Review

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Pancreatic neuroendocrine tumors

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Summary **Pancreatic neuroendocrine neoplasms (pNENs) are a heterogeneous group of tumors including well differentiated pancreatic neuroendocrine tumors (pNETs) and neuroendocrine carcinomas (pNECs). The incidence of pNENs has increased over the past few decades. Although, the understanding and interest for this tumor have also increased significantly, the debate about classification and diagnosis continues. Although the primary treatment for pNENs is surgical resection, there is still a lack of effective therapeutic options for patients with advanced unresectable pNENs. Although many therapeutic methods have proven effective, the choice of treatment and specific programs are still unclear. Our article presents an overview of pNENs, with a focus on their diagnostic work-up, clinical presentation and treatment options.**

Keywords: Pancreatic neuroendocrine neoplasms, surgery, diagnosis, prognosis

1. Introduction

Pancreatic neuroendocrine neoplasms (pNENs), originating from diffuse neuroendocrine cells, are a clinically rare and heterogeneous disease of the pancreas. pNENs comprise only 1% to 2% of all pancreatic neoplasms, but have increased significantly in incidence over the past few decades (*1,2*). Increasing interest in research on neuroendocrine neoplasms (NENs) has grown in the past 10 years, however, our understanding of this disease is not thorough and is controversial. This review will summarize the epidemiology, clinical features and management of sporadic pNENs.

2. Epidemiology

Islet cell tumors were initially used to describe pNENs, furthermore the pNENs were redefined by the World Health Organization (WHO) in 2010. Although this tumor is rare, the incidence has been substantially increasing more than twice as much in the last 20-30 years (*1,3*). This increase is due in large part to increased physician awareness and improvements in diagnostic imaging. Most of the pNENs were sporadic in adults between the sixth and eighth decades, sometimes it was associated with hereditary diseases, such as multiple endocrine neoplasia (MEN) 1, Von Hippel Lindau (VHL) and Neurofibromatosis type 1 (NF-1). PNETs represent a heterogeneous group of neoplasms in tumor behavior and a wide spectrum of clinical manifestations (*1,4-6*). pNENs are classified as two general categories, functional and nonfunctional, based on whether the patients present a clinical syndrome caused by the hypersecreted hormones. Patients with functional pNENs were diagnosed earlier than patients with nonfunctional pNENs (mean age of presentation 55 *vs*. 59 years) due to the different specific hormonal syndromes including gastrin, insulin, glucagon, somatostatin, vasoactive intestinal polypetide (VIP), growth hormone-releasing factor and adrenocorticotrophic hormone (*7*). The nonfunctional pNENs account for 40-90% pNENs (*8,9*). As a result, PNETs often present as a significant clinical challenge to diagnosis and prognosis for physicians.

3. Clinical presentation and Classification

For the functional pNENs, the clinical presentations are mainly determined by the hypersecreted hormones

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Table 1. WHO classification of neuroendocrine tumors 2010: Functional classification

Name	Cell type	Hormones secreted	Malignancy (%)	Pancreatic involvement (%)	Syndrome
Insulinoma	B	Insulin	10	99	Hypoglycemic symptoms, whipple triad
Gastrinoma	G	Gastrin	60-90	25	ZES (peptic ulcer, epigastric pain, diarrhea)
VIPoma	D1	Vasoactive intestinal peptide	40-70	90	Watery diarrhea, hypokalemia, dehydration, achlorhydria
Glucagonoma	A	Glucagon	50-80	100	Rash, migratory erythema, diabetes mellitus, cachexia
Somatostatinoma	D	Somatostatin	70	55	Diabetesmellitus, cholelithiasis, and diarrhea
GRFoma	PP	Growth hormone-releasing hormone	60	30	Acromegaly
ACTHoma	NT	ACTH	95	4-16	Cushing's syndrome
Carcinoid	EC	Serotonin, tachykinins	60-88	1	Diarrhea,flushing,pain, asthma, and heart disease

