

Long-term Follow-up of Patients with Multiple Endocrine Neoplasia Type 1

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Abstract. Whether early surgical treatment of non-functioning pancreas islet cell tumor (NFPT) provides a favorable quality of life and life expectancy in patients with multiple endocrine neoplasia type 1 (MEN1) remains controversial. We analyzed the long-term clinical courses and surgical outcomes of 14 Japanese patients with MEN1-associated NFPTs. NFPTs smaller than 20 mm in diameter did not show any apparent growth over a long monitoring period. Furthermore, these small NFPTs did not metastasize to regional lymph nodes or the liver. On the other hand, the development of additional NFPTs or metastasis was found in five of six patients with large (35 mm or larger) NFPTs. Among the seven patients who underwent a partial pancreatectomy, six patients developed impaired glucose tolerance or diabetes. The accumulation of more prospective data is needed to clarify the optimal surgical indications for patients with NFPTs, especially among the Japanese population, which has a relatively low insulin secretion potency compared with non-Hispanic white and African-American populations.

Key words: MEN1, Tumor growth, Surgical indication, Pancreatectomy, Diabetes

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MULTIPLE endocrine neoplasia type 1 (MEN1) is a relatively rare autosomal dominantly inherited disorder characterized by hyperplastic and neoplastic disorders of endocrine organs, such as the parathyroid, anterior pituitary and gastroenteropancreatic endocrine tissues [1]. Less frequent manifestations include adrenal cortex adenoma, foregut carcinoid tumor and subcutaneous lipoma. Some cutaneous tumors, such as collagenoma and facial angiofibroma, are also seen. A clinical diagnosis of MEN1 is made when at least two lesions in three principal organs (parathyroid, anterior pituitary and pancreas/duodenum) are confirmed [2].

Patients with MEN1 are at an increased risk of premature death. In earlier studies, the average life-span

of patients was about 50 years [3, 4]. The predominant cause of death was peptic ulcer and subsequent complications caused by gastrinoma and hyperparathyroidism. Since medical management for peptic ulcers has been dramatically improved by the introduction of H2 blockers, the risk of such premature death has greatly decreased. In recent studies, the most significant determinant of prognosis in patients with MEN1 was the malignant transformation of gastroenteropancreatic tumors and thymic/bronchial carcinoid tumors [5–8]. Pancreas islet cell tumor occurs in about 50% of patients and often metastasizes to the liver and other organs. Thus, the early detection of such tumors is crucial to achieving a better clinical course and possibly to obtaining a better life expectancy. Periodic biochemical and imaging studies are therefore recommended [2].

The standard treatment for functioning pancreas islet cell tumors is surgery. Surgery is also the golden standard for the treatment of non-functioning pancreas islet cell tumor (NFPT), but its indications and timing are

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controversial [9–11]. In this study, we analyzed the long-term clinical courses and surgical outcomes, particularly the postoperative development of diabetes, of Japanese patients with MEN1-associated NFPTs.

Patients and Methods

Forty-three patients with MEN1 who were followed-up for more than two years between 1995 and 2004 in our hospital were analyzed. A diagnosis of MEN1 was made in probands with evidence of neoplastic lesions in at least two out of three principal organs (parathyroid, anterior pituitary and pancreas/duodenum). Among family members, a diagnosis was made with evidence of at least one lesion or confirmation of an *MEN1* germline mutation. The patient characteristics are summarized in Table 1. Patients were periodically examined using abdominal CT scanning (average interval, 17 months). An NFPT was diagnosed when the plasma or serum hormone levels (gastrin, insulin, glucagon and somatostatin) were within normal limits and no clinical symptoms attributable to hormonal excess were present.

Results

During the study period, 26 NFPTs were identified in 14 patients. The location, size and longitudinal course of each tumor are shown in Fig. 1 and Table 1. The average age at the time of NFPT diagnosis was 48 years (29–59 years), and the average tumor size was 20 mm (5–78 mm). Seven of the tumors were located in the pancreas head, 9 were located in the pancreas body, and 10 were located in the pancreas tail. Among the 26 tumors, 7 tumors in 5 patients (average size, 40 mm [15–78 mm]) were surgically removed within 3 months of diagnosis. In one case (Fig. 1 and Table 1, patient C), a 57-year-old man with a 50-mm tumor in the pancreas tail, multiple metastases to the liver were found at the time of the initial examination. After resection of the primary pancreatic tumor, he received a series of transcatheter arterial embolizations and combined therapy with interferon and a somatostatin analog for the treatment of the metastatic tumors. The patient died 2 years after undergoing surgery.

