REVIEW

The Current Strategy for Managing Pancreatic Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type 1

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Multiple endocrine neoplasia type 1 (MEN1) is an inherited autosomal dominant disease presenting with pancreatic neuroendocrine tumors (pNETs), parathyroid tumors, or pituitary tumors. Using the PubMed database, we reviewed the literature on information regarding the proper diagnosis and treatment of MEN1-associated pNET. Many cases of MEN1-associated pNET are functioning pNETs. Gastrinomas and insulinomas tend to occur frequently in the duodenum and pancreas, respectively. In addition to diagnostic imaging, the selective arterial secretagogue injection test (SASI test) is useful for localizing functioning pNET. The standard treatment is surgical resection. However, in the case of a functioning pNET, the tumor should first be accurately located using the SASI test before an appropriate surgical method is selected. In cases of a MEN1-associated non-functioning pNET that exceeds 2 cm in diameter, the incidence of distant metastasis is significantly increased, and surgery is recommended. In cases of unresectable pNET, a somatostatin analog has been shown to demonstrate antitumor effects and is considered to be a promising treatment. In addition, molecular-targeted drugs have recently been found to be effective in phase III clinical trials. **(Gut Liver 2012;6:287-294)**

Key Words: Multiple endocrine neoplasia type 1; Pancreatic neuroendocrine tumor; Multiple tumors; Selective arterial secretagogue injection test

INTRODUCTION

Multiple endocrine neoplasia (MEN) is an autosomal dominant inherited disease presenting with tumorous lesions, mainly in various endocrine organs. In 1954, Wermer[1] first indicated that patients with multiple tumors in the parathyroid gland, pituitary gland, and pancreatic islets of Langerhans were actually suffering from an autosomal dominant inherited syndrome instead of simple concomitant onset of the tumors. In 1961, Sipple[2] reported a syndrome complicated with medullary thyroid carcinoma and pheochromocytoma. A syndrome consisting of mainly pancreatic neuroendocrine tumor (pNET), parathyroid tumor, pituitary tumor, etc., that was formally called "multiple endocrine adenomatosis," which was found to be hereditary by Wermer,[1] was subsequently classified as MEN type 1 (MEN1). A syndrome consisting of mainly medullary thyroid carcinoma and pheochromocytoma, as reported by Sipple,[2] was classified as MEN2.

Patients with MEN1-associated pNET often have multiple tumors or malignant tumors that determine patients' prognosis for survival. Therefore, it is considered important to make a cautious diagnosis and select the most appropriate treatment method for each patient. In light of this, we used the PubMed database to review the literature on MEN1-associated pNET and examine the diagnosis and treatment methods appropriate for MEN1-associated pNET.

ETIOLOGY OF MEN1

MEN1, which was identified by Chandrasekharappa et al.[3] in 1997 as the gene that causes MEN1, is located on the long arm of chromosome 11 (11q13). This gene, which is also called *menin*, consists of about 10 exons dispersed over a region of approximately 7,000 base pairs, and encodes a 610-amino acid protein.[3] Menin mRNA has been found in all normal human tissues thus far examined. Menin protein has also been found in pancreatic exocrine cells, where *MEN1* tumors do not develop.[4]

Menin protein is mainly located in the nucleus where it binds with nuclear proteins, including JunD, NFκB, and Smad3, as well as with histone deacetylase and histone methyl-transferase. It is thought to be involved in cell growth, apoptosis, DNA repair, and transcriptional regulation.[5,6]

In patients with MEN1, the inactivated *MEN1* gene has existed heterozygously from the time of ontogeny, while the other normal gene has lost function through somatic mutation, thus causing tumor formation of specific cells.

In familial and non-familial MEN1, the detection rate of *MEN1* mutations is 90% and 70%, respectively,[7] and the lifetime incidence of MEN1 is nearly 100% in those with the mutations. Therefore, if a patient clinically suspected of having MEN1 cannot be definitely diagnosed, a genetic test is required.

CLINICAL FEATURES OF pNET IN MEN1 PATIENTS

It is reported that the prevalence of MEN1 is estimated to be approximately 1 in 10,000 to 30,000, and that non-familial MEN1 patients account for approximately 15% of total MEN1 patients.[8] In people with *MEN1* mutations, a few percent of those 10 years of age and under develop MEN1, and while, by 40 years of age, nearly 100% of them develop the disease.[9] Hyperparathyroidism is the most frequent initial disease in MEN1 (85%), and in people in their 40s, the incidence of parathyroid adenoma is higher than that of other tumor types.[10] Pituitary adenoma and pNET are the second most frequent diseases.

