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BRIEF ARTICLE

Biochemically curative surgery for gastrinoma in multiple endocrine neoplasia type 1 patients

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Abstract

AIM: To search for the optimal surgery for gastrinoma and duodenopancreatic neuroendocrine tumors in patients with multiple endocrine neoplasia type 1.

METHODS: Sixteen patients with genetically confirmed multiple endocrine neoplasia type 1 (MEN 1) and Zollinger-Ellison syndrome (ZES) underwent resection of both gastrinomas and duodenopancreatic neuroendocrine tumors (NETs) between 1991 and 2009. For localization of gastrinoma, selective arterial secretagogue injection test (SASI test) with secretin or calcium solution was performed as well as somatostatin receptor scintigraphy (SRS) and other imaging methods such as computed tomography (CT) or magnetic resonance imaging (MRI). The modus of surgery for gastrinoma has been changed over time, searching for the optimal surgery: pancreaticoduodenectomy (PD) was first performed guided by localization with the SAST test, then local resection of duodenal gastrinomas with dissection of regional lymph nodes (LR), and recently pancreas-preserving total duodenectomy (PPTD) has been performed for multiple duodenal gastrinomas.

RESULTS: Among various types of preoperative localizing methods for gastrinoma, the SASI test was the most useful method. Imaging methods such as SRS or CT made it essentially impossible to differentiate functioning gastrinoma among various kinds of NETs. However, recent imaging methods including SRS or CT were useful for detecting both distant metastases and ectopic NETs; therefore they are indispensable for staging of NETs. Biochemical cure of gastrinoma was achieved in 14 of 16 patients (87.5%); that is, 100% in 3 patients who underwent PD, 100% in 6 patients who underwent LR (although in 2 patients (33.3%) second LR was performed for recurrence of duodenal gastrinoma), and 71.4% in 7 patients who underwent PPTD. Pancreatic NETs more than 1 cm in diameter were resected either by distal pancreatectomy or enucleations, and no hepatic metastases have developed postoperatively. Pathological study of the resected specimens revealed co-existence of pancreatic gastrinoma with duodenal gastrinoma in 2 of 16 patients (13%), and G cell hyperplasia and/or microgastrinoma in the duodenal Brunner's gland was revealed in all of 7 duodenal specimens after PPTD.

CONCLUSION: Aggressive resection surgery based on accurate localization with the SASI test was useful for biochemical cure of gastrinoma in patients with MEN 1.

Key words: Gastrinoma; Duodenopancreatic neuroendocrine tumors; Multiple endocrine neoplasia type 1; Selective arterial secretagogue injection test; Somatostatin receptor scintigraphy; Pancreas-preserving total duodenectomy; Pancreaticoduodenectomy

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INTRODUCTION

Controversy has surrounded the treatment strategy for gastrinoma and neuroendocrine tumors (NETs) in patients with multiple endocrine neoplasia type 1 (MEN 1) and Zollinger-Ellison syndrome (ZES)[1-14]. It has been confirmed that ZES in patients with MEN 1 is caused mostly by duodenal gastrinomas[15,16]. Some surgeons have not recommended surgery for duodenopancreatic gastrinoma, because of both low biochemical cure rate of gastrinoma and early recurrence of gastrinoma after surgery[8,9]. In contrast, surgeons who have performed aggressive duodenopancreatic resection have reported a higher biochemical cure rate of gastrinoma after surgery, although these studies included relatively small numbers of patients[4-7,11-14].

We have performed curative resection surgery for gastrinoma in 41 patients with ZES guided by localization using the selective arterial secretagogue injection test (SASI test)[17,18]. Guided by localization with the SASI test, pancreaticoduodenectomy (PD) was performed for 10 patients, of whom 3 patients were classified as MEN 1, and all of them have been cured of gastrinoma postoperatively. Pathological examination of the duodenopancreatic specimens resected from the MEN 1 patients revealed single or multiple gastrinomas < 10 mm only in the duodenum, but not in the pancreas head. Thus, we have changed the modus of resection surgery for gastrinomas in patients with MEN 1 from PD to transduodenal excisions of the duodenal gastrinomas or partial duodenectomy (LR) with dissection of the regional lymph nodes, while seeking for less invasive and optimal surgical resection for gastrinomas in MEN 1 patients. Recently, we have performed pancreas-preserving total duodenectomy (PPTD) for MEN 1 patients with multiple gastrinomas and/or numerous microgastrinomas in the duodenum[19,20]. Here, we report the results of our surgical strategy for both gastrinoma and pancreatic NETs in MEN 1 patients, and discuss the optimal surgery for patients with MEN 1 and gastrinomas from a viewpoint of the staging of both gastrinoma and pancreatic NET in these patients.

MATERIALS AND METHODS

Patients

Sixteen patients with genetically confirmed MEN 1 and gastrinoma underwent resection surgery for gastrinomas and pancreatic NETs by a team comprising a chief surgeon (senior author) and co-surgeons (co-authors) at the Departments of Surgery of Graduate School of Medicine, Kyoto University, Osaka Saiseikai Noe Hospital and Kansai Electric Production Company Hospital between March 1991 and March 2010.

