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Pancreatic Neuroendocrine Tumors in the 21st Century – An Update

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Abstract

Pancreatic Neuroendocrine Tumors (PNETs) are rare, reported to account for less than 1-2% of all pancreatic tumors. This, however, is likely an underestimation, as improved radiologic techniques and heightened awareness have resulted in an increase in the detection of incidentalomas, with estimations of true prevalence as high as 10%. The term "PNET" is an umbrella name encompasses a heterogenous group of neoplasms each with distinct clinical presentations, diagnostic radiographic features, management principles, and tumor/patient outcomes. In this context, accurate diagnosis is challenging, and management guidelines unclear. A high degree of clinical suspicion is required for best patient management. This manuscript provides a comprehensive of PNETs in the 21st century, in which we review the terminology, epidemiology classification, aetiopathogenesis, radiographic and histopathologic diagnostic features, management for localized and metastatic disease, as well as a review of features defining functional and non-functional PNETS, and finally describe prognostic features.

Keywords: Pancreatic neuroendocrine tumor; Insulinoma; Gastrinomas

Introduction

Pancreatic Neuroendocrine Tumours (PNETs) are a heterogeneous group of rare neoplasms that account for less than 3% of all pancreatic tumors [1]. These neoplasms are most commonly sporadic, though they may be associated with a number of genetic syndromes including Multiple Endocrine Neoplasia-1 and von Hippel Lindau syndrome. The prevalence of PNETs has been increasing, from 15 to 24% in the 1980s to 60% more recently [2]. This trend may be due to greater awareness, more specific systems of classification, and increased radiological imaging. Though grouped together as a single neoplastic category: these heterogenous tumors arise from different neuroendocrine cells, may produce diverse secretory products resulting in multiple clinical presentations, progress along aberrant pathways from indolent to aggressive, and have differing outcomes. This manuscript describes the current terminology, epidemiology, and classification of these tumors, followed by a discussion of their aetiopathogenesis and associated syndromes. The principles of diagnosis including pathology with World Health Organization updates, and management of PNETs are deliberated. Finally, the prognostic determinants with propositions for future directions are discussed.

Terminology

The proper terminology to describe these tumours has been a source of contention for a number of years, with multiple nomenclature and staging systems causing confusion. The term 'carcinoid' ('carcinoma-like') was first proposed over 110 years ago by Obendorfer to describe functional neuroendocrine tumours in the gastrointestinal tract with a slow-growing nature [3-5]. Clinically, the term 'carcinoid' was restricted to describe neoplasms that secrete serotonin (5HT) whereas pathologists more broadly applied the term to well-differentiated endocrine tumours of lung, gut, and pancreas [5]. It was recognized that the generalized term 'carcinoid tumour' was insufficient to effectively convey the spectrum of biological behavior of these lesions ranging from benign to malignant. The name "pancreatic neuroendocrine tumor" is synonymous with 'islet cell tumour' and 'well-differentiated pancreatic endocrine carcinoma'. Traditional benign vs. malignant classification of these tumors is often impossible at initial diagnosis, as they can show extremely

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Table 1: WHO classification of PNETs.

Classification	WHO Grade	Features
Well-differentiated neuroendocrine tumor, grade 1	G1	<2 mitoses per 10 HPF Ki67 labeling index ≤2%
Well-differentiated neuroendocrine tumor, grade 2	G2	2-20 mitoses per 10 HPF Ki67 labeling index 3-20%
Poorly-differentiated neuroendocrine carcinoma (small cell carcinoma, large cell endocrine carcinoma), grade 3	G3	>20 mitoses per 10 HPF Ki67 labeling index >20%

Table 2: TNM staging of PNETs.

Stage	Tumor	Node	Metastases
0	**Tis** Carcinoma in situ	**N0** No nodal metastases	**M0** No metastases
IA	**T1** Limited to pancreas ≤2cm dimension		
IB	**T2** Limited to pancreas >2cm dimension		
IIA	**26** Beyond pancreas No celiac axis/SMA involvement		
IIB	**T1, T2, or 26**	**N1** Regional node metastases	
III	**T4** Involves celiac axis or SMA	**Any N**	
IV	**Any T**		**M1** Distal metastases

variable biological behavior. Whether these tumours should be called 'endocrine' or 'neuroendocrine' continues to be debated. Originally, the tumours were called 'neuroendocrine' based on the hypothesis that they were derived from embryonal neural crest cells. When this hypothesis was discredited due to the endodermal origins of these neoplasms, they were termed 'endocrine tumours'. The most recent switch, back to 'neuroendocrine', was due to the recognition of the neural and epithelial elements present such as expression of neuron-specific enolase, chromogranin A/B/C, and synaptophysin. The 'correct' term is, however, simply semantics as they as are essentially synonymous.

Epidemiology

PNETs are rare tumours, accounting for only 1 to 2% of all pancreatic neoplasms [6-8] yet an estimated prevalence of up to 9.9% of pancreatic malignancies are neuroendocrine in nature [9]. Tumors may be functional or non-functional with the latter conferring up to half of all PNETs [10]. It is estimated that 2,500 new PNETs are diagnosed each year, with an overall incidence of 1-10/million. Despite this low incidence, PNETs have been detected in 0.5-1.5% of the population at autopsy [11]. It is expected the prevalence of PNETs will continue to increase due to the widespread use of high-quality radiological imaging thereby detecting incidental, non-functioning PNETs [12]; currently, up to 50% of tumors are incidentalomas [13]. However the true prevalence of these lesions remains obscure, as many are asymptomatic and less than one centimeter in diameter and thus may escape detection on imaging. Nevertheless, the overall incidence and prevalence of PNETs have increased over the past thirty years. These rising trends are most likely attributed to advancements and improvements in diagnostic imaging that are more sensitive to detecting smaller lesions [14,15]. An enhanced awareness of these neoplasms may additionally account for the increased number of tumours detected and accurately diagnosed [16]. In this context, it is estimated that the true incidence of PNETs is closer to 2-10%. Due to the rarity of these lesions, epidemiological information indicating populations at the greatest risk of developing a PNET remains sparse and unclear. These tumours have no gender preference and patients are typically between the ages 30-60 years, particularly 51-57 years. A slight predisposition for Japanese populations is suggested, as the annual incidence in Japan is 2.23/100,000 compared with an American incidence of 0.32/100,000. It is, however, well recognized that patients with syndromes including multiple endocrine neoplasia- 1(MEN-1), von Hippel Lindau (vHL), neurofibromatosis type 1 (NF-1) and tuberous sclerosis (TSc) have a higher risk of developing PNETs; the clinical features and syndromic PNETs may differ from their sporadic counterparts [17,18]. Of all patients with PNETs, 1-2% will have a familial syndrome. These syndromes are explored in further detail in section 4b.

Classification

Developing a comprehensive, clinically significant system for classifying PNETs is challenging due to their heterogeneity, as they differ in morphology, clinical course, hormonal function, treatment response, and prognosis. Clinically, these neoplasms are often classified as functioning and non-functioning. Three-quarters of patients present with symptoms caused by PNETs secreting an excess of certain hormones and therefore these tumours are classified as 'functional'. These 'functional' tumours can further be sub classified based on the hormone produced. This is discussed in section 7. The two most generally accepted classification systems are from the World Health Organization (WHO) and the European Neuroendocrine Tumour Society (ENETS). In both, important criteria for malignancy include tumour size, perineural/vessel invasion, tumour cell proliferation, metastatic disease, and local invasion. Both systems have been validated for prognostic stratification. The American Joint Committee on Cancer (AJCC) has proposed a classification/staging system for PNETs; however, prospective evaluation is required prior to its universal acceptance. In 2000, the World Health Organization (WHO) created a classification system aimed at predicting patient outcome that used stage and grade-related criteria including tumour size, the presence of metastases, mitotic rate, perineural invasion, angioinvasion, and Ki67 proliferation index. Unfortunately inter-pathologist reproducibility was low using this system. In response to this concern, the WHO released a new classification structure in 2010,

which is currently being used. This new classification categorizes PNETs into a) well-differentiated neuroendocrine tumours (NET, Grades 1 and 2) and b) poorly-differentiated neuroendocrine carcinoma (NEC, Grade 3) as seen in Table 1. NETs are further sub-classified as low-grade (0-1 mitosis/10 HPFs, Ki67 0-2%, Grade 1) or intermediate (2-20 mitoses/10 HPFs, Ki67 3-20%, Grade 2). NEC is characterized by more than 20 mitoses/10 HPFs and Ki67 >20% [19,20]. However, the calculation of the Ki67 index remains challenging as there is poor inter-observer agreement with the usual 'eye-balling method' that is routinely used in histopathological evaluations [21]. Thus the development of a *minimum pathology dataset* as proposed by Klimstra et al. may be an option if universally adopted [22]. Due to the heterogenous biological behaviour, only microscopic analysis is considered acceptable in grading and staging as it is validated with poorly-differentiated carcinoma having a significantly worse prognosis. The ENETS also has created a TNM staging system to classify these tumours. The 'tumor' element is divided into T0 (no primary tumor evident), T1 (limited to pancreas, <2cm), T2 (limited to pancreas, >2cm), (beyond pancreas without celiac axis or SMA), and T4 (involving celiac axis or SMA). The 'nodal' status may be either N0 (no lymph node involvement) or N1 (positive involvement). Finally, 'metastasis' status is either M0 (no metastases) or M1 (distant metastases present). Based on these criteria, the ENETS system stages PNETs from I-IV as illustrated in Table 2. On univariant analysis higher stages of IIIa, IIIb and IV were significant for worse prognosis, and on multivariant analysis stage IV was significant.

