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Neuroendocrine Tumors of the Pancreas: Diagnosis and Management

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Abstract

Pancreatic neuroendocrine tumors (pNETs) are rare, heterogeneous malignancies with varied presentation and management. PNETs are categorized into syndromic and non-syndromic based on clinical manifestations secondary to the secretion of bioactive peptides. Approximately 10% of pNETs are associated with an inherited syndrome with an established genetic predisposition to tumor development. Generic non-invasive biomarker testing can be utilized for monitoring disease progression and treatment response, but these are non-specific and may be falsely elevated due to various factors. Non-invasive imaging modalities are effective methods of localization, but angiography, endoscopic ultrasound, and intraoperative palpation with ultrasound are beneficial adjuncts for localization. Overall survival and prognosis vary considerably based on tumor pathology, differentiation, and proliferation index, but many malignant tumors are clinically silent and are recognized after locoregional or metastatic spread. Surgical resection with negative margins can be curative for tumors identified at an early stage. For unresectable or metastatic disease, locoregional therapy and systemic treatment are options. In this review, we discuss the clinical presentation, diagnosis, and potential management options of pNETs.

Keywords

Pancreatic neuroendocrine tumor (pNET); diagnosis; classification; management; imaging; surgical interventions

1. Introduction

Neuroendocrine neoplasms (NENs) are present in a wide range of body systems. Dense core granules constitute the 'neuro' component of the classification, while synthesis and secretion of monoamines constitute the 'endocrine' component of the classification [1–3]. Neuroendocrine tumors of the pancreas are a heterogenous disease with heterogeneous presentation patterns, comprising 1-2% of all pancreatic lesions [4,5]. Pancreatic neuroendocrine tumors (pNETs) can be divided into syndromic and non-syndromic tumors based on hormone production and comprise approximately 7% of gastropancreatic NENs [6].

2. Genetic Syndromes Associated with Pancreatic Neuroendocrine Tumors

While a majority of pNETs are sporadic, approximately 10% are associated with an inherited syndrome, including multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau (VHL), neurofibromatosis type 1 (NF-1), and Mahvash disease [7,8].

2.1. MEN1

MEN1, also known as Wermer syndrome, is a high-penetrance, autosomal-dominant, endocrine syndrome caused by a germline-inactivating mutation of the *menin* gene located on chromosome 11 [9]. A majority of patients exhibit clinical and biochemical manifestations by the age of fifty. Classically, patients have pituitary, neuroendocrine,

and parathyroid tumors. In addition, MEN1 patients often develop non-syndromic pNETs, and in those patients, MEN1 mutation is the most common genetic alteration seen [9].

2.2. VHL

Von Hippel-Lindau (VHL) syndrome is an autosomal dominant, high penetrance mutation of the VHL tumor suppressor gene located on chromosome 3, resulting in characteristic growth of cysts and tumors, including hemangioblastomas, cysts of the kidney and pancreas, renal cell carcinoma, pheochromocytoma, and pNETs [10].

2.3. NF-1

NF-1 is an autosomal dominant, complete penetrance mutation of the NF-1 tumor suppressor gene located on chromosome 17. Characteristic findings of the disease include axillary and inguinal freckling, lisch nodules, skeletal abnormalities, neurological abnormalities, and malignancies, including Wilms tumor, rhabdomyosarcoma, leukemia, gastrointestinal stromal tumors, breast cancers, retinoblastoma, and pNETs [11,12].

2.4. Mahvash Disease

Mahvash disease is an autosomal recessive pNET syndrome secondary to biallelic inactivating mutations of the glucagon receptor gene, *GCGR* [13]. Patients develop hyperglucagonemia without the symptoms associated with glucagonomas or alpha-cell hyperplasia [14]. The most common presenting symptom is vague abdominal pain with characteristic diffuse hypertrophy of the pancreas with associated pNETs [13].

3. Genomic Profile of pNETs

Aside from the inactivation of MEN1, VHL, TSC1/2, and hyper-activation of PI3K/mTOR signaling, genomics studies identified additional pNET-specific markers [15]. Next-generation sequencing of a large cohort of pNET tissues has identified recurring themes exemplified by telomere length shortening through the inactivation of DAXX and ATRX [15]. The International Cancer Genome Consortium (ICGC) studied well-differentiated pNETs and identified several novel findings. These findings include defining a mutational signature characterizing pNETs, demonstrating a higher-than-expected prevalence of germline mutations in patients lacking a family or personal history of cancer, identifying novel mutational mechanisms and confirming the heavy involvement of chromatin remodeling and the PI3K/mTOR pathway in pNET development [15].

4. Serum Biomarkers

Serum biomarkers allow for biochemical, non-invasive evaluation and surveillance of patients with suspected pNETs. Most serum biomarkers are broadly associated with neuroendocrine tumors (NETs) providing restricted information regarding individual tumor behavior. Current pNET biomarkers are monoanalyte assessments providing limited information regarding cellular activity, as components of tumor progression, including growth factor signaling and metabolic status, are not accounted for [16,17]. In order to overcome these limitations, liquid biopsies have been proposed for multianalyte assessments of pNETs [18].

4.1. Chromogranin A

Chromogranin A (CgA) is a serum glycoprotein biomarker released by neurons and neuroendocrine cells that is utilized in the diagnosis of pNETs and is also used for monitoring tumor status and treatment response and in surveillance. Although possessing a sensitivity of 95% and a sensitivity of 71%, CgA is a poor diagnostic biomarker when used by itself [19,20]. Confounding factors that may result in an elevated CgA include chronic gastritis, renal failure, liver failure, inflammatory bowel disease, and proton-pump inhibitor use. Notably, CgA levels increase with tumor size, metastasis, and tumor stage of pNETs, and, therefore, possess a limited role in the diagnosis and treatment of early-stage pNETs [19,21]. However, in patients with elevated preoperative CgA on presentation, trending CgA may be a reliable indicator for response to treatment, post-operative recurrence, and the presence of metastatic disease [22,23].

