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REVIEW ARTICLE

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From diagnosis to treatment: navigating the course for pancreatic neuroendocrine neoplasms

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ABSTRACT

Introduction: Pancreatic neuroendocrine neoplasms (pNENs) represent an increasingly significant, unique and complex subgroup of neuroendocrine diseases. Their heterogeneity is reflected in wide variations in biological behaviour, metastatic potential, functionality and aetiology. This review synthesizes the current understanding of pNENs, from diagnosis to treatment.

Discussion: Recent advances in understanding of these neoplasms have led to significant changes in their classification, now distinguishing three grades of well-differentiated tumours from poorly differentiated neuroendocrine carcinomas. These neoplasms are rare and can occur sporadically or within the context of hereditary syndromes, however, due to advances in diagnostic modalities and ageing population their incidence worldwide is on the rise. They can present as functional neoplasms, secreting biologically active hormones and inducing hormonal syndromes, or as non-functional neoplasms. Surgery remains the primary curative-intent approach for localized and locally advanced tumours, while systemic treatment is often the only option for patients with advanced disease. Multifaceted nature of pNENs demands a multidisciplinary approach that incorporates personalized diagnostic and therapeutic strategies. While clinical guidelines provide an essential framework, they must remain adaptable to accommodate individual patient circumstances and evolving evidence.

Conclusions: This review addresses existing gaps, unresolved controversies and areas of inconsistency in diagnostic workup and management of pNENs. It underscores the need for continued investigation to refine our understanding and improve patient outcomes.

KEY MESSAGES

The growing worldwide incidence of pancreatic neuroendocrine neoplasms demands profound and up-to-date knowledge on diagnostic and therapeutic modalities. Their complex and versatile pathology necessitates a multidisciplinary approach to ensure optimal management for each individual patient. In localized disease, treatment is guided by tumour size and functionality, with active surveillance or surgery as mainstays. In advanced disease, systemic therapy remains the cornerstone of care.

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1. Introduction

1.1. Background

Neuroendocrine neoplasms (NENs) are a unique and diverse group of diseases that span a spectrum from indolent to highly aggressive malignancies [1]. Although all NENs possess the potential for malignancy, their biological behaviour and metastatic risk can vary dramatically, posing significant challenges in diagnosis and management [2]. Histologically, these neoplasms are distinguished by their affinity for silver staining and the expression of hallmark neuroendocrine markers such as synaptophysin (SYP) and chromogranin A (CgA) [1].

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Although NENs can arise throughout the body, gastroenteropancreatic system represents the most common primary site [3,4]. Historically, these tumours were often referred to as carcinoids, a term introduced in 1907 by German pathologist Siegfried Oberndorfer to describe growths with benign clinical behaviour but carcinoma-like microscopic features [5]. Today, the term gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) is preferred for clarity [6], though carcinoid is still commonly used to describe well-differentiated neuroendocrine tumours of the luminal gastrointestinal tract.

GEP-NENs, though rare, are an increasingly significant group of neoplasms, with a steadily rising global incidence over the past few decades. This rising trend is largely attributed to advancements in diagnostic methods, improved imaging technologies, greater awareness among clinicians and pathologists, as well as an ageing population and potential yet unidentified environmental factors [5,7,8].

A rising trend in incidence of the pancreatic subtype of GEP-NENs has been observed [9]. A recent study based on a United States database revealed an increase in incidence rates from 0.27 to 1.00 per 100,000 between 2000 and 2016, largely attributed to a growing proportion of early-stage diagnoses in recent years [10]. Pancreatic neuroendocrine neoplasms (pNENs) account for approximately 2–5% of all pancreatic neoplasms [11]. They range from well-differentiated pancreatic neuroendocrine tumours (pNETs) to poorly differentiated pancreatic neuroendocrine carcinomas (pNECs), demonstrating a spectrum of differentiation [12]. Although typically less aggressive than pancreatic ductal adenocarcinoma, they may metastasize to lymph nodes and distant sites and exert locoregional effects due to their size and anatomical location [13].

1.2. Objective and methods

The increasing incidence of pNENs calls for ongoing refinement of diagnostic and therapeutic strategies. This narrative review aimed to synthesize current knowledge on the aetiology, classification, clinical presentation, diagnosis and management of pNENs, with a particular focus on sporadic cases, which represent the majority. Hereditary syndromes were included only where relevant to the broader understanding of the disease.

Relevant literature was identified through a comprehensive search of two major electronic databases: PubMed and Google Scholar. The search strategy combined Medical Subject Headings and free-text keywords related to pNENs, including terms such as '*pancreatic neuroendocrine neoplasms*', '*pancreatic neuroendocrine tumours*', '*neuroendocrine carcinoma*', '*well-differentiated*', '*poorly differentiated*', '*tumour grading*', '*functional tumours*', '*non-functional tumours*', '*diagnosis*', '*imaging*', '*biomarkers*', '*surgery*' and '*systemic therapy*'. Boolean operators (AND/OR) were used to refine results.

The search included English-language articles published up to June 2025, covering clinical trials, reviews, meta-analyses, consensus statements, retrospective and prospective studies and practice guidelines. Only studies involving human subjects were considered. No formal quality appraisal or meta-analysis was conducted, consistent with the narrative review design.

As such, this review is subject to limitations, including potential selection bias and the lack of standardized quality assessment. The exclusion of non-English publications may have omitted relevant data. Many of the referenced studies are retrospective in nature and subject to publication bias, and existing clinical guidelines often rely on limited or low-level evidence, contributing to variability in recommendations. Despite these limitations, efforts were made to include a broad and representative range of key studies to ensure a balanced overview of the current evidence on pNENs.

2. Factors behind the disease

Approximately 10% of pNENs are associated with hereditary syndromes, while the majority arise sporadically, primarily in older adults, with the highest incidence observed in the sixth decade of life [14,15]. Although the precise drivers of sporadic pNEN development remain to be fully elucidated, several risk factors have been proposed, including socio-economic status, a family history of cancer, smoking, alcohol consumption and type two diabetes mellitus [16,17].

Advances in molecular profiling, including next-generation sequencing (NGS) techniques such as whole-genome and exome analysis, along with preclinical studies, have identified key genetic

alterations and pathways involved in both sporadic and hereditary pNENs. In sporadic pNETs, *MEN1* mutations are the most frequent, occurring in over 40% of cases [18–21]. Mutations in *ATRX* and *DAXX* are also common and, like *MEN1*, typically involve two-hit inactivation. These alterations are associated with alternative lengthening of telomeres, chromosomal instability and poor prognosis. Tumours with ATRX/DAXX loss often present with larger size, higher-grade, lymph node involvement and distant metastasis [12,22,23]. Other alterations frequently affect mTOR pathway genes such as *TSC1*, *TSC2*, *PTEN*, *PIK3CA* and *DEPDC5* [18–21]. By contrast, pNECs are distinguished by mutations in the *TP53* and *Rb1* genes, with occasional mutations in *KRAS* and *SMAD4* [24]. These insights are not only prognostic but increasingly critical to clinical decision-making, as they provide the foundation for tailoring therapy selection and sequencing—an aspect that remains underutilized and is addressed in later sections of this review.

Among the hereditary cases, multiple neuroendocrine neoplasia type one (MEN-1) syndrome is the most prevalent, followed by von Hippel-Lindau syndrome, Tuberous Sclerosis Complex and Neurofibromatosis type one [25]. Up to 80% of patients with MEN-1 syndrome develop pNETs, the majority of which are non-functional, with gastrinomas being the most common among functional types [26]. Notably, no hereditary syndromes have been associated with pNECs [27].

Hereditary pNETs typically present at an earlier age compared to their sporadic counterparts and are often multifocal [28]. While comparative studies are limited, recent retrospective data suggest that hereditary cases have better overall survival (OS) than sporadic ones [15]. In sporadic pNETs, older age and the presence of metastatic disease are consistently associated with poorer outcomes. Supporting this, a study of patients with Zollinger-Ellison syndrome (ZES)—a clinical manifestation of gastrinomas—found that those with MEN-1–associated ZES had significantly improved OS and progression-free survival (PFS) compared to sporadic cases [29].

3. Classification

3.1. Tumour grade and differentiation

The clinical behaviour and prognosis of pNENs are heavily influenced by various factors, including tumour grade, differentiation and disease stage [30,31]. Tumour grade reflects the rate of tumour cell proliferation, assessed using the mitotic index (mitoses per 10 high-power fields (HPF) or per 2 mm^2) and the Ki-67 index (percentage of dividing nuclei expressing Ki-67 protein). Differentiation describes how closely neoplastic cells resemble their normal counterparts [32,33].

First introduced in 2017 and retained in the 2022 World Health Organization (WHO) classification, the current system categorizes pNENs by grade (G1–G3) and histologic differentiation (well-differentiated pNETs versus poorly differentiated pNECs) [33,34]. The revision reflects growing evidence that grade alone does not fully capture differences in clinical behaviour or prognosis. Although G3 neoplasms are relatively rare, they vary widely in aggressiveness depending on their degree of differentiation [35,36]. Well-differentiated G3 pNETs are now recognized as a distinct entity, morphologically similar to lower-grade pNETs but differing molecularly from pNECs. Accurate classification is crucial, as it informs subsequent treatment choices discussed later in this article. Yet, distinguishing G3 pNETs from pNECs remains challenging in practice, and misclassification can adversely affect management.

Emerging evidence supports the view that pNETs and pNECs are biologically separate entities rather than a spectrum [37]. At diagnosis, metastases are found in about one-third of low-grade pNETs and 80% of high-grade pNETs, while nearly all pNECs present with metastatic disease [38,39]. Even G3 pNETs, with a Ki-67 index reaching up to 50%, are more closely related to lower-grade pNETs than to pNECs [37]. pNECs, in contrast, are poorly differentiated with significant atypia and geographic necrosis, making careful histopathologic assessment and immunohistochemistry essential for distinguishing them from G3 pNETs [33,40]. Figure 1 provides an overview of the latest WHO classification for pNENs and the immunohistochemical characteristics used to differentiate high-grade pNENs.

The WHO classification expands beyond pNETs and pNECs by including a third category known as mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) [33,34]. These rare neoplasms consist of both neuroendocrine and non-neuroendocrine components, each accounting for at least 30% of the

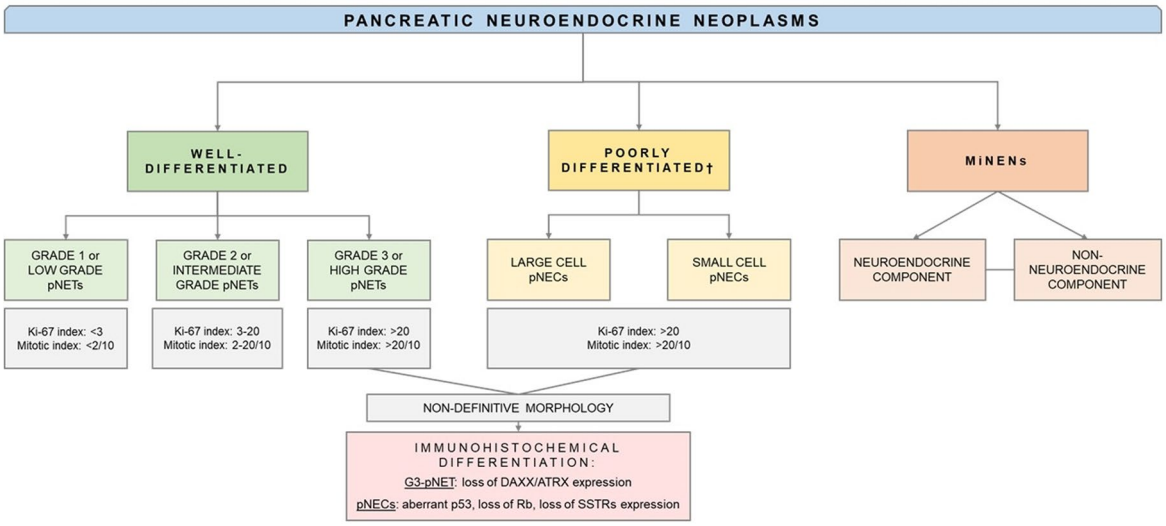

Figure 1. Summary of the 2022 WHO classification and immunohistochemical differentiation of high-grade pNENs [27,33,34]. Ki-67 index is expressed in percentages; mitotic index is expressed in mitoses per 10 HPF or per 2 mm^2. Abbreviations: pNETs—pancreatic neuroendocrine tumours; pNECs—pancreatic neuroendocrine carcinomas; MiNENs—mixed neuroendocrine-non-neuroendocrine neoplasms, SSTRs—somatostatin receptors. †All pNECs are by definition high-grade neoplasms.

Table 1. The TNM classification for pNETs, 8/9th edition AJCC/UICC [45,46].

TNM	
Stage	
T1	Tumour limited to pancreas, ≤2 cm
T2	Tumour limited to pancreas, >2 cm but ≤4 cm
T3	Tumour limited to pancreas, >4 cm; or invading duodenum or bile duct
T4	Tumour invades adjacent structures
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to liver
M1b	Metastasis in at least one extrahepatic site
M1c	Both hepatic and extrahepatic metastases
I	T1 N0 M0
II	T2–3 N0 M0
III	T4 N0 M0
	T1–4 N1 M0
IV	T1–4 N0–1 M1

Abbreviations: T—tumour; N—node; M—metastasis.

neoplasm's cellular makeup. The non-neuroendocrine component is most often ductal adenocarcinoma, though acinar carcinoma is less common. In most cases, all components of MiNENs are high-grade [41,42].

3.2. Disease stage

The staging of pNENs is based on the tumour, node, metastasis (TNM) classification system. Currently, two major TNM systems exist. One was proposed by the European Neuroendocrine Tumour Society (ENETS), and the other was developed by the American Joint Committee on Cancer (AJCC) and endorsed by the International Union for Cancer Control (UICC) [43]. The latest version is the 9th edition of the AJCC/UICC classification for GEP-NENs. For pNETs, this edition remains unchanged from the 8th edition, which was previously aligned with the ENETS system (Table 1) [44–46]. However, this classification does not apply to pNECs, which are staged using the prognostic framework for exocrine pancreatic carcinomas [45,46].

4. Clinical presentation

Clinically, pNENs are classified as functional or non-functional based on their ability to secrete biologically active hormones and induce hormonal hypersecretion syndromes. While pNETs can be either functional or non-functional, pNECs are predominantly non-functional [27].

The defining criterion for functional pancreatic neuroendocrine neoplasms (F-pNENs) is the presence of a hormone-specific clinical syndrome supported by biochemical evidence of elevated hormone levels [47]. Non-functional pancreatic neuroendocrine neoplasms (NF-pNENs) are more prevalent, representing 60–90% of all cases [48,49].

