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Surgical management of sporadic pancreatic neuroendocrine tumor

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ABSTRACT

Recently, new treatment guidelines and classifications were proposed for the management of pancreatic neuroendocrine tumors (P-NETs), and are now being used in clinical practice. The World Health Organization classification published in 2010 emphasized the importance of a grading system for P-NETs based on parameters of proliferative activity, such as mitotic count and Ki-67 labeling index, proposed by the European Neuroendocrine Tumor Society. For surgical treatment of P-NETs, it is important to select a strategy based on the degree of tumor malignancy. However, there are still no clear indications for organ-preserving pancreatic resection or lymph node dissection. This article outlines the surgical management and clinicopathological features of P-NETs. There are various surgical options, such as tumor enucleation, spleen-preserving distal pancreatectomy (SpDP), distal pancreatectomy with splenectomy, pancreatoduodenectomy, and duodenum-preserving pancreatic head resection. Hepatectomy is the first choice for liver metastasis from well-differentiated neuroendocrine carcinoma without extrahepatic metastasis. Other treatment options are radiofrequency ablation, transarterial chemoembolization/ embolization, and liver transplantation. Systematic chemotherapy, biotherapy such as somatostatin analogue and interferon-α, and targeted therapy are used for recurrence after surgery and unresectable tumors. This article also gives details of the surgical techniques available for tumor enucleation and SpDP.

Key words: pancreatic neuroendocrine tumor, enucleation, spleen-preserving distal pancreatectomy, Liver metastasis

Introduction

Pancreatic neuroendocrine tumors (P-NETs) are comparatively rare neoplasms, and account for only 1%–2% of all pancreatic neoplasms. The incidence of P-NETs is approximately 1 per 100 000 people[1)-5)]. The incidence in autopsy cases ranges from 0.26% to 1.4%[6),7)]. An autopsy study of 800 elderly subjects obtained specimens cut every 5 mm and found tiny neuroendocrine tumors (NETs) in more than 10% of the cases[8)].

P-NETs include benign neoplasms without metastasis or invasion, as well as high-grade malignant neoplasms. The assessment of tumor malignancy is important for determining the surgical strategy for P-NETs. In 2000 and 2004, the World Health Organization (WHO) classified P-NETs into three categories – well-differentiated NETs (benign or uncertain behavior), well-differentiated neuroendocrine carcinoma (NEC), and poorly differentiated NEC – according to the presence or absence of metastasis, direct invasion, arterial or venous invasion, perineural invasion, hormonal syndrome, tumor size, histological differentiation, and Ki-67 index[9),10)].

Table 1. A grading system for neuroendocrine tumors proposed by the European Neuroendocrine Tumor Society [11, 12].

Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≦2
G2	2-20	3-20
G3	>20	>20

[a] Ten HPF : High power field = 2 mm2 , at least 40 fields, evaluated in areas at highest mitotic density

[b] MIB 1 antibody: Percent of 2,000 cells in areas of highest nuclear labeling

Table 2. The pathological classification of neuroendocrine tumors by World Health Organization classification [9, 10, 14]

WHO (2000/ 2004)	WHO (2010)
1. Well-differentiated endocrine tumor (WDET)	Neuroendocrine tumor
1.1. Benign behavior	NET G1
Confined to the pancreas, nonangioinvasive, < 2cm in size, ≦2 mitoses and ≦2% Ki-67 positive cells/ 10HPF	NET G2
1.2. Uncertain behavior	
Confined to the pancreas, ≧2cm in size, >2 mitoses and >2% Ki-67 positive cells/ 10HPF, or angioinvasive	
2. Well-differentiated endocrine carcinoma (WDEC)	
Low grade malignant with gross local invasion and/or metastases	
3. Poorly-differentiated endocrine carcinoma (PDEC)/ small cell carcinoma, high grade malignant	Neuroendocrine carcinoma
	Large cell NEC
	Small cell NEC

NET; Neuroendocrine tumour, NEC; Neuroendocrine carcinoma

The European Neuroendocrine Tumor Society (ENETS) proposed guidelines for the treatment and prognostic stratification of gastroenteropancreatic NETs in 2006 by histological differentiation according to the WHO classification, the TNM classification, and grading based on proliferative activity, such as Ki-67 labeling index and mitotic count[11), 12)] (Table 1).

The American Joint Committee on Cancer (AJCC) proposed a new TNM classification for P-NETs in 2009[13)]. This classification is used for pancreatic ductal adenocarcinoma; the AJCC applied the same classification for P-NETs.

In the WHO classification published in 2010[14)], the grading system proposed by the ENETS[11), 12)] was considered important. Well-differentiated NETs were classified into NET G1 and NET G2, and poorly differentiated carcinoma was classified into NEC[14)] (Table 2). The 2000/2004 WHO histological classification included TNM elements such as tumor size and metastasis[9), 10)], but in the 2010 WHO classification[14)], the TNM classification (AJCC-TNM) was adopted for these factors. There are two major differences between the AJCC-TNM classification and the ENETS-TNM classification: the definition of the T stages and the consideration of tumor grading based on proliferative activity. Both TNM classifications are effective prognostic indicators[15) – 19)]. However, they are not free of problems[20), 21)]. The fact that there are two TNM classifications actually causes confusion among many practitioners.

P-NET G3 was newly added to the well-differentiated pancreatic neuroendocrine neoplasm category of the WHO classification published in 2017[22)] (Table 3). Grade 3 (ki-67 > 20%) tumors include biologically distinct subtypes. For example, Sorbye et al. reported that Grade 3 tumors with Ki-67 < 55% had a lower response rate to platinum-based chemotherapy (15% vs. 42%, P < 0.001), but better survival than Grade 3 tumors with Ki-67 ≥ 55% (14 months vs. 10 months, P<0.001)[23)]. Raj et al. reported that the response rate to platinum-based chemotherapy was 10% in Grade 3 well-differentiated P-NETs and 37% in poorly differentiated pancreatic NEC and that overall survival was significantly longer in Grade 3 well-differentiated P-NETs compared with G3 pancreatic NEC[24)]. Well-differentiated P-NETs are more likely to have loss of nuclear expression of DAXX or ATRX, and preserved expression of Rb and p53[25), 26)]. Therefore, well-differentiated P-NET G3 is an entity that should be distinguished from poorly differentiated NEC.

In the 2017 WHO classification, the same TX-T3 factors used in the ENETS-TNM classification were applied for the T-factor in the TNM classification of well-differentiated pancreatic neuroendocrine neoplasms[22)] (Table 4). Distant metastases were subclassified as M1a for liver metastasis alone, M1b for extrahepatic metastasis alone, and M1c for concurrent liver metastasis and extrahepatic metastasis. Stage subclassifications were eliminated and replaced with a simple system divided into stages I, II, III, and IV. The TNM classification for pancreatic ductal adenocarcinoma was applied for pancreatic NEC[22)].