4.2. Neuron-Specific Enolase

Also secreted by neurons and neuroendocrine cells, neuron-specific enolase (NSE) can be utilized in conjunction with CgA as a predictive and prognostic indicator [19,24]. The prognostic value of CgA and NSE for the treatment of pNETs with everolimus was evaluated in a study by Yao *et al.* [25]. In this study, patients with elevated baseline NSE had shorter median PFS and OS than those with non-elevated baseline NSE. Furthermore, median PFS was prolonged in patients with early NSE response to treatment compared to patients without early response to treatment. The same PFS and OS trends were identified with CgA [25].

4.3. Pancreatic Polypeptide

Pancreatic polypeptide (PP) is a secondary biomarker for pNETs, due to variable success in its utilization. PP is a 36 amino acid hormone typically produced by islet cells located in the head and uncinate process of the pancreas. PP can be falsely elevated in the post-physical exercise state, hypoglycemic state, and after food ingestion [19]. There have been reports of pNETs that exclusively secrete PP; however, these tumors are exceedingly rare [19,26,27].

4.4. Liquid Biopsy

Liquid biopsy identifies personalized tumor characteristics through analysis of tumor extracellular vesicles, circulating tumor DNA, RNA, tumor-educated platelets, and circulating tumor cells (CTCs) [17,18]. While liquid biopsies offer the advantage of personalized diagnostics, there are notable challenges **(Table 1)** [18]. For example, CTCs comprise a small component of blood sampling and are detectable in < 50% of patients [17]. The neuroendocrine neoplasms test (NETest) is a multianalyte, liquid biopsy assessment which evaluates 51 individual circulating genes in 1 cc of blood. Precision and accuracy are 4x and 10x greater than CgA, respectively. NETest can be used to analyze disease progression, monitor treatment efficacy, and supplement assurance of complete surgical resection versus residual disease [26]. Malczewska *et al.* determined that the NETest accurately correlates with the grading, staging, and progression of gastroenteropancreatic NENs [27]. In a meta-analysis by Oberg *et al.*, NETest is predicted to reduce the need for radiologic surveillance by 50% [28]. Liu *et al.* evaluated the clinical utility of NETest

and determined that NETest diagnostic accuracy was 95% concordant in patients with image-detected disease. As a result, they estimated that the use of NETest could result in a reduction of healthcare spending of 240 million to 1.69 billion (United States Dollars [USD]) [17,29]. At the present time, liquid biopsy is still not a widely accepted standard of care in pNET management. Ultimately, further prospective studies would be beneficial to determine the role of liquid biopsy in pNET [30].

5. Staging and Grading

The American Joint Committee on Cancer (AJCC) and the European Neuroendocrine Tumor Society (ENETS) have provided two widely accepted staging classification systems utilized for the management of pNETs (Table 2) [31–33]. The ENETS Tumor Node Metastasis (TNM) staging classification was initially established in 2006, and the AJCC staging system was last updated in 2018 (8th edition) [31]. In 2017, the World Health Organization (WHO) updated the grading criteria for pNETs. pNETs are initially categorized as well-differentiated or poorly-differentiated. Well-differentiated pNET are further categorized as grade 1 to grade 3 based on mitotic rate and Ki-67 proliferation index (Table 3). The mitotic rate is calculated based on the mitosis in 50 high-power fields reported based on mitosis per 10 high-power fields. The Ki-67 proliferation index is calculated based on examining ≥ 500 cells in an area of high nuclear labeling [34].

Table 1: Advantages and disadvantages of liquid biopsy [17,18].

Advantages	Disadvantages
Non-invasive	Not standard of care
Lower cost than tissue sampling	Detection limitations in blood samples (CTCs, DNA, RNA limited compared to other blood components)
Monitoring of drug response	
Monitoring of tumor progression	

CTC – Circulating tumor cells; DNA – Deoxyribonucleic acid; RNA – Ribonucleic acid.

Table 2: AJCC 7th, AJCC 8th, ENETS edition staging classification [31–33].

	AJCC 7th edition staging classification	AJCC 8th edition staging classification	ENETS staging classification
T1	≤ 2 cm, limited to the pancreas	< 2 cm, limited to the pancreas	≤ 2 cm, limited to the pancreas
T2	> 2 cm, limited to the pancreas	2–4 cm, limited to the pancreas	> 2 cm and < 4 cm, limited to the pancreas
T3	Beyond pancreas, but no involvement of SMA	> 4 cm, limited to the pancreas, duodenum, or CBD	> 4 cm, limited to the pancreas, duodenum, or CBD
T4	Involvement of SMA or CA	Tumor invades adjacent structures	Tumor invades adjacent structures or infiltration of large blood vessels
N0	No nodal involvement	No nodal involvement	No nodal involvement
N1	Regional lymph node metastasis	Regional lymph node metastasis	Regional lymph node metastasis
M0	No distant metastasis	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis	Distant metastasis
M1a		Metastasis is confined to the liver	
M1b		Metastasis in at least one extrahepatic site	
M1c		Both hepatic and extrahepatic metastases	

SMA – superior mesenteric artery; CA – celiac artery; CBD – Common bile duct.

Table 3: World Health Organization (WHO) pNET grading classification [34].