4.1. Functional neoplasms

The clinical presentation of F-pNENs depends on the hormone produced in excess by the neoplastic cells. Up to sixteen different syndromes have been described, with insulinomas and gastrinomas being the most common [50,51]. Although uncommon, F-pNENs can produce multiple bioactive hormones simultaneously, leading to the concurrent manifestation of more than one syndrome in a single patient. Clinical presentations of these functional syndromes are summarized in Table 2.

4.2. Non-functional neoplasms

NF-pNENs often present with non-specific symptoms, in contrast to functional neoplasms. Most NF-pNENs, excluding the aggressive pNECs, are frequently indolent and slow-growing, often remaining asymptomatic for a long time [11]. When symptoms do occur, they are usually caused by the neoplasm's growth, leading to local compression, invasion of adjacent structures or metastasis. Common symptoms include abdominal pain, obstructive jaundice and weight loss, while less frequent manifestations include loss of appetite, nausea and intra-abdominal bleeding [49]. The absence of hormone-related symptoms means these neoplasms are frequently diagnosed at advanced stages, when they are large and distant metastases are already present [55]. The frequent late presentation complicates management and highlights the need for improved strategies to facilitate earlier detection and refine risk stratification.

Table 2. Clinical presentations and primary locations of F-pNENs.

Tumour type (hormone)	Primary location	Clinical presentation
Insulinoma (insulin) [52–54]	Evenly distributed throughout the pancreas	Hypoglycaemia[a] symptoms (usually fasting): a) Neurogenic symptoms (i.e. sweating, tremor, palpitations) b) Neuroglycopenic symptoms (i.e. confusion, fatigue, visual changes, coma) Frequent small meals may cause weight gain
Gastrinoma (gastrin) [55,56]	Gastrinoma triangle[b] (predominantly in the duodenum, followed by the pancreas)	ZES: a) Gastroesophageal reflux disease b) Peptic ulcer disease (multiple ulcers in uncommon sites, e.g. third part of the duodenum, small bowel) c) Chronic diarrhoea
Glucagonoma (glucagon) [57,58]	Distal pancreas (tail)	Pathognomonic dermatitis (necrolytic migratory erythema), diabetes mellitus, other manifestations (i.e. weight loss, diarrhoea, anaemia, deep vein thrombosis, depression)
VIPoma (vasoactive intestinal peptide) [59]	Distal pancreas (body, tail)	Varner-Morrison syndrome/WDHA syndrome: a) Watery diarrhoea (up to 3 l/day) b) Hypokaliemia c) Achlorhydria
Somatostatinoma (somatostatin) [60,61]	Pancreas, ampulla, duodenum	Somatostatinoma syndrome (diabetes mellitus, gallstones, steatorrhea/diarrhoea)[c]
Other rare forms	Secretion of somatoliberin, adrenocorticotropin, parathyroid hormone related peptide, serotonin, tachykinins, etc., causing symptoms.	

[a]Hypoglycaemia in a non-diabetic patient is defined by Whipple's triad: low blood glucose, hypoglycaemia symptoms and symptom relief after carbohydrate intake.
[b]The gastrinoma triangle is formed by connecting three points: the junction of the second and third parts of the duodenum, the cystic duct and common bile duct junction, and the body and neck of the pancreas junction.
[c]Somatostatinomas are often silent, diagnosed incidentally or present with non-specific symptoms.

5. Diagnostic approach

The diagnostic approach to pNENs is a multifaceted process combining clinical evaluation, blood-based markers, advanced imaging, with histopathological or cytological examination remaining the gold standard for definitive diagnosis [62].

5.1. Biochemical diagnostics

Circulating neuroendocrine markers, detectable in plasma and/or serum, are divided into two groups where non-specific or general markers are expressed by almost all pNENs and specific markers are primarily associated with F-pNENs [63,64]. Hormonal markers such as insulin, gastrin, glucagon, vasoactive intestinal peptide and somatostatin are commonly used in the diagnosis and monitoring of F-pNENs [65].

General circulating markers are widely used in clinical practice to monitor and support the diagnosis of NENs. CgA, the most common marker, is expressed in both normal and neoplastic neuroendocrine cells [61]. However, its diagnostic utility is constrained by limited sensitivity and specificity. Its sensitivity is more acceptable in functional and advanced NENs [65,66]. Despite its limitations, CgA remains valuable for assessing disease progression, tumour burden and treatment response in non-functional pancreatic neuroendocrine tumours (NF-pNETs) when measured consistently with the same assay [67,68]. Other markers, such as neuron specific enolase (NSE) and pancreatic polypeptide, are also relevant, with NSE linked to poor differentiation and shorter PFS, even when CgA levels are normal [69].

Molecular biomarkers like circulating tumour cells, microRNAs and the NETest are transforming NEN diagnosis and management through more precise detection and monitoring. The NETest, with its superior sensitivity and specificity in analysing NEN-specific gene expression, remains limited by high cost and accessibility [65,70]. Researchers are exploring affordable alternatives, such as serum ß-human chorionic gonadotropin, for evaluating treatment response and disease progression in pNENs [71].

Taken together, circulating markers are useful for monitoring and prognostication but lack the specificity needed for reliable diagnosis, making imaging and pathology indispensable. Emerging molecular biomarkers show promise for improving diagnostic accuracy and disease monitoring, but their clinical utility remains limited by cost, accessibility and the need for robust validation.

5.2. Diagnostic imaging

Imaging is central to the evaluation of pNENs, offering critical information for diagnosis, staging and treatment planning. Broadly, modalities are categorized as morphological imaging, which assesses anatomical structures, and functional imaging, which captures receptor expression or metabolic activity.

5.2.1. Morphological imaging techniques

Multiphasic contrast-enhanced computed tomography (CT) is a widely used first-line modality due to its availability, high spatial resolution and ability to assess both primary tumour and metastases. Detection rates range from 69% to 94%, depending on tumour size and vascularity [72]. CT is particularly useful for whole-body staging, but its sensitivity for detecting bone metastases is limited, and lymph node evaluation is constrained by size-based criteria [72,73].

Abdominal ultrasound (US) is commonly used as an initial imaging step given its accessibility, though its detection rate for primary neoplasms is low (i.e. around 40%) even with contrast enhancement [72]. While more effective for identifying liver metastases, its role in comprehensive evaluation remains limited.

In contrast, endoscopic ultrasound (EUS), particularly with contrast enhancement, offers the highest sensitivity for detecting small lesions such as insulinomas and gastrinomas [72,74,75]. It also enables tissue sampling through fine-needle aspiration (FNA) or fine-needle biopsy (FNB), with FNB demonstrating superior diagnostic yield and greater accuracy in preoperative Ki-67 index assessment [76,77]. Additionally, EUS accurately maps lesion location and proximity to critical structures like the main pancreatic duct (MPD), which is essential for surgical planning.

Magnetic resonance imaging (MRI) provides superior contrast resolution compared to abdominal US and CT, as well as avoids ionizing radiation. It is particularly effective in detecting liver, brain and bone

metastases [78] and is often used when CT results are inconclusive [79]. Magnetic resonance cholangiopancreatography further enhances lesion characterization by delineating their relationship to the pancreatic and bile ducts, improving surgical planning. Additionally, diffusion-weighted imaging (DWI) is useful for identifying small lesions and is suitable for patients who cannot receive contrast agents [78,80].

5.2.2. Functional imaging techniques

Many well-differentiated pNENs express somatostatin receptors (SSTRs), enabling their detection through SSTR-based functional imaging. Radiolabelled somatostatin analogues (SSAs) are commonly used for identifying primary tumours, detecting metastases and identifying candidates for SSTR-targeted therapies [81].

Historically, somatostatin receptor scintigraphy (SRS) with indium-111 (^{111}In)-pentetreotide (Octreoscan), was the cornerstone of functional imaging. However, it has largely been replaced by positron emission tomography (PET) combined with CT (SSTR-PET/CT) using gallium-68 (^{68}Ga) based tracers (e.g. ^{68}Ga-DOTATATE, DOTA-NOC and DOTA-TOC), which offers significantly higher spatial resolution and sensitivity [82,83]. SSTR-PET/CT provides high diagnostic accuracy and greater sensitivity than conventional CT for detecting distant metastases, especially in bones, though it is less effective for pulmonary lesions [84]. It also improves detection of lymph node metastases that are challenging to assess on CT or MRI [72]. For liver metastases, however, MRI with hepatocyte-specific contrast remains superior [85]. Prior to local treatment, liver MRI with DWI and hepatocyte-specific contrast is recommended, either alongside SSTR-PET/CT or as part of hybrid SSTR-PET/MRI imaging [68,86].

While an unenhanced low-dose CT in PET/CT may suffice for anatomical orientation and attenuation correction, contrast-enhanced imaging, either as part of PET/CT or via dedicated CT and/or MRI, is crucial for comprehensive tumour evaluation, including local resectability and metastatic anatomy [85,87].

As Ki-67 index increases, SSTR expression typically decreases, reducing the utility of SSTR-based imaging. Conversely, fluorine-18-fluorodeoxiglucose (^{18}F-FDG)-PET/CT becomes more effective due to increased glucose metabolism in high-grade tumours. A positive ^{18}F-FDG-PET/CT result strongly correlates with poorer disease outcomes and can also offer valuable prognostic information in lower-grade pNENs [82,88]. Using both SSTR-PET/CT and ^{18}F-FDG-PET/CT offers complementary insights into tumour biology.

In insulinomas, which may lack significant SSTR expression, glucagon-like peptide one receptor (GLP-1R)-PET/CT, has shown promise, especially in benign cases. However, its utility in malignant insulinomas is limited due to downregulation of GLP-1R [82].

From a clinical standpoint, morphological and functional imaging provide complementary insights—one defining anatomical extent, the other capturing tumour biology. Both are central to staging and treatment planning, yet their sequencing is not standardized. Although practice must be tailored to individual patient characteristics, the absence of unified recommendations highlights the need for a clearer framework to guide diagnostic workup of suspected pNENs. A recent international Delphi consensus sought to address this by providing expert guidance on the sequencing of SSTR-PET and EUS biopsy. For example, SSTR-PET was recommended as the preferred initial test in surgical candidates with >2 cm, multifocal or functional pancreatic neuroendocrine tumours (F-pNETs), while biopsy was considered unnecessary before resection unless there was concern for high-grade features, metastatic disease, inconclusive findings or alternative diagnoses [89]. These statements aim to harmonize practice in the absence of high-level evidence.

5.3. Pathological analysis

Pre-treatment assessment of pathological tumour grade in pNENs is important for determining prognosis and informing management decisions. ENETS guidelines recommend sampling the most accessible site, with liver metastases prioritized when available. If metastases are absent or inaccessible, EUS-FNA or EUS-FNB of the primary tumour is suggested, with CT-guided biopsy as an alternative [68].

Histopathological evaluation, typically performed on surgical or endoscopic biopsy samples, relies on morphological analysis of the neoplasm and immunohistochemistry. Currently, CgA and SYP are regarded as the most specific immunohistochemical markers for neuroendocrine differentiation. Well-differentiated

neoplasms generally show high levels of CgA expression, while poorly differentiated pNECs display reduced or focal expression [63,90].

Immunohistochemical staining for SSTR-2 is valuable for assessing tumour differentiation [7]. The Ki-67 marker plays a central role in grading pNENs by evaluating the proliferative activity of neoplastic cells. Additionally, other markers are used to distinguish between G3 pNETs and pNECs (see Classification section). In some cases, neoplastic cells produce hormones that do not enter the bloodstream but can be detected using specialized staining techniques [63,90].

5.4. Radiomics: a new look at pNENs

While the invasive nature and vulnerability to sampling error limit reliability of tissue biopsy, the diagnostic accuracy of imaging modalities is often constrained by subjective interpretation [91]. Radiomics presents a more objective approach by extracting quantitative features from medical images and converting them into high-dimensional data that may capture underlying tumour biology. Integrated with machine learning, radiomics has shown promise in predicting pNEN grade and may support treatment planning and follow-up [92–95]. It has also demonstrated high sensitivity in detecting small pNETs on CT, suggesting utility in early detection and opportunistic screening [96]. Beyond diagnosis, radiomics may help overcome the limitations of size-based surgical thresholds by identifying small but aggressive tumours and larger indolent ones and assist in evaluating metastatic lesions [97].

Despite this promise, clinical translation remains limited. Radiomics features vary with scanner settings, reconstruction methods, software and segmentation, which remains a major source of variability. Standardization initiatives such as the Image Biomarker Standardization Initiative, which defines feature calculation and reporting standards, and harmonization methods such as ComBat, which adjust feature distributions across centres, have improved comparability, but cross-centre variability continues to hinder reproducibility [98–100]. Most studies are small, retrospective and single-centre, with little external or prospective validation [101], and current artificial intelligence models remain exploratory and imprecise. For now, radiomics in pNENs should be regarded as experimental until validated in large, prospective multicentre studies.

6. Treatment options

pNENs have diverse treatment options shaped by tumour differentiation, pathological grade, clinical stage and hormonal symptoms. Recent advancements in surgical techniques and systemic therapies have led to a shift towards individualized management, with treatment strategies crafted by a multidisciplinary team of pNEN specialists.

6.1. Surgical treatment

Surgical resection remains the primary curative-intent approach for localized and locally advanced pNENs and can also offer significant benefits for patients with metastatic disease, particularly by alleviating symptoms and improving survival outcomes [102]. Given the rarity and specificity of pNENs, their management should be centralized in specialized high-volume centres to minimize morbidity and mortality.

6.1.1. Localized disease

6.1.1.1. Sporadic F-pNETs. Surgery with radical intent is recommended for medically fit patients with localized sporadic G1 or G2 F-pNETs, regardless of tumour size, due to the significant clinical syndromes these tumours can cause [86,103–107]. Surgical resection not only alleviates symptoms caused by hormone overproduction but also serves to prevent metastases [102]. However, medical control of the hormonal syndrome must be achieved before surgery to reduce perioperative risks.

Insulinomas are typically benign and curable with surgery, with enucleation often sufficient, provided tumour size, location and MPD proximity are carefully assessed. Routine lymphadenectomy is not indicated due to their minimal malignant potential [86,104,106]. By contrast, gastrinomas are more frequently

malignant and often involve lymph nodes, making peritumoural lymphadenectomy necessary and formal pancreatic resection more appropriate than enucleation [86,104,106,108,109]. Other F-pNETs are exceptionally rare, making standardized management difficult, though surgical resection remains the only curative option [51,104,106].

