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REVIEW

Non-functional neuroendocrine tumors of the pancreas: Advances in diagnosis and management

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Abstract

Nonfunctional neuroendocrine tumors of the pancreas (NF-PNETs) are a heterogeneous group of neoplasms. Although rare, the incidence of NF-PNETs is increasing significantly. The classification of PNETs has evolved over the past decades and is now based on a proliferation grading system. While most NF-PNETs are slow growing, tumors with more aggressive biology may become incurable once they progress to unresectable metastatic disease. Tumors of higher grade can be suspected preoperatively based on the presence of calcifications, hypoenhancement on arterial phase computed tomography, positron emission technology avidity and lack of octreotide scan uptake. Surgery is the only curative treatment and is recommended for most patients for whom complete resection is possible. Liver-directed therapies (thermal ablation, transarterial embolization) can be useful in controlling unresectable hepatic metastatic disease. In the presence of unresectable progressive disease, somatostatin analogues, everolimus and sunitinib can prolong progression-free survival. This article provides a comprehensive review of NF-PNETs with special emphasis on recent advances in diagnosis and management.

Key words: Pancreas; Neuroendocrine tumor; Neuroendocrine carcinoma; Islet cell; Octreotide

Core tip: Pancreatic neuroendocrine tumors (PNETs) are a fascinating and diverse group of neoplasms. While the clinical features of functional PNETs are frequently discussed, the majority of PNETs are actually non-functional. Although typically slow growing, tumors with more aggressive biology may progress to unresectable metastatic disease. Surgery should be considered for all patients for whom complete resection is possible, while liver directed therapies are useful for managing hepatic metastases. For patients with progressive metastatic disease, strong evidence supports the use of somatostatin analogues, everolimus and sunitinib in prolonging survival. The purpose of this article is to provide a comprehensive review of NF-PNETs.

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INTRODUCTION

Pancreatic neuroendocrine tumors (PNET) are a rare heterogeneous group of neoplasms that arise from progenitor islet cells. PNETs may be classified as either functional (F-PNET) or non-functional (NF-PNET), depending on their ability to secrete biologically active hormones and elicit characteristic symptomatology. NF-PNETs exhibit a wide range of malignant potential, ranging from slow-growing and non-infiltrative tumors to locally invasive and rapidly metastasizing ones, thereby making standardization of the diagnosis, surgical and medical management, follow-up surveillance and prognosis challenging. Fortunately, significant advances in diagnostic modalities, tumor localization and therapeutic options have been made over the past decade. This article provides a comprehensive review of NF-PNETs and an update on advances in their diagnosis and management.

EPIDEMIOLOGY

Although neuroendocrine neoplasms can occur nearly anywhere in the body, gastroenteropancreatic neuroendocrine tumors (GEP-NET) and pulmonary neuroendocrine tumors comprise the majority. PNETs comprise approximately 7% of all NETs[1]. However, compared to other pancreatic pathology, PNETs are relatively rare, comprising only 1%-2% of all pancreatic neoplasms. The incidence of PNETs increases significantly after the age of 40 with a peak incidence around age 65[1]. There is only a slight male predominance[2]. Between 60%-90% of all PNETs are non-functional and given their frequently asymptomatic nature the majority of patients present with distant metastasis[2,3].

By all measures, the incidence of PNETs is increasing. The Surveillance, Epidemiology and End Results (SEER) program has shown that the incidence has increased from 0.17 per 100000 people in 1973 to 0.47 per 100000 people in 2007[1]. Likewise, a six-fold increase in the incidence was found in Ontario, Canada between 1994 and 2009 (from 0.1 to 0.6 per 100000 persons)[4]. Autopsy studies would also suggest that the prevalence of PNETs is higher than previously suspected[5]. Interestingly, this trend of increasing incidence of PNETs seems to be true of all neoplasms of neuroendocrine origin[4,6] and may be partly related to increased incidental discovery due to more frequent use and improving sensitivity of cross-sectional imaging.

STAGING AND PROGNOSIS

In 2000, the World Health Organization (WHO) first established guidelines that distinguished between well-differentiated tumors with benign behavior (localized to pancreas, size < 2 cm, low mitotic rate and Ki-67, no angioinvasion or perineural invasion), tumors with uncertain behavior (limited to the pancreas, angioinvasion or perineural invasion, size ⩾ 2 cm) and tumors with clearly malignant behavior (gross local invasion or distant metastases)[7]. In 2010, the WHO revised their previous grading system to a proliferation based grading system (Table 1). Based on mitotic counts and Ki-67 indices, well-differentiated tumors included those of low and intermediate grade while poorly differentiated tumors included high grade tumors. It was concluded that mitotic count and Ki-67 should be performed on all specimens and that the grade would reflect the higher value when discordant[8]. In fact, Ki-67 and differentiation has been found to be some of the most important factors in determining prognosis[9].

Based on results of a consensus conference in 2005, the European Neuroendocrine Tumour Society (ENETS) proposed a classification scheme for all foregut NETs that combined a TNM staging system with a histologic grading system[10]. The most commonly used staging system, however, is from the 7th edition American Joint Committee on Cancer (AJCC)[11]. Revised in 2010, this system applies to all neoplasms of the pancreas, both endocrine and exocrine, and is based on TNM staging (Table 1). Importantly, the AJCC system does not incorporate histological grading criteria.

Both the ENETS and the AJCC system have been validated and provide important prognostic information for patients with PNETs[12]. However, some have called into question whether the AJCC system provides adequate discriminatory value. Specifically, validation studies by Strosberg *et al*[13,14] showed no survival difference between stages Ⅰ and Ⅱ as well as stages Ⅲ and Ⅳ. In addition, Rindi *et al*[15] studied a large international cohort of resected PNETs and found no significant differences in survival between stage Ⅱ and Ⅲ. A large range of outcomes was seen in patients of all stages, suggesting poor discriminatory ability, and they concluded that the ENETS staging system was superior[15]. Qadan *et al*[16] utilized SEER to demonstrate that no significant survival differences could be replicated between stages Ⅱ and Ⅲ or Ⅲ and Ⅳ, and suggested a revised TNM staging system with potentially improved prognostic capabilities.