Classification	Mitotic rate	Ki-67 proliferation index
Well-differentiated pNETs:		
NET G1	< 2	< 3
NET G2	2-20	3-20
NET G3	> 20	> 20
Poorly-differentiated pNETs:		
NEC G3 (small and large cell subtypes)	> 20	> 20

NEC - Neuroendocrine carcinoma; NET - Neuroendocrine tumors; pNET - Pancreatic neuroendocrine tumor; G - Grade.

6. Syndromic pNETs

PNETs are categorized as syndromic or non-syndromic. Most pNETs are non-syndromic and consequently are identified incidentally on imaging or as a result of mass effect. Syndromic tumors are usually smaller than non-syndromic tumors due to the early onset of symptoms from an overproduction of hormones that result in symptoms associated with hormonal excess [8].

6.1. Insulinoma

Insulinomas are sporadic, solitary islet cell tumors, accounting for approximately 60% of syndromic pNETs. These neoplasms typically occur in the fifth decade of life with an incidence of 1/1-4,000,000. These tumors are commonly hypervascular and measure less than 2 cm in size [35]. Tumor distribution is consistent with the distribution of the beta cells in the pancreas and tumors are located throughout the body and tail. Because insulinomas arise from the beta cells of the pancreas, patients characteristically exhibit fasting hypoglycemia [3,36,37]. There must be a high suspicion for insulinoma when Whipple's triad consisting of neuroglycopenic symptoms, fasting blood glucose of < 50mg/dL, and relief of symptoms with glucose treatment is present. The gold standard for diagnosing an insulinoma has been a 72-hour observed fast. Nearly 100% of patients experience hypoglycemia with associated symptoms by 72 hours, 80% experience symptoms at 24 hours, and 30% experience symptoms at 12 hours [3]. Hirshberg *et al.* determined that a supervised 48-hour fast in conjunction with plasma insulin and proinsulin level measurements every 6 hours was diagnostic in greater than 97% of patients with insulinoma and suggested this regimen replace the 72-hour fast [38]. To rule out exogenous sources of insulin, additional biochemical considerations include proinsulin ≥ 5 pmol/L, β - hydroxybutyrate ≤ 2.7 mmol/L, C-peptide ≥ 0.6 nmol/L in addition to an insulin ≥ 3mU/mL and a negative plasma sulfonylurea level **(Table 4)** [36]. The majority of insulinomas are benign, and surgical resection is curative. 10% of these tumors are malignant, with a greater likelihood of malignancy in tumors associated with MEN1 [3]. MEN1-associated insulinomas tend to develop earlier, often present with a multicentric disease, and are associated with a greater likelihood for recurrence than malignant insulinomas not associated with MEN1 syndrome [35]. Furthermore, tumor size > 2 cm, Ki-67 > 2%, and chromosomal instability have been reported as possible poor prognostic indicators for metastatic disease and poor PFS [36,39].

Table 4: Common Diagnostic Criteria for Insulinoma [36].

Common Diagnostic Criteria for Insulinoma
Insulin ≥ 3mU/mL
Proinsulin ≥ 5 pmol/L
β - hydroxybutyrate ≤ 2.7 mmol/L
C-peptide ≥ 0.6 nmol/L
Negative plasma sulfonylurea

6.2. Glucagonoma

Glucagonomas are rare, solitary tumors that develop predominantly in the body and tail of the pancreas, consistent with the distribution of pancreatic alpha cells. Most lesions are greater than 3 cms in size at diagnosis, and approximately 50% of patients present with metastatic disease to the liver [40]. Excessive glucagon secretion from the tumor results in weight loss, stomatitis, cheilitis, and glossitis. Furthermore, there is a classic triad of symptoms associated with glucagonomas consisting of necrolytic migratory erythema, diabetes mellitus, deep vein thrombosis (DVT), and depression **(Table 5)** [40,41]. Biochemical considerations for diagnosis include a fasting plasma glucagon level of > 500 pg/mL. Most glucagonomas are sporadic; however, approximately 5-15% are associated with MEN1. The 10-year survival is heavily impacted by the presence of metastatic disease, with a 100% survival rate in localized, surgically resectable disease, which decreases to 50% with metastasis [41].

6.3. Gastrinoma

Gastrinomas are a slow-growing pNET that commonly cause Zollinger-Ellison syndrome (ZES), characterized by the hypersecretion of gastrin and severe peptic ulcer disease. The term gastrinoma refers to a NEN which secretes gastrin, while ZES is a consequence associated with the syndromic tumor [42]. Other symptoms include abdominal pain, diarrhea, nausea, vomiting, and bleeding **(Table 6)** [43]. While approximately 75-80% of these tumors arise sporadically, up to 30% are associated with an inherited genetic mutation, particularly MEN1 [44–46]. Although slow-growing, approximately 60% are metastatic on presentation. Approximately 80-90% of primary tumors can be localized in the 'gastrinoma triangle,' the boundaries of which are defined by the confluence of the cystic and common bile duct, the second and third portions of the duodenum, and the neck and body of the pancreas [43,44]. Although slow-growing, 60-90% of patients present with metastatic disease in the liver or lymph nodes [43]. 5- and 10-year survival is significantly impacted by genetic mutations associated with the gastrinoma, particularly MEN1 [47]. Primary tumor size, liver metastasis, and the extent of liver metastasis are poor prognostic indicators for overall survival (OS) [48].

Table 5: Symptoms of glucagonoma.