This article describes surgical strategies and options for the treatment of P-NETs.

Table 3. 2017 WHO classification and grading of pancreatic neuroendocrine neoplasms (PanNENs) [22].

Classification/grade	Ki-67 proliferation index[a]	Mitotic index[a]
Well-differentiated PanNENs: pancreatic neuroendocrine tumours (PanNETs)		
PanNET G1	< 3%	< 2
PanNET G2	3-20%	2-20
PanNET G3	> 20%	> 20
Poorly differentiated PanNENs: pancratic neuroendocrine carcinomas (PanNECs)		
PanNEC (G3)	> 20%	> 20
Small cell type		
Large cell type		
Mixed neuroendocrine –non-neuroendocrine neoplasm		

[a] The ki-67 proliferation index is based on the evaluation of ≧ 500 cells in areas of higher nuclear labelling (so-called hotspots). The mitotic index is based on the evaluation of mitoses in 50 high-power fields (HPF: 0.2mm^2 each) in areas of higher density and is expressed as mitoses per 10 high power fields (2.0 mm^2). The final grade is determined based on whichever index (Ki-67 or mitotic) places the lumen in the highest grade category. For assessing Ki-67, casual visual estimation (eyeballing) is not recommended: manual counting using printed images is advocated.

Table 4. TNM classification of tumours of the neuroendocrine pancreas* [22].

T-Primary Tumor	M-Distant Metastasis
TX Primary tumour cannot be assessed T0 No evidence of primary tumour T1 Tumour limited to pancreas**, less than 2cm in greatest dimension T2 Tumour limited to pancreas**, 2cm or more but less than 4cm in greatest dimension T3 Tumour limited to pancreas**, more than 4cm in greatest dimension or Tumour invading duodenum or bile duct T4 Tumour perforates visceral peritoneum (serosa) or other organs or adjacent structures	M0 No distant metastasis M1 Distant metastasis M1a Hepatic metastasis only M1b Extrahepatic metastasis only M1c Hepatic and extrahepatic metastases
N- Regional Lymph Nodes	**Stage**
NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Regional lymph node metastasis	Stage Ⅰ T1 N0 M0 Stage Ⅱ T2, T3 N0 M0 Stage Ⅲ T4 N0 M0 Any T N1 M0 Stage Ⅳ Any T Any N Any M
	*The TNM classification of PanNECs follows the criteria for classifying ductal adenocarcinomas. ** This includes invasion of the peripancreatic adipose tissue.

Surgical strategies for P-NETs

Surgical treatment for P-NETs varies according to the site and size of the tumor, whether single or multiple, benign or malignant, and associated with multiple endocrine neoplasia type 1 or not. Patients with nonfunctioning P-NETs < 1.0 mm, which are occasionally found at autopsy, are certainly not candidates for treatment. Approximately 70%–90% of enlarging P-NETs have malignant features, such as invasion and metastases[22)-28)]. However, there are no definite indications regarding whether nonfunctioning P-NETs should be removed or observed based on size, since P-NETs are so rare that there is little evidence clarifying the size of tumors that should be treated[29)-31)]. Functional P-NETs such as insulinoma and gastrinoma should be treated surgically, even if the tumor is < 1 cm. Despite the small size, gastrinoma has malignant potential[32)-35)].

According to the ENETS guidelines, surgical resection is indicated for nonfunctioning P-NETs in patients who have symptoms, patients with a diagnosis of NET G2, and patients who desire to have surgery. They also recommend non-operative management as one of the therapeutic options for nonfunctioning P-NETs ≤ 2 cm if major pancreatic resection is required, and surgery is indicated if the tumor diameter increases by > 0.5 cm or to > 2 cm[36)]. In contrast, according to the National Comprehensive Cancer Network guidelines, surgery is generally indicated for all patients, but observation may also be an option for patients with small P-NETs detected incidentally depending on factors such as comorbidities, surgical risk, and tumor location[37)]. The Japanese guidelines proposed by the

Japan Neuroendocrine Tumor Society recommend that all patients with nonfunctioning P-NETs are candidates for surgery regardless of tumor diameter as long as they are managed in the hospital where pancreatic surgery can be done safely and do not have contraindications to surgery such as severe comorbidities[38].

Considering that some nonfunctioning P-NETs ≤ 2 cm are still highly malignant with metastatic potential[39)-41)]and that analyses using the United States National Cancer Database have shown that surgical resection of nonfunctioning P-NETs ≤ 2 cm improves survival[40),42)], surgery should be indicated for all nonfunctioning P-NETs. However, in studies that followed patients with nonfunctioning P-NETs ≤ 2 cm (median or mean size: 10 to 14 mm) that were asymptomatic (i.e., no epigastric pain, jaundice, pancreatitis, or symptoms associated with excessive hormone secretion) and had no invasion of peripancreatic tissue or lymph node or extrahepatic metastasis on imaging for a period of 31 to 45 months (median or mean), tumor growth of ≥ 20% was reported in only 0% to 13% of patients and no metastases or disease-specific deaths were reported, even in patients who underwent surgery after observation[43)-46)]. In a Japanese study that followed 19 patients with nonfunctioning P-NETs with a median size of 12 mm for a median period of 45 months, five-year progression-free survival was 83%[47)]. The results of these studies suggest that observation with careful monitoring of progress may be feasible for a select group of patients with tumors ≤ 2 cm. Several studies have concluded that patients with nonfunctioning P-NETs < 15 mm, many of which are NET G1, are ideal candidates for observation[46),47)]. Moreover, Zhang et al. found that although surgical resection improves survival in patients with nonfunctioning P-NETs ≥ 15 mm, the significance of surgery is unclear in patients with nonfunctioning P-NETs < 15 mm[48)]. Using size as an indicator, a cutoff of 15 mm may be one means of determining whether observation is also an option. In addition, studies have shown that survival outcomes are significantly worse for G2/3 nonfunctioning P-NETs ≤ 2 cm than for G1 tumors ≤ 2 cm and improved survival can be anticipated with surgical resection in patients with G2/3 nonfunctioning P-NETs ≤ 2 cm[49),50)]. As such, surgery should always be performed for P-NET G2/3 patients regardless of tumor size.