CLINICAL PRESENTATION

Unlike other solid tumors (including F-PNETs), NF-PNETs can remain asymptomatic before they reach

Table 1 Current pancreatic neuroendocrine tumor classification and staging systems

WHO 2010/ENETS grading			
Grade	Differentiation	Ki-67 index (%)	Mitotic count/10 HPF
G1 (low)	Well	≤ 2	< 2
G2 (intermediate)	Well	3-20	2-20
G3 (high)	Poorly	> 20	> 20
ENETS T staging[1]			
T stage	Description		
TX	Cannot be assessed		
T0	No evidence of tumor		
T1	< 2 cm, limited to pancreas		
T2	2-4 cm, limited to pancreas		
T3	> 4 cm, limited to pancreas		
T4	Involving adjacent organs or large blood vessels		
AJCC T staging[1]			
T stage	Description		
TX	Cannot be assessed		
T0	No evidence of tumor		
T1	≤ 2 cm, limited to pancreas		
T2	> 2 cm, limited to pancreas		
T3	Involves adjacent organs		
T4	Involving celiac axis or superior mesenteric artery		
Stage	ENETS staging	AJCC staging	
ⅠA	T1 N0 M0	T1 N0 M0	
ⅠB		T2 N0 M0	
ⅡA	T2 N0 M0	T3 N0 M0	
ⅡB	T3 N0 M0	T1-3 N1 M0	
ⅢA	T4 N0 M0	T4 N1 M0	
ⅢB	T1-4 N1 M0		
Ⅳ	T1-4 N0-1 M1	T1-4 N0-1 M0	

[1]Both AJCC and ENETS share common N and M staging: N0, no regional lymph node metastatic; N1, regional lymph node metastasis; M0, no distant metastasis; M1, distant metastasis. WHO: World Health Organization; ENETS: European neuroendocrine tumor society; AJCC: 7th edition American joint committee on cancer.

Table 2 Clinical features of functional pancreatic neuroendocrine tumors

Tumor	Percentage	Secreted hormone	Malignant	Clinical features	Biochemical evaluation
Insulinoma	40%-60%	Insulin	< 10%	Hypoglycemia	Insulin, pro-insulin, C-peptide, 72 h fasting insulin/glucose ratio
Gastrinoma	20%-50%	Gastrin	60%-90%	PUD, GERD, diarrhea	Fasting gastrin (off PPI), secretin stimulation test
Glucagonoma	Rare	Glucagon	50%-80%	Necrolytic migratory erythema, diabetes, venous thrombosis, depression	Glucagon
Somatostatinoma	Rare	Somatostatin	> 70%	Diabetes, hypochlorhydria, cholelithiasis, diarrhea	Somatostatin (not widely available)
VIPoma	Rare	Vasoactive Intestinal Peptide	40%-70%	Watery diarrhea, hypokalemia, achlorhydria	VIP

PUD: Peptic ulcer disease; GERD: Gastroesophageal reflux disease; PPI: Proton pump inhibitor.

a significant tumor burden. When they become symptomatic, their symptomatology is typically related to mass effect from the primary tumor or the metastasis. Many PNETs occur in the head of the pancreas where symptoms may include jaundice, abdominal pain, or weight loss. Other less frequent symptoms may include anorexia, nausea, intra-abdominal bleeding, or a palpable mass. Many will be asymptomatic and found incidentally on cross-sectional imaging performed for other indications. The vast majority of metastases occur in the liver, though other sites including bone, peritoneum, adrenal, brain and spleen have been reported[17]. Liver metastases more frequently occur with non-functional tumors and patients with symptoms. When liver metastases occur, most are multifocal and bilobar[17].

F-PNETs present with symptoms caused by the specific hormone produced. Common F-NETs include insulinoma, which presents with hypoglycemia, and gastrinoma, which presents with peptic ulcer disease, gastroesophageal reflux disease or secretory diarrhea. Less common F-NETs include VIPomas, glucagonomas, and somatostainomas. These tumors are summarized in Table 2 but are not discussed further in this review. NF-PNETs either do not produce hormones, produce hormones at a low enough level to not cause

symptoms, or are associated with hormones that do not cause symptoms, such as pancreatic polypeptide, chromogranin A, ghrelin, calcitonin or neurotensin.

While most NF-NETs are sporadic, approximately 10% of NETs will be associated with an inherited genetic syndrome[18]. Multiple endocrine neoplasia type 1 (MEN1) is an inherited autosomal dominant disease characterized by hyperparathyroidism (nearly 100%), PNETs (up to 75%) and pituitary tumors (less than 50%)[19]. NF-PNETs are the most common pancreatic neoplasms in MEN1, followed by gastrinomas, and then insulinomas. Patients with MEN1 frequently present with multiple PNETs throughout the pancreas[20]. Von Hippel-Lindau (VHL) disease is an autosomal dominant disorder that is associated with pancreatic tumors or cysts. In order of frequency, patients develop pancreatic cysts, NF-PNETs (10%-20% of patients), cystadenomas, hemangioblastomas and adenocarcinoma; F-PNETs are rare[20]. PNETs in neurofibromatosis type 1 (NF1) are relatively rare (0%-10%) but are almost exclusively duodenal somatostatinomas in the periampullary region[21]. Other functional and non-functional PNETs may rarely occur[22-24]. PNETs associated with tuberous sclerosis (TS) are relatively uncommon and may be either functional or non-functional[25].

DIAGNOSIS

Patients with PNETs require a thorough evaluation for symptoms classically associated with functional tumors as well as symptoms directly related to the primary or metastatic tumor. Past medical and family history should be carefully reviewed. A comprehensive physical examination should be undertaken. Ultimately, the diagnosis of PNETs depends on comprehensive biochemical and radiographic evaluation.