According to a recent nationwide survey on gastroenteropancreatic neuroendocrine tumors in Japan,[11] MEN1 was concur-

rently found in 10% of pNET patients. As for the breakdown of pNET in MEN1 patients, gastrinoma was the most frequent (25%), followed by insulinoma (14%). Interestingly, non-functioning pNET (6.1%) occurred less frequently in Japan than in Western countries.[11] VIPoma and glucagonoma were also found, although rarely, as other functioning pNET that present with specific symptoms due to the hormones produced. Table 1 summarizes the characteristics of the MEN1-associated functioning pNET reported in literature.[10-16]

In cases of gastrinoma, refractory multiple ulcers and diarrhea, etc., develop due to increased gastrin concentrations in the blood (Table 2).[14,17,18] This disease is called Zollinger-Ellison syndrome (ZES). In gastrinoma, the incidence of concurrent MEN1 is as high as 20% to 38%;[16,19] and therefore, gastrinoma should be treated with MEN1 in mind. Gastrinoma is often found in the duodenum of MEN1 patients. Since gastrinoma occurs as multiple tumors that are usually smaller than 0.5 mm in size, it is sometimes difficult to detect by imaging.

Insulinoma often presents with symptoms of hypoglycemia caused by an elevation of insulin levels in the blood. Insulinoma usually develops as an isolated disease; however, a patient with multiple pancreatic tumors is likely to have MEN1. Like gastrinoma, it is usually difficult to identify all the pancreatic tumors by imaging studies in MEN1 patients.

The most characteristic sign of glucagonoma is necrotic migratory erythema. While glucagonoma is usually considered malignant due to distant metastasis, MEN1-associated cases apparently have tiny tumors with fewer symptoms.[20]

Most of endocrine tumors with MEN1 are benign, while

Table 1. The Characteristics of Functioning Pancreatic Neuroendocrine Tumors in Patients with MEN1

Tumors	Incidence of tumor type in MEN1, %	Incidence of MEN1 involvement in tumor, %	Site	Malignancy, %
Gastrinoma	40-47[10,12]	19-25[11,16]	Duodenum (>80%) Pancreas[15]	50-60[13,15]
Insulinoma	10-12[10,12]	12-14[11,12]	Pancreas[15]	12-20[15]
VIPoma	<2[13,15]	1[14]	Pancreas Duodenum (10%)[15]	40[14,15]
Glucagonoma	<3[13,15]	3[14]	Pancreas[15]	70[14,15]
Somatostatinoma	<2[13,15]	1[14]	Pancreas Duodenum/jejunum (44%)[15]	70-80[14,15]

MEN1, multiple endocrine neoplasia type 1.

Table 2. The Symptoms and Signs of Functioning Pancreatic Neuroendocrine Tumors

Tumors	Symptoms and signs
Gastrinoma	Abdominal pain, diarrhea, heartburn, nausea, vomiting, gastrointestinal bleeding[17,18]
Insulinoma	Neuroglycopenic symptoms and hypoglycemia, corrected by administration of glucose[17,18]
VIPoma	Severe watery diarrhea, hypokalemia, achlorhydria[14,17,18]
Glucagonoma	Necrolytic migratory erythema (rash), diabetes, thromboembolic disease[14,17,18]
Somatostatinoma	Steatorrhea, cholelithiases, diarrhea, diabetes[14,17,18]

MEN1-associated pNET is considered to be relatively high risk for malignancy. It is reported that pNET is an important determinant of survival in MEN1 patients and the most important cause of MEN1-related death.[21,22] Therefore, the surveillance for MEN1-associated pNET is recommended for patients as follows: 1) asymptomatic individuals with MEN1 mutation, 2) individuals with a clinical diagnosis of MEN1, and 3) symptomatic individuals at risk for MEN1 with an affected parent who have not undergone genetic testing. A diagnostic interval of 1 to 3 years is widely considered to be appropriate for asymptomatic individuals because of the low MEN1-associated tumor proliferation rate.[18]

DIAGNOSIS

1. Diagnosis of MEN1

MEN1 is diagnosed when at least 2 of the main tumorous diseases (parathyroid tumor, pNET, and pituitary tumor) are found. However, these tumors may occur at different times; therefore, whenever one of these endocrine tumors is detected, the other sites should be monitored over time. As mentioned earlier, genetic testing for MEN1 mutation may be useful, if a definite diagnosis is difficult, or if it is a familial case. Nevertheless, such tests should be implemented cautiously, since it could become a social issue.