Surgical treatment of primary tumors

In the WHO classifications published in 2000[9)]and 2004[10)], NETs were classified into benign behavior or uncertain behavior and well-differentiated NEC or poorly differentiated NEC. However, the WHO classification published in 2010 emphasized grade as recommended by ENETS[11),12)], and NETs were classified into NET G1, NET G2, or NEC (G3) based on mitotic count and Ki-67 labeling index[14)]. The prognosis of Grade 2/3 P-NETs is significantly worse than that of Grade 1 P-NETs[17),18),51)-55)]. Even if the tumor is small, radical surgery with regional lymph node dissection should be performed for Grade 2/3 P-NETs[52),56)].

Determination of TNM classification and grade is important in deciding on a surgical strategy for the primary tumor because these are risk factors for postoperative recurrence.

Predictors of lymph node metastasis and grade (Tables 5, 6)

Tables 5 and 6 show predictors of lymph node metastasis[41),57)-80)]and grade[46),50),67),69),71),72),78),79),81)-94)].

The relationship between tumor diameter and lymph node metastasis has been well researched. Many studies have shown that the rate of lymph node metastasis is significantly higher for tumors > 15 to 20 mm[41),58)-69)]. Tumors > 15 to 20 mm are also more likely to be Grade 2/3[46),50),67),69),84)-90)], and thus tumor diameter is an important predictor of grade as well as lymph node metastasis. However, several studies have shown that tumor diameter is not an independent predictor of lymph node metastasis[41),60),61),69)]. Some studies have shown that even P-NETs < 10 mm are accompanied by lymph node metastasis in 10% to 30% of patients[39),40),41),65)], and this may be partially attributable to the presence of patients with lymph node metastasis regardless of tumor diameter. Consequently, it is important to evaluate factors other than tumor diameter.

Nodal features suggestive of lymph node

Table 5. Reported predictive factors for lymph node metastasis of P-NETs

	Reference No.	
	Statistically significant difference	
	Presence	Absence
Category Ⅰ		
Lymph node		
Enlargement (≥ 1 cm)/hypervascularization (CT)	57[UM]	
A short axis measuring > 1 cm/abnormal round morphology/central necrosis (CT)	58[UM]	
Tumor size		
>/≥ 15 mm	41[U]/ 59[U], 60[U] , 61[U]	41[M], 60[M], 61[M]
> 17 mm/> 18 mm	62[U]/ 63[UM]	
>/≥ 20 mm	64[U], 65[UM], 66[UM] / 67[U]	68[U], 69[M]
Tumor enhancement pattern		
Hypoenhancement on arterial phase (CT)	70[U]	
Hetero/hypo-attenuation in the late arterial phase (30 s) (CT)	60[UM]	
Iso/hypo-attenuation in the pancreatic phase (44 s)	71[U]	
Tumor to pancreas contrast ratio on portal venous phase (75 s) < 1.238 (CT)	58[UM]	
Main pancreatic duct involvement (MRCP/CT)	61[UM]	
Tumor shape irregular (CT)	72[U]	
Laboratory findings		
Neutrophil to lymphocyte ratio (NLR) ≥ 2.056	73[UM]	
Pathological factor		
Grade G2/G3	41[U], 57[UM], 60[U], 61[U], 63[U], 74[UM],	41[M], 60[M], 61[M]
Poorly/moderately differentiation	68[UM]	
Lymph vascular invasion	41[U], 68[U]	41[M]
Positive CK19 expression	75[U], 76[U]	
No hormonal expression for immunohistochemical study	77[U]	
Gastrin/serotonin expression for immunohistochemical study	77[U]	
Category Ⅱ		
Symptomatic (Non-functioning tumor)	68[U], 74[UM], 78[U], 79[U]	69[M], 57[U]
Tumor location Pancreatic head	41[U], 57[U], 63[U], 66[UM], 69[M]	41[M], 57[M], 58[U], 60[U], 61[U], 63[M], 65[U], 74[U], 80[U]
Vascular invasion (CT)	58[U]	58[M]
Tumor margin poorly defined (CT)	58[U]	58[M]
Intratumoral calcification (CT)	80[UM]	58[U], 60[U]
Tumor thrombus	73[U]	73[M]
Perineural invasion	68[U]	68[M]

Definitions of Categories I and II:
Category I: Factors identified as potential predictors of lymph node metastasis by statistical or clinical analysis
Category II: Potential predictors of lymph node metastasis on which further research is warranted
U: univariate analysis; M: multivariate analysis

metastasis have also been investigated. Partelli et al. found that enlargement of the lymph nodes to ≥ 1 cm and/or hypervascularization of peripancreatic lymph nodes on contrast-enhanced CT were independent predictors of lymph node metastasis[57]. Choi et al. found that a nodal short axis diameter greater than1cm, an abnormal round morphology, and central necrosis were independent predictors of lymph node metastasis[58].

Many studies have shown that tumor contrast

Table 6. Reported predictive factors for Grade 2/3 P-NETs

	Reference No.	
	Statistically significant difference	
	Presence	Absence
Category I		
Diagnosis of G2/3 by EUS-FNA	81, 82, 83	
Tumor growth (≥ 20% or 5 mm increase in size)	46[U]	
Imaging findings		
Tumor size		
≥ 15 mm/> 17.5 mm	46[UM]/84	
>/≥ 20 mm	50[U], 85[U], 69[M],86[U], 87[U]/67[U], 88[U], 89[UM]	
≥ 30 mm	90[U]	
Tumor enhancement pattern		
Non-homogenous hyper-attenuation on arterial phase (20-30 s)	91[U]	
Iso/hypo-attenuation in the pancreatic phase (44 s)	71[U]	
Tumor to pancreas contrast ratio on arterial phase (CT) < 1.1 (Predictive factor for grade 2/3)	67[U]	
Late contrast enhancement (peak attenuation observed in the venous phase) (CT)	67[U]	
Peripancreatic tissue invasion (MRI/CT)	86[U], 90[U]/85[UM]	
Vascular invasion (MRI/CT)	84[U], 86[U], 90[U] /87[U], 85[UM]	88[U]
MPD involvement (MRI/EUS)	90[U]/89[UM]	
ADC value (MRI) ≤ 1.22/1.21/0.930×10^3 mm^2/s	84/ 92/ 93	
ADC ratio [ADC value of the tumor (solid portion)/ ADC value of the parenchyma] < 0.94	91	
Category II		
Symptomatic (non-functioning tumor)	78[U],79[U]	69[M]
Heterogenous enhancement (MRI/ CT)	84[U], 94[U] / －	92[U]/67[U], 86[U], 88[U]
MPD dilatation ≥ 4 mm (MRI/CT)	86[U], 94[U]/87[U], 85[U]	84[U],90[U], 92[U]/85[M], 88[U], 91[U]
Ill-defined borders (MRI/CT)	84[U], 94[U]/85[U]	90[U], 94[U]/85[M], 88[U]
Tumor shape irregular/lobular (CT/EUS)	72[U], 85[U], 91[U]/ －	85[M]/89[U]
Lymphadenopathy (≥ 10 mm) (with irregular margin and heterogenous enhancement) (CT)	85[U], 87[U]	85[M]
Internal echo pattern (EUS) heterogenous	89[U]	89[M]

