Review Article

Practical management and treatment of pancreatic neuroendocrine tumors

Naoko Iwahashi Kondo, Yasuharu Ikeda

Department of Gastroenterological Surgery, National Hospital Organization Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka City, Japan
Correspondence to: Naoko I. Kondo, MD, PhD. Department of Gastroenterological Surgery, National Hospital Organization Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka City, 8111395 Japan. Email: kondo-n@surg2.med.kyushu-u.ac.jp.

Abstract: Pancreatic neuroendocrine tumors (NETs) are uncommon disease, about which little is known. Pancreatic NETs are usually slow growing and their malignant potential are often underestimated. The management of this disease poses a challenge because of the heterogeneous clinical presentation and varying degrees of aggressiveness. Recently, several guidelines for the management of pancreatic NETs have been established and help to devise clinical strategy. In the treatment algorithms, however, a lot of uncertain points are included. Practical treatment decisions of pancreatic NETs are still sometimes made in a patient- and/or physicians-oriented manner. The tumor grading system proposed by the European Neuroendocrine Tumor Society (ENETS) gives important prognostic information, however, the implication of grading regarding medical treatment strategies to choose has not yet been clarified. Moreover, the place of surgical treatment is unclear in the overall management course of advanced pancreatic NETs. In some cases, practical management and treatment have to be individualized depending on predominant symptoms, tumor spread, and general health of the patients. Current issues and a few points to make a strategy in the management of pancreatic NETs would be reviewed.

Keywords: Pancreas; neuroendocrine; treatment; neuroendocrine tumor (NET)

Submitted Nov 11, 2013. Accepted for publication Dec 26, 2013.
doi: 10.3978/j.issn.2227-684X.2013.12.05
View this article at: http://dx.doi.org/10.3978/j.issn.2227-684X.2013.12.05

Introduction

Even though pancreatic neuroendocrine tumors (NETs) are slow growing and are not as aggressive as invasive ductal carcinomas of the pancreas, once unresectable metastases has occurred, it would become life-threatening sooner or later and cure would be highly unlikely. The US Surveillance Epidemiology and End Results (SEER) database from the year 1973 to 2004 suggests that pancreatic NETs are account for 3.6% of all NETs (1). Pancreatic NETs are rare subgroup of pancreatic tumors and represent about 1-2% of all pancreatic neoplasms (2). The incidence and prevalence of overall NETs has increased substantially, and the incidence of pancreatic NETs alone has also increased in the data of each primary tumor site (3). Recently, increased incidental lesions of the pancreatic NETs may be led by the increasing of availability of advanced imaging examinations (4,5). The developments of imaging modalities that allow the hemodynamics monitoring of the pancreatic tumors have made accurate diagnoses of the most of pancreatic NETs easy because the typical pancreatic NETs are hypervascular.

In the European Neuroendocrine Tumor Society (ENETS) consensus guidelines, the grading of proliferative rate of the tumor cells based on combination the mitotic rate and Ki67 labeling index is advocated (6). Moreover, the newest World Health Organization (WHO) classification incorporates grading and staging, and provides a basis for prognostic prediction (7). These grading systems are helpful to assess the predictive malignant potential in the patients with pancreatic NETs. It would be expected to apply more practically at each disease stage.

Some controversial issues in the diagnoses or treatments of pancreatic NETs, especially in the treatments of advanced

pancreatic NETs, still remain. Here, we review pancreatic NETs from a perspective of practical strategies and make a few points in regard to diagnoses and treatments in the following sections.

Diagnosis

Diagnosis of functioning or nonfunctioning pancreatic NETs

Pancreatic NETs are divided into two groups: those associated with a functional syndrome and those that are not associated with a functional syndrome. The functional symptoms are related to the type of hormone secreted: insulin, gastrin, glucagons, vasoactive intestinal peptide, somatostatin or combination of them (4). Nonfunctioning pancreatic NETs, however, frequently secrete a number of other substances, for instances, chromogranins, neuron-specific enolase, subunits of human chorionic gonadotropin, neurotensin, and grehlin, but by definition of nonfunctioning pancreatic NET these hormones are not secreted or do not lead to a clinical syndrome (8-11). Although the clinical relevance of the distinction between functioning and nonfunctioning pancreatic NETs has recently been questioned as the treatment of these tumors follow the same general principles (12), the distinction is sometimes important for clinical presentation, diagnosis, and treatment of these tumors.

