Pancreatic Neuroendocrine Tumors: an Update

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Abstract Pancreatic neuroendocrine tumors (pNETs) are rare and comprise only 1–2 % of all pancreatic neoplastic disease. Although the majority of these tumors are sporadic (90 %), pNETs can arise in the setting of several different hereditary genetic syndromes, most commonly multiple endocrine neoplasia type 1 (MEN1). The presentation of pNETs varies widely, with over 60 % having malignant distant disease at the time of initial diagnosis involving the liver or other distant sites. Functioning pNETs represent approximately 10 % of all pNETs, secrete a variety of peptide hormones, and are responsible for several clinical syndromes caused by profound hormonal derangement. Surgery remains the cornerstone of therapy and the only curative approach. It should be pursued for localized disease and for metastatic lesions amenable to resection. Multimodality therapies, including liver-directed therapies and medical therapy, are gaining increasing favor in the treatment of advanced pNETs. Their utility is multifold and spans from ameliorating symptoms of hormonal excess (functional pNETs) to controlling the local and systemic disease burden (non-functional pNETs). The recent introduction of target molecular therapy has promising results especially for the treatment of progressive well-differentiated G1/G2 tumor. In this review, we summarize the current knowledge and give an update on recent advancements made in the therapeutic strategies for pNETs.

Keywords Neuroendocrine tumor · pNET · Pancreatic cancer

Introduction

Pancreatic neuroendocrine tumors (pNETs) are rare, having an estimated incidence of 0.43 per 100,000 and representing only 1–2 % of all pancreatic neoplasms [1, 2]. Recent evidence suggests that pNETs originate from pluripotent pancreatic stem cells of the ductal/acinar system and are characterized by a series of distinctive genetic mutations [3].

Commonly identified, in order of frequency, are mutations of MEN1 (44 %), DAXX (25 %), ARX (18 %), and genes of the mTOR pathway (16 %) [4]. Characteristic is the almost complete absence of the KRAS mutation which is distinctly different than pancreas adenocarcinoma where KRAS mutations are common.

A particular trait of pNETs is the capacity to produce and secrete different hormones including insulin, gastrin, vasoactive intestinal peptide (VIP), glucagon, and somatostatin [5]. These pNETs are classified as functional and make up 10 % of pNETs. The other 90 % are non-functional and therefore do not cause symptoms from deregulated and excess hormone production.

Although rare, functional pNETs give rise to very distinctive syndromes [5–7]. Insulinomas are the most common functional pNETs (35–40 %) and are characterized by episodic hyperinsulinemia leading to symptomatic hypoglycemia [5, 6].

Gastrinomas (16–30 %) are responsible for excessive gastrin secretion that culminates in refractory peptic ulcer disease and secretory diarrhea also known as Zollinger-Ellison syndrome [5, 6].

Glucagonomas (less than 10 %) often present with a typical dermatitis known as migratory necrolytic erythema characterized by necrotic erythematous lesions that eventually resolve

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in pigmented scarring [8, 9]. In addition, glucose intolerance, weight loss, diarrhea, and deep vein thrombosis can be observed.

VIPomas (less than 10 %) lead to increased secretion of vasoactive intestinal polypeptide causing large volume of watery diarrhea culminating in symptomatic hypokalemia [10].

Somatostatinomas are perhaps the least common functional pNETs (less than 5 %) and have the potential to cause diabetes mellitus, diarrhea/steatorrhea, gallbladder disease, anemia, and weight loss [5–7].

Non-functional pNETs are often diagnosed late in the disease process or incidentally as a result of imaging studies done for different reasons. Typical symptoms of non-functional pNETs include abdominal pain, back pain, weight loss, jaundice, possibly pancreatitis, and are likely due to the mass effect exerted by the pNETs lesions on the surrounding structures [11]. At the time of diagnosis, 20 % of patients present with locally advanced disease, and approximately 60 % of patients present with metastatic disease [9].