Table 2. 2010 WHO grading system for pNENs

Items	Grade 1 (G1)	Grade 2 (G2)	Grade 3 (G3)
Ki-67 index	< 3%	3-20%	> 20%
Mitotic count	< 2/10 HPF	2-20/10 HPF	> 20/10 HPF
Differentiation	Well differentiated	Well differentiated	Poorly differentiated

produced by the tumor (Table 1). Insulinomas are the most common pNENs type, followed in decreasing order by gastrinomas, glucagonomas, VIPomas, somatostatinomas, and other rare types (*10*). For the nonfunctional pNENs, the clinical presentations are more likely to be associated with the symptoms of local compression and metastatic lesions, such as obstructive jaundice, pain and liver metastasis. In addition, an increasing percentage of pNENs were diagnosed in asymptomatic patients who received diagnostic evaluation for unrelated problems (*11*). From the perspective of biological characteristics, except for the insulinomas which are predominantly benign, most pNENs are slow growing but ultimately malignant.

The classification and staging of pNENs is not uniform and has undergone a great number of changes. Up to now, there are three guidelines for the pNENs, which are widely used including World Health Organization (WHO) grading scheme (*12*), European Neuroendocrine Tumors Society (ENETS) classification (*13*) and c (AJCC) staging system (*14*). The 2010 WHO classification system combined the differentiation and grading features to classify the biological aggressiveness of pNENs based on the proliferative activity of the tumor as measured by mitotic count and the expression of nuclear antigen Ki-67. Grade 1 tumors have fewer than 2 mitoses per 10 high power fields and less than or equal to 3% Ki-67 staining. Grade 2 tumors have 2-10 mitoses per 10 high power fields or 3-20% Ki-67 staining. Grade 3 tumors have greater than 20 mitoses per 10 high power fields or greater than 20% Ki-67 staining. Grade 1 and 2 lesions are well differentiated and classified as neuroendocrine neoplasms (NET), while Grade 3 lesions are poorly differentiated and classified as neuroendocrine carcinomas (NEC) (Table 2). This classification system is simple and useful to standardize diagnosis and treatment. However, previous studies demonstrated that some pNENs with a high proliferative activity, but well-differentiated degree, are also classified into NEC (*15,16*). Furthermore, this subtype of pancreatic NEC, named well differentiated NET G3 normally, presented significantly better disease-specific survival than in the poorly differentiated subtype, which suggests that the biological behaviors of the two are different (*17-19*). Therefore, a separation of well differentiated NET G3 from poorly differentiated NEC G3 is emerging. The AJCC and ENETs guidelines both have TNM/staging systems. However, the two staging systems differ from each other in the definitions of T stage groupings and are used in the United States and Europe respectively. Confusion often arises because of the coexistence of the two parallel staging systems in practice (*20*). Furthermore, each staging system showed some shortcomings which was observed in the previous studies (*21-24*). So, based on the data of the Surveillance, Epidemiology, and End Results (SEER) registry (2529 patients) and a multicentric series from China (1143 patients), we proposed a modified ENETS staging classifications by maintaining the ENETS T, N, and M definitions and adopting the AJCC staging definitions (Table 3). This modified ENETS staging classification may be more suitable for pNENs than either the AJCC or ENETS systems (*25*). In addition,

Table 3. The European Neuroendocrine Tumors Society (ENETS) staging definitions, and the modified ENETS (mENETS) staging definitions for pancreatic neuroendocrine tumors with cross-tabulation of stage distributions

ENETS staging classification	
T1	Tumor limited to the pancreas, < 2 cm
T2	Tumor limited to the pancreas, 2-4 cm
T3	Tumor limited to the pancreas, > 4 cm, or invading duodenum or common bile duct
T4	Tumor invades adjacent structures
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis

ENETS				mENETS*			
Stage	T	N	M	Stage	T	N	M
I	T1	N0	M0	I	T1	N0	M0
IIA	T2	N0	M0	IIA	T2	N0	M0
IIB	T3	N0	M0	IIB	T3	N0	M0
IIIA	T4	N0	M0	IIIA	T4	N0	M0
IIIB	Any T	N1	M0	IIIB	Any T	N1	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

*The mENETS staging classification was proposed by maintaining the ENETS T, N, and M definitions and adopting the AJCC staging definitions.

the T stage definitions of the TNM/staging system in the 8th edition of the AJCC has been changed and will be used in 2018.

