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Treatment Strategy for Pancreatic Neuroendocrine Neoplasms (pNEN)

Koji KUBOTA, Akira SHIMIZU*, Tsuyoshi NOTAKE, Shinsuke SUGENOYA, Kiyotaka HOSODA
Koya YASUKAWA, Hikaru HAYASHI, Ryoichiro KOBAYASHI and Yuji SOEJIMA

*Division of Gastroenterological, Hepato-Biliary-Pancreatic, Transplantation and Pediatric Surgery,
Department of Surgery, Shinshu University School of Medicine*

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I Introduction

Neuroendocrine neoplasms (NEN) were previously classified under the disease concept vaguely referred to as carcinoids. The term carcinoids were removed from the 2000 World Health Organization (WHO) classification of pancreatic and gastrointestinal tract diseases and the disease concept of neuroendocrine tumors (NET) was defined. In the 2010 WHO classification, tissue grading was reconsidered using the Ki-67 index and mitotic count, which represents mitotic cell patterns that correlate with clinical symptoms. Moreover, the notation in the 2017 WHO classification of gastrointestinal and pancreatic neuroendocrine tumors was changed from NET to NEN. New concepts were also proposed, including the reclassification of neuroendocrine carcinomas (NEC) into well-differentiated G3 NET and poorly-differentiated NEC. This was accompanied by a revision of the Clinical Practice Guidelines for Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN) 2019 in Japan¹⁾ (hereinafter, Japan NeuroEndocrine Tumor Society; JNETS Guidelines, 2nd Edition). An observation approach was included as a treatment option

for some of the non-functional pancreatic neuroendocrine tumors, although conditional. There have also been changes to surgical treatments, including the addition of surgical indications to the newly proposed G3 NET. Given the differences between the National Comprehensive Cancer Network (NCCN) guidelines²⁾ and the European Neuroendocrine Tumor Society (ENET) guidelines³⁾, this article provides a review of surgical treatments for pancreatic NEN (pNEN).

II Pancreatic Neuroendocrine Neoplasms (pNEN)

The generic term for neuroendocrine tumors of the pancreas is pNEN. For pNEN, the degree of differentiation is first evaluated pathologically. Well-differentiated tumors are classified as pancreatic neuroendocrine tumors (pNET), and poorly-differentiated tumors as pancreatic neuroendocrine carcinomas (pNEC). Within pNET, tumors are divided into functional pancreatic endocrine tumors with clinical manifestations of excess hormone production of tumors and non-functional pancreatic endocrine tumors without clinical manifestations. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) were defined as tumors where the same tumor contains at least 30% each of pNEN and another epithelial tumor (**Fig. 1**).

III Functional Pancreatic Neuroendocrine Tumor ; F-pNET

Treatment concepts for F-pNETs have two objectives: (1) improving hormonal symptoms through

* Corresponding author : Akira Shimizu
Division of Gastroenterological, Hepato-Biliary-Pancreatic,
Transplantation and Pediatric Surgery, Department of Surgery,
Shinshu University School of Medicine, 3-1-1 Asahi,
Matsumoto, Nagano 390-8621, Japan
E-mail : ashimizu@shinshu-u.ac.jp

