Chapter

An Overview of Pancreatic Neuroendocrine Tumors

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Abstract

Pancreatic neuroendocrine tumors are a group of endocrine tumors that constitute 7% of all pancreatic neoplasms. They can be benign or malignant. Their presentation can vary from slow growing, non infiltrative, indolent masses to rapidly progressing, highly aggressive, metastasizing tumors. In the past, there was paucity of scientific data available about the diagnosis and treatment strategy of these neoplasms but in recent years, ongoing research has inferred much data regarding classification, prognostic stratification and therapy of pancreatic neuroendocrine tumors. In this chapter we will discuss epidemiology, clinical presentation and classification, diagnosis and management of these tumors. We will also deliberate about the latest developments in treatment of pancreatic neuroendocrine tumors with focus on recent studies done on this topic.

Keywords: pancreatic neuroendocrine tumors, pancreatic NET, GEP-NET, Gastroenteropancreatic tumor

1. Introduction

Neuro-endocrine tumors constitute 0.5% of all malignancies [1]. Gastro-entero-pancreatic neuro-endocrine tumors (GEP-NET) originate from neuro-endocrine cells of the embryological gut and they constitute a group of heterogeneous tumors that demonstrate divergent tumor biology, different diagnostic behavior, management principles and tumor-patient outcomes [2].

2. Incidence and epidemiology

GEP-NET comprises 2% of all gastrointestinal tumors [3]. Pancreatic neuroendocrine tumors (PNETs) are one of the most common neuroendocrine tumors [4]. But they are relatively rare tumors and comprise about 7% of all cancers that occur in the pancreas [5]. According to The American Cancer Society's estimates for 2020, about 4,032 people in the United States will be diagnosed with pancreatic NET.[8]

With better imaging modalities coming into play, the incidence of pancreatic NETs is increasing over the years as they are often found incidentally when radiological tests such as CT or MRI scans are done for other diseases. There has also been increased sensitivity of lab tests that have escalated the ability to distinguish these tumors from other malignancies. The increased prevalence over the past few decades, is attributed to multifactorial causes mainly as a consequence of increased awareness and improved diagnostic technique [6]. It is estimated that nowadays almost 50% of PNET diagnoses are incidentalomas [7]. An aging population and heightened awareness of the disease have also contributed to an increase in the detection of incidentalomas [8].

Majority of pNET are sporadic, i.e. non inherited while 10–30% pNET are associated with a genetic syndrome like multiple endocrine neoplasia (MEN) type 1, which is most commonly associated with it [9]. Other rare genetic conditions include MEN4, Von Hippel–Lindau disease, neurofibromatosis 1 (von Recklinghausen's syndrome), and tuberous sclerosis, which are linked to genetic type pNET [10].

There is no gender predilection for pNET although some studies have suggested a slight preponderance for men. These tumors can present at any age but the incidence of sporadic tumors rises from fifth decade and peaks around 80s [11].

3. Classification and staging

In the past NETs were classified based upon the site of origin in embryological gut as foregut, midgut and hindgut tumors. It has been rather challenging to classify these tumors due to their heterogeneity, difference in their morphology, clinical presentation, molecular biology, hormone profile and treatment response.

Clinically these tumors have been classified as functioning and non functioning tumors. In 2007 WHO introduced a new classification system for neuroendocrine tumors which categorized them according to tumor's proliferation indices like mitotic index or Ki67 score as well differentiated tumors and poorly differentiated carcinomas [12]. In 2010 it also included histopathological features as a criteria for classification apart from proliferation indices, which lead to revision of the existing guidelines and NETs were further divided into three grades based upon ENETS classification (**Table 1**) [14]. Well differentiated tumors comprised of grade 1 and grade 2 NET, while poorly differentiated tumors were grade 3 NET also described as neuroendocrine carcinoma (NEC). The difference between the two has been illustrated in **Table 2** [14].

In 2017, the classification was re-revised to include NET grade1, 2 and 3 in the well differentiated category and the poorly differentiated category was NEC grade 3. See **Table 3** [15].

European neuroendocrine society has also devised a staging for GEP-NET. American cancer society has included tumor resectability as classification criteria (**Figure 1**) [17].

Mixed adenoneuroendocrine carcinoma (MANEC) of pancreas are a group of extremely rare tumors, with incidence approximately 0.2% and only a few cases are reported in literature [18]. They have both adenocarcinoma and neuroendocrine components with each component accounting for more than 30% of the tumor [19]. Due to rarity of this, tumor the clinical behavior is not studied much. It has been proposed that the treatment should depend on the aggressiveness of the cell type of the tumor [20]. In various cases studied, surgery has been considered as the first line of treatment for resectable tumors. Post operative treatment includes adjuvant chemotherapy and/or radiotherapy [21].