Aetiopathogenesis

A neuroendocrine tumour arises in any organ derived from primitive endoderm, including pancreatic islet cells, or diffuse neuroendocrine cells of the gut, thyroid gland, respiratory system, or thymus [23]. As such, PNETs were originally believed to arise from the islets of Langerhans [5,24]. The islet cells make up 1-2% of the total pancreatic mass and include a number of cell types that each secrete a certain hormone, including beta cells (insulin), alpha cells (glucagon), delta cells (somatostatin), and PP cells (pancreatic polypeptide) [25]. An alternative theory which is gaining acceptance suggests PNETs are derived from the ductal epithelial stem cells. In this theory, precursor pluripotent stem cells from the neural crest mature and secrete one or multiple hormones [26]. Most sporadic PNETs are solitary, well-demarcated, and well-differentiated tumours with a slow-growing, indolent course [23,27]. These tumours usually grow in the pancreatic duct lumen without epithelial invasion. Vascular invasion of non-functional-PNETs indicates malignant potential [24]. Within these tumours, tumour-associated macrophages account for the largest immune cell population and are associated with poor clinical features [28]. In the presence of multiple tumours, genetic syndromes should be considered as the underlying etiology.

Molecular mechanisms

The genetic basis of sporadic PNETs has yet to be fully elucidated; however, varied observations may contribute to a greater understanding regarding the molecular development and progression of these neoplasms. Traditionally, malignant neoplasms have been associated with multiple genetic mutations. Paradoxically, PNETs are regarded as being relatively mutationally inert. Genetic instability has been implicated in the development and progression of PNETs, with genetic losses occurring more commonly than gains. Four chromosomal abnormalities have been detected using single nucleotide polymorphism studies in 60% of PNETs. Such losses accumulate as the tumour progresses, and are associated with tumour volume and stage [29]. Malignant behaviour is linked with loss of chromosomes 3q, 6pq, and 10 pq, and gains of 5q, 12a, 18q, and 20q. These tumors contain microsatellite losses, with a median fractional loss of 0.37, significantly different from the median fractional loss of 0 amongst benign tumors. This is significant, as a fractional allelic loss of greater than 0.2 is associated with increased progression and mortality [30]. Chromosome 1 and 11q loss with gain of 9q are thought to occur early in development as they have been observed in tumours <2cm, suggesting genetic instability may be associated with development of malignancy [5,29]. Several genetic mutations have been described in association with PNETs. A study investigating the genetic basis of PNETs identified 157 somatic mutations in 149 genes with a mean of 16 mutations per tumor, and the most common somatic mutations were *MEN1* (44.1%), *DAXX* (25%), *ATRX* (17.6%), *PTEN* (7.3%), *TS47* (8.8%) and *PIK3CA* (1.4%) [31]. The most frequent mutation is *MEN1,* which occurs in the syndromic PNETs. 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* [32,33]. Markers that may predict a more aggressive malignancy include cytokeratin 19, E-cadherin, and CEACAM1. Many PNETs are positive for somatostatin receptor which is involved in hormone secretion, apoptosis and endocrine proliferation [34,35]. Impaired G1/S checkpoint is reported in PNETs. It is hypothesized that mutations of PTEN in PI3K/mTOR signaling and p53 expression lead to tumor progression. Over expression of cyclin D1 is common in PNETs, reported in 43%, and *PTEN* mutations are identified in 7.4% of sporadic PNETs all of which had concurrent mutations of either *MEN1* or *DAXX*. Increased activity of protein kinase B (AKT) is reported in 61 to 76% of gastroenteropancreatic neuroendocrine tumors, with inhibition of AKT signaling reducing PNET proliferation. Abnormal activation of mTOR, a component of the PI3K pathway, is common in PNETs and therapeutic targeting of this pathway with sirolimus decreases relapse rates. The DAXX/p53 pathway is also implicated in PNETs. While a mutation in *TP53* is rare in well-differentiated PNETs and is possibly a late event for poorly-differentiated tumours, mutation of the DAXX adaptor protein causes disassociation of MDM2/USP7, degradation of MDM2, and subsequent p53 stabilization, causing arrest of the G2/S checkpoint. DAXX normally functions with ATRX; mutation of either of these proteins is mutually exclusive and correlated with alternative lengthening of telomeres. These mutations are present in 45% of PNETs and are not identified in pancreatic neuroendocrine carcinoma. Patients with mutation of *MEN1* and *DAXX/ATRX* have double the median survival compared with other mutations. The Ras-Raf-MEK-ERK pathway is implicated in the pathogenesis of PNETs. While KRAS mutations are not present in these tumors, low levels of Raf1 are reported in PNETs which is hypothesized to contribute to invasion and migration via activation of focal adhesion kinase (FAK). The PNET molecular profile is thus opposite of Pancreatic Neuroendocrine Carcinoma (PNEC), where this pathway is activated and Raf1 inhibition causes antitumor activity. PNECs have 60% more mutations than PNETs and have a higher likelihood of TGF-β, CDKN2A and TP53 mutations compared with PNETs and they are thus proposed to arise through different independent pathways [31]. In gastrinomas, deletion or hypermethylation of p16/MTS1 and/or deletion of p16INK4a has been reported; however, this mutation is not recognized in insulinomas. By contrast, 93% of both benign and

malignant insulinomas have loss of heterozygosity (LOH) on 22q. PNET metastases often have gain of function in chromosomes 4 and 7, with loss of 21q. Specific factors involved in this metastatic process include VEGF-C, MAGE-1, p27, thrombomodulin, and SRC kinases [32]. Despite an improved understanding of the genetic basis of these tumours, the clinical implications remain unclear, as traditionally genetic testing could only be done on tissue samples post-resection. Recently, it has been shown that an analysis of microsatellite loss could be performed on EUS-FNA samples in which a mean fractional allelic loss with >0.2, was associated with disease progression, thus providing an insight into future tumor behavior. Further investigation is warranted to determine the reliability of this technique in terms of tumor outcomes.