Common symptoms of glucagonoma	4 D's of glucagonoma
Weight loss	Dermatitis (necrolytic migratory erythema)
Diarrhea	Diabetes
Mucosal abnormalities (stomatitis, cheilitis, and glossitis)	DVT
	Depression

DVT – Deep vein thrombosis.

Table 6: Symptoms associated with gastrinomas [43].

Symptoms associated with gastrinomas	
PUD	Nausea
Abdominal pain	Vomiting
Diarrhea	Bleeding

PUD – Peptic ulcer disease.

6.4. VIPoma

Vasoactive intestinal peptide tumors (VIPomas) are a pNET arising from the D2 islet cells of the pancreas with an estimated incidence of 1/10,000,000. These tumors are predominantly located in the tail of the pancreas. VIPomas have classic symptoms of watery diarrhea, hypokalemia, and hypochlorhydria or achlorhydria, referred to as WDHA syndrome [49]. Secretory diarrhea associated with VIPomas is defined by diarrhea > 700 mL/day with a serum VIP level of > 200 pg/mL; this secretory diarrhea occurs from the excretion of sodium, chloride, potassium, and water while preventing resorption [50]. Additionally, VIP gastric secretion promotes blood flow to the gastrointestinal (GI) tract, resulting in hyperglycemia, and has vasodilatory effects on smooth muscle.

6.5. Somatostatinoma

Somatostatinomas arise from the delta cells of the pancreas and account for 5% of pNETs with an incidence of 1/40,000,000. Somatostatinomas localize in the head of the pancreas in 36% of cases and the tail of the pancreas in 32% of cases [51]. Neoplasm symptoms are related to the functional effects of somatostatin and include inhibition of thyroid-stimulating hormone, growth hormone, glucagon, cholecystokinin, secretin, gastrin, vasoactive intestinal polypeptide, motilin, glucagon, and neurotensin. As a result, patients experience impaired gastric acid secretion with associated delayed gastric emptying, reduced bowel motility, and impaired bile flow with poor gallbladder contractility [51,52]. Patients often present with abdominal pain, jaundice, and steatorrhea due to the aforementioned inhibitory effects of somatostatin [53]. A minority of patients exhibit inhibitory syndrome, a characteristic triad of cholelithiasis, steatorrhea, and diabetes mellitus related to the suppressive effects of somatostatin [54]. Biochemical diagnostic criteria include an elevated fasting serum somatostatin level of > 14 mmol/L or an elevated 5-hydroxy indole acetic acid (5-HIAA) on 24-hour urine collection. However, fasting somatostatin levels may be elevated in other conditions, including medullary thyroid malignancy, pheochromocytoma, paragangliomas, and lung malignancies. Additionally, urine 5-HIAA may be falsely elevated due to medications and a diet rich in serotonin-containing food [55,56]. These tumors are predominantly malignant, and in 25% of patients, the tumor will secrete another hormone in addition to somatostatin [51,57]. The 5-year survival of localized and resectable disease is reported to range between 60-100%; however, 5-year survival is significantly decreased to 15-60% in patients with metastatic disease. Tumor size greater > 3 cm, hormonal inactivity, and poor differentiation on histology are all poor prognostic indicators of OS [54,58,59].

7. Non-Syndromic pNETs

Non-syndromic pNETs constitute approximately 2-10% of all pancreatic neoplasms and 60-90% of pNETs, demonstrating an incidence of < 1/100,000. These tumors are often detected in very late stages of the disease process, given that the tumor remains clinically silent until causing mass effects, including jaundice from biliary obstruction, intra-abdominal bleeding from vessel erosion, and anorexia from obstruction of the GI tract. They may also be detected incidentally on imaging [60,61]. Common sites of metastasis include the liver, bone, peritoneum, adrenal, brain, and spleen [61].

8. Tumor Localization

Modern imaging modalities have significantly improved the rate of identification and localization of pNETs. Nearly 50% of pNETs are found incidentally on cross-sectional imaging [62,63]. Regardless of the type of pNET, localization initially begins with non-invasive modalities. Common localization methods include cross-sectional imaging, peptide-stimulated imaging, and intraoperative localization.

8.1. CT/MRI

Successful preoperative localization with computed tomography (CT) has been reported to be 70-80% [64]. A helical contrasted-enhanced CT is particularly beneficial for tumors greater than 2 cm and further detection of liver or intra-abdominal metastases. For tumors greater than 2 cm, contrast-enhanced CT has a sensitivity of 63-82% and a specificity of 83-100% [65,66]. Gadolinium contrast-enhanced magnetic resonance imaging (MRI) is an alternative to CT, with a detection rate of approximately 85% [64]. Tumors typically demonstrate low signal intensity on T1-weight images and high signal intensity on T2-weighted images. Sensitivity and specificity for gadolinium contrast-enhanced MRI are over 85% and 75%, respectively. Finally, multiphasic MRI may help detect tumors < 2 cm in size and improves the detection of small liver metastasis in comparison to CT [67,68]. Limitations of MRI include incompatibility with implantable devices and motion artifacts.

8.2. Somatostatin Receptor Scintigraphy

Previously, if a tumor could not be localized on cross-sectional imaging, then somatostatin scintigraphy was pursued. This modality can be utilized in all pNET, except insulinomas, due to the low levels of somatostatin receptors expressed on these tumors. 111IN pentetreotide, a radiolabeled somatostatin analog octreotide, is utilized for tumor localization. This modality is particularly beneficial for NEN that are located outside of the pancreas. The reported sensitivity of this imaging modality ranges from 75-100% in detecting NENs [63,67]. The utility of 111IN-labeled GLP-1R agonists in detecting insulinomas has been evaluated using single photon emission computed tomography (SPECT) and CT scans [69]. Notably, however, this imaging modality is particularly beneficial for benign insulinomas, as only 33% of their malignant counterparts demonstrate the GLP-1R receptor that is the target of the radiolabeled scan [70].