Syndromic pNET

It is widely recognized that pNETs can be associated with several genetic syndromes. In fact, approximately 10 % of all pNETs arise in the setting of a known familial syndrome including multiple endocrine neoplasia type I (MEN1) and type IV (MEN4), von Hippel-Lindau disease (VHL), neurofibromatosis type I (NF1), or tuberous sclerosis complex (TSC) [6, 12]. Syndromic pNETs tend to be multi-focal throughout the pancreas. Characteristic of syndromic pNETs are summarized in Table 1.

Diagnosis

Patient's history and physical examination are of paramount importance, especially in the setting of functional pNETs. Evidence of endocrine dysfunction or a family history of syndromes known to be associated with pNETs should prompt a thorough evaluation. Nevertheless, non-functional pNETs may be difficult to differentiate from adenocarcinoma as they both present with symptoms related to the mass effect [13].

Biochemical evaluation is an invaluable aid in the diagnosis of functional pNETs and should be tailored based on the specific syndrome encountered (e.g., insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma, etc. [Table 2]).

Insulinoma can be suspected based on the presence of the Whipple triad: (1) symptoms of hypoglycemia during fasting or exercise, (2) glucose levels <45 mg/dL (2.5 mmol/L) at the time of symptoms, and (3) resolution of symptoms following glucose administration.

The diagnosis of insulinoma is confirmed by a 72-h fast with measurement of glucose and insulin levels at the time of symptoms [14]. It is important to exclude surreptitious insulin use by assuring the presence of normal serum C-peptide level [15].

Gastrinoma is diagnosed by measurement of serum gastrin level and confirmed by the administration of a secretin stimulation test [16–19].

The diagnosis of glucagonoma, VIPoma, and somatostatinoma requires serum level measurement of their respective hormones (glucagon, VIP, and somatostatin) [10, 20].

Several studies report on the utility of tumor markers, such as chromogranin A (CgA) and neuron specific enolase (NSE) in the setting of pNETs [21–23]. It is worth noting that CgA is hindered by a moderate specificity (sensitivity: 72–100 %; specificity: 50–80 %), and NSE has been reported to have a poor sensitivity (sensitivity: 30–40 %; specificity: ~100 %) limiting their utility as reliable diagnostic tools. Nevertheless, characteristic of serum CgA levels is their direct correlation with tumor burden and metastatic disease; therefore, CgA levels are often used to evaluate progression or response to therapy [21, 22, 24].

Tumor Localization

Several non-invasive and invasive techniques have been utilized to localize and stage pNETs. Multi-slice computed tomography (CT) using a triple-phase contrast protocol (arterial, pancreatic, and portal-venous phase) is often the primary imaging modality in light of its acceptable sensitivity (62–83 %) and good specificity (83–100 %) [25]. Major limitations of triple-phase CT are evident in the setting of lesions that are only a few millimeters in size (too small to be seen) or in the rare subgroup of pNETs that present as cystic lesions (approximately 10 %). In this latter scenario, the misdiagnosis rate has been reported as high as 43 % [26].

Magnetic resonance (MR) imaging techniques are particularly useful for lesions that are too small to be seen by CT or for the identification and follow-up of liver metastatic disease, where MR has been shown to be superior to CT [27–29]. The reported sensitivity of MR ranges from 85 to 100 % with a specificity of 75 to 100 % [25, 27].

Somatostatin receptor scintigraphy (SRS) takes advantage of cellular somatostatin receptor expression by both functional and non-functional pNETs. This test utilizes radiolabelled somatostatin analogs and can visualize pNETs with good sensitivity ranging from 75 to 100 % [27, 30]. There are four major applications for SRS: (1) pNETs are highly suspected but conventional cross-sectional imaging failed to locate any lesions, (2) in the setting of glucagonoma as this tumor tends to present outside the pancreatic anatomic boundary, (3) to evaluate the level of uptake when considering radiotherapy with labeled somatostatin analog, and (4) in the evaluation of

