

Nonfunctional Pancreatic Neuroendocrine Tumors: Advances in Diagnosis, Management, and Controversies

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In this article, we aimed to review the literature on the clinics and management of nonfunctional pancreatic neuroendocrine tumors (NPNET). Pancreatic neuroendocrine tumors (PNET) are rare tumors with a <1/100,000 incidence and constitute approximately 2 to 10% of all pancreatic tumors. Nonfunctional PNETs are difficult to detect at early stages since they have no symptoms. Except those detected accidentally during different diagnoses, the majority of PNETs are detected in the advanced stages, with symptoms related to tumor size or liver metastasis. We reviewed the studies published in the English medical literature through PubMed and summarized the clinical features and current approaches to the treatment and follow-up of the NPNET. The common imaging techniques used for the detection of tumor localization, size, locoregional, and metastatic involvement are contrasted computed tomography, magnetic resonance imaging, endoscopic ultrasonography, and somatostatin receptor scintigraphy. Surgical resection is the only curative treatment. However, in advanced locoregional disease and liver metastasis, interventional ablative therapies such as palliative reductive surgery, selective hepatic arterial embolization, radiofrequency ablation; and systemic therapies, such as peptide receptor radionuclide therapy, chemotherapy, somatostatin analogous therapy, interferon, VEGF inhibitor, and mTOR inhibitor may be used as symptom relieving or may improve progression-free survival and total survival. Current knowledge on NPNET shows that the treatment should be personalized considering the prognostic features and life expectancy of the patient.

Key words: Nonfunctional pancreatic neuroendocrine tumor – Surgical resection – Diagnosis criteria – Treatment options

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Gastroenteropancreatic neuroendocrine tumors (GEP-NET) are produced as a result of the malignant transformation of the neuroendocrine cells that regulate the secretion and motility of the gastrointestinal tract. The incidence of GEP-NET was found to be 3.65/100,000, according to the 2000–2007 American SEER database, and approximately 7% of those were classified as (0.43/100,000) pancreatic neuroendocrine tumors (PNET).¹ Approximately 2 to 10% of the pancreatic tumors consist of PNETs.² Although it seems to be a rare tumor in clinics, a histologic PNET finding may be observed in 1 to 10% of the series in some autopsy studies.³ PNETs are commonly known as slow progressing tumors; however, their metastatic potential is high. In both population- and center-based studies, distant metastasis has been reported in 60 to 77% of the patients with PNET.^{4–6} The most frequent PNET-related metastasis is observed in the liver.

PNETs are classified as functional or nonfunctional according to their functions. Functional PNETs are labeled insulinoma, gastrinoma, or glucagonoma, according to the hormones they secrete, and may appear with symptoms related to excessive hormone secretion. Nonfunctional PNETs on the other hand, secrete some molecules such as chromogranin, neuron-specific enolase, pancreatic polypeptide, and ghrelin, but do not result in clinical manifestations related to hormone secretion. Since they show quiescent progression for a long time, they are detected in the advanced stages with symptoms related to the physical size of the tumor and metastasis. The main complaints observed in PNET are abdominal pain (35–78%), weight loss (20–35%), anorexia and nausea (45%), icterus (17–50%), intra-abdominal hemorrhage (4–20%), and mass observed in the examination (7–40%).⁷ Functional PNETs appear more frequently in previous studies, whereas recent studies include nonfunctional PNETs with rates approximating 90%.^{4,8} A retrospective trend study also shows a more than 2-fold increase in the incidence of nonfunctional PNETs compared to 16 years previous.⁹ Asymptomatic PNETs may have a role in this relative increase due to the advances in imaging techniques and related accidental detection of the tumors.

Hereditary Syndromes

Although PNETs are generally sporadic, they have been related to several hereditary syndromes, such as multiple endocrine neoplasia type I (MEN-1), von Hippel-Lindau (VHL), neurofibromatosis-1 (NF-1)

and tuberous sclerosis. Concerning the MEN-1 patients, clinical findings are detected in 20 to 80% and microscopic PNET can be found in almost all patients.¹⁰ The majority of the MEN-1 related PNETs are of the nonfunctional type. PNETs are observed at a rate of 10 to 17% in von Hippel-Lindau (VHL) disease, and 98% of these are nonfunctional as well.¹⁰ Nonfunctional or functional PNETs may be observed although rare in NF-1 and tuberous sclerosis.

