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Pancreatic Neuroendocrine Neoplasms: Classification and Novel Role of Endoscopic Ultrasound in Diagnosis and Treatment Personalization

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ABSTRACT

The incidence and prevalence of pancreatic neuroendocrine neoplasms are steadily increasing. These tumors are highly heterogeneous, with treatment options ranging from observation to surgery, and various medical therapies. The choice of treatment is influenced by factors such as tumor stage, grade (proliferative activity), and the presence of hormone-related syndromes. Endoscopic ultrasound (EUS) is becoming increasingly valuable for assessing pancreatic neuroendocrine neoplasms, offering detailed morphological, vascular, and functional information through techniques such as contrast enhancement and elastography. It also allows biopsies that are useful for both histopathological and molecular analyses. These tumors are highly heterogeneous, with treatment options ranging from observation to various medical therapies and surgery. Recent data suggest that small, non-functioning PanNENs with low proliferation rates may be safely monitored, whereas more aggressive or functioning tumors typically require surgery. EUS-guided ablation is a promising alternative for patients with functional pancreatic neuroendocrine neoplasms who are unsuitable for surgery, although randomized trials are needed. In non-resectable pancreatic neuroendocrine neoplasms, treatment options include somatostatin analogs, targeted therapies (e.g., everolimus, sunitinib), chemotherapy, and radioligand therapy. This review discusses key factors in planning personalized treatment strategies for pancreatic neuroendocrine neoplasms.

Abbreviations: ALT, alternative lengthening of telomeres; CE-EUS, contrast-enhanced EUS; CT-scan, computed tomography; ENETS, European Neuroendocrine Tumor Society; EUS, endoscopic ultrasound; EUS-E, EUS elastography; FNA/B, fine-needle aspiration/biopsy; MEN1, Multiple Endocrine Neoplasia type 1; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; MRI, magnetic resonance imaging; MVD, microvessel density; NEC, neuroendocrine carcinomas; NET, neuroendocrine tumor; NF1, neurofibromatosis type 1; NF, non-functioning; PanNENs, pancreatic neuroendocrine neoplasms; PDAC, Pancreatic Ductal Adenocarcinoma; PFS, progression-free survival; RFA, radiofrequency ablation; RLT, radioligand therapy; SRI, somatostatin receptor imaging; SSAs, somatostatin analogs; TNM, tumor, node, metastasis; TT, targeted therapies; TTP, time to progression; VHL, Von Hippel-Lindau disease.

1 | Introduction and Terminology

1.1 | Epidemiology

Pancreatic neuroendocrine neoplasms (PanNENs) are a distinct subset of pancreatic neoplasms that arise from pancreatic islet cells. PanNENs are relatively rare, accounting for about 1%–2% of all pancreatic neoplasms; however, their incidence has been increasing, likely due to improved diagnostic techniques and greater awareness. The overall incidence is estimated to be approximately 1.5 per 100,000 individuals per year [1].

Although PanNENs may occur in the context of genetic syndromes, such as Multiple Endocrine Neoplasia type 1 (MEN1), Von Hippel-Lindau disease (VHL), and neurofibromatosis type 1 (NF1), most cases are sporadic [2].

The risk factors for the occurrence of sporadic PanNENs largely reflect those associated with an increased risk of developing Pancreatic Ductal Adenocarcinoma (PDAC) [3], such as smoking, overweight, and diabetes.

1.2 | Classification

PanNENs are classified based on several criteria including functionality, histopathological features, and genetic characteristics. These features are key factors to consider when personalizing the treatment of PanNENs.

1.2.1 | Functional Versus Non-Functional Tumors

Functional PanNENs account for no more than 20% of all PanNENs, and secrete hormones that can cause specific clinical syndromes. Examples include insulinomas (secreting insulin), gastrinomas (secreting gastrin), glucagonomas (secreting glucagon), somatostatinomas (secreting somatostatin), and VIPomas (secreting vasoactive intestinal peptides). Most PanNENs are non-functioning (NF) and are often detected incidentally or due to mass effects (e.g., abdominal pain and jaundice) [4].

