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Neuroendocrine Tumors of the Pancreas

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LEARNING OBJECTIVES

1. Assess the basic aspects of PNET tumor biology, pathogenesis, and classification.
2. Explain the epidemiology and evaluate the prognosis of PNET patients.
3. Engage in rational clinical management of PNETs.

ABSTRACT

This literature review briefly summarizes the epidemiology, pathophysiology, clinical management, and outcomes of patients with pancreatic neuroendocrine tumors (PNETs) and highlights recent advances in PNET research. PNETs are rare neoplasms, compared with carcinomas arising from pancreatic exocrine tissue. They, like other neuroendocrine tumor types, display variable malignant potential, hormone-related syndromes (functionality), localization, and genetic background. Although tumor origin and molecular pathogenesis remain poorly understood, recently established grading and staging systems facilitate patient risk stratification, and thereby directly impact clinical decision making.

Although the optimal clinical management of PNETs involves a multidisciplinary approach, surgery remains the only curative treatment for early-stage disease. Surgery may also have a role in patients with advanced-stage disease, including those with hepatic metastases. Alternative therapeutic approaches applied to PNETs, including chemotherapy, radiofrequency ablation, transarterial chemoembolization, biotherapy, polypeptide radionuclide receptor therapy, antiangiogenic therapy, and selective internal radiotherapy, have failed to demonstrate a long-term survival benefit. Surgery remains the primary therapeutic option for patients with PNETs. Research on PNETs is desperately needed to improve the therapeutic options for patients with this disease. ***The Oncologist*** 2009;14:456–467

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INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) comprise a group of rare neoplasms arising from the neuroendocrine system of the gut. The annual incidence is estimated at 1–4 in 100,000, showing a trend of a higher incidence over recent decades [1–4].

At least 14 different cell types of the neuroendocrine system of the gut have been described to date. This cell type heterogeneity likely accounts for the wide variety of syndromes associated with hormone overproduction and oversecretion [5, 6]. Correspondingly, GEP-NETs are classified as "functional" (F-NETs) or "nonfunctional" (NF-NETs) based on the presence or absence, respectively, of a specific clinical syndrome associated with hormone oversecretion. Hormone secretion, however, does not uniformly result in a clinical syndrome, for example, as in the case of pancreatic polypeptide (PP) secretion. GEP-NETs may have benign, uncertain, or malignant behavior. Furthermore, they may arise sporadically or be associated with genetic syndromes, fox example, multiple endocrine neoplasia type 1 (MEN-1).

Pancreatic neuroendocrine tumors (PNETs) are a subgroup of GEP-NETs with unique tumor biology, natural history, and clinical management [7–9]. PNETs are rare pancreatic neoplasms, compared with their more common exocrine counterparts. It is estimated that <3% of primary pancreatic neoplasms result from neuroendocrine tumors [10–12]. The overall prognosis and long-term survival for PNET patients are far better than for patients with exocrine pancreatic cancer [13, 14]. The overall 5-year survival rate is in the range of 30% in NF-PNETs to 97% in insulinoma, one category of F-PNET [15].

INCIDENCE

The incidence of PNETs is <1 in 100,000 in Asian and European population-based studies [3, 10, 16–20]. Recently, Halfdanarson et al. [21] reported an annual incidence of 2.2 in 1,000,000, covering a period of 27 years. These data also showed a male gender preference (males, 2.6; females, 1.8) and a higher incidence in PNETs in recent decades [21].

Remarkably, the incidence of PNETs according to autopsy studies is as high as 10% [22]. Furthermore, 19% of all pancreatic lesions incidentally detected by computed tomography (CT) are PNETs [23]. These data suggest a higher incidence of clinically "silent" and benign PNETs than symptomatic and malignant PNETs.

Importantly, the incidence of multiple primary malignancies in patients with sporadic PNETs compared with general population is remarkably high. Specifically, malignant gastrinomas and malignant NF-PNETs are associated with a wide range of other tumors, for example, ovarian, breast, endometrial, bladder, prostate, or esophageal cancer [24].