The patients who have even small primary functioning pancreatic NETs sometimes present hormonal manifestation and the localization of tumors is difficult to be depicted by CT or MRI imaging (13). Insulinomas are the most common functioning pancreatic NETs. The sizes of tumors are ≤2 cm at presentation in approximately two thirds of cases, making them notoriously difficult to localize radiologically (14). Recent data suggest that glucagon-like peptide 1-receptor scans might be helpful in localization of these tumors, especially of benign insulinomas (15,16). Ito *et al.* reported that gastrinomas are the second common functioning pancreatic NETs in Japanese population (17). In the past, approximately 70-80% of gastrinomas were thought to occur in the pancreas, particularly in its head. Currently, gastrinomas are more frequently found in the duodenum rather than in the pancreas. Gastrinomas are found the duodenum in more than 60% of patients with sporadic Zollinger-Ellison syndrome (ZES) and in more than 85% patients with multiple endocrine neoplasia type 1 (MEN 1) with the presence of ZES (18). Klöppel G *et al.* described that the reason for this change is that in the past many of the small duodenal gastrinomas were overlooked, but their large peri pancreaticoduodenal lymph node metastases were regarded as primary pancreatic gastrinoma or primary lymph node gastrinoma (19). Recently, pancreatic gastrinomas are revealed to be more aggressive and much more likely to distant metastases than duodenal gastrinomas (8,20,21). Therefore, to make precise diagnoses of localization of these small tumors are more important in the management. Somatostatin receptor scintigraphy (SRS), selective arterial secretagogue injection (SASI) test, and/or arterial stimulating venous sampling (ASVS) are useful functional diagnostic technique to identify localization of the tumors.

Nonfunctioning pancreatic NETs represent 30-50% of all pancreatic NETs and malignancy occurs in 60-90% (22,23). There is a correlation between tumor size and malignancy in tumors of nonfunctioning pancreatic NETs (24). Characteristically, nonfunctioning pancreatic NETs are large, and 60% to 85% of them having liver metastases at the time of diagnosis (8,10,11,25). The presence of nonfunctioning pancreatic NET is suggested by the presence of a hypervascular pancreatic tumor in a patient without hormonal symptoms. Elevated serum levels of chromogranin A and/or pancreatic polypeptide or positive SRS are frequently corroborative that the tumor has neuroendocrine features.

Diagnosis of sporadic or inherited pancreatic NETs

Pancreatic NETs sometimes occur in patients with various autosomal dominant disorders, for instances, MEN 1, von Hippel-Lindau syndrome (VHL), or neurofibromatosis 1 (NF-1) (8,26). Multiple endocrine neoplasia type 1 (MEN 1) is the most frequent of these inherited disorders, in patients with pancreatic NETs (26,27). In patients with MEN 1-related pancreatic NETs, it is sometimes necessary to consider different strategies from MEN 1-nonrelated pancreatic NETs. For example, pancreatic tumors are invariable multiple in MEN 1, on the contrary, are single in sporadic ZES (18). The precise identification of location of the functioning pancreatic NET is necessary, considering that tumors maybe multiple, is necessary for cure resection in patients with MEN 1. Hyperparathyroidism is the most common clinical manifestation in patients with MEN 1 (28), often resulting in that the treatment for hyperparathyroidism prior to the treatment for pancreatic tumors. The second most inherited disorder in patients with pancreatic NETs is VHL. Although pancreatic tumors are

nonfunctioning and slow growing in the most of patients with VHL, patients with lesions greater than 3 cm are more likely to develop metastases (29).

Diagnosis of resectability of pancreatic NETs

Imaging of the primary tumor and the extent of the disease is essential to determine whether surgical resection for possible cure or possible cytoreductive surgery is adequate. In a patient with a large pancreatic NET, tumor sometimes involves superior mesenteric vessels, or vascularization into tumor such as direct arterial flows from Aorta sometimes developed. When intraoperative control of blood flows is regarded as difficult, other management should be considered. Surgical resectability should be assessed cautiously based on hemodynamic CT/MRI and angiography.

