J Hepatobiliary Pancreat Surg (2009) 16:639–647
DOI 10.1007/s00534-009-0099-1

ORIGINAL ARTICLE

Nonfunctioning neuroendocrine pancreatic tumors: our experience and management

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Received: 25 October 2008 / Accepted: 24 December 2008 / Published online: 14 April 2009

Abstract
Background and purpose We present our experience in the treatment of nonfunctioning neuroendocrine pancreatic tumors (NFNPTs) to define the clinical and pathological characteristics and to suggest proper management.
Methods The records of 17 patients with NFNPTs operated on between 1998 and 2008 were retrospectively reviewed, and all tumors were classified clinicopathologically as benign, uncertain, and malignant, based on the World Health Organization (WHO) classification of neuroendocrine tumors.
Results There were four benign, six uncertain, and seven malignant NFNPTs. The most frequent symptoms were abdominal pain (five patients) and obstructive jaundice (one patient). Most of these symptomatic patients had malignant tumors. Mean tumor size of benign, uncertain, and malignant tumors were 1.0 ± 0.3, 3.2 ± 1.6, and 5.3 ± 2.4 cm, respectively. Metastatic lesions of malignant tumors were lymph node (six patients), liver (four patients), and adrenal gland (one patient). Six of seven patients with malignant tumors underwent curative rejection. There were recurrences in four of six patients with curatively rejected malignant tumors. Two patients underwent more rejection, three patients received systemic chemotherapy, and two patients underwent radiofrequency ablation and transcatheter arterial chemoembolization for liver metastases. Survival of patients with malignant tumors was significantly shorter than that of patients with benign and uncertain tumors. However, three patients with malignant tumors had long survival of more than 3 years, even with metastases or recurrences.
Conclusions Aggressive surgical resection should be performed in patients with resectable NFNPTs, even with metastases. Even when a tumor was unresectable or there were recurrences, long-time palliation could be achieved by a multidisciplinary approach.

Keywords Pancreas · Nonfunctioning neuroendocrine tumor · WHO classification

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Introduction

Neuroendocrine pancreatic tumors (NPTs) are rare, accounting for only 1–5% of pancreatic tumors [1]. Nonfunctioning neuroendocrine pancreatic tumors (NFNPTs) account for 15–52% of NPTs and are not associated with specific clinical symptoms, as they do not produce an excess of any active polypeptide hormone [2, 3]. Because there were no specific clinical symptoms of hormone excess, NFNPTs are often discovered at an advanced stage, such as a huge mass, gross local invasion, and distant metastases. The malignancy of NFNPTs has been confirmed by criteria including local invasion, regional lymph node or distant metastases, and histologic evidence of vascular, lymphatic, or perineural invasion. However, malignancy cannot be easily predicted on the basis of histology alone, except for poorly differentiated carcinomas that resemble small cell carcinoma of the lung. Thus, the diagnosis of malignancy should be made according to the gross features of local invasion or the presence of metastases [4, 5]. In 2004, the World Health Organization

(WHO) classified well-differentiated NPTs as having benign, uncertain, or low-grade malignant behavior, based on criteria including tumor size, mitotic rate, Ki67 proliferative rate, angioinvasion, perineural invasion, gross local invasion, and metastases [6]. According to this classification, the malignancy rate of NFNPTs is reported to be between 37.5 and 72% [2, 3, 5, 7–9].

In this article we present the results of 17 patients with NFNPTs whom we have seen in the last 10 years and whose tumors were classified based on the WHO classification. The purpose of this study was to analyze the clinicopathological characteristics and prognosis of 17 NFNPTs and suggest proper management of the tumors.

Table 1 WHO classification of endocrine tumors

Well-differentiated endocrine tumor
Benign behavior
Confined to the pancreas, non-angioinvasive, no perineural invasion
<2 cm in size, <2 mitoses/10 HPF and <2% Ki67-positive cells
Uncertain behavior
Confined to the pancreas and or more of the following features:
≥2 cm in size, 2–10 mitoses/10 HPF, >2% Ki67-positive cells, angioinvasion, perineural invasion
Well-differentiated endocrine carcinoma
Low-grade malignant
Gross local invasion and/or metastases
Poorly differentiated endocrine carcinoma
High-grade malignant
>10 mitoses/10 HPF

Patients and methods

A total of 17 patients with NFNPTs were treated between 1998 and 2008 at the Department of Surgery II, Nagoya University Hospital. The diagnosis of NPTs was established by histopathologic examination and immunohistochemistry. Tumors were considered nonfunctional if the patients had no evidence of clinical symptoms of hormonal excess, and if analyzed, plasma hormone levels of gastrin, insulin, glucagon, vasoactive intestinal peptide (VIP), somatostatin, pancreatic polypeptide, and serotonin were normal.