2. Imaging diagnosis of MEN1-associated pNET

1) Conventional imaging studies: detection of pNET

As is the case for sporadic pNET that does not involve MEN1,

MEN1-associated pNET is also a plethoric tumor involving many tumor vessels. Therefore, imaging diagnosis of MEN1-associated pNET includes an early-phase staining pattern on enhanced computed tomography (CT) (Figs 1A and 2A), and tumor staining image on angiography. CT imaging, in particular, is useful for delineating neuroendocrine tumors in extrapancreatic lesions. Furthermore, while contrast magnetic resonance imaging shows an early-phase staining pattern, it may be useful for differentiating solid pseudopapillary neoplasms or metastatic tumors from pNET, especially in non-functioning pNET.

MEN1-associated pNET is characterized by multiple tumors sporadically distributed across the pancreas. Though multiple intrapancreatic tumors are often tiny, endoscopic ultrasonography (EUS) and intraductal ultrasonography can delineate such minute tumors due to their excellent spatial resolution (Figs 1B and 2B). Since EUS, in particular, can be used for outpatients, it is valuable for monitoring patients over time and the delineation of multiple minute intrapancreatic lesions.

Intraoperative ultrasonography (IOUS) is useful for estimating the character of a tumor and to measure the distance between a tumor and the main pancreatic duct which is very important information to determine whether enucleation can be undergone safely or not. In addition, the form and size of pNET can be measured more correctly with IOUS than any other preoperative imaging techniques (Table 3).[23-26]
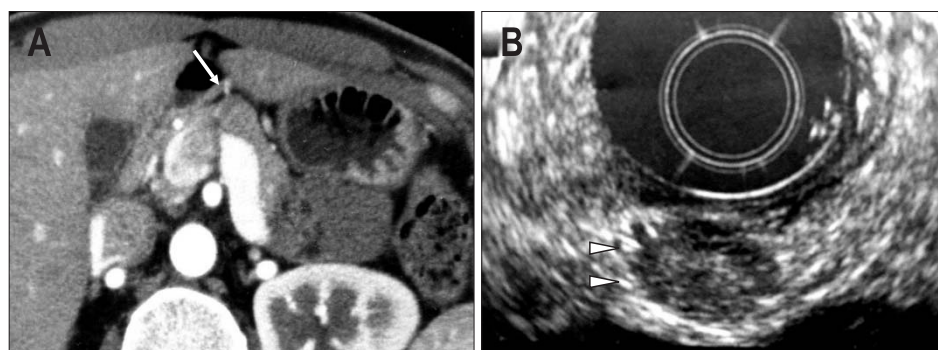
Fig. 1. A case of MEN1-unassociated insulinoma (34-year-old female). (A) Abdominal imaging computed tomography (CT). A tumor with a slight early phase stain pattern is observed at the pancreatic head and body border (arrow). (B) Endoscopic ultrasonography. A tumor is observed at the site shown using CT (arrowheads). No other tumors are detected in the pancreas.
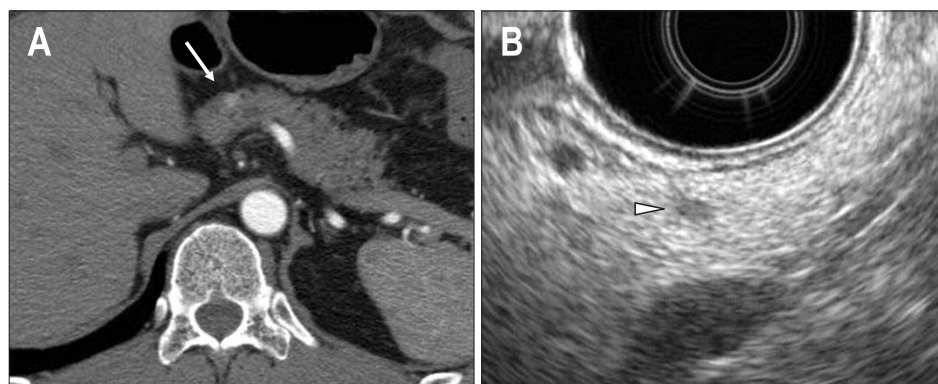
Fig. 2. A case of MEN1-associated insulinoma (44-year-old male). (A) Abdominal imaging computed tomography (CT). A tumor with an early phase stain pattern is observed at the pancreatic head and body border (arrow). (B) Endoscopic ultrasonography. In addition to the lesion shown using CT, small tumors are found at the pancreatic head, body, and tail. The case is considered to have multiple pancreatic lesions. The arrowhead shows a 3-mm lesion in the pancreatic body.