Surgical management

Surgical treatment of localized pancreatic NETs

It would be incontestable that surgical resection of a functioning pancreatic NETs should be considered whenever possible (8,10,30), except in patients with MEN 1 with the presence of ZES. The reason of this exception is that patients with MEN 1 with the presence of ZES are almost never cured without extensive resections (26,31-33). In patients with sporadic gastrinomas, pancreatectomies with lymphadenectomy are recommended for possible cure due to their high incidence of nodal involvement (34).

The positive impact of resection on survival in patients with nonfunctioning pancreatic NETs has been repeatedly demonstrated (35-39). However, the extent of surgery and lymphadenectomy could be limited in small pancreatic NET (<2 cm), because such small nonfunctioning pancreatic NETs are often indolent neoplasms without lymph node metastasis. It has also been suggested that most small tumors have an indolent course and may be amenable to observation (24,40,41). In addition to size of tumor, tumor grade and differentiation are candidates of indicators of biologic behavior and are associated with survival (39,42,43). Partelli S *et al.* reported that nodal metastases were occurred in 30% of patients with nonfunctioning pancreatic NETs and were associated with decreased 5-year disease-free survival. They also reported that independent factors associated with nodal metastasis were radiological nodal status and tumor grade (44). Further studies would likely to clarify how to decide proper management for each patient with nonfunctioning pancreatic NETs depending on predictive biologic behavior. Tumor characteristic are a central consideration for treatment decisions of pancreatic NETs.

Surgical treatment of pancreatic NETs with resectable synchronous metastases

Most of the pancreatic NETs have already metastases at the time of diagnosis (45). Liver metastases are the most common (1,46) and account for 90% of metastases in patients with pancreatic NETs on disease progression (47). When the metastatic lesions of the liver are possible to be achieved total removal of the tumor with negative margins, aggressive surgical resection of both primary and metastatic lesions is recommended because the presence of liver metastasis is suggested to be one of the major prognostic factors (48,49). Sarmiento JM *et al.* reviewed articles and described more than half of the patients with liver metastases from NETs underwent a major hepatic resection and 40% of them had concurrent resection of the primary tumor (50). Norton JA *et al.* reported that aggressive surgery including pancreatectomy, splenectomy, superior mesenteric vein reconstruction, and liver resection can be done with acceptable morbidity and low mortality rates for patients with advanced NETs (51). Following to surgery, consideration for medical treatment such as everolimus, sunitinib or cytotoxic agents should be given to patients with clinically significant progressive disease (52).

Surgical treatment of pancreatic NETs with unresectable synchronous liver metastases and no extrahepatic metastases

Metastatic lesion in the liver is often difficult to remove totally with negative margins and 86% of patients with liver metastasis already have unresectable multiple liver metastases and/or extrahepatic metastases (53). The incident rate of synchronous liver metastases from all pancreatic NETs has been reported approximately 30% (48,54). Cytoreductive hepatic surgery in patients with functioning pancreatic NETs may be indicated to reduce the amount of hormone and improve the clinical symptoms and prognosis, and may associate with increased long-term survival (55-57). Cytoreductive surgery can be performed safely with minimal morbidity and mortality and results in regression of symptoms and prolonged survival in the majority of patients (58).

As for another strategy, nonsurgical hepatic regional

therapy such as trans-catheter arterial embolization (TAE), trans-catheter arterial chemoembolization (TACE), radioembolization, or ablative therapy, in combination with resection of primary pancreatic tumor is possible to be considered (49,59). The clinical efficacy of surgery to primary pancreatic tumor has been controversial (18). Both the National Comprehensive Cancer Network (NCCN) guideline for pancreatic NETs (52) and ENETS consensus guidelines for unresectable liver metastases from digestive NETs (60) describe the management in patients with pancreatic NETs with unresectable liver metastases and no extrahepatic metastases. Although they recommend hepatic regional therapy with systemic treatment, they have made no mention about surgery to the primary tumor. Molecular-targeted therapy with everolimus or sunitinib has been established in the treatment for the patients with unresectable pancreatic NETs (61,62). In the studies of these agents, however, it should be known that most of the patients had previous surgical treatment including resection of primary pancreatic tumor. Resection of the primary tumor may prevent from some complications which are developed on disease progression (49,63) and may be associated with improved the response to radiologic therapy and overall survival (64). Recently, mortality rates of pancreatectomies have been decreased and acceptable (59,65-67).