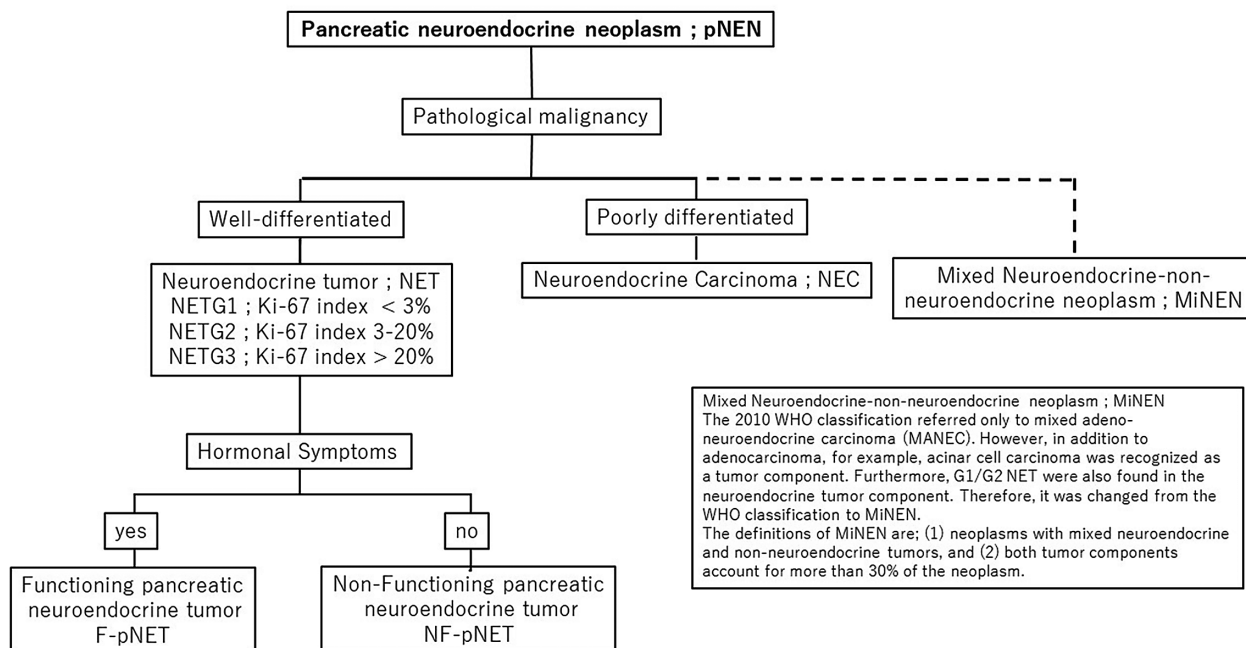
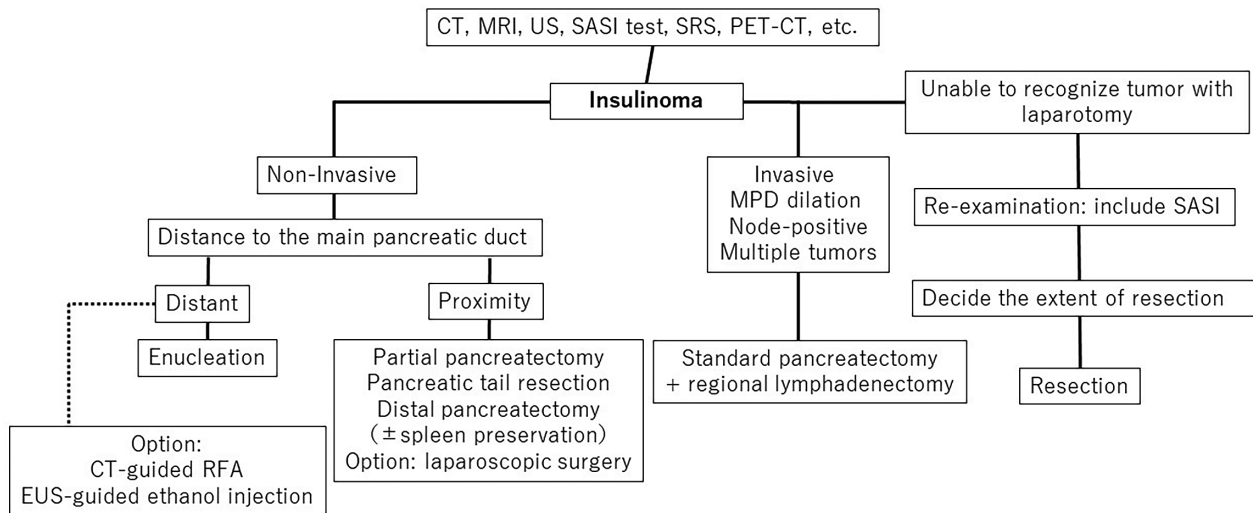


Fig. 1 Concept of pNEN

tumor resection (occasionally reducing the dose), and (2) radical resection of the tumor.