Biochemical

Neuroendocrine markers are important not only for confirming diagnosis, but also as screening tools for future surveillance. The most commonly utilized neuroendocrine markers include chromogranin A (CgA), pancreatic polypeptide (PPP), pancreastatin, and neuron-specific enolase (NSE). CgA is a glycoprotein used commonly as a tumor marker in histopathology but also has elevated circulating levels in patients with both functional and non-functional PNETs[26,27]. However, falsely elevated levels can be observed in patients with chronic renal insufficiency, liver failure and with proton-pump inhibitor (PPI) use[28,29]. Recent recommendations by the North American Neuroendocrine Tumor Society[30] and a Canadian national expert group[29] have recommended utilizing CgA in the diagnosis and surveillance of advanced PNETs. PPP may be elevated in up to 63% of PNETs[31] and has a specificity of 84% when used during surveillance[32]. Pancreastatin may provide additional diagnostic utility, especially in patients on PPIs or with normal CgA levels[33,34]. Laboratory evaluation should also include tests to rule out F-NETs, including insulinoma and gastrinoma, if suspected (Table 2). Screening for MEN1 with serum parathyroid hormone and calcium levels should be performed in appropriate patients (*e.g.*, diagnosis at young age, multifocal tumors, and/or with relevant personal or family history).

Localization

Cross-sectional imaging should be performed in all patients suspected of having a PNET. Computed tomography (CT) remains the initial imaging modality of choice given its good sensitivity, specificity and availability. PNETs typically are well-circumscribed lesions that appear hyperenhancing on contrast-enhanced scans. In fact, there is some evidence that hypoenhancement on arterial phase imaging is associated with more aggressive tumors and worse prognosis (Figure 1)[35]. Similarly, the presence of calcifications within these tumors on CT is associated with higher grade and the presence of lymph node metastases (Figure 2)[36]. Magnetic resonance imaging (MRI) is an alternative modality with the advantage of less radiation exposure. PNETs should be low signal intensity on T1 weighted images and high signal intensity on T2 weighted images. In addition, MRI may be more sensitive than CT for detecting smaller pancreatic lesions and liver metastases[37,38]. While ultrasound has a limited role in the diagnosis of PNETs, intraoperative ultrasound (IOUS) is very sensitive in identifying small PNETs[39], and endoscopic ultrasound (EUS) is a valuable technique for detection, localization and diagnosis through fine needle aspiration of identified lesions[40].

Somatostatin receptor scintigraphy (SRS), also known as an octreotide scan, is a whole body functional imaging study that uses ^{111}indium labeled pentetreotide, a somatostatin analogue. Advantages include identification of unknown metastatic sites and providing important information on functional expression of somatostatin receptors which may guide systemic therapy decisions[41]. Although less available at most institutions compared to SRS, newer functional imaging studies utilizing ^{68}Gallium labeled 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid-d-Phe(1)-Tyr(3)-octreotide ((68)Ga-DOTA-TOC) show promising results that may be superior to conventional SRS[42,43]. Although standard positron emission technology (PET) with ^{18}flourodeoxyglucose is not typically useful in the diagnosis of NF-PNETs, PET with newer radiolabeled tracers may prove more advantageous[44,45]. In general, well differentiated tumors are positive on Octreotide scan and negative on PET scan, with the opposite being true for poorly differentiated grade 3 tumors[46].