For patients with symptoms of hormone hypersecretion, the primary tumours may remain occult despite advanced preoperative imaging [110]. Historically, blind distal pancreatectomy was performed when insulinomas could not be localized or palpated during surgery [111]. However, guidelines now prioritize surgical exploration with intraoperative US, which significantly enhances tumour localization and surgical precision [86,104].

6.1.1.2. Sporadic NF-pNETs. The management of sporadic NF-pNETs is challenging due to their variable biology and uncertain malignant potential [109,112]. Advances in high-resolution imaging have significantly increased the detection of small (≤2 cm), asymptomatic NF-pNETs, shifting management from routine surgery to a more selective approach [113]. Although surgery remains the standard for localized disease and is generally recommended for sporadic and MEN-1-related NF-pNETs [114], studies have shown that a non-operative approach can be safe for carefully selected small tumours [102,115,116]. However, most evidence derives from small, non-randomized series, limiting generalizability.

At the same time, studies indicate that even small NF-pNETs can exhibit aggressive behaviour, including lymph node or distant metastases and recurrence, negatively impacting OS and cancer-specific survival [117–120]. This underscores the potential long-term benefits of surgical resection. Preoperative examinations lack accuracy in predicting nodal involvement, as current imaging modalities show high specificity but very low sensitivity for detecting lymph node metastases [121]. Still, surgery may not improve survival in patients with localized, well- to moderately-differentiated tumours with lymph node metastases only [122].

The growing trend towards the 'watch-and-wait' strategy emphasizes the importance of individualized approach, where clinical practice guidelines are not rigidly applied but rather serve as adaptable tools to guide decisions tailored to each patient's unique circumstances. Data analysis from the National Cancer Database indicates that surgery improves survival for localized tumours 1–2 cm and >2 cm in size, but not for those <1 cm, after adjusting for covariates [123].

Clinical guidelines broadly endorse surveillance for small, asymptomatic, localized sporadic NF-pNETs, while recommending surgical removal for tumours larger than 2 cm due to their higher risk of metastasis, local invasion and nodal involvement [68,103–107,118]. Tumours 1–2 cm in size fall into a 'grey zone', requiring a tailored approach based on tumour grade, location, growth behaviour and patient-specific factors [68,104,105]. For tumours exceeding 2 cm, most guidelines recommend regional lymph node removal [103–107], though ENETS raises this threshold to 3 cm [68]. Recommendations from international societies are summarized in Table 3.

Adding to this, a multicentre retrospective study demonstrated a strong correlation between tumour size and the risk of lymph node metastasis in NF-pNETs. Tumours larger than 2 cm were identified as independent risk factors for lymph node metastases and reduced disease-free survival, supporting surgical intervention in fit patients [124].

The interim analysis of the Asymptomatic Small Pancreatic Endocrine Neoplasms (ASPEN) study, the largest prospective multicentre study of small asymptomatic NF-pNETs (≤2 cm), reported surveillance to be safe over a median follow-up of 2 years, with minimal tumour growth and no cases of distant metastases [125,126]. Follow-up remains short and cannot exclude late progression, a well-recognized risk in indolent tumours. Notably, nearly all tumours with aggressive histological features and nondilated MPD exceeded 1 cm [126]. These results provide short-term reassurance but fall short of establishing long-term safety.

Analysis from the SEER database [127] and a retrospective multicentre study [128] highlight that tumour size alone is an imperfect surrogate for tumour aggressiveness and insufficient for determining eligibility for the 'watch-and-wait' strategy. The latter study recommends personalized management and surveillance for G1 tumours under 2 cm, G2 tumours under 1 cm and a 1.5 cm cut-off for unknown-grade tumours due to higher Ki-67 indices in tumours ≥1.5 cm and strong tumour diameter predictive ability for lymph node metastases [128].

Table 3. Comparison of clinical guidelines for managing localized sporadic NF-pNETs.

	Clinical guideline	Recommendations
Europe	ENETS (2023) [68]	No MPD dilatation **≤1 cm and asymptomatic:** Active surveillance **>1 and ≤2 cm:** Personalized approach considering type of surgical approach needed and patients' comorbidities **>2 cm:** Resection + routine lymphadenectomy, if >3 cm MPD dilatation **Any size:** Resection + routine lymphadenectomy, if >3 cm
	ESMO (2020) [103]	**≤2 cm and incidentally discovered:** Imaging-based surveillance *(suggested for elderly patients, those with important comorbidities, or deep localization in the pancreatic head; surgery recommended for young patients or when signs of local invasiveness are present)* **>2 cm:** Standard pancreatectomy (PD/DP) + regional lymphadenectomy
North America	NCCN (2.2024) [104]	Grade 1/2 **≤1 cm, Grade 1 and incidentally discovered:** Observation **>1 to ≤2 cm:** Observation *(consider for grade 1, incidentally discovered tumours; base decision on surgical risk, tumour site and comorbidities)*, **or** pancreatectomy ± lymphadenectomy, **or** enucleation ± lymphadenectomy **>2 cm, invasive, or node-positive:** Pancreatectomy + lymphadenectomy
	NANETS (2020) [105]	**<1 cm, asymptomatic and imaging consistent with pNETs:** Observation **1–2 cm:** Observation *(consider age, comorbidities, tumour growth over time, estimated risk of symptom development, details of imaging, grade, the extent of surgical resection required, patient's wishes, access to long-term follow-up)* **or** resection **>2 cm:** Formal resection + lymphadenectomy
Asia	JNETS (2019) [106]	**<1 cm, incidentally discovered, asymptomatic and no radiographic evidence of metastasis/invasion** (e.g. hepatic or lymphatic involvement, pancreatic duct stenosis, biliary stricture): Follow-up with informed consent **<1 cm not reaching criteria for observation:** Resection including enucleation **≥1 and <2 cm:** Resection including enucleation + lymphadenectomy **≥2 cm:** Standard resection + lymphadenectomy
	China (2020) [107]	Grade 1/2 **<2 cm:** Imaging-based surveillance with informed consent **or** resection *(especially for grade 2, significant progression/volume increase >20%, evidence of lymph node metastasis/local invasion, MPD dilatation, or obstructive jaundice)* **≥2 cm:** Regular pancreatectomy + lymphadenectomy

Abbreviations: ENETS—European Neuroendocrine Tumour Society; ESMO—European Society for Medical Oncology; NCCN—National Comprehensive Cancer Network; NANETS—North American Neuroendocrine Tumour Society; JNETS—Japanese Neuroendocrine Tumour Society; MPD—main pancreatic duct; PD—pancreatoduodenectomy; DP—distal pancreatectomy; pNETs—pancreatic neuroendocrine tumours.

Finally, patients eligible for the 'watch-and-wait' strategy require structured follow-up to monitor for changes necessitating surgical intervention. 2016 ENETS guidelines recommend EUS and MRI/CT every 6 months, transitioning to annual evaluations for patients with stable disease and a low Ki-67 index [129]. ESMO advises annual high-quality imaging [103], Japanese Neuroendocrine Tumour Society suggests follow-ups every 6–12 months [106], and Chinese guidelines advocate more frequent monitoring, with follow-ups every 3 months in the first year, transitioning to 6-month intervals for 3 years and annually thereafter if the disease remains stable [107].

In summary, while surveillance is increasingly endorsed for small, low-grade, asymptomatic NF-pNETs, supporting evidence is limited, largely retrospective and prone to selection bias. Prospective data, such as the ASPEN trial, offer short-term reassurance but cannot establish long-term safety. Tumour size alone is insufficient for risk stratification, with biological features, imaging characteristics and patient-specific factors providing more reliable guidance. Until high-quality, long-term prospective data are available, surveillance should be reserved for carefully selected patients within structured follow-up, and guided by multidisciplinary expertise. Even with growing guideline support, the 'watch-and-wait strategy' rests more on pragmatic consensus than on solid evidence, and its uncertainty must be acknowledged.

6.1.2. High-Grade pNENs

The role of surgical resection in G3 pNENs remains controversial, as evidence is largely limited to retrospective series, few of which account for the updated subcategories [105,130]. Outcomes appear to differ

by subtype. In pNECs without metastases, surgery provides limited benefit and should be considered cautiously [131]. By contrast, surgery for G3 pNETs, regardless of metastatic status, has shown favourable outcomes [131] and is an independent predictor of improved prognosis [132]. Another study also suggested a survival benefit in selected pNEC patients, though negative prognostic factors such as vascular infiltration, lymph node involvement and distant metastases were highlighted [133]. Reflecting these differences, the European Society of Endocrine Surgeons (ESES) recommends surgery for G3 pNETs without metastases and selective resection for localized pNECs within a multimodal framework [134].

6.1.3. Surgical management approaches and alternative strategies

The surgical management of pNETs includes standard pancreatic resections with lymphadenectomy and parenchyma-sparing procedures [135,136]. Standard resections include pancreatoduodenectomy, commonly performed for tumours in the pancreatic head, and distal pancreatectomy, with or without spleen preservation, for tumours in the body or tail. For larger central tumours or multiple tumours confined to the pancreas, total pancreatectomy may be necessary [136,137].

Conservative surgical techniques, including tumour enucleation and central pancreatectomy, aim to preserve healthy pancreatic tissue to minimize the risk of postoperative pancreatic exocrine and endocrine insufficiency. However, they often fall short in achieving sufficient lymphadenectomy compared to standard resections [138,139]. Enucleation can therefore be an option for small, benign tumours (e.g. insulinomas and NF-pNETs <2 cm) located >2–3 mm from the MPD [105,140,141]. On the other hand, small, low-grade pNETs in the neck or proximal body of the pancreas that cannot be enucleated due to proximity to MPD may undergo central pancreatectomy [105]. Because these procedures carry a higher risk of postoperative pancreatic fistula, the benefits of parenchyma preservation must be carefully weighed against this risk [139,142–144].

Surgery for pNETs can be performed using open, laparoscopic or robotic techniques. Minimally invasive surgery (MIS) offers benefits like shorter hospital stays, reduced blood loss and lower recurrence rates [145]. Robotic surgery, an advancement in MIS, addresses limitations of laparoscopy by enhancing manoeuvrability with wristed instruments, enabling precise manipulation and providing 3D visualization [146]. A meta-analysis found robotic distal pancreatectomy as effective as laparoscopic surgery, with added advantages including higher spleen preservation and fewer conversions to open surgery [147]. MIS should be prioritized whenever feasible [68,103], though laparoscopic pancreatoduodenectomy remains challenging due to its complexity. In such cases, robotic surgery serves as a superior MIS option [136,146,148].

For low-grade, small pNETs, particularly for patients unfit for surgery, EUS-guided radiofrequency ablation (EUS-RFA) is emerging as a promising alternative. By inducing coagulation necrosis in targeted tumour tissue while sparing surrounding healthy tissue, EUS-RFA achieves high efficacy with low risk for adverse events [149–152]. Although still investigational, early results are encouraging and reflect a broader trend towards tailoring local therapies to balance oncologic control with preservation of pancreatic function.

6.1.4. Advanced disease

Advanced pNETs often manifest as large masses that invade extrapancreatic structures or major vessels and are frequently accompanied by metastases. Complete surgical resection remains the only potentially curative treatment, particularly for large tumours or low-volume metastases. In locally advanced disease, surgical intervention may require resection of adjacent organs and vascular reconstruction, which, while potentially improving outcomes, also increases the risk of postoperative complications [134,153–155].

Multiple guidelines recommend surgery for locally advanced and/or metastatic pNETs when complete resection is feasible and clinically appropriate, considering patient health and tumour characteristics [68,104,107]. Additionally, several low-quality studies have examined neoadjuvant protocols for downsizing advanced borderline resectable or unresectable pNETs using peptide-receptor radionuclide therapy (PRRT) and chemotherapy. While PRRT shows higher partial response rates, the optimal treatment

regimen remains unclear [134,156,157]. These findings suggest some of these patients may achieve resectable disease and undergo curative resection.

6.1.4.1. Management of liver metastases. In pNENs, the liver is the most common site of distant metastases [158,159]. Liver failure resulting from extensive tumour replacement is the leading cause of death in these patients [160]. The conventional treatment of metastatic pNETs includes a combination of surgical resection, locoregional and systemic therapies [161].

Surgical treatment focuses on reducing tumour burden while preserving liver function. Patients with G1 or G2 pNETs, resectable neuroendocrine liver metastases (NELMs) and no extrahepatic disease may undergo curative resection. This can involve staged or synchronous removal of the primary tumour and liver metastases. However, cure is rare due to frequent recurrence. In palliative care, cytoreduction (debulking) helps slow disease progression and relieve hormonal or mass-effect symptoms [162,163]. A 70% hepatic clearance threshold is widely accepted as beneficial [164].

Surgical strategies often combine non-anatomical resections of superficial metastases with ultrasound-guided ablations for deeper lesions. Additional locoregional therapies including transarterial embolization, chemoembolization and yttrium-90 radioembolization offer effective, lower-morbidity alternatives to surgical metastasectomy and are viable for patients unsuitable for surgery [102,165,166].

Furthermore, orthotopic liver transplantation is a promising investigational option for select patients with unresectable NELMs, provided the primary tumour and lymph node metastases are fully resected [167,168].

6.1.4.2. The role of primary tumour resection in unresectable liver metastases. The benefit of primary site resection in patients with unresectable NELMs remains uncertain. Studies suggest it may relieve hormonal and local tumour symptoms while improving disease control [169]. Systematic reviews also link primary tumour resection to longer survival compared to non-operative management [169–171]. However, these results are primarily based on retrospective studies, which are susceptible to selection bias. For severe symptoms like gastric outlet or biliary obstruction, endoscopic resection or surgical bypass can be considered as treatment options [172].

6.2. Systemic treatment

Systemic treatment is essential for managing advanced pNENs when curative surgery or locoregional therapies are not viable or pose significant risks, aiming to control hormone overproduction, alleviate symptoms and suppress tumour growth. Treatment selection and sequencing should be personalized, considering patient, tumour and therapeutic goals, ideally guided by a multidisciplinary team discussion [173,174].

Interestingly, systemic treatments for syndromic pNENs, including those linked to MEN-1 syndrome, are largely consistent with those used for sporadic pNENs, despite the absence of robust evaluation in large patient cohorts [175,176].

6.2.1. Systemic treatment modalities

SSAs exert their therapeutic effects in pNETs through binding to SSTRs, primarily SSTR-2 and, to a lesser extent, SSTR-5 [81,177]. In addition to their antisecretory effects in functional tumours, SSAs also have antiproliferative properties that suppress tumour growth and stabilize disease [178].