Insulinoma : This condition triggers hypoglycemic symptoms, as represented by the triad of Whipple symptoms that are caused by excessive secretions of insulin. Many patients experience some interference in their daily life due to chronic high insulin status. Surgical treatment is indicated when the diagnosis is confirmed, and surgery is recommended in all of the guidelines¹⁻³⁾. Approximately 90 % of insulinomas are benign tumors and are likely to be cured by surgery⁴⁾⁵⁾. There are some differences in the interpretations in each of the guidelines. In the 2nd edition of the JNETS guidelines, enucleation is recommended for tumors without distant metastases, without invasive findings, and that are distant from the main pancreatic duct⁶⁾⁷⁾. If damage to the main pancreatic duct is suspected, a procedure that preserves the pancreas as much as possible (including partial pancreatectomy, segmentectomy, distal pancreatectomy with/without spleen preservation) may be selected. Less invasive laparoscopic surgery is also an option at some medical institutions. Even if the tumor cannot be identified intraoperatively, surgery should be performed on that assumption. The recommendation is that not only diagnostic imaging but also selective

arterial secretagogue injection (SASI) testing with calcium be performed preoperatively. If tumors cannot be identified intraoperatively without SASI tests, intraoperative ultrasonography may be helpful. However, there is still a possibility that tumors may not be detected. Resection of the pancreas is not recommended if SASI tests are not performed preoperatively, the location of the intraoperative tumor (or even if it can be identified as a tumor) is not understood, or the culprit site is unclear. After abdominal closure, SASI tests must be performed to identify the culprit site and map the extent of resection. If the lesions cannot be confirmed to be tumors, lesions causing hyperinsulinemia, such as minute insulinoma, hyperplasia of the islets of Langerhans, and non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS), may be identified within the resected specimen⁸⁾⁹⁾. Standard pancreatectomy with lymphadenectomy is recommended for invasive findings, multiple lesions, lesions with dilated pancreatic ducts, and positive lymph node metastases. For the most part, surgical method selection is the same as described in the NCCN guidelines. Somatostatin receptor scintigraphy (SRS) or positron emission tomography/computed tomography (PET/CT) or PET/magnetic resonance imaging (MRI) is also recommended



selective arterial secretagogue injection test: SASI test
 somatostatin receptor scintigraphy: SRS
 noninsulinoma pancreatogenous hypoglycemia syndrome: NIPHS

Fig. 2 Surgical treatment algorithm for insulinoma

preoperatively². In addition to resection, the ENET guidelines introduce endoscopic ultrasonography (EUS)-guided ethanol injection and CT-guided radiofrequency ablation (RFA)¹⁰⁻¹² (Fig. 2). For insulinomas, treatment is difficult since whether or not the hyperinsulinemia improves intraoperatively even after the resection of tumors is not known. Based on this finding as well, confirming the localization of culprit lesions preoperatively by SASI tests provides reassurance. Although not mentioned in the guidelines, there have been reports of increases in glucose from continuous intraoperative glucose monitoring¹³ or an insulin/glucose ratio of 0.3 or less as being a guide for resection of culprit lesions¹⁴.

Gastrinoma: Refractory peptic ulcers and reflux esophagitis due to gastric hyperacidity are observed since the condition presents with the so-called Zollinger-Ellison syndrome (ZES). Gastrinoma is a highly malignant tumor with a high rate of lymph node metastases. Resection of the primary lesion and lymphadenectomy are necessary^{15,16}. Surgery is the only treatment method that can be expected to lead to a cure. Gastrinomas are often seen within the gastrinoma triangle comprising the duodenum and pancreas and adjacent lymph nodes¹⁷. However, since

5.6 % of instances arise outside the pancreas and duodenum¹⁸, systemic evaluation such as with SRS is required prior to surgery. Surgical procedures are almost identical to those described in the 2nd edition of the JNETS guidelines and the NCCN guidelines, and evaluations are performed depending on the location, the presence or absence of invasion, and the number of tumors. If neither pancreas or duodenum are invaded, enucleation and partial resection are chosen; however, lymphadenectomy is required for all procedures. Moreover, in patients with invasion or multiple lesions, pancreaticoduodenectomy, total duodenectomy, distal pancreatectomy, and central pancreatectomy are considered. However, the ENET guidelines do not recommend extensive surgery, such as pancreaticoduodenectomy, in gastrinomas complicated with multiple endocrine neoplasia type 1 (MEN1). The reason for this is that ZES can be controlled with pharmacotherapy^{19,20} and there is a possibility of numerous early and late complications with pancreaticoduodenectomy. This point significantly differs from the 2nd edition of the JNETS guidelines. Total pancreatectomy should be avoided for patients with glucagonoma associated with MEN, but the recommendation is that curative outcomes are