All patients were examined for MEN 1 gene mutations by a co-author (MK) at the Medical Gene Research Center, Kyoto University. A diagnosis of ZES was established by confirming the co-existence of gastric hyperacidity and hypergastrinemia. Levels of gastrin were > 80 pg/mL in patients who had undergone distal or total gastrectomy and > 200 pg/mL in patients who had not undergone distal gastrectomy[21]. Gastric hyperacidity was confirmed using 24 h pH monitoring, and was diagnosed when the percentage of the time that the gastric pH was 0-4 was > 70%[21]. Either the secretin test or the calcium test was performed for all patients[22-24]. The secretin test was performed by bolus intravenous injection of secretin (3 U/kg body weight). Blood samples were collected from a cubital vein before and 2, 4, and 6 min after secretin injection. An increase in serum immunoreactive gastrin concentration (IRG) both of > 20% of the basal serum IRG and > 80 pg/mL, 4 min after secretin injection was considered positive. The calcium test was performed by injecting 1.17 mEq calcium solution (1 mL of 0.39 mEq calcium gluconate hydrate) diluted with 2 mL physiological saline over 30 s into a cubital vein[22-24]. The intraoperative secretin test was performed using the same method as the preoperative secretin test, and results were obtained within 60 min using rapid radioimmunoassay of serum gastrin levels[25].

Localization of gastrinoma

For localization of gastrinoma, the SASI test with secretin (Secrepan® 30 units) or calcium solution (0.39 mEq calcium gluconate diluted with 2 mL physiological saline) was performed for all patients as described previously[17,18,26]. The principle of the SASI test is to identify the feeding artery of gastrinoma by stimulating gastrinoma to release gastrin using a secretagogue[17]. We used secretin until 2004, since then we have used calcium gluconate hydrate solution, because production of secretin in Japan ended in 2004[10]. CT, MRI or US have been used primarily for detection of distant metastases, such as hepatic metastases or large lymph nodes[1,10,11].

PPTD

PPTD was performed using a new technique described

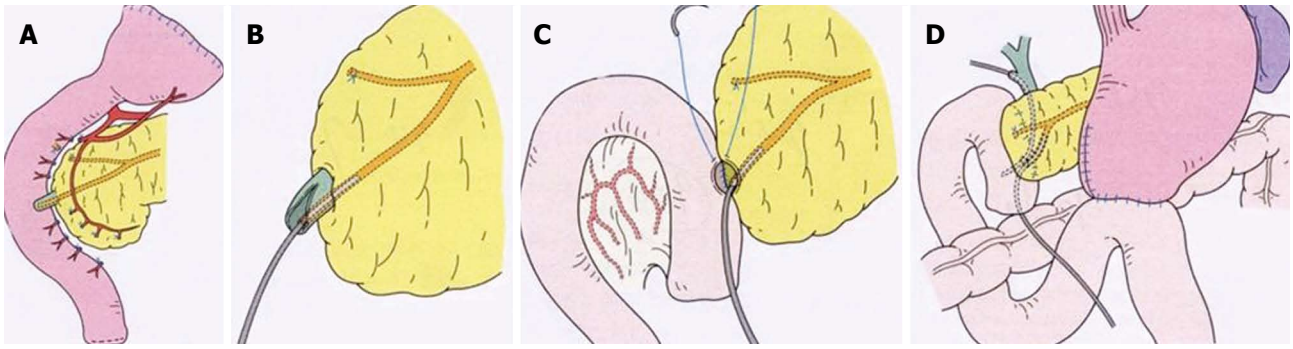

Figure 1 Pancreas-preserving total duodenectomy technique. A: The duodenum is separated from the head of the pancreas by cutting the branches of the pancreaticoduodenal arcade vessels. The choledochal trunk is saved and only the membrane of the major papilla is shaved sharply. The accessory pancreatic duct is ligated and cut; B: Papillotomy is performed on the major papilla at 0, and then a catheter is inserted into the main pancreatic duct for stenting; C: Bilio-jejunal reconstruction. The edge of the common bile duct is sewn to a small opening on the jejunum with 4-0 absorbable knotted sutures; D:The final reconstruction schema of the alimentary tract.

elsewhere[20]; briefly, when resecting the entire duodenum, only a mucosectomy is performed on the duodenal major papilla portion, retaining the structure of the major papilla, and after an 8 mm long sphincterotomy, the opened papilla is anastomosed to the incisional opening of the jejunum[20]. Details of the procedure are shown in Figure 1.

