Surgical management of primary pancreatic neuroendocrine tumors

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Abstract: Pancreatic neuroendocrine tumors (PanNETs) are the second most common malignancy of the pancreas, and their incidence is increasing. PanNETs are a diverse group of diseases which range from benign to malignant, can be sporadic or associated with genetic mutations, and be functional or nonfunctional. In as much, the treatment and management of PanNETs can vary from a "Wait and See" approach to orthotopic liver transplantation (OLT). Despite this, surgical resection is still the primary treatment modality to achieve cure. This review focuses on the surgical management of PanNETs.

Keywords: Pancreatic neuroendocrine tumors (PanNETs); pancreatic neoplasm; pancreatic islet cell carcinoma; pancreas surgery

Introduction

Pancreatic neuroendocrine tumors (PanNETs), also known as "islet cell tumors", are neuroendocrine tumors that arise from the embryonic endodermal ductal-acinar system. These neoplasms have a reported incidence of 1 to 1.5 per 100,000 in the world and 35 per 100,000 in the United States (US) (1). PanNETs comprise approximately 1.3–3% of pancreatic malignancies; however, their incidence has increased up to seven fold partially due to increased discovery of incidentalomas on cross-sectional imaging (2,3). The Surveillance, Epidemiology and End Results (SEER) specifically has shown that the incidence of sub-two centimeter PanNETs, in particular, have increased (4-6).

PanNETs are classified into two distinct groups, functional (F-PanNET) and nonfunctional (NF-PanNET), and their management is uniquely tied to the qualities of each tumor. Surgical resection remains the only curative treatment, and five-year survival is >90% in patients with localized disease and 15–27% for those with unresectable disease (7). Although consensus guidelines exist, surgical management requires a more in-depth assessment and a tailored approach to individual patients and their tumor type. In addition, with the greater detection of smaller, incidentally found PanNETs, there is a pressing need for development of appropriate surveillance and surgical treatment algorithms to guide management. This review describes the surgical management of localized and advanced PanNETs, as well as surveillance strategies for patients being observed.

Workup and diagnosis

Due to the predominantly indolent nature of these tumors, the diagnosis of many PanNETs can be delayed for months to years. As a result, up to 11% of cases are diagnosed with advanced metastatic disease (8). F-PanNETs often produce symptoms that raise clinical concern for a particular syndrome and work-up includes analysis of serum hormone levels (*Table 1*). In patients who are asymptomatic, relevant

Table 1 Surgical management of nonfunctional and functional PanNETs

Tumor type	Incidence (per 100,000/year)	Malignancy rate (%)	Overall survival (%)	Presentation	Serum markers	Management Preoperative	Management Intraoperative
Non-functional	1–5	60–90	5-year: 43	Incidental finding; signs/symptoms from mass effect	CgA >36.4 ng/mL; NSE[a] >8.6 ng/mL	Rule-out functional tumors	–
Functional PanNETS							
Insulinoma	1–3	5–15	10-year: benign—78; malignant—29	Whipple's triad; symptomatic hypoglycemia; low serum glucose; symptoms resolve with glucose	Fasting[b]: glucose <50 mg/dL; insulin >5–10 mU/mL; C-peptide ≥0.2 nmol/L; negative sulfonylurea screen	Octreotide scans poor due to low somatostatin expression; diazoxide for glucose control; octreotide/lanreotide	IOUS if unable to localize pre-operatively; (identifies up to 90%); enucleation for superficial lesions* or formal pancreatectomy; pancreatic biopsy if no tumor identified following exploration and IOUS
Gastrinoma	0.5–1.5	60–90	5-year: 86–94[d]	Zollinger-Ellison syndrome; duodenal/pre-pyloric ulcers; diarrhea; heartburn	Gastrin >1,000 pg/mL[c]	PPI or H2-blocker +/– octreotide/lanreotide to prevent gastric hypersecretion; genetic testing for multiple or family history	Thorough exploration including IOUS of liver and pancreas, Kocherization of the duodenum; lateral duodenotomy and peritoneal exploration if no tumor identified; formal pancreatectomy w/LN dissection
VIPoma	0.05–0.2	70–90	5-year: 69	Verner-Morrison syndrome[e]; watery diarrhea; hypokalemia; achlorhydria	VIP >190 pg/mL[f]	Correct electrolytes, hydration; octreotide/lanreotide for symptom control	Formal pancreatectomy w/LN dissection
Glucagonoma	0.01–0.1	60–75	10-year[g]: localized—100; metastatic—52	Necrolytic migratory erythema; normochromic, normocytic anemia; glucose intolerance	Fasting: glucagon >500 pg/mL	Biopsy of necrolytic erythema; octreotide/lanreotide; manage hyperglycemia/diabetes	Resection w/LN dissection
Somatostatinoma	0.0025	40–60	5-year: 75	Diabetes mellitus; cholelithiasis; steatorrhea	Somatostatin >100 pg/mL	Octreotide for symptom control	Resection with cholecystectomy