Table 1 Characteristics of syndromic pancreatic neuroendocrine tumors

Syndrome	Genetic mutation	Protein	Incidence of pNETs	Clinical manifestation
MEN1	MEN1 gene 11q13	Menin	80 %	Gastrinoma 50 % Insulinoma 20 % VIPoma 3–5 % Glucagonoma <5 %
MEN4	CDKN1B gene 12p13.1-p12	CDK1 p27Kip1	Unclear	MEN1-like type syndromes and higher incidence of adrenal, renal, gonadal, and thyroid tumor
VHL	VHL gene 3p25	VHL	10–20 %	Mostly not functional-pNETs
NF1	NF 1 gene 17q11.2	Neurofibromin 1	<5 %	Mostly somatostatinoma
TSC	TSC1 gene 9q34 TSC2 gene 16p13	Hamartin (TSC1) Tuberin (TSC2)	1–2 %	pNETs are rare and poorly characterized

pNET pancreatic neuroendocrine tumor, *MEN* multiple endocrine neoplasia, *CDK1 p27Kip1* cyclin-dependent kinase inhibitor 1B, *VHL* Von Hippel-Lindau, *NF* neurofibromatosis, *TSC* tuberous sclerosis

metastatic disease. It is important to note that insulinomas are not well visualized with SRS as their level of expression of somatostatin receptors is either low or absent.

Positron emission tomography (PET) uses ¹⁸F-fluorodeoxyglucose (FDG) to evaluate the metabolic rate of the tumor. PET is best suited for the identification of rapidly progressive tumors. Usually, high FDG avidity correlates with poorly differentiated pNETs and increased mortality risk [31, 32]. Recently, the use of ⁶⁸Ga-labeled somatostatin analogs has been proposed by several authors and shown to be superior to both SRS and conventional cross-sectional imaging [33–36]. Furthermore, the simultaneous use of PET and CT imaging techniques (PET-CT) has been shown to have a sensitivity ranging from 94 to 100 % [34, 37].

Endoscopic ultrasound (EUS) has gained popularity during the last decade. Not only do EUS techniques benefit from a good sensitivity and high specificity, respectively, 82 and 92 %, but they also allow for tissue biopsy and offer the possibility of lesion tattooing [38, 39]. The latter has been shown to be an invaluable advantage especially in the presence of small pNETS when a laparoscopic approach is planned [40].

Staging

The development of an accurate staging system for pNETs remains an area of active investigation. To date, at least three formal staging systems have been proposed by three different major organizations, including the World Health Organization (WHO), the European Neuroendocrine Tumor (ENETS), and the American Joint Commission on Cancer (AJCC) [41–43]. Although each of these staging systems utilizes slightly different criteria, their ability to predict survival is quite similar [44–46].

Tumor grade and differentiation held an important role in the evaluation and staging of pNETs. Reportedly, well to

moderately differentiated tumor (G1/G2) appears to have a more indolent course and appear to be more responsive to therapeutic intervention. Poorly differentiated (G3) tumors are highly aggressive, often present with disseminated unresectable disease, and show poor response to chemotherapy-based treatments. Nevertheless, tumor mitotic counts and the Ki-67 index are being increasingly recognized as important predictors for tumor response to therapy and overall outcome.

Treatment

Resectable Disease

Surgery remains the backbone of therapy for pNETs and the only truly curative approach. However, pNETs can often present with advanced disease precluding surgical resection and limiting interventions to palliation of symptoms originating from hormone excess (functional-pNETs) and, when appropriate, control of disease burden (e.g., cytoreductive surgery, tumor direct therapy, and systemic medical therapy).

Several surgical approaches are described in the literature for treatment of local resectable disease. The choice of the specific procedure is based on the location of the tumor and its anticipated malignant potential.

Complete oncologic resection is obtained via distal pancreatectomy with or without splenectomy, pancreaticoduodenectomy, and in selected cases total pancreatectomy. These approaches allow for complete removal of the neoplastic lesions and ensure adequate lymph node harvest.