Well differentiated net	Ki67 index	Mitotic index
NET G1	<=2%	<2/hpf
NET G2	3–20%	2–20/hpf
Poorly differentiated net		
NEC	>20%	>20/hpf

Table 1.
Who classification 2010 [13].

Characteristics	NET G3	NEC
Pathological differentiation	Well differentiated	Poorly differentiated
Ki 67 index	>20% (usually 30–55%)	>20%(usually 50%)
Mitotic index	>20/hpf	>20/hpf
necrosis	Rare	present
Genetic syndrome MEN1, VHL	occasionally	rare
Functionality	occasionally	rare
Neuroendocrine marker expression	positive	weak
Somatostatin receptor scintigraphy uptake	strong	weak
Loss of ATR x and DAXX protein expression	present	rare
Abnormal p53, SMAD4 and Rb expression	rare	present
Response to platinum agents	worse	better
Prognosis	Relatively good	poor

Table 2.
The difference between NET Grade3 and NEC grade3 [15].

Well differentiated net	Ki67 index	Mitotic index
NET G1	<3%	<2/hpf
NET G2	3–20%	2–20/hpf
NET G3	>20%	>20/hpf
Poorly differentiated net		
NEC	>20%	>20/hpf

Table 3.
Who classification 2017 [13].

AJCC Staging Classification		ENETS Staging Classification	
T1	Tumor limited to the pancreas, <2 cm	T1	Tumor limited to the pancreas, <2 cm
T2	Tumor limited to the pancreas, >2 cm	T2	Tumor limited to the pancreas, 2-4 cm
T3	Tumor extends beyond the pancreas, but not involving the celiac axis or SMA	T3	Tumor limited to the pancreas, >4 cm, or invading duodenum or CBD
T4	Tumor involves the celiac axis or SMA	T4	Tumor invades adjacent structures
N0	No regional LN metastasis	N0	No regional LN metastasis
N1	Regional LN metastasis	N1	Regional LN metastasis
M0	No distant metastasis	M0	No distant metastasis
M1	Distant metastasis	M1	Distant metastasis

Stage	T	N	M	Stage	T	N	M
IA	T1	N0	M0	I	T1	N0	M0
IB	T2	N0	M0	IIA	T2	N0	M0
IIA	T3	N0	M0	IIB	T3	N0	M0
IIB	T1-3	N1	M0	IIIA	T4	N0	M0
III	T4	N0-1	M0	IIIB	Any T	N1	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

	ENETS I	ENETS II	ENETS III	ENETS IV
AJCC I	25	59	0	0
AJCC II	0	4	37	0
AJCC III	0	0	18	0
AJCC IV	0	0	0	282

CBD = common bile duct; LN = lymph node; SMA = superior mesenteric artery.

Figure 1.
Comparison of TNM classification of pancreatic NENs according to ENETS versus UICC/AJCC (TNM classification) [16].

4. Etiopathogenesis

4.1 Cellular biology of net

As such pNETs were classically thought to arise from pancreatic islet cells or the islets of Langerhans, hence the term islet cell tumors was coined [22]. Islet cells are the endocrine cells of the pancreas and they constitute 1–2% of total pancreatic mass. They are therefore distinct from the exocrine cells, from which pancreatic ductal adenocarcinomas arise. They are composed of various cell types and responsible for secretion of hormones like beta cells (insulin), alpha cells (glucagon), delta cells (somatostatin), and PP cells (pancreatic polypeptide) [23]. However, current theory says that pNETs in fact arise from the APUD (amine precursor uptake and decarboxylation) cells [24]. The presence of neurosecretory granules is the characteristic feature of APUD cells and these neurosecretory granules have autocrine, paracrine and neuromodulatory functions, in addition to the endocrine property. These cells are thought to originate in the embryologic neural crest, but more recent research suggests that they originate in the embryologic endoderm [25].

The most common genes involved in pancreatic neuroendocrine tumors are mentioned in **Table 4**.

Other specific genes suggested to be implicated in the etiopathogenesis of NETs include BIN1, Serpine 10, BST2, IGFBP3, LCK, MET, fibronectin, PDGF, IGF- 1, fibroblast growth factor, TGF-alpha and–beta, EGFR, and stem cell factor receptor [27].