Table 3. The Characteristics and Sensitivities of the Diagnostic Modalities for pNET

Modalities	Sensitivity, %	Characteristics
CT/MRI[24-26]	14-77	The detection rate of CT/MRI has been improving over time. MRI may be useful for differentiating solid pseudopapillary neoplasms or metastatic tumors from pNET, especially in non-functioning pNET.
EUS[25]	79-100	Most sensitive preoperative test for detection of the tumor.
SASI test[24,26]	90-96	Exact localization of functioning pNET
Intraoperative palpation[24,26]	88-90	Very useful especially for MEN1-associated gastrinoma in the duodenum.
IOUS[23,24,26]	88-100	The form and size of tumors can be measured more correctly, however, it is difficult to distinguish functioning tumors from non-functioning tumors.

pNET, pancreatic neuroendocrine tumor; CT, computed tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasonography; SASI test, selective arterial secretagogue injection test; MEN1, multiple endocrine neoplasia type 1; IOUS, intraoperative ultrasonography.
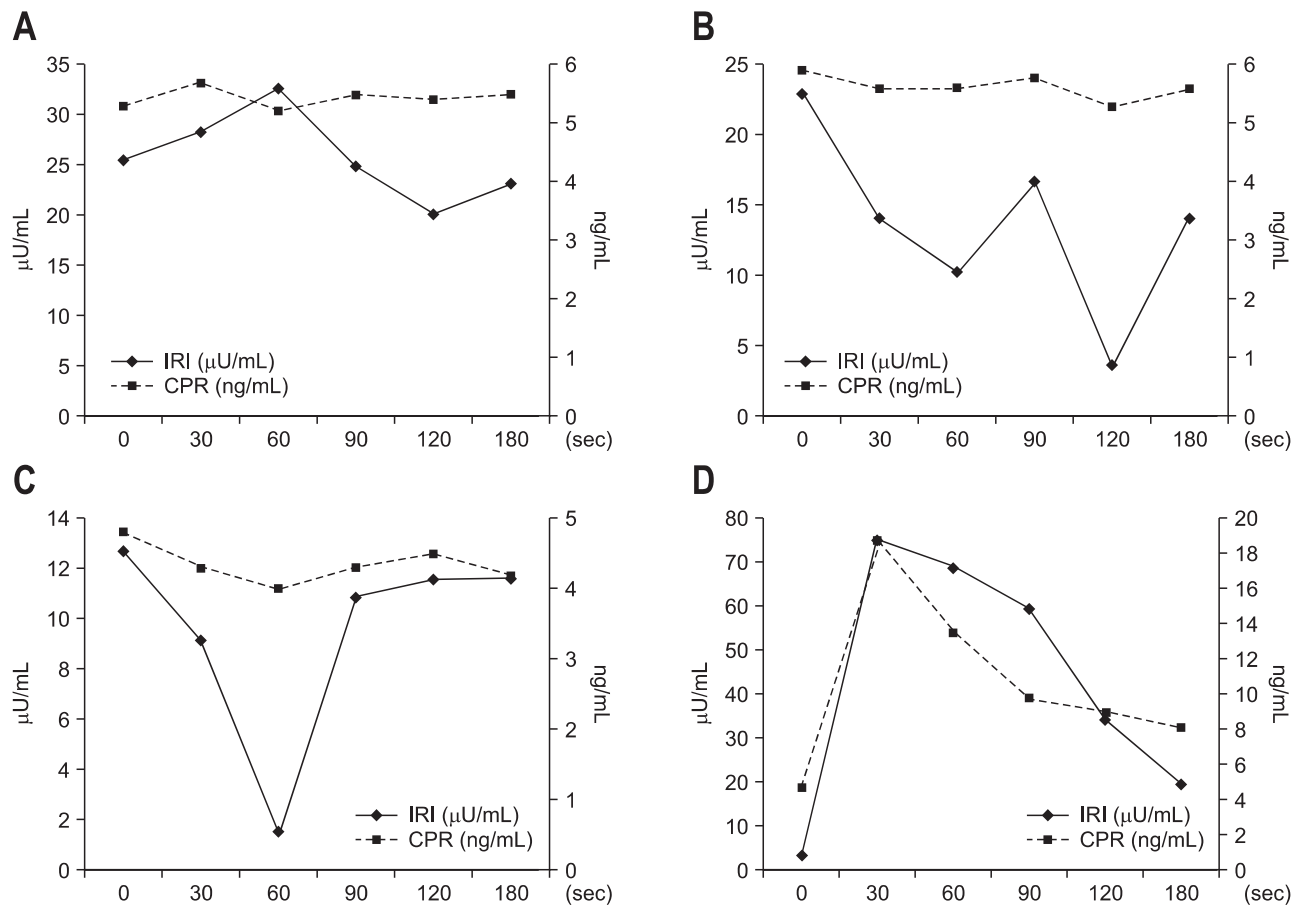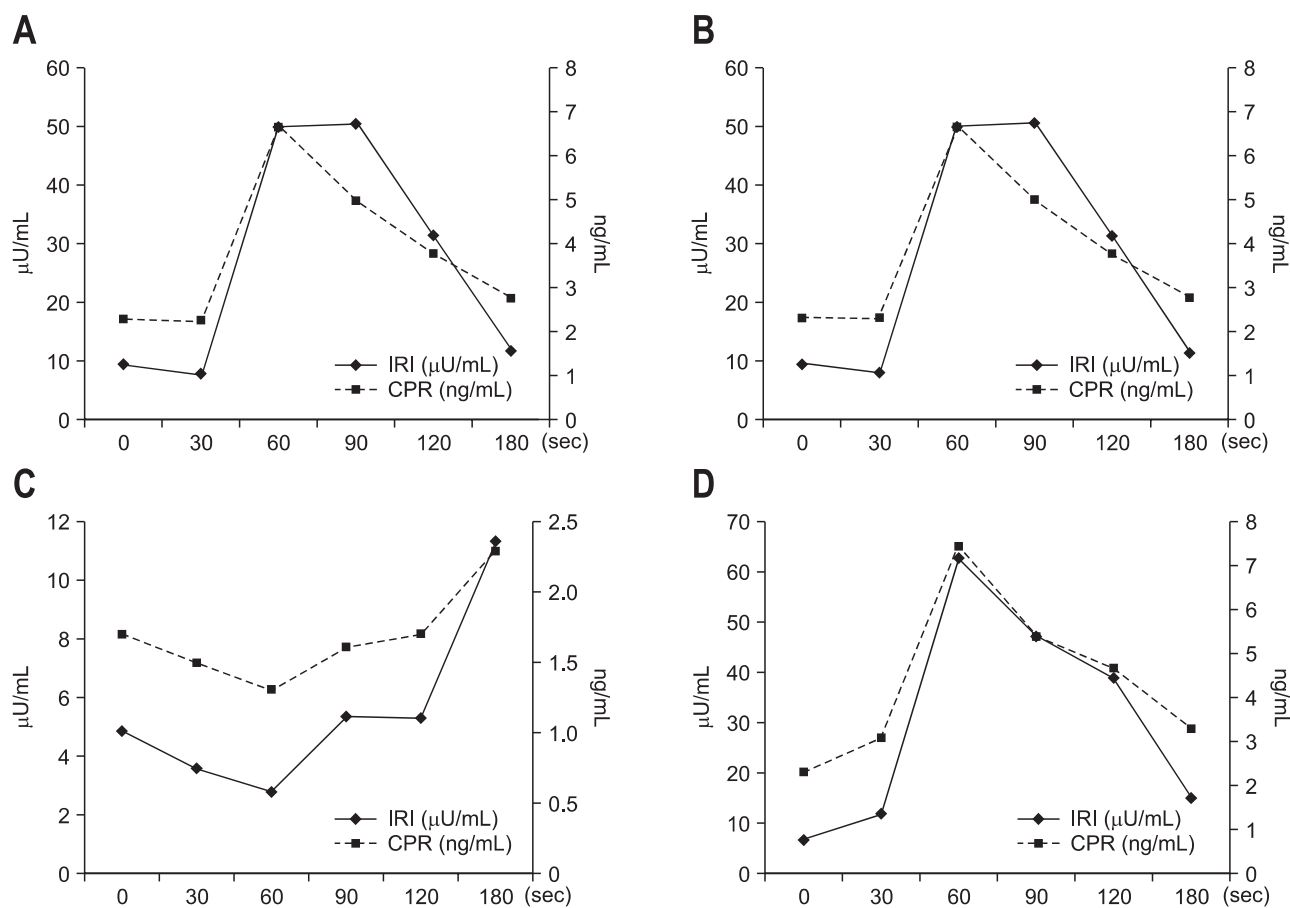