Although multiple studies address PNET incidence and natural history, definitive data are still lacking because most study designs limit any conclusions that can be drawn as a result of inherent bias. For example, benign PNETs are excluded from national cancer databases, and thus are most likely underrepresented in recent epidemiological studies [25] or studies from large referral centers [26]. This may in part explain the shift in relative incidence from F-PNETs to NF-PNETs in recent years. Whereas in early single-center series, NF-PNETs comprise 18%–66% of all neuroendocrine tumors of the pancreas [27–32], recent large, single-center or epidemiologic studies classify 68%–90% as NF-PNETs [21, 26, 33–35].

ORIGIN

By definition, PNETs express neuroendocrine markers—for example, synaptophysin [36], neuron-specific enolase (NSE) [37], and/or chromogranin A (CgA) [38])—namely, proteins associated with the secretory apparatus of endocrine cells. The true cell or cells of origin of PNETs, however, are not fully understood. The adult endocrine pancreas is anatomically organized into a million "micro-organs," called islets of Langerhans, referring to Paul Langerhans who described them in 1869. Human islets display a remarkable variability concerning cellular composition and morphology and differ significantly from model organisms, particularly rodents. The average human islet consists of approximately 3,000 cells producing insulin (β cells, 54%), glucagon (α cells, 34%), somatostatin (δ cells, 10%), vasoactive intestinal polypeptide (VIP) (δ_2 cells), PP (PP cells), and substance P/serotonin (enterochromaffin cells). Gastrin-producing G cells are present in fetal but not normal adult pancreatic islets [6, 39].

In theory, each pancreatic endocrine cell type could give rise to a PNET. Additionally, PNETs may rarely produce nonpancreatic hormones ectopically. Immunocytochemistry may elucidate the expression of specific hormones.

Hormone-producing PNETs (Table 1) can be divided into: (a) common types, that is, insulinoma (17%) and gastrinoma (15%), and (b) rare functional tumors, VIPoma (2%), glucagonoma (1%), carcinoids (serotonin, 1%), somatostatinoma (1%), and exceedingly rare neoplasms like PPoma, adrenocorticotropic hormone (ACTH)oma, growth hormone releasing factor (GRF)oma, calcitonin-producing tumors, parathryroid hormone–related peptide-producing tumors, and others [22, 40–47].

The wide variety of hormone-producing PNETs is evidence for the heterogeneity of tumor cell origin. Mixed neuroendocrine/non-neuroendocrine tumors have also been

Table 1. Summary of PNET characteristics [15, 122]

Tumor (secreted product)	Clinical presentation	Pancreatic localization (%)	Malignancy (%)	MEN-1–associated (%)	Incidence in MEN-1 (%)
Insulinoma (insulin)	Whipple's triad[a]	>97	<10	5–10 [90]	21
Gastrinoma (gastrin)	Zollinger-Ellison syndrome[b]	25–60	60–90	20–30 [57]	54
VIPoma (vasoactive intestinal polypeptide)	Verner-Morrison syndrome[c]	>90	40–70	6	17
Glucagonoma (glucagon)	Glucagonoma syndrome[d]	>95	50–80	1–20	3
Somatostatinoma (somatostatin)	Somatostatinoma syndrome[e]	55	>70	45–50	<5
GRFoma (growth hormone releasing factor)	Acromegaly	30	>60	16	?
ACTHoma (ACTH)	Ectopic Cushing syndrome	4–16	>95	Rare	Rare
Carcinoid (serotonin/?)	Carcinoid syndrome[f]	1.4 [44] to 7.9 [123]	60–80	Rare	Rare
PTH-related peptide-producing NET (PTHrP)	Hypercalcemic symptoms	Rare	84	Rare	Rare
Calcitonin-producing NET	Hypocalcemic symptoms	Rare	>80	16	?
Well-differentiated NF-PNETs (e.g., PP or none)	Mass effect (jaundice, hemorrhage, etc.)	100%	60	8 [35]	55 [124]
Poorly differentiated PNETs	Mass effect/syndromes reported	Rare	100%	?	?