1.2.2 | Histopathological Classification

- *Well-differentiated PanNENs are defined as Neuroendocrine Tumors* (NETs) and they exhibit well-defined cellular architecture. According to the updated WHO classification they are graded based on mitotic count and Ki-67 proliferation index into Grade 1 (G1): Ki-67 index < 3% and/or < 2 mitoses per 10 high-power fields (HPF); Grade 2 (G2): Ki-67 index between 3% and 20% and/or 2–20 mitoses per 10 HPF; Grade 3 (G3): Ki-67 index > 20% and/or > 20 mitoses per 10 HPF.
- *Poorly differentiated PanNENs are defined as Neuroendocrine Carcinomas* (NECs) and high-grade tumors (G3) with aggressive behavior, high mitotic rate, and often show extensive necrosis. When a PanNEN lesion is mixed with an exocrine pancreatic neoplasm, a mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) is diagnosed. The WHO classification is summarized in Table 1 [5].

1.2.3 | Genetic and Molecular Classification

The somatic genetic mutations most commonly associated with PanNENs include alterations in MEN1, DAXX/ATRX, and mTOR pathway genes. Mutations in DAXX and ATRX occur in approximately 40%–60% of PanNENs patients. These genes encode chromatin remodeling proteins that are involved in maintaining genomic stability, particularly in the regulation of heterochromatin at telomeres. When mutated, DAXX and ATRX are unable to properly regulate telomere function, leading to the activation of the alternative lengthening of telomeres (ALT) pathway, an abnormal mechanism that allows cancer cells to maintain telomere length and continue proliferating indefinitely. The presence of DAXX or ATRX mutations is strongly correlated with more aggressive clinical behavior and worse prognosis, including higher tumor grade, increased metastatic potential, and reduced overall survival rates [6] (Table 1).

1.2.4 | Staging

The TNM staging system (tumor, node, metastasis) is useful for determining the extent of disease and guiding treatment decisions. This system considers the size of the primary tumor (T), involvement of regional lymph nodes (N), and the presence of distant metastasis (M) [7]. Most PanNENs are diagnosed incidentally as stage I, but it is common to diagnose patients with non-functioning (NF) PanNENs at a metastatic stage without relevant symptoms.

TABLE 1 | World Health Organization (WHO) classification for pancreatic neuroendocrine neoplasms.

Classification	Cell morphology	Ki67 proliferative index	Mitotic count
NET G1	Well-differentiated	< 3%	< 2
NET G2		3%–20%	2–20
NET G3		> 20%	> 20
NEC G3	Poorly-differentiated	> 20%	> 20
Small-cell type			
Large-cell type			
MiNEN	Well- or poorly-differentiated	NA	NA