Syndromic associations

Though they are often spontaneous, PNETs may be associated with one of several underlying genetic conditions. Patients diagnosed with a PNET secondary to any of these conditions follow a more indolent course, and tumours are often multifocal. These include von Hippel Lindau (vHL), Multiple Endocrine Neoplasia-1 (MEN-1), Tuberous sclerosis (TS), and Neurofibromatosis-1 (NF-1). Von Hippel Lindau (vHL) is caused by an autosomal dominant mutation of the vHL tumor suppressor gene on chromosome 3p25 that increases the patient's susceptibility to neoplasms in the central nervous system and visceral organs, including neuroendocrine tumours [5,36]. Loss of heterozygosity at this chromosome has been demonstrated in 30% of sporadic PNETs though it is suggested the VHL gene doesn't play a direct role in these sporadic lesions. The VHL gene is responsible for the regulation of ubiquitination of hypoxia-inducible factors (HIF) 1 and 2, which causes upregulation of VEGF, PDGFR-beta, TGF-alpha, and erythropoietin. Mutation of this protein in vHL syndrome results in the development of hemangioblastomas, renal and hepatic cysts, adrenal/pulmonary/hepatic hemangiomas, renal cell carcinomas, and pheochromocytomas. 10-17% of patients with vHL will develop a PNET, and these tumours are non-functional and often asymptomatic [29,36-38]. The average age at diagnosis is 29-38 years, and 67-70% has unifocal tumours [38]. It is suggested pancreatic screening should begin at age 15, when screening begins for renal cell carcinoma with follow-up every 2-3 years. These PNETs are often locally invasive; however, they have a lower rate of metastases, at 11-20%, potentially due to constant screening resulting in earlier diagnosis than sporadic non-functional PNETs. The decision of when to operate can be a challenge due to the presence of multiple tumours and recurrences. Criteria for predicting metastases includes: tumour size >3cm, exon mutations, and a tumour doubling time <500d. The presence of these factors favors early surgical intervention. However, these PNETs are slow-growing which contributes to their overall good prognosis; the death rate of PNET with vHL is 0.3%. Multiple Endocrine Neoplasia type 1 (MEN-1) results when the tumour suppressor gene on chromosome 11q13 is inactivated and is characterized by primary hyperparathyroidism in >95% secondary to parathyroid hyperplasia or adenoma, pituitary tumours in 20-40%, and PNETs. Over 1,300 mutations of the *MEN1* gene have been identified, leading to dysfunction of the Menin protein. This gene is mutated in one-third of sporadic non-functioning PNETs, insulinomas, and gastrinomas and does not affect tumour size of metastases. It is additionally hypothesized that additional oncogenes and tumour suppressor genes may be at 11q, downstream from MEN-1, that play a role in PNET development. The *Menin* gene interacts with a number of downstream proteins, regulating transcription, genomic stability, cell division and the cell cycle [39]. It is not yet understood from which cells MEN-1-associated PNETs arise, though it is thought they arise from the acinar and ductal cells rather than the islets themselves. The lifetime risk of developing a PNET in the context of MEN-1 is nearly 100% [40], though 54-93% of MEN-1 patients are asymptomatic [41]. Patients more often present with hyperparathyroidism or hyperpituitarism, with the PNET being diagnosed incidentally after confirmatory diagnosis of MEN-1. As such, continued screening should be offered to these patients. The most common type of PNET in patients with MEN-1 is non-functioning, gastrinoma, insulinoma, and VIPoma, which occur in 55%, 50-60%, 20%, and 3-5% respectively. These tumours occur at a younger age, usually 30-50 years. Up to 50% of these patients will develop metastases [42], and 30-50% of patients will already have liver metastases at the time of symptomatic presentation [43]. PNETs associated with MEN-1 have a higher rate of recurrence than sporadic PNETs and consequently are the most significant cause of death in patients with MEN-1. There remains no reliable clinical, histologic, or molecular marker to predict the aggressiveness of a MEN-1-associated PNET. Early and aggressive treatment is suggested to prevent metastases; however, most will develop recurrences [42]. PNETs are often multiple with tiny lesions that may only be detected with EUS/intraductal ultrasonography. Unresectable advanced PNET burden are controlled through hormone regulation, hepatic metastases management, and systemic chemotherapy. There remains no consensus on the best treatment guidelines for non-functional PNETs associated with MEN-1. If the lesion is >3cm in diameter it should be resected due to the increased risk of liver metastases; however, this has not improved survival. Additionally, no best-practice guidelines have been established for the management of smaller tumours. The timing and extent of surgical intervention for gastrinoma is also debated. Some authors argue aggressive interventions such as Whipple's procedure are not indicated due to high postoperative morbidity with unclear benefits; additionally, chemoembolization cannot be used to treat liver metastases after this procedure due to the risk of an ascending infection. This procedure therefore should be reserved for healthy patients with large tumours in the pancreatic head with positive nodes not amenable to simple resection [38]. These lesions are often multicentric, suggesting pharmacological interventions such as H2-blockers or protein pump inhibitors rather than surgical resection are indicated [18,31,42]. In contrast, insulinomas in patients with MEN-1 should undergo surgical resection including subtotal pancreatic resection with splenic preservation combined with enucleation providing there are no metastases, as cure rates of 83-100% can be achieved [42,44]. A distal pancreatectomy is often required to decrease recurrence risk. In these patients, enucleation alone is less effective as tumours are often small and multifocal. It is proposed laparoscopic surgery may be an option for insulinomas, with intraoperative laparoscopic ultrasound to identify pre-operatively unidentified tumours [44]. Metastases are less common in PNETs associated with MEN-1 than their sporadic counterparts. The risk of hepatic metastases is decreased by 62% for gatrinomas, 50% for VIPomas and glucagonomas, 30% for somatostatinomas, and 80% for non-functional PNETs. The only exception is insulinomas, in which hepatic metastases occur more frequently. Patients diagnosed with MEN-1 generally have a shortened lifespan, with a mean survival of 46-54 years. The 5- and 10-year survival in patients with MEN-1 with PNETs is 82% and 75% respectively. This can be further broken down based on hormonal activity, with 10-year survival in insulinomas/gastrinomas of 82-91%,

non-functional PNETs of 62% and gluaconomas, VIPomas, and somatostatinomas of 54% [38]. Tumor size in non-functional PNETs among MEN-1 positive patients is an important prognostic feature, with a diameter greater than 1.5-2cm associated with increased risk of malignancy. Positive outcomes in MEN-1 PNETs are likely attributable to early diagnosis. Tuberous Sclerosis is the result of a mutation of either TSC-1, which codes for hamartin, or TSC-2, which codes for tuberin, and is characterized by hamartoma development resulting in neurological and dermatologic disorders. Both functional and non-functioning PNETs have been reported with tuberous sclerosis, particularly in patients with TSC-2 mutations; however, it is not clear whether this relationship is a causal or a casual association. Neurofibromatosis type-1 (NF-1) is an autosomal dominant genetic disorder caused by alterations, including nonsense, frameshift, splice mutations, translocations, and partial or complete deletions, of the NF1 gene on chromosome 17q11.2 that encodes expression of neurofibromin. Neurofibromin regulates p21 activation to affect cell proliferation, growth and signalling. The most common PNET in NF-1 patients are somatostatinomas, but these tumours are usually functionally silent and present due to mass effect. PNETs in NF-1 are overall rare (0-10%).

Diagnosis

Serologic studies

Chromogranin-A, a glycoprotein in the secretory granules of neuroendocrine cells, is expressed in the majority of PNETs. The sensitivity depends on tumor burden, ranging from 50-100% and the majority of studies show a relationship between the level of chromogranin-A and patient prognosis. False positives may be due to Parkinson's disease, hypertension, glucocorticoids, chronic atrophic gastritis, renal/liver failure, or pregnancy. An exception is insulinomas, in which elevated chromogranin-A is rare. Other serologic markers include neuronal serum enolase, human chorionic gonadotropin, and pancreatic polypeptide, which are elevated in 20-40% of PNETs [45]. Specific elevated hormone levels (insulin, gastrin, glucagon, VIP) can be assessed in the serum of symptomatic patients with functional PNETs. Diagnostic criteria are explored in their respective sections under the heading "Functional PNETs".

Radiologic studies

Several radiological imaging techniques can be used for PNET detection, characterization, and staging. These radiological interventions can be divided by their use into the 'anatomic techniques' that determine the location and extent of the tumour, which include CT, MRI and EUS, and the 'functional techniques' that define metastatic spread and biological behaviour, which includes scintigraphy (Octreoscan) and PET [46]. Functional PNETs are more difficult to diagnose radiologically than non-functional, as these tumors are small and seldom alter the pancreatic contour [47]. The most common radiological tools used in the work-up of PNETs are Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), and all patients should have at least one of these to localize the tumour, determine its resectability and assess metastatic spread [48]. The sensitivity of these modalities has been reported to range from 14-77%. On such imaging, PNETs are solid, hypervascular lesions, differing from the hypovascular appearance of adenocarcinoma. Features suggestive of PNET include calcification, cystic degeneration and the absence of ductal obstruction, vascular encasement or desmoplastic reaction. Findings suggestive of malignancy in PNET include necrosis, calcification, and retroperitoneal invasion [48]. By contrast, pancreatic adenocarcinomas are hypervascular, only 2% are calcified, and often have ductal obstruction. CT scanning can be combined with Single-Photon Emission Computed Tomography (SPECT) to improve attenuation correction, increase specificity, improve tumour localization, and assess for and detect invasion. Identification of regions of uptake using both CT/SPECT aids in the differentiation between true- and false-negatives [49]. On Magnetic Resonance Imaging (MRI), PNETs exhibit low signal intensity on T1 weighted imaging (T1WI) with intermediate-to-high intensity on T2 weighted imaging (T2WI). Because of the rich vasculature, contrast-enhanced imaging shows enhancement on arterial phase, either homogenously for tumours <2cm or heterogeneously in a ring-like appearance for larger tumours. CT scans are optimized with angiography and images should be obtained 25-30s following contrast administration for the arterial phase, and 60 seconds post-administration for the portal venous phase. MRI sensitivity is reported between 74-100%. The sensitivity of CT and MRI for detecting metastases is up to 94%. These metastases often have low-density T1WI though patient-to-patient variability exists [49]. MRI imaging can be combined with Diffusion-Weighted Imaging (DWI) to improve visualization of small lesions. A recent study that investigated the fusion of DWI with T2 imaging found significant improvements in interpretation, strong inter-interpreter reliability, and an increased overall confidence [50]. Endoscopic Ultrasonography (EUS) is an investigational technique that can be used in the evaluation of small <1cm cystic pancreatic lesions. When combined with biphasic thin-section helical CT, diagnostic sensitivity approaches 100%. EUS allows for anatomic identification of the PNET in relation to the pancreatic duct for pre-operative planning. EUS is better for visualization of intra-pancreatic lesions compared with extra-pancreatic lesions. Unlike other imaging modalities, EUS identifies lesions as small as 2-3mm, and is the preferred diagnostic modality of choice for the detection of small insulinomas. EUS evaluation may be combined with Fine Needle Aspiration Biopsy (FNAB), allowing the retrieval of a specimen for pathological examination. It is a technique often used for screening patients with MEN-1 or VHL who are prone to pancreatic lesions. It has a reported sensitivity of 82% and specificity of 95%; however, it is unable to evaluate metastatic spread and its accuracy is highly operator-dependent. Differentiation between pancreatic nodules and peripancreatic lymph nodes is often difficult using this technique. Somatostatin receptors are expressed on 80-90% of PNETs; therefore, somatostatin receptor scintigraphy has become a standard technique for detection and staging [51,52]. As somatostatin has a short half-life, the analog octreotide labelled with indium-111 (111-DTPA octreotide) is the most common technique for detecting all gastropancreatic neuroendocrine tumours, with sensitivity of 67-100%. Though rare, octreotide has also been labelled with Gallium-67 citrate to improve detection of PNETs [53]. Insulinomas are an exception as they are poorly detected by this technique. Scintigraphy scans the entire body; therefore, identification of distant metastases can be identified with this one technique. Scintigraphy combined with CT imaging has a higher sensitivity than CT and MRI for detecting metastatic disease, with a sensitivity of 90%. OctreoScan can be also combined with Positron Emissions Tomography (PET) scans to visualize lesions not seen by CT or MRI and to differentiate malignant from benign based on uptake functional images. PET (FDG-PET) alone may play a role in assessing poorly differentiated neuroendocrine tumours, which are often negative on OctreoScan. Radiopharmaceuticals used with PET to detect PNETs include fluorodeoxyglucose, Gallium-68, fluorodehydroxyphenylalanine,