[a] Hypoglycemic symptoms, low blood glucose levels, reversible upon glucose intake [125].
[b] Diarrhea, hypergastrinemia, gastric acid hypersecretion, peptic ulcer diathesis [126].
[c] WDHA syndrome: watery diarrhea, hypokalemia, achlorhydria [127].
[d] 4D syndrome: necrolytic migrating erythematous dermatitis, diabetes, deep vein thrombosis, depression [128].
[e] (Questionable) elevated somatostatin serum levels, diabetes, hypochlorhydria, cholelithiasis, dia-/steatorrhea, anemia, weight loss [42, 129].
[f] Flushing, diarrhea, cardiac valvular diseases, bronchospasms [130].
Abbreviations: ACTH, adrenocorticotropic hormone; GRF, growth hormone releasing factor; NF, nonfunctional; PNET, pancreatic neuroendocrine tumor; PP, pancreatic polypeptide; PTH, parathyroid hormone; PTHrP, PTH-related peptide; VIP, vasoactive intestinal polypeptide.

described, lending credence to this theory [48]. Nonetheless, β-cell turnover remains under intense investigation; however, conclusive data for mechanisms of adult β-cell regeneration (stem cells versus cell replication versus transdifferentiation) are still missing [49]. In contrast, compelling data also exist for nonislet origins of F-PNETs [50]. Thus, the cellular origin of PNETs is complex and remains to be elucidated.

Genetics, Etiology, and Pathogenesis

The molecular basis of PNET pathogenesis is poorly characterized. The majority of PNETs are sporadic, but PNETs may also be associated with genetic syndromes such as MEN-1, von Hippel-Lindau (VHL) disease, neurofibromatosis 1 (NF-1), and tuberous sclerosis (TSC). The genetic background of these syndromes may shed light on the molecular mechanisms of PNET pathogenesis [9].

MEN-1 is a result of a chromosomal aberration that has been mapped to chromosome region 11q13. The corresponding gene, *MEN-1*, codes for the protein menin [51, 52]. To date, over 300 *MEN-1* germline mutations have been identified [53]. The tumor-suppressing mechanisms mediated by menin remain unclear, although menin was shown to be involved in the regulation of gene transcription, cell proliferation, apoptosis, and genome stability [54].

PNETs occur in the majority of MEN-1 patients, typically as numerous pancreatic microadenomas. A minority of these microadenomas acquire the potential to grow and give rise to clinically relevant lesions. When present they are typically in multifocal duodenal and/or pancreatic locations [55]. PNETs are responsible for premature death in MEN-1 patients [56]. Suspicion of MEN-1 based on medical history (young onset, two organ manifestations, family history) should lead to tests for hyperprolactemia and primary hyperparathyroidism, and, if positive, these should be followed by genetic characterization [46, 57]. In the case of genetically proven MEN-1, regular screening for PNETs, including assessment of biochemical serum markers (PP, CgA, gastrin, insulin, glucagon) and imaging studies (en-

doscopic ultrasound), is recommended [55, 58]. Surgical therapy of MEN-1–associated PNETs differs significantly from surgery for sporadic PNETs because of multifocality [55, 59].

VHL disease is an autosomal dominant inherited syndrome characterized by proliferation of vascular tissue (angiomatosis, hemangioblastoma), renal cell carcinoma, pheochromocytoma, and pancreatic lesions. The *VHL* gene locus is on chromosome 3p25–26. Some data point to involvement of loci on 3p centromeric to the *VHL* gene [60]. Loss of heterozygosity of *VHL* leads to hypoxia-induced upregulation of angiogenic factors.

The reported range of VHL patients who develop pancreatic lesions is broad (20%–75%). The majority (91%) show true cysts, whereas the minority (12%) develop PNETs [61, 62].

NF-1 and TSC were casually reported to be associated with pancreatic and duodenal NETs [63–67]. However, the rarity of these entities has prevented further characterization thus far [58].

The genetic background of sporadic PNETs is complex. Although a number of candidate genes, including *MEN-1*, *RAR-β*, *hMLH1*, *RASSF1*, *Her2/neu*, *Cyclin D1*, $p16^{INK4a}$/$p14^{ARF}$, $p18^{INK4c}$, $p27^{Kip1}$, *p53*, and those encoding tyrosine kinase receptors, have been implicated in PNET pathogenesis, the genetic and proteomic mechanisms of tumor progression are poorly understood [9]. Interestingly, recent data suggest that PNETs have significant molecular differences when compared with other GEP-NETs, arguing for a critical reconsideration of the current World Health Organization (WHO) classification, which combines these entities into one classification system [68–70].

Further investigations using high-throughput analyses and large tumor banks may elucidate the molecular pathogenesis of PNETs.