The medical records of 17 patients were retrospectively reviewed with regard to patient demographics, clinical features, pathologic findings, operative details, medical treatment, and survival. The tumors were classified as benign, uncertain, and malignant behavior, based on the WHO classification of endocrine tumors (Table 1).

Overall survival intervals were calculated from the time of surgical exploration. Cumulative overall survival curves were calculated and compared using the Kaplan–Meier method and log-rank test, respectively. A value of $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

Table 2 shows the demographic and clinical features, pathological findings, operative details, outcomes, and WHO classification of 17 patients with NFNPTs. There were nine men and eight women with a mean age of 56.7 years (range 30–75 years) at the time of operation. One patient had multiple endocrine neoplasia type I (MEN-I), and one had von Hippel–Lindau disease. Twelve patients were asymptomatic, with the tumors found incidentally on radiological investigation. Five patients presented with abdominal pain and one patient with obstructive jaundice.

Pathological findings

Five tumors were located in the head of the pancreas, six in the body, four in the tail, and one in the body and tail of the pancreas. One patient with MEN-I had multiple tumors throughout the pancreas, ranging from 0.7 to 5.2 cm in size. Six patients had lymph node metastases, four had liver metastases, and one had adrenal gland metastases at the initial operation.

Immunohistochemical staining was performed in 14 patients. Twelve tumors were positive for chromogranin A, four tumors for CD56, and three tumors for synaptophysin. Immunohistochemical-staining assay for Ki67 was performed in 16 patients, and the percentage of Ki67-positive cells was determined. Five of seven "malignant" tumors showed high expression of Ki67 of more than 5% (Fig. 1).

According to the WHO classification, four tumors were classified as benign, six as uncertain, and seven as malignant. Six of seven "malignant" tumors were classified as low-grade malignant, and one as high-grade malignant.

Mean tumor size of benign, uncertain, and malignant tumors was 1.0 ± 0.3, 3.2 ± 1.6, and 5.3 ± 2.4 cm, respectively. Tumor size was significantly large in the "malignant" tumors in contrast with "benign" or "uncertain" tumors ($P < 0.05$). Four of five symptomatic patients had malignant tumors.

Treatment

One of four patients with "benign" tumors underwent enucleation. Two patients with benign tumors also tried to undergo enucleation; however, as intraoperative ultrasound

Table 2 Clinical and pathological status of 17 patients with NFNPTs

Case					Size (cm)	Local invasion Metastases	Surgical procedure	Angio-invasion	Perineural invasion	Mitoses	Ki67(+) cells (%)	WHO classification	Recurrence (Treatment)	Prognosis (months)
No.	Age	Sex	Symptom	Location										
1	56	M	No	Pb	0.7	No	MP	No	No	<2	<1	Benign behavour	No	101 alive
2	56	F	No	Pb	0.8	No	MP	No	No	<2		Benign behavour	No	114 alive
3	68	F	No	Pt	1.0	No	Enucleation	No	No	<2	<1	Benign behavour	No	120 alive
4	52	M	No	Ph	1.5	No	PHRSD	No	No	<2	<1	Benign behavour	No	8 alive
5	66	M	No	Pb	1.4	No	DP	No	Yes	<2	5	Uncertain behaviour	No	15 alive
6	70	M	No	Ph	3.6	No	PHRSD	No	No	<2	<1	Uncertain behaviour	No	86 alive
7	50	F	No	Pt	5.0	No	DP	Yes	No	<2	3	Uncertain behaviour	No	41 alive
8	46	F	No (MEN-I)	Ptbh	0.7–5.2	No	DP Enucleation	No	No	<2	<1	Uncertain behaviour	No	120 died
9	68	M	No	Ph	2.2	No	PHRSD	Yes	Yes	<2	<1	Uncertain behaviour	No	7 alive
10	34	F	Abdominal pain	Pt	1.8	No	SPDP				3	Uncertain behaviour	No	8 alive
11	41	M	Abdominal pain	Pb	2.0	LN	DP	Yes	Yes	<2	<1	Low grade malignant	No	22 alive
12	66	F	Abdominal pain Jaundice	Ph	4.5	LN, Liver	PD Hepatectomy	Yes	Yes	2–10	30	Low grade malignant	Liver (No treatment)	7 died
13	69	F	Abdominal pain	Pt	6.0	LN	DP	Yes	Yes	2–10	10	Low grade malignant	No	1.7 died
14	75	F	No	Ph	6.0	LN, Liver	PD Hepatectomy	Yes	No	2–10	<1	Low grade malignant	Liver (TACE)	24 alive
15	38 (von Hippel–Lindau disease)	M	No	Ptb	10.0	LN, Liver Adrenal gland	DP Adrenalectomy	Yes	Yes	2–10	10	Low grade malignant	(Chemotherapy, RFA)	45 alive
16	52	M	No	Pb	5.0	Liver	DP Hepatectomy	Yes	No	2–10	5	Low grade malignant	Liver, Peritoneum (Hepatectomy, RFA, TACE)	99 alive
17	30	M	Abdominal pain	Pb	4.2	LN	DP	Yes	No	>10	40	High grade malignant	Local, Peritoneum (Resection, Chemotherapy)	40 died