Abbreviations: MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

2 | The Novel Role of Endoscopic Ultrasound (EUS) in the Diagnosis of PanNENs

The diagnosis of Pancreatic Neuroendocrine Neoplasms (PanNENs), especially when they are small, can be particularly challenging. The latest European guidelines for the management of PanNENs [4] recommend a diagnostic workup including CT (computed tomography), MRI (magnetic resonance imaging), somatostatin receptor imaging (SRI) (preferably using PET/CT), and EUS. However, these guidelines do not specify whether all tests should be performed for every patient or their sequence. Consequently, CT-scan and EUS are considered diagnostically equivalent. Nevertheless, several studies have demonstrated the superiority of EUS over CT-scan in detecting PanNENs, especially for small lesions. A 2016 study showed that CT scan failed to find 68.4% of lesions < 10 mm detected by EUS and 15% of lesions < 20 mm [8]. A 2015 meta-analysis, despite several biases like the inclusion of retrospective studies with small and heterogeneous sample sizes, estimated that EUS is able to detect about 26% more PanNENs over CT-scan [9]. Morphologically, PanNENs can appear as either solid lesions or with central cystic degeneration on B-mode EUS, varying according to the tumor's aggressiveness. Well-differentiated, low-grade PanNENs typically present as homogenous, hypoechoic, oval-shaped lesions with well-defined margins and a space-occupying pattern. In contrast, high-grade or poorly differentiated PanNENs present as heterogenous, irregularly margined lesions with internal necrotic areas and an infiltrative pattern [10]. Differential diagnosis during EUS includes pancreatic metastases, serous cystadenomas, accessory spleens, and well-differentiated adenocarcinomas. EUS offers ancillary techniques, such as elastography (EUS-E) and contrast-enhanced EUS (CE-EUS), which can enhance diagnostic accuracy and predict tumor behavior. Elastography allows real-time evaluation of tissue stiffness, which correlates with the histopathological features of lesions. Iglesias García et al. reported high sensitivity (100%) and specificity (88%) of EUS-E for distinguishing pancreatic adenocarcinoma from PanNENs, but it is a highly operator-dependant technique with high inter-observer variability [11]. On the other hand, CE-EUS is a user-friendly technique without side effects, providing valuable information for differential diagnosis. Typically, PanNENs exhibit an early hyper-enhancing pattern with rapid washout, reflecting increased arteriolar vascularity, which is characteristic of well-differentiated, low-grade tumors (Figure 1). Higher-grade, poorly differentiated tumors, however, show low microvessel density (MVD) and appear hypo-enhancing in the arterial phase on CE-EUS [12–14]. This is due to the fact that PanNENs exhibit a microvascular density (MVD) much higher than that of typical carcinomas, sometimes up to thirtyfold greater, resembling the vascular richness of normal glandular tissues, which is vital for the extensive exchange between the blood and endocrine cells [15]. In PanNENs, which vary in their degree of aggressiveness and typically showcase dense vascular networks, the relationship between MVD and tumor behavior deviates from other tumor types. In contrast to other neoplasms, a higher MVD in PanNENs often indicates better differentiation and lesser aggression, while a lower vascular density is associated with increased malignancy [13]. One of the most important problems in performing the EUS-CE is that the evaluation of enhancement is left exclusively to the subjective opinion of the endoscopist. In last years, some software has been developed that tries to give a quantitative evaluation of the quantity and velocity of contrast uptake by providing objective parameters [14]. To-date these software are available only for research purposes, but maybe in the next future they could become a daily clinical practice tool to stratify the risk of PanNENs patients.

A key role of EUS is the ability to perform biopsy sampling with needles that provide material for cytological (Fine Needle