Classification and Prognosis

Although GEP-NETs have been a well-recognized entity for decades, the heterogeneity of localization and tumor biology make it a challenge to classify these tumors with optimal prognostic relevance. Whereas the presence of metastases remains the ultimate sign of malignant behavior, clearly a classification system that predicts such malignant behavior based upon histological criteria would be more clinically relevant. The WHO introduced a histological classification system for GEP-NETs (including PNETs) in 2000 [71–73]. Based on the work of Capella et al. [74], this system was intended to discriminate benign tumors from low-grade, well-differentiated, malignant tumors.

For the WHO classification system, tumor localization, extension, proliferative capacity, and angio-/perineural invasion must be assessed. This grading system enables discrimination of well-differentiated endocrine tumor (WDET) with benign and uncertain behavior, well-differentiated endocrine carcinoma (WDEC), and poorly differentiated endocrine carcinoma (PDEC) (Table 2).

Table 2. WHO classification of pancreatic neuroendocrine tumors [73]

1. Well-differentiated endocrine tumor (WDET)
1.1. Benign behavior
Confined to the pancreas, <2 cm in diameter, ≤2 mitoses per 10 HPF, ≤2% Ki-67–positive cells, no angioinvasion or perineural invasion
1.2. Uncertain behavior
Confined to the pancreas and one or more of the following features:
≥2 cm in diameter, >2 mitoses per 10 HPF, >2% Ki-67–positive cells, angioinvasion, perineural invasion
2. Well-differentiated endocrine carcinoma (WDEC)
Low-grade malignant
Gross local invasion and/or metastases
3. Poorly differentiated endocrine carcinoma (PDEC)
High-grade malignant
>10 mitoses per HPF

Abbreviations: HPF, high-power field; WHO, World Health Organization.

While some authors question the clinical relevance of the WHO histological classification [75], several studies have demonstrated its prognostic value [7, 76–80]. Furthermore, early attempts at correlating WHO classification and DNA microarray analysis results are promising. Duerr et al. [69] were able to show "benign clusters" and "malignant clusters" of PNET gene expression associated with WDET and WDEC, respectively.

The tumor–node–metastasis (TNM) staging system for pancreatic adenocarcinoma (American Joint Committee on Cancer, Sixth Edition), when applied to PNETs, also provides survival discrimination by stage for surgical and nonsurgical patients [14]. The demand for standardized oncologic stratification of patients with GEP-NETs led the European Neuroendocrine Tumour Society (ENETS) to propose a TNM staging system for foregut GEP-NETs, including a grading system based solely upon the tumor's proliferative capacity measured by mitotic count and/or Ki-67 index (Table 3) [81].

Recently, the suggested TNM classification was retrospectively validated for 202 foregut NETs (131 PNETs). Based upon the survival analysis, the authors, acknowledging limitations concerning the retrospective study design

Table 3. Proposal for a TNM classification and disease staging and grading for pancreatic neuroendocrine tumors [81]

TNM			
T: primary tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor limited to the pancreas and size <2 cm		
T2	Tumor limited to the pancreas and size 2–4 cm		
T3	Tumor limited to the pancreas and size >4 cm or invading duodenum or bile duct		
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery)		
	For any T, add (m) for multiple tumors		
N: regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M: distant metastases			
MX	Distant metastases cannot be assessed		
M0	No distant metastases		
M1	Distant metastases		
Stage			
I	T1	N0	M0
IIa	T2	N0	M0
IIb	T3	N0	M0
IIIa	T4	N0	M0
IIIb	Any T	N1	M0
IV	Any T	Any N	M1
Grade	Mitotic count (10 HPF)	Ki-67 Index (%)[a]	
1	<2	≤2	
2	2–20	3–20	
3	>20	>20	

[a] Percentage of 2,000 tumor cells.
Abbreviations: HPF, high power field; TNM, tumor–node–metastasis.

and small cohort, concluded at least equivalence for the TNM staging system compared with previous classification systems [82].

Nonetheless, the factors associated with long-term survival after resection of PNETs remain controversial. Bilimoria et al. [83] recently conducted a multivariate analysis of long-term survival on the largest cohort of patients (n = 3,851) after PNET resection reported to date. Identified factors adversely affecting survival were age (>55 years), NF-PNET, poor tumor differentiation, distant metastases, and surgical procedure (pancreaticoduodenectomy). A prognostic score that incorporated age, histological grading, and the presence or absence of distant metastases significantly predicted long-term survival outcome. That study [83] could not reproduce tumor size or nodal status as independent predictors of poor long-term survival outcome, as reported by earlier smaller multivariate analyses [76, 84]. Because the U.S. national cancer database captures only malignant PNETs, this result might be biased by the selection of larger tumors (81% of analyzed tumors were >2 cm).