and 5-hydroxytryptophan. The Selective Arterial Secretagogue Injection (SASI) test has two parts: first, percutaneous transhepatic portal venous sampling followed by arterial calcium stimulation with hepatic venous sampling. Percutaneous transhepatic portal venous sampling involves the placement of a venous catheter through the liver to the portal vein to permit hormone sampling from the splenic vein, SMV, and portal vein. This technique has a sensitivity of 70-95%. Arterial calcium stimulation with hepatic venous sampling, also called an Imamura test, is conducted by serial injection of calcium into the splenic, gastroduodenal, and inferior pancreaticoduodenal arteries, with samples taken from the hepatic vein pre- and post- each injection. SASI with calcium is a preoperative tool to locate MEN-1 associated insulinomas.

Pathology

On gross examination, PNETs are most commonly tan to pink, well-demarcated soft tumour; however they have been reported to be hard and white/gray when associated with fibrosis or amyloid. Less common appearances include papillary, angiomatous, and cystic. Rarely, PNETs with attendant tubules or ductules are recognized [54]. Larger tumors may reveal areas of haemorrhage and/or necrosis. Insulinomas are generally <2cm in diameter, the smallest of all PNETs, and non-functional PNETS usually present as a larger tumour. Cytological features of PNETs include round-to-ovoid cells, an eosinophilic/granular cytoplasm, dispersed chromatin in the nucleus and nucleoli. On microscopic examination, well-differentiated tumours may demonstrate a number of architectural patterns including solid, nesting, trabecular, gyriform, glandular, tubular/acinar, pseudorosettes and mixed. Well-differentiated tumours exhibit tumour cell monomorphism with little to no cytologic atypia and a low mitotic and proliferative index. Occasionally clear cells, vacuolated cells, and oncocytes may be seen. The histological architecture is not indicative of the functional state except for the presence of amyloid, which is more typical in insulinomas, and psammoma bodies indicating somatostatinoma. Malignancy is evidenced by the presence of local spread, vascular invasion, nodal involvement and/or organ metastases rather than histopathological features.

Immunohistochemistry

As PNETs are epithelial in origin, they are often immunoreactive to keratin 8 and 18, and 50% are immunoreactive to vimentin. As with other neuroendocrine tumours, PNETs usually stain positive for neuroendocrine markers such as chromogranin A and synaptophysin, thus differentiating them from pancreatic adenocarcinomas. One of both of these markers is positive in approximately 90% of PNETs [55]. Well-differentiated PNETs are positive for both chromogranin and synaptophysisin; however, poorly differentiated PNETs may be only positive for synaptophysin [56]. As discussed previously, chromogranin A is the most frequently secreted and measured hormone in PNETs. Levels are correlated with the tumour burden, with 60-100% sensitivity in metastatic disease yet less than 50% in localized disease. Insulinomas and somatostatinomas may be negative for chromogranin A, though are often reactive to chromogranin B or C; however, antibodies to B and C are usually commercially unavailable [55]. False positives can result from renal insufficiency, Parkinson's disease, untreated hypertension, pregnancy, steroid use, and achlorhydria. Other markers that have been described to define neuroendocrine differentiation include protein gene product 9.5, CD57 and neuron specific enolase [55]. PNETs have been shown to stain strongly to PDGFRA (33%), CK19 (26%), CD56 (25%), CD20 (5%), S100 (6%), and CK7 (2%). Pancreatic polypeptide has a sensitivity of 63% and specificity of 81%. A recent PNET study investigated the prognostic role of geminin, a negative regulator of DNA proliferation that has been reported to confer a negative prognosis in a variety of malignancies including breast cancer, renal cell carcinoma, prostatic adenocarcinoma, salivary gland carcinoma, and lung cancer. The study suggested geminin is a greater predictor of disease-free survival than Ki67 or ENETS staging.

Management

The management of PNETs depends on the type of tumour present, and best-practice management is difficult to determine as the rarity of these lesions inhibits prospective randomized controlled studies [57]. Conservative management is a reasonable option for many patients, particularly for small incidental asymptomatic non-functioning PNETs and older patients with significant comorbidities who are not good surgical candidates [58]. The European Neuroendocrine Tumor Society suggests conservative "wait-and-see" management for non-functional PNETs that measure less than two centimeters. No strong data supports a survival advantage for surgery in patients with small, likely benign non-functioning PNETs therefore a careful risk vs. benefit analysis must precede surgical interventions. When treatment is sought, goals may include surgical excision, tumour growth inhibition, symptomatic relief, and an improved quality of life. Treatment options can be divided into two categories based on their desired outcome: a) to reduce tumour mass, using strategies including surgery, chemotherapy, and arterial embolization, and b) to reduce symptoms, using somatostatin analogues and interferon therapy [59].

Tumour Mass Reduction

Surgical resection remains the only curative treatment for PNETs and alleviates symptoms associated with hormone secretion and mass effect. Surgical options include radical excision with a curative intent, palliative excision aimed at symptomatic relief, and surgical treatment of complications. The 5-year overall survival rate of resected PNETs is significantly greater than unresected ones, from 77% to 46%. Complete excision with a curative intent plays a central role for patients with localized tumours at presentation. Major aggressive resection, including either pancreaticoduodenectomy or distal pancreatectomy, may effectively treat tumour-related endocrinopathies and local symptoms due to mass effect. These surgical procedures, however, are associated with a high incidence of exocrine or endocrine pancreatic insufficiency. Some authors suggest that sporadic malignant tumours, or tumors over 3cm, are best managed with Whipple's resection or distal pancreatectomy, with resection of adjacent organs and vasculature as indicated in relation to tumor size and its localization. One notable exception is patients with MEN-1 with non-functional PNETs, in whom multiple microadenomas are often found throughout the pancreas; thus restricting the effectiveness of limited tumour resection. Among these patients, subtotal (80%) distal pancreatectomy with enucleation of any pancreatic head tumor is often recommended.

