreatic neuroendocrine tumors (PancNETs): recent insights and advances. J Gastroenterol 2012;47(9): 941–60.

7. Jensen RT, Cadiot G, Brandi ML, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology 2012;95(2):98–119.
8. Kulke MH, Anthony LB, Bushnell DL, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas 2010;39(6):735–52.
9. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology 2008;135(5):1469–92.
10. Gullo L, Migliori M, Falconi M, et al. Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. Am J Gastroenterol 2003;98(11):2435–9.
11. Ito T, Sasano H, Tanaka M, et al. Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. J Gastroenterol 2010;45(2):234–43.
12. Jensen RT, Berna MJ, Bingham DB, et al. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. Cancer 2008;113(7 Suppl):1807–43.
13. Pipeleers-Marichal M, Somers G, Willems G, et al. Gastrinomas in the duodenums of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome. N Engl J Med 1990;322(11):723–7.
14. Chamberlain RS, Canes D, Brown KT, et al. Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg 2000;190(4):432–45.
15. Hoeffel C, Job L, Ladam-Marcus V, et al. Detection of hepatic metastases from carcinoid tumor: prospective evaluation of contrast-enhanced ultrasonography. Dig Dis Sci 2009;54(9):2040–6.
16. Massironi S, Conte D, Sciola V, et al. Contrast-enhanced ultrasonography in evaluating hepatic metastases from neuroendocrine tumours. Dig Liver Dis 2010; 42(9):635–41.
17. de Herder WW, Kwekkeboom DJ, Valkema R, et al. Neuroendocrine tumors and somatostatin: imaging techniques. J Endocrinol Invest 2005;28(11 Suppl International):132–6.
18. Kwekkeboom DJ, Krenning EP, Scheidhauer K, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: somatostatin receptor imaging with (111)In-pentetreotide. Neuroendocrinology 2009;90(2):184–9.
19. Ambrosini V, Campana D, Bodei L, et al. 68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. J Nucl Med 2010;51(5):669–73.
20. Frilling A, Sotiropoulos GC, Radtke A, et al. The impact of 68Ga-DOTATOC positron emission tomography/computed tomography on the multimodal management of patients with neuroendocrine tumors. Ann Surg 2010;252(5):850–6.
21. Grama D, Eriksson B, Mårtensson H, et al. Clinical characteristics, treatment and survival in patients with pancreatic tumors causing hormonal syndromes. World J Surg 1992;16(4):632–9.
22. Park BJ, Alexander HR, Libutti SK, et al. Operative management of islet-cell tumors arising in the head of the pancreas. Surgery 1998;124(6):1056–61 [discussion: 1061–2].
23. Sheppard BC, Norton JA, Doppman JL, et al. Management of islet cell tumors in patients with multiple endocrine neoplasia: a prospective study. Surgery 1989; 106(6):1108–17 [discussion: 1117–8].
24. Sotoudehmanesh R, Hedayat A, Shirazian N, et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. Endocrine 2007;31(3):238–41.
25. Kisker O, Bartsch D, Weinel RJ, et al. The value of somatostatin-receptor scintigraphy in newly diagnosed endocrine gastroenteropancreatic tumors. J Am Coll Surg 1997;184(5):487–92.

26. Guettier JM, Kam A, Chang R, et al. Localization of insulinomas to regions of the pancreas by intraarterial calcium stimulation: the NIH experience. J Clin Endocrinol Metab 2009;94(4):1074–80.
27. Hashimoto LA, Walsh RM. Preoperative localization of insulinomas is not necessary. J Am Coll Surg 1999;189(4):368–73.
28. Lo CY, Lam KY, Kung AW, et al. Pancreatic insulinomas. A 15-year experience. Arch Surg 1997;132(8):926–30.
29. Arnold R, Wied M, Behr TH. Somatostatin analogues in the treatment of endocrine tumors of the gastrointestinal tract. Expert Opin Pharmacother 2002;3(6):643–56.
30. Boukhman MP, Karam JH, Shaver J, et al. Insulinoma–experience from 1950 to 1995. West J Med 1998;169(2):98–104.
31. Norton JA, Cromack DT, Shawker TH, et al. Intraoperative ultrasonographic localization of islet cell tumors. A prospective comparison to palpation. Ann Surg 1988;207(2):160–8.
32. Nikfarjam M, Warshaw AL, Axelrod L, et al. Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital. Ann Surg 2008;247(1):165–72.
33. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology 1995;108(6):1637–49.
34. Andersen DK. Current diagnosis and management of Zollinger-Ellison syndrome. Ann Surg 1989;210(6):685–703.
35. Berna MJ, Hoffmann KM, Long SH, et al. Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the National Institutes of Health and comparison with 537 cases from the literature. evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. Medicine (Baltimore) 2006;85(6):331–64.
36. Roy PK, Venzon DJ, Shojamanesh H, et al. Zollinger-Ellison syndrome. Clinical presentation in 261 patients. Medicine (Baltimore) 2000;79(6):379–411.
37. Klose KJ, Heverhagen JT. Localisation and staging of gastrin producing tumours using cross-sectional imaging modalities. Wien Klin Wochenschr 2007; 119(19–20):588–92.
38. Noone TC, Hosey J, Firat Z, et al. Imaging and localization of islet-cell tumours of the pancreas on CT and MRI. Best Pract Res Clin Endocrinol Metab 2005;19(2): 195–211.
39. Stabile BE, Morrow DJ, Passaro E Jr. The gastrinoma triangle: operative implications. Am J Surg 1984;147(1):25–31.
40. Morrow EH, Norton JA. Surgical management of Zollinger-Ellison syndrome; state of the art. Surg Clin North Am 2009;89(5):1091–103.
41. Norton JA, Alexander HR, Fraker DL, et al. Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases, or survival in patients with Zollinger-Ellison syndrome? Ann Surg 2004;239(5):617–25 [discussion: 626].
42. Bartsch DK, Langer P, Rothmund M. Surgical aspects of gastrinoma in multiple endocrine neoplasia type 1. Wien Klin Wochenschr 2007;119(19–20):602–8.
43. Fendrich V, Langer P, Waldmann J, et al. Management of sporadic and multiple endocrine neoplasia type 1 gastrinomas. Br J Surg 2007;94(11):1331–41.
44. Norton JA. Gastrinoma: advances in localization and treatment. Surg Oncol Clin N Am 1998;7(4):845–61.
45. Norton JA, Cornelius MJ, Doppman JL, et al. Effect of parathyroidectomy in patients with hyperparathyroidism, Zollinger-Ellison syndrome, and multiple endocrine neoplasia type I: a prospective study. Surgery 1987;102(6):958–66.