Pathological examination of the resected specimens

Resected duodenopancreatic tissues including any suspected NETs or lymph nodes were fixed in a 10% formalin solution and embedded in paraffin. Paraffin-embedded sections were stained with Masson-Fontana, Grimelius, and Hellerstrom-Hellman silver stains. Immunohistochemical staining was performed with Simple Stain MAX-PI (Multi) (mouse and rabbit/horseradish peroxidase) reagent (Nichirei, Tokyo, Japan) using polyclonal rabbit anti-human gastrin serum (Dako, Glostrup, Denmark).

Criteria of biochemical cure of gastrinoma

Cure of gastrinoma was defined as a normal fasting serum IRG < 150 pg/mL in patients without a history of gastrectomy and < 80 pg/mL in patients with a history of gastrectomy, and/or a negative secretin test or a negative calcium test during the 6 mo follow-up surveillance period. Survival curve analysis was performed using the Kaplan-Meier method.

RESULTS

PD

Between 1991 and 1997, PD was performed for 3 patients with ZES based on localization guided only by the SASI test, because imaging methods (CT, MRI, US) did not visualize any tumor in the abdomen (Table 1). In 3 patients, the SASI test localized the gastrinoma in the upper part of the duodenum and/or the head of the pancreas, thus PD was performed for all patients. Preoperative localization by the SASI test was correct, and gastrinomas were proved in the duodenum; that is, 7 duodenal gastrinomas in 1 patient (No. 2) and only 1 duodenal gastrinoma in 2 patients (Nos. 1 and 3). Metastatic lymph nodes associated with the duodenal gastrinoma were identified in 2 patients. Two patients (Nos. 1 and 2) had multiple nonfunctioning NETs in the head of the pancreas (Table 1). The preoperative serum IRG of these patients ranged between 310 and 800 pg/mL, and the postoperative serum IRG decreased in all patients to < 33 pg/mL. The postoperative secretin test was negative in all patients. One patient died of other causes 4 year after undergoing the PD. Two patients are alive and well, and biochemical cure of gastrinoma has continued for 18 year 5 mo and 12 year, postoperatively.

LR

Since 1996, 5 patients have successively undergone local resection of duodenal gastrinoma through duodenectomy after a 7 year intermission. 1 patient (No. 9) underwent DX in 2009 based on localization by the SASI test, duodenoscopy revealed duodenal submucosal NETs in 3 patients, and CT visualized a few metastatic lymph nodes more than 2 cm with a pancreatic NET more than 1 cm in 2 patients (Table 2). Localization by the SASI test was correct in all of them. In case No. 9, gastrinoma was located not only in the duodenum, but also in the head of the pancreas. Size of duodenal gastrinoma was between 1-15 mm in diameter. Any pancreatic NETs > 1 cm were treated by enucleation and/or distal pancreatectomy. In 3 patients, metastatic lymph nodes were associated with duodenal gastrinoma.

Most of these patients were biochemically cured of gastrinoma after the first LR, but ZES recurred in 2 patients (Nos. 5 and 6). In patient No. 5, the serum IRG increased from 140 to 170 pg/mL 8 year postoperatively, and in patient No. 6, the serum IRG increased from 68 to 400 pg/mL 6 year postoperatively. Based on localization by the SASI test, a second LR was performed for these patients, and their serum IRG levels decreased to within normal ranges postoperatively. They have been biochemically cured of gastrinoma since the second LR for 5 year, 8 mo and 2 year, 7 mo, respectively, postoperatively.

Patient No. 9 had undergone a distal pancreatectomy

Table 1 Results of pancreaticoduodenectomy for patients with multiple endocrine neoplasia type 1

No.	Age	Gender	ZES	Ulcer diseases	Ulcer related operation	MEN 1 related diseases	Pre-PD IRG (pg/mL)	Localization of gastrinoma			Operation	Post-PD IRG (pg/mL)	Gastrinoma			Metastases		Pancreas NET	Prognosis present status (post-op yr)	Postoperative secretin or calcium test
								SASI	GIF	CT			Location	Number	Size (mm)	N	L			
1	44	M	+	DU 1984	-	Pit NET 1987	310	GDA IPDA	ND	ND	PitX T PitX PD	1989 Mar 1990 Mar 1991 Mar	26	D	1 5	1	0	5	Alive well with Pit NET, PNET (18 yr 5 mo)	Negative
2	39	F	+	GU perf 1982 Ileus 1983 JU 1990	GX 1982 JX 1983	HPT 1991 Nov	800	GDA IPDA	ND	ND	PD, PX St ParX	1991 Mar 1991 Nov	33	D	7 1-7	1	0	6	DOD (4 yr) no recur	Negative
3	21	M	+	DU, GU 1997	-	Pit NET 1997	583	GDA	ND	ND	PD PitX	1997 Aug 1997 Oct	25	D	1 10	0	0	0	Alive wll (12 yr) no recur	Negative