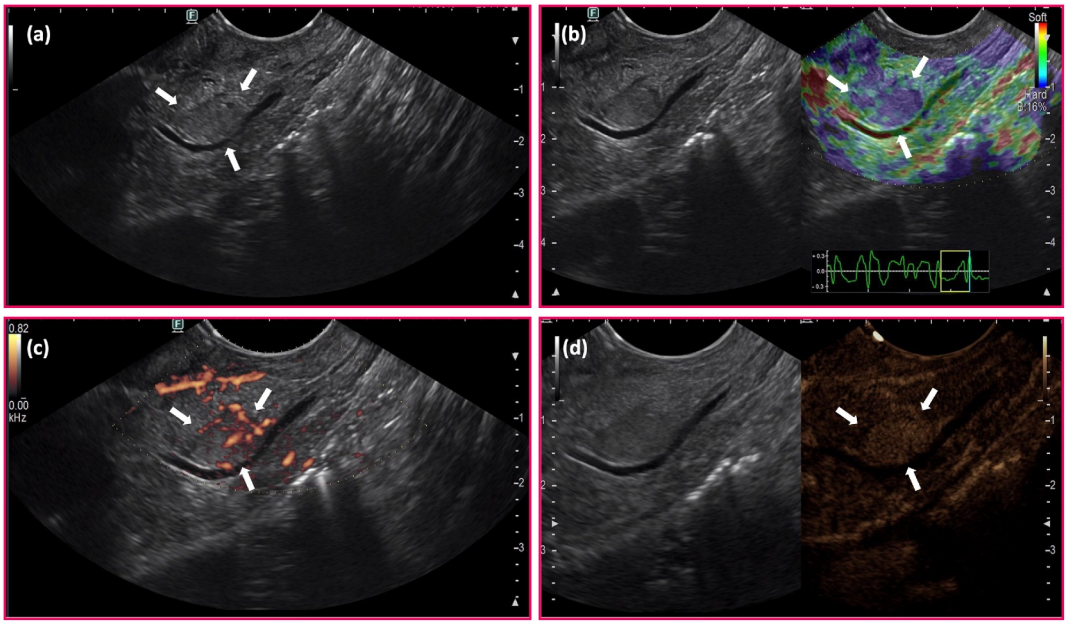

FIGURE 1 | Endoscopic ultrasound (EUS) typical aspect of a pancreatic neuroendocrine neoplasm: (a) B-mode, (b) EUS-elastography, (c) Fine Doppler, and (d) EUS-contrast enhancement.

Aspiration, FNA) or histological (Fine Needle Biopsy, FNB) evaluation. This biopsy not only aids in differential diagnosis but also allows grading of the tumor, providing both diagnostic and prognostic information. The sensitivity and specificity of EUS-FNA for PanNENs are 73.2%–100% and 83.3%–93%, respectively [16]. A 2016 retrospective study highlighted that tumor location in the pancreatic head and intratumoral fibrosis of > 30% were significantly associated with diagnostic failure [17]. Numerous studies have examined the concordance between EUS-FNA/B and post-surgical grading, with varying results. A 2022 meta-analysis showed an overall EUS-surgery concordance rate of 80.3% with a higher risk of undergrading compared to over-grading (14.7% vs. 3.5%, $p < 0.001$), with lesion size being the most significant factor associated with misgrading [18].

In the near future, EUS-guided biopsies are likely to provide additional information for further patient stratification and therapy response prediction. For instance, preoperative assessment of DAXX/ATRX expression and alternative lengthening of telomeres (ALT) activation could be performed, which are parameters associated with tumor aggressiveness [19]. Recently, EUS-FNB has shown potential for transcriptomic analysis of specimens from PDAC [20], and this approach has also been explored for PanNENs, although the results are still preliminary [21]. Significant investments are being made to develop artificial intelligence algorithms to predict PanNEN behavior using EUS, and promising results are expected in the coming years [22].

3 | Treatment of PanNENs

3.1 | The Role of EUS in the Treatment of PanNENs

In recent years, EUS has increasingly carved out a significant role in the treatment of PanNENs, thanks largely to the development of new technologies. Consequently, there has been a growing number of scientific articles on the role of EUS-guided ablative treatments for PanNENs [23]. The EUS-guided techniques tested include radiofrequency ablation (RFA), ethanol ablation, and microwave ablation (MWA) [24], although the latter two have only anecdotal case reports. Prospective and retrospective studies are available for RFA; however, randomized controlled clinical trials (RCT) are still lacking.

EUS-RFA uses a high-frequency alternating current to generate heat, leading to coagulation of the target tissue and 360° destruction of tumor cells. The electrified surface of commercially available RFA needles ranges between 5 and 20 mm in size. While there is no officially established size limit for performing the procedure, it is widely recognized that smaller lesions are more likely to be completely ablated. Many authors agree that the probability of achieving a radical treatment is significantly higher for lesions smaller than 2 cm in diameter. A recent meta-analysis [25] summarizing 11 studies (5 prospective) and 292 patients reported that the procedure was technically feasible in 99.2% of the cases. The pooled rates of complete and partial radiological responses following the procedure were 87.1% and 11.4%, respectively, with an overall success rate of 98.5%.

The pooled rate of adverse events (AEs) was 20% (mainly mild abdominal pain or pancreatitis), with a severe adverse event rate of 0.9%. The EUS-RFA competitor is surgical resection for the treatment of localized diseases, which has a much higher rate of AEs. Currently, no RCTs comparing EUS-RFA with surgical resection are available; however, one is underway [26] and may provide high-grade evidence in the coming years.