For pNETs, this antiproliferative activity has been well-documented for lanreotide [179], though prospective studies on octreotide are lacking. Despite this, antitumour activity is considered a class effect of SSAs, making both lanreotide and octreotide recommended as first-line treatments for SSTR-positive G1 pNETs and G2 pNETs with a Ki-67 index ≤10%, non-bulky disease and unaggressive behaviour [180]. There is also limited evidence to support the use of SSAs in patients with relatively aggressive tumours, such as those with a Ki-67 index ≥10% [181]. While SSAs have a very tolerable safety profile, resistance can develop, posing challenges in patient management [182]. Moreover, negative SSTR imaging typically predicts SSA ineffectiveness [183], guiding patients with such imaging results, progression on standard-dose SSAs or aggressive disease to alternative systemic treatments.

Everolimus, an oral mTOR inhibitor, and sunitinib, a multitargeted tyrosine kinase inhibitor, are key targeted therapies for advanced pNETs. Both therapies have demonstrated efficacy in well-differentiated pNETs through phase three trials [184,185], with sunitinib further validated in a phase four study [186]. In the absence of comparative studies, and given their similar median PFS, the choice between these agents should be guided by the safety profile best suited to the individual patient [68,187]. More recently, the phase three CABINET trial showed that cabozantinib, an oral multikinase inhibitor, significantly improved PFS in patients with progressive pNETs previously treated with PRRT or targeted therapies such as everolimus or sunitinib, supporting its role as a new treatment option in this setting [188]. Although cabozantinib's toxicity profile necessitates careful patient selection and monitoring, it presents itself as an emerging key agent in later-line treatment settings. Especially patients with progressive, well-differentiated, non-resectable pNENs who have failed or do not tolerate other approved therapies are most likely to benefit from cabozantinib [173,188–190].

Despite their benefit in disease control, sunitinib and everolimus are less likely to induce significant tumour shrinkage compared to chemotherapy and PRRT [105,191]. Consequently, cytotoxic chemotherapy remains an essential component of pNEN treatment, especially for patients with bulky, symptomatic or rapidly progressing pNETs. Similarly, the aggressive nature of pNECs demands the prompt initiation of chemotherapy [187,191].

Cytotoxic chemotherapy for G1 and G2 pNETs commonly involves alkylating agents like streptozocin (STZ) or temozolomide (TEM), often combined with antimetabolites such as 5-fluorouracil (5-FU) or capecitabine (CAP) [192,193]. While STZ-based regimens have long been the standard of care, the capecitabine/temozolamide (CAPTEM) regimen has gained popularity due to its favourable toxicity profile and convenient oral administration [191,194]. Meanwhile, platinum-based chemotherapy remains the frontline treatment for pNECs [195]. For the recently recognized G3 pNET category, the optimal regimen remains debated [196]. However, CAPTEM is frequently recommended as a first-line option for tumours with a Ki-67 index below 55%, given their limited response to platinum-based regimens compared to pNECs [180].

Finally, theranostics, a key advancement in precision medicine, uses radiopharmaceuticals to first detect tumours via PET or single photon emission computed tomography (SPECT) imaging and then treat them with cytotoxic radionuclides [197]. Radiolabelled SSAs, with high affinity for SSTRs, are ideal for PRRT due to their uptake by receptor-expressing tumour cells and rapid clearance from blood, ensuring precise delivery of ionizing radiation [198]. In pNEN diagnosis, gallium-labelled SSAs are used, while PRRT utilizes SSAs labelled with β-emitters like lutetium (^{177}Lu) combined with DOTA chelators (e.g. ^{177}Lu-DOTA-TATE) [199].

Early clinical data support the efficacy of PRRT in pNETs. Preliminary phase two trial results indicate that ^{177}Lu-DOTA-TATE PRRT nearly doubles 12-month PFS compared to sunitinib, with final data pending [200], while a retrospective study [201], building on NETTER-1 [202] and Erasmus MC [203] findings, confirms its effectiveness. Already approved in the United States and Europe for advanced, well-differentiated (G1 and G2), SSTR-positive GEP-NENs [204], ^{177}Lu-DOTA-TATE PRRT also shows promise in G3 pNETs with a Ki-67 index below 55% [205].

Further comparative evidence comes from a multicentre retrospective cohort study of 508 patients with advanced G1–G3 enteropancreatic NETs progressing on SSAs, who subsequently received PRRT, chemotherapy or targeted therapy. Median PFS was 2.2 years with PRRT (vs 0.6 years with chemotherapy or targeted therapy; hazard ratio (HR) 0.37). In the pNET subgroup, the adjusted HR was 0.41, corresponding to an absolute PFS gain of 1.6 years. Similar benefits were observed across functioning and non-functioning tumours, intestinal primaries and G1–G2 disease (Ki-67 ≤ 10%) [206]. While limited by its retrospective design, this study highlights the potential of earlier PRRT use, contrasting with current practice where treatment is typically reserved for later lines.

Prospective trials are now strengthening this evidence base by evaluating PRRT earlier in the treatment course. The NETTER-2 trial is the first randomized study to assess PRRT as a first-line treatment in patients with advanced, well-differentiated, higher-grade (G2 ≥ 10% and G3) GEP-NETs. The primary analysis demonstrated that first-line ^{177}Lu-DOTATATE combined with octreotide LAR prolonged median PFS by more than 14 months compared with high-dose SSAs (22.8 versus 8.5 months), establishing a new standard of care in this population and addressing a critical unmet need where no evidence-based standard

previously existed [207]. PRRT with ^{177}Lu-DOTATATE has also demonstrated efficacy and safety as a neoadjuvant therapy for high-risk resectable or potentially resectable NF-pNETs [208].

Despite advancements in systemic therapies, adjuvant therapy is not currently indicated for patients with completely resected pNETs. Recent practice guidelines emphasize the lack of robust, high-level evidence to support the use of systemic therapy regimens, including chemotherapy, radiotherapy or chemoradiotherapy, in improving recurrence or survival outcomes after complete surgical resection of pNETs [68,104,105].

6.2.2. The challenge of treatment sequencing

6.2.2.1. Barriers to defining a standard sequencing approach. The optimal sequencing of systemic therapies for advanced pNENs remains undefined due to limited comparative data. Most patients eventually receive all available treatments in varying orders, based on individual clinical and tumour characteristics as well as treatment goals (e.g. tumour stability versus tumour response) [174,180,187,192]. While updated guidelines offer general frameworks, significant discrepancies persist, particularly regarding second-line treatment recommendations. Figure 2 illustrates differences among international guidelines for systemic therapy in advanced G1–G2 SSTR-positive pNETs.

A recent comparative analysis of these guidelines highlights this variability and the ongoing lack of consensus, emphasizing the need for prospective trials to clarify sequencing strategies [209]. However, the authors acknowledge that global differences in drug approval processes make a universal

G1-G2 pNETs (SSTR-positive)

Favourable phenotype (e.g., asymptomatic, stable or slow-growing, low tumour burden)

Guideline	**ENETS**	**ESMO**	**NCCN**	**ASCO**
1st line	**SSAs[a]**	**SSAs[a]**	Observation/**SSAs**	**SSAs[a]**
Progression?	MTAs/PRRT	Chemo/MTAs	MTAs/PRRT/Chemo[b]	PRRT/Chemo/MTAs
Progression?	Chemo	PRRT		

G1-G2 pNETs (SSTR-positive)

Unfavourable phenotype

1st line	**Chemo**	**Chemo** (MTAs)	MTAs/PRRT/Chemo[b]	**Chemo** (PRRT/MTAs[c])
Progression?	MTAs/PRRT	PRRT		

Note: Of the major guidelines, only ENETS specify therapy sequencing for unfavorable phenotypes. ASCO prefer chemotherapy, while ESMO recommend chemotherapy for bulky disease without prior progression and reserve PRRT for use after approved therapies fail.

Figure 2. Variability in guideline recommendations for the management of advanced G1-G2 somatostatin receptor-positive pNETs across disease course. Note: For somatostatin receptor-negative tumours (not shown), therapies such as SSAs and PRRT are not applicable. However, the overall treatment algorithm remains similar and is still guided by clinical phenotype. Abbreviations: SSAs—somatostatin analogues; SSTR—somatostatin receptor; MTAs—multitarget agents; PRRT—peptide-receptor radionuclide therapy; chemo—chemotherapy; ENETS—European Neuroendocrine Tumour Society; ESMO—European Society for Medical Oncology; NCCN—National Comprehensive Cancer Network; ASCO—American Society of Clinical Oncology. [a]Preferably for Ki-67 < 10%. [b]Including platinum-based chemotherapy. [c]For patients ineligible for chemotherapy, PRRT and multitarget agents are recommended.

sequencing algorithm unlikely and emphasize the importance of flexibility in applying guidelines to individual patient contexts. Nonetheless, drawing from multiple international guidelines, Figure 3 presents a proposed treatment algorithm for advanced pNETs.

To date, no randomized trial has definitively established the optimal sequencing of therapies in pNENs. The SEQTOR trial initially set out to compare everolimus followed by STZ/5-FU versus the reverse sequence, but slow enrolment shifted the focus to a direct comparison of first-line treatments [210]. PFS was similar between the two arms. However, first-line STZ/5-FU achieved a significantly higher overall response rate than everolimus (30% versus 11%), indicating greater antitumour activity. Other large prospective comparative studies are underway, including the COMPOSE trial (NCT04919226; comparing PRRT with either chemotherapy or everolimus) and the COMPETE trial (NCT03049189; PRRT versus everolimus), though neither is designed to evaluate treatment sequencing.

Beyond the lack of trial data, biological complexity further challenges sequencing decisions. Possible intrapatient tumour heterogeneity, particularly the emergence of clones lacking treatment targets like SSTRs, also complicates sequencing by limiting the applicability of certain therapies and negatively impacting prognosis [211].

6.2.2.2. Treatment sequencing beyond efficacy. While disease biology and therapeutic efficacy currently guide sequencing decisions, safety and tolerability data remain essential to tailoring treatment. A recent review of clinical trial data outlines the safety profiles of available therapies in advanced NENs, providing useful context for clinical decisions [212]. Despite therapeutic advances, many patients continue to experience significant symptom burden [213]. Given the chronicity of many therapies and the often indolent disease course, patient-reported outcomes (PROs), quality of life (QoL) and treatment-related toxicities are becoming central considerations in the systemic management of pNENs. PRRT and SSAs are typically associated with improved global QoL, particularly through effective symptom control. PRRT also demonstrate significant improvements in several QoL domains according to some randomized trials (like NETTER-1); however, they carry a risk of long-term haematologic toxicity, including myelodysplastic syndromes, which must be weighed in decision-making, especially in patients with risk factors for cytopenias or prior myelotoxic therapy [173,214,215].

Targeted therapies (e.g. everolimus and sunitinib) may prolong PFS but are associated with adverse effects like hyperglycaemia, diarrhoea and hypertension. These may all negatively impact QoL.

Step	Decision point		Recommended action
1	Confirm diagnosis: Well-differentiated pNET, metastatic/unresectable		Assess grade (G1-G3), Ki-67, SSTR status, symptoms, tumour burden
2	Assess comorbidities, patient preference, MDT input		Individualize therapy, consider QoL, toxicity, shared decision-making
A	Low tumour burden, slow progression	SSTR-positive	SSAs (octreotide or lanreotide)
		SSTR-negative	MTAs (everolimus or sunitinib)
B	Intermediate tumour burden/progression		Consider MTAs (everolimus or sunitinib)
C	High tumour burden, rapid progression, symptomatic		Initiate cytotoxic chemotherapy (CAPTEM or STZ-5FU)
D	SSTR-positive, progression after SSAs/MTAs/chemotherapy		Consider PRRT
E	Reassess at progression		Sequence next-line therapy based on prior response, toxicity, and patient factors

Figure 3. Proposed decision-making framework for systemic treatment of advanced pNETs. Abbreviations: pNET—pancreatic neuroendocrine tumour; SSTR—somatostatin receptor; MDT—multidisciplinary team; QoL—quality of life; SSAs—somatostatin analogues; MTAs—multitarget agents; CAPTEM—capecitabine/temozolamide; STZ–5-FU—streptozocin/5-fluorouracil; PRRT—peptide-receptor radionuclide therapy.

Chemotherapy regimens, including CAPTEM, offer higher response rates in selected patients but are linked to increased grade 3–4 toxicities, necessitating careful patient selection and monitoring [173,213,214,216].

The American Society for Clinical Oncology emphasizes that shared decision-making, incorporating patient preferences, comorbidities and anticipated impact on QoL, is essential in therapy selection for pNENs. PROs and QoL data should be routinely integrated into clinical discussions, as they directly inform the balance between efficacy and tolerability, especially in the context of multiple treatment possibilities and the need for chronic therapy [173,213]. Recent literature further highlights the importance of open patient–clinician communication and the use of standardized QoL assessments to optimize patient-centred care [216–218].

6.2.3. The future is molecular: advancing personalized therapy

Despite advances in NGS, pNEN management still relies primarily on histologic differentiation and the Ki-67 index. Molecular profiling remains underutilized, and most clinical trials lack genomic stratification—for example, everolimus studies often disregard mTOR pathway mutations, while antiangiogenic trials rarely account for the upregulation of angiogenic factors [21]. Nonetheless, NGS enables comprehensive detection of somatic mutations (e.g. DAXX, MEN1, mTOR, ATRX) and rare actionable alterations (FGFR3, HER2/Neu amplifications, FTRK fusions). Such information could help predict prognosis and guide therapy selection. Loss of DAXX/ATRX, for example, may indicate worse prognosis and thus potentially propagate more intensive therapy [21,219]. Molecular markers may also guide decisions such as selecting small pNETs that warrant resection or tailoring surveillance based on individual risk.

Currently, SSTR expression is the only clinically established predictive biomarker for therapy selection in pNENs, guiding eligibility for PRRT. Further advances in NGS may soon identify molecular subgroups with enhanced response or resistance to PRRT [220–224]. There is also emerging evidence that methylguanine methyltransferase (MGMT) deficiency may predict response to TEM-based chemotherapy [173,225]. In addition, converging pathways appear to drive pNEN progression, raising opportunities to target shared regulatory nodes with combination therapies that may reduce toxicity and resistance [18]. In the near future, NGS could influence selection of therapy by identifying specific mutations for targeted therapies and integrating them with functional imaging or histopathology to optimize patient-centred treatment [221,226]. Broader patient representation in clinical trials and greater collaboration across institutions will be essential for translating molecular insights into effective precision therapies.

6.2.4. The complexity of managing advanced functional neoplasms

Managing advanced unresectable F-pNENs involves the dual challenge of controlling tumour growth and hormonal symptoms [227]. Comprehensive evaluation of the functioning syndrome, along with patient and tumour characteristics, guides therapy selection, as many treatments impact both hormone production and tumour proliferation [68,228]. However, while some antitumour treatments effectively target tumour growth, they may not sufficiently control hormone excess, necessitating combination therapies for optimal management [229].