46. Halfdanarson TR, Rabe KG, Rubin J, et al. Pancreatic neuroendocrine tumors (PANCNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol 2008;19(10):1727–33.
47. Thomas-Marques L, Murat A, Delemer B, et al. Prospective endoscopic ultrasonographic evaluation of the frequency of nonfunctioning pancreaticoduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. Am J Gastroenterol 2006;101(2):266–73.
48. Triponez F, Goudet P, Dosseh D, et al. Is surgery beneficial for MEN1 patients with small (< or = 2 cm), nonfunctioning pancreaticoduodenal endocrine tumor? An analysis of 65 patients from the GTE. World J Surg 2006;30(5):654–62 [discussion: 663–4].
49. Triponez F, Dosseh D, Goudet P, et al. Epidemiology data on 108 patients from the GTE with isolated nonfunctioning tumors of the pancreas. Ann Surg 2006; 243(2):265–72.
50. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012;97(9): 2990–3011.
51. Norton JA. Neuroendocrine tumors of the pancreas and duodenum. Curr Probl Surg 1994;31(2):77–156.
52. Lipp RW, Schnedl WJ, Stauber R, et al. Scintigraphic long-term follow-up of a patient with metastatic glucagonoma. Am J Gastroenterol 2000;95(7):1818–20.
53. Abood GJ, Go A, Malhotra D, et al. The surgical and systemic management of neuroendocrine tumors of the pancreas. Surg Clin North Am 2009;89(1): 249–66, x.
54. Krejs GJ, Orci L, Conlon JM, et al. Somatostatinoma syndrome. Biochemical, morphologic and clinical features. N Engl J Med 1979;301(6):285–92.
55. Tanaka S, Yamasaki S, Matsushita H, et al. Duodenal somatostatinoma: a case report and review of 31 cases with special reference to the relationship between tumor size and metastasis. Pathol Int 2000;50(2):146–52.
56. Maithel SK, Fong Y. Hepatic ablation for neuroendocrine tumor metastases. J Surg Oncol 2009;100(8):635–8.
57. Norton JA, Kivlen M, Li M, et al. Morbidity and mortality of aggressive resection in patients with advanced neuroendocrine tumors. Arch Surg 2003;138(8):859–66.
58. Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 2003;197(1):29–37.
59. Mayo SC, Herman JM, Cosgrove D, et al. Emerging approaches in the management of patients with neuroendocrine liver metastasis: role of liver-directed and systemic therapies. J Am Coll Surg 2013;216(1):123–34.
60. de Jong MC, Mayo SC, Pulitano C, et al. Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. J Gastrointest Surg 2009;13(12):2141–51.
61. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg 2009;250(3):440–8.
62. Pawlik TM, Vauthey JN. Surgical margins during hepatic surgery for colorectal liver metastases: complete resection not millimeters defines outcome. Ann Surg Oncol 2008;15(3):677–9.
63. Mazzaglia PJ, Berber E, Milas M, et al. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. Surgery 2007;142(1):10–9.

64. Le Treut YP, Grégoire E, Belghiti J, et al. Predictors of long-term survival after liver transplantation for metastatic endocrine tumors: an 85-case French multicentric report. Am J Transplant 2008;8(6):1205–13.
65. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? J Hepatol 2007;47(4):460–6.