4. Diagnosis

The diagnosis of pNENs depends on the pathological examination. The other techniques, such as the imaging examination and tumor markers, also plays an important role in the preoperative diagnosis and observation of the disease.

5. Imaging examination

Imaging techniques for detecting of pNENs include morphological and functional imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), somatostatin receptor scintigraphy (SRS) and positron emission tomography (PET).

5.1. *Computed tomography (CT) and magnetic resonance imaging (MRI)*

CT/MRI are the most used and generally readily available techniques for the diagnosis of pNENs, especially for nonfunctional pNENs, and has sensitivity and specificity over 80%. The images of CT/MRI can be routinely reformatted in 2D or 3D image volumes to better display vascular anatomy and contribute to surgical strategy. For the pNENs, CT has a mean sensitivity and specificity of 73% and 96% respectively. For the liver metastases, mean sensitivity and specificity is 82% and 92% (*13,26*). When the MRI techniques are chosen, the sensitivity and specificity is 93% and 88% for the detection of pNENs, and the mean detection rate is 82% for the liver metastases (*13,27*). Generally, the radiological specialist tends to use MRI rather than CT for imaging of the liver and pancreas due to improved tissue contrast (*28*). However, the CT is superior to MRI on the imaging of anatomy and cost, and in most centers, CT also would be the first choice for the detection of pNENs. The drawback of CT/MRI is that the sensitivity will be decreased in small tumors with a diameter less than 2 cm (*29*).

5.2. *EUS*

EUS provides high resolution imaging of the pancreas, and is suitable to detect small size (2-5 mm) pNENs with mean detection rates of over 90% (*30*). Furthermore, EUS can guide fine-needle biopsy for cytology or core biopsy and provide a histologic diagnosis for lesion of the pancreas and duodenum (*31*). However, the availability of EUS is limited by the requirement of a highly skilled endoscopist.

5.3. *Functional imaging techniques*

Most pNENs (about 70%) express high levels of somatostatin receptors, mainly somatostatin receptor type 2 (SSTR2) (*32*), and can therefore be imaged with a radiolabeled form of the somatostatin analogue octreotide (also known as somatostatin receptor scintigraphy, SRS), such as ^{111}In-DTPA-octreotide and ^{99m}Tc-EDDA/hydrazinonicotinyl-Tyr3-octreotide. SRS provides for scanning of the whole body and allows detection of metastases outside of the abdominal region. Furthermore, SRS can offer functional information based on the levels of somatostatin receptor expression and contributes to selection of appropriate candidates for somatostatin-based therapies (*33*). However, SRS is limited by the expression of somatostatin receptors. Poorly differentiated pNENs and insulinomas are less likely to be detected and the SRS does not provide information on anatomy and surgical resectability (*34*).

Currently, the sensitivity of SRS has improved with the addition of single photon emission computed tomography (SPECT). A novel class of somatostatin analogs labeled with the positron-emitting radionuclide 68Ga for PET/CT imaging has emerged as the current gold standard for NETs (*13,35*). Combining the advantages of PET/CT and affinity for the somatostatin receptor, the sensitivity of 68Ga for PET/CT imaging for pNENs was reported to be around 90%, even if false positive findings or false negative findings may occur (*29,36*).

6. Tumor markers

Tumor markers, including serum tumor markers and immunohistochemical tumor markers, are useful for the diagnosis and prognosis, especially with nonfunctional pNENs. Plasma chromogranin A (CgA), a most widely used serum marker, was found elevated in 88-100% of pNENs. However, the diagnostic value of CgA is moderate in pNENs. The diagnostic sensitivity of CgA is less than 50% in patents with small tumors, and increases to 60-100% in patients with metastases (*37*). Therefore, serum CgA was used to reflect tumor burden, evaluate therapeutic response, and predict survival outcomes for pNENs (*37,38*). Other serum markers, including plasma neuron-specific enolase (NSE), pancreatic polypeptide (PP), pancreastatin and subunits of human chorionic gonadotropin, are also limited due to the similar phenomenon in the application of CgA (*39*). There are no immunohistochemical markers specific for pNENs. The most used label for the diagnosis of neuroendocrine tumors are synaptophysin and chromogranin. For functional pNENs, the specific peptides can be used as a label for the diagnosis of a subset of pNENs, such as insulin and glucagon.