Ph head of pancreas, *Pb* body of pancreas, *Pt* tail of pancreas, *LN* lymph node, *MP* middle pancreatectomy, *PHRSD* pancreatic head resection with segmental duodenectomy, *DP* distal pancreatectomy, *SPDP* spleen-preserving distal pancreatectomy, *PD* pancreticoduodenectomy, *TACE* transcatheter arterial chemoembolization, *RFA* radiofrequency ablation

revealed that the tumors were close to main pancreatic ducts, they underwent middle pancreatectomy. Another tumor localized in the pancreatic head was resected by pancreatic head resection with segmental duodenectomy (PHRSD) [10].

Of the six patients with "uncertain" tumors, two with tumors localized in the pancreatic head underwent PHRSD. Four patients with tumors localized in the pancreatic body or tail underwent distal pancreatectomy (DP) or spleen-preserving distal pancreatectomy (SPDP).

Of the seven patients with "malignant" tumors, two underwent pancreaticoduodenectomy (PD), and five underwent DP. Four patients underwent combined resection of other organs with metastases, including liver (three patients) and left adrenal gland (one patient). Curative resection was performed in six of seven patients with "malignant" tumors. One patient who underwent DP died on postoperative day 52 because of sepsis initiated by pancreatic fistula (case 13). One patient with multiple liver metastases had palliative resection (case 15). This case was complicated by von Hippel–Lindau disease. The primary tumor, 10 × 7 cm in size, was located in the pancreatic body and tail, and metastatic lesions were present in liver, left adrenal gland, and paraaortic lymph nodes (Fig. 2). Distal pancreatectomy combined with splenectomy, left adrenalectomy, and lymphadenectomy was performed. For the treatment of liver metastases, transcatheter arterial chemoembolization (TACE) with epirubicin and mitomycin C was performed, but could not be continued due to allergy to the contrast media. Alternatively, systemic chemotherapy with dacarbazine (200 mg/m^2/day), 5-fluorouracil (5-FU) (500 mg/m^2/day), and epirubicin (30 mg/m^2/day) was performed for 3 consecutive days every 3 weeks. The patient was given four courses of combined chemotherapy with these three drugs and the next nine courses of monotherapy with dacarbazine (400 mg/m^2/day) every 4 weeks. Nausea/vomiting and neutropenia were observed after combined chemotherapy, but there was only a mild degree of nausea/vomiting after monotherapy. No measurable response could be obtained, but the tumor stabilized. Radiofrequency ablation (RFA) was also performed, and the patient is still alive 45 months after the primary operation.