Information from references (8-28). *, superficial lesions are defined as distance between tumor and main pancreatic duct ≥3 mm without focal stricture or dilation and <2 cm in size. [a], CgA + NSE are traditionally used in combination due to their combined diagnostic power, alternatives include pancreastatin, pancreatic polypeptide, neurotensin, protein S, ghrelin, motilin, enolase; [b], supervised fast is conducted and serum levels of glucose, insulin and C-peptide are assessed every 6 hours or when symptoms occur; [c], hypergastrinemia (>10× the upper limit of normal) in conjunction with gastric pH <2 is diagnostic of Zollinger-Ellison Syndrome; [d], OS for sporadic gastrinoma is 86–94%; however, for gastrinoma associated with MEN1 OS is nearly 100% at 20 years; [e], Werner-Morrison Syndrome is also referred to as WDHA Syndrome or pancreatic cholera; [f], VIP Normal VIP levels range from 0–190 pg/mL and fluctuate frequently, all levels should be confirmed more than once as a single level is not reliable for ruling in or ruling out VIPoma; [g], 10-year post-operative overall survival as calculated by Kaplan-Meier method. PanNET, pancreatic neuroendocrine tumor; CgA, Chromogranin A; NSE, neuron-specific enolase; VIP, vasoactive intestinal polypeptide; EUS, endoscopic ultrasound; IOUS, intraoperative ultrasound; PPI, proton-pump inhibitor; H2, histamine-2 receptor; LN, lymph node.
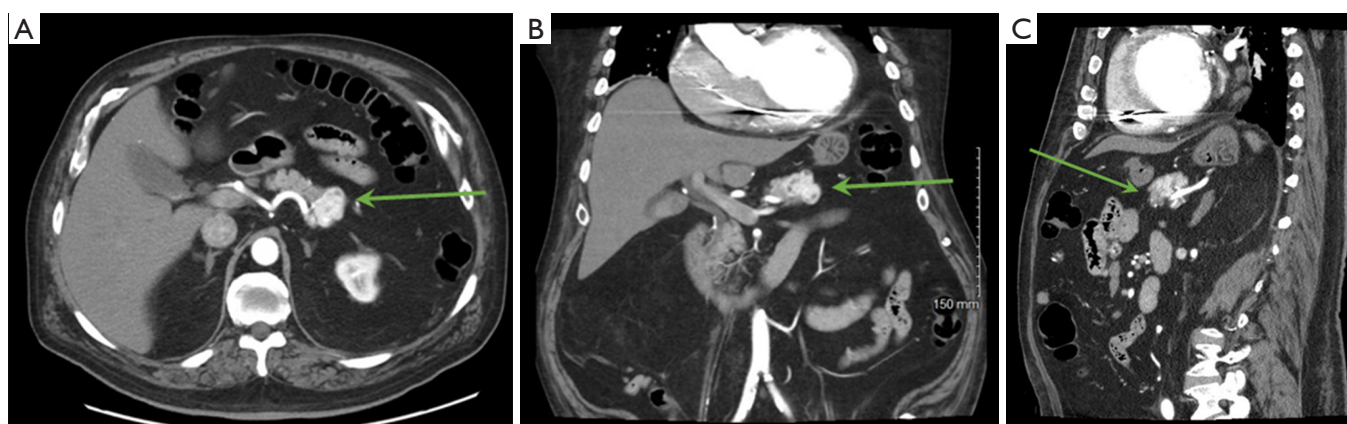
Figure 1 Computed Tomography with PanNET: CT of a 4.7 cm pancreatic neuroendocrine tumor within the pancreas body (green arrows). Note the hyperenhancement on arterial phase. (A) Transverse view; (B) coronal view; (C) sagittal view. PanNET, pancreatic neuroendocrine tumor.
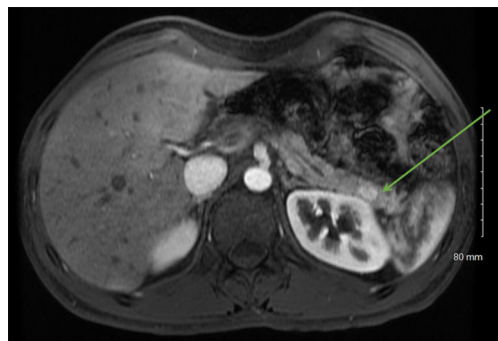