Multiple studies have elucidated the underlying genetic mechanism regarding molecular development and progression of these tumors but still much remains unexplored in this area. Loss of chromosomes 3q, 6pq, and 10 pq, and gains of 5q, 12a, 18q, and 20q is associated with malignant behavior in these tumors [28]. In tumors less than 2 cm in size, it has been observed that Chromosome 1 and 11q loss with gain of 9q is associated with genetic instability [29].

4.2 Olecular pathology of PNET and its role in prognosis

Most recent advancements in assessment of pancreatic NET is the development of microRNA profiling which corresponds to various proliferation indices and also propensity of tumor to cause local spread and distant metastasis [30]. MicroRNA are non-coding RNA sequences having length of 21–25 nucleotides. They regulate genes at post translational level [31]. They can act as oncogenes or tumor suppressor genes and play a significant role in proliferation of tumors or their dissemination [32]. They can act as diagnostic as well as a prognostic marker.

There is very limited data available regarding microRNA profiling of pNET. In one large study done on pancreatic NET, 28 different miRs have been shown to

Gene	Prevalence in PNET	Prevalence in PDAC
MEN1	44%	0%
ATRX/DAXX	43%	0%
mTOR	15%	0.8%
TP53	3%	85%
KRAS	0%	100%
CDKN2A	0%	25%
TGFBR1/SMAD3/SMAD4	0%	38%

Table 4.
Common genes in pancreatic neuroendocrine tumors vs. pancreatic adenocarcinoma [26, 27].

be differentially expressed with 18 of them being higher expressed and 10 lower expressed as compared to healthy pancreatic tissue [33]. There is a higher expression of miR-103, miR-107 and miR-193b and lower expression of let-7 miR and miR-155 in pancreatic neuroendocrine neoplasias [34]. Tumor proliferation is denoted by expression levels of miR-196a, miR-21 and miR-642 while miR-210 and miR-21 seem to correlate with metastatic disease and tumor recurrence is predicted by expression of both miR-196a and miR-27b [35, 36].

Circulating tumor cell count also plays an important role in delineating the prognostic value of pNETs, especially before and during the treatment. Liquid biopsy is emerging as a newer and more profound biomarker test which provides valid cytochemical, morphological, pathological and molecular information regarding response of anti tumor therapy for pNET [37]. Circulating tumor cells (CTC) are shed from the primary or metastatic component of the tumor and they are evaluated by liquid biopsy [38]. CTC are considered as prognosticators in many solid malignancies but their role in neuroendocrine tumors was highlighted first by Khan et al. in 2011 [39] patients with advanced NETs who were starting either systemic or local therapy were enrolled. It was found that patients with one or more circulating tumor cells (CTC) were more likely to have worse progression free and overall survival.

Further placental growth factor (PIGF) is also evaluated as a prospective biomarker in NET. pIGF is a derivative of VEGF, which shows increased expression in NETs. It was found that PlGF levels were elevated in pNET samples and serum as compared to control pancreatic tissue and control serum. It was concluded that elevated PIGF levels are seen in pNET and it has also been projected that increase PIGF levels correlate with shorter time to progression [40].

5. Clinical presentation

Since non functional pNET represent up to 90% of PanNETs, they present with high hormone levels without symptoms. However, upto 60% of these patients have a metastatic disease at diagnosis, while 21% present with a locally advanced disease [41].

Non specific symptoms of pNET include abdominal pain, weight loss, or mass effect related to the pancreatic tumor or to the distant spread. Less frequently it is associated with complaints of jaundice, hemorrhage from tumors, and a palpable mass. Symptoms often do not appear until metastases develop [42].

Usually endocrine tumors of the pancreas present with typical symptoms due to hormonal hypersecretion, such as insulinoma, gastrinoma, VIP-oma, glucagonoma and somatostatinoma. In upto 40%-50, cases may present as non-functioning tumors or secrete pancreatic polypeptide (PP) and neurotensin [43]. The various pancreatic NET subtypes with their incidence, clinical presentation and survival are mentioned below (**Table 5**).