Recurrence of disease was seen in four of six patients with curatively resected "malignant" tumors. In one patient a tumor recurred locally 18 months after the initial operation (case 17). The tumor invaded the left adrenal gland, left kidney, and transverse colon. He underwent tumor resection with adrenalectomy, nephrectomy, and hemicolectomy, but the tumor recurred in the peritoneum 3 months after the reoperation. He received systemic chemotherapy with dacarbazine, 5-FU, and epirubicin. Nausea/vomiting, neutropenia, and alopecia were observed, but chemotherapy could be continued. Although tumor in the peritoneum was once reduced after six courses of chemotherapy, 6 months later multiple recurrences developed in the peritoneum, and the patient died 40 months after the

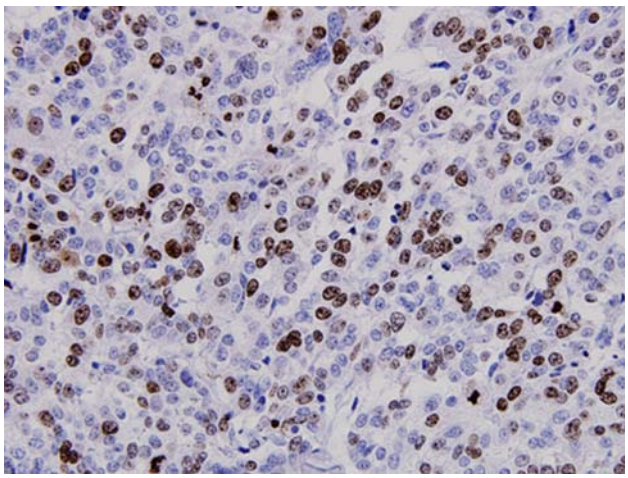

Fig. 1 Immunohistochemical-staining assay for Ki67 (30% Ki67-positive cells) of "malignant" NPT with liver metastases (case 12)

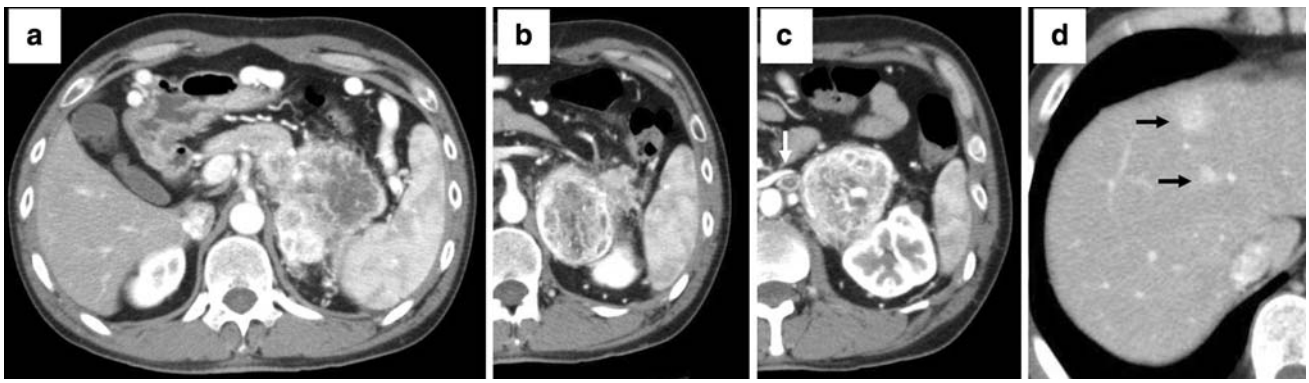

Fig. 2 Abdominal CT scan shows hypervascular tumor, 10 × 7 cm in size, in the pancreatic body and tail (**a**). Metastatic lesions were present in the left adrenal gland (**b**), paraaortic lymph nodes (**c** *arrow*), and liver (**d** *arrow*)