All the resected tumors were pathologically examined using hematoxylin-eosin staining and immuno-

Table 1. Patient characteristics

No. of patients followed between 1995–2004 (M/F)	43 (17/26)
with either a family history or an <i>MEN1</i> mutation (M/F)	36 (17/19)
age at diagnosis of MEN1 (yr, mean \pm SD) (range)	41.7 \pm 14.8 (14–74)
proband/family member	23/20
No. of patients with NFPT (M/F)	14 (7/7)
age at diagnosis of NFPT (yr, mean \pm SD) (range)	48.4 \pm 9.8 (29–59)
size of tumor (mm, mean \pm SD) (range)	20 \pm 18 (5–78)
follow-up period after NFPT diagnosis (mo, mean \pm SD) (range)	78 \pm 36 (27–115)

staining for specific proteins, such as chromogranin A, NSE, insulin, and glucagons. All the tumors were positive for chromogranin A and NSE and some were positive for insulin, glucagons and pancreatic polypeptide.

Indolent character of primary NFPTs

In general, we performed surgery to resect NFPTs that were larger than 20 mm in diameter. Two patients with large NFPTs (Fig. 1, patients E and F) refused surgery and preferred to receive periodical examinations. We followed 13 primary tumors for between 24 and 115 months. During the follow-up period, only one tumor showed a significant increase in size (>20%; 31 mm \rightarrow 38 mm over the course of 109 months; Figs. 1 and 2, patient E); none of the other tumors exhibited significant growth.

Occurrence of newly developed NFPTs during follow-up

During the follow-up period, newly developed NFPTs were found in 6 patients (Fig. 1, patients A, B, D, E, H and K). All of these patients, except for patient H, had been diagnosed as having NFPTs at the beginning of the follow-up period. Among the 6 patients whose primary tumors were 35 mm or larger (Fig. 1, patients A to F), newly developed tumors or metastases were found in 5 patients. On the other hand, among the 8 patients whose primary tumors were 25 mm or smaller, newly developed tumors occurred in only patient K (Fig. 1).

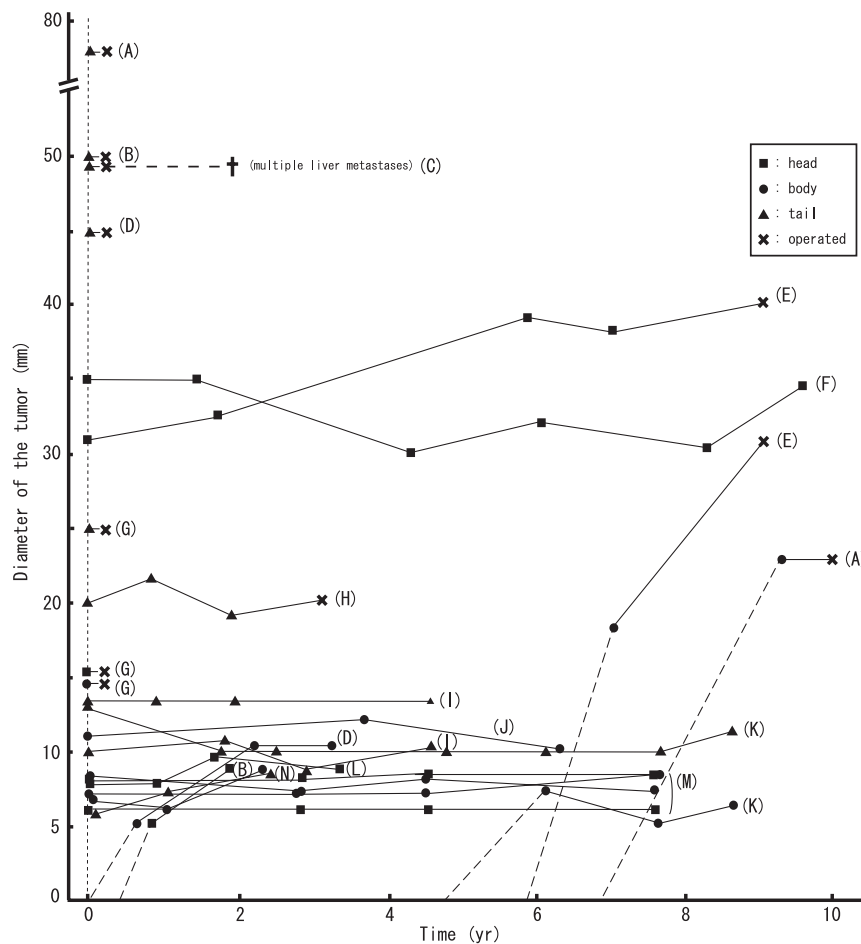


Fig. 1. Localization, size and longitudinal course of NFPTs in patients with MEN1. The ordinate axis indicates the diameter of each tumor, as estimated using computed tomography (CT). The abscissas axis indicates the time since the NFPT was identified using CT.