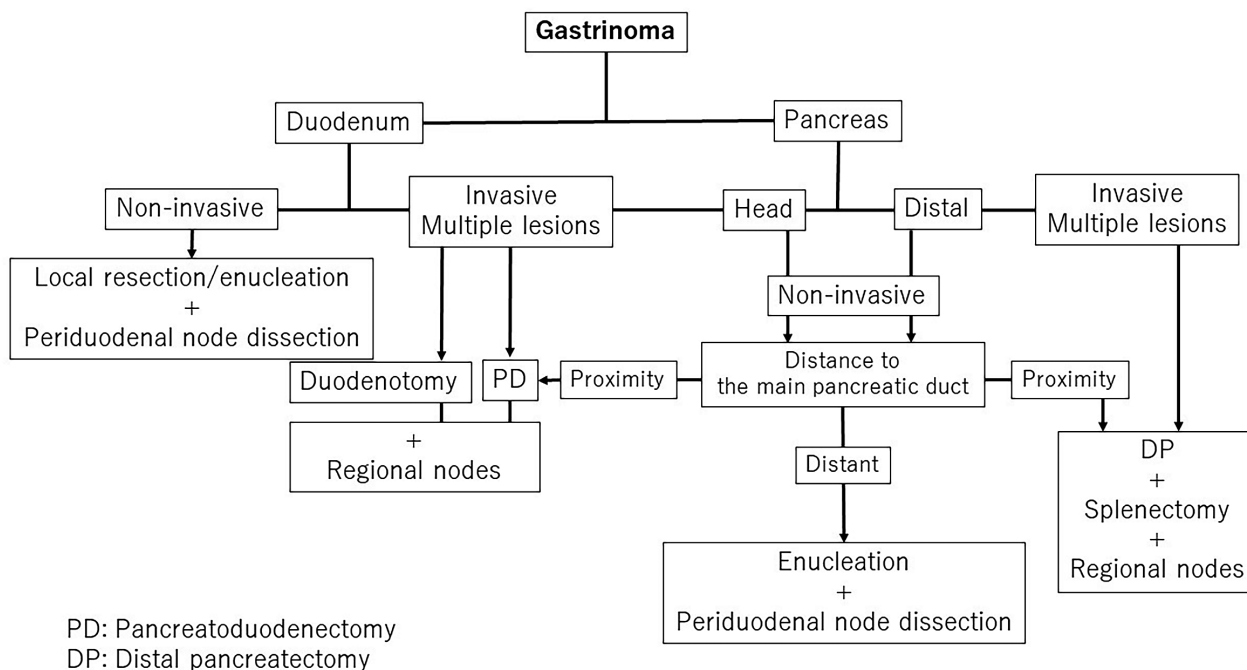


Fig. 3 Surgical treatment algorithm for gastrinoma

focused on when selecting the procedure²¹⁾²²⁾ (Fig. 3).

Rare functional pancreatic NET: In addition to insulinoma and gastrinomas, there are rare F-pNET, such as glucagonomas, vasoactive intestinal peptide (VIP) omas, somatostatinomas, growth hormone releasing factor (GRF) omas, pancreatic polypeptide (PP) omas, adrenocorticotrophic hormone (ACTH) omas, and parathyroid hormone (PTH) omas. All of these tumors are highly malignant and are associated with poor prognoses²³⁾. Surgery is the only curative treatment. Lymph node metastases are frequent in all of these tumors, and standard pancreatectomy with lymphadenectomy is recommended. Although these tumors are often large, spleen-preserving distal pancreatectomy and partial pancreatectomy or enucleation should be performed to preserve organ function in small tumors less than 2 cm. Lymphadenectomy should not be omitted.