Minimally-Invasive Techniques for Resection PNET

Laparoscopic surgery of the pancreas was first introduced in 1994, since which sufficient evidence in the international literature has proven its suitability in the management of low-risk PNETs. The feasibility of a complete resection with optimal oncologic

outcome using laparoscopic techniques remains debateable. Laparoscopic surgery, without proper pre-operative imaging, has a localization failure rate of 19%. Laparoscopic distal pancreatectomy is recommended for tumors of the pancreatic body or tail, with five surgical variations: i) spleen and splenic vessel preserving distal pancreatectomy, ii) spleen-preserving distal pancreatectomy, iii) distal pancreatectomy with splenectomy, iv) central pancreatectomy, and v) laparoscopic pancreaticoduodenectomy. With proper preparation, laparoscopic resection success rates reach 60-100%. The morbidity rate of laparoscopic surgery is between 8-50% and improves with technology and surgical skill. No significant difference in mortality, morbidity, reoperation, or readmission has been found when a laparoscopic vs. an open resection was used. A study by Fernandez-Cruz et al examined laparoscopic vs. open surgery, and found advantages in pain management, cosmetics, reduced hospital admission times, and faster recovery. A specific laparoscopic technique for PNET management is enucleation, a technique that is reported to decrease the risk of postoperative complications such as diabetes, as a great amount of pancreatic parenchyma is spared. This technique, however, increases the risk of causing a pancreatic fistula, most commonly when the tumour is in the pancreatic duct. The decision to choose enucleation vs. resection additionally depends on tumour location, focality, and intraoperative ultrasound findings. Large or fast-growing tumours are not suitable for enucleation and require open excision. Ideal tumors for laparoscopic enucleation are well-circumscribed lesions <3cm with noninvasive features located along the pancreatic periphery [60]. Prediction of which tumors will have a benign natural history is challenging. Enucleation can be an open or laparoscopic procedure. It is suggested subtotal (80%) distal pancreatectomy should be performed in conjunction with enucleation for syndromic non-functional PNETS >2cm or for functional PNETs of any size. The postoperative morbidity rate of laparoscopic enucleation is 20-30%. A second minimally invasive technique, central pancreatectomy, has also been reported that, with enucleation, has a lower morbidity and shorter hospital stay than a standard pancreatectomy.

Robotic-assisted surgery has been used to perform pancreaticoduodenectomy, central pancreatectomy, and distal pancreatectomies. This technique offers several advantages, most notably a three-dimensional and significantly magnified view of the surgical field and a 540 degree range of motion. Aside from the expense and technical expertise required, other limitations of robotic surgery include technical issues such as collisions between the robotic arms and the inability of changing table position after robot docking.

Ablative techniques

Unresectable primary tumors may be treated with radiofrequency ablation performed percutaneously with ultrasonographic guidance, or intraoperatively. Solitary small tumors (<3cm), ideally located distal from peripancreatic structures are the best candidates for this technique. Thermal-induced pancreatitis and injury to peri-tumoral structures (duodenum, pancreatic duct, and blood vessels) are potential adverse effects. Another technique, ethanol ablation**,** causes dehydration, protein denaturation and vascular occlusion of the tumor resulting in coagulation necrosis; however, the technique poses the risk of late recurrence, incomplete ablation, and progression.

Treatment of lymph node metastases

Rates of metastases among small tumors <1.5cm and <3cm are 8% and 31% respectively. The significance of lymph node metastases on patient outcomes remains uncertain; therefore, guidelines for the management of lymph nodes in PNETs remain controversial. A small (n=136) retrospective study showed higher rates of lymph node metastases among large tumors (>1.5cm), tumors involving the pancreatic head, tumors with a high (>20%) Ki67 index, and tumors with vascular invasion; lymph node metastases was associated with a shorter disease free survival (4.5 years vs. 14.6 years without nodal involvement). These authors concluded that lymph node metastases are predictive of poor outcome. While some authors have also reported a relationship between tumor size and lymphadenopathy, others have failed to show this correlation. Recommendations from the National Comprehensive Cancer Network suggest lymph node resection is indicated for tumors between 1-2cm in size. The exact extent of lymph node resection, whether regional, radical, extended or lymph node 'picking' is still unclear.

Treatment of Liver Metastases

The presence of metastases is the most definitive indicator of a malignant PNET. The risk of metastatic spread depends on the functional status of the tumour and the hormone being expressed. Complete resection and/or hepatic debulking for metastases are associated with improved quality of life and survival [61]. Among all PNETs, 60-80% will present with metastatic spread [62]. The most common site of metastases is the liver; however, hepatic dysfunction is rare despite the large tumour mass [63]. Optimal treatment of liver metastases remains controversial, with options including cytoreduction, debulking surgeries, transplantation, or observation with or without pharmaceutical interventions. Cytoreductive surgery is indicated if metastases are localized or if >90% of the tumor burden is resectable. This number is recently contested, with Maxwell et al suggesting that a target threshold of 70% may increase patient eligibility for cytoreduction and increase patient survival [64]. If left untreated, the median survival of a patient with hepatic metastases from a PNET is 2-4 years; this number is improved when the patient is aggressively treated, whether through resection or debulking. Resection of a metastasis should be considered if less than 50% of the liver is involved and a minimum of 90% of the tumour burden can be safely resected. Such conditions account for approximately 10% of cases. The rate of hepatic recurrence is up to 76% within 2 years. The risk/benefit ratio for aggressive resection must be evaluated in relation to its morbidity and mortality, versus pharmacotherapy or locoregional techniques. Hepatectomy with transplantation may be considered for patients younger than 55-60 years of age. This option should be reserved for patients with no extrahepatic disease, who are unresponsive to other therapies, and the tumour should be well-differentiated with a low Ki67 index. Few orthotopic liver transplantations have been attempted which have incurred high rates of mortality and recurrence. The perioperative mortality rate, which ranges from 11-28%, may be reduced by choosing a staged procedure. Post-transplant, the rate of recurrence is up to 63% within months. If the hepatic metastasis is unresectable, patients may benefit from surgical excision of the primary lesion to decrease the risk of biliary obstruction, gastric outlet obstruction, or haemorrhage. This may, however, depend on the extent of metastases, as one study found no significant difference in the survival of patients with more than 50% liver involvement treated surgically or nonsurgically [65]. Data from the Surveillance, Epidemiology, and End Results from 882 patients with non-functional PNETs indicates that resection of the primary tumor improves patient survival from 0.83 years to 5.42 years [66]. These results, however, may be confounded given

its retrospective study design, as patients selected for resection may have been healthier with less tumor burden. Ablation techniques to the liver include radiofrequency ablation, cryoablation, microwave ablation, and alcohol ablation. Radiofrequency ablation can be used as a monotherapy or in combination with other therapies including surgery. This technique is indicated when less than 10 lesions are present, with none over 4cm. These techniques are used to treat metastases less than 5cm. Hepatic arterial embolization is based on the observation 75-80% of blood supporting PNETs is derived from the hepatic artery. This staged procedure involves sequential catheterization of hepatic arterial branches to one liver lobe then 6-8 weeks later, cannulation and embolization of the branches to the other lobe. This procedure is contraindicated in patients with portal vein thrombosis, cirrhosis, or a history of biliary reconstruction. Side effects secondary to ischemic hepatitis include nausea, abdominal pain, fever, and fatigue. Symptomatic response rates in non-functional PNETs with liver metastases are 50-100%, with tumour volume response rates from 25-86%. This response may last from 6-42 months. A longer response is associated with isolated hepatic metastatic disease, prior resection of the primary tumour, involvement of less than 75% of the liver, and a tumour size <5cm. Hepatic artery embolization can be combined with intra-arterial chemotherapeutics like doxorubicin or cisplatin. Radioembolization using yttrium-90 radiolabeled microspheres may be distributed by arterial injection, delivering direct intratumoral radiation. This technique has a response rate of 12-18% with a median survival of 22-36 months [67].

Treatment of Advanced PNET

Aggressive surgical management with improved survival of patients with advanced PNETs includes pancreatectomy, splenectomy and SMV reconstruction. In some patients with symptomatic, low-volume advanced disease, careful observation without treatment may be sufficient until symptoms of progression present. In patients with symptomatic disease, a number of palliative measures may be used to improve the patient's quality of life. The 5-year survival for patients presenting with advanced PNETs ranges from 25-75%. Surgical debulking may help to relieve symptoms of mass effect or hormone excess and is an appropriate choice if a minimum of 90% of the tumour is resectable. For patients who do not fit this criterion, or who are not good surgical candidates, a number of non-operative techniques exist including radiofrequency ablation, cryotherapy, hepatic artery embolization, and/or chemoembolization. Chemoembolization involves direct injection of chemotherapeutics including doxorubicin or cisplatin directly into the liver. This technique has the best results when combined with systemic chemotherapy, with a mean survival of 3.5 years. Whereas systemic cytotoxic agents remain the primary treatment for poorly-differentiated and/or rapidly progressing PNETs, for most patients with advanced unresectable well or moderately-well differentiated PNET treatment options include observation, nonsurgical liver-directed therapy, and systemic therapy to control tumor growth and symptoms related to the disease. The systemic options include somatostatin analogs, peptide receptor radionuclide therapy, interferon-alpha and systemic chemotherapy and targeted therapy. These pharmacological interventions may be used for non-resectable PNETs, in patients unsuitable for surgery, or for patient's symptomatic post-surgical resection.