Tumor Classification and Grading Systems, and Prognosis

In terms of classification, it is irrelevant whether the PNETs are functional or nonfunctional. The well-differentiated neuroendocrine tumors and poorly-differentiated small or large cell carcinomas are separately evaluated in the 2010 gastrointestinal system tumor classification of WHO. Neuroendocrine tumors are graded as G1 (mitosis count, <2/10 HPF (*high power field*) and/or Ki-67, ≤2%) and G2 (mitosis count, 2–20/10 HPF and/or Ki-67, 3–20%) according to the mitosis count or Ki-67 proliferative index. All neuroendocrine carcinomas are graded as G3 (mitosis count, >20 and/or Ki-67 >20%; Table 1).¹¹

However, the *European Neuroendocrine Tumor Society* (ENETS)¹² and *American Joint Committee on Cancer* (AJCC)¹³ have also suggested TNM-based PNET classification and grading systems in relation to prognosis (Table 2 and 3). Although ENETS and AJCC TNM classification systems are different in terms of some aspects, it has been proven in retrospective studies that both gave valid postulations for survival rates according to the grading systems.^{14,15} When the 2 TNM classification systems are compared regarding their prognoses, the 5-year total survival was found to be 100%, 88%, 85%, and 57% with ENETS and 92%, 84%, 81%, and 57% with AJCC for grades 1, 2, 3, and 4, respectively.¹⁵ Liver/bone metastasis is the most common factor affecting prognosis. Other factors may be counted as lymph node involvement, invasion depth, presence of certain histologic markers, necrosis, high serum alkaline phosphatase level, advanced age, and WHO and TNM scoring systems.¹⁶

Diagnostic Methods

Nonfunctional PNETs are generally large in size and have a heterogeneous structure. Irregular calcification, necrosis, and cystic changes may be observed.

Table 1 2010 WHO classification of pancreatic neuroendocrine tumors^{11,16}

Histologic type	Mitosis count	Ki-67 (%)
Well-differentiated NET, G1 (carcinoid)	2/10 HPF	≤2
Well-differentiated NET, G2	2 to 20/10 HPF	3 to 20
Poor-differentiated NEC, G3 (large or small cell type)	>20/10 HPF	>20

HPF, high power field; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

Local and vascular invasion and distant metastasis are commonly observed conditions. Confirmation of PNET necessitates Chromogranin A (CgA) and synaptophysin positivity in immunohistochemical staining in the histopathologic examination.⁷ Diagnosis is made upon the presence of the primary tumor and various imaging techniques for the evaluation of nodal or metastatic situations. Routine sectional imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), and somatostatin receptor scintigraphy (SRS) are the techniques that are routinely used in the diagnosis of the disease.

CT and MRI

Since PNETs have a hypervascular structure, the best imaging is obtained via contrast agent admin-

istration. The sensitivity of helical multiphasic contrasted CT is over 80%, and even 100% sensitivity has been reported for tumors larger than 3 cm.^{16,17} A typical pancreatic CT scan consists of the noncontrasted phase, contrasted arterial phase, and portal venous phase.¹⁸

The advantageous aspects of MRI may include nonexposure to ionized radiation and excellent soft tissue contrast resonance. Diagnostic PNET studies via MRI report 80% sensitivity and 100% specificity.¹⁹ The PNETs are visualized as hypervascular lesions of low T1 signal intensity or moderate T2 signal intensity in the MRI; larger necrotic tumors may give heterogeneous signal distribution.¹⁸ MRI has been reported to be more effective in detecting liver metastasis compared to CT or SRS.²⁰

Endoscopic ultrasonography (EUS)

EUS is another method for the diagnosis of pancreatic lesions, especially for the lesions smaller than 1 cm. The sensitivity of EUS is reported to be 79 to 100%.²¹ Furthermore, EUS plays an important role in the early detection and follow-up of multifocal PNETs that are common among patients with MEN-1 and VHL syndromes.²²

EUS-guided thin needle biopsy provides the preoperative histopathologic examination and plays an important role in the discrimination of guided

Table 2 ENETS TNM grading system for pancreatic tumors¹²

T grade (primary tumor)			
T _x	Primary tumor is not assessed		
T0	No finding of primary tumor		
T1	Tumor is limited to the pancreas and <2 cm		
T2	Tumor is limited to the pancreas and 2 to 4 cm		
T3	Tumor is limited to the pancreas and >4 cm or duodenum or biliary tract invasion is positive		
T4	Tumor has invaded the neighboring organs (stomach, spleen, colon, adrenal gland) or walls of the large vessels (celiac artery or superior mesenteric artery)		
N—lymph node status			
N _x	Regional lymph nodes are not assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis is positive		
M—distant metastasis			
M _x	Distant metastasis is not assessed		
M0	No distant metastasis		
M1	Distant metastasis is positive		
Grade I	T1	N0	M0
Grade IIA	T2	N0	M0
Grade IIB	T3	N0	M0
Grade IIIA	T4	N0	M0
Grade IIIB	Any T	N1	M0
Grade IV	Any T	Any N	M1