Figure 2 Magnetic resonance image with PanNET: Transverse view T2 weighted MRI with PanNET in pancreatic tail approximately 1.1 cm × 1.0 cm × 1.1 cm (green arrow). PanNET, pancreatic neuroendocrine tumor.

hormone studies should still be obtained if F-PanNET has not yet been ruled out.

The North American Neuroendocrine Tumor Society (NANETS) recommends the use of chromogranin A (CgA), a serum peptide secreted by 60–100% of NF-PanNETs, in the diagnosis of and the surveillance for recurrent PanNETs. However, the utility of CgA, in routine testing has been shown to be non-specific (specificity 65.5%) (9). Furthermore, CgA alone has insufficient sensitivity to diagnose small lesions and can be falsely elevated in patients with chronic kidney disease, liver failure, and the use of proton-pump inhibitors (PPIs) (10). Less often utilized serum peptides associated with NF-PanNETs include pancreastatin, ghrelin, neurotensin, motilin, pancreatic polypeptide (PPP), and enolase (10-14,29,30).

Imaging

High-quality cross-sectional imaging should be performed to evaluate pancreas lesions. A multiphasic computed tomography (CT) scan or magnetic resonance imaging (MRI) is commonly utilized (14). Primary and metastatic PanNETs are most often well-circumscribed lesions that are highly vascular and demonstrate hyperenhancement during the arterial phase (*Figure 1*). The hepatic arterial phase of the pancreas protocol has a sensitivity of 83–88% for PanNET lesions (15). Hypoenhancement on arterial phase and the presence of calcifications within the lesion are associated with higher grade histology and the presence of lymph node metastases (31). Compared to CT, contrast enhanced MRI (*Figure 2*) is more sensitive and specific for identifying smaller pancreatic lesions and liver metastases (32).

Functional imaging studies assist in staging, tumor localization, and therapeutic guidance. Such imaging techniques take advantage of the presence of somatostatin receptors—most commonly receptor subtypes 2 and 5 (SSTR-2, SSTR-5). The presence of these receptors in PanNETs is 76% and 93%, respectively (33). The most common functional imaging study used was indium-111-labeled somatostatin receptor scintigraphy (Octreoscan). More recently, positron-emission tomography (PET)/CT scan using gallium-68 (Ga-68) labeled somatostatin analogues (DOTATOC, DOTANONC and DOTATATE) is becoming more readily available and has better sensitivity (86–100%) and specificity (79–100%) compared to Octreoscan (34). However, one notable limitation of Ga-68 labeled somatostatin analogues is their inability to detect

insulinomas, having a sensitivity of only 25% (35). At our institution, the Ga-68 dotatate scan is used to help stage patients with PanNETs (36).

Resection of nonfunctional PanNETs

Surgical management of PanNETs is indicated for nonfunctional tumors ≥2 centimeters, tumors that are functional, symptomatic, or have evidence of aggressive features (local invasion, lymphatic metastases). With the increasing incidence of PanNETs <2 cm, there is concern for the potential to surgically overtreat, with patients being "Victims of Modern Imaging Technology" (37). Pancreatic surgery, despite having low mortality, is associated with high morbidity rates of almost 50% (38). Postoperative complications range from short term pancreatic fistula, intraabdominal fluid collections, or surgical site infections to long term pancreatic endocrine or exocrine insufficiencies.

Surgical options for the approach to PanNET resection depends on tumor size, anatomical location, and proximity to the pancreatic duct. These factors guide the surgeon in approaching the tumor with planned enucleation, pancreaticoduodenectomy (PD), distal pancreatectomy (DP), central pancreatectomy, or total pancreatectomy (TP). Additionally, patients that undergo splenectomy with DP should receive perioperative vaccines. The previously mentioned morbidities and mortality vary across these surgical techniques.