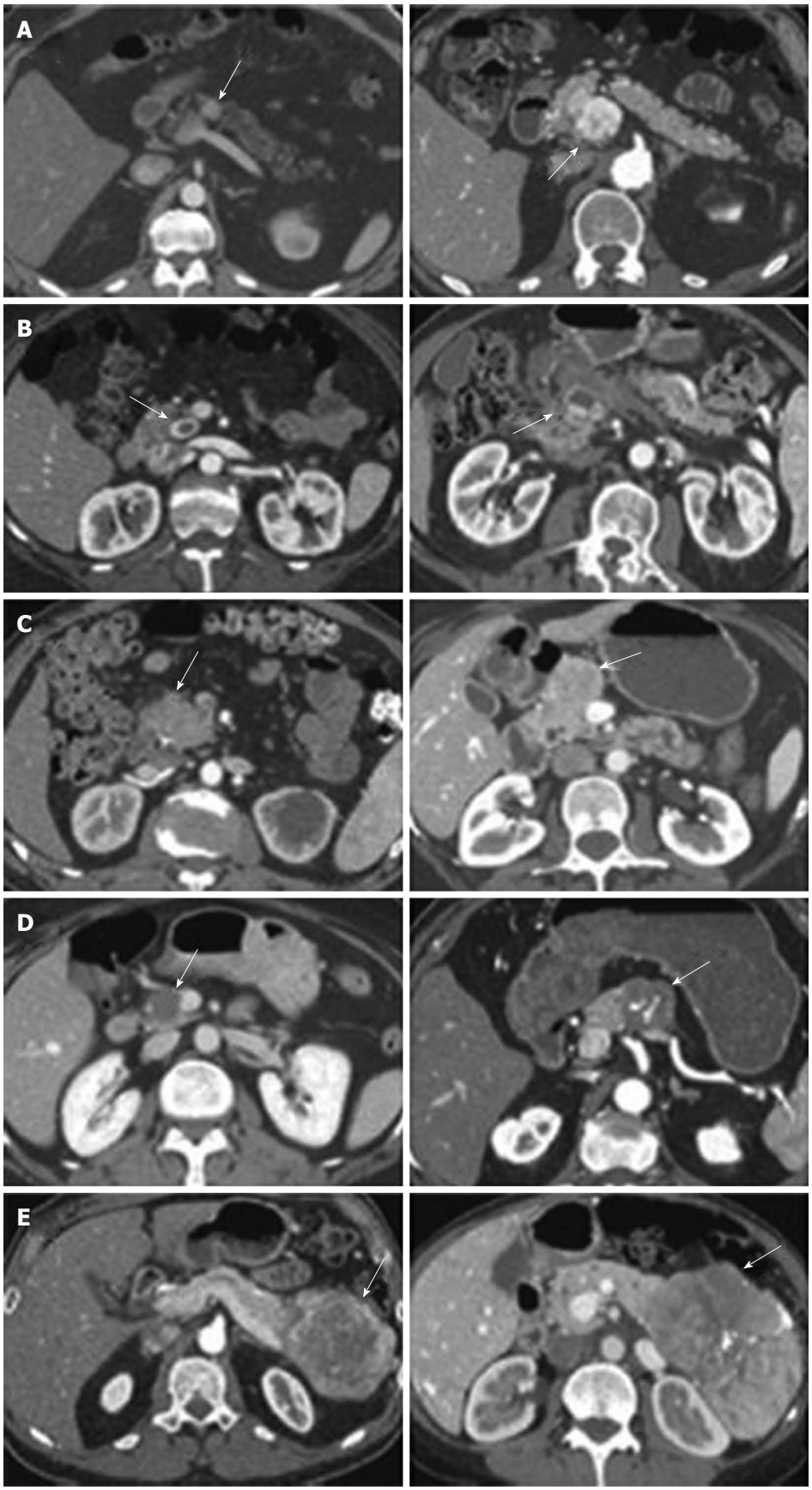


Figure 1 Representative images of the 5 types of pancreatic neuroendocrine tumor enhancement pattern on arterial phase computed tomography. Two images are shown for each type. A: Hyperenhancing, solid; B: Cystic with hyperenhancing rim; C: Isoenhancing or no mass visualized; D: Homogeneously hypoenhancing; E: Heterogeneous but mostly hypoenhancing with some peripheral enhancement. Groups D and E had worse survival after resection compared with groups A, B, and C (From Worhunsky *et al*[35]. Pancreatic neuroendocrine tumours: hypoenhancement on arterial phase computed tomography predicts biological aggressiveness. *HPB* 2014; 16: 304-311). Arrows indicate PNET.

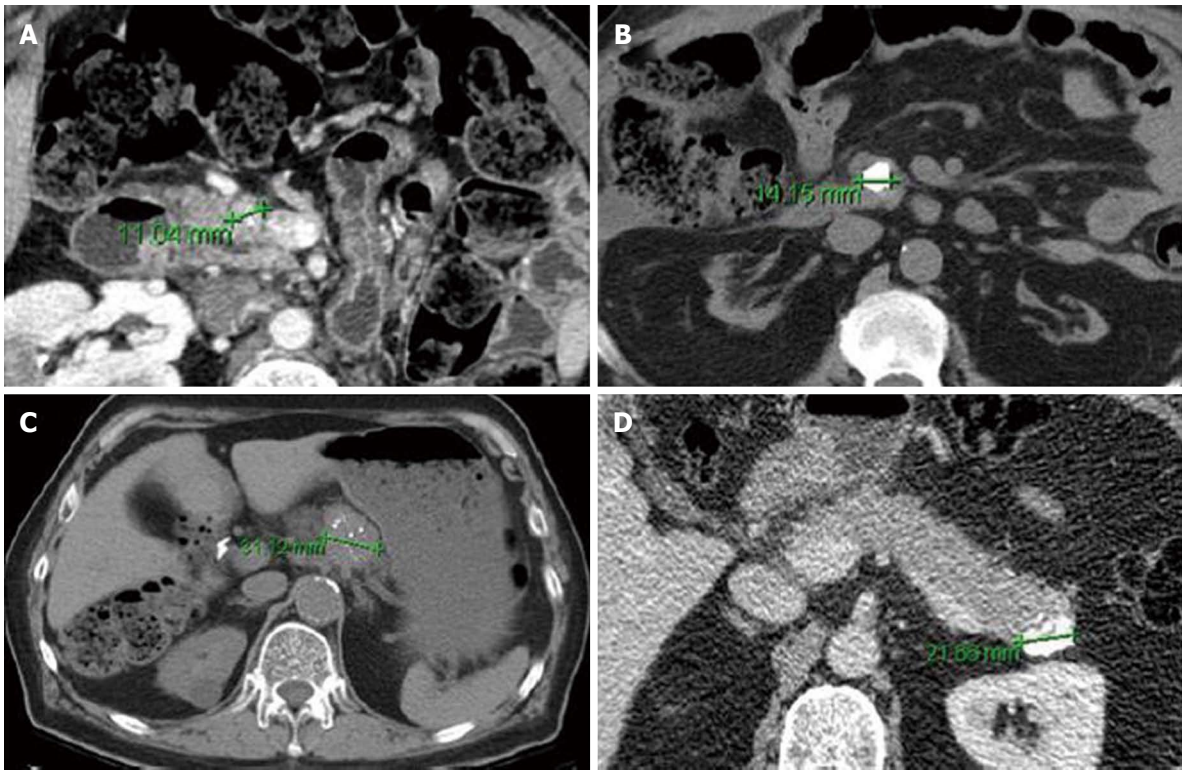


Figure 2 Axial computed tomography images of Pancreatic neuroendocrine tumor with punctate (A, C) and dense/coarse calcifications (B, D). Despite their small size, all lesions were associated with either lymph node metastasis (A-C) or intermediate (G2) grade (B-D) on pathologic evaluation (From Poultsides *et al*[36]. Pancreatic Neuroendocrine Tumors: Radiographic Calcifications Correlate with Grade and Metastasis. *Ann Surg Onc* 2012; 19: 2295-2303).

SURGICAL MANAGEMENT

Primary

Surgery remains the only curative treatment for NF-PNETs and is the mainstay of treatment in most cases. Appropriate candidates who undergo surgery have a significant survival advantage compared with those who do not. Hill *et al*[47] demonstrated a median survival difference of 114 mo *vs* 35 mo for patients who underwent resection compared to those who did not but were recommended to, across all patients with localized, regional and metastatic disease.