8.3. PET

Fluorodeoxyglucose (FDG) positron emission tomography (PET) scans are typically not beneficial in the localization of pNETs due to the low metabolic activity demonstrated by the tumors utilizing FDG. FDG uptake is noted in poorly-differentiated pNETs and may be a poor prognostic indicator for tumor progression and increased mortality [68,71,72]. 68-Ga DOTATATE is a new PET tracer for NENs that can be utilized for the detection of small lesions. It has demonstrated

greater sensitivity than 111IN-pentetreotide scintigraphy [71,72]. However, there is no correlation between tumor uptake of Ga-DOTATATE and the histologic grade of the tumor [72]. Given the increased localization, shorter study length, decreased radiation, and reduced biliary excretion, Ga-DOTATATE has largely replaced 111IN pentetreotide [73].

8.4. Endoscopic Ultrasound

Endoscopic ultrasound (EUS) can provide high-resolution images of pNETs. The high-frequency transducer can identify small lesions (< 2 cm), which are often difficult to identify on CT. In a systematic review, EUS identified pNETs in 97% of cases, 28% of which were not detected by CT imaging [68,74]. EUS is also used to evaluate locoregional lymph nodes and can be used to obtain biopsies and tattoo small lesions for easier intraoperative identification of the pNET, which may be too small to palpate [75–78].

8.5. Intraoperative Palpation

In the rare event that no imaging modality can identify the tumor, intraoperative palpation may be an effective localization method. In a retrospective study of 59 patients where imaging modalities were ineffective in localizing the pNET, intraoperative palpation successfully localized 98.2% of tumors. 100% were identified when intraoperative palpation was accompanied by intraoperative ultrasound [79].

8.6. Intraoperative Ultrasound

Intraoperative ultrasound can identify small, focal, non-palpable lesions located within the pancreas and can identify small liver metastasis. Furthermore, intraoperative ultrasound can be used to assess the distance of the tumor to the pancreatic duct, particularly in targeted treatments such as enucleation [79,80].

9. Surgical Management of pNETs

Surgical management of pNETs is individualized based on the type of pNET, tumor location, and tumor burden on presentation. A wide range of surgical resection options are available, ranging from a precise tumor enucleation to formal resection with negative margins and regional lymphadenectomy.

9.1. Enucleation

Enucleation is a focal resection, which can be performed using an open, laparoscopic, or robotic approach [81,82]. For lesions in the head or uncinate process of the pancreas, intraoperatively, the head of the pancreas may be exposed by performing a Kocher maneuver, followed by potential division of the gastroepiploic vascular pedicle for further exposure of the medial head and uncinate process of the pancreas. For neoplasms localized in the body or tail of the pancreas, the greater omentum is divided for sufficient exposure. Once adequate exposure is achieved, prolene or silk sutures are placed in the pancreas for retraction, the tumor is localized, and the enucleation is undertaken by the removal of the mass [82,83]. Caution should be displayed to prevent injury to surrounding structures, including the common bile duct, gastroduodenal artery, and portal vein behind the head and neck of the pancreas; the superior mesenteric vein behind the neck and body of the pancreas; and the splenic vessels and capsule with the dissection of the tail of the pancreas [82].

Enucleation is reserved for select patients with benign, solitary neoplasms that are < 2 cm in size and are > 2 mm from the main pancreatic duct without focal stricture or dilation [82,84,85]. Enucleation is most commonly performed for insulinomas [86,87]. Gastrinomas have also demonstrated favorable outcomes [82]. When pursuing this intervention for gastrinomas, lymphadenectomy is recommended due to the malignant potential [88]. Extreme caution should be exhibited when utilizing this intervention for non-syndromic pNETs due to malignant and metastatic potential. Enucleation with associated lymph node dissection may be considered in non-syndromic pNETs that are < 2 cm in size and demonstrate a low Ki-67 mitotic index [82,85,88].

9.2. Spleen-Preserving Distal Pancreatectomy vs. Distal Pancreatectomy with Splenectomy

For pNETs located in the body and tail of the pancreas, typically consisting of insulinomas, VIPomas, and glucagonomas, a spleen-preserving distal pancreatectomy (SPDP) canbe pursued. For pNETs located in the body and tail of the pancreas with malignant potential, a distal pancreatectomy is done in conjunction with splenectomy (DPS) due to the proximity of the two organs. NCCN guidelines recommend DPS for all glucagonomas due to malignant potential. Furthermore, distally located non-functioning pNETs and VIPomas that are > 2 cm in size or possess evidence of lymph node metastasis should also be excised with DPS. However, in insulinomas, which are predominantly benign, an SPDP provides adequate resection. Acomparative study by Huang *et al.* showed comparable 5-year OS in patients with non-functioning pNET who had grade 1/2 and stage T1/T2 disease who underwent SPDP vs. DPS [89].

9.3. Whipple Procedure

For tumors with concern for malignant potential located in the head of the pancreas, a pancreaticoduodenectomy (PD), or Whipple procedure, should be performed [90]. Studies comparing laparoscopic versus open PD for pNET demonstrated shorter recovery time and reduced length of hospitalization. However, a more extensive lymph node harvest was feasible with open PD [91]. Patients can undergo a classic Whipple (CW) or pylorus-preserving Whipple (PPW). While PPW is associated with shorter operative time and lower blood loss, there is an increased risk for delayed gastric emptying [92,93]. Other complications associated with the procedure include pancreatic fistula, post-operative hemorrhage, wound infection, and intra-abdominal abscess [94].