Since NETs are usually abundant in arterial flow, TACE or TAE is common as hepatic regional therapy. Timing of sequential TACE/TAE has remained unclear. In our institute, pre- and postoperative TACE/TAE has been performed sequentially every 1-3 months based on the patient's condition (59). Systemic treatment alone rather than trans-arterial hepatic treatment following pancreaticoduodenectomy in patients for tumor located in the pancreatic head might be recommended because liver abscess may be more likely to develop than in patients for tumor located in pancreatic tail theoretically. The role of ablation therapy in the overall management remains poorly defined (68).

Surgical treatment of recurrence from pancreatic NETs

Some experts try to reoperate for patients with recurrence from pancreatic NETs. A proportion of patients could benefit by aggressive surgical approaches and have long-term survival or long-term palliation (69,70). The detail analyses to select patients who can receive the surgical benefits have not been done.

Medical management

In addition to surgery, diverse types of medical treatment are used in the management course for patients with pancreatic NETs as well as gastrointestinal NETs. The main aim of the treatment should be clearly defined before choosing treatment, there are two main aim of treatment: to ameliorate hormonal symptoms and to improve the survival. Observation without any agents might be the best management for patients with stable disease for long time or the elderly patients.

Medical treatment of functioning pancreatic NETs

In patients with functioning NETs, medical management can often provide release symptoms by inhibition of the secretion of bioactive agents. Administration of diazoxide (8,71,72) or long-acting somatostatin analogs (octreotide, lanreotide) (73,74) can control hypoglycemic symptoms in about 50% of patients with insulinoma. Histamine H2-receptor antagonists and proton pump inhibitors can control the acid hypersecretion in most patients with ZES (31,75). For patients with other functioning pancreatic NETs, long-acting somatostatin analogs are generally successful in the initial management (76-78).

Medical treatment with molecular-targeted therapy

Tumor grading is paramount for selecting patients who should receive chemotherapy, and platinum-based chemotherapy is recommended in patients with NEC G3 (79). In some patients with NET G1/G2, molecular-targeted treatment or chemotherapy may provide a benefit. The European Society for Medical Oncology (ESMO) guidelines 2012 recommended use of molecular-targeted agents in advanced pancreatic NETs G1/G2 (80). According to the North American Neuroendocrine Tumor Society (NANETS) guidelines, the level of recommendation is listed as "consider" to use of everolimus in metastatic functioning NETs because there has been no sufficient evidence to recommend routine use of it (81).

Everolimus, an oral inhibitor of mammalian target of rapamysin (mTOR) (82), and sunitinib, an inhibitor of VEGF and platelet-derived growth factor receptors (83), are now registered worldwide for the treatment of pancreatic NETs. These two agents have similar tumor-stabilizing effects in pancreatic NETs. Since there has been no trial that compared the two agents directly, choice of

the agent in each case could be suggested in perspective of side-effects. For example, in patients with poorly controlled hormonal symptoms, congestive heart failure, poorly controlled hypertension, high risk of gastrointestinal bleed, or a history of myocardial infarction or stroke, everolimus is thought be the preferred choice agent. In patients with poorly controlled diabetes mellitus, pulmonary disease, or high risk of infection, sunitinib would be a more appropriate choice (84). To evaluate of response these agents, several biomarkers are investigated. It has been suggested that chromogranin A and neuron-specific enolase are useful as prognostic markers in patients with advanced pNET treated with everolimus (85). Soluble vascular endothelial growth factor receptor 2 and 3, interleukin-8, and stromal cell-derived factor 1alpha have been reported to have a potential as biomarkers associated with response to sunitinib (86). Based on recent data, treatment algorithms have been expected to update for advanced pancreatic NETs.