ZES: Zollinger-Ellison syndrome; PD: Pancreaticoduodenectomy; SASI: Selective arterial secretagogue injection test; GIF: Gastrointestinal fibroscopy; CT: Computed tomography; IRG: Serum immunoreactive gastrin concentration; N: Lymph node metastasis; L: Liver metastasis; NET: Neuroendocrine tumor; postop: Postoperative; F: Female; M: Male; DU: Duodenal ulcer; GU: Gastric ulcer; JU: Jejunal ulcer; perf: Perforation; GX: Partial gastrectomy; JX: Partial jejunectomy; Pit: Pituitary; PitX: Extirpation of pituitary tumor; T PitX: Total resection of pituitary gland; HPT: Hyperparathyroidism; St ParX: Subtotal parathyroidectomy; GDA: Gastroduodenal artery; IPDA: Inferior pancreatoduodenal artery; ND: Not detected; PX: Partial resection of the pancreas; D: Duodenum; P: Pancreatic; DOD: Died of other disease; Dsmt: Duodenal submucosal tumor; diff: Diffuse; D-EUS: Duodenal endoscopic ultrasonography; no recur: No recurrence.

for multiple insulinoma 31 year before visiting our clinic. She also had a history of a total parathyroidectomy with a forearm subcutaneous parathyroid transplantation and gamma knife therapy for a pituitary NET. Her serum IRG was 49 500 pg/mL. Multiple submucosal gastric NETs and multiple duodenal submucosal NETs were identified by gastroduodenoscopic examination. A few large metastatic lymph nodes around the head of the pancreas were visualized using CT; therefore, advanced stage of gastrinoma was suspected. The SASI test localized the gastrinoma in the duodenum and/or the head of the pancreas. We performed LR and an enucleation NET in the head of the pancreas with dissection of the peripancreatic lymph nodes. A partial resection of the middle part of the stomach for multiple gastric tumors was also performed. Her serum IRG decreased to < 150 pg/mL and plasma chromogranin A concentration was normalized. Pathological examination revealed 3 duodenal gastrinomas and 1 pancreatic gastrinoma with 3 metastatic lymph nodes from duodenopancreatic gastrinoma. The gastric NET was a type Ⅱ NET.

PPTD

PPTD was first performed for case No. 10, in whom a substantial numbers of NETs were palpated intraoperatively and a few large metastatic lymph nodes were detected, without any pancreatic head tumors. Pathological study revealed numerous submucosal microgastrinomas throughout the duodenum. Her serum IRG did not decrease to within normal range and she developed hepatic metastases 3 year after the PPTD. In order to save the head of the pancreas, PPTD was performed for the following 6 patients in whom the SASI test diagnosed gastrinoma in the pancreatic head and/or the duodenum and considerable numbers of duodenal NETs were suspected during surgery (Table 3). In one patient (case 16) the SASI test localized gastrinoma not only in the head of the pancreas and/or the duodenum, but also in the tail of the pancreas, so PPTD and a distal pancreatectomy were performed curatively, and the patient has since been free of gastrinoma. Any serious postoperative morbidity was experienced in this series of patients.

Hyperplasia of G cells or microgastrinomas in the duodenal Brunner's gland

In 7 PPTD patients, duodenal gastrinomas were numerous in only 2 patients, and there were 4 or more in 2 additional patients. In 3 other patients, only 1 tumor was diagnosed as gastrinoma, and the other submucosal tumors were mostly diagnosed as hyperplasia of the duodenal Brunner's gland. Not expecting these results, we carefully re-examined the duodenal mucosal membrane with anti-gastrin antibody and identified clusters of gastrin-producing cells in or adjacent to the Brunner's gland, some of which were diagnosed as microgastrinoma. The clusters of gastrin-producing cells were found in all 7 duodenal specimens after PPTD (Figure 2).

Five patients post-PPTD have been cured of gastrinoma for lengths of time ranging from 2 year to 6 year 8 mo. However, in 2 patients in whom their preoperative serum IRG levels were as high as 18 200 pg/mL or

Table 2 Results of extirpation or partial duodenectomy for duodenal gastrinomas in patients with multiple endocrine neoplasia type 1