Definitions of Categories I and II:
Category I: Factors identified as potential predictors of Grade 2/3 P-NETs by statistical or clinical analysis
Category II: Potential predictors of Grade 2/3 P-NETs on which further research is warranted
U: univariate analysis; M: multivariate analysis

enhancement pattern is a predictor of lymph node metastasis and NET G2/3. A typical NET G1 exhibits homogeneous tumor staining reflecting hypervascularity in the early arterial phase or late arterial phase (pancreatic parenchymal phase) (20 to 44 s after injection of contrast medium)[60),71),95)－99)]. In addition, they typically exhibit peak contrast enhancement in the early arterial (20 to 26 s) or late arterial (30 to 45 s) phase[71),97),100)], followed by contrast medium washout in the portal venous phase (65 to 75 s) or equilibrium phase (180 s)[71),97),99)]. In contrast, highly malignant tumors (NET G2/3) do not exhibit tumor staining in the arterial phase[60),71),99),101)], and exhibit peak contrast in the portal venous phase or equilibrium phase[67),97),102)].

Invasion of the main pancreatic duct[61),89),90)], invasion of peripancreatic tissue[85),86),90)], and vascular invasion[84)－87),90)] have also been identified as predictors of lymph node metastasis or NET G2/3.

These studies indicate that it is necessary to consider not only tumor diameter but also features of peripancreatic lymph nodes, tumor contrast

enhancement patterns, and invasion of the main pancreatic duct, invasion of peripancreatic tissue, and vascular invasion when determining tumor malignancy.

Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNA) is a method for grading tumors by direct collection of tumor tissue. However, one flaw of this method is that it underestimates the grade of NET G2/3 tumors with internal heterogeneity as the less malignant NET G1. Nevertheless, studies have shown that a preoperative pathological diagnosis of NET G2/3 by EUS-FNA often matches the postoperative pathological diagnosis[81)-83)].

Jung et al. found that tumors that grow by at least 20% or 5 mm in diameter are more likely to be NET G2/3, and that tumors that grow rapidly during observation must be treated as NET G2/3 as well[46)].

Many studies have shown that NET G1 exhibit high apparent diffusion coefficient (ADC) values on diffusion-weighted magnetic resonance imaging (MRI), and cutoff points ranging from 0.930 to 1.22 were found to have clinical utility[84),92),93)]. In addition, Toshima et al. examined the ratio of ADC values of tumors and pancreatic parenchyma of the proximal side of the tumor to control for variation in ADC values by MRI scanner, and found that tumors with an ADC ratio (ADC value of the tumor/ADC value of the pancreatic parenchyma) of < 0.94 were often graded as NET G2/3, and ADC ratio was an independent predictor of grade[91)].

Another study showed that SUVmax on FDG-PET is high in NET G3, and a cutoff value of 2.5 has clinical utility for differentiating between NET G3 and G1/2 patients[103)]. Although differences between PET scanners may influence FDG-PET results as well, it can at least be assumed that tumors with low SUVmax are less malignant.

Some studies have shown that patients with nonfunctioning P-NETs who exhibit symptoms such as abdominal pain, jaundice, and weight loss are significantly more likely to have lymph node metastasis or NET G2/3[68),74),78),79)]. However, other studies have shown no significant difference[57),69)]. Findings common to all these studies are that symptomatic nonfunctioning P-NETs often have a large tumor diameter and more advanced stage, with differences in these features manifesting as differences in grade of malignancy. However, Birnbaum et al. found that symptomatic patients, even those with tumors < 2 cm, were significantly more likely to have NET G2 or perineural invasion, and that lymph node metastasis also tended to be more common in symptomatic patients (25% vs. 9%, P = 0.19)[78)]. In a study of 16 symptomatic patients with nonfunctioning P-NETs ≤ 2 cm, Sallinen et al. found that 7 patients with lymph node metastasis or liver metastasis had obstruction of the bile duct or main pancreatic duct[50)]. Particular care is necessary in the evaluation of symptomatic patients with bile duct or main pancreatic duct invasion, even if the tumor size is ≤ 2 cm.

Although many studies have shown that lymph node metastasis is significantly more common in tumors of the pancreatic head[41),57),63),66),69)], many other studies have shown no significant difference[6),41),57),58),60),61),63),74),80)]. As no study has shown that tumors of the pancreatic head are more likely to be NET G2/3, it is possible that lymph node metastasis of the tumors of the pancreatic head are more likely to occur than that of the tumors of the body or tail, if they are the same grade. At this point, it is necessary to evaluate lymph node metastasis risk comprehensively with consideration to other risk factors rather than relying on tumor location alone.

Although the extent of cystic component is not an independent predictor of NET G2/3[85),91)], tumors with lymph node metastasis and NET G2/3 rarely have a large cystic component (≥ 50% of total tumor size)[104),105)]. Differential diagnosis from cystic tumors such as IPMN and MCN is also challenging for these types of NETs[104)].

Selection of surgical procedure (Tables 7, 8, 9)

There are currently no clear indications for organ-preserving resection, such as enucleation and spleen-preserving distal pancreatectomy (SpDP), in patients with P-NETs[57),106)-111)].

Standard pancreatectomy with lymph node dissection is the treatment of choice when the tumor diameter is over 2 cm or lymph node metastasis or Grade 2/3 tumor is suspected preoperatively.