Rapid growth of newly developed tumors

Some of the newly developed tumors showed rapid growth. In patient E, who refused surgery for a large pancreas head tumor, a newly developed tumor (18 mm) that was found in the pancreas body grew to a size of 31 mm (Figs. 1, 2). In patient A, a tumor (23 mm) and lymph node metastasis were found 9 years after surgery for the primary tumor.

Development of diabetes after pancreatectomy (Table 2)

Among the 7 patients (patients A, B, C, E, G, H, and N) who had histories of partial pancreatectomies, only one patient remained euglycemic (patient G). Patient B, who had acromegaly and had undergone transsphenoidal surgery, had an elevated fasting glucose level

(114 mg/dL). He is currently receiving octreotide injections to suppress tumor growth and hormone production from a remnant pituitary tumor. Recent laboratory results show a plasma IGF-1 level of 700–800 ng/mL. Thus, his glucose intolerance may have been caused by the uncontrolled acromegaly and octreotide injections, rather than the pancreatectomy. Patient C also received octreotide injections for the treatment of metastatic liver tumors. Among the 7 patients who did not receive a pancreatectomy or who received only tumor enucleation, only one patient (patient F) is currently diabetic.

Discussion

NFPT is the most common pancreas islet cell tumor

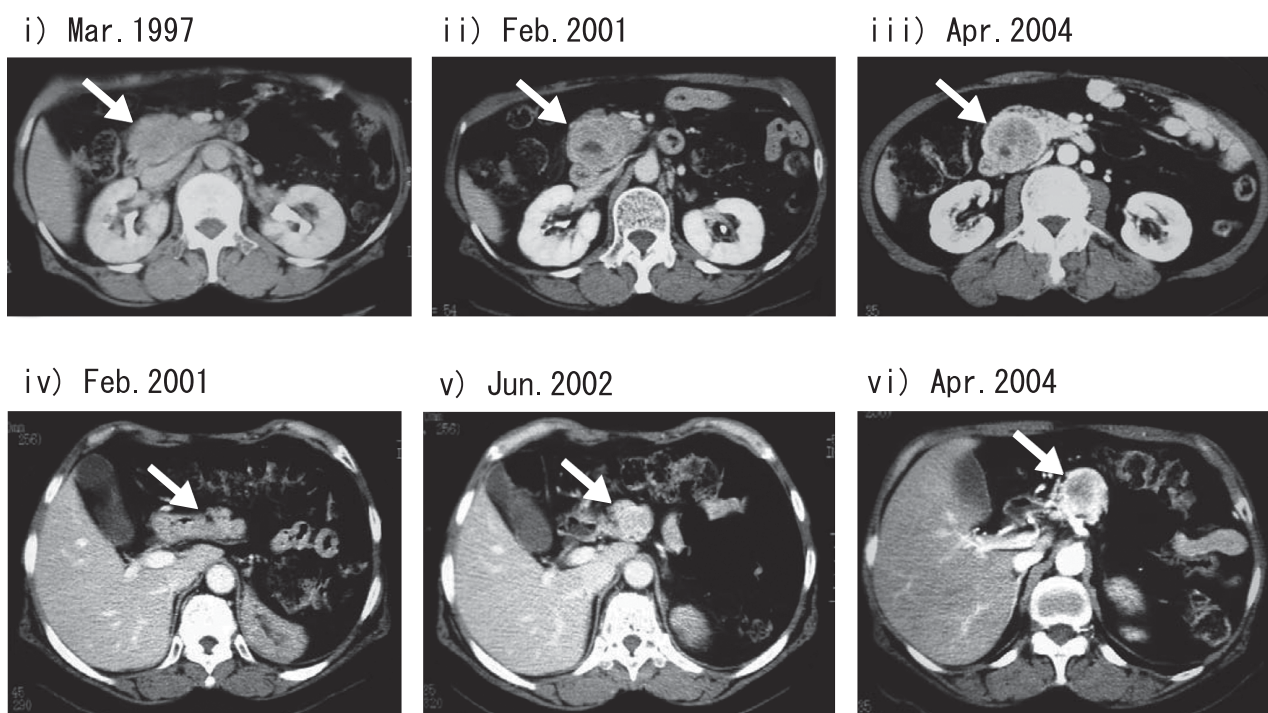


Fig. 2. Growth of primary and secondary NFPTs in patient E. Panels i) to iii) show the growth of the primary pancreas head tumor identified in 1997, and panels v) and vi) show the rapid growth of a secondary tumor in the pancreas body, which was not seen in panel iv).