9.4. Beger Procedure

The Beger procedure is a duodenal-preserving pancreatic head resection typically used in the setting of chronic pancreatitis that can be utilized for small pNETs with a low risk of malignancy located in the head of the pancreas, such as an insulinoma [95,96]. The Beger procedure entails the removal of the head of the pancreas while preserving the duodenum with a subsequent pancreaticojejunostomy and distal jejunojejunostomy [97].

9.5. Hepatectomy in Resectable Metastatic Disease

The liver is the most common site of pNET metastases, with a lifetime risk of liver metastases ranging between 28% and 77% [98,99]. General surgical guidelines for hepatectomy for metastatic disease include the ability to perform complete (R0) resection, grade 1 or 2 tumors, lack of right-sided heart failure, metastases isolated to a resectable portion of liver without carcinomatosis or extra-hepatic disease, and considerations of perioperative morbidity and mortality [100]. Several meta-analyses demonstrated improved OS when liver resection was undertaken for patients with resectable metastatic disease to the liver associated with NEN [101–103]. Surgical resection demonstrated improved symptoms and OS compared to non-surgical targeted hepatic treatments [103]. However, other reviews determined no significant superiority of liver resection to other targeted therapies as it pertains to OS, PFS, or quality of life [104,105]. Notably, these reviews included all NEN or midgut NEN.

9.6. Lymphadenectomy

Nodal metastases is a poor prognostic indicator of OS in pNETs. In a retrospective study of 136 patients by Hashim *et al.*, 38% of the patient population demonstrated nodal metastasis. Risk factors for nodal metastasis included Ki67 mitotic index > 20%, tumor invasion into surrounding structures, tumors located in the head of the pancreas, and tumor size > 1.5 cm. As a result, regional lymphadenectomy was recommended in addition to pancreatectomy [106]. In an eight-institution study by Lopez-Aguiar *et al.*, routine regional lymphadenectomy was recommended, as a range of 9-23% of patients with non-syndromic pNETs demonstrated nodal metastases without risk factors. In this study, tumor size ≥ 2 cm, Ki-67 mitotic index ≥ 3%, location in the head of the pancreas, and moderate differentiation were determined to be risk factors for lymph node metastasis in non-syndromic pNETs [107]. The NCCN guidelines recommend peripancreatic lymphadenectomy for gastrinoma, glucagonoma, VIPoma, somatostatinoma, and non-functioning pNET [88].

10. Locoregional Intervention

Locoregional interventions allow for targeted treatment of primary or metastatic pNET. Various types of locoregional therapies are in use, including transarterial embolization (TAE), transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and microwave ablation (MWA).

10.1. Transcatheter Arterial Embolization (TAE) and Transarterial Chemoembolization (TACE)

TAE and TACE are commonly utilized for the treatment of pNET liver metastases. TAE includes embolization with lipiodol, bland microspheres, or gel foam particles [108]. TACE includes the delivery of high-dose targeted chemotherapy and embolization [109,110]. The procedure is typically tolerated well, but complications include the development of liver abscesses, gallbladder necrosis, bowel ischemia, and pleural effusions [111]. In a retrospective study by Grozinsky-Glasberg *et al.*, which included NENs of all origins, TAE/TACE demonstrated a median OS of 22 months [112]. In a five-patient study by Akahori *et al.* specific to the patient with liver metastasis from pNETs, TACE employed a combination of cisplatin, and degradable starch microspheres demonstrated a median OS of 36 months (range of 3-70 months) [111]. Ultimately, further investigation should be pursued specifically for this patient population.

10.2. Radiofrequency Ablation (RFA)

RFA is commonly utilized for metastatic liver lesions associated with pNETs not located near vital structures or on the liver surface [113]. The process creates heat from high-energy radiofrequency resulting in targeted coagulative necrosis [114]. RFA is beneficial for symptomatic relief in patients with metastatic liver lesion volumes ≤ 20% of total liver volume, ≤ 14 metastases, grade 1 or 2, and lesions ≤ 3 cm in size [108,109]. While survival is not extended due to this intervention, 70% of patients reported symptomatic relief for an average of 10 - 11 months [109,115]. Complications of the procedure are rare but include bleeding, hepatic abscess development, and pneumothorax [109,116].

Regarding the utility of RFA for primary tumors, a pilot study of 10 patients by Rossi *et al.* from the University of Pavia in Italy demonstrated RFA to be an effective treatment method for small pNETs in patients who cannot undergo surgical intervention. RFA was performed percutaneously, endoscopically, or laparoscopically in pancreatic tumors, which were ≤ 2.9 cm. All tumors demonstrated complete ablation, defined as the absence of tissue on CT imaging and normalization of serum hormones, with 1 or 2 RFA sessions [117]. In a systematic review by Imperatore *et al.*, 61 patients were evaluated who underwent up to 3 sessions of endoscopic ultrasound-guided (EUS)-RFA. The response to EUS-RFA was favorable in 96% of patients on 11-month follow-up, with tumor size being the most significant predictive factor for failure. Lesions size ≤ 18 mm predicted response to EUS-RFA, irrespective of the functional status of the tumor. Response to EUS-RFA was determined by post-operative imaging [118]. Ultimately, further prospective studies should evaluate the utility of RFA for pNETs.