Table 7

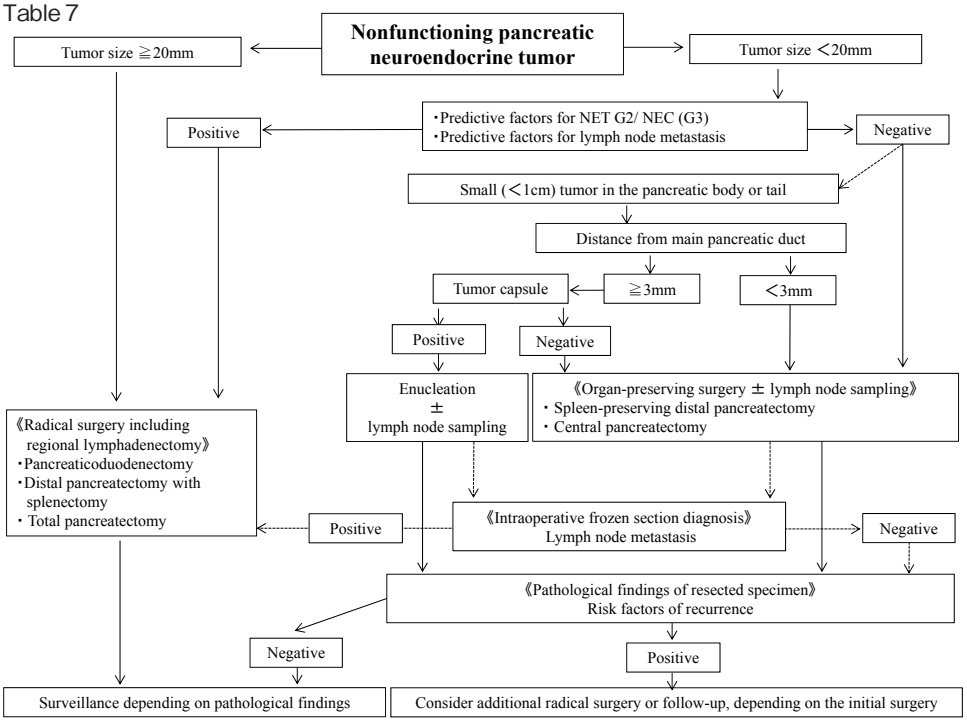
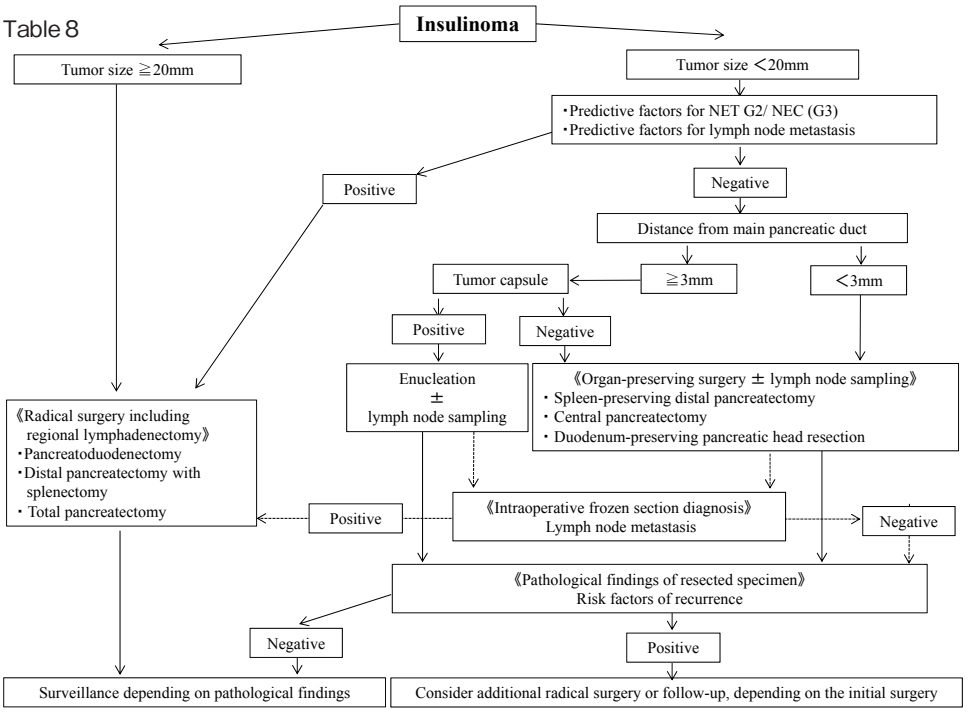


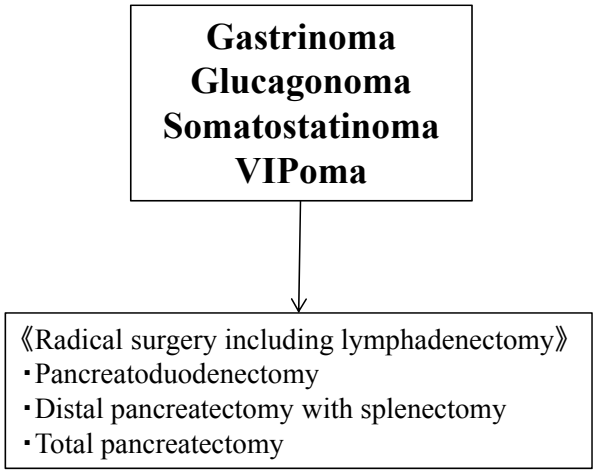
Table 8



Essentially, pancreaticoduodenectomy is the treatment of choice for tumors of the pancreatic head, and distal pancreatectomy with splenectomy is the treatment of choice for tumors of the pancreatic body and tail (Tables 7, 8).

Standard pancreatectomy with lymph node dissection is also selected for functioning tumors other than insulinomas (Table 9)[32)－35), 112)－115)]. Gastrinomas are particularly malignant, and even small gastrinomas have metastatic

Table 9



potential[33),35)]. Insulinomas ≤ 2 cm with no malignant features are almost always benign and are associated with favorable postoperative survival, so patients with such tumors are good candidates for organ-preserving surgery (Table 8)[116)]. Studies in which hormone production was evaluated by immunohistochemical study have shown that glucagon- and somatostatin-producing tumors are less likely to metastasize to the lymph nodes than gastrin- or serotonin-producing tumors[77)]. However, glucagonomas and somatostatinomas that cause symptoms due to overproduction of hormones are often first detected in patients with advanced disease that has already metastasized to the liver[112)-114)].

Organ-preserving surgery is indicated for patients without risk factors such as lymph node metastasis (Table 5) or NET G2/G3 (Table 6). In specific terms, tumors that meet criteria such as size of < 15 mm, no peripancreatic lymph node features suggestive of lymph node metastasis, round or oval tumor morphology, well-defined tumor margins with no invasion of the main pancreatic duct or peripancreatic tissues, homogeneous tumor staining pattern on arterial-phase dynamic CT, low ADC relative to the pancreatic parenchyma on diffusion MRI, and lack of 20% or 5-mm growth during observation are relatively good candidates for organ-preserving surgery.

However, even patients with tumor diameter < 10 mm may have lymph node metastasis[39)-41),65)], and conversely, some patients with a tumor diameter of 15 to 20 mm may still be candidates for organ-preserving surgery as long as they do not have any other poor prognostic predictors such as lymph node metastasis or NET G2/3[60),61)]. Consequently, it is probably necessary to pay attention to factors other than tumor diameter as well.