Enucleation is a technique limited to nonfunctional tumors less than 2 cm or peripheral insulinomas. One of the caveats with enucleation is that lymph nodes are not often sampled and the decision to proceed is examining the risk of having locoregional lymph node involvement. Enucleation mainly involves blunt dissection along the pancreas for superficial lesions. The pancreatic capsule is routinely closed but is left to surgeon discretion. Falconi *et al.* reported that atypical resection/enucleation had a lower incidence of endocrine or exocrine insufficiency, but did have a higher incidence of pancreatic fistula that were clinically relevant (grade B-C based on the International Study Group on Pancreatic Fistula) (39). A meta-analysis by Finkelstein in 2016 supported these findings across eleven studies with a total of 1,491 patients and also found that enucleation had shorter operative time and lower blood loss (40).

Surgical resections of DP, PD, and TP with nodal dissection are indicated for large, malignant lesions, or PanNETs close to the pancreatic duct where injury

to the duct is likely. For non-functional PanNETs between 1–2 cm, treatment remains controversial. Studies have shown that 7–26% of small, nonfunctional PanNETs 1–2 cm in size can have lymph node involvement (41). Hashim *et al.* found that 12% of tumors <1 cm in size had positive lymph nodes (42). Furthermore, patients with tumors >1.5 cm were almost 5× as likely to have regional lymph node metastases than smaller tumors (odds ratio 4.7, 95% CI: 1.81 to 12.35, P=0.002). Based on these data, not every tumor <2 cm can be observed. To help further evaluate which patients are at risk of having lymph node metastasis, Lopez-Aguiar *et al.* developed a novel lymph node risk score for NF-PanNETs <2 cm using data from the US Neuroendocrine Tumor Study Group. The authors found a significant association for lymph node-positivity with tumors located in the pancreatic head/uncinate and Ki-67 >3%, based on this, they developed a 3-tiered risk system. Patients in the low risk group had an incidence of 3.2%, intermediate with 13.8%, and high with 20.5% of positive lymph nodes (43). At our institution, we consider resection of NF-PanNETs between 1–2 cm if they have high Ki-67 (>3%), increase in size, or evidence of local invasion.

There have been multiple studies looking at the utility of minimally invasive techniques in pancreatic surgery. Zhang *et al.* found in a retrospective multi-institutional matched study that the incidence of minimally invasive DP for PanNETs is becoming more popular in comparison to open pancreatectomy (44). Furthermore, minimally invasive surgery resulted in similar oncologic outcomes compared to open, while having equivalent to lower blood loss, lower Clavien-Dindo III or greater complications, and shorter hospital stay. These data were also seen several other studies (45,46).

Resection of functional PanNETs

Functional PanNETs are sub-classified based on the endocrine hormone they secrete and resulting clinical syndrome they produce. F-PanNETs are less prevalent (1) with an annual incidence of 1–5 per 100,000 people (16). As seen in *Table 1*, the incidence of the all F-PanNETs varies, and so do the preoperative workup, management, and outcomes. All F-PanNETs should be respected. The following sections will focus on specific F-PanNETs.

Insulinomas

Insulinomas can be visualized by cross-sectional imaging,

but are often <2 cm, with workup being prompted by the clinical syndrome produced. Despite the multiple imaging modalities available, 20–50% of insulinomas are not localized preoperatively (47,48). Surgical resection is the treatment of choice for insulinomas. Preoperative management as shown in *Table 1* includes Diazoxide to inhibit the release of insulin, promote glycogenolysis, palliate Whipple's Triad, and is used for palliation in patients with advanced disease (16). Although, octreotide is used to control the symptoms of many functional PanNETs, for insulinomas, it can be dangerous if used as initial treatment as it can exacerbate the hypoglycemic episodes. Enucleation can be used for lesions that are exophytic and away from the main pancreatic duct due to the relative low incidence of lymph node involvement. For any lesion close to the pancreas duct, having a larger size, or if there is evidence of local invasion or nodal involvement, a formal pancreatectomy is warranted. In the OR, if a discrete tumor is not identified, a pancreatic biopsy should be taken to rule out other disease etiologies such as beta cell hyperplasia or adult nesidioblastosis, and the procedure should be aborted. If a lesion is still suspected, intraoperative ultrasound can help identify lesions in up to 90% of cases (47,48). With routine use of cross-sectional imaging, these scenarios are rare.