10.3. Microwave Ablation

MWA utilizes ultrasound, CT, or MRI for electrode-guided frictional heating of the tumor, causing cell death by coagulation necrosis. Ablation time with MWA is typically reduced compared to RFA secondary to deeper tissue penetrance [119,120]. It has been theorized that MWA is more suitable than RFA for hepatic lesions near major vascular structures due to a reduced heat sink effect associated with MWA. This phenomenon leads to reduced ablation volume due to the cooling effect of blood flow [121,122]. In a 100-patient, single-institution, prospective study by Martin *et al.*, MWA was associated with a 0% 90-day mortality for patients with metastatic hepatic lesions. In this study, no patients developed bleeding complications, and one developed a hepatic abscess due to the procedure. Eleven patients in the study had liver metastasis secondary to NENs [123].

MWA has traditionally been utilized for hepatic metastases of pNET; however, its utility in primary pNET for patients with poor functional status is slowly being investigated [124–126]. In a seven-patient trial by Egorov *et al.*, MWA was utilized to ablate syndromic insulinomas in patients with poor functional status. While patients did experience regression of symptoms, two patients required intervention for pseudocyst and abscess development, and one died from myocardial infarction two months following the intervention. Tumor location was uniformly in the head with tumor size ≤ 2.1 cm [124]. In a case report by Chen *et al.*, a 60-year-old with stage IV non-small cell lung cancer and the concomitant development of a syndromic pancreatic insulinoma underwent a single session of MWA, achieving complete symptomatic resolution with near complete ablation of the tumor [125]. A continued investigation should be pursued into the role of MWA in managing and treating pNET.

11. Systemic Therapy

While margin-negative surgical resection remains the optimal treatment for localized pNETs, systemic therapies are available for locally advanced and metastatic disease. In patients with syndromic pNETs, systemic therapies for symptom control are also available.

11.1. Somatostatin Analogs

For syndromic pNETs that possess somatostatin receptors, patients should receive octreotide or lanreotide for symptom and tumor control. Octreotide and lanreotide are somatostatin analogs that act on the somatostatin receptors inhibiting gastroenteropancreatic endocrine system hormones [127]. Given that both drugs demonstrate the same mechanism of action, NCCN guidelines recommend either drug for symptom and tumor control [88]. The 2009 PROMID trial showed that monthly 30 mg intramuscular injections of octreotide LAR delays tumor progression time in patients with well-differentiated metastatic gastroenteropancreatic neuroendocrine tumors compared to the placebo. Stable disease was noted in 66.7% of patients after six months of use vs. 37.2% in the placebo group. In this randomized, double-blind, placebo-controlled trial, patients were given octreotide LAR 30 mg intramuscularly monthly until tumor progression or patient death [128]. Subsequently, in 2014, the CLARINET trial demonstrated that lanreotide improved PFS in patients with advanced, well or moderately-differentiated, non-syndromic, somatostatin receptor-positive NEN. The estimated PFS at 24 months was 65.1% in the lanreotide group vs. 33% in the placebo group. In this randomized, double-blind, placebo-controlled, multinational trial, patients would receive a 120 mg dose of lanreotide subcutaneously every 28 days for 96 weeks or placebo [129].

11.2. Molecularly Targeted Therapies

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor that has been approved for treating pNETs. The RADIANT-3 Study, a randomized-controlled trial using everolimus 10 mg daily vs. placebo in pNETs (grade 1 and 2) showed a statistically significant improvement of PFS from 11 months in the everolimus group compared to 4.6 months in the placebo group [130]. Sunitinib is a receptor tyrosine kinase (RTK) inhibitor that limits vascular endothelial growth factor (VEGF) signaling in pNETs. In a randomized, double-blind, control trial, a 37.5 mg daily dose of sunitinib improved mPFS (11.4 months vs. 5.5 months), OS (10% vs. 25% death rate), and objective response rate (ORR) (9.3% vs. 0%) [131].

11.3. Cytotoxic Chemotherapy

The NCCN recommends cytotoxic chemotherapy for bulky, higher grade, symptomatic or progressive tumors, including 5-Fluorouracil (5-FU)/Doxorubicin/streptozocin, streptozocin/doxorubicin, streptozocin/5-FU. 5-FU/oxaloplatin/leucovorin (FOLFOX), and capecitabine/oxaloplatin (CAPOX) [88].

Streptozocin, an alkylating agent, was the first approved chemotherapeutic agent for pNETs [88,132,133]. Moertel *et al.* demonstrated in a multicenter, randomized trial that streptozocin in conjunction with doxorubicin exhibited a more favorable rate of tumor regression, time to tumor progression, and median survival compared to streptozocin and 5-FU in patients with advanced pNET [132].

Dacarbazine is another alkylating agent that showed clinical activity in pNET, which was demonstrated in a phase II trial of 42 patients with advanced pancreatic islet cell carcinomas; the objective response rate was 30%. The side effects profile of

both streptozocin and dacarbazine limited their usage in this disease [134].

The combination of capecitabine plus temozolomide (CAPTEM) is now the most common regimen used to treat bulky or symptomatic pNET due to its good response rate and favorable adverse events profile. CAPTEM efficacy was noted in a phase II trial which showed that the combination in the pNET population was superior to single-agent temozolomide. In this trial, there was a trend toward better median OS (58.7 versus 53.8 months, HR 0.82, 95% CI 0.51-1.33) with combined therapy, with a higher ORR (40 versus 34%, p = 0.42) and longer duration of response (16.6 versus 12.6 months) [135].

Oxaliplatin-fluoropyrimidine regimens are also active in pNET. Two-phase II trials using FOLFOX or CAPOX showed a 50% partial response rate and 50% stable disease [136].