No.	Age	Gender	ZES	Ulcer diseases	Ulcer related operation	MEN 1 related diseases	Pre-first duodenectomy IRG (pg/mL)	Localization of gastrinoma			Operation	Post-duodenectomy IRG (pg/mL)	Gastrinoma			Metastases		Pancreas NETs	Prognosis present status (post-op yr)	Postoperative secretin or calcium test
								SASI	GIF	CT			Location	Number	Size (mm)	N	L			
4	49	M	+	GU 1984 JU 1995	GX 1984	HPT Pit NET	3,180	GDA	ND	PNET	DX, DP, St ParX 1996 Sep	50	D	9	1-7	0	0	1 (gluc)	Alive well, after TParX (2004 Jul) PitX (2006 Oct) (13 yr 10 mo)	Negative
5	61	F	+	GU 1974 JU 1975	GX 1974 JX 1975	HPT	400 ↓ 230 (post Par X)	GDA GDA	ND ND	ND ND	St Par X 1984 Apr DX 1996 Apr DX 2004 Nov	230 → 140 170 → 70	D D	5 1	2-4 4	0 0	0 0	2 0	Alive well, (14 yr 4 mo) no recur	Negative
6	56	F	+	DU 1997	-	HPT	580 ↓ 385 → 885 (post Par X)	GDA	ND	ND	PX 1997 Feb St Par X 1999 Jul DX 2001 Jan DX 2007 Jan	885 → 68 400 → 54	D D	3 2	1-2 1-3	1 0	0 0	3 0	Alive well, with mult PNET (9 yr 8 mo)	Negative
7	44	F	+	GU 1992	-	PNET HPT					PPPD 1993 Jan St Par X 1993 Apr	137	-	-	-	0	0	1	Alive well, (9 yr 4 mo)	Negative
							811	GDA	Dsmt	ND	DX 2001 Apr	811 → 28	D	1	9	0	0	0	no recur	
8	33	M	-	- -	-	HPT	3240	GDA	Dsmt	ND	ParX 1993 St ParX 2003 May DX, DP 2003 Jul	44	D	1	10	1	0	mult (gluc)	Alive well, (7 yr) No recur	Negative
9	54	F	+	GU, DU 2005	-	Ins (multi) HPT Pit NET GNET	49 500	n n	Dsmt Gsmt	Dsmt Gsmt LNMets	DP 1978 TParX, TX 1989 PitX,γ-K 1989, 1995 DX, GX, LNX 2009 Feb	149	D P(H)	2 1	6, 12 15	3	0	1	Alive well, (1 yr 6 mo) no recur	Negative

ZES: Zollinger-Ellison syndrome; SASI: Selective arterial secretagogue injection test; GIF: Gastrointestinal fibroscopy; CT: Computed tomography; IRG: Serum immunoreactive gastrin concentration; N: Lymph node metastasis; L: Liver metastasis; NET: Neuroendocrine tumors; postop: Postoperative; F: Female; M: Male; GU: Gastric ulcer; JU: Jejunal ulcer; DU: Duodenal ulcer; GX: Partial gastrectomy; JX: Partial jejunectomy; HPT: Hyperparathyroidism; P: Pancreatic; Pit: Pituitary; G: Gastric; NET: Neuroendocrine tumor; Ins: Insulinoma; mult: Multiple; ParX: Parathyroidectomy; GDA: Gastroduodenal artery; ND: Not detected; Dsmt: Duodenal submucosal tumor; PX: Partial resection of the pancreas; LN: Lymph node; DX: Extirpation of duodenal gastrinoma and/or partial resection of duodenum; St Parx: Subtotal parthyroidectomy; T Parx: Total parathyroidectomy; TX: Transplantation of parathyroid gland; PPPD: Pylorus preserving pancreaticoduodenectomy; DP: Distal pancreatectomy; D: Duodenum; gluc: Glucagonoma; Mets: Metastasis; P(H): Pancreas head; LNX: Dissection of regional lymph nodes; NN: Not needed; NP: Not performed; no recur: No recurrence.

Table 3 Results of pancreas-preserving total duodenectomy for duodenal gastrinomas in patients with multiple endocrine neoplasia

No.	Age	Gender	ZES	Ulcer diseases	Ulcer related operation	MEN 1 related diseases	Pre-PPTD IRG (pg/mL)	Localization of gastrinoma			Operation	Post-PPTD IRG (pg/mL)	Gastrinoma			Metastases		Pancreas NETs	Prognosis (post-op yr)	Post-PPTD secretin or calcium test
								SASI	GIF	CT			Location	Number	Size (mm)	N	L			
10	51	F	+	DU 1997 Dec	-	HPT	54800 ↓ 18200 (post ParX)	GDA, IPDA	ND	#6 LN #13 LN	St ParX 2003 Apr PPTD, DP 2003 Nov	216	D	num	1-4	2	0	9 (1; gluc)	Alive well with L Mets (IRG 900) (6 yr 8 mo)	Positive
11	30	M	-	-	-	HPT Pit NET	820 ↓ 206 (post ParX)	GDA, IPDA	ND	PNET (uncus tail)	T ParX, TX 2004 Apr PPTD, DP 2004 Jul	110	D	1	5	0	0	1	Alive well (6 yr) no recur	Negative
12	33	M	+	DU 2004 Mar	-	HPT	3050 ↓ 710 (post ParX)	GDA, IPDA	Dsmt	ND	T ParX, TX 2003 Aug PPTD, DP 2004 Aug	57	D	1	5	0	0	multi	Alive well (6 yr) no recur	Negative
13	48	F	-	-	-	HPT	687	IPDA, DPA	Dsmt diff PNET (D-EUS)	#13 LN PNET (< 3 mm) diff	PPTD 2007 Apr T ParX, TX 2007 Sep	59	D	num	1-5	1	0	multi diff	Alive well (2 yr 11 mo) no recur	Negative
14	33	M	+	JU perf 2007 Jan	Patch	HPT	13900 (post ParX)	GDA	Dsmt diff PNET (D-EUS)	#17 LN Dsmt	T ParX, TX 2001 Dec PPTD 2007 Nov	255	D	1	8	2	0	multi diff	Alive well witn N Mets (IRG 371) (2 yr 8 mo)	Positive
15	57	F	+	DU perf 2006 Jan JU perf 2006 Jul Ileus 2007 May JU perf 2008 Jul	GX JX	HPT	720 ↓ 646 (post ParX)	GDA, IPDA	ND	ND	T ParX, TX 2007 Mar PPTD, TG 2008 Aug	42	D	7	2	1	0	0	Alive well (2 yr) no recur	Negative
16	32	M	+	Es bleeding 2002 Oct DU JU perf 2006 Jan		HPT	1630	DGA, SPA	ND	PNET (17 mm)	ParX, PPTD 2008 P(T)X Aug	450	D, P(T)	3, 1	3, 10, 11 10	3	0	3 (> 5 mm)	Alive well (2 mo) no recur	Negative
				JU perf 2008 Nov	JX GX, JX		1000	DGA, SPA	ND	PNET (5-10 mm)	DP, P(H)X 2009 Jul	94	P(b)	1	4	0	0	multi		