7. Surgical management

Surgical resection is the only curative strategy for pNENs. However, because of the wide range of biological behavior and recurrence risk, the surgical treatment strategy should be considered for the functional and nonfunctional pNENs, in addition, pNETs and pNECs.

For the functional pNENs or pNETs, surgical treatment tends to be positive. In addition to radical surgery, cytoreductive surgery can also be recommended for control of secretion of activated hormones and improvement of the survival of patients with advanced pNET (*40,41*). Different from the surgical indication of pancreatic cancer, the partial hepatectomy and non-radical operations are often performed in pNET patients with liver metastases and local progressive disease (*42*). For the nonfunctional pNENs with synchronous liver metastasis, a consensus from the Chinese study group for neuroendocrine tumors (CSNET) agree with a biopsy prior to treatment (*43*). The consensus including surgical strategy is as follows: Curative surgery is recommended for G1/G2 p-NET with type I LM (single metastasis regardless of size) and R1 resection also seems to improve overall survival rate. Cytoreductive surgery is recommended for G1/G2 p-NET with type II LM (isolated metastatic bulk accompanied by smaller deposits) in select patients, and should meet stated requirements. Surgical resection for G1/G2 p-NET with type III LM (disseminated metastatic spread) and p-NEC with LM should be avoided, and insufficient evidence exists to guide the surgical treatment of G3 p-NET with LM. For local progressive disease, aggressive surgery, including superior mesenteric vein reconstruction or major pancreatic resection combined with multiple organ resection, can be done with an acceptable morbidity and mortality rate and improved survival of patients (*44,45*).

Unlike functional pNENs and advanced pNETs which will affect the quality of life and survival of patients, the small nonfunctional pNETs present a more indolent behavior. In consideration of an increasing incidence of small pNETs and only 6% of small (< 2 cm) pNETs will be metastatic at diagnosis, some suggest a conservative strategy (*46,47*). The guidelines ENETS recommends that both surgical treatment and observation are suitable for asymptomatic sporadic nonfunctional pNET ≤ 2 cm (*13*), while the guidelines of National Comprehensive Cancer Network (NCCN) recommends surgical resection for nonfunctional pNETs > 1 cm. The CSNET also provided a consensus statement about the management of small (≤ 2 cm) nonfunctional pNETs (*48*). First, the pathological confirmation should be obtained before the optimal treatment strategy is decided. Second, a more aggressive approach is suggested to be taken, except for some selected patients with nonfunctional pNETs < 1 cm, incidentally discovered and unacceptable surgical risks, all others with NF-pNETs ≤ 2 cm should undergo tumor resection and careful postoperative surveillance.

For the patients with poorly differentiated pNEC, the role of surgery is limited, because many cases are unresectable and most resectable cases have a high risk of recurrence or metastasis (49,50). Therefore, systemic medical management is the main therapeutic option for this disease.

8. Systemic medical management

While the primary treatment for pNENs is surgical, the treatment of patients with advanced or metastatic disease requires a multidisciplinary approach. Many therapeutic modalities play a pivotal role in controlling both symptoms and tumors and prolonging survival in the majority of patients. Nonsurgical therapeutic approaches include chemotherapy, biotherapies, targeted therapies, peptide receptor radiotherapy (PRRT), local ablation and interventional therapy (*51-53*).

9. Cytotoxic chemotherapy

The pNENs demonstrate a relative sensitivity to chemotherapy. However, there is no established standard chemotherapy for this disease and the chemosensitivity varies with type and differentiation status. The poorly differentiated (G3) pNECs have a better response than the well differentiated (G1/G2) pNETs. First-line therapy is traditionally platinum with etoposide for pNECs and present a response rates from 31% to 67% (*54,55*). pNECs Patients with a lower proliferative rate (Ki-67 < 55%) had a lower response rate to chemotherapy (15% *vs*. 42%) but a better overall survival (OS) (14 *vs*. 10 months) compared with patients with a Ki-67 over 55% (*54*). Well differentiatied pNETs proliferate slowly and are generally resistant to most chemotherapeutic agents with reported response rates varying from 8% to 45% (*56*). Given these findings, the oral alkylating agent temozolomide, particularly in combination with capecitabine, has shown promise. In a series of 30 patients treated with temozolomide in combination with capecitabine, 70% of patients demonstrated a radiographic tumor response (*57*). However, the effect of temozolomide was relative to the state of O6-methylguanine-DNA methyltransferase (MGMT), a low expression of MGMT in tumor cells will increase susceptibility to the temozolomide.