The management of advanced F-pNENs typically starts with hormonal control, with SSAs as the first-line therapy. SSAs are usually maintained throughout the disease course, even in cases of tumour progression and can be combined with supportive measures to manage symptoms [187]. However, caution is required in insulinomas, where SSAs may worsen hypoglycaemia. Instead dietary modifications, diazoxide or everolimus are preferred alternatives [50,228]. For gastrinomas, high-dose PPIs effectively control acid hypersecretion, while SSAs can reduce gastrin levels and provide antiproliferative effects when needed [68].

For controlling tumour growth, SSAs are also commonly used as a first-line option, particularly in slowly progressive, low-proliferative, well-differentiated F-pNETs [50]. If patients progress on SSAs, have negative SSTR expression or present with more aggressive disease, alternative systemic therapies such as PRRT, targeted treatments or chemotherapy may be employed [187].

7. Conclusions and future directions

pNENs are a diverse group of tumours that demand personalized management within a multidisciplinary framework. Advances in classification, imaging and therapies have improved outcomes, yet major challenges remain, particularly in managing small non-functional tumours, advanced-stage disease and defining optimal treatment sequencing.

Imaging continues to play a central role in pNEN evaluation. Standardized use of morphological and functional imaging, along with emerging tools like radiomics, holds promise for improving diagnosis, grading and treatment planning. However, clinical adoption of radiomics requires further validation and harmonization across imaging protocols.

The optimal management of small NF-pNETs remains controversial. Improved risk stratification is needed to guide treatment decisions and define surveillance protocols, while minimally invasive options like EUS-guided ablation warrant further investigation. In advanced disease, the roles of neoadjuvant and liver-directed treatments remain incompletely defined, while the sequencing of systemic therapies continues to lack robust evidence. Future trials should prioritize comparative data and incorporate PROs to better support personalized care.

Despite advances in genomics, molecular profiling remains underutilized in clinical practice and trial design. Integrating molecular and imaging biomarkers may enhance risk prediction, therapy selection and surveillance strategies. Expanding clinical trial diversity and fostering multicentre collaboration will be critical to translating these insights into routine precision care.

Authors contributions

CRediT: **Lara Mastnak**: Data curation, Formal analysis, Writing – original draft, Writing – review & editing; **David Badovinac**: Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

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References

[1] Wang R, Zheng-Pywell R, Chen HA, et al. Management of gastrointestinal neuroendocrine tumors. Clin Med Insights Endocrinol Diabetes. 2019;12:1179551419884058. doi: 10.1177/1179551419884058.
[2] Schott M, Klöppel G, Raffel A, et al. Neuroendocrine neoplasms of the gastrointestinal tract. Dtsch Arztebl Int. 2011;108(18):305–312. PMID: 21629514. doi: 10.3238/arztebl.2011.0305.
[3] Oronsky B, Ma PC, Morgensztern D, et al. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia. 2017;19(12):991–1002. doi: 10.1016/j.neo.2017.09.002.
[4] Yang Z, Tang LH, Klimstra DS. Gastroenteropancreatic neuroendocrine neoplasms: historical context and current issues. Semin Diagn Pathol. 2013;30(3):186–196. doi: 10.1053/j.semdp.2013.06.005.
[5] Pinchot SN, Holen K, Sippel RS, et al. Carcinoid tumors. Oncologist. 2008;13(12):1255–1269. doi: 10.1634/theoncologist.2008-0207.

[6] Vogele D, Schmidt SA, Gnutzmann D, et al. Gastroenteropancreatic neuroendocrine tumors—current status and advances in diagnostic imaging. Diagnostics. 2023;13(17):2741. doi: 10.3390/diagnostics13172741.
[7] Takayanagi D, Cho H, Machida E, et al. Update on epidemiology, diagnosis, and biomarkers in gastroenteropancreatic neuroendocrine neoplasms. Cancers. 2022;14(5):1119. doi: 10.3390/cancers14051119.
[8] Das S, Dasari A. Epidemiology, incidence, and prevalence of neuroendocrine neoplasms: are there global differences? Curr Oncol Rep. 2021;23(4):43. doi: 10.1007/s11912-021-01029-7.
[9] Ishida H, Lam AK. Pancreatic neuroendocrine neoplasms: updates on genomic changes in inherited tumour syndromes and sporadic tumours based on WHO classification. Crit Rev Oncol Hematol. 2022;172:103648. doi: 10.1016/j.critrevonc.2022.103648.
[10] Sonbol MB, Mazza GL, Mi L, et al. Survival and incidence patterns of pancreatic neuroendocrine tumors over the last 2 decades: a SEER database analysis. Oncologist. 2022;27(7):573–578. doi: 10.1093/oncolo/oyac049.
[11] Mullen B, Sy AL, Dias Goncalves P, et al. Navigating the diagnostic gray zone: a challenging case of pancreatic high-grade neuroendocrine neoplasm. Diagn Pathol. 2024;19(1):123. doi: 10.1186/s13000-024-01546-6.
[12] Maluchenko A, Maksimov D, Antysheva Z, et al. Molecular basis of pancreatic neuroendocrine tumors. Int J Mol Sci. 2024;25(20):11017. doi: 10.3390/ijms252011017.
[13] Cloyd JM, Poultsides GA. The landmark series: pancreatic neuroendocrine tumors. Ann Surg Oncol. 2021;28(2):1039–1049. doi: 10.1245/s10434-020-09133-x.
[14] Luo G, Javed A, Strosberg JR, et al. Modified staging classification for pancreatic neuroendocrine tumors on the basis of the American Joint Committee on Cancer and European Neuroendocrine Tumor Society Systems. J Clin Oncol. 2017;35(3):274–280. doi: 10.1200/JCO.2016.67.8193.
[15] Soczomski P, Jurecka-Lubieniecka B, Krzywon A, et al. A direct comparison of patients with hereditary and sporadic pancreatic neuroendocrine tumors: evaluation of clinical course, prognostic factors and genotype–phenotype correlations. Front Endocrinol. 2021;12:681013. doi: 10.3389/fendo.2021.681013.
[16] Haugvik SP, Hedenström P, Korsæth E, et al. Diabetes, smoking, alcohol use, and family history of cancer as risk factors for pancreatic neuroendocrine tumors: a systematic review and meta-analysis. Neuroendocrinology. 2015;101(2):133–142. doi: 10.1159/000375164.
[17] Bogaards M, May AM, Hassan FA, et al. Lifestyle factors and development and natural course of gastroenteropancreatic neuroendocrine tumors: a review of the literature. Neuroendocrinology. 2023;113(4):381–394. doi: 10.1159/000527741.
[18] Maharjan C, Ear P, Tran C, et al. Pancreatic neuroendocrine tumors: molecular mechanisms and therapeutic targets. Cancers. 2021;13(20):5117. doi: 10.3390/cancers13205117.
[19] Shen X, Wang X, Lu X, et al. Molecular biology of pancreatic neuroendocrine tumors: from mechanism to translation. Front Oncol. 2022;12:967071. doi: 10.3389/fonc.2022.967071.
[20] Mafficini A, Scarpa A. Genomic landscape of pancreatic neuroendocrine tumours: the International Cancer Genome Consortium. J Endocrinol. 2018;236(3):R161–R167. doi: 10.1530/JOE-17-0560.
[21] Chatani PD, Agarwal SK, Sadowski SM. Molecular signatures and their clinical utility in pancreatic neuroendocrine tumors. Front Endocrinol. 2020;11:575620. doi: 10.3389/fendo.2020.575620.
[22] Singhi AD, Liu TC, Roncaioli JL, et al. Alternative lengthening of telomeres and loss of DAXX/ATRX expression predicts metastatic disease and poor survival in patients with pancreatic neuroendocrine tumors. Clin Cancer Res. 2017;23(2):600–609. doi: 10.1158/1078-0432.CCR-16-1113.
[23] Marinoni I, Kurrer AS, Vassella E, et al. Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors. Gastroenterology. 2014;146(2):453–460. e5. doi: 10.1053/j.gastro.2013.10.020.
[24] Segaran N, Devine C, Wang M, et al. Current update on imaging for pancreatic neuroendocrine neoplasms. World J Clin Oncol. 2021;12(10):897–911. doi: 10.5306/wjco.v12.i10.897.
[25] Papadopoulou-Marketou N, Tsoli M, Chatzellis E, et al. Hereditary syndromes associated with pancreatic and lung neuroendocrine tumors. Cancers. 2024;16(11):2075. doi: 10.3390/cancers16112075.
[26] Kamilaris CDC, Stratakis CA. Multiple endocrine neoplasia type 1 (MEN1): an update and the significance of early genetic and clinical diagnosis. Front Endocrinol. 2019;10:339. doi: 10.3389/fendo.2019.00339.
[27] Lam AK, Ishida H. Pancreatic neuroendocrine neoplasms: clinicopathological features and pathological staging. Histol Histopathol. 2021;36(4):367–382. doi: 10.14670/HH-18-288.
[28] Geurts JL. Inherited syndromes involving pancreatic neuroendocrine tumors. J Gastrointest Oncol. 2020;11(3):559–566. doi: 10.21037/jgo.2020.03.09.
[29] Massironi S, Rossi RE, Laffusa A, et al. Sporadic and MEN1-related gastrinoma and Zollinger–Ellison syndrome: differences in clinical characteristics and survival outcomes. J Endocrinol Invest. 2023;46(5):957–965. doi: 10.1007/s40618-022-01961-w.
[30] Yang M, Zhang Y, Zeng L, et al. Survivals of patients with surgically treated and high-grade pancreatic neuroendocrine carcinomas: a comparative study between two American Joint Committee on Cancer 8th tumor-node-metastasis staging systems. Eur J Surg Oncol. 2019;45(6):1054–1060. doi: 10.1016/j.ejso.2019.01.010.
[31] Shyr BS, Shyr BU, Chen SC, et al. Impact of tumor grade on pancreatic neuroendocrine tumors. Asian J Surg. 2022;45(12):2659–2663. doi: 10.1016/j.asjsur.2022.01.094.
[32] Cives M, Strosberg JR. Gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin. 2018;68(6):471–487. doi: 10.3322/caac.21493.

[33] Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms. Endocr Pathol. 2022;33(1):115–154. doi: 10.1007/s12022-022-09708-2.
[34] WHO Classification of Tumours Editorial Board. WHO classification of endocrine and neuroendocrine tumours. Lyon (France): IARC; 2022.
[35] Basturk O, Yang Z, Tang LH, et al. The high grade (Who G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogeneous and includes both well differentiated and poorly differentiated neoplasms. Am J Surg Pathol. 2015;39(5):683–690. doi: 10.1097/PAS.0000000000000408.
[36] Hijioka S, Hosoda W, Mizuno N, et al. Does the WHO 2010 classification of pancreatic neuroendocrine neoplasms accurately characterize pancreatic neuroendocrine carcinomas? J Gastroenterol. 2015;50(5):564–572. doi: 10.1007/s00535-014-0987-2.
[37] Taskin OC, Clarke CN, Erkan M, et al. Pancreatic neuroendocrine neoplasms: current state and ongoing controversies on terminology, classification and prognostication. J Gastrointest Oncol. 2020;11(3):548–558. doi: 10.21037/jgo.2020.03.07.
[38] Fang JM, Shi J. A clinicopathologic and molecular update of pancreatic neuroendocrine neoplasms with a focus on the new World Health Organization classification. Arch Pathol Lab Med. 2019;143(11):1317–1326. doi: 10.5858/arpa.2019-0338-RA.
[39] Pellat A, Coriat R. Well differentiated grade 3 neuroendocrine tumors of the digestive tract: a narrative review. J Clin Med. 2020;9(6):1677. doi: 10.3390/jcm9061677.
[40] Fang JM, Li J, Shi J. An update on the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. World J Gastroenterol. 2022;28(10):1009–1023. doi: 10.3748/wjg.v28.i10.1009.
[41] Wang F, Lou X, Qin Y, et al. Mixed neuroendocrine nonneuroendocrine neoplasms of the pancreas: a case report and literature review of pancreatic mixed neuroendocrine nonneuroendocrine neoplasm. Gland Surg. 2021;10(12):3443–3452. doi: 10.21037/gs-21-564.
[42] Baía CAQ, Sousa A, Sousa F, et al. Unexpected pancreatic mixed neuroendocrine-nonneuroendocrine neoplasms (MiNEN)—reflection on a case report. J Surg Case Rep. 2024;2024(2):rjae026. doi: 10.1093/jscr/rjae026.
[43] Yang M, Ke NW, Zhang Y, et al. Functional and non-functional pancreatic neuroendocrine tumours: ENETS or AJCC TNM staging system? Oncotarget. 2017;8(47):82784–82795. doi: 10.18632/oncotarget.20007.
[44] Chauhan A, Chan K, Halfdanarson TR, et al. Critical updates in neuroendocrine tumors: version 9 American Joint Committee on Cancer staging system for gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin. 2024;74(4):359–367. doi: 10.3322/caac.21840.
[45] Brierley JD, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. 8th ed. Oxford: Wiley Blackwell; 2017.
[46] Amin MB, Edge SB, Greene FL, et al. editors. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.
[47] Yan J, Yu S, Jia C, et al. Molecular subtyping in pancreatic neuroendocrine neoplasms: new insights into clinical, pathological unmet needs and challenges. Biochim Biophys Acta Rev Cancer. 2020;1874(1):188367. doi: 10.1016/j.bbcan.2020.188367.
[48] Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology. 2008;135(5):1469–1492. doi: 10.1053/j.gastro.2008.05.047.
[49] Cloyd JM, Poultsides GA. Non-functional neuroendocrine tumors of the pancreas: advances in diagnosis and management. World J Gastroenterol. 2015;21(32):9512–9525. doi: 10.3748/wjg.v21.i32.9512.
[50] Magi L, Marasco M, Rinzivillo M, et al. Management of functional pancreatic neuroendocrine neoplasms. Curr Treat Options Oncol. 2023;24(7):725–741. doi: 10.1007/s11864-023-01085-0.
[51] Albers MB, Sevcik M, Wiese D, et al. Characteristics, therapy, and outcome of rare functioning pancreatic neuroendocrine neoplasms. Sci Rep. 2024;14(1):18507. doi: 10.1038/s41598-024-68290-1.
[52] Okabayashi T, Shima Y, Sumiyoshi T, et al. Diagnosis and management of insulinoma. World J Gastroenterol. 2013;19(6):829–837. doi: 10.3748/wjg.v19.i6.829.
[53] Hofland J, Refardt JC, Feelders RA, et al. Approach to the patient: insulinoma. J Clin Endocrinol Metab. 2024;109(4):1109–1118. doi: 10.1210/clinem/dgad641.
[54] Giannis D, Moris D, Karachaliou GS, et al. Insulinomas: from diagnosis to treatment. A review of the literature. J BUON. 2020;25(3):1302–1314.
[55] Anderson CW, Bennett JJ. Clinical presentation and diagnosis of pancreatic neuroendocrine tumors. Surg Oncol Clin N Am. 2016;25(2):363–374. doi: 10.1016/j.soc.2015.12.003.
[56] Rossi RE, Elvevi A, Citterio D, et al. Gastrinoma and Zollinger Ellison syndrome: a roadmap for the management between new and old therapies. World J Gastroenterol. 2021;27(35):5890–5907. doi: 10.3748/wjg.v27.i35.5890.
[57] Song X, Zheng S, Yang G, et al. Glucagonoma and the glucagonoma syndrome (review). Oncol Lett. 2018;15(3):2749–2755. doi: 10.3892/ol.2017.7703.
[58] Wu S, Bai J, Xu J, et al. Necrolytic migratory erythema as the first manifestation of pancreatic neuroendocrine tumor. World J Surg Oncol. 2014;12(1):220. doi: 10.1186/1477-7819-12-220.
[59] Abdullayeva L. VIPoma: mechanisms, clinical presentation, diagnosis and treatment (review). World Acad Sci J. 2019;1:229–235. doi: 10.3892/wasj.2019.22.
[60] Williamson J, Thorn C, Spalding D, et al. Pancreatic and peripancreatic somatostatinomas. Ann R Coll Surg Engl. 2011;93(5):356–360. doi: 10.1308/003588411X582681.