Insulinomas represent a particular case of pNETS, as they have the lowest malignant potential amongst all pNETS, and can often be treated with less invasive procedure such as enucleation. Although a general consensus has yet to be reached, several authors suggest reserving enucleation only for

Table 2 Functional pNETs diagnostic criteria

Tumor	Secreted hormone responsible for clinical syndrome	Diagnostic criteria (symptomatic disease)	Prevalence amongst functional pNETs
Insulinoma	Insulin	72 h fast: plasma glucose <45 mg/dL; insulin $\geq 6 \mu\text{U/mL}$; insulin/glucose ratio >0.3; C-peptide level 0.2 nmol/L; proinsulin level $\geq 5 \text{ pmol/L}$; absence of sulfonylurea	35–40 %
Gastrinoma (Zollinger-Ellison)	Gastrin	Elevated fasting serum level of gastrin off PPIs with concomitant gastric pH <2.5; secretin stimulation test with paradoxical increase in serum gastrin by $\geq 200 \text{ pg/mL}$	16–30 %
VIPoma (Verner-Morrison)	Vasoactive intestinal peptide	Serum VIP level >75 pg/mL in the presence of high-volume watery diarrhea (unexplained by other causes)	<10 %
Glucagonoma	Glucagon	Fasting serum glucagon level >500 pg/mL	<10 %
Somatostatinoma	Somatostatin	Fasting serum somatostatin >160 pg/mL and pancreatic or duodenal mass, or presence of symptoms/clinical signs (e.g. diabetes, steatorrhea, cholelithiasis)	<5 %

PPIs proton pump inhibitors, VIP vasoactive intestinal peptide

insulinoma or small non-functional pNETs (less than 2 cm in size) that are distant from the pancreatic duct. Nevertheless, when appropriate cases are selected, enucleation offers similar survival outcomes compared to more radical oncologic resection [47–50]. Major concerns with this surgical approach are the occurrence of pancreatic fistulas and the inability to properly assess the regional lymph nodes [47–50]. Lastly, central pancreatectomy can be performed for pNETs lesions that lie in the pancreatic neck or body and are in close proximity with the pancreatic duct [51–54].

In general, pNETs lesions are particularly suitable to minimal-invasive surgical approaches, and laparoscopic pancreatectomies are described with increased frequency in the literature with encouraging results [55–58].

Advanced Disease

The role of surgery in the setting of locally advanced and metastatic pNETs remains a matter of controversy. Evidence suggests that tumor debulking may be beneficial only if more than 90 % of tumor burden can be removed [59, 60].

A debulking procedure should include removal of the primary disease, regional lymph nodes, and distant metastasis. The advantages of an appropriate debulking are multifold, spanning from resolution of symptoms (in patients that where symptomatic pre-operatively) to associated 5- and 10-year survival rate up to 61 and 35 %, respectively [61].

Nevertheless, according to recent studies, less than 15 % of patients presenting with metastatic disease are eligible for a debulking procedure [59, 62] as no survival advantage has been shown in patients receiving suboptimal debulking (<90 % of disease burden) [62–64]. Unfortunately, even after removal of all metastatic disease with microscopic negative margin (R0), the recurrence (or persistence) rate remains high with 1-year and 5-year disease free survival (DFS) of 53.7 and 10.7 %, respectively [23].

Metastatic liver disease occurs in greater than 50 % of pNETs and can be tackled using several described approaches. The appropriate approach is chosen mostly based on lesion distribution within the liver parenchyma, numbers, size, presence of extra-hepatic disease, patient's comorbidities, and functional status.

Partial hepatectomy should be pursued in the setting of clearly resectable metastatic liver disease either preceding or concomitantly with pancreatic resection [59, 60, 65–68]. In the situation, when a pancreaticoduodenectomy is necessary to treat the primary pancreatic lesion, a staged procedure where hepatectomy is performed first should be considered. This will decrease the occurrence of hepatic abscesses caused by pre-existing contamination of the biliary tract through the bilio-enteric anastomosis [69].