10. Somatostatin analogs (SSAs)

SSAs have shown a significant impact on functional pNENs patients with hormonal symptoms. Furthermore, SSAs also have cytostatic effects that can stabilize metastatic disease without tumor regression in most cases. The SSAs currently available in clinical practice are octreotide and lanreotide. Two phase III controlled studies of SSAs antiproliferative response in neuroendocrine tumor trials, CLARINET trial and PROMID trial, both have significantly better progression-free survival (PFS) (*58,59*). Although, SSAs have long been the workhorse in medical NET therapy, combination with newer targeted therapeutic agents is the most used type of treatment and may further improve outcomes (*60*).

11. Peptide receptor radiotherapy (PRRT)

PRRT is a newer treatment option that can be used for tumors that express a high density of somatostatin receptors on somatostatin receptor imaging. This is approved for use in Europe and is being studied in trials in the United States. One series of 504 patients with gastroenteropancreatic NETs treated with Lu-177 labeled PRRT reported complete and partial tumor response in 2% and 28% of patients respectively (*61*). The first phase III trial of PRRT, NETTER-1, demonstrated a significant increase in the median PFS duration of patients with midgut NETs who received DOTATATE compared with those treated with LAR octreotide. This trial succeeded in establishing an additional effective therapeutic agent against these tumors (*62*).

12. Targeted therapy

12.1. *Agents for antiangiogeneis*

pNENs are highly vascularized neoplasms and express an abundance of VEG-F and platelet-derived growth factor (PDGF) receptors. This characteristic is associated with the overexpression of both ligand and related receptor of vascular endothelial factor (VEGF) (*63*), particularly in hepatic metastases (*64*). Sunitinib is an oral, small-molecule, multi-targeted tyrosine kinase inhibitor with activity against VEG-F and PDGF. A recent phase III trial randomized 171 patients with advanced well differentiated pNENs compared therapy with sunitinib versus placebo (*65*). The study was discontinued early because of the clear advantage of sunitinib versus the placebo group. Bevacizumab is a humanized monoclonal antibody that inhibits VEG-F and has not yet been approved by the FDA for use in pNENs. Combination therapy with bevacizumab has also been investigated in pNENs. Combination therapy with mTOR inhibitor temsirolimus and bevacizumab showed a response rate (RR) of 41% (*66*).

12.2. *mTOR inhibitors*

As aberrant mTOR pathway genes have been found in 16% of pNETs, it is expected, then, that inhibiting mTOR signaling would inhibit tumor growth in at least a subset of patients. The oral mTOR inhibitor everolimus has been extensively studied in GEP-NETs. A randomized phase III study evaluating the efficacy of everolimus in advanced pNENs had been demonstrated to prolong PFS duration in patients with advanced-stage pNENs when compared with placebo (*67*). As a result of the significant improvement in PFS, everolimus was approved by the FDA for treatment of patients with advanced pancreatic NETs.

13. Conclusion

pNENs are a group of pancreatic neoplasms with high heterogeneity and a better prognosis than exocrine pancreatic cancer. The incidence of pNENs is increasing and the marjority of pNENs are nonfunctional. Localization and staging of pNENs are essential for correct management. Surgical resection remains the only curative modality for pNENs. However, the selecting and operative approach for pNENs is a complex decision that must consider a myriad of factors. An expanding number of systemic treatment options are available for clinicians treating pNENs.

Cytotoxic chemotherapy and/or SSA used to be the primary treatment for patients with unresectable tumors, but the role of cytotoxic chemotherapy continues to be debated, followed by peptide receptor radionuclide therapy. Targeted drugs inhibiting angiogenesis and mTOR pathways have been developed. There are still many unanswered questions about optimized classification, staging and treatment of pNENs.

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