Table 3 AJCC TNM grading system for pancreatic tumors¹³

T grade (primary tumor)			
Tx	Primary tumor is not assessed		
T0	No finding of a primary tumor		
Tis	In situ carcinoma		
T1	Tumor is limited to the pancreas and ≤ 2 cm		
T2	Tumor is limited to the pancreas and >2 cm		
T3	Tumor has progressed beyond the pancreas but there is no celiac or mesenteric artery involvement		
T4	Tumor shows celiac or superior mesenteric artery involvement.		
N—lymph node status			
Nx	Regional lymph nodes are not assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis is positive		
M—distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis is positive		
Grade 0	Tis	N0	M0
Grade IA	T1	N0	M0
Grade IB	T2	N0	M0
Grade IIA	T3	N0	M0
	T1	N1	M0
Grade IIB	T2	N1	M0
	T3	N1	M0
Grade III	T4	Any N	M0
Grade IV	Any T	Any N	M1

nonfunctional PNETs from pancreatic adenocarcinomas and other pancreatic lesions.²³

Somatostatin receptor scintigraphy (SRS)—Octreoscan

Most of the PNETs include somatostatin receptors on their cell membranes. Therefore, it is possible to visualize the PNET cells via radioactive-labeled somatostatin analogues. Indium 111 labeled DTPA-octreotide (a synthetic somatostatin analogue) is a routinely used agent in SRS; SRS is therefore known as octreoscan. SRS is highly effective in diagnosing nonfunctional PNETs, gastrinomas and glucagonomas; however, it cannot effectively detect insulinoma or poorly-differentiated tumors since they have a weak somatostatin receptor expression.²⁴ The advantage of SRS is that it can scan not only the abdominal region, but the whole body rapidly, with regard to the presence of a metastasis. In patients with suspicious extra hepatic metastasis, SRS may both confirm the diagnosis and affect the treatment plan.²⁵ The accuracy rate of SRS has been increased by the usage of SPECT (*single photon emission computed tomography*).²⁶

Biochemical marker scanning

Although no biomarker has been defined specific to PNETs, increase in the plasma levels of various

nonspecific biomarkers may indicate the presence of a neuroendocrine tumor. The most facilitating marker among these is plasma CgA. The sensitivity and specificity of CgA in GEP-NETs are approximately 60% and 80%, respectively.²⁷ Furthermore, increase in the plasma levels of CgA has been related to a progression in the disease and metastasis, and thus it may be used in the follow-up of the disease.^{27,28} In addition to CgA, markers such as pancreatic polypeptide (pp), plasma neuron-specific enolase, pancreastatin, and human chorionic gonadotropin α and β may be used in the diagnosis of GEP-NET. However, their sensitivities are less. In nonfunctional PNETs, concomitant usage of plasma CgA and pp markers may significantly increase the sensitivity of the test. In a study, the sensitivity of plasma CgA alone was shown to be 68% and the combination of CgA and pp has resulted in 93% sensitivity in the detection of nonfunctional PNETs.²⁹

Surgical Treatment

The treatment of PNETs are planned according to several factors, such as the grade of the tumor, whether it is well or poorly differentiated, severity of the symptoms and the presence of a hereditary syndrome. The main curative treatment is surgical resection. In advanced locoregional disease and liver

metastasis, palliative reductive surgery, other interventional therapies, and medical therapies may be used.

Primary tumor resection

Surgical resection is recommended for both the sporadic and MEN-1 related nonfunctional PNETs where the tumor size is greater than 2 cm, because the risk of locoregional and distant metastasis is increased.^{30,31} In a retrospective study based on the American SEER data base, the survival rates were demonstrated to increase significantly via aggressive treatment.³² In this study, tumor resection was recommended for 425 patients and performed on 310. Among those, the survival was 114 months, and among the remaining 115 with no resection, the survival was 35 months ($P < 0.001$). In the same study, the odds ratio of mortality was calculated to be 0.48 in the resection group compared to the non-resection group.³² However, surgical resection is controversial in patients with a tumor size smaller than 2 cm, having a benign appearance and showing slow progression. There are even studies suggesting aggressive treatment in nonfunctional and accidentally detected PNETs smaller than 2 cm due to the unknown metastatic potential.³³ In some other studies, follow-up via EUS or MRI are recommended in such cases since resection-free survival is generally high.^{34,35} The risk/benefit ratio of surgical intervention, particularly in multifocal MEN-1 related PNETs with a known nature, should be carefully considered, because the risk of glucose intolerance and diabetes may be high in patients with MEN-1 and undertaken distal pancreatectomy.³⁶