In 2023, a multicenter retrospective study [27] compared the two methods for insulinoma treatment using propensity score matching. This study confirmed that the clinical efficacy of EUS-RFA and surgery was comparable (100% in the surgery group vs. 95.7% in the EUS-RFA group). However, there was a significant difference in the overall and severe AEs rates (61.8% vs. 18% and 15.7% vs. 0%, respectively).

Despite these studies, the current European Neuroendocrine Tumor Society (ENETS) guidelines [28] still recommend surgical resection for patients with pancreatic insulinoma, reserving EUS-RFA as an alternative for highly selected cases not suitable for surgery. These guidelines do not assign any role to EUS-RFA in the treatment of NF-PanNEN.

3.2 | Management of PanNEN < 2 cm: Surgery Versus Observation

The surgical approach for PanNENs reflects their biological heterogeneity and complexity. For localized disease, treatment options range from active surveillance to tailored surgical resection and extended pancreatic resection. Although the risk of recurrence after curative resection is generally low, it can increase depending on tumor grade and stage [29].

The management of small lesions depends on diagnostic assessment, with the first step being to exclude the presence of an associated syndrome such as insulinoma, which is the most prevalent functioning tumor. If insulinoma is diagnosed, surgical resection is the treatment of choice. Enucleation is preferred when feasible to spare pancreatic parenchyma. One of the main factors in deciding whether to perform enucleation or a standard resection is the distance between the nodule and the main pancreatic duct. If this distance is less than 3 mm, the risk of damaging the pancreatic duct during the procedure—and consequently the risk of developing a pancreatic fistula or pancreatitis—significantly increases. Therefore, in such cases, it is advisable to opt for a standard resection. Most small PanNENs are asymptomatic and NF. For these lesions, a wait-and-see approach is recommended by the ENETS guidelines [4]. However, controversies remain regarding their management, and surgery is performed in up to 30% of cases [30]. This skepticism toward guidelines may stem from evidence in large US databases that challenge the safety of a watchful strategy [31]. Recently, preliminary prospective data from the ASPEN study suggested that active surveillance is safe for these patients, although it cautions about potential signs of aggressiveness such as main pancreatic duct dilation [32]. The management of lesions measuring between 1 and 2 cm remains controversial. Given the scarcity of elements defining the risk of specific lesions, a personalized approach is preferable, considering factors

such as age, comorbidities, type of pancreatic resection, and associated risks.

3.3 | Management of PanNEN > 2 cm

Surgery is clearly indicated for PanNENs > 2 cm. The surgical strategy must consider the high probability of cure in patients with G1 and G2 PanNENs. However, a careful assessment must always be made regarding the choice of surgical procedure to be performed. In fact, parenchyma-sparing procedures such as enucleation or central pancreatectomy lack adequate lymphadenectomy. For tumors > 2 cm, the risk of nodal metastases exceeds 50% [33], necessitating formal pancreatic resection to avoid stage migration [34] and nodal recurrence [35]. Unfortunately, the pre-surgical prediction of nodal metastases is challenging despite numerous imaging tests [36].

3.4 | Considerations Regarding Perioperative Therapy

The recurrence risk after surgery is low, with approximately 6% of patients experiencing early recurrence. Some tumors show local invasiveness or large sizes, which complicate surgical resection [37]. These patients may benefit from preoperative neoadjuvant therapy to reduce the recurrence risk and shrink tumors, making surgery easier. Preliminary experience suggests neoadjuvant treatment for high-risk PanNENs (defined by the presence of at least one of the following characteristics: tumor size > 4 cm, nearby organ/s invasion, Ki67 > 10%, vascular invasion, single liver metastasis, nodal involvement) [38]. A recent prospective study demonstrated that ^{177}Lu-Dotate is safe and effective as a neoadjuvant treatment for resectable or borderline resectable high-risk PanNENs, with a partial response rate of 58% [39].

