Practical management and treatment of pancreatic neuroendocrine tumors

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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)

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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 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
pancreatectoduodenectomy 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
(81,72) 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
rapamycin (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 1 alpha 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.

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References


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