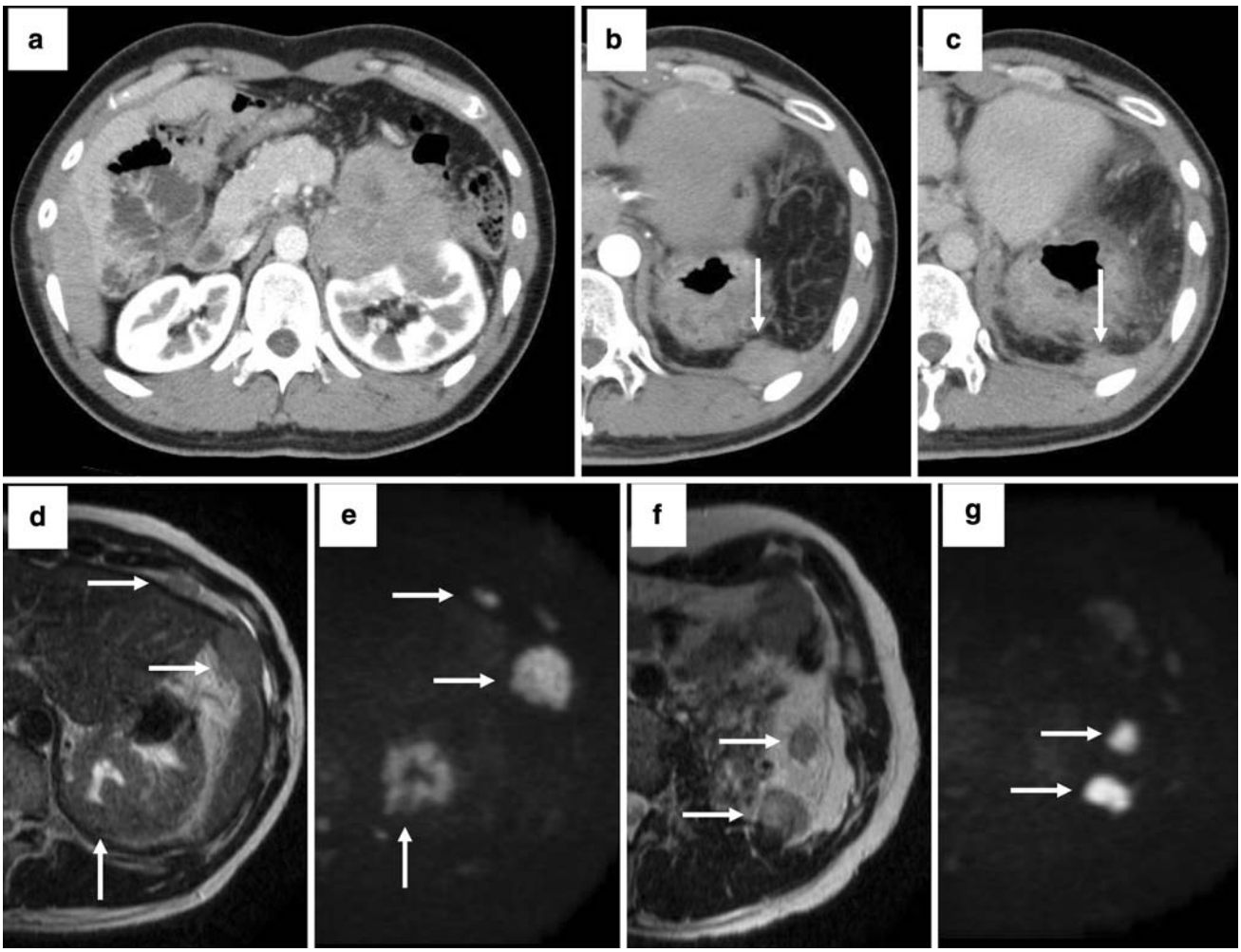

Fig. 3 **a** Tumor recurred locally 18 months after the initial operation and invaded the left adrenal gland, left kidney, and transverse colon. **b** Patient underwent tumor resection with adrenalectomy, nephrectomy, and hemicolectomy, but the tumor recurred in the peritoneum 3 months after reoperation (*arrow*). **c** Tumor in the peritoneum was once reduced after six courses of systemic chemotherapy with dacarbazine, 5-FU, and epirubicin (*arrow*). **d–g** However, 6 months later, multiple recurrences in the peritoneum were demonstrated by magnetic resonance imaging (*arrows*)

primary operation (Fig. 3). One patient died of multiple liver metastases 7 months after the operation without any treatment (case 12). In one patient who underwent resection of primary pancreatic tumor and synchronous hepatic metastases, recurrence developed in the liver 29 months later, and repeated partial hepatic resection was performed (case 16). Multiple hepatic recurrences were seen after the second operation, and TACE was repeated four times. Then it recurred in the peritoneum also, so we performed resection of the peritoneal tumor and partial hepatectomy with RFA. Recurrences in the liver and peritoneum were documented again after the operation, but the tumors grew slowly. TACE has been repeated for liver metastases, and he is still alive more than 8 years after the primary operation. Another patient received TACE and is still alive more than 2 years after the operation (case 14).