A major controversy regarding the surgical approach for patients with localized high-grade G3 PanNEN or PanNEC involves a high risk of recurrence. These patients are challenging to manage because of the limited evidence for an integrated approach. Retrospective studies have not shown a clear benefit of adjuvant therapy [40], though it seems advisable after radical resection of poorly differentiated carcinomas.

3.5 | Somatostatin Analogs (SSAs)

Patients with PanNENs who are not eligible for curative surgical resection may undergo various systemic therapies that often have overlapping indications [41] (Table 2).

SSAs are widely used as first-line therapies for patients with advanced PanNENs and low Ki67 expression. They serve dual purposes: antiproliferative treatment for both NF and functioning PanNENs and symptom control for hormone-mediated symptoms in functioning tumors. The most commonly used SSAs in clinical practice are octreotide LAR and lanreotide autogel, which target somatostatin receptor subtypes 2 and 5 (SSTR2 and SSTR5). The choice of SSAs depends on somatostatin receptor expression and the overall burden of the metastatic disease [42]. The ideal therapeutic targets for SSAs in their antiproliferative role are advanced PanNENs with a low burden of metastatic liver disease, and Ki67 < 10%.

In the PROMID RCT [43], which primarily included metastatic G1 midgut NETs with a low burden of disease, a median prolongation of time to progression (TTP) of 8.3 months was demonstrated in patients treated with SSAs compared with placebo. Furthermore, the CLARINET RCT [44], which also included PanNENs and patients with a higher tumor burden, showed a significant difference in the estimated rates of progression-free survival (PFS) at 24 months of SSAs compared to placebo (65.1% vs. 33.0%).

3.6 | Targeted Therapies (TTs)

TTs for PanNENs aim to inhibit the overexpressed molecular pathways involved in tumor formation and progression. Currently, approved TTs for PanNENs include Everolimus and Sunitinib (and surufatinib, although only in certain guidelines) [45]. Everolimus inhibits tumor growth by targeting the mTOR pathway (PI3K-AKT-mTOR). PanNENs, which are highly vascularized with pronounced neoangiogenesis, are effectively treated with sunitinib, a multi-targeted tyrosine kinase inhibitor that inhibits the VEGF pathway.

According to the ESMO guidelines [41], patients with metastatic G1-G2 PanNENs progressing after SSAs or G3 PanNENs post-chemotherapy should receive TTs as second-line treatment. Additionally, well-differentiated G2 tumors with high Ki67 expression or a lack of somatostatin receptors may be treated with TTs as a first-line option. These recommendations are based on multiple studies. The RADIANT-3 trial showed a median PFS improvement of 6.4 months in patients with advanced PanNEN treated with everolimus compared to placebo [46]. Similarly, a RCT showed significant benefits of Sunitinib over placebo in unresectable advanced PanNENs, with PFS of 11.4 months compared to 5.5 months, and objective response rates of 9.3% versus 0% [47]. Combination therapy with TT and SSAs did not show superiority over monotherapy [48].

A major issue with TTs is the development of resistance to treatment. Numerous studies have been conducted and are ongoing to understand the specific mechanisms of resistance [42, 49, 50].

3.7 | Chemotherapy

Chemotherapy is crucial for the treatment of selected patients with PanNENs. While the optimal timing remains unclear, first-line chemotherapy is indicated for metastatic disease with a high disease burden and grade (Ki67 > 10%). Streptozocin-based regimens have been the traditional choice for these tumors [51]. However, recently, other regimens have been preferred. Currently, the most widely used regimen involves a combination of Capecitabine and Temozolomide. Initially, Temozolomide was tested in the monotherapy setting, but recently, a prospective

TABLE 2 | Summary of the main treatments available for pancreatic neuroendocrine neoplasms.