[61] Bevere M, Gkountakos A, Martelli FM, et al. An insight on functioning pancreatic neuroendocrine neoplasms. Biomedicines. 2023;11(2):303. doi: 10.3390/biomedicines11020303.
[62] Cuthbertson DJ, Shankland R, Srirajaskanthan R. Diagnosis and management of neuroendocrine tumours. Clin Med. 2023;23(2):119–124. doi: 10.7861/clinmed.2023-0044.
[63] Bocchini M, Nicolini F, Severi S, et al. Biomarkers for pancreatic neuroendocrine neoplasms (PanNENs) management—an updated review. Front Oncol. 2020;10:831. doi: 10.3389/fonc.2020.00831.
[64] Guo X, Gao S, Li Z, et al. The role of biomarker in pancreatic neuroendocrine tumor: a narrative review. J Pancreatol. 2021;4(3):122–129. doi: 10.1097/JP9.0000000000000076.
[65] Franchina M, Cavalcoli F, Falco O, et al. Biochemical markers for neuroendocrine tumors: traditional circulating markers and recent development—a comprehensive review. Diagnostics. 2024;14(12):1289. doi: 10.3390/diagnostics14121289.
[66] Pulvirenti A, Rao D, Mcintyre CA, et al. Limited role of chromogranin A as clinical biomarker for pancreatic neuroendocrine tumors. HPB. 2019;21(5):612–618. doi: 10.1016/j.hpb.2018.09.016.
[67] Zyromski NJ, Lewellen KA, Maatman TK, et al. Circulating chromogranin A is associated with disease extent, progression and recurrence in patients with non-functioning pancreatic neuroendocrine tumor (NF-PNET). Pancreas. 2025;54(4):e281–e286. doi: 10.1097/MPA.0000000000002428.
[68] Kos-Kudła B, Castaño JP, Denecke T, et al. European Neuroendocrine Tumour Society (ENETS) 2023 guidance paper for nonfunctioning pancreatic neuroendocrine tumours. J Neuroendocrinol. 2023;35(12):e13343. doi: 10.1111/jne.13343.
[69] Ma ZY, Gong YF, Zhuang HK, et al. Pancreatic neuroendocrine tumors: a review of serum biomarkers, staging, and management. World J Gastroenterol. 2020;26(19):2305–2322. doi: 10.3748/wjg.v26.i19.2305.
[70] Rossi RE, La Salvia A. NETest and gastro-entero-pancreatic neuroendocrine tumors: still far from routine clinical application? A systematic review. Genes. 2025;16(2):161. doi: 10.3390/genes16020161.
[71] Komarnicki P, Musiałkiewicz J, Stańska A, et al. Circulating neuroendocrine tumor biomarkers: past, present and future. J Clin Med. 2022;11(19):5542. doi: 10.3390/jcm11195542.
[72] Sundin A, Arnold R, Baudin E, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine and hybrid imaging. Neuroendocrinology. 2017;105(3):212–244. doi: 10.1159/000471879.
[73] Tamm EP, Bhosale P, Lee JH, et al. State-of-the-art imaging of pancreatic neuroendocrine tumors. Surg Oncol Clin N Am. 2016;25(2):375–400. doi: 10.1016/j.soc.2015.11.007.
[74] Melita G, Pallio S, Tortora A, et al. Diagnostic and interventional role of endoscopic ultrasonography for the management of pancreatic neuroendocrine neoplasms. J Clin Med. 2021;10(12):2638. doi: 10.3390/jcm10122638.
[75] James PD, Tsolakis AV, Zhang M, et al. Incremental benefit of preoperative EUS for the detection of pancreatic neuroendocrine tumors: a meta-analysis. Gastrointest Endosc. 2015;81(4):848–856.e1. doi: 10.1016/j.gie.2014.12.031.
[76] Crinò SF, Ammendola S, Meneghetti A, et al. Comparison between EUS-guided fine-needle aspiration cytology and EUS-guided fine-needle biopsy histology for the evaluation of pancreatic neuroendocrine tumors. Pancreatology. 2021;21(2):443–450. doi: 10.1016/j.pan.2020.12.015.
[77] Leeds JS, Nayar MK, Bekkali NLH, et al. Endoscopic ultrasound-guided fine-needle biopsy is superior to fine-needle aspiration in assessing pancreatic neuroendocrine tumors. Endosc Int Open. 2019;7(10):E1281–E1287. doi: 10.1055/a-0990-9611.
[78] Pellegrino F, Granata V, Fusco R, et al. Diagnostic management of gastroenteropancreatic neuroendocrine neoplasms: technique optimization and tips and tricks for radiologists. Tomography. 2023;9(1):217–246. doi: 10.3390/tomography9010018.
[79] Baur AD, Pavel M, Prasad V, et al. Diagnostic imaging of pancreatic neuroendocrine neoplasms (pNEN): tumor detection, staging, prognosis, and response to treatment. Acta Radiol. 2016;57(3):260–270. doi: 10.1177/0284185115579932.
[80] Chiti G, Grazzini G, Cozzi D, et al. Imaging of pancreatic neuroendocrine neoplasms. Int J Environ Res Public Health. 2021;18(17):8895. doi: 10.3390/ijerph18178895.
[81] Hu Y, Ye Z, Wang F, et al. Role of somatostatin receptor in pancreatic neuroendocrine tumor development, diagnosis, and therapy. Front Endocrinol. 2021;12:679000. doi: 10.3389/fendo.2021.679000.
[82] Prosperi D, Gentiloni Silveri G, Panzuto F, et al. Nuclear medicine and radiological imaging of pancreatic neuroendocrine neoplasms: a multidisciplinary update. J Clin Med. 2022;11(22):6836. doi: 10.3390/jcm11226836.
[83] Dromain C, Déandréis D, Scoazec JY, et al. Imaging of neuroendocrine tumors of the pancreas. Diagn Interv Imaging. 2016;97(12):1241–1257. doi: 10.1016/j.diii.2016.07.012.
[84] Bauckneht M, Albano D, Annunziata S, et al. Somatostatin receptor PET/CT imaging for the detection and staging of pancreatic NET: a systematic review and meta-analysis. Diagnostics. 2020;10(8):598. doi: 10.3390/diagnostics10080598.
[85] Ebner R, Sheikh GT, Brendel M, et al. ESR essentials: role of PET/CT in neuroendocrine tumors—practice recommendations by the European Society for Hybrid, Molecular and Translational Imaging. Eur Radiol. 2025;35(4):1903–1912. doi: 10.1007/s00330-024-11095-7.

[86] Hofland J, Falconi M, Christ E, et al. European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. J Neuroendocrinol. 2023;35(8):e13318. doi: 10.1111/jne.13318.
[87] Hope TA, Bergsland EK, Bozkurt MF, et al. Appropriate use criteria for somatostatin receptor PET imaging in neuroendocrine tumors. J Nucl Med. 2018;59(1):66–74. doi: 10.2967/jnumed.117.202275.
[88] Koffas A, Giakoustidis A, Papaefthymiou A, et al. Diagnostic work-up and advancement in the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. Front Surg. 2023;10:1064145. doi: 10.3389/fsurg.2023.1064145.
[89] Casey M, Tozzi F, Wang J, et al. Appropriate use of tissue sampling and somatostatin receptor PET imaging in the diagnosis of pancreatic neuroendocrine tumors: results of an International Delphi Consensus. Surg Endosc. 2025;39(6):3435–3446. doi: 10.1007/s00464-025-11667-8.
[90] Konukiewitz B, Jesinghaus M, Kasajima A, et al. Neuroendocrine neoplasms of the pancreas: diagnosis and pitfalls. Virchows Arch. 2022;480(2):247–257. doi: 10.1007/s00428-021-03211-5.
[91] Wang X, Qiu JJ, Tan CL, et al. Development and validation of a novel radiomics-based nomogram with machine learning to preoperatively predict histologic grade in pancreatic neuroendocrine tumors. Front Oncol. 2022;12:843376. doi: 10.3389/fonc.2022.843376.
[92] McCague C, Ramlee S, Reinius M, et al. Introduction to radiomics for a clinical audience. Clin Radiol. 2023;78(2):83–98. doi: 10.1016/j.crad.2022.08.149.
[93] Gu D, Hu Y, Ding H, et al. CT radiomics may predict the grade of pancreatic neuroendocrine tumors: a multicenter study. Eur Radiol. 2019;29(12):6880–6890. doi: 10.1007/s00330-019-06176-x.
[94] Bian Y, Jiang H, Ma C, et al. CT-based radiomics score for distinguishing between grade 1 and grade 2 nonfunctioning pancreatic neuroendocrine tumors. AJR Am J Roentgenol. 2020;215(4):852–863. doi: 10.2214/AJR.19.22123.
[95] Ye JY, Fang P, Peng ZP, et al. A radiomics-based interpretable model to predict the pathological grade of pancreatic neuroendocrine tumors. Eur Radiol. 2024;34(3):1994–2005. doi: 10.1007/s00330-023-10186-1.
[96] Lopez-Ramirez F, Soleimani S, Azadi JR, et al. Radiomics machine learning algorithm facilitates detection of small pancreatic neuroendocrine tumors on CT. Diagn Interv Imaging. 2025;106(1):28–40. doi: 10.1016/j.diii.2024.08.003.
[97] Javed AA, Zhu Z, Kinny-Köster B, et al. Accurate non-invasive grading of nonfunctional pancreatic neuroendocrine tumors with a CT derived radiomics signature. Diagn Interv Imaging. 2024;105(1):33–39. doi: 10.1016/j.diii.2023.08.002.
[98] Tixier F, Lopez-Ramirez F, Blanco A, et al. CT image reconstruction parameters impact the predictive value of radiomics features in grading pancreatic neuroendocrine neoplasms? Bioengineering. 2025;12(1):80. doi: 10.3390/bioengineering12010080.
[99] Mali SA, Ibrahim A, Woodruff HC, et al. Making radiomics more reproducible across scanner and imaging protocol variations: a review of harmonization methods. J Pers Med. 2021;11(9):842. doi: 10.3390/jpm11090842.
[100] Haarburger C, Müller-Franzes G, Weninger L, et al. Radiomics feature reproducibility under inter-rater variability in segmentations of CT images. Sci Rep. 2020;10(1):12688. doi: 10.1038/s41598-020-69534-6.
[101] Bezzi C, Mapelli P, Presotto L, et al. Radiomics in pancreatic neuroendocrine tumors: methodological issues and clinical significance. Eur J Nucl Med Mol Imaging. 2021;48(12):4002–4015. doi: 10.1007/s00259-021-05338-8.
[102] Sulciner ML, Clancy TE. Surgical management of pancreatic neuroendocrine tumors. Cancers. 2023;15(7):2006. doi: 10.3390/cancers15072006.
[103] Pavel M, Öberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(7):844–860. doi: 10.1016/j.annonc.2020.03.304.
[104] Bergsland E, Rose JB, Benson AB, et al. Neuroendocrine and adrenal tumors, version 2.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2024; https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
[105] Halfdanarson TR, Strosberg JR, Tang L, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical management of pancreatic neuroendocrine tumors. Pancreas. 2020;49(7):863–881. doi: 10.1097/MPA.0000000000001597.
[106] Ito T, Masui T, Komoto I, et al. JNETS clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms: diagnosis, treatment, and follow-up: a synopsis. J Gastroenterol. 2021;56(11):1033–1044. doi: 10.1007/s00535-021-01827-7.
[107] Wu W, Chen J, Bai C, et al. The Chinese guidelines for the diagnosis and treatment of pancreatic neuroendocrine neoplasms (2020). J Pancreatol. 2021;4(1):1–17. doi: 10.1097/JP9.0000000000000064.
[108] Kartik A, Armstrong VL, Stucky CC, et al. Contemporary approaches to the surgical management of pancreatic neuroendocrine tumors. Cancers. 2024;16(8):1501. doi: 10.3390/cancers16081501.
[109] Liu JB, Baker MS. Surgical management of pancreatic neuroendocrine tumors. Surg Clin North Am. 2016;96(6):1447–1468. doi: 10.1016/j.suc.2016.07.002.
[110] Kulke MH, Bendell J, Kvols L, et al. Evolving diagnostic and treatment strategies for pancreatic neuroendocrine tumors. J Hematol Oncol. 2011;4(1):29. doi: 10.1186/1756-8722-4-29.