The exact surgical management must be individualized for each patient based on their particular tumor and staging. In general, most NF-PNETs should be resected. However, given the increase in incidentally discovered asymptomatic NF-PNETs, there is growing interest in the role of observation for patients with small indolent tumors. Lee *et al*[48] retrospectively analyzed 77 patients who underwent nonoperative observation of small, sporadic NF-PNETs without evidence of local invasion or metastasis. Median initial size was 1.0 cm and there was no documented disease specific progression or mortality during a median follow-up of 45 mo. In addition, Bettini *et al*[49] found that of 51 patients with incidentally diagnosed NF-PNETs < 2 cm, only 6% were malignant and there were no disease specific deaths on long term follow-up. Other population-based analyses have attempted to investigate this question but have been limited by methodological concerns[50-52]. Until better data are available, the ENETS guidelines states that intensive observation could be considered for NF-PNETs < 2 cm but risks and benefits must be carefully weighed in each patient[53].

Small low grade PNETs may safely undergo enucleation regardless of location in the pancreas, provided they are far away from the pancreatic duct and the integrity of this structure can be maintained during enucleation[54]. Enucleation may be performed in an open, laparoscopic or robotic fashion; the technique does not have an appreciable impact on morbidity, mortality, length of hospital stay or survival[55]. For larger or more aggressive NF-PNETs, formal resection is recommended. Tumors in the head of the pancreas typically require pancreaticoduodenectomy (PD) while body and tail lesions may be resected *via* distal pancreatectomy with or without splenic preservation. Distal pancreatectomy can often be performed *via* minimally invasive techniques which are associated with decreased morbidity, operative blood loss and hospital length of stay with similar rates of negative margins[56]. Minimally invasive PD has been slow to gain popularity given its greater learning curve and longer operating times. However, recent evidence suggests that it is a feasible option at select centers with potential benefits in morbidity and perhaps oncologic outcomes[57,58].

Several reports now have stressed the prognostic importance of lymph node involvement in patients

with NF-PNETs[59-61]. Krampitz *et al*[61] found that positive lymph nodes were associated with a shorter time interval to the development of liver metastases, and in long term follow-up, a shorter disease specific survival. Similarly, Hashim *et al*[60] found that lymph node positivity was associated with PNETs of greater size, location in the head, high Ki-67 and with lymphovascular invasion. Furthermore, positive lymph nodes were associated with decreased median disease free survival. These data support the use of routine lymphadenectomy during resection for PNETs. Controversy exists over which lesions may forego lymphadenectomy during simple enucleation. Curran *et al*[59] analyzed the SEER database and found no lymph node metastases in any low grade PNETs < 1 cm. In contrast, Gratian *et al*[50] found that among tumors < 0.5 cm in the national cancer database, 33% presented with regional lymph node metastases and 11% with distant metastases. Formal resection with adjacent lymphadenectomy, as opposed to enucleation, is the procedure of choice for PNETs greater than 2 cm, of higher grade, or with radiographic calcifications.

Several authors have described the role of aggressive extended resections for advanced PNETs[62-65]. For example, Norton *et al*[62] describe acceptable morbidity, low mortality, and excellent overall survival rates, albeit high recurrence rates, in patients with advanced PNETs. Norton *et al*[63] also described good outcomes for patients with PNETs with major vessel involvement undergoing simultaneous vascular reconstruction. Surgeons at experienced hepatopancreaticobiliary centers may follow standard oncologic principles, including multivisceral and vascular resections, in order to accomplish R0 resections.

Liver metastases

All patients with liver metastases from PNETs should be considered for surgical intervention. Although resection can be associated with high recurrence rates, it does improve progression free survival as well as symptom control[66-71]. Saxena *et al*[66] performed a meta-analysis of 1469 GEP-NETs metastatic to the liver and found 3, 5, and 10 year overall survival rates of 83%, 70.5%, and 42%, respectively, following hepatic resection. Predictors of poor outcomes included poor histologic grade, incomplete resection and extrahepatic disease[66]. When patients are not candidates for resection, alternative methods, such as thermal ablation or hepatic artery embolization, are helpful strategies that improve local control and palliate symptoms[67,69,71,72]. Insufficient data exists to recommend one liver-directed strategy over another[73]. Liver transplantation has been described for well selected patients with metastatic GEP-NET[74]. However, liver transplantation for neuroendocrine liver metastases of pancreatic origin is associated with worse overall outcomes and is not typically recommended[75].

In the setting of metastatic disease, controversy remains regarding the role of surgery for the primary tumor[53,76,77]. Capurso *et al*[77] performed a systematic review on this topic and found improved overall survival in patients undergoing resection of the primary in 2 of 3 retrospective cohort studies identified. One potential benefit of removal of the primary tumor is allowing providers to focus treatment on the liver metastatic sites with hepatic artery therapies. Primary tumors that are symptomatic should generally undergo resection for palliation of symptoms[78].

SYSTEMIC THERAPY

The goal of systemic therapy is to prolong survival in patients with recurrence or relapse as well as improve quality of life by controlling symptoms. Currently, there is no evidence to support the use of various systemic modalities in an adjuvant fashion following complete surgical resection of PNETs.

Somatostatin analogues

Nearly 80% of NF-NETs express somatostatin receptors, making them a suitable target for therapy with somatostatin analogues. In addition to their favorable safety profile and effectiveness in controlling symptoms, recent evidence has suggested improvements in oncologic outcomes as well. The PROMID trial[79] was a placebo-controlled double blinded randomized controlled trial (RCT) of long acting release (LAR) octreotide in patients with metastatic well differentiated midgut NETs. Median progression free survival was 14.3 mo in patients receiving octreotide *vs* 6 mo in the placebo group. More recently, the CLARINET trial randomized 204 patients with enteropancreatic NETs to receive long acting lanreotide or placebo and found significantly prolonged progression free survival in the lanreotide group (65.1% *vs* 33.0% at 24 mo); this finding was confirmed in a subset of patients with PNETs (Figure 3)[80].