Gastrinomas

Approximately 75% of gastrinomas are sporadic, while the remaining are associated with Multiple Endocrine Neoplasia Type-1 (MEN1). Gastrinomas are most commonly malignant (60–90%), and distant metastases, particularly to the liver, is the strongest predictor of long-term survival (17). With surgical resection though, 15-year disease free survival can reach up to 98% (49). During workup of gastrinomas, proton pump inhibitors, histamine-2 receptor blockers, and somatostatin may be necessary, with the occasional use of Carafate to decrease gastrin hypersecretion to prevent gastric or duodenal perforation.

Surgical resection for gastrinomas always includes a formal pancreatectomy with regional lymph node dissection due to a high rate of nodal metastasis at operation. Intraoperatively, a thorough exploration should be performed and include ultrasound of the liver and pancreas with kocherization of the duodenum. If the lesion still cannot be found despite a clinical diagnosis, at the time of exploration, a lateral duodenotomy is performed with digital palpation for duodenal tumors, and peritoneal exploration

for extra-pancreatic locations. Prior to performing a duodenotomy, endoscopy with transillumination should be performed first as creating a duodenotomy prevents subsequent insufflation.

VIPomas

Vasoactive Intestinal Polypeptide (VIP)-secreting tumors (VIPomas) are rare tumors as seen in *Table 1*. They are located 80–95% of the time in the pancreas, while 10% are localized to the periganglionic, adrenal, or neural regions (50,51). Typical preoperative imaging modalities are used, but portal venous sampling can be used to confirm pancreatic location. Preoperatively, patients need to be resuscitated to correct electrolyte derangements commonly associated with the diarrhea including hyponatremia, hypokalemia, and a metabolic acidosis. Additionally, octreotide can be used to control symptoms in preparation for the operating room. Surgical resection with a formal pancreatectomy is the treatment of choice with regional lymph node dissection due to the high incidence of malignancy.

Glucagonomas

Glucagonomas have a low incidence however, 70% of patients at the time of diagnosis have necrolytic migratory erythema, and 70% of glucagonomas are malignant and frequently have metastasis at diagnosis (18). Labs can assist in diagnosis but is typically confirmed by biopsy of the necrolytic migratory erythema (52). Surgical resection with regional lymph node dissection is the treatment of choice and consideration can be given to perform a metastasectomy when possible. For patients with necrolytic migratory erythema, somatostatin analogues can be used for treatment.

Somatostatinomas

Somatostatinomas are typically malignant and can be found in the duodenum, pancreas, or jejunum. Soga *et al.* showed that 5-year OS following resection is 100% for localized disease (19). They are typically large, solitary lesions located in the head of the pancreas and identifiable on cross-sectional imaging. Surgical resection of the lesion remains the primary treatment. Due to the increased incidence of cholelithiasis in patients with somatostatinoma should undergo a cholecystectomy at the time of resection.

Surgical management of PanNETs with genetic associations

PanNETs can be associated with an inherited genetic abnormality, and the most common associations include MEN1, von Hippel-Lindau disease (VHL), tuberous sclerosis (TS), and von Recklinghausen Disease—Neurofibromatosis 1 (NF1) (20). When a patient is diagnosed with PanNET, a thorough family history should be performed, and genetic counseling considered. Additionally, their surgical management is complicated by the potential requirement for multiple resections predisposing patients to endocrine insufficiencies such as diabetes (39). MEN1 will be discussed separately.

VHL is an autosomal dominant mutation in the *3p25* gene with an incidence of PanNETs in 10–17% of patients. Patients present younger and greater than 98% are non-functional (53). They are also prone to the development of pancreatic cysts which makes imaging the pancreas difficult. Concurrent diseases in VHL include hemangioblastomas, retinal angiomas, pheochromocytomas, and clear cell renal carcinomas. Surgical resection is recommended like for sporadic PanNET patients. Blansfield *et al.* reviewed outcomes of 108 patients with VHL and PanNETs, and recommended observation if lesions were less than three centimeters, had a low mutational burden of exon 3, and slow doubling time (54). They recommend screening with cross-sectional imaging of PanNETs meeting these criteria every 6–12 months.

TS and NF1 are two less common genetic associations with PanNETs. TS is caused by an autosomal dominant mutation in 9q34 and is associated with the rare (1 per 10,000) development of PanNETs. These are most commonly non-functional malignant PanNETs. Management is the same as sporadic PanNETs.

NF1 is a mutation in a tumor suppressor protein on 17q11.2, and these patients commonly develop pheochromocytoma. PanNETs in NF1 are rare (7 reported to date) (55), and management is the same as sporadic. Preoperative workup should include ruling out pheochromocytomas as missing this lesion could result in disastrous intraoperative complications.