6. Diagnosis

6.1 Biochemical

Chromogranin A is a secretory glycoprotein present in neurosecretory granules of pancreatic NET. Majority of pNET show elevated chromogranin A levels. The sensitivity depends upon the tumor burden and the levels of chromogranin A are directly correlated with the prognosis of the patient. In insulinomas elevated

Tumor/Syndrome	Incidence	Associated Symptoms	Malignancy	Associated peptide	Survival
Insulinoma [45]/ Hypoglycemia Syndrome	1–4 per million per year	Confusion, sweating, dizziness, weakness, relief with eating	10% patients develop metastasis	insulin	Complete resection leads to cure
Gastrinoma [46]/zollinger ellison syndrome	1–2 per million per year	Diarrhea with or without severe peptic ulcertion	60% patients develop metastasis, likelihood correlated with size of primary	gastrin	Complete resection leads to 10 year survival 90%
Glucagonoma [47]	0.1 per million per year	Weight loss, diabetes mellitus,necrolytic migratory erythema	60% patients develop metastasis	glucagon	Most favorable prognosis with complete resection, even in cases with liver metastasis
VIPoma [48]/ verner morrison syndrome	0.05% to 2.0%	Profuse watery diarrhea, hypokalemia, hypochlorhydria	70%patients develop metastasis Usually at diagnosis	Vasoactive intestinal polypeptide	Complete resection associated with 5 year survival 95%, With metastasis 60%
Somatostatinoma [49]	1 in 40 million	Cholelithiasis, weight loss, steatorrhea, diarrhea, diabetes mellitus, achlorhydria	50% patients develop metastasis	Somatostatin	Complete resection associated with 5 year survival 95%,, With metastasis 60%
ACTHoma [50]	<0.1	Cushing syndroma		ACTH	
PTHrPoma/ pNET causing hypercalcemia [32]	<0.1	Symptoms due to raised Ca levels		PTHrP	
GRFoma [32]	<0.1	acromegaly		GRF	
Non syndromic pancreatic neuroendocrine syndrome [32]		Symptoms due to pancreatic mass or liver metastasis	50% patients develop metastasis		Complete resection associated with 5 year survival 50%

Table 5.
Incidence, clinical presentation and survival of pancreatic NET subgroups [27–32, 44].

chromogranin A levels are rare. Other serologic markers include neuronal serum enolase, human chorionic gonadotropin, and pancreatic polypeptide, which are elevated in 20–40% of PNETs. (See **Table 6**) [52].

When any NET is suspected then fasting gut hormones such as chromogranin B, pancreatic polypeptide and urinary 5HIAA (a breakdown product of serotonin) are also useful baseline tests. False positive chromogranin A levels are caused due to treatment with a proton pump inhibitor, Parkinson's disease, hypertension, glucocorticoids, renal failure and atrophic gastritis, while various dietary factors and drugs can cause an elevated urinary 5HIAA [53].

Additional blood tests for secreted peptides can be useful if a clinical syndrome is suspected and calcium, prolactin and parathyroid hormones should be tested in possible MEN1 cases. For Nonfunctioning pNETs, pancreatic polypeptide is a useful test. For insulinomas the gold standard diagnostic tool is supervised fasting with serial blood glucose analysis. Diagnosis requires the fulfillment of Whipple's triad of hypoglycemia, symptoms and correction of symptoms with glucose, in the presence of non-suppressed insulin levels. Factitious hypoglycemia due to administration of insulin or sulfonylureas must be ruled out [54].

6.2 Radiological

Cross sectional imaging plays an important role in the workup of PNETs by characterizing the primary tumor and determining the extent of disease. Location of the tumor and its spread can be delineated by the use of multimodality imaging which includes computed tomography (CT), MRI and various nuclear medicine scans. Endoscopic ultrasound (EUS), digital subtraction angiography and venous sampling can also be used [55]. The sensitivity of CT and MRI is more than 80% for the detection of PNETs which is more sensitive than an octreotide-based scintigraphic scans [56].

EUS acts as an indispensable accompaniment to CT or MRI and has superior resolution. For tumors with size as small as 2 mm, EUS shows sensitivity of more than 90% and when combined with cross sectional imaging the sensitivity reaches upto 100%. Addition of EUS is recommended when cross-sectional imaging fails to define the pancreatic mass, when the location of primary cannot be delineated or biopsy is needed to confirm the diagnosis before commencing the treatment [57].

Syndrome	Test	Result
Gastrinoma	Fasting gastrin Gastrin secretion studies	Raised basal serum gastrin, High gastric acid secretion
Insulinoma	Fasting Insulin, Glucose, C peptide (sulfonyl urea screen negative)	Raised fasting insulin/glucose ratio, proinsulin or c peptide
Glucagonoma	Fasting gut hormones, ski biopsy	Raised serum pancreatic glucagons and enteroglucagon
VIPoma	Fasting gut hormone	Raised fasting VIP
Ppoma	Fasting gut hormone	Raised fasting pancreatic polypeptide
Somatostatinoma	Fasting gut hormone	Raised fasting somatostatin
All NET	Serum chromogranin	Raised chromogranin A
Ectopic hormones	GHRH, ACTH, HCG-alpha and beta	Raised but low incidence

Table 6.
Biochemical tests for pNET [33, 51].