Table 2. Clinical characteristics of patients with NFPTs

Patient	Age ¹	Sex	Tumor size (mm) ^{2,3}	Tumor localization ³	Surgery	Glucose tolerance			
						before surgery ⁶	after surgery ⁶	HbA1c ⁸	Medication ⁹
A	57	F	78, 23	tail, body	distal pancreatectomy	NA	DM	7.0	SU + BG
B	29	M	50, (9)	tail, (head)	distal pancreatectomy	NGT	IGT	6.0	(LAR)
C	57	M	50	tail	subtotal pancreatectomy	NGT	DM	8.0	INS (OCT)
D	52	M	45, (10)	tail, (body)	enucleation	NGT	NGT	5.0	
E	51	F	38, 31	head, body	pancreaticoduodenectomy	NGT	DM	7.4	INS
F	49	F	35	head	—	DM		6.1	BG
G	43	F	25, 15, 15	tail, body, head	distal pancreatectomy + enucleation	NGT	NGT	4.2	
H	49	M	20	tail	distal pancreatectomy	DM	DM	7.0	INS
I	59	M	13, 10	tail, tail	—	NGT		5.4	
J	59	F	11	body	—	NGT		5.2	
K	36	F	13, 8	tail, body	—	NGT		5.2	
L	46	M	9	head	—	NGT		5.6	
M	34	F	8, 6, 7, 8	head (2), tail (2)	enucleation of insulinoma ⁴	NGT		4.4	
N	57	M	9, 9	tail, body	pancreaticoduodenectomy ⁵	NGT ⁷	DM	6.6	none

¹ Age at diagnosis of NFPT.

² Diameter of the tumor at the last evaluation.

³ Newly developed tumors after primary surgery are indicated in parentheses.

⁴ Received surgery at age 13.

⁵ Received surgery for a gastrinoma at age 54.

⁶ DM, diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; NA, data not available.

⁷ Before pancreaticoduodenectomy.

⁸ Value at the last measurement. Normal range, 4.3–5.8%.

⁹ INS, insulin; SU, sulfonylurea; BG, biguanide; LAR, long-acting octreotide; OCT, octreotide.

seen in patients with MEN1 [12, 13]. Reducing the risk of malignant transformation is the primary reason for surgical intervention for NFPT. Which treatment modality provides patients with the most favorable quality of life and life expectancy remains debatable. Some reports on preferable surgical treatment for sporadic NFPTs have been made [14–18], but whether these procedures are directly applicable to MEN1-associated NFPTs is uncertain. In sporadic NFPTs, surgical resection of the tumor can lead to a complete cure, but this is not the case for patients with MEN1, a life-long disease. Also, the clinical course of MEN1-associated NFPTs may not be the same as that of sporadic NFPTs [19].

A number of studies have reported a link between the size of MEN1-associated gastrinomas and the risk of distant metastasis [8, 20]. Accordingly, many experts have recommended that surgical treatment for gastrinomas should be performed only for large tumors [5, 21, 22]. For NFPT, the possibility of a correlation between tumor aggressiveness and size has been argued. Several studies have suggested that larger tumors are more aggressive, and have recommended that surgery should be considered only for NFPTs larger than 2–3 cm, while smaller tumors should be carefully surveyed [10, 23, 24]. Recently, Triponez *et al.* reported that surgery for NFPTs smaller than 2 cm is not beneficial for MEN1 patients, with regard to their life expectancy [25]. On the other hand, a poor correlation between tumor size and malignant behavior has also been documented [26]. Some groups advocate an aggressive surgical approach for MEN1-associated NFPTs [27–30]. The rationale for such aggressive management is based on the high malignant potency of NFPTs in MEN1. Indeed, malignant pancreatic tumor is the leading cause of mortality in patients with MEN1 [5–8], and NFPTs are widely recognized to have a higher malignant potential than functioning pancreas islet cell tumors. Nevertheless, the benefit of early surgical treatment of NFPTs in patients with MEN1 has not been fully established. Also, few studies have focused on the quality of life of patients who have undergone a pancreatectomy.