Conclusions

Appearance of the novel agents such as everolimus and sunitinib has produced more variety in the treatment of metastatic pancreatic NETs. Management of pancreatic NETs should be decided with considering that they have varying degrees of aggressiveness, symptoms and malignant potentials, and sometimes are associated with inherited disorder. Further studies of predictive prognostic factors and outcome by each treatment would be needed to advance treatment and survival for patients with pancreatic NETs.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934-59.
2. Halfdanarson TR, Rabe KG, Rubin J, et al. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol 2008;19:1727-33.
3. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61-72.
4. Yao JC, Eisner MP, Leary C, et al. Population-based study of islet cell carcinoma. Ann Surg Oncol 2007;14:3492-500.
5. Cheema A, Weber J, Strosberg JR. Incidental detection of pancreatic neuroendocrine tumors: an analysis of incidence and outcomes. Ann Surg Oncol 2012;19:2932-6.
6. Rindi G, Klöppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006;449:395-401.
7. Bosman FT, Carneiro F, Hruban RH, et al. eds. WHO Classification of tumors of the digestive system (4th edition). Lyon: IRAC Press, 2010:322-6.
8. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology 2008;135:1469-92.
9. Klöppel G, Anlauf M. Epidemiology, tumour biology and histopathological classification of neuroendocrine tumours of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 2005;19:507-17.
10. Oberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol 2005;19:753-81.
11. Falconi M, Plockinger U, Kwekkeboom DJ, et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology 2006;84:196-211.
12. Modlin IM, Moss SF, Gustafsson BI, et al. The archaic distinction between functioning and nonfunctioning neuroendocrine neoplasms is no longer clinically relevant. Langenbecks Arch Surg 2011;396:1145-56.
13. Aspestrand F, Kolmannskog F, Jacobsen M. CT, MR imaging and angiography in pancreatic apudomas. Acta Radiol 1993;34:468-73.
14. de Herder WW, Niederle B, Scoazec JY, et al. Well-differentiated pancreatic tumor/carcinoma: insulinoma. Neuroendocrinology 2006;84:183-8.
15. Wild D, Mäcke H, Christ E, et al. Glucagon-like peptide 1-receptor scans to localize occult insulinomas. N Engl J Med 2008;359:766-8.
16. Wild D, Christ E, Caplin ME, et al. Glucagon-like peptide-1 versus somatostatin receptor targeting reveals 2 distinct forms of malignant insulinomas. J Nucl Med 2011;52:1073-8.
17. Ito T, Tanaka M, Sasano H, et al. Preliminary results of a Japanese nationwide survey of neuroendocrine gastrointestinal tumors. J Gastroenterol 2007;42:497-500.
18. Kulke MH, Anthony LB, Bushnell DL, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas 2010;39:735-52.
19. Klöppel G, Anlauf M. Gastrinoma--morphological aspects. Wien Klin Wochenschr 2007;119:579-84.

20. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology 1995;108:1637-49.
21. Gibril F, Doppman JL, Reynolds JC, et al. Bone metastases in patients with gastrinomas: a prospective study of bone scanning, somatostatin receptor scanning, and magnetic resonance image in their detection, frequency, location, and effect of their detection on management. J Clin Oncol 1998;16:1040-53.
22. Dralle H, Krohn SL, Karges W, et al. Surgery of resectable nonfunctioning neuroendocrine pancreatic tumors. World J Surg 2004;28:1248-60.
23. Fendrich V, Waldmann J, Bartsch DK, et al. Surgical management of pancreatic endocrine tumors. Nat Rev Clin Oncol 2009;6:419-28.
24. Bettini R, Partelli S, Boninsegna L, et al. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery 2011;150:75-82.
25. Plöckinger U, Wiedenmann B. Diagnosis of non-functioning neuro-endocrine gastro-enteropancreatic tumours. Neuroendocrinology 2004;80 Suppl 1:35-8.
26. Jensen RT, Berna MJ, Bingham DB, et al. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. Cancer 2008;113:1807-43.
27. Gibril F, Schumann M, Pace A, et al. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. Medicine (Baltimore) 2004;83:43-83.
28. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86:5658-71.
29. Blansfield JA, Choyke L, Morita SY, et al. Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). Surgery 2007;142:814-8; discussion 818.e1-2.
30. Akerström G, Hellman P. Surgery on neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007;21:87-109.
31. Jensen RT, Niederle B, Mitry E, et al. Gastrinoma (duodenal and pancreatic). Neuroendocrinology 2006;84:173-82.
32. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999;341:635-44.
33. Norton JA, Jensen RT. Resolved and unresolved controversies in the surgical management of patients with Zollinger-Ellison syndrome. Ann Surg 2004;240:757-73.
34. Anlauf M, Garbrecht N, Henopp T, et al. Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinico-pathological and epidemiological features. World J Gastroenterol 2006;12:5440-6.
35. Hill JS, McPhee JT, McDade TP, et al. Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. Cancer 2009;115:741-51.
36. Gomez-Rivera F, Stewart AE, Arnoletti JP, et al. Surgical treatment of pancreatic endocrine neoplasms. Am J Surg 2007;193:460-5.
37. Zerbi A, Capitanio V, Boninsegna L, et al. Surgical treatment of pancreatic endocrine tumours in Italy: results of a prospective multicentre study of 262 cases. Langenbecks Arch Surg 2011;396:313-21.
38. Franko J, Feng W, Yip L, et al. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. J Gastrointest Surg 2010;14:541-8.
39. Martin RC, Kooby DA, Weber SM, et al. Analysis of 6,747 pancreatic neuroendocrine tumors for a proposed staging system. J Gastrointest Surg 2011;15:175-83.
40. Lee LC, Grant CS, Salomao DR, et al. Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): role for nonoperative management. Surgery 2012;152:965-74.
41. Gaujoux S, Partelli S, Maire F, et al. Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. J Clin Endocrinol Metab 2013;98:4784-9.
42. Scarpa A, Mantovani W, Capelli P, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. Mod Pathol 2010;23:824-33.
43. Toste PA, Kadera BE, Tatishchev SF, et al. Nonfunctional pancreatic neuroendocrine tumors <2 cm on preoperative imaging are associated with a low incidence of nodal metastasis and an excellent overall survival. J Gastrointest Surg 2013;17:2105-13.
44. Partelli S, Gaujoux S, Boninsegna L, et al. Pattern and clinical predictors of lymph node involvement in nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs). JAMA Surg 2013;148:932-9.
45. Chen H, Hardacre JM, Uzar A, et al. Isolated liver metastases from neuroendocrine tumors: does resection

prolong survival? J Am Coll Surg 1998;187:88-92; discussion 92-3.
46. Chamberlain RS, Canes D, Brown KT, et al. Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg 2000;190:432-45.
47. Gaujoux S, Gonen M, Tang L, et al. Synchronous resection of primary and liver metastases for neuroendocrine tumors. Ann Surg Oncol 2012;19:4270-7.
48. Oh TG, Chung MJ, Park JY, et al. Prognostic factors and characteristics of pancreatic neuroendocrine tumors: single center experience. Yonsei Med J 2012;53:944-51.
49. Hodul PJ, Strosberg JR, Kvols LK. Aggressive surgical resection in the management of pancreatic neuroendocrine tumors: when is it indicated? Cancer Control 2008;15:314-21.
50. Sarmiento JM, Que FG. Hepatic surgery for metastases from neuroendocrine tumors. Surg Oncol Clin N Am 2003;12:231-42.
51. Norton JA, Kivlen M, Li M, et al. Morbidity and mortality of aggressive resection in patients with advanced neuroendocrine tumors. Arch Surg 2003;138:859-66.
52. National Comprehensive Cancer Nework (NCCN) Clinical Practice Guidelines in Oncology. Version 1.2012 Neuroendocrine tumors of the pancreas. Available online: http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
53. Eriksson B, Arnberg H, Lindgren PG, et al. Neuroendocrine pancreatic tumours: clinical presentation, biochemical and histopathological findings in 84 patients. J Intern Med 1990;228:103-13.
54. Zerbi A, Falconi M, Rindi G, et al. Clinicopathological features of pancreatic endocrine tumors: a prospective multicenter study in Italy of 297 sporadic cases. Am J Gastroenterol 2010;105:1421-9.
55. McEntee GP, Nagorney DM, Kvols LK, et al. Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery 1990;108:1091-6.
56. Modlin IM, Lewis JJ, Ahlman H, et al. Management of unresectable malignant endocrine tumors of the pancreas. Surg Gynecol Obstet 1993;176:507-18.
57. Wessels FJ, Schell SR. Radiofrequency ablation treatment of refractory carcinoid hepatic metastases. J Surg Res 2001;95:8-12.
58. Hodul P, Malafa M, Choi J, et al. The role of cytoreductive hepatic surgery as an adjunct to the management of metastatic neuroendocrine carcinomas. Cancer Control 2006;13:61-71.
59. Kondo NI, Ikeda Y, Maehara S, et al. Role of resection of the primary pancreatic neuroendocrine tumor in the multidisciplinary treatment of patients with unresectable synchronous liver metastases: a case series. JOP 2013;14:415-22.
60. Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012;95:157-76.
61. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501-13.
62. Duran I, Kortmansky J, Singh D, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. Br J Cancer 2006;95:1148-54.
63. Solorzano CC, Lee JE, Pisters PW, et al. Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. Surgery 2001;130:1078-85.
64. Gupta S, Johnson MM, Murthy R, et al. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. Cancer 2005;104:1590-602.
65. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. Ann Surg 1995;221:721-31; discussion 731-3.
66. Gordon TA, Burleyson GP, Tielsch JM, et al. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. Ann Surg 1995;221:43-9.
67. Brennan MF, Moccia RD, Klimstra D. Management of adenocarcinoma of the body and tail of the pancreas. Ann Surg 1996;223:506-11; discussion 511-2.
68. Mazzaglia PJ, Berber E, Milas M, et al. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. Surgery 2007;142:10-9.
69. Fendrich V, Langer P, Celik I, et al. An aggressive surgical approach leads to long-term survival in patients with pancreatic endocrine tumors. Ann Surg 2006;244:845-51; discussion 852-3.
70. Saxena A, Chua TC, Zhao J, et al. Liver-directed therapy for neuroendocrine neoplasm hepatic metastasis prolongs survival following progression after initial surgery. J Surg Oncol 2012;105:342-50.
71. Gill GV, Rauf O, MacFarlane IA. Diazoxide treatment for insulinoma: a national UK survey. Postgrad Med J