Radionucleide therapy

Peptide receptor radionuclide therapy (PRRT) also makes use of PNETs' octreotide receptor expression by coupling radionuclides to somatostatin analogues. Typical radionuclides include ^{90}yttrium and ^{177}lutetium. Response rates range only between 10%-40% with toxicity (primarily bone marrow and renal) rates in a similar range so PRRT should be reserved for cases not responsive to less toxic therapies[81-83]. Furthermore, having been pioneered at the Erasmus Medical Center in the Netherlands, PRRT is still only available at select centers in Europe and North America and randomized data are lacking.

Chemotherapy

Indolent and well differentiated NETs are typically resistant to traditional systemic chemotherapy which

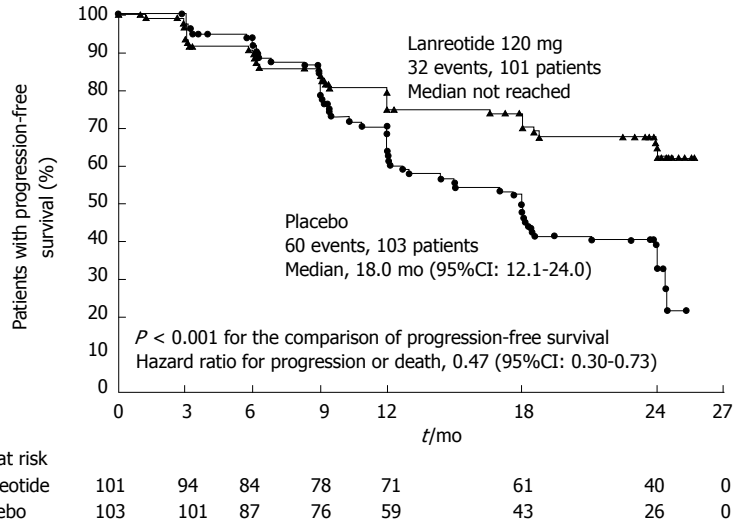


Figure 3 Results of the Clarinet trial which randomized patients with enteropancreatic neuroendocrine tumors to lanreotide *vs* placebo. From: Caplin *et al*[80]. Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *N Engl J Med* 2014; 371: 224-233.

is therefore reserved for patients with high grade, poorly differentiated tumors or with rapidly progressive unresectable disease[84]. However, NETS of pancreatic origin, generally respond better to chemotherapy than other GEP-NETs. Streptozocin was one of the first agents shown to have activity patients with metastatic PNETs, either as monotherapy or in combination with doxorubicin or fluorouracil[85-87]. Currently, platinum based therapy remains the standard of care for patients with high grade metastatic PNETs. Various combinations exist but the most common regimen utilized consists of cisplatin and etoposide. Nevertheless, data supporting the use of this regimen is limited and more evidence is needed to clarify its role as aggressive first line therapy[88].

More recent research has focused on the use of oral temozolamide with or without capecitabine given its ease of administration and favorable side effect profile. A retrospective review of 30 patients with well or moderately differentiated PNETs treated with this regimen demonstrated a 70% response rate and a median PFS of 18 mo[89]. Additional research is becoming available regarding the safety and efficacy of this regimen[90,91].

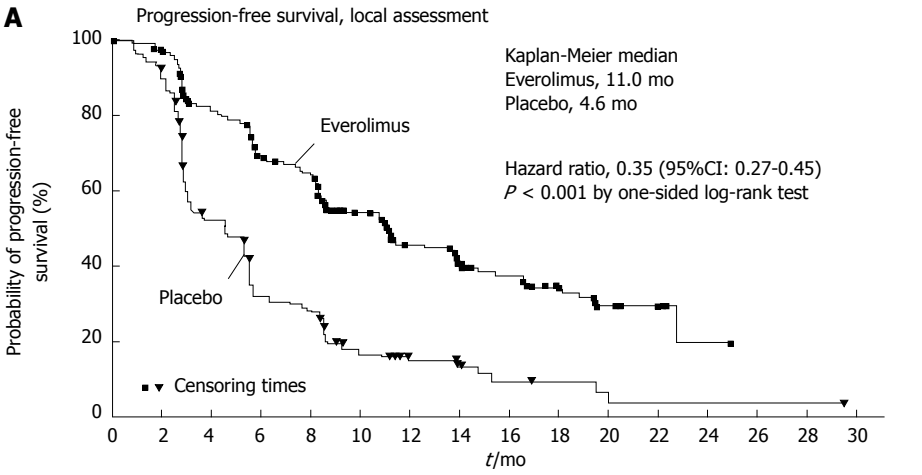
Targeted therapy

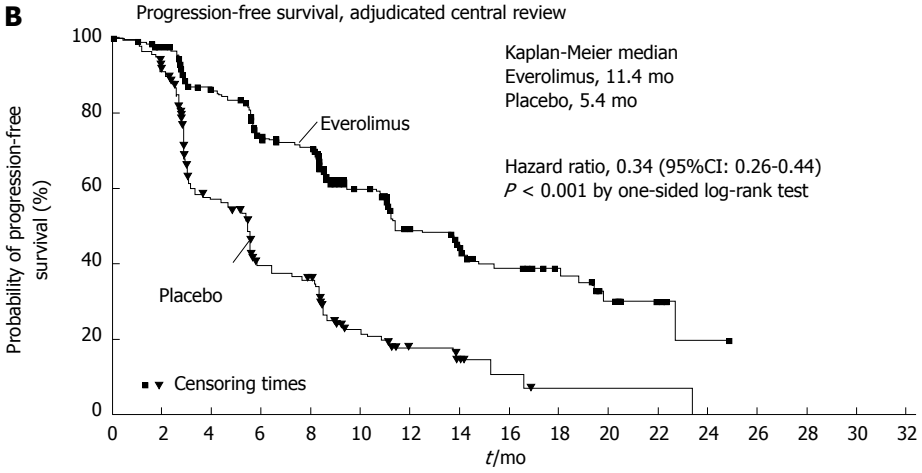
Increasingly, PNETs have been found to be responsive to targeted therapies. The purpose of these molecular agents is to stabilize disease progression in metastatic unresectable cases[92]. Much focus has been placed on Everolimus, an oral mTOR (mammalian target of rapamycin) inhibitor. Previously, Everolimus had been found to have clinical benefit in patients who progressed while on systemic cytotoxic chemotherapy[93]. The RADIANT-3 trial was an international, multisite, RCT comparing daily Everolimus to placebo in patients with low or moderate grade NF-PNETs. Although response rates were low, PFS was longer in the Everolimus group (11.0 mo *vs* 4.6 mo) (Figure 4)[94]. Similarly, the RADIANT-2 trial evaluated Everolimus in conjunction with long acting octreotide and found improved PFS in the Everolimus plus octreotide LAR group *vs* octreotide LAR alone(16.4 mo *vs* 11.3 mo)[95]. Common adverse effects included stomatitis, rash and diarrhea. Some have suggested this regimen should be first line therapy for most NETs[96].