Treatment	Available RCTs	Fundamental evidences	Who should be treated	Fundamental adverse events
Surgery	No RCT. ASPEN registry study (small asymptomatic PanNENs)	ASPEN: Active surveillance for small PanNENs is safe. In the surveillance group, 2% of patients underwent surgery for increasing tumor size, increased MPD dilatation, and patient's preference in 2	Resectable, well differentiated G1 or G2 patients with F- or NF-PanNENs	Pancreatic fistula Bleeding Infections Diabetes Exocrine pancreatic insufficiency Delayed gastric emptying
Somatostatin analogs (SSAs)	CLARINET (2014, enteropancreatic NETs) PROMID (2009, midgut NETs) CLARINET FORTE (2021, enteropancreatic NETs)	– 24 months PFS: 65.1% versus 33% (placebo group) – Disease progression/death risk reduction: 53%	Locally advanced or metastatic G1 or low G2 (Ki67 < 10%)	Diarrhea Abdominal pain Cholelithiasis
EUS-guided radiofrequency ablation (EUS-RFA)	No RCTs. One retrospective propensity score-matching study	Technical feasibility: 99.2% Overall success rate: 98.5%	Localized insulinomas in patients unable to undergo surgery	Abdominal pain acute pancreatitis Bleeding Pancreatic duct stricture
Targeted therapies (sunitinib/everolimus)	RADIANT-1 (2010, PanNENs) RADIANT-3 (2011, PanNENs) SUN1111 (2011, PanNENs)	– Median PFS (EVE): 11 versus 4.6 months (placebo group) – Median PFS (SUN): 11.4 versus 5.5 months (placebo group)	Metastatic G1-G2 PanNENs progressing after SSAs or G3 PanNENs progressing post-chemotherapy	Stomatitis Rash Diarrhea Vomiting Fatigue Anemia
Capecitabine/Temozolomide	ECOG-ACRIN E2211 (2018, PanNENs)	– Median PFS: 22.7 versus 14.4 months (CAP-TEM vs. TEM alone) – Higher response rates in patients with MGMT deficiency	Advanced progressive PanNENs after SSAs and/or other treatments	Pancytopenia Nausea Fatigue
Cisplatin/etoposide Carboplatin/etoposide	No recent RCTs specific to PanNENs	Increased median PFS and response rate respect to placebo (but no RCTs)	High-grade G3 PanNENs or small/large-cell NEC with liver or distant metastasis	Nausea Vomiting Myelosuppression Nephrotoxicity
FOLFOX/CAPOX ± bevacizumab	No RCTs specific to PanNENs. Retrospective studies available	Retrospective studies: Significant activity in aggressive PanNECs, with robust response but relatively short duration. The addition of bevacizumab has shown improved efficacy	G3 poorly differentiated GEP-NETs	Neuropathy Neutropenia Thrombocytopenia Fatigue Gastrointestinal symptoms Nausea

(Continues)

TABLE 2 | (Continued)

Treatment	Available RCTs	Fundamental evidences	Who should be treated	Fundamental adverse events
Radioligand therapy (RLT)	NETTER-1 (midgut NETs, 2017)	NETTER-1: Increased PFS rate (65.2% vs. 10.8%) and response rate (18% vs. 3%) of RLT respect to LAR alone in progressive NET	Metastatic progressive PanNENs, particularly those expressing somatostatin receptors	
	NETTER-2 (GEP-NETs, 2024)	NETTER-2: Increased PFS and response rate of RLT groups respect to control group as first line treatment	New recent insights as neoadjuvant therapy	Vomiting Bone marrow suppression Kidney toxicity

