Nonfunctional Pancreatic Neuroendocrine Tumors

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KEYWORDS

• Pancreas • Neuroendocrine • Nonfunctional • Neuroendocrine liver metastases
• PanNET

KEY POINTS

- Pancreatic neuroendocrine tumors are rare, heterogeneous tumors that compose 3% of all pancreatic neoplasms and 7% of all neuroendocrine tumors.
- The incidence of pancreatic neuroendocrine tumors has been increasing over the past 20 years because of the increased diagnosis of pancreatic incidentalomas.
- Ninety percent of pancreatic neuroendocrine tumors are nonfunctional tumors that are often malignant and present with symptoms of mass effect or metastatic disease.
- Formal surgical resection is the treatment of choice for most locoregional disease; however, surgical decision making must include many variables.
- Hepatic metastasis is common, and resection is recommended in the absence of extrahepatic disease.
- Interventional liver-directed therapies and targeted systemic therapies offer promising alternatives for patients with advanced disease, improving morbidity and increasing progression-free survival.

INTRODUCTION

Neuroendocrine tumors (NETs) are a group of rare, diverse neoplasms, which can be found throughout the body. They are most commonly located in the gastrointestinal tract and lung but are also found in the pancreas.[1] Historically known as islet cell tumors, they are now classified as pancreatic NETs (PanNETs) by the World Health Organization (WHO). When compared with adenocarcinomas, PanNETs account for a relatively small percentage of pancreatic neoplasms,[2,3] but their incidence has been increasing over the past 20 years. Based on the Surveillance, Epidemiology, and End Results (SEER) database, the incidence of NETs in the United States increased

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Surg Clin N Am 94 (2014) 689–708
http://dx.doi.org/10.1016/j.suc.2014.02.010 **surgical.theclinics.com**
0039-6109/14/$ – see front matter

nearly 5-fold over the past 3 decades and was 5.25 per 100,000 in 2004.[4] PanNETs account for 7% of all NETs[5] and have an incidence of 0.43 per 100,000 people in 2007,[5] a greater than 2-fold increase in the incidence of PanNETs since the 1980s. The increased frequency of abdominal imaging, specifically computed tomography (CT) and ultrasound, has increased the incidence of abnormal pancreatic findings detected in asymptomatic patients. Of these patients, 17% will ultimately undergo pancreatectomy.[6] This increase in pancreatic incidentalomas may reflect a historical underestimation of the prevalence of this disease; autopsy studies suggest that the prevalence of PanNETs may be higher than we expect, with prevalence rates of 3% to 10%.[7–9]

RELEVANT ANATOMY/PATHOPHYSIOLOGY

Traditionally, PanNETs have been thought to arise from the islets of Langerhans that perform the endocrine function of the pancreas. More recent investigation, however, has demonstrated that these neoplasms originate from pluripotent cells in the pancreatic ductal/acinar system.[10] All PanNETs express neuroendocrine markers, such as synaptophysin, neuron-specific enolase, and chromogranin A (CgA) (present in 88%–100% of patients with PanNETs). A multitude of cellular and molecular alterations have been implicated in the pathogenesis of PanNETs, involving at least 14 different types of cells and genetic alterations in the MEN-1 gene, the p16/MTS1 tumor-suppressor gene, the DPC4/Smad 4 gene, amplification of the Her-2/neu proto-oncogene, and alterations in transcription factors Hox C6, growth factors, and their receptor expressions.[11] Several of these genetic alterations have been shown to correlate with tumor aggressiveness and may have prognostic significance.[12] This molecular heterogeneity translates to heterogeneity in the clinical presentation, including both the multiple syndromes of overproduction and hypersecretion of hormones that have traditionally characterized these tumors as well as hormonally silent tumors. Thus, PanNETs are often classified as functional or nonfunctional based on the presence or absence of a particular clinical syndrome associated with hormone hypersecretion. According to the SEER database, from 1973 to 2000, most PanNETs diagnosed were nonfunctional tumors (90.8%); the remaining 9% included malignant functional tumors, such as gastrinomas (4.2%), insulinomas (2.5%), glucagonomas (1.6%), and VIPomas (0.9%).[13,14] In addition to variability in the production of pancreatic endocrine hormones, PanNETs exhibit a broad range of growth rates, malignant potential, and overall prognosis. Although commonly perceived to be indolent tumors because they have a far better prognosis than pancreatic adenocarcinoma, most patients with PanNETs (60%–70%) present with metastatic disease.[4,13,14] Even when they are resectable, many patients ultimately succumb to the disease. Following surgical resection of PanNETs, the 5-year survival for PanNETs other than insulinomas is roughly 65%, with a 10-year survival of 45%.[14]

In 2000, the WHO introduced a classification system based on clinical and histopathologic features that divides PanNETs into well-differentiated endocrine tumors with either benign or uncertain behavior, well-differentiated endocrine carcinomas, or poorly differentiated endocrine carcinomas.[15] More recent classification systems have acknowledged the increasing importance of a proliferative index, specifically expression of the nuclear antigen Ki-67, and evidence of its prognostic value for PanNET.[15–17] In 2010, the WHO revised the classification of PanNETs to reflect a proliferation-based grading system in conjunction with the traditional histopathologic diagnostic criteria (**Table 1**). They delineated a 3-tier grading system of PanNETs designating tumors as well-differentiated NETs versus poorly differentiated