[111] Hirshberg B, Libutti SK, Alexander RH, et al. Blind distal pancreatectomy for occult insulinoma, an inadvisable procedure. J Am Coll Surg. 2002;194(6):761–764. doi: 10.1016/S1072-7515(02)01177-8.
[112] Dąbkowski K, Starzyńska T. Management of small, asymptomatic, non-functioning pancreatic neuroendocrine tumours: follow-up, ablation, or surgery? Endokrynol Pol. 2023;74(1):25–30. doi: 10.5603/EP.a2022.0080.
[113] Paik W, Lee K. Management of Small Nonfunctioning Pancreatic Neuroendocrine Neoplasms: Current Opinion And Controversies. J Clin Med. 2022;12(1):251. doi: 10.3390/jcm12010251.
[114] Hain E, Sindayigaya R, Fawaz J, et al. Surgical management of pancreatic neuroendocrine tumors: an introduction. Expert Rev Anticancer Ther. 2019;19(12):1089–1100. doi: 10.1080/14737140.2019.1703677.
[115] Partelli S, Cirocchi R, Crippa S, et al. Systematic review of active surveillance *versus* surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms. Br J Surg. 2017;104(1):34–41. doi: 10.1002/bjs.10312.
[116] Sallinen V, Le Large TYS, Galeev S, et al. Surveillance strategy for small asymptomatic non-functional pancreatic neuroendocrine tumors—a systematic review and meta-analysis. HPB. 2017;19(4):310–320. doi: 10.1016/j.hpb.2016.12.010.
[117] Vega EA, Kutlu OC, Alarcon SV, et al. Clinical prognosticators of metastatic potential in patients with small pancreatic neuroendocrine tumors. J Gastrointest Surg. 2021;25(10):2593–2599. doi: 10.1007/s11605-021-04946-x.
[118] Finkelstein P, Sharma R, Picado O, et al. Pancreatic neuroendocrine tumors (panNETs): analysis of overall survival of nonsurgical management versus surgical resection. J Gastrointest Surg. 2017;21(5):855–866. doi: 10.1007/s11605-017-3365-6.
[119] Kuo EJ, Salem RR. Population-level analysis of pancreatic neuroendocrine tumors 2 cm or less in size. Ann Surg Oncol. 2013;20(9):2815–2821. doi: 10.1245/s10434-013-3005-7.
[120] Chivukula SV, Tierney JF, Hertl M, et al. Operative resection in early stage pancreatic neuroendocrine tumors in the United States: are we over- or undertreating patients? Surgery. 2020;167(1):180–186. doi: 10.1016/j.surg.2019.04.061.
[121] Partelli S, Muffatti F, Andreasi V, et al. A single-center prospective observational study investigating the accuracy of preoperative diagnostic procedures in the assessment of lymph node metastases in nonfunctioning pancreatic neuroendocrine tumors. Ann Surg. 2022;276(5):921–928. doi: 10.1097/SLA.0000000000005615.
[122] Ye J, Wu H, Li J, et al. Impact of surgery on non-functional pancreatic neuroendocrine tumors ≤2 cm: analyses with propensity score–based inverse probability of treatment weighting. Front Surg. 2022;9:890564. doi: 10.3389/fsurg.2022.890564.
[123] Assi HA, Mukherjee S, Kunz PL, et al. Surgery versus surveillance for well-differentiated, nonfunctional pancreatic neuroendocrine tumors: an 11-year analysis of the National Cancer Database. Oncologist. 2020;25(2):e276–e283. doi: 10.1634/theoncologist.2019-0466.
[124] Perinel J, Nappo G, Zerbi A, et al. Sporadic nonfunctional pancreatic neuroendocrine tumors: risk of lymph node metastases and aggressiveness according to tumor size: a multicenter international study. Surgery. 2022;172(3):975–981. doi: 10.1016/j.surg.2022.04.013.
[125] Partelli S, Ramage JK, Massironi S, et al. Management of asymptomatic sporadic nonfunctioning pancreatic neuroendocrine neoplasms (ASPEN) ≤2 cm: study protocol for a prospective observational study. Front Med. 2020;7:598438. doi: 10.3389/fmed.2020.598438.
[126] Partelli S, Massironi S, Zerbi A, et al. Management of asymptomatic sporadic non-functioning pancreatic neuroendocrine neoplasms no larger than 2 cm: interim analysis of prospective ASPEN trial. Br J Surg. 2022;109(12):1186–1190. doi: 10.1093/bjs/znac267.
[127] Yang Z, Zhang D, Shi G. Reappraisal of a 2-cm cutoff size for the management of nonfunctional pancreatic neuroendocrine tumors: a population-based study. Front Endocrinol. 2022;13:928341. doi: 10.3389/fendo.2022.928341.
[128] Hijioka S, Yamashige D, Esaki M, et al. Factors affecting nonfunctioning small pancreatic neuroendocrine neoplasms and proposed new treatment strategies. Clin Gastroenterol Hepatol. 2024;22(7):1416–1426.e5. doi: 10.1016/j.cgh.2024.03.029.
[129] Falconi M, Eriksson B, Kaltsas G, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology. 2016;103(2):153–171. doi: 10.1159/000443171.
[130] Borbon LC, Tran CG, Sherman SK, et al. Is there a role for surgical resection of grade 3 neuroendocrine neoplasms? Ann Surg Oncol. 2022;29(11):6936–6946. doi: 10.1245/s10434-022-12100-3.
[131] Yoshida T, Hijioka S, Hosoda W, et al. Surgery for pancreatic neuroendocrine tumor G3 and carcinoma G3 should be considered separately. Ann Surg Oncol. 2019;26(5):1385–1393. doi: 10.1245/s10434-019-07252-8.
[132] Yang M, Zeng L, Hou S, et al. Surgical outcomes, long-term survivals and staging systems of World Health Organization G3 pancreatic neuroendocrine tumors. J Clin Med. 2022;11(18):5253. doi: 10.3390/jcm11185253.
[133] Luo X, Yang M, Tian B, et al. Surgical outcomes and prognostic factors of G3 pancreatic neuroendocrine carcinomas: a consecutive analysis based on previous study results. J Clin Med. 2022;11(11):3176. doi: 10.3390/jcm11113176.

[134] Van Beek DJ, Van Den Heede K, Borel Rinkes I, et al. Surgery for advanced pancreatic neuroendocrine neoplasms: recommendations based on a consensus meeting of the European Society of Endocrine Surgeons (ESES). Br J Surg. 2024;111(2):znae017. doi: 10.1093/bjs/znae017.
[135] Jeune F, Taibi A, Gaujoux S. Update on the surgical treatment of pancreatic neuroendocrine tumors. Scand J Surg. 2020;109(1):42–52. doi: 10.1177/1457496919900417.
[136] Ferraro V, Tedeschi M, Laera L, et al. The role of laparoscopic surgery in localized pancreatic neuroendocrine tumours. Curr Treat Options Oncol. 2021;22(4):27. doi: 10.1007/s11864-021-00824-5.
[137] Heidsma CM, Tsilimigras DI, Van Dieren S, et al. Indications and outcomes of enucleation versus formal pancreatectomy for pancreatic neuroendocrine tumors. HPB. 2021;23(3):413–421. doi: 10.1016/j.hpb.2020.06.015.
[138] Cherif R, Gaujoux S, Couvelard A, et al. Parenchyma-sparing resections for pancreatic neuroendocrine tumors. J Gastrointest Surg. 2012;16(11):2045–2055. doi: 10.1007/s11605-012-2002-7.
[139] Hüttner FJ, Koessler-Ebs J, Hackert T, et al. Meta-analysis of surgical outcome after enucleation *versus* standard resection for pancreatic neoplasms. Br J Surg. 2015;102(9):1026–1036. doi: 10.1002/bjs.9819.
[140] Heeger K, Falconi M, Partelli S, et al. Increased rate of clinically relevant pancreatic fistula after deep enucleation of small pancreatic tumors. Langenbecks Arch Surg. 2014;399(3):315–321. doi: 10.1007/s00423-014-1171-0.
[141] Brient C, Regenet N, Sulpice L, et al. Risk factors for postoperative pancreatic fistulization subsequent to enucleation. J Gastrointest Surg. 2012;16(10):1883–1887. doi: 10.1007/s11605-012-1971-x.
[142] Iacono C, Verlato G, Ruzzenente A, et al. Systematic review of central pancreatectomy and meta-analysis of central *versus* distal pancreatectomy. Br J Surg. 2013;100(7):873–885. doi: 10.1002/bjs.9136.
[143] Xiao W, Zhu J, Peng L, et al. The role of central pancreatectomy in pancreatic surgery: a systematic review and meta-analysis. HPB. 2018;20(10):896–904. doi: 10.1016/j.hpb.2018.05.001.
[144] Zhou Y, Zhao M, Wu L, et al. Short- and long-term outcomes after enucleation of pancreatic tumors: an evidence-based assessment. Pancreatology. 2016;16(6):1092–1098. doi: 10.1016/j.pan.2016.07.006.
[145] Bousi SE, Zachiotis M, Papapanou M, et al. Robotic versus laparoscopic versus open surgery for non-metastatic pancreatic neuroendocrine tumors (pNETs): a systematic review and network meta-analysis. J Clin Med. 2024;13(21):6303. doi: 10.3390/jcm13216303.
[146] Dittrich L, Biebl M, Malinka T, et al. Minimally invasive pancreatic surgery—will robotic surgery be the future? Eur Surg. 2021;53(4):158–165. doi: 10.1007/s10353-020-00689-2.
[147] Guerrini GP, Lauretta A, Belluco C, et al. Robotic versus laparoscopic distal pancreatectomy: an up-to-date meta-analysis. BMC Surg. 2017;17(1):105. doi: 10.1186/s12893-017-0301-3.
[148] Kim HS, Han Y, Kang JS, et al. Comparison of surgical outcomes between open and robot-assisted minimally invasive pancreaticoduodenectomy. J Hepatobiliary Pancreat Sci. 2018;25(2):142–149. doi: 10.1002/jhbp.522.
[149] Rimbaș M, Dumitru AC, Tripodi G, et al. EUS-guided radiofrequency ablation therapy for pancreatic neoplasia. Diagnostics. 2024;14(19):2111. doi: 10.3390/diagnostics14192111.
[150] Marasco M, Galasso D, Larghi A, et al. When should we adopt EUS-guided radiofrequency ablation in pancreatic neuroendocrine tumors? J Clin Med. 2023;12(14):4581. doi: 10.3390/jcm12144581.
[151] Armellini E, Facciorusso A, Crinò SF. Efficacy and safety of endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors: a systematic review and metanalysis. Medicina. 2023;59(2):359. doi: 10.3390/medicina59020359.
[152] Khoury T, Sbeit W, Fusaroli P, et al. Safety and efficacy of endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine neoplasms: systematic review and meta-analysis. Dig Endosc. 2024;36(4):395–405. doi: 10.1111/den.14681.
[153] Birnbaum DJ, Turrini O, Vigano L, et al. Surgical management of advanced pancreatic neuroendocrine tumors: short-term and long-term results from an international multi-institutional study. Ann Surg Oncol. 2015;22(3):1000–1007. doi: 10.1245/s10434-014-4016-8.
[154] Chang JY, Ruff SM, Cloyd JM. Treatment strategies for borderline resectable pancreatic neuroendocrine tumors: a narrative review. Chin Clin Oncol. 2024;13(2):25. doi: 10.21037/cco-23-145.
[155] Abdalla TSA, Klinkhammer-Schalke M, Zeissig SR, et al. Prognostic factors after resection of locally advanced non-functional pancreatic neuroendocrine neoplasm: an analysis from the German Cancer Registry Group of the Society of German Tumor Centers. J Cancer Res Clin Oncol. 2023;149(11):8535–8543. doi: 10.1007/s00432-023-04785-0.
[156] Perysinakis I, Aggeli C, Kaltsas G, et al. Neoadjuvant therapy for advanced pancreatic neuroendocrine tumors: an emerging treatment modality? Hormones. 2016;15(1):15–22. doi: 10.14310/horm.2002.1636.
[157] Li Y, Fan Z, Zhang F, et al. Neoadjuvant therapy in pancreatic neuroendocrine neoplasms: A systematic review and meta-analysis. Front Oncol. 2022;12:981575. doi: 10.3389/fonc.2022.981575.
[158] Cloyd JM, Wiseman JT, Pawlik TM. Surgical management of pancreatic neuroendocrine liver metastases. J Gastrointest Oncol. 2020;11(3):590–600. doi: 10.21037/jgo.2019.11.02.
[159] Sharma A, Muralitharan M, Ramage J, et al. Current management of neuroendocrine tumour liver metastases. Curr Oncol Rep. 2024;26(9):1070–1084. doi: 10.1007/s11912-024-01559-w.
[160] Williams JK, Schwarz JL, Keutgen XM. Surgery for metastatic pancreatic neuroendocrine tumors: a narrative review. Hepatobiliary Surg Nutr. 2023;12(1):69–83. doi: 10.21037/hbsn-22-238.