Surgical management of PanNETs associated with MEN1

MEN1 is an autosomal dominant genetic abnormality and caries a prevalence of PanNET of 1–10 per 100,000 patients. Additionally, 20–25% of patients diagnosed with gastrinomas and 4% of patients with insulinomas have MEN1 (20). MEN1 is also associated with pituitary adenomas, parathyroid lesions, and PanNETs, with the most common functional lesion being gastrinomas. These patients often have multifocal microscopic functional and/or non-functional PanNETs at time of diagnosis.

MEN1 most commonly presents in patients during their second to third decades of life and primary hyperparathyroidism is typically the first endocrine disorder diagnosed. Following workup and treatment of hyperparathyroidism, they should be assessed for PanNETs, which occur in 50–75% of patients with MEN1 (56). Currently, guidelines recommend screening with MRI or CT for PanNETs in MEN1 patients beginning at ten years old and subsequently every ten years. Biochemical screening starts at 20 years old (56). Malignant degeneration of PanNETs with subsequent metastasis is the most common cause of death (56). Patients typically present at an earlier age with PanNETs, and the majority are gastrinomas. Surgical management is controversial as they will often recur, and resection is rarely curative.

For MEN1 patients with a gastrinoma, only rarely is a solitary lesion identified as they are often multiple and scattered throughout the pancreas. For these patients, surgery does remain an option. Originally described by Dr. Norman Thompson, the Thompson Procedure involves performing a DP for body tail lesions, enucleation of head lesions, duodenotomy for excision of duodenal gastrinomas, and lymph node dissection. This procedure aims to avoid pancreatic endocrine and exocrine insufficiency associated with the surgical alternative i.e., TP (52). From Thompson's initial description in 1996, he described 68% of patients were eugastrinaemic at 19-year follow-up. Additionally, only one patient had recurrence requiring hepatic resection and there was no mortality associated with the surgery.

Patients who have MEN1 and known hyperparathyroidism, parathyroidectomy has been proven to reduce end organ effects of hypergastrinemia and is often performed before a pancreatectomy (57). Additionally, symptoms from gastrinomas can be well controlled with anti-acids (58). The second most common functional PanNET associated with MENI are insulinomas. Like for sporadic insulinomas, treatment consists of surgical resection, but more aggressive surgical management should be undertaken with resection due to their higher incidence of malignancy in MEN1.

MEN1 is also associated with NF-PanNETs. Almost all patients with MEN1 have multi-focal, asymptomatic

NF-PanNETs (20,59). They confer a worse prognosis than F-PanNETs, and malignant PanNETs are the most common cause of death in patients with MEN1 (14). Currently ENETs recommends surgical resection for radiographically visible PanNETs, but due to the high rate of recurrence and risk for insufficiencies strategies should be individualized (34).

Resection versus observation?

Surveillance for PanNETs that do not meet obvious criteria for surgery remains a controversial area with mixed evidence for optimal management. This group are typically nonfunctional lesions <2 cm in size. As a result, there are no official guidelines or recommendations. Bettini *et al.* found that NF-PanNET size is correlated with malignancy, with only 6% of PanNETs <2 cm being malignant (60). In contrast, Gratian *et al.* showed, 5-year OS for surveillance *vs.* partial pancreatectomy to be 27.6% *vs.* 83.0% for PanNETs less than two centimeters using the National Cancer Database (NCDB) (8).

All in all, there is concern regarding the morbidity associated with pancreatic resections; therefore, the risks and benefits of surgical management versus surveillance must be weighed. Kazanjian *et al.* found that among 70 patients that underwent resection for PanNETs, complications occurred in 48% of patients undergoing PD, 12.5% after DP, and 0% in those undergoing enucleation (61).

In contrast, Sadot *et al.* in a matched case-control study of 104 patients with PanNETs <2 cm who underwent observation versus 77 patients with resection at initial diagnosis showed no evidence of metastasis or death from disease in the observed group (62). They did find that 26 of the 104 observation patients eventually underwent surgery with a median of 30-month observation for patient preference, increase in tumor size, physician's preference, and/or pancreatic ductal dilatation. This demonstrated that observation can be feasible in the carefully selected patient with small PanNETs and is supported by multiple other studies (62).