Survival

The mean follow-up period was 50 months (range 2–120 months). One patient with "uncertain" tumor died of other disease 10 years after the operation. The other nine patients with "benign" and "uncertain" tumors are all alive without recurrence. The cumulative 5-year survival rate of patients with "malignant" tumors was 48%, which was statistically significantly lower than the survival rate of patients with "benign" and "uncertain" tumors ($P = 0.02$; Fig. 4).

Discussion

NFNPT is a relatively rare disease, and we have experienced only 17 cases during the last 10 years. NFNPTs have

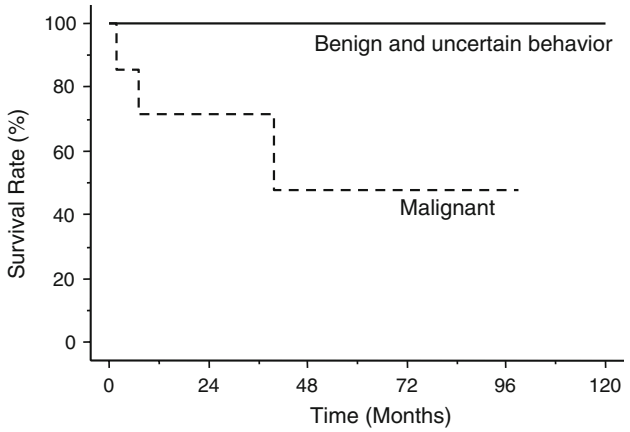

Fig. 4 Kaplan–Meier survival curves of patients with "malignant" NFNPTs ($n = 7$) and patients with "benign" and "uncertain" NFNPTs ($n = 10$) ($P = 0.02$)

no specific clinical symptoms of hormone excess, so they are often not diagnosed until the advanced stage when large in size and with distant metastases, most commonly to the liver. Several patients presented with abdominal pain, weight loss, nausea, jaundice, and abdominal mass; however, these symptoms are not specific to these tumors. In our study, four of seven patients (57%) with "malignant" tumors were symptomatic, but only one of ten patients (10%) with "benign" or "uncertain" tumors was symptomatic ($P < 0.05$).

Recently, with the development of imaging modalities, we have had more opportunity to find relatively small-sized NFNPTs. NFNPT under contrast-enhanced CT typically shows a hyperdense mass in the arterial contrastographic phase. Other tumors, such as acinal cell carcinoma of the pancreas, pancreatic metastases of renal cancer, and intrapancreatic accessory spleen, also show hyperdensity, and the differential diagnosis between NFNPTs and these tumors is sometimes difficult. NFNPTs are rarely demonstrated by means of contrast-enhanced CT as hypodense or cystic tumors, and cannot be differentiated from other solid tumors [11].

Preoperative differentiation between benign and malignant NPTs is often difficult except in cases with distant metastases or invasion to adjacent organs. Sugiyama et al. reported that a hypoechoic mass with an irregular central echogenic area on EUS or complete obstruction of the main pancreatic duct on ERCP suggested malignancy [12]. NPTs have been considered to be malignant in the presence of local invasion, lymph node, or distant metastases, and histologic evidence of vascular, lymphatic, or perineural invasion. However, the WHO has classified well-differentiated NPTs as benign, uncertain, and malignant, and defined "malignant" as tumors with gross local invasion to adjacent organs and metastases [6]. Indeed, from our data, neither recurrence nor progression of disease was seen in patients with "benign" and "uncertain" tumors, and the difference in survival was significant between patients with "benign" or "uncertain" tumors and "malignant" tumors. Therefore, the WHO classification is useful for predicting the prognosis of patients after operation. Especially histopathologic proliferative activity (Ki67) is considered to be the most important variable to predict tumor growth and prognosis [7]. Most of the tumors with high Ki67 expression in our study had synchronous metastases, and recurrence of tumor occurred repeatedly after the curative resection.