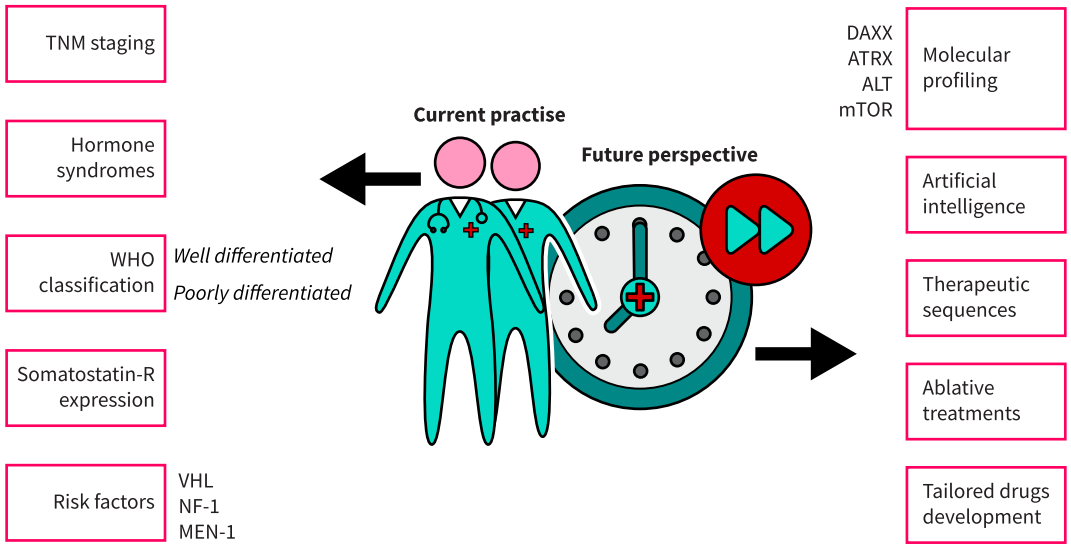

FIGURE 2 | Summary of the actual and future possibilities available to personalize the management of patients with pancreatic neuroendocrine neoplasms.

randomized phase II study assessed the activity of Capecitabine plus Temozolomide versus Temozolomide alone, demonstrating that the median PFS was 14.4 months for Temozolomide versus 22.7 months for Capecitabine/Temozolomide (hazard ratio = 0.58) [52]. Other regimens used in the treatment of patients with advanced PanNET include oxaliplatin-based regimens such as FOLFOX or CAPOX, alone or in combination with bevacizumab [53]. Chemotherapy is currently the treatment of choice for patients with G3 PanNETs. Platinum doublet chemotherapy with cisplatin or carboplatin plus etoposide is a staple therapy for patients with poorly differentiated grade 3 NECs. However, the activity of these regimen(s) in patients with well-differentiated PanNETs is less clear [54].

3.8 | Radioligand Therapy (RLT)

One of the most impactful therapeutic perspectives in recent years is radioligand therapy (RLT). This is a technique that uses radiolabeled, beta-emitting somatostatin analogs (such as [^{90}Yttrium-DOTATOC and ^{177}Lu-Dotatate]) that bind to somatostatin receptors on the surface of tumor cells. This binding leads to the internalization of the radiopeptide and subsequent cell death. The efficacy of RLT has been documented in numerous retrospective and prospective [55]. However, the highest level of evidence currently available on this topic is from the NETTER-1 trial [56]. This RCT enrolled patients with well-differentiated metastatic midgut NETs that had progressed after SSA therapy and randomized them to receive either ^{177}Lu-Dotatate or high-dose LAR. The trial demonstrated the superiority of RLT over the control group in terms of PFS (65.2% vs. 10.8%) and response rates (18% vs. 3%).

One of the major uncertainties regarding RLT is its optimal placement in the timeline of disease progression. Recently, several papers [57], including a new RCT named NETTER-2 [58], have been published, demonstrating the role of this therapy in reducing tumor masses, improving PFS and overall survival of patients, with a higher rate of achieving radical surgical resectability.

4 | Conclusion

PanNENs are a unique group of tumors whose incidence is on the rise, with distinct epidemiological and clinical characteristics and heterogeneous behavior driven by specific features that allow personalized treatment and predict prognosis. Their management

poses a challenge for the treating physicians and require multidisciplinary approach in expert centers. Ongoing research with artificial intelligence examination of images and on the genetic and molecular underpinnings of these tumors hold promise for more targeted and effective therapies in the future (Figure 2).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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