11.4. Radioactive Polymer Microspheres

Peptide receptor radionuclide therapy (PRRT) utilizes radioactive nuclides, such as β-emitting Yttrium-90 or Lutetium-177, attached to a somatostatin analog [137]. The premise of this therapy is based on the expression of somatostatin receptors on most NENs. Lutetium-177 has a tissue penetration of 2 mm, making it ideal for smaller tumors. Furthermore, in addition to the β-emission, Lutetium-177 exhibits γ-emission, allowing for imaging and verification of targeted therapy following administration. Yttrium-90 has deeper tissue penetration at 12 mm and is more suitable for neoplasms with heterogenous receptors [138]. As an emerging therapy, studies regarding its efficacy in combination with other treatment modalities are limited. However, studies have demonstrated increased OS and PFS by 15-35% based on the tumor type and the radionuclide [137]. In a retrospective study by Ezzidinn *et al.*, 68 patients with advanced grade 1 and grade 2 pNETs underwent PRRT with Lu-octreotate and demonstrated favorable outcomes in terms of OS and PFS [139]. PRRT is reserved for treating advanced, metastatic pNETs that failed to be controlled using long-acting somatostatin analogues [140]. A new phase II trial (OCLURANDOM Trial) compared second-line sunitinib vs. PRRT in progressive advanced/metastatic pNETs, showed superior results favoring PRRT. This trial is helpful evidence in establishing the best treatment sequence when managing those patients with progressive pNETs [141].

12. Conclusion

PNETs are rare and heterogeneous tumors with different biological behaviors, and therefore require correct diagnosis and classification for appropriate management.

PNETs may be syndromic or non-syndromic based on clinical symptoms and hormonal secretion. Considerable variability in terms of malignancy risk and the metastatic potential exists between the different types of pNETs, which should be accounted for in managing these tumors. Several genetic mutations also exist which predispose patients to the development of pNETs. OS and progression of the disease vary drastically based on the malignant potential of the neoplasm; however, 5-year OS was 83%, 67%, and 28% for localized, regional, and metastatic disease [142]. Significant advancements have been made regarding the diagnosis and surveillance of pNETs, including new novel biomarkers and imaging. Low-grade pNETs with low malignant potential that are found incidentally on imaging may be simply observed. Surgical excision is the only curative intervention and should be appropriately tailored to include lymphadenectomy based on the malignant potential of the tumor. The extent of the pancreatectomy required and the need for reconstruction are determined by the location of the lesion; at times, concomitant liver resection may be indicated when liver metastasis is present. Various locoregional treatments exist for targeted primary tumor management as well as hepatic metastases. Systemic therapies are also available for symptom control and tumor management. In this review, we discussed the diagnosis and management of pNETs. However, ultimately further studies should be pursued for optimal management and treatment of these neoplasms, accounting for variables such as genetic predisposition, type of pNET and associated malignant potential, location, tumor biology, and metastases.

Abbreviations

5-FU – 5-Fluorouracil; 5-HIAA.- 5- Hydroxy indole acectic acid; AJCC – American Joint Commission on Cancer; CA – Celiac artery; CAPOX – Capecitabine/oxaliplatin; CAPTEM – capecitabine plus temozolamide; CBD – Common bile duct; CgA - Chromogranin A; CT – Computed tomography; CTCs – Circulating tumor cells; CW – Classic Whipple; DNA – Deoxyribonucleic acid; DPS – Distal pancreatectomy and splenectomy; DVT – Deep Vein Thrombosis; ENETS – European Neuroendocrine Tumor Society; EUS – Endoscopic ultrasound; FDG – Fluorodeoxyglucose; FOLFOX – 5-FU/Doxorubicin/streptozocin; GI – gastrointestinal; ICGC – International Cancer Genome Consortium; MEN1 – Multiple endocrine neoplasia type 1; MRI – Magnetic resonance imaging; mTOR – Mammalian target of rapamycin; MWA – Microwave ablation; NANETS – North American Neuroendocrine Tumor Society; NCCN – National Comprehensive Cancer Network; NEC – Neuroendocrine carcinoma; NENs – Neuroendocrine neoplasms; NET – Neuroendocrine tumor; NETest – neuroendocrine neoplasms test; NF1 - Neurofibromatosis type 1; NSE – Neuron-specific enolase; ORR – Objective response rate; OS – Overall survival; PD – Pancreaticoduodenectomy; PET – Positron emission tomography; PFS – Progression-free survival; pNET – pancreatic neuroendocrine tumor; PP – Pancreatic polypeptide; PPW – Pylorus-preserving Whipple; PRRT – peptide receptor radionuclide therapy; RFA – Radiofrequency ablation; RNA – Ribonucleic acid; RTK – Receptor tyrosine kinase; SACST – Selective arterial calcium stimulation test; SMA – Superior mesenteric artery; SPDP – Spleen-preserving distal pancreatectomy; SPECT - single photon emission computed tomography; SPDP – Spleen-preserving distal pancreatectomy; TAE – Transarterial embolization; TACE – Transarterial chemoembolization; TNM – Tumor, Node, Metastasis; USD – United States Dollars; VEGF – Vascular endothelial growth factor; VHL – von Hippel-Lindau; VIP – Vasoactive intestinal peptide; VIPomas – Vasoactive intestinal

peptide tumors; WHO – World Health Organization; ZES – Zollinger Ellison Syndrome

Authors' Contributions

All authors conceptualized and outlined this work. LG and EWB prepared the first draft. All authors reviewed, revised, and provided final approval.

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Conflicts of Interest

Najeeb Al Hallak is on the speakers' bureau for IPSEN. All other authors declare no conflict of interest.

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