Somatostatin analogs

Octreotide and lanreotide are somatostatin analogs that bind to somatostatin receptors that are expressed in most neuroendocrine tumors and inhibit the secretion of multiple hormones. Somatostatin analogs have not only shown efficacy in the management of symptoms associated with hormone hypersecretion but are also effective in controlling the tumor growth. Recent reports suggest that somatostatin analogs help to stabilize the disease and prolong the progression free interval [68,69]. For example, the PROMID study group conducted a randomized placebo-controlled, double-blind study to assess the ability of octreotide Long-Acting Repeatable (LAR), to control the growth of well-differentiated metastatic neuroendocrine tumors [68]. The results showed that median time to tumor progression was significantly longer in the group treated with octreotide LAR compared with the placebo group (14.3 versus 6 months with HR of 0.34; 95% CI, 0.20 to 0.59). After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group compared with 37.2% in the placebo group. The findings of the PROMID study was subsequently confirmed by the CLARINET investigators in a placebo-controlled randomized phase involving patients with grade 1 or 2 nonfunctioning, somatostatin receptor-positive neuroendocrine tumors of pancreas and gastrointestinal tract [69]. This study randomly assigned 204 patients to receive either 120 mg lanreotide or placebo. The estimated rates of progression-free survival at 2 years were 65.1% in the lanreotide group compared with 3.0% in the placebo group (HR for progression or death, 0.47; 95% CI: 0.30 to 0.73). Side effects include mild nausea, abdominal discomfort, bloating, loose stools, and fat malabsorption.

Peptide receptor radioligand therapy

A variant of somatostatin treatment is peptide receptor radioligand therapy or targeted radiotherapy using radiolabeled somatostatin analogs. Yttrium and lutetium are the most commonly used radionuclides for targeted radiotherapy [70,71]. These therapies are most useful in patients with somatostatin-receptor positive tumors. In a large observational study 1,109 patients were treated with median two cycles of ^{90}Y-DOTA-TOC [71]. The objective radiographic response rate was 34.1%, biochemical response rate was 15.5%, and clinical response rate was 29.7%. The median survival was 94.6 months and survival was correlated with any type of response. Transient bone marrow suppression and renal dysfunction were major toxicities. Tumoral uptake in the initial imaging study was predictive for overall survival (HR, 0.45; 95% CI, 0.29 to 0.69). Another study evaluated the efficacy and toxicity of ^{177}Lu-DOTATATE in over 500 patients. Complete and partial tumor remissions occurred in 2% and 28% of 310 patients with gastroenteropancreatic NET, respectively. Minor tumor response noted in 16% patients. Median time to progression was 40 months. Median overall survival from start of treatment was 46 months, and from diagnosis was 128 months. In addition to radiolabeled somatostatin analogs, 131I-metaiodobenzylguanidine (^{131}I-MIBG) therapy in MIBG positive metastatic neuroendocrine tumors has demonstrated activity [72].

Chemotherapy

Streptozocin with either 5-fluorouracil or doxorubicin is one of the standard chemotherapy regimens in the management of advanced low-grade PNET [25]. In a randomized trial that compared two streptozocin-based regimen, combination of streptozocin and doxorubicin was associated with a significantly better combined biochemical and radiographic response rate (69% vs. 45%) and median overall survival (2.2 vs.1.4 years) compared with streptozocin and 5-FU [61,73]. Nevertheless, due to major toxicities such as

severe myelosuppresion and renal dysfunction, currently the use of streptozocin-based regimens has declined. Similar to streptozocine, decarbazine (DTIC) and its orally active analog Temozolomide are alkylating agents that have shown activity in PNET. For example, a phase II trial assessed decarbazine (DTIC) in 50 patients with advanced symptomatic or progressive PNET and showed a response rate of 33% in 42 patients with measurable disease and median overall survival of 19.3 months [74]. However, due to better side effect profile and dosing convenience, temozolomide-based regimens have replaced the use of DTIC in PNET. The optimal temozolomide-based regimen and dosing schedule is not known. It has been used as a monotherapy or in combination with: a) capecitabine, with an overall response rate of 70% and median progression-free survival of 18 months, and b) thalidomide with an overall response rate of 45%. Temozolomide has also been evaluated in combination with everolimus and bevacizumab in advanced PNET with response rate of 40% and 33% and median progression free survival of 15.4 months and 14.3 months, respectively [75,76]. Long-term use of temozolomide has been associated with lymphopenia and pneumocystis pneumonia, therefore prophylaxis is recommended in these patients. Oxaliplatin is a third generation platinum compound that in combination with fluoropyrimidine and bevacizumab has shown efficacy in selected patients with well differentiated and poorly differentiated PNET [77]. Oxaliplatin has also been combined with gemcitabine, with a response rate of 27%. Other chemotherapeutics that have been failed to affect the course of PNETs include endostatin, irinotecan & cisplatin and capecitabine & rofecoxib.

Targeted therapy

Sunitinib and everolimus are approved for the treatment of unresectable PNETS. Sunitinib is a potent inhibitor of VEGFR-1, VEGFR-2, FL26, KIT, PDGFRα, and PDGFRβ [36,67,78]. Of note, the mechanism of angiogenesis in neuroendocrine tumours is not well understood as these malignancies do not have the same dense vascularization as other solid organ cancers [79]. A phase II trial that evaluated activity of sunitinib in patients with advanced neuroendocrine tumors found an overall response rate of 16.7%, with 62.1% demonstrating some response and the time to progression while was 7.7 months. Subsequently, a randomized, double-blind, placebo-controlled phase 3 trial involving 171 patients with advanced, well-differentiated pancreatic neuroendocrine tumors demonstrated superiority of sunitinib over placebo [80]. The response rate was 9.3% in the sunitinib group compared with no response in the placebo group. The median progression-free survival of the group treated with sunitinib was 11.4 months compared with 5.5 months in the placebo group (HR, 0.42; 95% CI, 0.26 to 0.66; P<0.001). Although follow-up period was short, mortality rate was also lower in the group treated with sunitinib compared with the placebo group (10% versus 25%) [HR, 0.41; 95% CI, 0.19 to 0.89; P=0.02]. The most frequent adverse events in the sunitinib group were diarrhea, nausea, vomiting, asthenia, and fatigue. Nevertheless, there were no differences in the quality-of-life index between the two groups. Two other oral multi-targeted tyrosine kinase inhibitors, sorafenib and pazopanib, have also demonstrated efficacy in well-differentiated PNET [81]. In addition, the VEGF inhibitor bevacizumab has been used to treat advanced PNETs, with 18% response rate. When combined with oxaliplatin and fluorouracil, the response rate increases to 19% in one study, and 50% in another.

The mTOR pathway is involved in a number of the genetic syndromes associated with PNETs including von Hippel Lindau, tuberous sclerosis, neurofibromatosis-1 and MEN-1; sporadic PNETs express IGF-1, which stimulates mTOR pathway and thereby tumor growth and proliferation [82]. Everolimus is an oral inhibitor of mTOR. A phase II trial found a 22% response rate, with 70% stable disease when combined with octreotide. Later a phase 3 trial showed that everolimus in patients with PNET was associated with 65% reduction in the estimated risk of progression or death [83]. In RADIANT-3 trial 410 patients who had advanced, low-grade or intermediate-grade pancreatic neuroendocrine tumors with radiologic progression within the previous 12 months were randomized to everolimus, or placebo. The median progression-free survival was 11.0 months with everolimus compared with 4.6 months with placebo (HR, 0.35; 95% CI, 0.27 to 0.45; P<0.001). Most drug-related adverse events were mostly mild to moderate and included stomatitis, rash, diarrhea, fatigue, and hyperglycemia. Everolimus has been combined with bevacizumab for low- to intermediate-grade PNETs, octreotide, temozolamide, and pasireotide [61,84]. Given the fact that both VEGF pathway and mTOR inhibitors are active in pancreatic NET, a phase 2 trials evaluated the benefit of adding bevacizumab to everolimus in 150 patients with advanced PNET [85]. Although combination therapy was associated with higher response rate of 31% compared with 12% and superior progression free survival of 16.7 compared with 14 months, it was associated with higher rates of severe adverse effects. Contrary to everolimus, temsirolimus appears to have little activity as single agent treatment in PNET [86].

Interferon-alpha-2b

Interferon-alpha-2b is used in the treatment of PNETs because of its role in anti-proliferation, anti-angiogenesis, apoptosis and differentiation in both functional and non-functional tumours. Interferon can stabilize tumour growth in 10-15% of patients. Interferon therapy can be used as a monotherapy or, for better effects, in combination with octreotide. Adverse effects may include fatigue, myelosuppression, or depression and currently its use has declined.