Fig. 3. The selective arterial secretagogue injection test data from the case in Fig. 1. (A) Gastroduodenal artery. (B) Splenic artery. (C) Superior mesenteric artery, and (D) dorsal pancreatic artery. Step-up is found only in (D).
IRI, immunoreactive insulin; CPR, C-peptide immunoreactivity.

2) Functional imaging studies: exact localization of functioning pNET

Nevertheless, even the combination of these diagnostic imaging techniques cannot necessarily delineate all of the multiple lesions. In the case of functioning pNET, selective arterial secretagogue injection test (SASI test) can be useful for the localizing tumors, since hormone is secreted by the tumor cells in response to secretin or calcium stimulant under arteriography. SASI test was developed by Imamura et al.[27] to locate gastrinoma using secretin as stimulant. Subsequently, Doppman et al.[28] applied this method for localizing insulinoma by changing the stimulant from secretin to calcium. In this test, a catheter is placed inside a hepatic vein under abdominal angiography in order to measure gastrin or insulin in the hepatic venous blood, and then secretin or calcium is injected into the artery responsible for each pancreatic region. The tumor is located in the region where

Fig. 4. The selective arterial secretagogue injection test data from the case in Fig. 2. (A) Gastroduodenal artery. (B) Splenic artery. (C) Superior mesenteric artery, and (D) dorsal pancreatic artery. Step-up is found in (A), (B), and (D). In this case, a parathyroid tumor is found in addition to the pancreatic endocrine tumor.
IRI, immunoreactive insulin; CPR, C-peptide immunoreactivity.

gastrin or insulin has increased. The injection is usually made into the splenic artery, the gastroduodenal artery, or the superior mesenteric artery.[28,29] Furthermore, according to another report, an additional injection into the dorsal pancreatic artery may improve diagnostic performance.[30] These tests can locate the nutrient vessel for the tumor, and are therefore useful in determining which surgical method to use in order to remove the entire tumor.[29] In addition, in some cases of MEN1-associated pNET, functioning tumors and non-functioning tumors exist at the same time. Therefore, in the case of MEN1-associated gastrinoma and insulinoma, SASI test should be performed before operation to localize functioning tumors exactly.

Our department conducts the SASI test using calcium. After the blood is collected, 0.025 meq/kg calcium gluconate is administered. Immunoreactive insulin or immunoreactive gastrin is measured before calcium administration and at 30, 60, 90, 120, and 180 seconds after calcium administration. For insulinoma, C-peptide immunoreactivity is also measured. Figs 3 and 4 show our SASI test data for MEN1-unassociated insulinoma and MEN1-associated insulinoma, respectively. As demonstrated by the results of CT and EUS, MEN1-unassociated insulinoma was

fed by a single vessel; and therefore, it was a solitary tumor. In contrast, in the case of MEN1-associated insulinoma, CT showed only 1 tumor; however, the SASI test revealed that the insulinoma was fed by multiple vessels and that multiple minute tumors existed in the pancreas.