Table 1
WHO classification of PanNETs

Grade	Ki-67 Index (%)	Mitotic Count/10 HPF
G1	≤2	<2
G2	3–20	2–20
G3	>20	>20
TNM	**Size (cm)**	**Muscularis Propria Invasion**
T1a	<1	–
T1b	1–2	–
T2	>2	+

In the World Health Organization (WHO) 2010, the higher grade is assumed if the Ki-67 index and mitotic count differ; in the WHO 2010 TNM, the tumor is classified as T2 if it is larger than 2 cm in diameter or if it invades the muscularis propria. T3 and T4 tumors are locally aggressive tumors (data not shown in the table).

Abbreviation: HPF, high-power field.

Data from Bosman F, Carneiro F, Hruban R, editors. WHO classification of tumors of the digestive system. Lyon (France): IARC Press; 2010.

neuroendocrine carcinomas. The well-differentiated NETs were further divided into grade 1 (Ki-67 <2%) and grade 2 (Ki-67 of 2%–20%). The poorly differentiated tumors are considered grade 3 (Ki-67 >20). Mitotic rate or Ki-67 should be assessed on all PanNETs. When both mitotic rate and Ki-67 are obtained, the higher grade is assigned. If the biopsy specimen is inadequate, a repeat biopsy is recommended.[18]

The European Neuroendocrine Tumor Society (ENETS) and the American Joint Committee on Cancer (AJCC) describe alternative classification systems for PanNETs. The ENETS' classification[19] for PanNETs combines a staging TNM classification including the tumor diameter along with a grading system based on the mitotic rate and Ki-67.[20] The AJCC's TNM classification is based on a staging system for exocrine pancreatic adenocarcinomas, differentiating tumors based on the extent of disease rather than the tumor grade to determine tumor resectability.[20] Although both systems emphasize different tumor characteristics, both classification systems have been demonstrated to be prognostic for relapse-free survival.[20] It is important to note that histopathology is not always predictive of malignancy, and the only true measures of whether a PanNET is benign or malignant include evidence of local invasion, metastases, and/or recurrent disease.

CLINICAL PRESENTATION

Most PanNETs are sporadic and tend to affect older individuals. Men have a slightly increased risk of developing PanNETs than women (55.2% vs 44.8%), and there is a Caucasian predominance in the United States (84.1% Caucasian vs 15.9% other background).[13] Functional tumors present with symptoms that result from the specific hormone being elaborated. The most common functional PanNETs are insulinomas composing 30% to 45% of functioning PanNETs[2,21] and gastrinomas composing 16% to 30%.[21] Glucagonoma, VIPomas, and somatostatinomas are rarer PanNETs, and other rare functional PanNETs also exist.[22] The presentation of these tumors is summarized in **Table 2** but is not discussed in further detail in this article.

Patients with nonfunctional tumors typically present with symptoms related to local mass effect or metastatic disease, indicating a more advanced stage of disease.[9]

Table 2
Summary of functional NETs

Tumor Type	Number[a]	Secretory Hormone	Clinical Features	Laboratory Tests	Symptomatic Treatment
Insulinoma	40%–60%	Insulin	Hypoglycemia; symptoms of catecholamine excess; 90% benign	Insulin level, C-reactive protein; 72-h inpatient fasting with monitoring of glucose and insulin levels	Dietary modifications; octreotide; diazoxide
Gastrinoma	20%–50%	Gastrin	Peptic ulcer disease; GERD; secretory diarrhea; most common PanNET in MEN-1; 60%–90% malignant	Fasting serum gastrin; gastric pH analysis, gastrin provocation testing (calcium or secretin challenge)	Proton pump inhibitor; octreotide
Glucagonoma	Rare	Glucagon	Glucose intolerance; migratory necrolytic erythema; weight loss; anemia; 90% malignant	Serum glucagon	Octreotide; insulin; zinc supplement (rash); TPN (malnutrition)
Somatostatinoma	Rare	Somatostatin	Diabetes; gallstones; secretory diarrhea	Clinical and pathologic diagnoses; increased somatostatinlike immunoreactivity in resected tumor	Octreotide
VIPoma	Rare	Vasoactive intestinal peptide	Choleralike, secretory diarrhea; hypokalemia; hypochlorhydria	Serum VIP	Octreotide

Abbreviations: GERD, gastroesophageal reflux disease; MEN-1, multiple endocrine neoplasia type 1; TPN, total parenteral nutrition; VIP, vasoactive intestinal polypeptide.

[a] Percentage among PanNETs.