IV Non-functional Pancreatic Neuroendocrine Tumor ; NF-pNET

Surgery is the fundamental treatment mentioned in all of the guidelines. However, there is no consensus as to whether resection should be performed for all patients with small NF-pNETs. In the 2nd edition

of the JNETS guidelines, the recommendation is to follow-up patients with tumors less than 1 cm in diameter and no incidental findings of metastases or invasion every 6 to 12 months and to consider surgery if the tumor grows larger²⁴⁾²⁵⁾. Follow-up is included as an option other than surgery for tumors less than 1 cm in the NCCN guidelines²⁾ and for tumors 2 cm or less in the ENETS guidelines³⁾. Since highly invasive procedures such as pancreaticoduodenectomy are an option, particularly when the tumor is located in the head of the pancreas, follow-up may be selected if preferred after providing a thorough explanation to the patient. Naturally, if such a course is taken, there must be no imaging findings that are suggestive of malignancies. There is also a need to determine whether follow-up is appropriate considering age and whether the patient has any complications. Standard pancreatectomy and regional lymphadenectomy are also indisputably indicated for large tumors 2 cm or more in diameter. However, for small tumors less than 2 cm, various pancreatic resection techniques can be chosen, ranging from enucleation to standard pancreatectomy, considering such factors as the location of the tumor and the main pancreatic duct (Fig. 4). There is, how-