The surgical approach may be performed via organ protective enucleation or central pancreatectomy, or as open or laparoscopic techniques in patients with small and benign type tumors.³¹ The advantage of enucleation and central pancreatectomy is that they do not result in pancreatic failure in the long term. The disadvantages of the method are negative surgical border ambiguity and the absence of routine lymphadenectomy. Lymph node sampling may be necessary for patients with uncertain clinical or pathologic findings for potential malignancy.³⁶

In cases where locoregional disease or with a tumor size larger than 2 cm are suspected, a distal pancreatectomy may be performed if the tumor is localized in the caudal region (with or without splenectomy); or pancreatic duodenectomy (Whipple's procedure) may be performed if the tumor is localized in the caput/corpus region, or lymph node dissection may be performed.^{31,36}

Surgery in liver metastasis

The first treatment option in liver metastasis is surgical resection. However, the complete resection of the liver metastasis is usually not possible and the risk of recurrence is generally high. It may be performed when the hepatic involvement is less than 50% and at least 90% of the tumoral tissue can be resected, or in the palliative treatment of symptomatic diseases.^{31,36} It has been observed that cases with proper criteria curative or palliative surgical resection increased survival, despite high recurrence rates. In a retrospective series including 72 patients with liver invasive PNET, the morbidity and mortality rates following surgery were found to be 50% and 0% respectively, and 1- and 5-year survival rates were found to be 97.1% and 59.9%.³⁷ Surgical resections of the primary pancreatic tumor and liver metastasis may be performed concomitantly or in consequent operations. However, in a double-center, retrospective study, the major complication (liver abscess) was more frequent in 2-step pancreatic duodenectomy and liver metastasis resections than concomitant resection (14.5% versus 7%, $P < 0.05$).³⁸ In another recent study on patients with primary GEP-NET and bilobar liver metastasis, 2-step surgery was performed where the first step was the resection of the primary tumor and the involvement in 1 lobe. A period of 8 weeks was then allowed for the hypertrophy of the liver, after which the other lobe was resected.³⁹ It was suggested that a radical surgical treatment may be performed in patients with high grade of liver involvement via this method, with acceptable morbidity rates.⁴⁰

Liver transplants

Liver transplantations have been performed on some rare liver metastasis patients as a treatment option. However, this approach is not quite acceptable when the donor insufficiency and rapid recurrence rates are considered. It may be a last option in patients over 50 years of age, patients with a proven absence of extrahepatic metastasis via comprehensive whole body imaging techniques, and in patients with positive histologic properties (well-differentiated, Ki-67 $< 5\%$) who are not candidates for resection and who have not responded to other therapies.⁴⁰

Other Interventional Locoregional Treatments

Selective hepatic arterial embolization

Metastatic liver lesions are hypervascular and are fed by the hepatic artery. The hepatic tissue on the other

hand is fed primarily by the portal vein. Hepatic arterial embolization aims to direct the tumoral lesions to ischemia without deteriorating the liver parenchyma. This method is used in liver metastases where surgical resection is not possible due to its diffuse and multifocal nature. The indicators of good prognosis are previous primary pancreatic tumor resection, less than 75% involvement of the liver, <5 cm tumor size and absence of extrahepatic metastasis.⁴¹ Embolization may be performed via gel foam powder infusion (single embolization), microspheres that secrete chemotherapeutic agents (chemoembolization), or microspheres that secrete radioactive isotope (radioembolization). There is no sufficient data demonstrating the superiority of any of these methods to one another.¹⁶ In a review published in 2009, the 5-year survival rates were 40 to 67% and 50 to 65% in single embolization and chemoembolization, respectively.⁴² In a series including 148 patients who were treated with radioembolization (Yttrium-90 resin microspheres) the median survival time was 70 months, the rate of complete response was 2.75%, the rate of partial response was 60.5%, and the progression-free diseases was reported to be 22.7%.⁴³

Radiofrequency ablation (RFA)