Symptomatic reduction

Somatostatin analogs including octreotide (Sandostatin), lanreotide, and pasireotide are useful treatments of the symptoms of PNETs, particularly VIPomas and glucagonomas. Somatostatin itself cannot be used due to its short half-life. In addition to blocking the release of hormones thereby decreasing symptoms such as diarrhea, flushing, or acromegaly, octreotide and somatostatin analogs also stabilize the disease and lengthen the time to progression [61,87,88]. It has been suggested that in asymptomatic patients these drugs should be started after a 12-month observation period in which growth pattern can be established; however, clinical trials are needed to support or refute this hypothesis. Adverse effects include biliary disorders (62%), gastrointestinal disorders (14-38%), injection site pain (20-50%), hypoglycaemia (4%), hyperglycemia (27%), and bradycardia (19%) [87]. In patients with insulinomas, somatostatin analogs may cause a transient worsening of hypoglycaemia as half of these tumours don't express somatostatin receptor II and the octreotide blunts the glucagon response. The other systemic treatments including peptide receptor radioligand therapy, cytotoxic agents, and targeted therapy that as discussed above are also effective in symptomatic management of PNET.

Functional PNETS

Functional PNETs are those that secrete hormones at clinically-detectable levels. The clinical probability of malignancy increase with

tumour size, with up to 90% of non-functioning tumours being malignant at presentation. The hormone expressed depends on the type of neuroendocrine cell within the PNET: alpha cells with glucagon, beta cells with insulin, delta cells with somatostatin, and PP with pancreatic polypeptide and VIP. Well-described clinical syndromes exist for hypersecretion of glucagon, insulin, somatostatin, and VIP; however, due to the rarity of these lesions, it may take years for an accurate diagnosis to be made. Uncommon hormones that have been reported include calcitonin, neurotensin, growth hormone-releasing factor, adrenocorticotropic hormone, and serotonin. On rare occasions, PNETs may present with overexpression of two or more hormones. Reported combinations include insulin & gastrin, VIP & calcitonin, and parathyroid releasing hormone & calcitonin [89]. The most common PNET, comprising 20-30%, secreting insulin is the insulinoma. These are single lesions, measuring less than two cm in 90% of cases. Insulinomas are benign in 90% of cases. The 8-10% of lesions over 2cm are at a higher risk of malignancy. Ten percent of patients with insulinomas have multiple lesions, and 5% are associated with MEN-1. Insulinomas present with hypoglycaemia and atypical seizures. Additional symptoms that may suggest an insulinoma include hunger, sweating and systemic involvement of the neurological (incoherence, confusion, blurred vision, headache, seizure, tremor, peripheral neuropathy), psychological (irritability, anxiety, psychosis, amnesia, personality changes), and cardiac (palpitations, diaphoresis) systems. Diagnosis is usually over 4 years after the onset of symptoms. Diagnosis is based on the presence of the Whipple's triad, which includes a) signs and symptoms of hypoglycaemia while fasting, b) serum glucose <45 mg/dL while symptomatic, and c) symptomatic relief with glucose administration. The biochemical diagnostic criteria include: a) glucose ≤45mg/dL with a 72h fasting plastma glucose, b) serum insulin ≥36mcU/L, C-peptide of ≥200pmol/L, serum proinsulin of ≥5pmol/L, B-hypoxybutyrate ≤2.7mmol/L, and the absence of sulfonylurea in the plasma or urine. These laboratory findings diagnose up to 99% of insulinomas and are considered the gold standard for diagnosis. Elevated C-reactive protein (CRP) or proinsulin rule out factitous causes of hypoglycaemia. These investigations should be followed-up for localization with imaging including CT, MRI, endoscopic ultrasound octreotide scintigraphy and hepatic venous sampling. However, up to 30% of insulinomas are not radiographically detectable. Treatment depends on the size of the tumour and may include enucleation for smaller lesions or complete resection. Intraoperative exploration of the entire pancreas with palpation and intraoperative ultrasonography is recommended. Some authors suggest subtotal distal pancreatectomy should always be performed with enucleation to reduce the risk of recurrence. Others propose that if there is no risk to the pancreatic duct, and the tumor measures <2cm, enucleation alone is acceptable whereas more aggressive resection is indicated if the tumor is close to the duct. Among patients with MEN-1, accurate preoperative diagnosis of the insulin-secreting tumors is essential, as they will often have non-functional PNETs. For patients who are poor surgical candidates, palliative treatments for symptom control include radiotherapy ablation, cryotherapy, hepatic artery embolization, and chemoembolization. Given the rarity of lymphadenopathy with insulinomas, lymph node dissection is usually not recommended. Predictors of poor outcome include tumor size >2cm, Ki67 less than 2%, and specific molecular features. PNETs that oversecrete gastrin are called gastrinomas and are more common in men, average age 45-50 years. They comprise 20% of PNETs. These lesions may be solitary though 20-40% has multiple lesions, each with a mean diameter of 4cm. Up to 60% of gastrinomas are malignant. The majority (90%) of gastrinomas are found in the gastrinoma triangle, which is bordered by the bile duct/cystic duct junction superiorly, pancreatic body medially, and duodenum inferiorly, with 20-60% confined to the pancreatic head 20% are associated with MEN-1. Secretion of gastrin causes the clinical syndrome Zollinger-Ellison syndrome, characterized by parietal hyperplasia, peptic ulcerations, and hypergastrinemia, and presents clinically with abdominal pain and diarrhoea. Patients may additionally present with esophagitis. Diagnostic biochemistry involves a fasting serum gastrin level >1000 pg/mL and a pH<2; however, two-thirds of patients won't have a gastrin level this high in which diagnostic criteria includes a) fasting gastrin >200 pg/mL, b) basal acid output >15mEq/h, and c) positive secretin stimulation test. While secretin does not stimulate gastric G-cells to produce gastrin, it does result in release of gastrin from a gastrinoma. Approximately 30% of gastrinomas that require exploration cannot be localized preoperatively. While some authors suggest surgical resection should be offered to all candidates, others suggest that as patients can obtain symptomatic relief with medical therapy (histamine-2 receptor block, protein pump inhibitor) and given the high risk of recurrence following surgery with the long life-expectancy without surgery, the need for mandatory surgical management remains controversial. Resection of these tumors is a long-term cure for one-third of patients; however, gastrinoma associated with MEN-1 are often multifocal and have a very high recurrence rate and nonoperative management is suggested for tumors less than 2cm in size. Enucleation combined with partial pancreatectomy and lymphadenectomy is indicated if there is no evidence of invasion or metastases; if either of these is present, a pancreatectomy with lymphadenectomy is recommended. The role of laparoscopy similarly remains debated; it is argued that these lesions are often poorly localised pre-operatively, though found more commonly in the pancreatic head, and often have lymph node metastases, which may limit the usefulness of this technique. Patients with ZES and MEN-1 are an exception, as any surgical procedures either than a pancreaticoduodenectomy have a 90% recurrence rate. Lymph node dissection is indicated for gastrinomas. Gastrinomas confer a 10-year survival of 90% post-resection. PNETs that secrete glucagon are termed 'glucagonoma' and represent only 1% of all PNETs. These alpha cell tumours have a slight female predominance (55%) and present in those over 45 years of age. These tumours are large, 2-6cm in diameter, and present as solitary neoplasms of the pancreatic tail or body. 70% of glucagonomas are malignant, with metastases present in up to 60%. The classic symptom of glucagonomas is necrolytic migratory erythema. Additional symptoms that may be observed are associated with the intrinsic activity of glucagon to enhance blood glucose levels and increase lipolysis; mainly diabetes, weight loss and diarrhoea. Biochemically, glucagonomas are diagnosed by serum glucagon concentration levels of >1000 pg/mL. These are slow-growing tumours and should be resected in suitable patients for best outcomes. Somatostatinoma is a tumour of the delta cells that accounts for less than 1% of all PNETs. These tumours are large, often over 5cm, with a tendency to develop in the pancreatic head. The majority (95%) of somatostatinomas are malignant, with metastases present in up to half at presentation. These tumours have been reported to present with abdominal pain/distension, weight loss, gastrointestinal bleeding, splenic vein compression, cholelithiasis, steatorrhea, indigestion, hypochlorhydria, anemia, and relapsing cholangitis [14,90]. The existence of a true 'somatostatin syndrome' has been questioned, as it is challenged that these symptoms may be