Well Differentiated Net [63]	Poorly Differentiated Net [64]
• "organoid" arrangements of the tumor cells • solid, nested, trabecular, or ribbon-like/gyriform, tubulo-acinar/pseudoglandular and mixed pattern • Uniform cells with round to oval nuclei, coarsely granular, 'salt and pepper' chromatin • pale to moderately eosinophilic cytoplasm • Has neurosecretory granules • Necrosis absent	• Sheets or nests of atypical cells • pleomorphic, hyperchromatic nuclei and abundant mitotic figures • 'Salt and pepper' appearance of chromatin is absent • Necrosis often present • small cell (molding nuclei, scant cytoplasm) or large cell (abundant amphophilic cytoplasm

Table 7.
Histopathological features of well and poorly differentiated tumors.

Since NETs have high levels of somatostatin receptor 2 (SSTR2) expression, Functional imaging comes into play in these tumors. For tumors lacking SSTR2, like insulinomas and poorly differentiated tumors, it is less useful [58]. It is used to detect primary tumors or metastatic disease which is not readily seen on cross-sectional imaging. Also, the uptake can predict response to octreotide analogs [59].

Indium-111 (111In) pentetreotide scan (Octreoscan) is a readily available nuclear scan that is effective at identifying nonfunctional PNETs, glucagonomas, and gastrinomas [60]. Although High-resolution positron emission tomography (PET) in combination with CT is superior in detecting small tumors and identifying occult metastases as compared to 111In pentetreotide. For identifying well-differentiated NETs, Octreoscan appears more sensitive than (18) FDG-PET, whereas (18) FDG-PET demonstrates superior sensitivity for poorly-differentiated NETs [61].

Somatostatin receptors are overexpressed in a proportion of NETs and Somatostatin receptor scintigraphy (SSRS) is useful in detecting these tumors. There are five subtypes of SSTR and 80% of pNETs, excluding insulinomas, express SSTR-2. Less than half of insulinomas express SSRT-2, therefore Single-photon emission computed tomography (SPECT) has sensitivity of 50% when combined with SSRS. In gastrinomas, VIPomas, glucagonomas and nonfunctional tumors SSRS combined with SPECT has a diagnostic sensitivity of 75% [20].

Currently both 18F-FDG PET/CT and 68Gallium (Ga)-labeled somatostatin analog PET/CTs such as 68Ga-DOTATOC or 68Ga-DOTATATE PET/CTs are used. FDGPET use is limited to poorly differentiated NETs, as well differentiated NETs are not FDG avid. It may also be used to demonstrate aggressive behavior or heterogeneity between lesions in a single patient. 68Ga-labeled somatostatin analog PETs have been shown to be superior to CT or SSRS in sensitivity and specificity, for detecting an unknown primary, staging at diagnosis, and for follow-up [62].

6.3 Histopathology

They can be classified as well differentiated and poorly differentiated NET. the major differences are elaborated further (**Table 7**).

7. DIfferential diagnosis

- Acinar cell carcinoma: It can be differentiated from pNET as it has granular PAS positive cytoplasm, BCL10, trypsin, chymotrypsin positive, Synaptophysin and chromogranin positivity <25% while pNET is PAS negative, BCL10, trypsin, chymotrypsin negative and Synaptophysin or chromogranin positivity over 25% [65].

- Solid-pseudopapillary neoplasm: It has pseudopapillary architecture, Chromogranin focal to negative, Galectin 3,Vimentin, CD10, Nuclear beta catenin positive while pNET has no pseudopapillary architecture, Chromogranin strongly positive, Galectin 3,Vimentin, CD10, Nuclear beta catenin negative [65].

- Pancreatoblastoma: It shows Trypsin, chymotrypsin positive, Chromogranin, synaptophysin scattered positive, Islet polypeptide markers negative or very focal while Trypsin, chymotrypsin negative, Chromogranin or synaptophysin widespread staining, Islet polypeptide markers frequently positive in pNET [65]

Insulinoma [27]: the differential diagnosis includes conditions with increased insulin levels in blood

- Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)
- Sulfonylurea-induced hypoglycemia
- Insulin autoimmune hypoglycemia
- Post-gastric bypass hypoglycemia
- Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS)
- Non-islet-cell tumors that secrete insulin-like growth factors (IGF)
- Factitious use of insulin

Glucagonoma [66].