Because prospective validation of either the WHO classification or TNM classification is still not available, clinical implementation of a standardized classification system is incomplete. Thus, comparability of classification data remains a fundamental obstacle to further investigation of the disease [85].

Numerous retrospective reports on the prognosis of PNET patients have been published. The marked hetero-

geneity among the patient populations as well as the large potential for referral bias, however, reduce the generalizability of the results [25].

After surgical therapy, patients with insulinomas generally have an excellent long-term survival outcome. Cure was achieved in 98% of patients after surgical resection in a large patient cohort from the Mayo Clinic in Rochester [86, 87]. The 5- and 10-year disease-specific survival rates of all patients with sporadic gastrinoma were reported at 100% and 95%, respectively, and 40% of the patients were reported to be free from disease at 5 years postoperatively [88]. In the case of NF-PNETs, 5-year overall survival rates are in the range of 26%–58% [25, 35]. After adjustment for age, similar survival data were obtained for sporadic and MEN-1–associated PNETs [30, 55].

Clinical Management: Diagnosis and Therapy

For PNET diagnosis and therapy, a multidisciplinary approach is optimal. The diagnostic assessment should include a biochemical assessment for a functional syndrome, localization of the primary, assessment of the nodal status, assessment of metastatic disease, the familial genetic background, and histological classification of the disease. Curative therapy is generally based upon complete surgical resection [89].

Palliative care encompasses medical control of hormonal syndromes through local and/or systemic cytoreductive therapies including surgery, local ablative interventions, systemic chemotherapy, and biological approaches, fox example, polypeptide radionuclide receptor therapy (PRRT).

The ENETS conference in 2006, despite including a critical review of multimodal approaches, resulted in minimal consensus about diagnostic and therapeutic approaches in the management of PNETs [35, 46, 57, 90, 91].

Insulinoma

A classic history of hyperinsulinemic–hypoglycemic syndrome often suggests the diagnosis of insulinoma. The gold standard for the definitive diagnosis of insulinoma is a positive 72-hour fasting test. This test excludes all differential diagnoses of hypoglycemia, except the very rare nesidioblastosis, or noninsulinoma pancreatogenic hypoglycemia syndrome (NIPHS) [92–94].

Preoperative localization of tumors >0.5 cm can often be achieved using transabdominal or endoscopic ultrasound, CT, and/or magnetic resonance imaging (MRI) [90]. Additionally, promising results for the localization and differential diagnosis of PNETs were recently reported for a contrast-enhanced ultrasound approach (CEUS) [95, 96]. Somatostatin receptor scintigraphy (SRS) is positive in 46% of all benign insulinomas. Malignant insulinomas typically show a more frequent expression of somatostatin receptor subtype 2/5, which may have an immediate impact on palliative treatment options [97]. Finally, percutaneous selective arterial calcium stimulation and portal venous sampling are used selectively when other localization studies fail to identify the tumor [98].

Given that 97% of insulinomas are located within the pancreatic parenchyma and the near 100% sensitivity of intraoperative ultrasound and palpation of the skilled surgeon [99], preoperative imaging may reasonably be limited to determining the presence or absence of metastatic disease. Furthermore, preoperative imaging should take into account cost, sensitivity, availability, and local expertise [15, 86].

Surgery involves a thorough exploration of the pancreas to determine the precise location of the insulinoma(s). Enucleation is the preferred procedure for insulinomas <2 cm, whereas central or distal partial pancreatectomy may be anatomically required, for example, for tumors contacting the main pancreatic duct. In the case of a sporadic, singular, superficially located insulinoma, laparoscopic approaches might be feasible [100]. Blind distal resections for "occult insulinoma" are obsolete. However, when further investigations reveal NIPHS, subtotal distal pancreatectomy may be required [101].

In MEN-1, some authors suggest enucleation of insulinomas in the pancreatic head and simultaneous distal subtotal pancreatectomy, as recommended for other subgroups of MEN-1–associated tumors. Whether splenectomy is required for prophylactic cancer surgery in MEN-1 patients remains a matter of debate [55].