Somatostatin receptor (receptor subtype 2 in particular) is frequently expressed in pNET. Based on this observation, somatostatin receptor scanning is useful for localizating both the primary tumor and metastatic lesions.[17]

TREATMENT OF pNET IN MEN1 PATIENTS

Differing reports have been published regarding resection of MEN1-associated gastrinoma with ZES for the following reasons: the symptoms can be controlled with H2 blocker or proton pump inhibitor, it is likely to be malignant, and complete cure is difficult considering frequent postoperative recurrence. At present, there are many authorities who do not recommend subjecting patients with MEN1-associated gastrinoma to aggressive surgery such as a Whipple resection because it is extensive, the long-term consequences are unclear, postoperative morbidity

can be significant.[17] Some groups recommend that surgical exploration should be reserved for patients with an imageable tumor 2 to 3 cm.[31] In addition, there is a report that patients with MEN1-associated gastrinoma have excellent long-term survival without surgery and, even with metastatic disease, they have a 15-year survival of 52%.[32] On the other hand, some reports have suggested that the tumor should be proactively removed except in cases with hepatic metastasis.[29] A previous report regarding multivariate analysis of metastatic gastroenteropancreatic neuroendocrine tumors revealed that age, the number of liver metastases, tumor slope and initial surgery were predictive of survival.[33] Therefore, one of the purpose of surgery for pNET is preventing hepatic metastasis. Various surgical procedures have been attempted. Akerström *et al.*[34] recommended Thompson's procedure for MEN1-associated gastrinoma. In this procedure, a duodenotomy is performed since gastrinoma is often found in the duodenum. The tumor is then located by palpation and IOUS and removed. The mass at the pancreatic head is enucleated, and then 80% of the pancreatic tail is resected and lymph node is removed.[34,35] Bartsch *et al.*[36] recommended pylorus-preserving partial duodenectomy, in order to prevent duodenal recurrence and to maintain postoperative quality of life. Imamura *et al.*[29,37] recommended pancreaticoduodenectomy or pancreas-preserving total duodenectomy after fully identifying the location of tumor with SASI test, in order to improve the prognosis for complete cure and to prevent hepatic metastasis, provided that the tumor is located at the pancreatic head or duodenum; a high biochemical cure (87.5%) was obtained for gastrinoma.[37] In this way, surgical treatment for MEN1-associated gastrinoma remains controversial. It is also true that a controlled study has not been done to determine the exact timing and role of surgery. Additional studies are needed to clearly define whether a more aggressive approach is indicated.

In the case of MEN1-associated insulinoma, surgery is usually performed due to the intense symptoms caused by hyperinsulinemia, even if the tumor cannot be identified by imaging.[34] MEN1-associated insulinoma occurring mostly in the pancreas is multiple and minute. Therefore, an SASI test should be performed preoperatively to determine the extent of resection. When only the preoperatively identified tumor is removed, recurrence rate would be high; and therefore, distal pancreatectomy is often conducted in addition to tumor enucleation.[18]

The treatment method for MEN1-associated non-functioning pNET has been debated. The above-mentioned nationwide survey on gastroenteropancreatic neuroendocrine tumors in Japan reported that the rate of distant metastasis is significantly high when a non-functioning pNET exceeds 2 cm in size.[11] According to the guidelines of European Neuroendocrine Tumor Society, surgery is recommended for MEN1-associated non-functioning pNET exceeding 2 cm in diameter, in order to prevent further progression.[38] However, more data is needed.

In contrast, unresectable malignant pancreatic endocrine tumors are mainly treated by controlling the symptoms of hormone excess, managing hepatic metastasis, and with systemic chemotherapy, as is the case for MEN1-unassociated pNET. A somatostatin analog that can inhibit secretion of various hormones has demonstrated anti-tumor effects (PROMID study),[39] and is considered a promising treatment. According to various reports, other systemic chemotherapy agents include streptozotocin, dacarbazine, and temozolomide.[40-42] A report on the latest molecular targeted drugs for pNET showed that the mTOR inhibitor everolimus extended the median progression-free survival from 4.6 to 11.0 months and reduced the progression risk by 65% (hazard ratio, 0.35; p<0.0001) in a worldwide Phase III study (RADIANT-3).[43] It is a very promising drug for unresectable pNET and will likely become the first choice of treatment. Additionally, the median progression-free survival of the group treated with the tyrosine kinase inhibitor sunitinib was 11.4 months, which was significantly longer than the 5.5 months of the placebo group in a Phase III study.[44]

CONCLUSION

MEN1-associated pNET is mostly functioning pNET such as gastrinoma and insulinoma, which frequently manifest as multiple minute tumors. For a functioning pNET, surgery and other therapeutic strategies should be determined after SASI test is conducted to identify the exact location of the tumors. In contrast, for MEN1-associated non-functioning pNET, surgery is recommended when the tumor exceeds 2 cm in diameter, since the likelihood of distant metastasis is high.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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