Local ablative therapies can be used as an alternative approach in patients who are not candidates for liver resection or in addition to cytoreductive surgery. Radiofrequency ablation (RFA), cryotherapy, microwave coagulation, and ethanol injection have all been described; however, RFA is by far the most commonly utilized technique [70, 71]. Local ablative therapy can be performed percutaneously, laparoscopically, or during an open procedure. These techniques are associated with a low complication rate of approximately 5–15 % (mainly hematoma or abscess) and can be employed multiple times for recurrent disease. Initial experiences with RFA have been encouraging, reporting symptom relief in 70–90 % of patients and 5-year survival of approximately 48 % [72, 73].

Transarterial embolization (TAE) and transarterial chemoembolization (TACE) are used with diffuse metastatic liver lesions where surgical or local ablative therapy is not possible. These techniques require angiographic visualization of the hepatic artery and identification of specific arterial branches feeding the metastatic lesions. TAE utilizes occlusive particles alone (often referred to as bland embolization) while TACE benefits from the addition of chemotherapeutic agents (e.g., 5-

fluorouracile, cisplatin, streptozocyn, anthracycline, etc.). TACE has been shown to offer a higher response rate and a slight survival advantage compared to TAE, although a general consensus is still lacking [30, 31, 74, 75]. Portal vein thrombosis, ascites, and liver failure are absolute contraindications for TAE/TACE. It is worth noting that diffuse metastatic disease, involving more than 50 % of the liver parenchyma, represents a relative contraindication to TAE/TACE as episodes of acute liver failure are known to occur [5, 62, 76].

In the setting of extensive liver disease, radioembolization (RE) is a valuable alternative to TAE/TACE. Radioactive yttrium-90 (Y90) microspheres are accurately delivered, through selective arterial catheterization, into the peritumoral vasculature. This technique allows accurate targeting of metastatic lesions with minimal peripheral tissue damage, as Y90 has a mean tissue penetrance of only 2.5 mm and contrary to TAE/TACE, does not require tissue ischemia [77, 78]. The experience with this technique is still in its infancy, especially in the setting of pNETs. However, early results are encouraging, showing a median survival of approximately 70 months and reporting stable lesions or partial response in 27 and 60.5 % of patients, respectively [79, 80].

Orthotopic liver transplantation (OLT) has been the subject of many investigations, and efforts are still ongoing to define the appropriate cohort who will benefit the most from this intervention. Eligible for OLT are patients with diffuse metastatic liver disease, who do not qualify for cytoreductive or ablative procedure or patients suffering from severe symptoms caused by hormonal derangement, who have failed medical therapy. Nevertheless, the long-term survival rates remain disappointing with a disease-free survival rates ranging from 20 to 48 % at 5 years [81–83]. In light of this relatively low cure rate, several authors suggest limiting OLT to patients younger than 50 years, with a Ki-67 index less than 2 % (low-grade tumor), with tumor staining positive for epithelial cadherin, and only in the absence of extrahepatic disease [81–85].

Medical Therapy

Medical therapy aims to control the disease burden (non-functional pNETs) and ameliorate symptoms of hormonal excess (functional pNETs). Its utility is particularly pronounced in the setting of advanced unresectable disease. Several strategies are available including cytoreductive chemotherapy, hormonal therapy (somatostatin analogues), peptide receptor radiotherapy, and most recently targeted molecular therapy.

Cytoreductive Chemotherapy

For over three decades, streptomycin, often used in combination with either 5-FU (5-fluorouracile) or doxorubicin, has been the primary chemotherapeutic agent, especially for tumors with well to moderate differentiation (G1/G2). Despite

initially encouraging reports, it has now become clear that streptomycin-based regimens are characterized by a poor response rate of approximately 39 % and by a 2-year progression-free and overall survival of 41 and 74 %, respectively [86].