Nonfunctioning tumors either do not produce any hormone, produce very small amounts of hormones that are insufficient to produce symptoms, or produce hormones that do not generate specific symptoms (pancreatic polypeptide, human chorionic gonadotropin subunits, calcitonin, or neurotensin).[23,24] Most nonfunctional tumors occur in the head of the pancreas and often produce symptoms of mass effect that mimic those of pancreatic adenocarcinoma, including jaundice, abdominal pain, weight loss, abdominal mass, nausea and vomiting, backache, and pancreatitis.[22,25,26] As previously mentioned, the number of pancreatic tumors discovered incidentally before any onset of symptoms is dramatically increasing because of the widespread use of abdominal imaging.[6,9,23] Bruzoni and colleagues[27] found that 19% of these pancreatic incidentalomas were NETs on the final pathology.

Although most PanNETs occur sporadically, nearly 10% are associated with predisposing genetic syndromes. These hereditary syndromes include multiple endocrine neoplasia type 1 (MEN-1 syndrome), von Hippel-Lindau disease (VHL), von Recklinghausen disease or neurofibromatosis type 1 (NF-1), and tuberous sclerosis complex (TSC).[2,9,14,21] These patients are generally diagnosed at a younger age, have multiple synchronous lesions throughout the pancreas, and have a family history of endocrine disorders or their associated cancers.[9,21] The most recognized of these hereditary syndromes is MEN-1.[2,9,14,21] Most patients with MEN-1 (80%–100%) develop nonfunctioning PanNETs, 50% to 60% develop gastrinomas, 20% insulinomas, and 3% to 5% VIPomas or glucagonomas.[2,9,14,21] Nonfunctional PanNETs, cystic pancreatic lesions, and mixed serous-NETs can be seen in 20% of patients with VHL.[2,14,21] In contrast to MEN-1 and VHL, PanNETs are relatively uncommon in patients with NF-1 and TSC (<10%).[2,14,21]

The evaluation of patients with PanNETs should include a comprehensive history assessing for signs or symptoms of tumor mass effect, metastatic disease, or specific functioning tumors. Eliciting a family history or genetic testing can determine whether the tumor is sporadic or associated with a genetic syndrome and can have a significant impact on preoperative planning. For example, patients with MEN-1 are more likely to have multiple tumors throughout the pancreas necessitating altered surgical planning.

DIAGNOSIS

When a tumor of neuroendocrine origin is suspected, a complete biochemical evaluation looking for the most commonly secreted pancreatic hormones should be performed to determine functionality. Levels of NET markers can be very helpful for diagnosis and determining the prognosis of nonfunctional PanNETs.[2,11] Serum chromogranin A, a 49-kd protein contained in the neurosecretory vesicles of the NET cells, is the most widely used as it reflects tumor burden. It is most helpful for well-differentiated NETs. Elevated plasma chromogranin A levels have been associated with a poor overall prognosis, and early decreases may be associated with favorable treatment outcomes. It can be helpful in screening for persistent, recurrent, or metastatic disease[11]; the recent North American Neuroendocrine Tumor Society's management guidelines recommend following chromogranin A levels in patients with advanced disease and in patients who have elevated CgA levels at diagnosis and to consider following levels in those who have undergone resection.[18] Elevated CgA levels can also be caused by renal or liver failure and the use of proton-pump inhibitors.

The PP cells of the islets of Langerhans secrete pancreatic polypeptide. It is found to be elevated in 63% of PanNETs[28] but has not been widely used because of its low

sensitivity. However, high pancreatic polypeptide levels at baseline may be useful in identifying false-negative CgA determinations in the diagnosis of PanNETs and has a high specificity for follow-up in predicting controlled disease (84%).[29] When there is concordance of CgA and PP levels in follow-up, the ability to predict an increase in tumor burden is increased (from 51%–54% independently to 81% together).[29] The diagnostic accuracy of CgA and PP may be lower in the MEN-1 patient population.[30]

Pancreastatin, a posttranslational fragment of CgA, has shown diagnostic value in monitoring carcinoid tumors. Its levels are not influenced by decreased acid production and, thus, may lead to fewer false-positive determinations. Recent studies have shown some promise in using pancreastatin as a diagnostic and prognostic tumor marker for NETs.[31]

Neuron-specific enolase (NSE) is another tumor marker that is found to be elevated in 50% of NETs, most commonly in pulmonary NETs. High levels of NSE have been associated with poorly differentiated NETs.[32] Synaptophysin, glucagon, progastrin-releasing peptide, and cytokeratin fragments have all been evaluated as potential tumor markers but have low sensitivity for detecting NETs.[33]

Screening for MEN-1 with measurement of parathyroid hormone and calcium levels is also recommended given the high prevalence of PanNETs (80%–100%) in this patient population.[2,23]

DIAGNOSTIC PROCEDURES

The diagnosis of PanNETs centers on biopsy and staging of the disease. Cross-sectional imaging studies with either a multiphasic CT scan or magnetic resonance imaging (MRI) dedicated to the evaluation of the pancreas play a key role.

CT

- It is recommended for the initial evaluation of PanNETs.
- PanNETs are well circumscribed, hypervascular lesions (**Fig. 1**).
- It has a sensitivity of 80% to 100% (decreased in tumors smaller than 2 cm, but most symptomatic nonfunctioning tumors are >3 cm).