One study on insulinomas found no difference in grade between tumors that did not show the typical tumor staining pattern in the arterial phase with those that did show the typical contrast pattern[117)]. This indicates that grading of insulinomas by contrast pattern alone should be avoided in favor of consideration alongside other findings when determining a surgical strategy.

Insulinomas < 20 mm that are located at the pancreatic margin far from the main pancreatic duct, are covered by a capsule, and have no other malignant features besides tumor diameter are good candidates for enucleation[29),116)]. SpDP or middle pancreatectomy are indicated for tumors of the pancreatic body or tail that are close to the main pancreatic duct, because injury of the main pancreatic duct may cause postoperative refractory pancreatic fistula and abdominal abscess. In that situation, duodenum-preserving pancreatic head resection (DPPHR) should be considered for tumors of the pancreatic head[29)]. Nonfunctioning tumors of the pancreatic body or tail without risk factors such as lymph node metastasis or NET G2/3 that are far from the main pancreatic duct, are ≤ 1 cm, and are asymptomatic on detection are relatively good candidates for enucleation[38),65),118)].

SpDP with conservation of the splenic artery and vein (Kimura's method) does not include adequate dissection of the splenic hilar lymph nodes, but the same extent of dissection performed in standard surgery is technically feasible for dissection of lymph nodes surrounding the pancreatic body. SpDP may also be indicated for some nonfunctioning tumors of the pancreatic body that are > 15 mm in diameter but have no other malignant features.

Advantages of organ-preserving surgery include prevention of postoperative diabetes[109),119)], preservation of pancreatic exocrine function[109),119),120)], and reduced risk of infection[120),121)], new malignancies[123)], and

Table10. Previously reported risk factors for recurrence after resection of the primary tumor without distant metastasis.

	Reference No.	
	Statistically significant difference	
	Presence	Absence
Category I		
Non-insulinoma	128[UM]	
Imaging findings		
Tumor size ≥ 4 cm	57[U], 68[U]	
Bile duct obstruction	129[UM]	
Pancreatic duct obstruction	129[UM]	
Pathological findings		
Ki-67 index		
≥ 2%	128[UM]	
> 20%	41[UM]	
Grade (WHO): G2/3	50[UM], 57[UM], 94[U], 128[U], 130[U], 78[UM]	
Final resection status: R1	57[U], 131[UM]	57[M]
Lymph node metastasis	41[UM], 50[U], 57[UM], 74[UM], 128[UM], 130[U], 131[U]	50[M], 68[U] , 78[M], 131[M] 132[U]
Angioinvasion	57[U], 74[UM], 132[U]	57[M]
Tumor necrosis	130[U]	
Well differentiated endocrine carcinoma (WHO 2004)	130[U]	
Poorly/moderately differentiation	68[U], 132[U]	
T stage: T3/4 (ENETS)	128[UM]	
Category II		
Symptomatic (non-functioning tumor)	78[U], 133[M]	50[U], 57[U], 74[U], 78[M]
Tumor size > 2 cm	74[U]	68[U], 74[M]
Perineural invasion	57[U], 74[U], 130[U], 131[U]	57[M], 68[U] , 74[M]
Lymphovascular invasion	130[U]	68[U], 131[U]
Elevation of CA19-9	74[U]	74[M]

Definitions of Categories I and II:
Category I: Factors identified as potential predictors of recurrence by statistical or clinical analysis
Category II: Potential predictors of recurrence on which further research is warranted
U: univariate analysis; M: multivariate analysis

thromboembolism[122),124)]. Consequently, it should be performed whenever possible when indicated.

As organ-preserving surgery does not include adequate lymph node dissection, sampling dissection of the peripancreatic lymph nodes should be performed intraoperatively when enlarged lymph nodes are detected around the tumor and standard surgery performed if metastasis is suspected.

Laparoscopic surgery has been widely performed for pancreatic neoplasms. The postoperative morbidity of laparoscopic surgery is comparable to that of open surgery[125)－127)].

Although different institutions must establish their own eligibility criteria, laparoscopic surgery is generally a good choice for less malignant tumors for which organ-preserving surgery would be indicated.

Risk factors for recurrence after primary tumor resection (Table 10)

Table 10 shows risk factors for recurrence after primary tumor resection[41),50),57),68),74),78),94),128)－133)]. Recurrence of nonfunctioning tumors after enucleation or middle pancreatectomy has been reported in patients with characteristics such as NET G2 and lymph node metastasis[110),119)]. Recurrence of insulinomas has also been reported in patients with risk factors for recurrence such as NET G2, lymph node metastasis, and lymphovascular

invasion[134),135)]. This indicates that depending on the surgical strategy (particularly enucleation or middle pancreatectomy), it may be necessary to consider and discuss the possibility of additional radical surgery with patients who have risk factors for recurrence such as lymph node metastasis, NET G2/3, moderately or poorly differentiated NETs, vascular invasion, or R1 resection as a result of histopathological evaluation after organ-preserving surgery. Potential cure through radical surgery is preferable to death resulting from local recurrence following organ-preserving surgery.

Surgical techniques for P-NETs

There are various surgical techniques for tumor enucleation and SpDP. Lymph node dissection should be performed for cases with lymph node metastases or obvious invasive findings. Pancreatoduodenectomy with combined portal vein resection or distal pancreatectomy with splenectomy is selected for advanced P-NET cases.

Enucleation for P-NETs

Enucleation is usually indicated for benign P-NETs. In particular, insulinomas, which are often diagnosed when < 2 cm, especially those measuring approximately 1 cm and projecting hemispherically from the surface of the pancreas and have a fibrous capsule surrounding the tumor[29),136)], tend to be resected using enucleation.

Enucleation can cause injury to the main pancreatic duct if the distance between the tumor and the main pancreatic duct is very small, and suturing of the pancreatic parenchyma after enucleation can cause stenosis of the main pancreatic duct. These injuries may result in postoperative refractory pancreatic fistula and abdominal abscess.

In such cases, SpDP with conservation of the splenic artery and vein (Kimura's method)[136)－138)]and segmental pancreatectomy[109)]are also indicated for tumors of the body and tail of the pancreas. DPPHR may also be considered if the tumor is located deep in the head of the pancreas.

Preoperative computed tomography (CT), angiography, and EUS should be used to determine the presence of infiltration to neighboring organs and capsule.

The number of multiple NETs in the pancreas and location of the tumors should be diagnosed preoperatively using CT, MRI, EUS, selective arterial calcium injection (SACI) test, and other modalities. Endoscopic ultrasonography is somewhat useful in detecting small P-NETs like insulinoma. The sensitivity of EUS for insulinoma is 83%–94%, and this increases to 96%–100% if EUS is combined with CT and MRI[127),139)－141)]. A SACI test should be applied if the tumor cannot be detected with these modalities.