RFA is used as a symptom-relieving or supportive treatment in nonresectable liver metastases. It may be performed via the relieving of small lesions during open or laparoscopic liver tumor resections or via the percutaneous route alone. The ablation of the tumoral tissue is provided by the application of inserting high temperatures into the tumor via an RFA needle in the guidance of ultrasound. In a series including 89 patients with neuroendocrine liver metastasis, the symptoms were relieved in 97% of the patients via laparoscopic RFA. Although the recent hepatic lesion development and extrahepatic metastasis was about 60%, the disease-free survival was 1.6 years and total survival was 6 years.⁴⁴

Peptide Receptor Radionuclide Therapy (PRRT)

PRRT is based on the systemic transmission of radioisotope labeled synthetic somatostatin analogue (Lutetium-177 or Yttrium-90) to the metastatic cells within the whole body.⁴⁵ The number of somatostatin receptors should be high in the tumor cells in order to be able to use this method. Although it is not counted in the primary therapies, PRRT is recommended when the systemic medical therapy is unsuccessful in the diffuse diseases with

extrahepatic metastasis.³⁶ In a cohort study where Yttrium-90 DOTATOC and consequent Yttrium-90 DOTATOC and Lutetium-177 DOTATOC treatments were performed on 2 separate groups of 486 patients, consequent radioisotope usage was shown to provide a longer survival rate (5.51 versus 3.96 years).⁴⁶

Medical Treatment

Somatostatin analogue therapy

Long-term somatostatin analogue therapy is an antiproliferative therapy used in patients with a slow progressive PNET and a low rate of liver involvement (less than 50%) in order to stop/slow down the progression of the disease. In a randomized, double-blind, placebo controlled study on patients with GEP-NET, the somatostatin analogue octreotide-LAR delayed the tumor progression compared to the placebo (14.3 months versus 6 months, hazard ratio = 0.34), and following 6 months of therapy, progression-free disease was observed in 66.7% of the therapy group compared to 37.2% of the placebo group.⁴⁷ Since the somatostatin analogue is well tolerated, it may be primarily used primarily; however, chemotherapy is recommended for nonfunctional PNET patients with well-differentiated tumors and a Ki-67 index of >15%.⁴⁸

Interferon

Similarly, interferon therapy is used to stop or stabilize the progression of the disease and may be used in metastatic nonfunctional PNETs. However, frequent side effects limit the wide and long-term usage of this therapy.³¹ In a randomized study performed on 80 patients with metastatic GEP-NET, the somatostatin analogue lanreotide, interferon- α or the combination was applied to the patients, and the stable disease was found to be between 18 to 28% in all groups.⁴⁸

Chemotherapy

Cytotoxic chemotherapy may be used in PNETs with diffuse liver metastasis, in patients with rapid local progression, in poorly-differentiated patients, in well-differentiated but high proliferative Ki-67 index patients, or in patients not responding to the somatostatin analogue therapy.³¹ In a retrospective examination of 84 patients with advanced-stage PNET, the response to the triple therapy of streptozocin, fluorouracil, and doxorubicin was 39%; pro-

gression-free survival was 18 months, and general survival was 37 months.⁴⁹ In another phase II study on advanced grade PNET patients with dacarbazine, the objective response rate was found to be 34%.⁵⁰

A recent ENETS consensus guideline has summarized the chemotherapeutic approach in GEP-NETs with hepatic and distant metastases.⁵¹

VEGF inhibitor

VEGF is a growth factor that plays a role in angiogenesis. The progression-free survival was found to be improved in advanced-stage, well-differentiated PNETs with VEGF inhibitor sunitinib (11.5 months versus 5.5 months); however, the clinical study was ceased due to serious adverse events and death observed in the placebo arm.⁵² Since there is no sufficient data on issues such as long-term resistance or side effects yet, it is not currently recommended as a first-step therapy.⁵¹

mTOR inhibitor

mTOR (mammalian target of rapamycin) is a serine/threonine protein kinase molecule that has a role in the tyrosine kinase pathway. The mTOR inhibitor everolimus was compared to a placebo in a phase III study including patients with advanced, low and moderate stage PNET. In this study, where the best possible supportive treatment was performed on both groups, everolimus provided a significantly improved survival rate (11 months versus 4.6 months) and was well tolerated.⁵³ However, since everolimus is a recent agent like sunitinib, it is not recommended as a first-step therapy. There is the suggestion that it be used as a second- or third-step therapy if no response to other therapies is observed.⁵¹

Conclusion

Gastroenteropancreatic neuroendocrine tumors are rare diseases and there is quite a controversy concerning the diagnosis of the disease. Although we tried to review the literature to have a wide understanding about the disease, more data are needed to have a better prognosis with treatment modalities.

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