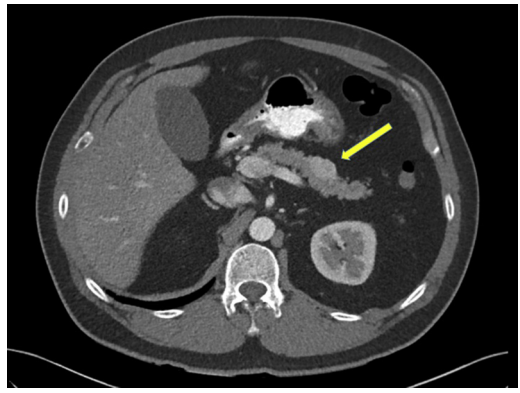

Fig. 1. PanNETs appear as well-circumscribed, hypervascular lesions on CT imaging. CT has a high sensitivity for detecting PanNETs greater than 2 cm in size and offers excellent anatomic and spatial detail. *Arrow* points to neuroendocrine tumor.

- The sensitivity of contrast-enhanced CT approaches 100% (imaging study of choice).
- Dual-phase (arterial and portal) imaging detects pancreatic neoplasms and delineates local vascular anatomy.
- Oral contrast allows optimum visualization of the duodenum, improving the detection of duodenal gastrinomas.

MRI

- PanNETs are typically characterized by low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. (Tumors <1 cm are not detected by MRI with gadolinium; 50% of tumors between 1 and 2 cm are identified.)[34]
- Larger tumors can be visualized without contrast.
- It has a greater sensitivity for liver metastases than CT or somatostatin receptor scintingraphy.[35]

Endoscopic Ultrasonography

- Able to detect small tumors as small as 2 to 3 mm in diameter
- Sensitivity of 79% to 82%, specificity of 95%[36,37]
- Enables histologic analysis with endoscopic ultrasonography (EUS)-guided fine-needle aspiration[38]
- Useful in MEN-1 detecting 55% to 100% of nonfunctional PanNETs in asymptomatic patients[39]
- Operator dependent

Somatostatin Receptor Scintigraphy (Indium In Pentetreotide [Octreoscan])

- Uses indium- 111-labeled somatostatin analogue resulting in high-resolution imaging of the pancreas
- Effective for visualizing gastrinomas (100%), glucagonomas, and nonfunctioning pancreatic tumors
- Not sensitive for detection of insulinomas and poorly differentiated NETs
- Additional advantage of whole-body scanning allowing for detection of metastatic disease outside of the abdomen (**Fig. 2**)
- Provides functional information on level of somatostatin receptor expression, which may be used to guide somatostatin-based therapies in patients with advanced disease
- Does not provide information on tumor size or surgical resectability
- Accuracy improved with fusion of somatostatin analogues to positron emission tomography isotopes in single-photon emission CT; allows differentiation between areas of pathologic and physiologic uptake in the abdomen

Fig. 3 provides a simple algorithm summarizing the diagnostic tests for PanNETs. Other diagnostic procedures, including visceral arteriography and selective intra-arterial stimulation, are used to localize occult functional tumors.

SURGICAL MANAGEMENT

Surgical resection is the only curative therapy for functional and nonfunctional PanNETs and is the cornerstone of the treatment of patients with PanNETs without evidence of metastatic disease or significant comorbidities. There is a significant survival benefit in patients with localized, regional, and metastatic disease who undergo resection (average overall survival 114 months vs 35 months) when compared with those

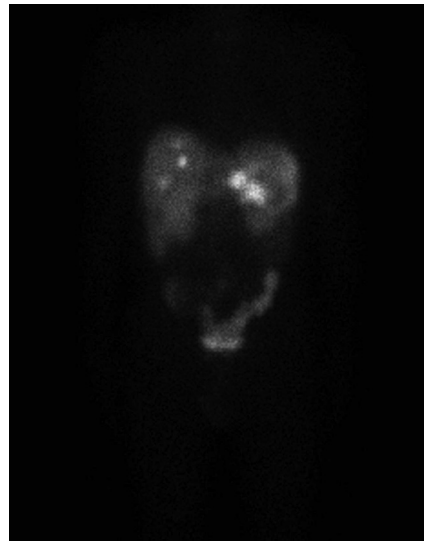

Fig. 2. Somatostatin receptor scintigraphy (indium In 111 pentetreotide [Octreoscan]) allows whole-body imaging and is sensitive for detecting metastatic disease, especially outside of the abdomen. It also allows assessment of somatostatin receptor expression levels that can be used to guide systemic therapy.

who did not undergo surgery.[40] Thus, surgical therapy should be considered if most (approximately 90%) of the gross disease can be resected safely. The primary exception to this rule is PanNETs associated with MEN-1 and Zollinger-Ellison syndrome whereby tumors tend to be multiple and nonfunctional and may warrant close surveillance and/or symptom management.