ZES: Zollinger-Ellison syndrome; PPTD: Pancreas preserving total duodenectomy; SASI: Selective arterial secretagogue injection test; op: Operation; GIF: Gastrointestinal fibroscopy; CT: Computed tomography; IRG: Serum immunoreactive gastrin concentration; N: Lymph node metastasis; L: Liver metastasis; NET: Neuroendocrine tumor; F: Female; M: Male; postop: Postoperative; DU: Duodenal ulcer; JU: Jejunal ulcer; perf: Perforation; Es: Esophagus; Patch: Omental patch; GX: Partial gastrectomy; JX: Partial jejunectomy; HPT: Hyperparathyroidism; Pit NET: Pituitary neuroendocrine tumor; ParX: Parathyroidectomy; GDA: Gastroduodenal artery; IPDA: Inferior pancreatoduodenal artery; DPA: Dorsal pancreatic artery; SPA: Splenic artery; ND: Not detected; Dsmt: Duodenal submucosal tumor; diff: Diffuse; D-EUS: Duodenal endoscopic ultrasonography; LN: lymph node; PNET: Pancreatic neuroendocrine tumor; St ParX: Subtotal parathyroidectomy; T ParX: Total parathyroidectomy; TX: Tranplantation of the parathyroid; DP: Distal pancreatectomy; PX: Partial resection of the pancreas; D: Duodenum; P(T): Pancreas tail; num: Numerous; gluc: Glucagonoma; mult: Multiple; NP: Not performed; diff: Diffuse; Met: Metastasis; no recur: No recurrence.

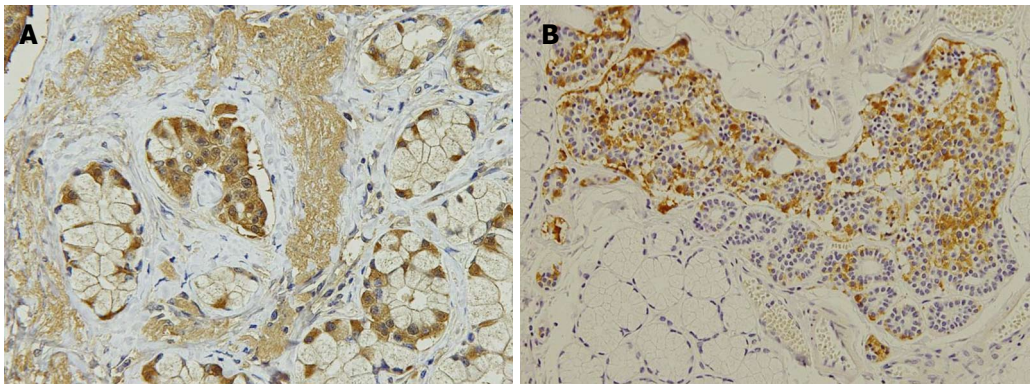

Figure 2 Hyperplasia (A) and a cluster of gastrin-producing cells (B) in the duodenal Brunner's glands (in patient No. 12, who underwent pancreas-preserving total duodenectomy for numerous duodenal microgastrinomas) were detected by immunohistochemical gastrin staining.