- Acrodermatitis Enteropathica
- Bacteremia
- Cirrhosis
- Non functioning neuroendocrine tumor
- Paraneoplastic Syndromes
- Pediatric Pellagra
- Psoriasis
- Type 1 and 2 Diabetes Mellitus

8. Management

Multidisciplinary teams (MDTs) have an important role in deciding the treatment of these tumors as they are slightly rare.

Treatment options range from curative surgery to palliation with medical therapies including somatostatin analogs, chemotherapy and targeted treatments [67].

Conservative management is indicated for incidentalomas, i.e. the tumors which are small, non functional and asymptomatic [68]. Although it is a controversy whether small nonfunctional tumors of under 2 cm should be resected, when they are likely to have less metastatic potential, but a more aggressive surgical approach is recommended for tumors over 2 cm [69].

8.1 Surgery

Surgery is the only curative treatment option and should be considered in all patients with localized disease as it not only cures the mass related symptoms but also the hormone related effects. Such patients should have their surgery carried out at specialist hepatopancreatobiliary centers. Surgery can be done for curative treatment like radical excision or palliative treatment that aims for symptomatic relief. It can also be used for surgical treatment of complications. The 5-year overall survival rate of resected PNETs is significantly greater than unresected ones, ranging from 77% to 46% [70]. Unfortunately, pancreatic surgery shows significant mortality, ranging from 1% to 10% [71] and morbidity. The perioperative and long-term complications include diabetes, pancreatic exocrine impairment in up to 50–60% patients, even in high volume centers [72, 73].

Careful observation and wait and watch policy can be employed for small non functioning pNET which helps in not only avoiding the pancreatic surgery but also helps curb the operation related complications, as most of the small NF-PanNETs are indolent despite a chance of 10% of nodal involvement [74, 75].

According to the updated ENET guidelines patients having NF-PanNETs ≤2 cm can be safely managed conservatively.

Indications of non operative approach:

- the presence of G1-low G2 tumor
- Tumor localized to pancreatic head
- no signs of malignancy at imaging.

In patients with G2 NF-PanNETs greater than or equal to 2 cm, surgery should be recommended. Other factors to be taken into consideration include patient's age, comorbidities, surgical risk, the tumor site, and desire for surgical intervention.

In cases of surveillance, EUS and MRI should be mandatory and to be repeated every 6 months (12 months if no changes are discovered). If an increase of 0.5 cm (or more) in the size of the lesion is seen on the imaging then the patient should be reevaluated for surgery [9].

The studies comparing observation with surgery in pNET are as follows:(**Table 8**).

In contrast to the ENETS guidelines, the American National Comprehensive Cancer Network (NCCN) guidelines recommend surgery to be done in a pNET bigger than 1 cm. Observation is indicated incidentally discovered, low-grade NF-PanNETs smaller than 1 cm. Additional factors for conservative management include the surgical risk, the tumor site, and the patient comorbidities, especially when dealing with small asymptomatic tumor [80]. NCCN states that more aggressive approach (routine surgery) is recommended in tumors greater than 1 cm as some small (<2 cm) high-grade tumors demonstrate frankly malignant behavior (9% to 39%) [81].

Study	No. of patients	Protocol	Result
Sadot et al. [76]	Incidentally discovered, sporadic, small (<3 cm), stage I–II PanNET 464 patients	Observation 104 patients vs. surgery 77 patients	No diff in os in both groups
Rosenberg et al. [77]	Incidentally discovered non functional pNET	Observation 15 patients vs. surgery 20 patients	Incidentally discovered NF-PNETs <2 cm in size can be observed safely with serial imaging.
Regenet et al. [78]	80 patients Non functional pNET	Observation 66 patients vs. 10 surgery	Tumor size has great impact on malignancy. he cutoff of 2 cm of malignancy used for small NF-PNETs could be decreased to 1.7 cm to select patients more accurately.
Zhang et al. [79]	Small non functioning pNET 249 patients`	Observation 56 vs. surgery 193	Resection of nonfunctioning PNETs over 1.5 cm is independently and significantly associated with a longer survival

Table 8.
Studies comparing observation versus surgery in small pNET.