Given the variable biology and behavior of PanNETs, deciding on the appropriate surgical therapy requires taking into account a myriad of factors, including risk of malignancy, presence/absence of metastases, as well as the patients' overall health and wishes. **Fig. 4** summarizes an algorithm that provides guidance on the surgical treatment of patients with solitary PanNETs. In general, nonfunctional PanNETs should undergo resection. However, evidence is emerging that with more accurate pathologic analysis of biopsy material, there are situations when small lesions can be observed. Most nonfunctional PanNETs are malignant as manifested by local invasion, lymph node involvement, and/or liver metastases. Patients without evidence of metastatic disease should be treated with formal resection and lymphadenectomy. Patients with low-grade metastatic disease should be treated with surgical resection (including resection of metastatic sites) in conjunction with adjuvant therapies, such as ablation, embolization, hormonal therapy, and chemotherapy. Patients with high-grade metastatic disease should receive medical therapy, often including cytotoxic chemotherapy.

All nonfunctional PanNETs greater than 3 cm should be resected if possible. Controversy exists as to whether enucleation is sufficient resection for nonfunctional PanNETs smaller than 3 cm. In a retrospective review of 318 patients with sporadic, nonfunctional, nonsyndromic PanNETs resected at a single institution, 9% to 37% of tumors less than 3 cm in size were associated with lymph node metastases. They also found on multivariate analysis that the presence of positive lymph nodes conferred a poorer survival.[41] Therefore, formal resection is preferred over enucleation

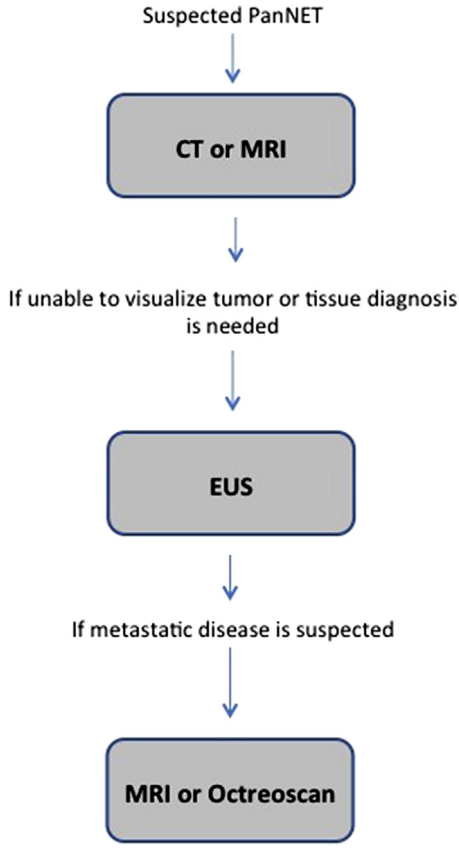

Fig. 3. Algorithm for diagnostic tests.

for nonfunctional PanNETs smaller than 3 cm in size. However, enucleation may be appropriate in elderly patients or those with significant comorbidities, a tumor with a low proliferative index, and patients who do not wish to have a formal resection.[42] Central pancreatectomy is another parenchyma-sparing procedure that can be considered for small benign lesions.[43]

For even smaller tumors less than 2 cm, surgical resection may not necessarily be mandated. The ENETS' guidelines state "no data exist with respect to a positive effect of surgery on overall survival in small (<2 cm), possibly benign or intermediate-risk pancreatic endocrine tumors" and advocate careful balancing of surgical risk before proceeding to resection over observation.[44] Lee and colleagues[45] described a cohort of 67 patients with small (median size 1 cm), incidentally found nonfunctional PanNETs who were observed for a median of 45 months. There were no cases of disease progression over this observation period. Therefore, for small tumors less than 2 cm with a low proliferative index (Ki-67), observation may be an appropriate option. **Table 3** summarizes the surgical options for management of PanNETs.

There have been descriptions and small series of minimally invasive approaches to most of the types of pancreatic resections. These approaches include laparoscopic and robotic techniques for both traditional, formal resections like pancreaticoduodenectomy to parenchyma-sparing operations like enucleations and central

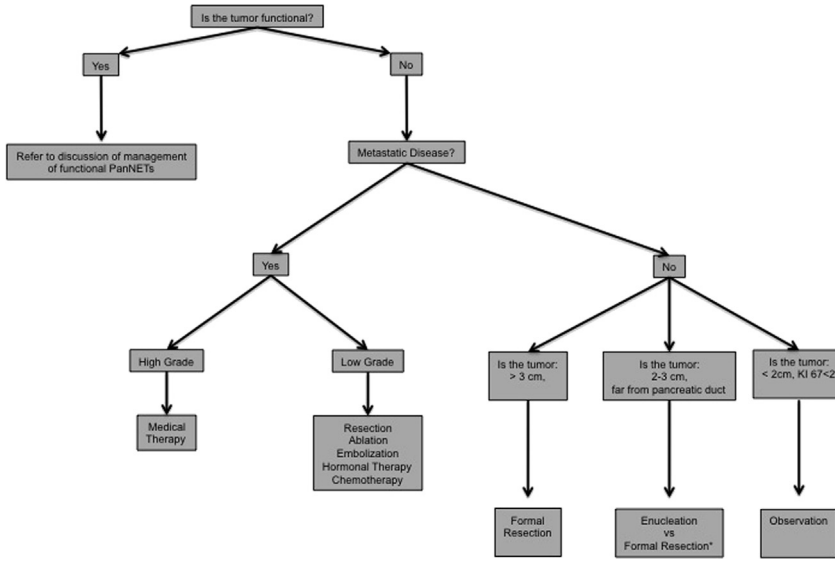

Fig. 4. Decision tree for surgical resection of PanNET. PD, pancreatic duct. * Refer to text for discussion of enucleation versus formal resection.