[161] Shimata K, Sugawara Y, Hibi T. Liver transplantation for unresectable pancreatic neuroendocrine tumors with liver metastases in an era of transplant oncology. Gland Surg. 2018;7(1):42–46. doi: 10.21037/gs.2017.12.11.
[162] Nigri G, Petrucciani N, Debs T, et al. Treatment options for PNET liver metastases: a systematic review. World J Surg Oncol. 2018;16(1):142. doi: 10.1186/s12957-018-1446-y.
[163] Yin B, Gao R, Xu Q, et al. Surgical management for pancreatic neuroendocrine neoplasms with synchronous hepatic metastases: a literature review. Surg Pract Sci. 2022;8:100055. doi: 10.1016/j.sipas.2021.100055.
[164] Mahuron KM, Singh G. Defining a new classification system for the surgical management of neuroendocrine tumor liver metastases. J Clin Med. 2023;12(7):2456. doi: 10.3390/jcm12072456.
[165] Siebenhüner AR, Langheinrich M, Friemel J, et al. Orchestrating Treatment Modalities in Metastatic Pancreatic Neuroendocrine Tumors—Need for a Conductor. Cancers. 2022;14(6):1478. doi: 10.3390/cancers14061478.
[166] Kennedy A, Bester L, Salem R, et al. Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver-Metastases Consensus Conference. HPB. 2015;17(1):29–37. doi: 10.1111/hpb.12326.
[167] Lai Q, Coppola A, Mrzljak A, et al. Liver transplantation for the cure of neuroendocrine liver metastasis: a systematic review with particular attention to the risk factors of death and recurrence. Biomedicines. 2024;12(11):2419. doi: 10.3390/biomedicines12112419.
[168] Kjaer J, Smith S, Hellman P, et al. Overall survival in patients with stage IV pan-NET eligible for liver transplantation. World J Surg. 2023;47(2):340–347. doi: 10.1007/s00268-022-06736-1.
[169] Zhou B, Zhan C, Ding Y, et al. Role of palliative resection of the primary pancreatic neuroendocrine tumor in patients with unresectable metastatic liver disease: a systematic review and meta-analysis. Onco Targets Ther. 2018;11:975–982. doi: 10.2147/OTT.S158171.
[170] Partelli S, Cirocchi R, Rancoita PMV, et al. A systematic review and meta-analysis on the role of palliative primary resection for pancreatic neuroendocrine neoplasm with liver metastases. HPB. 2018;20(3):197–203. doi: 10.1016/j.hpb.2017.10.014.
[171] Tsoli M, Spei ME, Wallin G, et al. Association of a palliative surgical approach to stage IV pancreatic neuroendocrine neoplasms with survival: a systematic review and meta-analysis. Cancers. 2020;12(8):2246. doi: 10.3390/cancers12082246.
[172] Johnston ME, Carter MM, Wilson GC, et al. Surgical management of primary pancreatic neuroendocrine tumors. J Gastrointest Oncol. 2020;11(3):578–589. doi: 10.21037/jgo.2019.12.09.
[173] Del Rivero J, Perez K, Kennedy EB, et al. Systemic therapy for tumor control in metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: ASCO guideline. J Clin Oncol. 2023;41(32):5049–5067. doi: 10.1200/JCO.23.01529.
[174] Panzuto F, Andrini E, Lamberti G, et al. Sequencing treatments in patients with advanced well-differentiated pancreatic neuroendocrine tumor (pNET): results from a large multicenter Italian cohort. J Clin Med. 2024;13(7):2074. doi: 10.3390/jcm13072074.
[175] Rogozik N, Kolasińska-Ćwikła A, Ćwikła JB, et al. Challenges in diagnosing and treating pancreatic neuroendocrine tumours in patients with a multiple endocrine neoplasia type 1 (MEN1) syndrome. OncoReview. 2018;8(1):42–47. doi: 10.24292/01.OR.270518.
[176] Marini F, Giusti F, Tonelli F, et al. Pancreatic neuroendocrine neoplasms in multiple endocrine neoplasia type 1. Int J Mol Sci. 2021;22(8):4041. doi: 10.3390/ijms22084041.
[177] Grozinsky-Glasberg S, Shimon I, Korbonits M, et al. Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. Endocr Relat Cancer. 2008;15(3):701–720. doi: 10.1677/ERC-07-0288.
[178] Plöckinger U, Wiedenmann B. Treatment of gastroenteropancreatic neuroendocrine tumors. Virchows Arch. 2007;451(S1): s 71–80. doi: 10.1007/s00428-007-0446-z.
[179] Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3):224–233. doi: 10.1056/NEJMoa1316158.
[180] Rodriguez-Freixinos V, Thawer A, Capdevila J, et al. Advanced pancreatic neuroendocrine neoplasms: which systemic treatment should I start with? Curr Oncol Rep. 2021;23(7):80. doi: 10.1007/s11912-021-01071-5.
[181] Merola E, Panzuto F, Fave GD. Antiproliferative effect of somatostatin analogs in advanced gastro-entero-pancreatic neuroendocrine tumors: a systematic review and meta-analysis. Oncotarget. 2017;8(28):46624–46634. doi: 10.18632/oncotarget.16686.
[182] Faggiano A. Long-acting somatostatin analogs and well differentiated neuroendocrine tumors: a 20-year-old story. J Endocrinol Invest. 2024;47(1):35–46. doi: 10.1007/s40618-023-02170-9.
[183] De Herder WW. When and how to use somatostatin analogues. Endocrinol Metab Clin North Am. 2018;47(3):549–555. doi: 10.1016/j.ecl.2018.04.010.
[184] Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):501–513. doi: 10.1056/NEJMoa1003825.
[185] Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514–523. doi: 10.1056/NEJMoa1009290.
[186] Raymond E, Kulke MH, Qin S, et al. Efficacy and safety of sunitinib in patients with well-differentiated pancreatic neuroendocrine tumours. Neuroendocrinology. 2018;107(3):237–245. doi: 10.1159/000491999.

[187] Riechelmann RP, Taboada RG, De Jesus VHF, et al. Therapy sequencing in patients with advanced neuroendocrine neoplasms. Am Soc Clin Oncol Educ Book. 2023;43(43):e389278. doi: 10.1200/EDBK_389278.
[188] Chan JA, Geyer S, Zemla T, et al. Phase 3 trial of cabozantinib to treat advanced neuroendocrine tumors. N Engl J Med. 2025;392(7):653–665. doi: 10.1056/NEJMoa2403991.
[189] Vitale G, Rybinska I, Arrivi G, et al. Cabozantinib in the treatment of neuroendocrine neoplasms: insights across different tumor origins. Neuroendocrinology. 2025;115(5):460–479. doi: 10.1159/000543953.
[190] Siebenhüner AR, Refardt J, Nicolas GP, et al. Impact of multikinase inhibitors in reshaping the treatment of advanced gastroenteropancreatic neuroendocrine tumors. Endocr Relat Cancer. 2025;32(6):e250052. doi: 10.1530/ERC-25-0052.
[191] Espinosa-Olarte P, La Salvia A, Riesco-Martinez MC, et al. Chemotherapy in NEN: still has a role? Rev Endocr Metab Disord. 2021;22(3):595–614. doi: 10.1007/s11154-021-09638-0.
[192] Lavingia V, Gohel S, Sirohi B. Systemic therapy for pancreatic neuroendocrine tumors. Indian J Surg Oncol. 2024;15(Suppl 2):305–314. doi: 10.1007/s13193-024-01908-y.
[193] Kunz PL, Graham NT, Catalano PJ, et al. Randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors (ECOG-ACRIN E2211). J Clin Oncol. 2023;41(7):1359–1369. doi: 10.1200/JCO.22.01013.
[194] Taherifard E, Bakhtiar M, Mahnoor M, et al. Efficacy and safety of temozolomide-based regimens in advanced pancreatic neuroendocrine tumors: a systematic review and meta-analysis. BMC Cancer. 2024;24(1):192. doi: 10.1186/s12885-024-11926-2.
[195] Ohmoto A, Fujiwara Y, Horita N, et al. Platinum-doublet chemotherapy for advanced gastroenteropancreatic neuroendocrine carcinoma: a systematic review and meta-analysis. Discov Oncol. 2022;13(1):40. doi: 10.1007/s12672-022-00499-w.
[196] Zappi A, Persano I, Galvani L, et al. Chemotherapy in well differentiated neuroendocrine tumors (NET) G1, G2, and G3: a narrative review. J Clin Med. 2023;12(2):717. doi: 10.3390/jcm12020717.
[197] Di Franco M, Zanoni L, Fortunati E, et al. Radionuclide theranostics in neuroendocrine neoplasms: an update. Curr Oncol Rep. 2024;26(5):538–550. doi: 10.1007/s11912-024-01526-5.
[198] Dash A, Chakraborty S, Pillai MRA, et al. Peptide receptor radionuclide therapy: an overview. Cancer Biother Radiopharm. 2015;30(2):47–71. doi: 10.1089/cbr.2014.1741.
[199] Starr JS, Sonbol MB, Hobday TJ, et al. Peptide receptor radionuclide therapy for the treatment of pancreatic neuroendocrine tumors: recent insights. Onco Targets Ther. 2020;13:3545–3555. doi: 10.2147/OTT.S202867.
[200] Baudin E, Walter TA, Beron A, et al. 887O First multicentric randomized phase II trial investigating the antitumor efficacy of peptide receptor radionucleide therapy with 177Lutetium-Octreotate (OCLU) in unresectable progressive neuroendocrine pancreatic tumor: results of the OCLURANDOM trial. Ann Oncol. 2022;33:s954. doi: 10.1016/j.annonc.2022.07.1013.
[201] Clement D, Navalkissoor S, Srirajaskanthan R, et al. Efficacy and safety of 177Lu-DOTATATE in patients with advanced pancreatic neuroendocrine tumours: data from the NETTER-R international, retrospective study. Eur J Nucl Med Mol Imaging. 2022;49(10):3529–3537. doi: 10.1007/s00259-022-05771-3.
[202] Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of 177Lu-dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376(2):125–135. doi: 10.1056/NEJMoa1607427.
[203] Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. Clin Cancer Res. 2017;23(16):4617–4624. doi: 10.1158/1078-0432.CCR-16-2743.
[204] Hennrich U, Kopka K. Lutathera®: the first FDA- and EMA-approved radiopharmaceutical for peptide receptor radionuclide therapy. Pharmaceuticals. 2019;12(3):114. doi: 10.3390/ph12030114.
[205] Carlsen EA, Fazio N, Granberg D, et al. Peptide receptor radionuclide therapy in gastroenteropancreatic NEN G3: a multicenter cohort study. Endocr Relat Cancer. 2019;26(2):227–239. doi: 10.1530/ERC-18-0424.
[206] Pusceddu S, Prinzi N, Tafuto S, et al. Association of upfront peptide receptor radionuclide therapy with progression-free survival among patients with enteropancreatic neuroendocrine tumors. JAMA Netw Open. 2022;5(2):e220290. doi: 10.1001/jamanetworkopen.2022.0290.
[207] Singh S, Halperin DM, Myrehaug S, et al. [177Lu]Lu-DOTA-TATE in newly diagnosed patients with advanced grade 2 and grade 3, well-differentiated gastroenteropancreatic neuroendocrine tumors: primary analysis of the phase 3 randomized NETTER-2 study. J Clin Oncol. 2024;42(3_suppl):LBA588. doi: 10.1200/JCO.2024.42.3_suppl.LBA588.
[208] Partelli S, Landoni L, Bartolomei M, et al. Neoadjuvant 177Lu-DOTATATE for non-functioning pancreatic neuroendocrine tumours (NEOLUPANET): multicentre phase II study. Br J Surg. 2024;111(9):znae178. doi: 10.1093/bjs/znae178.
[209] Panzuto F, Lamarca A, Fazio N. Comparative analysis of international guidelines on the management of advanced non-functioning well-differentiated pancreatic neuroendocrine tumors. Cancer Treat Rev. 2024;129:102803. doi: 10.1016/j.ctrv.2024.102803.
[210] Salazar R, Tafuto S, Krogh M, et al. LBA45 randomized open label phase III study comparing the efficacy and safety of everolimus followed by chemotherapy (CT) with streptozotocin (STZ)-5FU upon progression or the

reverse sequence, in advanced progressive panNETs: the SEQTOR study (GETNE 1206). Ann Oncol. 2022;33:S1412. doi: 10.1016/j.annonc.2022.08.044.
[211] Reccia I, Pai M, Kumar J, et al. Tumour heterogeneity and the consequent practical challenges in the management of gastroenteropancreatic neuroendocrine neoplasms. Cancers. 2023;15(6):1861. doi: 10.3390/cancers15061861.
[212] Chauhan A, Del Rivero J, Ramirez RA, et al. Treatment sequencing strategies in advanced neuroendocrine tumors: a review. Cancers. 2022;14(21):5248. doi: 10.3390/cancers14215248.
[213] Gosain R, Gupta M, Roy AM, et al. Health-related quality of life (HRQoL) in neuroendocrine tumors: a systematic review. Cancers. 2022;14(6):1428. doi: 10.3390/cancers14061428.
[214] Ronde EM, Heidsma CM, Eskes AM, et al. Health-related quality of life and treatment effects in patients with well-differentiated gastroenteropancreatic neuroendocrine neoplasms: a systematic review and meta-analysis. Eur J Cancer Care (Engl). 2021;30(6):e13504. doi: 10.1111/ecc.13504.
[215] Edfeldt K, Hellman P, Granberg D, et al. Improved health-related quality of life during peptide receptor radionuclide therapy in patients with neuroendocrine tumours. J Neuroendocrinol. 2023;35(10):e13342. doi: 10.1111/jne.13342.
[216] Modica R, Benevento E, La Salvia A, et al. Impact of treatment on quality of life in neuroendocrine neoplasm survivors. Endocr Relat Cancer. 2025;32(8):e240303. doi: 10.1530/ERC-24-0303.
[217] Panzuto F, Gallo A, Marini M, et al. Enhancing patient-centered care with AI: a study of responses to neuroendocrine neoplasms queries. Endocrine. 2025;89(3):921–929. doi: 10.1007/s12020-025-04294-9.
[218] Naraev BG, Mailman J, Halfdanarson TR, et al. Consideration of quality of life in the treatment decision-making for patients with advanced gastroenteropancreatic neuroendocrine tumors. Expert Rev Anticancer Ther. 2023;23(6):601–615. doi: 10.1080/14737140.2023.2207829.
[219] De Jesus-Acosta A, Mohindroo C. Genomic landscape of pancreatic neuroendocrine tumors and implications for clinical practice. J Clin Oncol Precis Oncol. 2024;8:e2400221. doi: 10.1200/PO.24.00221.
[220] Arakelyan J, Zohrabyan D, Philip PA. Molecular profile of pancreatic neuroendocrine neoplasms (PanNENs): opportunities for personalized therapies. Cancer. 2021;127(3):345–353. doi: 10.1002/cncr.33354.
[221] Halfdanarson TR, Capdevila J, Halperin DM, et al. Genetic profiling analysis design of well-differentiated aggressive grade 2 and 3 gastroenteropancreatic neuroendocrine tumors in the phase III randomized controlled COMPOSE trial. J Clin Oncol. 2023;41(4_suppl):TPS660–TPS660. doi: 10.1200/JCO.2023.41.4_suppl.TPS660.
[222] Tacelli M, Gentiluomo M, Biamonte P, et al. Pancreatic neuroendocrine neoplasms (pNENs): Genetic and environmental biomarkers for risk of occurrence and prognosis. Semin Cancer Biol. 2025;112:112–125. doi: 10.1016/j.semcancer.2025.03.005.
[223] Fazio N, La Salvia A. Precision medicine in gastroenteropancreatic neuroendocrine neoplasms: where are we in 2023? Best Pract Res Clin Endocrinol Metab. 2023;37(5):101794. doi: 10.1016/j.beem.2023.101794.
[224] Singh S, Hope TA, Bergsland EB, et al. Consensus report of the 2021 National Cancer Institute neuroendocrine tumor clinical trials planning meeting. J Natl Cancer Inst. 2023;115(9):1001–1010. doi: 10.1093/jnci/djad096.
[225] Loree JM, Chan D, Lim J, et al. Biomarkers to inform prognosis and treatment for unresectable or metastatic GEP-NENs. JAMA Oncol. 2024;10(12):1707–1720. doi: 10.1001/jamaoncol.2024.4330.
[226] Kong G, Boehm E, Prall O, et al. Integrating functional imaging and molecular profiling for optimal treatment selection in neuroendocrine neoplasms (NEN). Curr Oncol Rep. 2023;25(5):465–478. doi: 10.1007/s11912-023-01381-w.
[227] Ito T, Lee L, Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. Expert Opin Pharmacother. 2016;17(16):2191–2205. doi: 10.1080/14656566.2016.1236916.
[228] Wahba A, Tan Z, Dillon JS. Management of functional neuroendocrine tumors. Curr Probl Cancer. 2024;52:101130. doi: 10.1016/j.currproblcancer.2024.101130.
[229] Öberg K. Management of functional neuroendocrine tumors of the pancreas. Gland Surg. 2018;7(1):20–27. doi: 10.21037/gs.2017.10.08.