1997;73:640-1.
72. Goode PN, Farndon JR, Anderson J, et al. Diazoxide in the management of patients with insulinoma. World J Surg 1986;10:586-92.
73. Vezzosi D, Bennet A, Rochaix P, et al. Octreotide in insulinoma patients: efficacy on hypoglycemia, relationships with Octreoscan scintigraphy and immunostaining with anti-sst2A and anti-sst5 antibodies. Eur J Endocrinol 2005;152:757-67.
74. Jensen RT. Peptide therapy. Recent advances in the use of somatostatin and other peptide receptor agonists and antagonists. In: Lewis JH, Dubois A. eds. Current Clinical Topics in Gastrointestinal Pharmacology. Malden, MA: Blackwell Science, Inc., 1997:144-223.
75. Lew EA, Pisegna JR, Starr JA, et al. Intravenous pantoprazole rapidly controls gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. Gastroenterology 2000;118:696-704.
76. Plöckinger U, Wiedenmann B. Neuroendocrine tumors. Biotherapy. Best Pract Res Clin Endocrinol Metab 2007;21:145-62.
77. Oberg K, Ferone D, Kaltsas G, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: biotherapy. Neuroendocrinology 2009;90:209-13.
78. Oberg K, Kvols L, Caplin M, et al. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol 2004;15:966-73.
79. Costa FP, Gumz B, Pasche B. Selecting patients for cytotoxic therapies in gastroenteropancreatic neuroendocrine tumours. Best Pract Res Clin Gastroenterol 2012;26:843-54.
80. Öberg K, Knigge U, Kwekkeboom D, et al. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii124-30.
81. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas 2013;42:557-77.
82. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514-23.
83. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501-13.
84. Yao J, Phan AT. Optimising therapeutic options for patients with advanced pancreatic neuroendocrine tumours. Eur Oncol Haematol 2012;8:217-23.
85. Yao JC, Pavel M, Phan AT, et al. Chromogranin A and neuron-specific enolase as prognostic markers in patients with advanced pNET treated with everolimus. J Clin Endocrinol Metab 2011;96:3741-9.
86. Vinik AI, Raymond E. Pancreatic neuroendocrine tumors: approach to treatment with focus on sunitinib. Therap Adv Gastroenterol 2013;6:396-411.

Cite this article as: Kondo NI, Ikeda Y. Practical management and treatment of pancreatic neuroendocrine tumors. Gland Surg 2014;3(4):276-283. doi: 10.3978/j.issn.2227-684X.2013.12.05