pancreatectomies. The most commonly performed minimally invasive pancreatic operations are laparoscopic enucleations and laparoscopic distal pancreatectomy. Gagner and colleagues[46] first described their approach to the laparoscopic distal pancreatectomy with spleen preservation for insulinoma in 1996. It has become the gold standard for small, benign lesions or low-grade malignancies. In 2012, a meta-analysis showed that laparoscopic distal pancreatectomy resulted in decreased morbidity (39.3% vs 44.2%), with decreased estimated blood loss by approximately 350 mL and a decreased length of hospital stay by 4 days.[47] They found no difference in operative time, margin positivity, incidence of postoperative pancreatic fistula, and mortality.

Although laparoscopic pancreaticoduodenectomy was described before laparoscopic distal pancreatectomy in 1994,[48] the technique has been slow to gain popularity because of the complex technique and long operative times. However, a recent meta-analysis showed statistically significant differences with respect to less blood loss, lower transfusion rates, lower wound infection rates, lower morbidity rates, and shorter hospital stays. The laparoscopic approach is significantly longer compared with the open approach for pancreaticoduodenectomy.[49] There was no significant difference in oncological outcomes between laparoscopic pancreatectomy and the open technique.[49] Although there is often a learning curve involved, laparoscopic operations can be performed safely and offer a good alternative to formal open operations in the appropriate patients.

Robotic surgery has quickly evolved over the last decade, and several case series describing robotic approaches to distal pancreatectomy and pancreaticoduodenectomy have been published. Cirocchi and colleagues[50,51] reviewed these studies and concluded that although the operative times were longer for robotic distal pancreatectomy and pancreaticoduodenectomy, the robotic technique is feasible with similar morbidity and mortality to the laparoscopic and open techniques and is associated with a decreased length of hospital stay with distal pancreatectomies.[50] They

Table 3
Summary of operative management options for PaNETs

Procedure	Approach	Indications	Contraindications	Outcomes
Traditional resections				
Pancreaticoduodenectomy	Most commonly open Laparoscopic approach gaining popularity Robotic approach being investigated	Large tumors of the pancreatic head, uncinate, or neck	Involvement of the superior mesenteric artery Exclusion based on portal vein involvement may vary by institution	Significant survival benefit in patients who undergo resection[9]
Distal pancreatectomy	Open Laparoscopic	Large tumors of the pancreatic body or tail	Splenic preservation contraindicated for patients with suspected malignancy	Laparoscopic approach affords better postoperative pain, shorter hospital stay, shorter recovery, and better cosmesis[40]
Parenchyma-sparing resections				
Enucleation	Open Laparoscopic	Tumors $\leq$3 cm in size	Large tumors Nodal or metastatic disease Lesions in close proximity to the pancreatic duct	Similar morbidity and 5-y survival as traditional resections[53] Increased rate of pancreatic fistulas but less severe Decreased blood loss, operative time, and length of hospital stay
Central pancreatectomy	Open Laparoscopic	Small, benign, or low-grade tumors of the neck or proximal body of the pancreas	High-grade and/or advanced tumors	Better preservation of pancreas function with similar morbidity and mortality[43]

concluded that randomized trials were needed to compare oncologic outcomes and the cost-effectiveness of these procedures.

MANAGEMENT OF HEPATIC METASTASES

The liver is the predominant site of extranodal metastatic disease in PanNETs and is the predominant cause of mortality in many patients. Resection of hepatic metastases has been shown to improve outcomes in more than 90% of cases.[11,52–54] Survival rates of approximately 60% are reported at 5 years after hepatic metastasectomy compared with 30% in patients with untreated liver metastases,[54,55] with a median survival of 24 to 128 months. In patients without (or mild nonclinically significant) extrahepatic disease, resection should be considered for treatment. Asymptomatic patients who have resectable disease should also be considered for surgical debulking. **Table 4** summarizes the interventional treatment options for hepatic metastases in patients who are not candidates for surgical resection. In general, the use of these treatments either alone or in conjunction with surgical resection is recommended for locoregional control and symptom relief.[56–58] Liver transplantation is a viable option for symptomatic, well-differentiated gastrointestinal NETs when standard surgical resection is not an option or for disease that has not responded to other treatment options. The 5-year survival rate is 45%.[59] However, a primary PanNET was found to be a negative prognostic factor[60]; therefore, liver transplantation is not recommended in the treatment of NETs arising from the pancreas.

SYSTEMIC THERAPY

Patients with high-grade metastatic disease not amenable to surgical resection or liver-directed therapies can be treated with multiple medical therapeutic approaches. The goal of treatment is to improve quality of life and to extend progression-free survival as well as overall survival. Medical treatment can control the associated symptoms and signs of the specific tumors and shrink tumor mass.