8.2 Systemic therapy

In patients with resectable PanNETs, surgery with curative intent (that is, R0 or margins that are microscopically free of tumor) remains the treatment of choice. Unfortunately, as the majority of patients with PanNETs either present with metastatic disease or have disease recurrence within 2 years of surgery, effective systemic therapies are also needed [82].

8.3 Somatostatin analogs

Somatostatin analogs remain the cornerstone in treatment of advanced neuroendocrine tumors.

Long acting octrotide, lanreotide which bind both SSTR2 and SSTR5 and pasireotide which binds to SSTR1, 3, and 5 are currently approved for clinical use [83].

Trials studying the role of somatostatin analogues (**Table 9**).

Study	No. of patients	Protocol	Result
PROMID TRIAL [84]	85 patients with well-differentiated NETs	long-acting octreotide (n = 42) vs. placebo (n = 43)	Octreotide LAR significantly lengthens time to tumor progression compared with placebo. Ttp octreotide 14.3 month vs. placebo 6 month
CLARINET TRIAL [85]	204 patients with advanced, G1/G2 differentiated, nonfunctioning, somatostatin receptor–positive NETs	Lanreotide(n = 101) vs. placebo(n = 103)	Better PFS with lanreotide Median PFS lanreotide(32.8 month) vs. placebo(18 month)

Table 9.
Studies showing role of somatostatin analogues in pNET.

The use of pasireotide, a somatostatin analog was evaluated in a phase III randomized trial targeting SSTR5, in octreotide-resistant patients. It demonstrated no difference in the response rate (RR) compared with long-acting octreotide. The trial was stopped prematurely [86].

Chan et al., studied 1022 patients in 18 trials using more than 30 mg octreotide or 120 mg lanreotide over 28 days in a meta-analysis in 2017 [87]. Pasireotide has shown a more potent antiproliferative effect as compared to octreotide in preclinical data from NCI-H727 cells and from pancreatic NET primary cell cultures [88].

A similar study conducted by Cives et al. recently showed that pasireotide LAR provides better tumor control efficacy (PFS 11 months), when used as first-line therapy in patients with advanced NET [89]. Further, in patients with functionally active advanced GEP-NETs, pasireotide provided an improved tumor control rate at 6 months compared to octreotide [50]. In 160 patients with progressive grade 1 through 2 pancreatic NETs, the COOPERATE-2 trial tested the combination of everolimus and pasireotide vs. everolimus. It was seen that both overall and progression-free survival were similar in both arms (16.8 months vs. 16.6 months), although response rates were higher in the experimental arm [90].

Study Design	No of patients	protocol	Result
Kulke et al. 2008 [91] Phase 2	Out of 109 patients, pancreatic endocrine tumor, n = 66	oral sunitinib	ORR) in pancreatic endocrine tumor patients was 16.7% SD68% MEDIAN PFS 81% (1-year survival)
Raymond et al. [92] Phase 3	171 patients	Placebo (n = 85) vs. sunitinib(n = 86)	Median PFS was 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group. objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group
Yao et al. [93] Phase 2	200 patients	Everolimus(n = 115) Everolimus + octreotide LAR(n = 85)	Median PFS 9.6 months Median PFS 16.7 mo.
Yao et al. [94] Phase 2	30 patients	Everolimus + octreotide LAR	Median PFS 12.5 mo.
Yao et al. [95] Phase 3	410 patients	Everolimus (n = 207) vs. placebo (n = 203)	Median PFS 11 mo vs. 4.6 mo.
Duran et al. [96] Phase 2	15 patients	temsirolimus	median TTP 6 months and 1-year OS rate 71.5%
Hobday et al. [97] Phase 2	43 patients	sorafenib	Median PFS 6 month
Phan et al. [98] Phase 2	29 patients	Pazopanib + octreotide LAR	Median PFS 11.7 months

Table 10.
Studies showing the role of targeted therapy in treatment of pNET.