Advances in preoperative diagnostic modalities have allowed the detection of small P-NETs. Palpation and intraoperative ultrasonography should be performed to confirm the results of a preoperative diagnosis. An intraoperative diagnosis may be less accurate than a preoperative diagnosis, and requires a wider surgical field. This could lead to organ injury. Therefore, only tumors that are accurately diagnosed preoperatively should be resected[29)].

Preoperative stenting to the pancreatic duct through the papilla is useful for enucleation when the tumor is very close to the main pancreatic duct. Such stenting simplifies intraoperative detection of the main pancreatic duct. The surgeon can perform enucleation of the tumor safely without damaging the pancreatic duct[142)]. Another technique uses injection of dye into the main pancreatic duct, which enables the surgeon to note leakage from the pancreatic branch duct. This technique requires the surgeon to be very familiar with the surgical anatomy of the pancreas[143)].

Spleen-preserving distal pancreatectomy with conservation of the splenic artery and veins (SpDP)

Preservation of the spleen in distal pancreatectomy has recently attracted considerable attention. Since the first trial and success with conservation of the splenic artery and vein for tumors of the pancreas and chronic pancreatitis, this procedure (Kimura's procedure)[136),137)]has been performed very frequently. Splenic preservation can reduce the risk of hematological abnormalities, such as the elevation of serum platelet counts, thrombotic complications, and overwhelming postsplenectomy infection[137),144)－146)].

Enucleation is a common first-line therapy for benign P-NETs. However, enucleation can lead to injury of the main pancreatic duct if the distance between the tumor and the main pancreatic duct is very small, and so suturing of the pancreatic parenchyma after enucleation can cause stenosis of the main pancreatic duct. These injuries may result in postoperative refractory pancreatic fistula and abdominal abscess. SpDP with conservation of the splenic artery and vein (Kimura's procedure) may be desirable in such cases. Enucleation is also indicated if invasion to the pancreatic parenchyma is not clearly observed on imaging studies.

Surgical strategies for primary tumor with unresectable liver metastasis

Some reports have indicated a positive stance toward primary tumor resection for patients with P-NETs who have unresectable distant metastases because it is expected that this can improve the prognosis and quality of life of patients who have symptoms such as biliary and gastrointestinal obstruction, gastrointestinal bleeding, and abdominal pain[27),147)-150)]. Furthermore, primary tumor resection makes it easier to select liver-targeted therapy, such as transarterial embolization (TAE) or transarterial chemoembolization (TACE). However, some authors have indicated that the effect of primary tumor resection in patients with unresectable liver metastasis is merely palliative, rather than improvedoutcome[151),152)]. Therefore, resection of the primary tumor in patients with unresectable liver metastasis from P-NETs is controversial.

Bloomston et al. have also reported that cytoreductive surgery at primary tumor resection (R2 resection) did not improve outcome, and in fact increased the incidence of postoperative complications[153)]. It has also been reported that primary tumor resection should be avoided if liver metastasis shows a poorly differentiated histology, a Ki-67 labeling index of > 10%, and involves > 50% of the whole liver, because the outcome after primary tumor resection is very poor in such situations[151),154)].

Resection of the primary tumor may be indicated for resectable symptomatic tumors or tumors that are considered likely to become symptomatic in the near future, on the basis of prognostication from the extent of liver metastasis and the degree of tumor differentiation. In such cases, prophylactic cholecystectomy should be performed to prevent necrosis of the gallbladder following TAE/TACE. Palliative surgery such as a bypass operation may be indicated for bowel obstruction due to unresectable primary P-NETs.

Surgical treatment for liver metastasis

Hepatic resection combined with or without radiofrequency ablation is generally the first-line therapy for liver metastasis of P-NETs if there is no peritoneal dissemination or extra-abdominal metastasis, because they are usually slow-growing tumors[155)-157)]. Recently, the usefulness of ^{68}Ga-DOTATOC-PET/CT for detection of distant metastasis and staging has been reported[158),159)]. The 5- and 10-year survival rates for patients treated surgically for liver metastasis from NETs, including P-NETs, which account for 30-50% of all NETs in previous series, have been 61-86% and 35-50%[155),157),160)-167)], respectively.

There has so far been no randomized control study comparing surgical with non-surgical treatment for resectable liver metastasis from NETs. However, liver resection has been performed for resectable liver metastasis as first line-therapy, because the prognosis of patients who undergo liver resection is better than that of patients who do not, with 5-year survival rates of 0-40%[167)-170)]. Recently, the Surveillance, Epidemiology, and End Results program of the National Cancer Institute United States, has demonstrated that the prognosis of patients with distant metastasis from P-NETs, for whom surgery was recommended but who declined, was significantly worse than that of patients who underwent surgery[171)].

Partial resection, segmental resection, subsegmental resection, and lobectomy of the liver can also be considered based on the site and number of liver metastases. Combination chemotherapy with cisplatin and etoposide or irinotecan, instead of hepatectomy, is the first-line therapy for liver metastasis of NEC as defined by the 2010 WHO classification[172)].

Frilling et al. reported that prognosis and biological malignancy differed according to the localization and number of liver metastases[158),173)], and the ENETS guidelines suggest a therapeutic strategy that is based on this concept[172)].

The 5-year recurrence rate of liver metastasis after surgical treatment is very high, exceeding 80%. Most such recurrences occur within 2 years after surgery, and the most common sites are the liver, bone, lung, lymph nodes, peritoneum, and brain, the liver accounting for 80-90% of all recurrence sites[161),163)－165),167),168),174)]. Elias et al. reported that the preoperative detection rate for liver metastases by somatostatin receptor scintigraphy, CT, MRI, and abdominal ultrasonography was < 50% in comparison with final histological examination of liver specimens that had been systematically cut into 3- to 4-mm slices[175)]. Control of such micrometastases is a major problem to be resolved in the future, in order to improve liver surgery outcomes[176)].

Simultaneous resection of primary P-NETs and liver metastasis carries a potential risk of fatal morbidity, such as bleeding due to pancreatic fistula and liver failure, and requires careful treatment decision-making. Sarmiento et al. reported that the rates of major morbidities such as bile leakage and pancreatic fistula, and mortality after distal pancreatectomy combined with liver resection were 18% and 0%, respectively[160)]. Kianmanesh et al. reported two-step surgery for synchronous bilobar liver metastasis from digestive NETs including P-NETs of the distal pancreas. According to that report, at first-step surgery, distal pancreatectomy, partial resection of the left hepatic lobe, and ligation of the right portal vein were performed. For second-step surgery 8 weeks later, a right or extended right hepatectomy was performed. Using this strategy, morbidity and mortality rates were approximately 20% and 0%, respectively[177)]. With adequate surgical planning and in specialized centers, surgical treatment of synchronous liver metastasis and P-NETs of the distal pancreas may be performed safely. In relation to combined surgery, pancreatoduodenectomy, and extended liver surgery, one study found that combined surgery was associated with a high mortality rate of 38% (3/8 cases)[178)]. In this situation, careful decision-making about surgical indications is necessary.