Somatostatin Analogues

Octreotide is the prototypical somatostatin analogue used to treat patients with advanced PanNETs. Nearly 80% of NETs express somatostatin receptors as evidenced by radiotracer uptake on Octreoscans, providing an effective means of delivering cytotoxic treatments to neoplastic cells.[61] Radiolabeled somatostatin analogues bind to the somatostatin receptor, and a fraction of the ligand-receptor complex is internalized, delivering targeted radiotherapy to PanNETs.[62] The most frequently used radionuclides for therapy in PanNETs are indium, yttrium, and lutetium, which differ from one another in terms of emitted particles, particle energy, and tissue penetration.[63] Overall, tumor response rates have been reported between 30% and 50%; stable disease following treatment has been reported in up to 70%.[64,65] In the PROMID study, the use of octreotide-LAR (octreotide acetate long-acting injectable solution) increased the time to progression (14.3 months) as compared with placebo (6 months).[66] Stable disease was achieved in 66.7% and 37.2% of patients with octreotide-LAR and placebo, respectively. It was found to be effective in both functioning and nonfunctioning tumors. The duration of the therapy response is reported to be greater than 30 months; when kidney protective agents are used, the side effects of this therapy are few and mild.[65] Ongoing clinical trials are evaluating the efficacy of novel somatostatin analogues (SOM230 or pasireotide) that have 30 to 40 times higher binding affinity to somatostatin receptors than octreotide and lanreotide.[67]

Table 4
Summary of interventional liver-directed therapies for metastatic PaNETs

Treatment	Indications	Contraindications	Approach	Outcomes
Hepatic artery embolization	Palliation of patients who are not candidates for surgical resection Metastasis limited to the liver	Prior pancreaticoduodenectomy Significant hepatic insufficiency Portal vein thrombosis Poor performance status	Bland embolization: infusion of absorbable gelatin sponge (Gelfoam) powder Chemoembolization (TACE): infusion of cytotoxic drugs (doxorubicin, cisplatin, and streptozocin) or use of drug-eluting beads Radioembolization: use of radioactive isotopes (eg, yttrium-90)	Response rates generally exceed 50%[58–60]
Radiofrequency ablation, microwave ablation, and cryoablation	Patients with <10 lesions, each lesion <4 cm in size Small tumors deep in hepatic parenchyma	Large tumors	Used alone or in combination with surgical resection Percutaneous or laparoscopic approach	Morbidity benefit when compared with hepatic arterial embolization Recurrences common, but multiple treatments may be given with good tolerance
Infusional chemotherapy	Uncommon technique Used in conjunction with radiotherapy	Diffuse disease	Percutaneous infusion of 5-FU or melphalan with extraction of the drug from hepatic veins Multiple treatments possible	Good locoregional control with tumor response seen in 80% of patients when combined with radiotherapy[58]

Abbreviations: TACE, trans-arterial chemoembolization; 5-FU, 5-fluorouracil.

Peptide receptor radionucleotide therapy is a newer treatment option that couples cytotoxic drugs to somatostatin analogues to target PanNETs. Initially octreotide was used, but this has been largely replaced by yttrium-90 or lutetium-177 coupled analogues. This treatment has been shown to be effective for both symptom relief and tumor remission. Adverse effects are typically mild and limited primarily to toxicity to the bone marrow and kidneys.[68]

Cytotoxic Chemotherapy

Historically, well-differentiated PanNETs have been resistant to standard chemotherapy, with reported response rates varying from 8% to 45%.[69] Because of the limited efficacy of these agents, they were often started when patients demonstrated progressive disease despite somatostatin analogues. More recently, a randomized trial comparing the combination of streptozocin with doxorubicin versus streptozocin with fluorouracil demonstrated a mortality benefit as well as radiological and biochemical regression of disease in 69% of patients.[70] Therapy with streptozocin is limited by its toxicity and cumbersome administration schedule. Oral temozolomide (an alkylating agent) is better tolerated and has been shown to have comparable efficacy.[70] An 18-month median progression-free survival in patients with metastatic PanNETs was demonstrated in patients who received temozolomide and capecitabine.[62] Cytotoxic therapies should be considered in the palliation of patients with advanced PanNETs and symptoms related to tumor bulk.

Targeted Therapy

NETs have been shown to express a multitude of growth factors and their corresponding receptors leading to the development of targeted therapeutic agents. Recent phase III studies have shown tremendous promise for 2 drugs designed for targeted therapy in the treatment of PanNETs, everolimus and sunitinib. Both drugs are recommended for patients with progressive metastatic PanNETs.