Study Design	No of patients	protocol	Result
Broder et al. [63] Phase 2	52	streptozocin	A significant increase in 1-year survival rate and a doubling of median survival were shown for the responders as compared with the nonresponders
Moertel et al. [101] Phase 3	84	Streptozocin (n = 42) vs. streptozocin plus 5FU (n = 86)	Median OS was 26.5 months in the streptozocin plus 5FU group as compared with 16.5 months in the streptozocin group
Moertel et al. [102] Phase 3	105	Streptozocin/Doxo(n = 38) Streptozocin +5FU(n = 34) Chlorozotocin (n = 33)	Median OS 26.4 months Median OS 16.8 mo. Median OS 18 mo
Moertel et al. [103] Phase 2	14	Cisplatin + etoposide	
Turner et al. [104] Phase 2	47	Cisplatin/5-FU/ streptozocin	
Ramanathan et al. [105]	50	Dacarbazine	median OS 19.3 months
Bajetta et al. [106]	27	Capecitabine/oxaliplatin	
Kulke et al. [107] Phase 2	11	Temozolomide/thalidomide	Median OS 24 months
Chan et al. [108]	15	Bevacizumab Plus Temozolomide	median overall survival was 41.7 months for pancreatic NETs
Chan et al. [109]	43	Temozolamide and everolimus	the median progression-free survival duration was 15.4 months. Median overall survival was not reached
BETTER trial [110]	34	Bevacizumab with 5-FU/ streptozocin	Median PFS 23.7 months OS rate at 24 months was 88%.

Table 11.
Studies showing role of cytotoxic chemotherapy in pNET.

8.4 Targeted therapy

Molecular targeted therapies have emerged as a promising treatment modality for patients with well-differentiated PNETs in which disease progression is seen on a somatostatin analog or who are on best supportive care. Randomized studies have shown an improvement in PFS but not OS. Currently, sunitinib and everolimus are approved for use in PNETs (**Table 10**).

8.5 Cytotoxic chemotherapies

Much of the focus on treatment over the past half century has been on the use of conventional cytotoxic agents such as streptozocin [99] and temozolomide [100]. Sunitinib and everolimus are approved for use in PNETs (**Table 11**).

8.6 Peptide receptor radionuclide therapy (PRRT)

Majority of neuroendocrine tumors show increased level expression of somatostatin receptors (SSRs) 2 and 5 on the tumor cell surface and it forms the basis

Study	No. of Patients	Radioligand	Result
Valkema et al. [114]	58	90Y-DOTATOC	PFS 29 months OS 17 months
Kwekkeboom et al. [115]	310	177Lu-DOTATATE	PFS 33 months OS 46 months
Bushnell et al. [116]	90	90Y-DOTATOC	PFS 16 months OS 27 months
Cwikla et al. [117]	58	90Y-DOTATATE	PFS 17 months OS 22 months
Pfeifer et al. [118]	53	90Y-DOTATOC	PFS 29 months OS - months
Bodei et al. [119]	39	177Lu-DOTATATE	PFS 36 months OS - months
Ezziddin et al. [120]	74	177Lu-DOTATATE	PFS 26 months OS 55 months

Table 12.
Various retrospective studies have been conducted on PRRT.

of not only functional imaging but also tumor directed therapies like somatostatin analogues [111]. Beyond somatostatin analogues, PRRT, which is described as peptide receptor radioligand therapy or targeted radiotherapy using radiolabeled somatostatin analogs is emerging as an effective treatment modality in metastatic, well-differentiated, grade 1 and 2 GEP-NET [112]. Yttrium, a high-energy β particle emitter and Lutetium, a β and γ particle emitter with lower tissue penetration are most commonly studied radioligands [113] (**Table 12**).

131I-metaiodobenzylguanidine (131I-MIBG) therapy has shown promise in in MIBG positive metastatic neuroendocrine tumors, in addition to radiolabeled somatostatin analogs [121].

The toxicities associated with PRRT include myelosuppression and nephrotoxicity, both of which are reversible, acute pain due to radiation edema and nausea and vomiting, associated with the use of amino acids to reduce the risk of nephrotoxicity and very rarely myelodysplastic syndrome.

9. Prognosis

Depends upon Metastatic spread, large tumor size, and hormonal hypersecretion as well as gender, age, and histopathological high-grade, Ki67 (**Table 13**).

SEER Stage	5-year Relative Survival Rate
Localized	93%
Regional	77%
Distant	27%
All SEER stages combined	54%

Table 13.
5-year relative survival rates for pancreatic NET [8].

10. Conclusion

Pancreatic neuroendocrine tumors are a distinct group of tumors from other pancreatic malignancies. They present with vastly different spectrum of clinical features ranging from asymptomatic incidentalomas to symptoms related to hormone hypersecretion or due to mass effect. Due to rarity of these tumors and as the biological potential of these tumors remain unexplored, the management is largely consensus based and is still under a lot of research. Although surgery is the main modality of treatment but conservative management is also indicated in small non functioning tumors. Advanced pNET can be treated with chemotherapy or targeted agents. In this context, prospective studies with the creation of a large multi-center trials and an international registry are future recommendations.

Conflict of interest

The authors declare no conflict of interest.

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