Sunitinib is an oral, small-molecule, tyrosine kinase inhibitor with activity against vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) both of which are expressed abundantly in PNETs[97]. A placebo controlled, double blind, RCT of daily sunitinib in patients with well-differentiated PNETs with documented disease progression found improved PFS in patients receiving Sunitinib (11.4 mo *vs* 5.5 mo) (Figure 5)[98]. Finally, newer therapies that target the mTOR (*e.g.*, temsirolimus) and VEGF (*e.g.*, bevacizumab) pathways are currently being investigated and hold promise both as single agents and in combination[92,99].

CONCLUSION

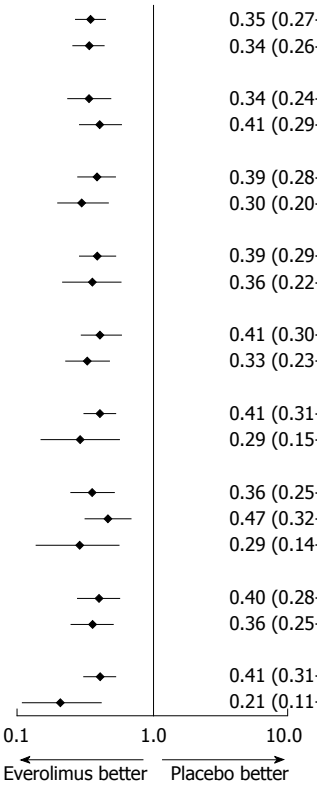
Nonfunctional neuroendocrine tumors of the pancreas are a heterogeneous group of neoplasms that are generally slow growing, however, they may become incurable when they progress to unresectable metastatic disease. Tumors of higher grade can be suspected preoperatively based on the presence of calcifications, hypoenhancement on arterial phase computed tomography, PET avidity and lack or octreotide scan uptake. Surgery is the only curative treatment and is recommended for most patients for whom complete resection is possible. Liver-directed therapies (thermal ablation, transarterial embolization) can be useful in controlling unresectable hepatic metastatic disease. In the presence of unresectable





C Progression-free survival in subgroups

Subgroups	No.	Hazard ratio (95%CI)	*P* value
Local investigator review	410	0.35 (0.27-0.45)	< 0.001
Central adjudicated review	410	0.34 (0.26-0.44)	< 0.001
Previous chemotherapy			
Yes	189	0.34 (0.24-0.49)	< 0.001
No	221	0.41 (0.29-0.58)	< 0.001
WHO performance status			
0	279	0.39 (0.28-0.53)	< 0.001
1 or 2	131	0.30 (0.20-0.47)	< 0.001
Age			
≤ 65 yr	299	0.39 (0.29-0.53)	< 0.001
> 65 yr	111	0.36 (0.22-0.58)	< 0.001
Sex			
Male	227	0.41 (0.30-0.58)	< 0.001
Female	183	0.33 (0.23-0.48)	< 0.001
Race			
White	322	0.41 (0.31-0.53)	< 0.001
Asian	74	0.29 (0.15-0.56)	< 0.001
Region			
America	185	0.36 (0.25-0.52)	< 0.001
Europe	156	0.47 (0.32-0.69)	< 0.001
Asia	69	0.29 (0.14-0.56)	< 0.001
Previous long-acting SSA			
Yes	203	0.40 (0.28-0.57)	< 0.001
No	207	0.36 (0.25-0.51)	< 0.001
Tumor grade			
Well differentiated	341	0.41 (0.31-0.53)	< 0.001
Moderately differentiated	65	0.21 (0.11-0.42)	< 0.001