Everolimus

mTOR (mammalian target of rapamycin) is a serine/threonine kinase involved in the regulation of cell growth and death through apoptosis. It is also capable of impacting multiple downstream pathways, including vascular endothelial growth factor (VEG-F) and other growth factors. There is a relationship between the TSC and the phosphatase and tensin homolog (PTEN), NF-1, and VHL genes that contribute to the development of neuroendocrine tumors. Downregulation of TSC2 and PTEN have been shown to be a poor prognostic factor in PanNETs, supporting an important role for the PI3K/Akt/mTOR pathway and its inhibition in the treatment of PanNETs.[69,71,72] Everolimus (RAD001), an oral mTOR inhibitor, has been shown to have antitumor activity in many solid tumors, including PanNETs. The RAD001 in Advanced Neuroendocrine Tumors-3 (RADIANT-3) study by Yao and colleagues[73] is a randomized phase 3 study evaluating the efficacy of everolimus in advanced PanNETs. In this international multisite study, 410 patients with low- or intermediate-grade, progressive, advanced PanNETs were randomized to receive everolimus, 10 mg oral daily, or placebo. The response rate was 5% in the everolimus arm compared with 2% in the placebo arm, with a median progression-free survival of 11.0 months with everolimus compared with 4.6 months with placebo (hazard ratio, 0.35; 95% confidence interval, 0.27–0.45; $P<.001$). The median overall survival has not been reached. The Food and Drug Administration (FDA) has approved everolimus for advanced PanNETs. Adverse events associated with everolimus are rare and most commonly include stomatitis, rash, diarrhea, fatigue, infections, and pneumonitis.

Sunitinib

PanNETs express an abundance of VEG-F and platelet-derived growth factor (PDGF) receptors. Three tyrosine kinase inhibitors have shown activity against VEG-F receptor: pazopanib, sorafenib, and sunitinib. Sunitinib is an oral, small-molecule, multi-targeted tyrosine kinase inhibitor with activity against VEG-F and PDGF. A phase II trial demonstrated a response rate of 17% with a stable disease rate of 68%.[74] In a multinational randomized controlled trial of 171 patients with advanced, well-differentiated, and progressive pancreatic neuroendocrine carcinomas, patients were randomized to receive sunitinib, 37.5 mg orally daily, or placebo. Sunitinib increased progression-free survival (11.4 months) versus placebo (5.5 months, $P<.0001$).[75] This study was terminated early because of more serious adverse events and deaths in the placebo group (25%) compared with the group receiving sunitinib; thus, the benefit in overall survival could not be determined. It can also be safely combined with somatostatin analogues without affecting the quality of life. Adverse events associated with sunitinib include diarrhea, nausea, asthenia, vomiting, fatigue, and hypothyroidism. The FDA and European Medicines Agency have approved sunitinib for the treatment of unresectable or metastatic, well-differentiated PanNETs with disease progression in adults.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that inhibits VEG-F and has recently been tested in combination with capecitabine and oxaliplatin for patients with advanced neuroendocrine tumors.[76] In patients with PanNETs, 30% exhibited partial responses with a median progression-free survival of 13.7 months. Prospective, randomized phase III studies combining bevacizumab with octreotide, temozolomide, CAPOX (oxaliplatin and capecitabine), FOLFOX (oxaliplatin and fluorouracil), and everolimus are still ongoing.[77,78]

SUMMARY

PanNETs are a heterogeneous group of tumors that pose a significant challenge because of the heterogeneous clinical presentations and varying degree of aggressiveness. The incidence of PanNETs is increasing, in part, because of the increased use of cross-sectional imaging and increased incidence of pancreatic incidentalomas. Most PanNETs are nonfunctional tumors, and most are malignant in nature. Surgery remains the only curative modality for PanNETs; resection of the primary tumor in localized, regional, and even metastatic disease can improve patient survival. Selecting an operative approach for PanNETs is a complex decision that must consider a myriad of factors, including functional status, benign or malignant nature, involvement with contiguous structures, presence of metastatic disease, proliferative index, and whether the tumor is sporadic or associated with a genetic syndrome. Indications for surgery in patients with nonfunctional PanNETs include local compressive symptoms caused by mass effect and prevention of malignant transformation or dissemination. In general, nonfunctional PanNETs, even those smaller than 3 cm, are best treated with formal resection and appropriate lymphadenectomy because a significant percentage of even small nonfunctional PanNETs will have lymph node metastases. However, in certain clinical scenarios (eg, low Ki-67, patient with significant comorbidities, patient who does not want an extensive resection, and so forth), nonfunctional PanNETs that are 3 cm or less in size that do not impinge on the common bile or pancreatic ducts can be enucleated. There is evidence to suggest observation is appropriate for selected patients with tumors smaller than 2 cm and a low proliferation index. PanNETs greater than 3 cm should be resected with an appropriate oncologic

operation based on the location within the pancreas. For lesions located in the head, uncinate, or neck of the pancreas, pancreaticoduodenectomy can be performed. For lesions located in the body or tail of the pancreas, distal pancreatectomy can be performed. For lesions in the neck and proximal body, either an extended pancreaticoduodenectomy or extended distal pancreatectomy may be performed depending on the specific anatomy. For select lesions in the neck and proximal body of the pancreas, central pancreatectomy may be performed. Patients with evidence of metastatic hepatic disease should be considered for metastasectomy if possible. In those patients who are not surgical candidates, early, aggressive treatment of unresectable liver metastases using interventional techniques may improve symptom relief and quality of life and should be considered for palliation of disease. For patients with advanced, metastatic disease not amenable to surgical resection, somatostatin analogues and targeted therapies offer promising therapeutic alternatives for decreasing morbidity and increasing progression-free survival.

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