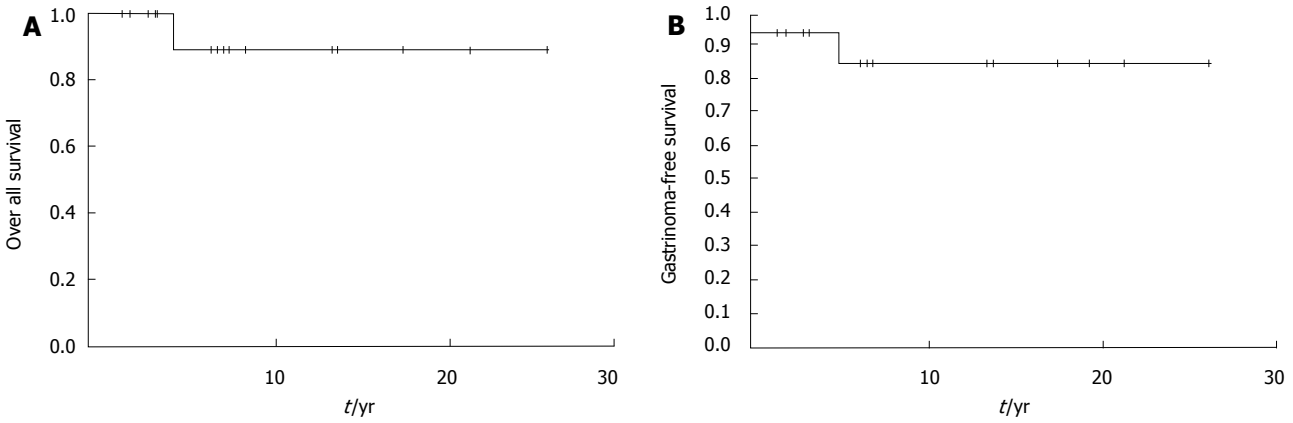

Figure 3 Survival curve of 16 patients with multiple endocrine neoplasia type 1 and neuroendocrine tumors. A: Overall survival after initial resection surgery. The survival rate at 10 years was 90.9%; B:Gastrinoma-free survival after initial resection surgery. The survival rate at 10 years was 82.0%.

13 900 pg/mL after parathyroidectomy, and advanced stages of gastrinoma were suspected, PPTD was noncurative (Table 3). In one of them, hepatic metastases have become apparent on CT film within 3 year postoperatively, and in the other patient, distant lymph nodes metastases have developed.

Results of surgery and survival curves

Of the 16 patients in this series, 7 patients had single duodenal gastrinoma and 9 patients had multiple gastrinomas. More specifically, 2, 4, 5, 6, and 9 duodenal gastrinomas were detected in 1 patient each; 7 duodenal gastrinomas in 2 patients; and numerous duodenal gastrinomas in 2 patients. In 2 patients (13%), pancreatic gastrinoma coexisted with duodenal gastrinoma which were localized by the SASI test.

To date, 14 patients have been cured of gastrinoma and 2 patients have been noncurative, postoperatively. The overall patient survival curve is shown in Figure 3A, with a survival rate of 90.9% at 10 years. The gastrinoma-free survival curve is shown in Figure 3B, with a survival rate of 82.0% at 10 years.

DISCUSSION

Controversy has surrounded the treatment strategy for gastrinoma and pancreatic NET in patients with MEN 1 and ZES[1-14]. It is difficult to determine whether aggressive surgical resection of both gastrinoma and pancreatic NETs improves survival rates and the long term biochemical cure of gastrinoma in MEN 1 patients, because of the rarity of the disease[1-4,10-14]. Many recently published articles support aggressive surgery, such as PD or multiple LR of a few duodenal gastrinomas and distal pancreatectomy for pancreatic NETs, for both biochemical cure of gastrinoma and prolongation of survival[1,4,10-14]. On the other hand, Gibril *et al*[27] reported the results of an important prospective study on the natural history of gastrinoma in patients with MEN 1, in which 57 patients with MEN 1 and ZES were followed for 8 year without performing surgical resection for duodenopancreatic NETs until the tumors grew to > 2.5 cm. In this study, 13 patients (23%) developed hepatic metastases and 3 patients died of duodenopancreatic NETs. They suggested that biochemical cure of gastrinoma might be impossible in patients with MEN 1 and that prolongation of survival of MEN 1 patients with an aggressive type of NETs would not be realized until the development of a tool to differentiate an aggressive type of NET from another slow growing type of NET. Their results themselves, we think, support the idea that early resection should be necessary for decreasing the rate of hepatic metastases from duodenopancreatic NETs

in MEN 1 patients.

The present study shows that aggressive surgical resection for gastrinoma in MEN 1 patients using PD or aggressive LR, or PPTD guided by localization with the SASI test, was useful for long term biochemical cure of duodenopancreatic gastrinoma, and that aggressive resection of pancreatic NETs was also useful for prevention of hepatic metastases. So, we would like to recommend early aggressive surgical resection of duodenopancreatic NETs for MEN 1 patients.

Goudet *et al*[28] performed a cohort study of 758 patients with MEN 1 and found that gastrinoma was a statistically significant high-risk factor for death of patients with MEN 1 secondary to the nonfunctioning pancreatic NETs, and suggested earlier resection surgery for both gastrinoma and nonfunctioning pancreatic NETs in patients with MEN 1. Gauger and Thompson reported a 94% 15 year survival rate of patients with functioning NETs (gastrinoma or insulinoma) in MEN 1 patients after local resections of duodenal gastrinomas and a distal pancreatectomy with enucleations of NETs in the head of the pancreas without any operative morbidity[2]. These results suggest that early resection of gastrinoma in MEN 1 patients is useful for normalization of serum gastrin levels and prevention of distant metastases.