Our present results indicate that most NFPTs have an indolent clinical course. None of the small NFPTs (20 mm or less) showed growth during the follow-up period. Furthermore, the patients with small NFPTs did not develop metastasis to either the regional lymph nodes or the liver. This finding is in agreement with a

recent report by Thomas-Marques *et al.* [12] showing that, in more than half of their patients, the diameter and number of NFPTs were stable during the follow-up period of their study. Since we experienced only two cases with liver metastases, we cannot provide any additional evidence as to whether tumor size and malignant potency are related. However, liver metastasis was only seen in patients with large NFPTs (78 mm and 50 mm). This finding was also true in a report by Lowney *et al.*, where the only patients with large tumors had liver metastasis [26].

On the other hand, some secondarily developed tumors in our cases showed relatively rapid growths. These tumors were seen in patients with histories of surgical resection for large primary tumors (patients A and E). Whether these rapidly growing tumors were metastasized from the primary tumor or *de novo* tumors is unclear, but the latter possibility is more likely since liver metastases were not seen in these patients. Also, in patient A, the secondary tumor appeared 9 years after the resection of the primary tumor (Fig. 1). These findings suggest that periodical follow-up after tumor resection is particularly important in patients with large NFPTs and that once a newly developed tumor is found, early surgical intervention or further close observation may be appropriate.

Aggressive surgical procedures certainly reduce the risk of metastatic disease and the development of other primary tumors arising from the residual pancreas. Some authors also claim that such procedures rarely result in the development of diabetes [31]. However, the impairment of glucose metabolism after a pancreatic resection is relatively common [32, 33]. Furthermore, an increased prevalence of diabetes in patients with MEN1 has recently been reported [34]. The effect of a pancreatectomy on glucose metabolism is particularly important in Asians, because this ethnic group is known to have lower beta cell function, compared to non-Hispanic whites and African-Americans [35, 36]. This fact raises the possibility that pancreatectomies may impair glucose metabolism more frequently in Asian patients. Although the available data was limited and was not adjusted for clinical parameters like age, sex, primary pancreatic disorders and preoperative glucose metabolism, Shibata *et al.* [37] reported that 3 of 7 Japanese patients who received a distal pancreatectomy developed substantial diabetes. In the present study, at least 5 of the 7 patients who received a partial pancreatectomy became diabetic. Three patients who

became diabetic after undergoing partial pancreatectomies were apparently euglycemic before surgery. On the other hand, among the 7 patients who did not receive a pancreatectomy or only underwent tumor enucleation, only one patient is currently diabetic.

Our study has several limitations. First, the number of patients was small and data was only obtained from a single institution, which may have caused an unintended bias with regard to the patients' backgrounds. However, we identified 14 out of 43 patients with MEN1, and this number is, to the best of our knowledge, one of the highest in Japanese patients' registries, since a nationwide registry system does not exist in Japan. A multicenter survey is certainly needed. Secondly, insulin secretion and insulin resistance was not estimated in each patient before and after pancreatectomy. Such evaluations will be essential to clarify the mechanism of the development of diabetes in the majority of patients who received a partial pancreatectomy. It should be noted that except for patient M, none of the patients were obese and their body mass indices were less than 25. Recently, Lee *et al.* reported that reduced insulin secretion, rather than insulin resistance, plays a major role in the development of diabetes in Korean patients who received distal pancreatectomies [38]. Reductions in insulin secretion almost certainly had a major contribution to the exacerbation of glucose metabolism in our patients who received pancreatecto-

mies. To clarify the beneficial effect of a pancreatectomy for preventing the occurrence of malignant tumor and the risk of developing diabetes and subsequent complications, especially in Asian patients, the accumulation of more data and a prospective follow-up study is needed.

In conclusion, based on our current results, we agree with the proposal made by Triponez *et al.* [25] and recommend that NFPTs smaller than 20 mm should be observed, based on their indolent clinical course, low malignant potential, and the possible risk of postoperative diabetes. However, a subgroup of patients may suffer from more aggressive and often lethal complications of the disease. Our limited experience is insufficient to draw a definite conclusion regarding the surgical indications for MEN1-associated NFPTs. The accumulation of further data and a longer follow-up period is needed to strengthen our conclusions, and reliable markers for distinguishing less aggressive NFPTs from aggressive ones are needed.

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