Symptomatic relief of hypoglycemic symptoms must be achieved by a high glucose diet and medical therapy. The most effective drug is diazoxide, whereas verapamil, diphenylhydantoin, and glucocorticoids may serve as alternatives. In the case of a positive SRS scan, somatostatin analogs might be used for suppressing insulin secretion [90].

Malignancy might be expected in tumors >2 cm. Consequentially, curative surgery encompasses radical removal of the primary, for example, pylorus-preserving duodenopancreatic resection, distal pancreatectomy (if required with splenectomy), lymphadenectomy, and removal of resectable liver metastases. In nonresectable hepatic or systemic disease, palliative tumor debulking may be justified to achieve hypoglycemic control and may prolong survival. However, the risk–benefit ratio has to be carefully estimated and other debulking procedures—radiofrequency ablation (RFA), cryotherapy, transarterial chemoembolization (TACE)—should be considered [90]. An option for systemic chemotherapy is the combination of doxorubicin and streptozotocin [102].

Gastrinoma

Secretory diarrhea, peptic (multiple, recurrent, that do not respond to medical therapy) and jejunal ulcers, hypertrophic gastric folds, severe esophagitis, and hypercalcemia are suggestive of Zollinger-Ellison syndrome (ZES) [103]. According to the ENETS consensus, a biochemical diagnosis requires determination of the fasting serum gastrin (FSG) level and gastric pH (to rule out achlorhydria) after cessation of proton pump inhibitor therapy for at least 1 week. If the FSG level is elevated less than tenfold and the gastric pH is <2, then a basal acid output (BAO) measurement should be performed. If repeated FSG measurements are performed on different days, $<0.5\%$ of ZES patients will have all normal values. If a BAO measurement is performed, $>85\%$ of patients with gastrinoma (without previous gastric acid–reducing surgery) will have a value >15 mEq/hour [57].

In all patients with ZES, serum parathormone, fasting calcium, and prolactin levels should be assessed to rule out MEN-1. Remarkably, 5%–15% of ZES patients develop additional hormonal syndromes (e.g., ectopic Cushing's, which is associated with a poor long-term prognosis). Thus, additional hormone assays may be indicated [57].

Tumor localization routinely involves upper gastrointestinal endoscopy, CT, SRS, or positron emission tomography (PET) with ^{67}Ga-DOTA-DPhe^{1}-Tyr^{3}-octreotide (^{67}Ga-DOTATOC) if available. If these tests fail to localize the gastrinoma, endoscopic ultrasonography and selective angiography with secretin stimulation and hepatic venous sampling should be considered. Liver metastases, when present, predict a significant likelihood of bone metastases. Finally, surgical exploration for gastrinoma should include pancreatic exploration with intraoperative ultrasonography, duodenal transillumination, and duodenotomy. Thus, laparoscopic approaches are typically not feasible.

Surgical therapy is generally recommended for sporadic, resectable disease. The ENETS minimal consensus recommended enucleation of pancreatic head tumors and excision of duodenal tumors [57]. However, the gastrinoma malignancy rate of 60%–90% has to be taken into account when nonradical approaches are chosen. Thus, histological confirmation of malignant gastrinoma after nonradical surgery is optimally followed by early reoperation for completion of radical resection.

Distal pancreatectomy removes the extremely rare distally located gastrinomas, because most tumors are located in the "gastrinoma triangle" (pancreatic head, duodenum, and surrounding lymph nodes) [104]. Lymphadenectomy should always be performed, even in the absence of a pancreatic or duodenal primary, because primary lymph node gastrinomas have been reported [57]. In young patients with diffuse, unresectable hepatic metastases, liver transplantation can be an ultimate curative option [105].

The type, timing, and role of surgery in MEN-1/ZES patients remain controversial. To prevent liver metastases and prolong long-term survival, some groups support aggressive and early surgical therapy, for example, pancreaticoduodenectomy or pancreas-preserving duodenectomy [106, 107]. In contrast, the ENETS consensus recommends surgical excision for MEN-1 gastrinomas >2 cm, because the natural history of small tumors is characterized by an excellent life expectancy [57, 88].