Klöppel et al. [13] considered that a size greater than 3 cm was predictive of aggressive development in nonfunctioning endocrine tumors. Several authors reported that survival was significantly higher in patients with tumors $\leq$3 cm than in those with tumors >3 cm [9, 14]. Our data have shown that mean tumor size of "malignant" tumors and no "malignant" tumors are 5.3 ± 2.4 and 2.3 ± 1.6 cm, respectively, and that a size >3 cm is statistically correlated with metastases ($P < 0.05$). Therefore, we consider that the treatment of choice for NFNPTs >3 cm should be radical en bloc resection with locoregional lymph node dissection following the principles of surgery for exocrine pancreatic cancer. Although the risk of malignancy increases with tumor size, malignant tumors as small as 1–3 cm have been reported [15–17]. In our study, one patient had a 2-cm malignant tumor with lymph node metastases. Therefore, we consider that pancreatic resection should be performed for any lesion >1 cm. When there is no macroscopic evidence of local invasion and metastases, we usually perform duodenum-, pancreas-, and spleen-preserving procedures, such as PHRSD, MP, and SPDP for these relatively small tumors. Enucleation can be an appropriate procedure for tumors $\leq$1 cm if the main pancreatic duct can be preserved because these small tumors are almost always benign.

Many patients with NFNPTs have synchronous metastases, typically in the liver. Aggressive surgical resection of liver metastases, if possible, offers the only hope for curative therapy and leads to long-term survival in patients with malignant NPTs [18–21]. Elias et al. reported 5-year survival of 71% for 47 patients with liver metastases treated with hepatectomy, and 31% for 65 patients treated with TACE [20]. When complete resection of liver metastases is not feasible, current recommendations dictate the removal of at least 90% of the disease to achieve adequate palliation for these patients [22]. In those cases, RFA can be used as an adjunct treatment to surgical resection [18]. Musunuru et al. [23] concluded that in patients with liver-only neuroendocrine metastases, surgical therapy with resection, RFA, or both were associated with improved survival compared with nonsurgical treatment.

For those patients who have diffuse liver metastases and are not candidates for surgical treatment, TACE is recommended because many of these metastases are hypervascular. Ho et al. showed that TACE resulted in average progression-free survival and overall survival times of 1.5 and 3.5 years, respectively, even when most of the patients had extrahepatic metastases, and almost all of them had diffuse liver involvement. Especially in patients with functional NPTs, hormonal syndromes could be relieved in most of them after TACE, even when they had extrahepatic metastases. They concluded that the presence of extrahepatic metastases should not limit the use of TACE [24]. In one patient, even with peritoneal recurrence, long survival was achieved by TACE for the treatment of liver metastases (case 16). When the tumor is refractory to TACE, RFA may be indicated as a cytoreduction therapy [25].

In addition, systemic chemotherapy is an appropriate therapeutic option for those patients with unresectable locally advanced and/or rapidly progressive metastatic tumors refractory to other treatment, such as TACE. In 1992, Moertel et al. [26] reported an objective tumor regression rate of 69% in patients with islet cell carcinoma treated with streptozocin and doxorubicin. Since then, combination chemotherapy with streptozocin and doxorubicin has been considered a standard treatment for progressive NPTs. However, this regimen was followed by a considerable number of toxic reactions, such as a severe degree of vomiting, haematological toxicity, and nephrotoxicity. In any case, streptozocin is not available in Japan. Ramanathan et al. [27] reported the result of a phase II study of dacarbazine as single agent in advanced pancreatic islet cell carcinoma. The response rate was 33% in 42 patients with measurable tumors, and in untreated patients the response rate was 50%. Arnold et al. [28] reported that the antiproliferative effect of dacarbazine monotherapy was observed in 40% of 40 patients with mostly nonfunctioning metastatic NPTs. Nausea and vomiting were the most adverse events after dacarbazine monotherapy, but were easily controlled. There were no observed severe toxicities, as have been seen after streptozocin-based chemotherapy. Bajetta et al. [29] conducted clinical trials evaluating a combination therapy with 5FU, dacarbazine and epirubicin in the treatment of patients with advanced unresectable neuroendocrine tumors. An objective response was observed in 20 of 82 patients (24.4%). Alopecia and neutropenia were the most frequent and the most severe adverse events, but no patients were withdrawn from the study because of adverse events. We performed dacarbazine-based chemotherapy for two patients with unresectable metastases. Nausea/vomiting, neutropenia, and alopecia were observed mostly after combined chemotherapy, but both patients could continue to receive chemotherapy. One patient with multiple liver metastases obtained disease stabilization and long survival.

Most clinical trials of chemotherapy have focused on locally advanced or metastatic unresectable tumors, and few data are available to support adjuvant chemotherapy. In our study, recurrence was seen in most patients with curatively resected "malignant" tumors. This indicates that surgical resection alone is not adequate, and adjuvant therapy after curative resection is required to prevent tumor recurrence. Dacarbazine monotherapy has less toxicity and could be one of the best regimens. Clinical trials are needed to assess the efficacy of adjuvant chemotherapy after curative resection.