Complete surgical resection is often difficult for liver metastasis, since 86% of patients with liver metastasis already have unresectable multiple liver metastases and extrahepatic metastases[179)]. For unresectable liver metastases, liver transplantation, transarterial chemoembolization/embolization[180),181)]systemic chemotherapy[182)], biotherapy such as somatostatin analogue and interferon-α[183)], peptide receptor radionuclide therapy (PRRT)[184)]and targeted therapy[185),186)]have been selected based on the presence or absence of extrahepatic metastasis, tumor proliferative activity, and somatostatin receptor status[134),155),169)]. It has been reported that a small number of patients with an inoperable primary tumor and metastasis can achieve down-sizing and curative resection by the use of PRRT[159),184)].

Liver transplantation for patients with liver metastases from P-NETs is indicated if the metastases are unresectable and no extrahepatic metastasis is present, although subsequent recurrence rates are very high[172)]. Lehnert et al. reviewed 103 patients who underwent liver transplantation for liver metastasis from NETs and reported that their 5-year overall and recurrence-free survival rates were 47% and < 24%, respectively; the postoperative mortality rate within 60 days after liver transplantation was 14%[187)]. Favorable prognostic factors after liver transplantation are a well-differentiated tumor histology, positive immunoreactivity for E-cadherin, a Ki-67 labeling index of < 5-10%, and liver metastasis involving < 40% of total liver volume[188)－190)]. Le Treut et al. reported that liver transplantation for P-NETs is associated with poor prognosis, along with upper abdominal exenteration, liver transplantation for liver metastasis from duodenal NETs, and hepatomegaly[191)]. In a review of liver transplantation for liver metastasis from P-NETs, however, Máthé et al. concluded that liver transplantation for patients < 55 years of age who did not undergo resection of the primary tumor and liver transplantation simultaneously had a relatively good outcome, with a 5-year survival rate of 61%[192)]. Thus, liver

transplantation may improve outcomes for selected patients.

Cytoreductive hepatic surgery, which removes 90% of liver metastases, may be indicated for hormonal symptoms that are resistant to medical therapy, to reduce the amount of hormone and improve clinical symptoms and prognosis, and may even increase long-term survival[193)-195)]. The rate of remission of hormonal symptoms by cytoreductive hepatic surgery has been reported to be approximately 90%[160), 161), 193), 196), 197)]. Furthermore, Chung et al. have reported that the rate of remission of hormonal symptoms by cytoreduction removing at least 70-90% of the tumor burden, followed by administration of an adjuvant long-acting somatostatin analog, was 87%[198)]. Although Osborne et al. have indicated improvement of prognosis using cytoreductive hepatic surgery[197)], there is insufficient evidence for the efficacy of cytoreductive hepatic surgery for patients other than those who have hormonal symptoms resistant to medical therapy.

Surgical treatment for other sites of metastasis

There are few reports about surgical treatment for lung metastasis from NETs[199)]. Although it is difficult to suggest any definitive therapeutic approach, patients who have no metastasis other than in the lung, metastatic tumors with low proliferative rates, and sufficient pulmonary function to tolerate lung resection may be suitable candidates for resection of lung metastasis.

In relation to peritoneal metastasis, 82-97% of patients with peritoneal metastasis from NETs have liver metastasis, and liver metastasis is a prognostic factor for patients with peritoneal metastasis[200), 201)]. In addition, extrahepatic metastasis such as peritoneal metastasis is a poor prognostic factor for patients with liver metastasis[165), 167)]. Therefore, therapy for liver metastasis and peritoneal metastasis may be important for improving prognosis. In terms of therapy for peritoneal metastasis, Ellias et al. reported that the 5- and 10-year survival rates for patients who had liver and peritoneal metastasis from well-differentiated NETs and who underwent resection of these metastases along with intraperitoneal chemotherapy using mitomycin C and 5-fluorouracil were 71% and 31%, respectively; the outcome was unaffected by whether peritoneal metastasis was present or not[157)]. Resection of peritoneal metastasis may be indicated if it can be done safely, as a part of combined therapy.

Local recurrence may also be an indication for surgery if the tumor is resectable. Schurr et al. reported that aggressive resection for recurrences including local recurrence had a tendency to improve overall and disease-free survival[202)].

Postoperative surveillance for P-NETs

Postoperative follow-up for at least 10 years is needed because long-term recurrence can occur after surgery[203)]. Laboratory investigations and ultrasonography are required every 3 months during the first 2 years and CT is required every 6 months. Thereafter, laboratory investigations and ultrasonography are recommended every 6 months and CT is recommended yearly[29)].

Multiple primary cancers such as breast, prostate, bladder, and ovarian cancer occurred in 13% of P-NETs and approximately 20% of gastrinoma and nonfunctioning P-NETs[31)]. Therefore, careful observation and follow-up are required due to the possibility of multiple primary cancers.

Blood levels of gastrin, insulin, glucagon, and others can be used as indicators of recurrence of functioning P-NETs. Neuron-specific enolase is used as a tumor marker for poorly differentiated NETs[204)]. Somatostatin receptor scintigraphy[205), 206)] and serum chromogranin A are used in postoperative follow-up[207)]. Serum chromogranin A is useful for determining recurrence and the effect of treatment, regardless of whether P-NET is functioning or nonfunctioning[208)-210)]. Single-photon emission CT imaging in somatostatin receptor scintigraphy gave a sensitivity of 92.3% for liver metastases. This value is superior to those for planar imaging (58.5%) and CT, MRI, and ultrasonography (80%)[211)].

Conflicts of interest

The authors have no conflicts of interest to declare.

Abbreviations

AJCC, American Joint Committee on Cancer; CT, computed tomography; DPPHR, duodenum-preserving pancreatic head resection; ENETS, European Neuroendocrine Tumor Society; EUS, endoscopic ultrasonography; FDG-PET, fluorodeoxyglucose positron emission tomography; FNA, Fine-needle aspiration; MRI, magnetic resonance imaging; NEC, neuroendocrine carcinoma; P-NET, pancreatic neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; SACI, selective arterial calcium injection test; SpDP, spleen-preserving distal pancreatectomy; TACE, transarterial chemoembolization; TAE, transarterial embolization; WHO, World Health Organization.

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