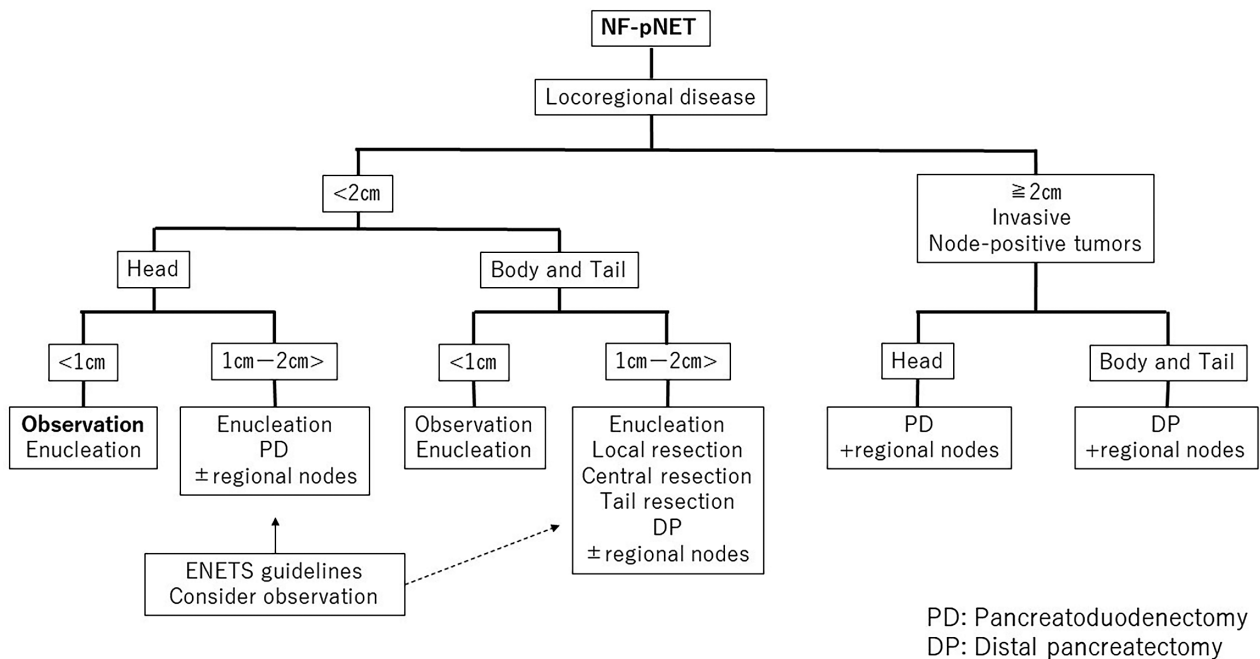


Fig. 4 Surgical treatment algorithm for NF-pNET

ever, no consensus on the extent of lymphadenectomy required. The 2nd edition of the JNETS guidelines also states that there is a need to investigate whether pancreatectomy with lymphadenectomy will lead to improved outcomes and quality of life (QOL) in all patients. This is because while there are numerous reports of very few nodal metastases in G1 pNETs less than 1 cm²⁶⁾⁻²⁸⁾, G1 pNETs less than 1 cm are also reportedly associated with widespread metastases²⁹⁾. At this point in time, the recommendation is to sample the surrounding lymph nodes, even if limited surgery is performed on NF-pNETs 2 cm or less.

V G3 pNET and pNEC

As previously mentioned, well-differentiated tumors with a Ki-67 index higher than 20 % are defined as pNET G3 and poorly-differentiated tumors as pNEC (G3) in the 2017 WHO classification. Within conventional NEC, there were groups responding differently to pharmacotherapy, and these were divided in two groups. The Ki-67 index for pNET G3 is modestly low, ranging from 20 % to 50 %, and response rates to platinum-based anticancer therapy, the standard treatment for NEC, are low. However,

the prognosis is relatively good. Conversely, the Ki-67 index for pNEC (G3) is usually at least 50 % and, although platinum-based pharmacotherapies are successful in some cases, survival prognoses are reported to be extremely poor³⁰⁾³¹⁾. Furthermore, a report on an investigation of gene expression patterns in both groups indicated that the gene expression patterns for pNET G3 were similar to those of pNET G1 and G2, whereas that for pNEC (G3) was similar to that of pancreatic ductal carcinoma³²⁾. The two tumor types did not show continuity in their development and malignant transformation as tumors, since the tumors were considered to have developed and originated from completely different cells. Prior to the 2017 WHO classification, NECs (known as pNET G3 and pNEC (G3) from 2017 onwards) were not indicated for surgery and the recommended treatment was platinum-based pharmacotherapy. However, following the 2017 revision of the WHO classification, the JNETS guidelines¹⁾ recommendations were also updated to state that the treatment policy for pNET G3 should conform to that of pNET G1/G2. This meant that surgery was added as a treatment option. Nevertheless, the prognoses for pNEC (G3) after resection remain extremely poor,

even in patients with resectable lesions, and the median overall survival does not exceed 12 months³³⁾⁻³⁵⁾. Since there have been no reports evaluating the outcomes of resection and prognostic factors for resection in only pNEC patients, whether surgery should be indicated or not and, if so, in which patients has not been clarified.

VI pNETs with Metastatic or Recurrent Lesions

If resection is feasible without the risk of leaving a residual lesion, multidisciplinary treatment with resection as the main treatment is indicated. An analysis of the vast amount of data in the United States Surveillance Epidemiology and End Results (SEER) registry revealed that surgical treatment that included the primary tumor and distant metastases was associated with improved outcomes³⁶⁾. However, most patients require multidisciplinary treatment and surgery alone is not expected to lead to a cure. In patients with pNET and liver metastases, recurrences within 3 years were reportedly associated with more lymph node metastases³⁷⁾, and favorable overall survival when hepatectomy and regional

lymphadenectomy were performed³⁸⁾⁻⁴⁰⁾. Thus, standard pancreatectomy with hepatectomy and regional lymphadenectomy is indicated in pNET patients with liver metastases. However, since simultaneous hepato-pancreatectomy is associated with excessive surgical invasiveness, not all patients are eligible for this procedure and it should be considered on a case-by-case basis considering the risks⁴¹⁾. Even in lesions for which curative resection is not feasible, surgery is indicated when improvements in prognosis and QOL are desired. In the United States, favorable prognosis was reportedly obtained with liver transplantation⁴²⁾.

VII Conclusions

This article focused on describing surgical options for pNEN. The extent and indications of lymphadenectomy and the role of hepatectomy in multidisciplinary treatment are controversial. The guidelines reported to date have been mainly from Europe and the United States, and the accumulation of more data from Japan is anticipated to lead to the dissemination of new evidence.

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