Medical control of acid hypersecretion is achieved by proton pump inhibitors in 98% of ZES patients. Therefore, tumor mass effects rather than hormonal excess is typically what is ultimately life limiting. The treatment of advanced, surgically incurable disease involves cytoreductive surgery, if $>90\%$ of the tumor mass can be removed, and/or RFA/TACE in the case of liver metastases [108, 109]. The combination of doxorubicin, streptozotocin, and 5-fluorouracil (5-FU) may serve as systemic chemotherapy [110].

The efficacy of biotherapy (somatostatin analogs, interferon-α) or PRRT has not yet been determined by ongoing clinical trials. So far, no study has shown prolonged survival for patients under palliative cytoreductive therapy.

Rare Functioning PNETs

Specific clinical symptoms and syndromes should be biochemically validated by confirmation of elevated serum levels of specific hormones. Global neuroendocrine parameters such as CgA and NSE should be assessed. SRS or ^{67}Ga-DOTATOC or other radionucleotide PET should be performed for evaluation of receptor status and localization. Additional imaging modalities include CEUS, CT, and MRI [46].

Curative surgery is recommended if disease is confined to the primary with or without technically resectable liver metastases. Lymph node dissection must be performed for suspicion of malignancy. Principally, surgery has to be performed after symptomatic control of hormone hypersecretion. Perioperative somatostatin infusion might be required to avoid a hormonal crisis.

Palliative surgery for control of hormone-related symptoms is justified, if $>90\%$ of the tumor mass can be removed. Liver transplantation should be taken into account in selected cases (exclusion of extrahepatic disease, standard surgery not feasible, or life-threatening symptoms refractory to maximal medical therapy). Local ablative therapy, such as TACE, RFA, cryotherapy, or laser therapy can serve as cytoreductive options.

Medical symptomatic control can be achieved with somatostatin analogs if SRS reveals receptor expression

(80%–90% of VIPoma/glucagonoma syndromes improve promptly). Somatostatin analogs may also have an antitumor growth efficacy. Interferon-α may be indicated in VIPomas not responding to somatostatin analogs.

Systemic chemotherapy should be considered in rapidly progressive systemic disease (streptozotocin plus 5-FU with or without doxorubicin) [46].

PRRT might be useful, if the tumor shows a high uptake on SRS. However, this approach is promising but remains experimental until clinical trials reveal a significant benefit for well-defined groups.

Well-Differentiated NF-PNETs

The diagnosis of nonfunctioning tumors is often delayed because of the lack of any hormonal syndrome. Generally, tumor mass effects determine clinical presentation. Therefore, localization is regularly achieved by conventional imaging modalities. Nevertheless, SRS is recommended to determine receptor expression status and rule out systemic disease. CgA and PP may serve as tumor markers, especially in the *MEN-1* genotype for NF-PNET screening [35].

In sporadic NF-PNETs, curative surgery is recommended if local and hepatic resectability is achievable and extrahepatic metastases are excluded. While tumors <2 cm might be enucleated, larger masses require aggressive, oncological surgical resection [35]. Nononcological resection of a small tumor with consecutive histological confirmation of malignancy must lead to early radical reoperation.

Liver transplantation for unresectable hepatic disease should be considered in highly selected patients. Even after careful patient selection, most transplanted patients experience recurrences within months, possibly because of undetected extrahepatic disease [105].

In the presence of the *MEN-1* genotype, the indications for surgery remain controversial. Whereas conservative groups recommend follow-up and enucleation of lesions >2 cm [111], more aggressive approaches encompass tumor enucleation in the head and prophylactic subtotal (80%) pancreatectomy [30, 59, 112].

Palliative surgery of liver metastases may be justified if $>90\%$ of the tumor mass can be reduced. No data support surgical debulking procedures if the primary is technically unresectable. The only exception to this is if tumor debulking is the only viable option to remedy tumor-related complications [35].

Even after complete (R0) resection of the primary and hepatic metastases, recurrence rates may be as high as 76%. The 5-year survival rate after hepatic surgery of patients with NF-PNET metastases is 47%–76% and is not significantly different in nonsurgically treated patients (30%–40%) [113, 114].