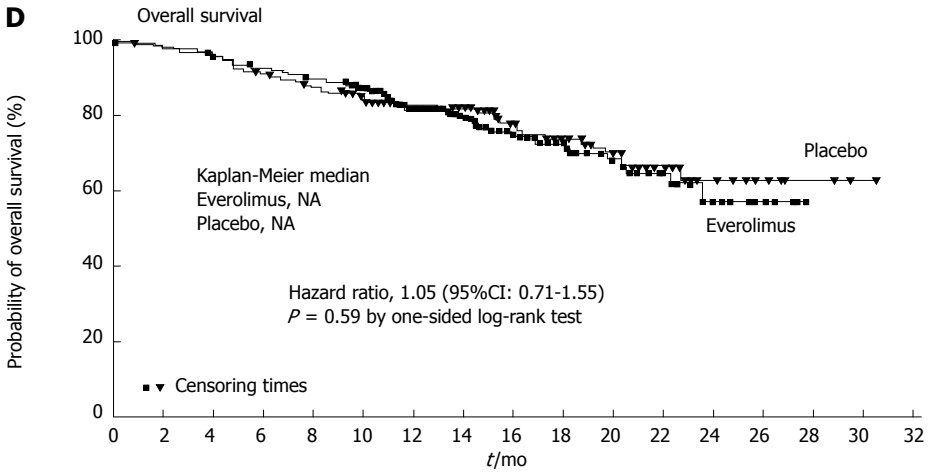
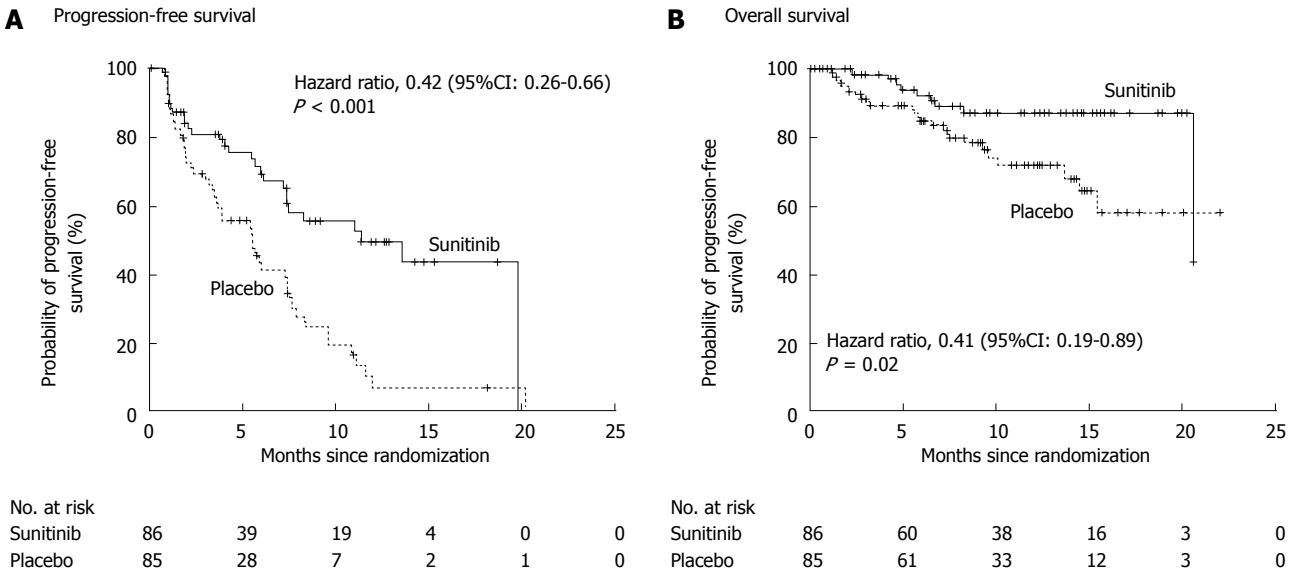


Figure 4 Results of the RADIANT-3 trial which randomized patients with nonfunctional neuroendocrine tumors of the pancreas to Everolimus *vs* placebo. From Yao *et al*[94]. Everolimus for Advanced Pancreatic Neuroendocrine Tumors. *N Engl J Med* 2011; 364: 514-523.



No. at risk						
Sunitinib	86	39	19	4	0	0
Placebo	85	28	7	2	1	0

No. at risk						
Sunitinib	86	60	38	16	3	0
Placebo	85	61	33	12	3	0

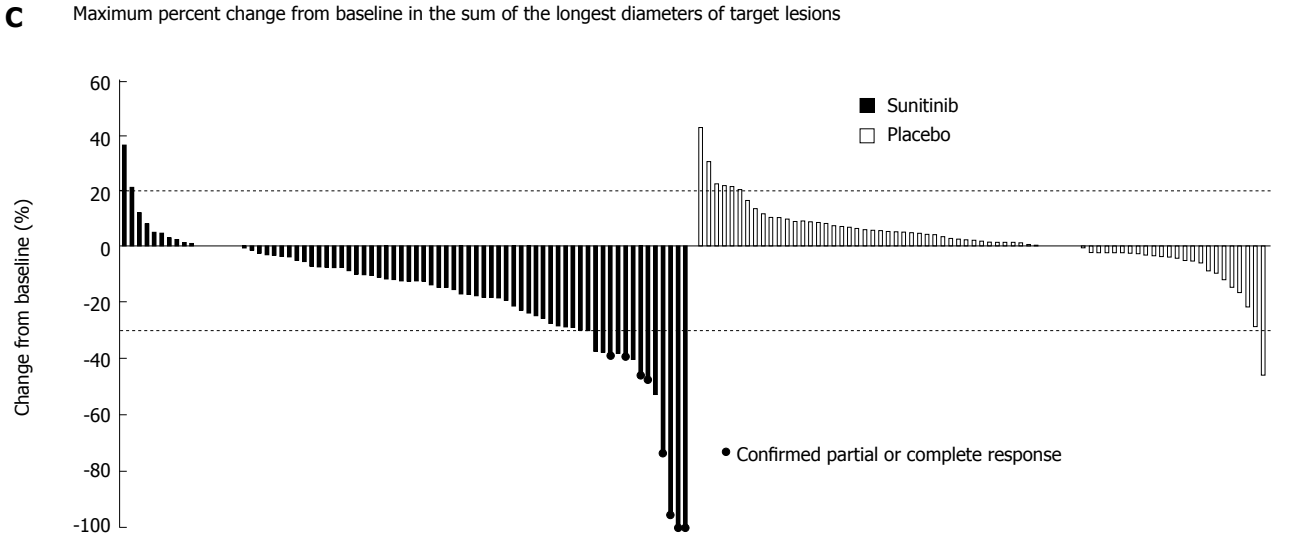


Figure 5 Results of a randomized controlled trial of Sunitinib *vs* placebo for well-differentiated pancreatic neuroendocrine tumors demonstrating (A) progression free survival and (B) overall survival. From: Raymond *et al*[98]. Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors. *N Engl J Med* 2011; 364: 501-513.

progressive disease, level 1 evidence suggests that somatostatin analogues, everolimus and sunitinib can prolong progression-free survival.

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