New synergistic chemotherapeutic strategies are currently being investigated, and favorable results can be obtained with the use of temozolamide (oral alkylating agent) and capecitabine (oral pro-drug of 5-FU). The initial experiences with temozolamide and capecitabine, in the setting of metastatic pNETs disease, show a radiographic response rate of approximately 60 %, with an estimated median progression-free survival of 14 months, and median overall survival of 83 months [87–89]. Another advantage of this synergistic regimen is its favorable toxicity profile compared to streptomycin [87].

High-grade, poorly differentiated pNETs are very aggressive tumors that often present with disseminated unresectable disease. Although, in rare occasions, high-grade tumor can be candidate for surgical resection, the majority are treated based on platinum regimen with response rates ranging from 42 to 67 % for the combination of cisplatin and etoposide [90].

Somatostatin Analogues and Peptide Receptor Radiotherapy

Overexpression of somatostatin receptors is characteristic of most pNETs (with the exception of insulinomas) and justifies the use of somatostatin analogues and peptide receptor radiotherapy.

Octreotide and lantreotide are the most commonly utilized somatostatin analogues (SSAs) and are exceptionally useful in the setting of functional pNETs.

SSAs bind to somatostatin receptors to effectively decreasing hormone release and ameliorating clinical symptoms caused by hormonal derangement [5, 91]. SSAs have also been shown to exert a cytostatic effect, which can result in disease stabilization and the lengthening of the median time to tumor progression [92].

Radioactive agents coupled with SSAs constitute the basis of peptide receptor radiotherapy (PRRT). This technique takes advantage of the SSAs specificity for somatostatin receptors to selectively deliver cytotoxic doses of a radioactive isotope (e.g., yttrium-90 or lutetium-177) to pNETs cells. Currently, under investigation, this therapy is mainly offered in the setting of progression of liver disease. A recent series reported on [67] pNETs patients with inoperable metastatic disease treated with ¹⁷⁷Lu-octreotate showing a partial response rate of 60.3 % with stabilization of disease in 13.2 % of cases. In the same study, the median progression-free survival and overall survival were 34 and 53 months, respectively [93]. Similar findings were reported by other authors [94–96], suggesting a potential role for this therapy in the setting of advanced pNETs.

Targeted Molecular Therapy

An increasing body of knowledge on specific mutation patterns present in pNETs has opened the way to the development of targeted molecular therapy.

Everolimus, an oral mTOR pathway inhibitor, was recently FDA-approved for the treatment of advanced pNETs. In a phase III clinical trial, patients treated with everolimus showed an improved median progression-free survival of 11 months compared to the placebo group (4.6 months) [97]. Although these results are encouraging, mutations of the mTOR pathways are present in only 16 % of pNETs, making everolimus beneficial for only a minority of patients [4].

Sunitinib, an oral tyrosine-kinase inhibitor, targets the vascular endothelial factor (VEGF) and may have broader application than everolimus. In fact, pNETs are highly vascular tumors that express high levels of VEGF receptors. Results obtained from a phase III clinical trial, showing a 2-fold increase in the median progression-free survival compared to placebo (11.5 vs. 5.5 months, respectively) [98], led to the approval of sunitinib by the FDA as the first-line therapy in advanced pNETs.

Conclusions

Pancreatic neuroendocrine tumors are rare, mostly sporadic, and tend to be non-functional. A small percentage of these tumors can arise in the setting of genetic syndromes (commonly MEN1) and can be responsible for several distinctive clinical syndromes caused by hormonal derangement. Though surgery remains the only curative approach, multimodality therapies are increasingly utilized in the treatment of pNETs especially when the presence of disseminated disease, which precludes a curative surgical intervention. The recent development of targeted molecular therapies is showing encouraging results; however, it is still limited to a minority of patients. The increasing body of knowledge on pNET's biology will likely open the door to new therapeutic targets especially in the setting of advanced disease.

Conflict of Interest No conflicts of interest are declared.

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