due to mass effect rather than somatostatin release. Due to the rarity of these tumours, best-practice management guidelines have not been determined [90]. A prophylactic cholecystectomy may be indicated for advanced disease, as up to 50% of cases may have gallstone disease related to the usage of somatostatin analogues. Resection confers a 5-year survival over 95% (60% in patient with metastases). Treatment with streptozocin, 5-fluorouracil, and doxorubicin has shown partial responses. Vasoactive Intestinal Peptide (VIP) secretion by PNET, a VIPoma, makes up <10% of PNETs with up to 90% arising in the pancreas, followed by the retroperitoneal sympathetic chain and adrenal gland. They are more common in women in the 4th decade of life. VIPomas typically occur in the pancreatic tail as large lesions, (mean 5cm) with 75% being malignant and metastases in 70%. Clinically VIPomas present with Verner Morrison Syndrome, a constellation of watery diarrhea (up to 20L/day), hypokalemia, achlorhydria, flushing (30%), and hypercalcemia (50%) [7,91]. Demonstration of an elevated VIP level is diagnostic; however, the fluctuations in VIP levels may cause a false negative, necessitating repeated fasting VIP levels. 44% of VIPomas are resectable, of which only 28% are aimed at cure. A localized tumour may be amenable to laparoscopic resection. When a complete resection is possible, 5-year survival approaches 95%. Somatostatin analogs stimulate SSTR2 to inhibit the secretion of neoplastic endocrine cells. Five-year survival for metastatic disease is 60%. Aside from these 'common' PNETs, a variety of lesions producing ectopic hormones have been described including a) ACTH, b) GHRH, c) PTH-like peptide, d) calcitonin and e) serotonin [27,91]. Overproduction of ACTH by a PNET has been reported in several case studies [92-94]. An ACTH-secreting PNET is an aggressive lesion with early metastatic spread to the nodes and liver and a 5-year survival of 16%. Early correction of hypercortisolemia is necessary to reduce the cushingoid symptoms and to prevent complications including diabetes, hypertension, psychiatric disorders and gastric ulcers [93]. Ectopic ACTH from a PNET is responsible for up to 16% of Cushing's syndromes [94]. Parathyroid hormone related peptide (PTHrP) has been reported to be expressed by well-differentiated PNETs, often that have already metastasized. PNETs secreting PTHrP confer a better survival than other PTHrP-secreting malignancies. Several cases of a calcitonin-releasing PNET have been reported [91,95]. Many of these report calcitonin co-secretion with insulin, somatostatin, VIP and PP. In a study by Schneider et al. [95] 37 calcitonin-secreting PNETs were identified, of which 60% presented with metastatic spread. Clinical symptoms include watery diarrhea and abdominal pain, and aggressive surgical resection is associated with a higher survival. PNETs secreting serotonin are rare and present with carcinoid syndrome, characterized by episodic flushing, diarrhea, and right-sided valvular heart disease. These lesions are responsive to somatostatin analogs for symptomatic improvement; however, tumour regression rarely occurs.

Non-functional PNETs

As the name would suggest, non-functional PNETs are functionally inactive pancreatic tumours. They often secrete peptides such as chromogranin, neuron-specific enolase, pancreatic polypeptide, ghrelin, and subunits of hCG which can be detected in the serum; however, unlike functional PNETs, cause no hormonal syndrome. These tumours are more common than functional PNETs, comprising 68-85% of all PNETs. While the reported yearly incidence of non-functioning PNETs is 1-5 cases/million, autopsy evidence reports an incidence of 1.5%. The incidence in males is equal to females, and they are most commonly discovered in the 5th decade of life [8,96]. These may be diagnosed in several ways, including a) as an 'incidentaloma' in which it is incidentally detected during investigations for nonspecific/unrelated symptoms, b) because of symptoms of 'mass effect' due to compression/obstruction such as jaundice, abdominal pain, nausea, steatorrhea, anorexia, or weight loss or, c) due to tumour-related complications such as bleeding. The indolent presentation of these lesions poses difficulties in diagnosis, localization, and subsequent treatment [97]. Distinguishing benign from malignant lesions can only be done with certainty in the presence of metastases. While 59-80% have liver metastases at diagnosis, no metastases have been reported in non-functional PNETs <10 mm. As such, the tumour dimension should guide treatment, as tumours <2cm are more likely to be benign, 2-4 cm are of uncertain behaviour, and >4cm more likely to be malignant. Larger tumours impart a greater risk of angioinvasion, perineural infiltration, and nodal metastases [98]. It is therefore proposed that tumours <2cm should be treated non-operatively due to the morbidity (2%) and mortality (5%) rates of pancreatic surgery [98]. These patients require a confirmed diagnosis with FNA sampling and/or a positive somatostatin receptor imaging study. Surveillance includes serial measurements on MR imaging every six months for two years then yearly thereafter [99]. The natural history of these small tumors is difficult to predict, with neither patient nor tumor characteristics indicative of tumor growth. For larger tumours, surgical treatment involves a spleen-preserving distal pancreatic resection to the portal vein level and/or enucleation. Multivariate Cox proportional hazard and ratios analysis of 128 nonfunctional PNETs identified patient age >55 years, grade 3 histology, and distant metastases as prognostic features; gender, race, BMI, symptoms, lymphovascular and perineural invasion, and size were not related to metastases or survival [100]. The 5-year survival rate is reported at 65%, with 45% surviving at 10 years. One study reported a 63% recurrence rate, with a median time-to-recurrence of 84 months; therefore, a strict follow-up regimen is mandatory.

Prognosis and Prognostic Factors

Identification of predictive and prognostic factors for the progression of PNETs is difficult to ascertain. Due to the rarity of these tumours, evidence is based primarily on small series. Metastatic spread, large tumour size, and hormonal hypersecretion are prognostic features, as are gender, age, and histopathological high-grade, Ki67. Histopathological examination provides relevant postoperative prognostic information, including tumour size, local invasion, pancreatic capsular penetration and the mitotic rate. Ki67 is a well-recognized prognostic factor, and is used in the WHO grading of these tumours. One study found the risk of progression increases 2% for every Ki67 unit increase. While calcification detected on imaging has traditionally been proposed to be associated with more aggressive PNETs, its true significance remains uncertain. Lymphadenopathy has shown prognostic significance on univariate analysis, but independently it may not correlate with prognosis. In this context, the role of lymphadenectomy remains unclear. Investigations to further elucidate these factors are required to guide individual patient management strategies [101]. Survivin, an inhibitor of apoptosis is abundant in the fetus and not normally expressed into adulthood except as an antigen in cancer, making it a promising drug target [101]. A higher level of nuclear survivin is correlated with a poorer outcome, and has been found to be an independent marker for poor survival [101]. Cytokeratin 19 (CK19) is an additional prognostic marker for PNETs; its expression can be used to classify patients into low risk (KIT neg/CK19 neg), intermediate risk (KIT neg/CK19 pos)

and high risk (KIT pos/CK19 pos) with 5-year disease-free survival of 100%, 80.6% and 47.6% respectively [102]. Alterations in microRNA, small noncoding RNA sequences that regulate post-transcription gene expression, are reported in association with PNETs. Serum microRNA-193b is upregulated in PNET tissues compared to pancreatic islets and may serve as a biomarker for disease detection. Specific microRNA is correlated with disease characteristics, with miR-642 associated with Ki67 score, and miR-210 with metastatic disease [103]. The reported median survival for patients diagnosed with PNETs was believed to be variable depending on the malignant potential of the tumour-type, with the early diagnosis of functional tumours lending to a better prognosis. It has, however, been found by one study that functional tumours are as likely to present with metastases as non-functional tumours, so the independent prognosis of functional vs. non-functional tumours remains controversial [104]. Among all PNETs, the median survival ranges between 38-104 months. Reported 5-year survival rates range 40-60%. The recurrence rate after resection is approximately 25%. Risk factors for the development of recurrence include MEN-1, tumour size over 4cm, the presence of hepatic metastases at presentation, and TNM stage III/IV. Patients with metastatic disease have a median survival of 23 months, compared with 70-124 months in those with isolated locoregional disease; however, when metastases are limited to the liver, 5- and 10-year survival is 46% and 38% respectively.

Conclusions and Future Directions

Pancreatic neuroendocrine tumors are a distinct entity from other pancreatic malignancies, and from neuroendocrine tumors elsewhere in the digestive tract. Due to the heterogeneity of tumors encompassed by this diagnosis, PNETs may present with a wide spectrum of clinical features, including signs and symptoms related to hormone hypersecretion or due to mass effect or as an asymptomatic incidental radiographic finding. Radiographic features vary depending on the subtype of tumor. As the biological potential of these tumors remains uncertain in most cases, with no predictive patient or tumoral characteristics, the overall management of PNETs still remains on a case-to-case basis; however, syndromic PNETs usually behave aggressively in contrast their sporadic counterpart. Though surgical resection is the primary modality of treatment in many cases, especially in symptomatic PNETs, conservative management is suggested for small non-functional tumors. Advanced symptomatic PNETs are treated by a multimodality approach that includes palliative resection of primary with metastatectomy, ablative therapies, hormone inhibitors and chemotherapeutics. The use of targeted-based therapies continues to evolve in PNETs. Given the rarity of PNETs, current guidelines for management are largely consensus-based rather than evidence-based. In this context, prospective studies with the creation of a large multi-center trials and an international registry are future recommendations.

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