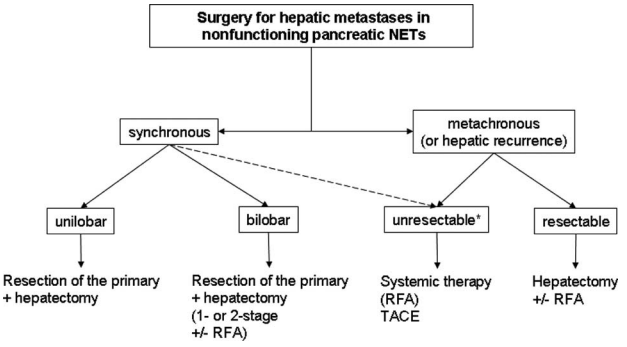

Figure 1. Suggested algorithm of different treatment options for liver metastases in NF-PNETs according to Falconi et al. [35]. Hepatectomy = Oncological resection. Abbreviations: NF-PNET, nonfunctional pancreatic neuroendocrine tumor; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Taking into account sufficient hepatic reserve, age, surgery-related morbidity, and mortality, the ENETS consensus conference [35] recommended an algorithm for the management of hepatic metastases (Fig. 1).

Locoregional ablative techniques (TACE, RFA) are recommended only in patients without extrahepatic metastases, whereas no conclusive clinical data are available concerning the effects on survival.

First-line biotherapy in SRS-positive NF-PNET patients is treatment with somatostatin analogs. Alternatively, interferon-α might be considered in SRS-negative tumors or after failure of somatostatin therapy. Systemic chemotherapy with streptozotocin in combination with 5-FU and doxorubicin should be considered after biotherapy has failed. No data are available to recommend adjuvant therapy [35].

Promising experimental approaches, such as selective internal radiation therapy with yttrium-90 microspheres [115], PRRT [116], antiangiogenic therapy [117], or new targeted chemotherapy regimens [118–120], have to be validated in the future by well-designed clinical trials.

Poorly Differentiated PNETs

Poorly differentiated PNETs are characterized by their aggressive tumor biology, absence of somatostatin receptors, and poor prognosis. NSE might be a good tumor marker, whereas CgA is usually negative. Conventional imaging techniques are mostly sufficient for localization of the primary and hepatic metastases, whereas ^{18}F-fluorodeoxyglucose PET may serve for additional information concerning systemic disease. Histological confirmation of the diagnosis by transcutaneous biopsies might be helpful for therapeutic decisions.

Surgery is only recommended for resectable primary tu-

Table 4. Recommendations for PNET follow-up

Tumor	Interval	Investigations
Benign WDET	Every 12 mos	CgA serum levels; if applicable, hormone levels
		Imaging studies (ultrasound)
Uncertain WDET	After 6 mos	SRS (in case of SRS-positive primary, once-only investigation)
	Every 12 mos	CgA; if applicable, hormone levels
		Imaging studies (ultrasound, CT, MRI)
WDEC–M0	Every 6 mos	CgA, NSE
		Imaging studies (ultrasound, CT, MRI, SRS)
WDEC–M1, PDEC	Every 3 mos	CgA, NSE
		Imaging studies (ultrasound, CT, MRI)

Abbreviations: CgA, chromogranin A; CT, computed tomography; MRI, magnetic resonance imaging; NSE, neuron-specific enolase; PDEC, poorly differentiated endocrine carcinoma; SRS, somatostatin receptor scintigraphy; WDEC, well-differentiated endocrine carcinoma; WDET, well-differentiated endocrine tumor.

mors, whereas the presence of hepatic metastases excludes a curative surgical approach. Cytoreductive procedures are generally not recommended, although TACE may be justified in selected patients.

Systemic chemotherapy with etoposide and cisplatin might be indicated in systemic disease, revealing remission in 55%–80% of patients, with a response duration of 8–11 months [91, 121].

Follow-up

Although evidence for reasonable follow-up or control of treatment efficacy is poor, we suggest a follow-up scheme closely related to the ENETS recommendations [35, 46, 57, 90, 91] and geared to WHO histological grading (Table 4).

Conclusion

As reported by the National Cancer Institute summit meeting in 2007 on GEP-NETs [85], standardized clinical management is often limited by different aspects of the disease, for example, its relative rarity, the limited understanding of tumor biology and behavior, heterogeneous clinical presentation, and the lack of prospectively evaluated risk stratification systems, and thus, incomplete implementation of staging systems. Thus, prospective tumor registries and tissue banks are required to scrutinize the value of different classification systems and search for biomarkers of GEP-NET biology, possibly resulting in new diagnostic and therapeutic strategies.

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Neuroendocrine Tumors of the Pancreas

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