The rate of screening for changes in tumor size or new concerning features is still debatable. EUS or cross-sectional imaging is the preferred surveying studies. The ENETs Guidelines recommend surgical intervention if lesions increase in size by 0.5 cm over a period of 6 to 12 months (34). This is an area that needs more studies however, the data does show it is safe to observe patients with small NF-PanNETs and Ki-67 <2% if patients have no genetic abnormalities or family history.

The Asymptomatic Small Pancreatic Endocrine Neoplasms (ASPEN) Trial in Europe is currently examining the best treatment for sporadic asymptomatic non-functioning pancreatic neuroendocrine neoplasms (NF-PNEN) ≤2 cm (63).

At the University of Cincinnati, resection is recommended for NF-PanNETs ≥2 cm and a multidisciplinary discussion is performed for lesions between 1–2 cm.

Surgical management of locally advanced (non-metastatic) PanNETs

PanNETs that are larger than 2 cm, invasive, or have radiographically evident positive lymph nodes are classified as locally advanced. Surgical management for these patients by the NCCN guidelines includes PD or DP with splenectomy and regional nodes based on tumor location if complete resection is possible (41). Patients with resectable localized disease have a median survival of approximately 7.1 years compared to those with locally advanced without undergoing resection have a median survival of 5.2 years (64).

In 2014, aggressive surgical resection for locally advanced PanNETs is possible even when tumors involve the portal or superior mesenteric vein as long as revascularization is achievable. Birnbaum *et al.* showed in a multi-institutional study, the role of extended resections for PNETs in 134 patients. They found among patients that underwent extended resection for local and/or metastatic disease severe morbidity was 21% and mortality was 5% (65). At the time of resection, ion, due to the likely use of somatostatin analogues postoperatively, cholecystectomy is recommended. In patients with locally advanced resectable disease, neoadjuvant systemic therapy is often utilized to test disease biology and potentially downstage tumors.

For patients that have a local recurrence, aggressive surgical management is still possible and result in improved long-term survival (66).

The data for locally advanced, non-metastatic disease is not sufficient to support debulking surgery. However, bypass operations for patients with severe symptoms including gastric outlet obstruction and biliary obstruction should be considered when endoscopic procedures are not possible.

Surgical management of metastatic PanNETs

Up to 77% of patients with PanNETs develop liver metastasis (67). Initial management of these patients begins with determining the differentiation of the tumor. Well-

Table 2 World Health Organization 2017 classification system

Classification	Differentiation	Grade	Ki67 (% of ≥500 cells)	Mitotic rate (2 mm^2)
PanNET	Well differentiated	G1	<3	<2
		G2	3–20	2–20
		G3	>20	>20
PanNEC[a]	Poorly differentiated	G3	>20	>20

Information from "Inzani F, Petrone G, Rindi G. The New World Health Organization Classification for Pancreatic Neuroendocrine Neoplasia. *Endocrinol Metab Clin North Am* 2018;47:463-70." . [a], PanNECs are further subclassified as large cell type and small cell type based. PanNET, pancreatic neuroendocrine tumor; PanNEC, pancreatic neuroendocrine carcinoma.

differentiated lesions that are G1 or G2 are potential candidates for metastatectomy (*Table 2*). Additionally patients with functional, resectable liver metastasis, absence of extra-hepatic intraabdominal disease, or Carcinoid syndrome are candidates for resection (34).

Sarmiento *et al.* first examined the feasibility of hepatic resection in 2003 showing that among 170 patients that underwent hepatic resection for metastatic PanNETs, 96% of patients had partial or complete response to their hormonal symptoms (68). Recurrences did occur in 84% of patients at 5 years and OS was 61% at 5 years. Following this in 2009, a Cochrane systemic review examined the benefit of cytoreductive surgery in patients with unresectable liver metastases. They found that there was insufficient data to recommend cytoreductive surgery (69,70). In 2012, Cusati *et al.* examined the outcomes of 72 patients with metastatic PanNETs that underwent R0 *vs.* R1 (>90%) resection. They found no significant differences in 5-year overall or disease free survival (21-23). Despite these data, current guidelines recommend that resection for metastatic PanNETs should be considered only when R0 resection it possible with "debulking surgery" remaining controversial.

In addition to hepatic resections, radiofrequency ablation (RFA), arterial embolization, and transarterial chemoembolization (TACE) are alternatives that are used to treat patients with metastatic disease (24). For patients with metastatic or locally advanced unresectable disease, systemic chemotherapy with streptozocin and doxorubicin or 5-flurouracil, everolimus, and long acting octreotide are treatment options (41).