A number of recent studies have investigated the efficacy of octreotide (somatostatin analogue) for the treatment of malignant NPTs [30–32]. In patients with functional NPTs, octreotide has been shown to decrease hormone hypersecretion and the resulting symptoms in a large percentage of treated patients. Actual tumor regression has been reported only rarely, but it is worth noting that disease stabilization can be obtained after treatment with octreotide. Saltz et al. [30] evaluated the antineoplastic activity of octreotide in 34 patients with advanced functional and nonfunctional neuroendocrine tumors. No patients experienced a major objective response, but stabilization of disease occurred in both functional (10 of 21 patients, 47%) and nonfunctional (7 of 13 patients, 54%) tumors. When TACE and systemic chemotherapy are not effective for unresectable NFNPTs, octreotide therapy can be considered for the purpose of disease stabilization. In Fig. 5, we presented a strategy for the treatment of NFNPTs in our institute. According to this strategy, we decide the most appropriate treatment for individual cases. In case 17, we performed aggressive complete resection with adrenectomy, nephrectomy, and hemicolectomy for the local recurrence. Multiple peritoneal recurrence occurred after the operation, and we selected systemic chemotherapy for the treatment. In case 15, we performed palliative resection because of unresectable liver metastases. We consider TACE to be the treatment of choice for unresectable liver metastases, but the patient could not undergo TACE because of allergy to contrast media. Therefore, he underwent systemic chemotherapy and RFA. In case 16, there was a recurrence in the liver and peritoneum, and we performed aggressive surgical resection combined with RFA. After the operation, TACE was repeated for unresectable liver metastases, and the patient achieved long survival. No patients received adjuvant chemotherapy in our study. Now we consider that adjuvant chemotherapy is needed even after curative resection of the malignant NPTs, especially in cases with high expression of Ki67.

In conclusion, the aggressive surgical approach should be considered as the treatment of choice for NFNPTs, even

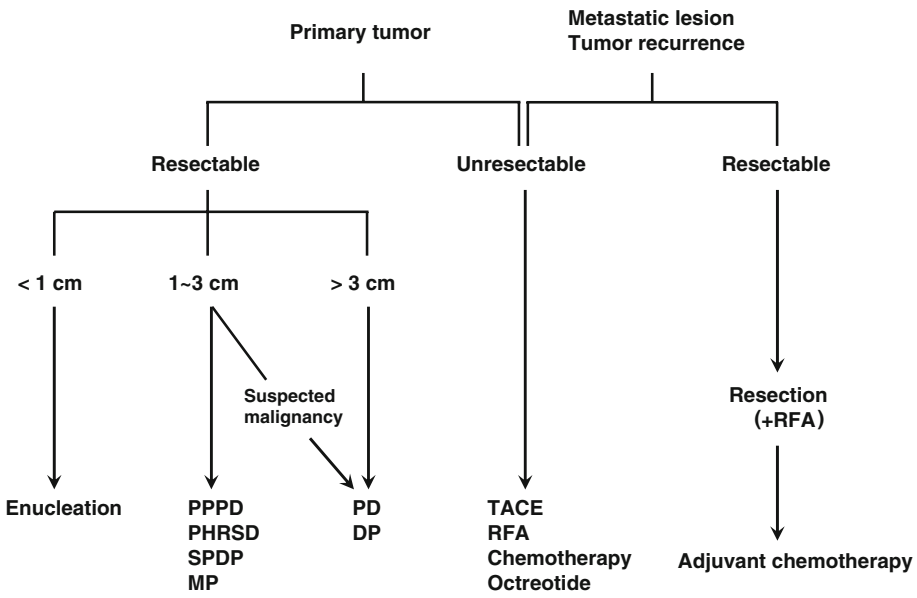

Fig. 5 Strategy for treatment of nonfunctioning neuroendocrine pancreatic tumors (NFNPTs) at the Department of Surgery II, Nagoya University Hospital, Japan

in the case of metastases. With recurrences, repeated resection, if possible, can be indicated to improve survival. Even when a tumor is unresectable, multidisciplinary approaches, such as RFA and TACE for liver metastases, systemic chemotherapy, and octreotide therapy should be considered to prolong survival and improve the quality of life.

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