Orthotopic liver transplantation (OLT) is a controversial subject in management of patients with metastatic PanNETs. The NCCN practice guidelines state OLT as investigational for metastatic PanNETs. Although a meta-analysis showed that OLT may provide survival

benefit, patient selection is critical due to the high rates of recurrence and scarcity of grafts (25,26).

Surveillance and adjuvant therapy

Recurrence following resection of a PanNET occurs in approx. 12–15% of patients and is linked with reduced OS (27,28). Focus has been shifted to detecting recurrence early and developing potential salvage therapies. Consensus guidelines currently vary in recommendations on surveillance post resection. NANETs recommend cross-sectional imaging 3 to 6 months initially, followed by every 6 to 12. ENETs and others tailor imaging based on tumor grade varying from 3 to 6 months on severity for life.

Recently, Zaidi *et al.* established a recurrence risk scoring system (RRS) from 1,006 international patients. They found that tumors >2 cm, Ki67 >3%, positive lymph nodes, and symptomatic tumors were predictive recurrence (*Table 3*) (71). Their RRS stratified patients into three categories and found a 33% predictability of recurrence in their high-risk group versus 2% and 14% in their low and intermediate-risk groups respectively.

Additionally, Dong *et al.* have studied predictive factors for patterns and time of recurrence following curative resection (28). In the retrospective review, of the 1,020 patients that underwent curative resection, 53.3% had recurrence within two years. They found that 49.4% recurred in the liver, 22.7% pancreatic, and the remaining in multiple other organs. Tumor factors that were predictive of liver recurrence included Ki-67, perineural invasion, and major vascular resection, while pancreatic recurrences were only associated with positive surgical margins.

Because of the high risk of recurrences, patients should undergo follow up every 3–12 months or sooner should the patients develop any symptoms. This evaluation includes a history and physical, biochemical testing, and cross-

Table 3 Summary of risk factors for PanNET recurrence

Variable	HR or OR (95% CI)	P value
Pancreas-only		
R1 versus R0 resection	5.12 (1.74–15.4)	0.003
Liver-only		
Ki-67 3–20%	2.85 (1.05–7.73)	0.0400
Ki-67 >20%	6.98 (1.21–4.35)	0.030
Perineural invasion	3.66 (1.53–8.72)	0.003
Major vascular resection	3.23 (1.13–9.23)	0.029
Any recurrence		
Underlying genetic syndrome	2.49 (1.19–5.20)	0.015
Ki-67 >20%	5.29 (1.57–17.79)	0.007
High-grade (G3)	1.43 (1.03–3.62)	0.040
Perineural invasion	2.38 (1.111–5.07)	0.026
Vascular invasion	3.45 (1.46–8.17)	<0.01
Symptomatic tumors (jaundice, pain, bleeding)	1.9 (1.1–35)*	0.041
Tumors >2 cm	2.6 (1.2–5.4)*	0.011
Ki67 >3%	6.7 (1.6–28.5)*	0.010
Positive lymph node disease	1.9 (1.1–3.6)*	0.039

*, denotes OR with (95% CI).

sectional imaging for every 6–12 months with increased vigilance the first two postoperative years.

Currently there are no recommendations for adjuvant therapy for resectable PanNETs.

The Eastern Cooperative Oncology Group (ECOG) Trial E2211, tested the combination of adjuvant capecitabine and temozolomide in patients with advanced PanNETs (72). They found that patients had improvement in OS and progression-free survival. Based on these data, there are currently studies under way to examine the benefits of adjuvant capecitabine and temozolomide in patients with high risk resectable PNETs (high Ki-67, lymph node positive, high grade, and lymphovascular invasion).

In the advanced setting and for recurrences, treatment with long acting octreotide analogues, mTOR inhibitors (Everolimus) and cytotoxic systemic chemotherapies is standard of care (73). Recently, the use of peptide receptor radionucleotide therapy with ^{177}Lu-Dotatate for advanced

midgut NETs was performed and found an improvement progression free survival compared to octreotide alone (74,75).

Conclusions

PanNETs are a heterogenous group of tumors that vary in type, workup, surgical management and outcomes. With the increasing incidence of these lesions, knowledge of the disease biology, genetic associations, perioperative management/workup, and novel treatment strategies under way are crucial for the surgeon.

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Footnote

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