Identification of gastrinoma among multiple NETs in the duodenopancreatic region of patients with MEN 1 is essentially impossible by imaging techniques alone[17,18]. The SASI test localizes gastrinomas or metastatic lymph nodes by judging whether or not gastrin is secreted from NETS in the area of interest by stimulation with a secretagogue, so it can differentiate functioning gastrinoma among multiple NETs in MEN 1 patients.

On the other hand, SRS and other imaging methods [CT or MRI or ultrasonography (US)] are useful for identification of hepatic metastases, although it is difficult to tell the absence of gastrinoma in the area of interest. We have used secretin for stimulating gastrinoma to release gastrin during the SASI test for a long time, but now we use calcium gluconate hydrate solution (Calcicol®), because secretin has not been produced in Japan since 2004. We compared the results with both secretagogues and found the results were identical[21].

In 1991, imaging methods were not sensitive for visualizing < 1 cm gastrinoma; thus we performed resection surgery of both gastrinoma and microgastrinoma based on localization with the SASI test. When the SASI test localized gastrinomas in the feeding area of the gastroduodenal artery, we performed PD. In the first 3 patients with MEN 1, the SASI test localized < 1 cm gastrinomas in the head of the pancreas and/or the duodenum, so we performed PD for them and all of them were cured of gastrinoma; 2 patients have been alive and healthy for more than 12 year, although a patient died of other causes 4 year postoperatively (Table 1). In the resected specimens of the first 3 patients, < 1 cm gastrinomas were located only in the duodenum and not in the pancreas. In those days, endocrine surgeons working in the USA or EU gradually found that the gastrinomas in patients with MEN 1 were localized mostly in the duodenum and rarely in the pancreas[15,16]. Thompson et al have started to perform LR for duodenal gastrinoma and distal pancreatectomy with enucleation of NET in the head of the pancreas in MEN 1 patients[1]. According to our results and theirs, we also started to perform local excisions of duodenal gastrinomas and enucleation or a distal pancreatectomy for pancreatic NETs, which are less invasive compared to PD. Since then, 6 patients have undergone LR for duodenal gastrinomas, which has been successful in all patients, although in 2 patients duodenal gastrinoma recurred and second LR was performed 8 year 8 mo and 6 year after the first LR.

We performed PPTD for 7 patients in whom duodenal gastrinomas were thought to number more than 5 during surgery. The duodenal gastrinomas were numerous in only 2 of 7 patients and the duodenal tumors in the other 5 patients were mostly diagnosed as hyperplasia of the duodenal Brunner's glands postoperatively (Table 3). Not expecting these results, we immunohistochemically stained the duodenal wall with anti-gastrin antibody and found a cluster of gastrin-producing cells or microgastrinomas in or adjacent to the Brunner's gland. The clusters of gastrin-producing cells in the Brunner's gland were found in all of the duodenal specimens after PPTD.

Klöppel *et al*[29] have reported that in patients with MEN 1, mutations in the menin gene can cause hyperplasia of gastrin-producing cells in the duodenal Brunner's glands, which are the precursor lesion of gastrinoma. Our results are consistent with their report. Thus, in the duodenum of MEN 1 patients with substantial numbers of duodenal gastrinomas and/or microgastrinomas, de novo gastrinoma might develop during the patient's lifetime.

Of the 16 patients in the present study, 7 patients (43.8%) had 1 duodenal gastrinoma and 9 patients (56.2%) had multiple duodenal gastrinomas. Gastrinoma did not recur in patients belonging to the former group, but recurred in 2 patients (22.2%) belonging to the latter group who had 3 and 5 duodenal gastrinomas, respectively. PPTD may be useful for preventing both residual microgastrinoma and recurrence due to development of de novo duodenal gastrinoma in MEN 1 patients with substantial numbers of gastrinomas and microgastrinomas.

In 7 patients who underwent PPTD, no postoperative complications, such as pancreatic leakage, acute pancreatitis, abscess or surgical site infections, have been experienced. Thus, PPTD is less invasive surgery compared to PD. On the other hand, dissection of the regional l ymph nodes may be incomplete by PPTD compared to PD. As duodenal gastrinoma metastasizes to the regional lymph nodes independent of size, any regional lymph nodes around both the pancreas head and the common hepatic artery have to be dissected. Lymph nodes along the superior mesenteric artery have to be resected when they are palpated hard[20].

When considering the optimal surgery for patients with MEN 1 and gastrinoma, we must first seriously consider the risk of hepatic metastases from pancreatic NETs[1,7-9,14,28,30]. Hepatic metastases from pancreatic

NETs are more serious than those from duodenal gastrinoma, and the rate of hepatic metastases from pancreatic NETs is at least several times more frequent than those from duodenal NETs[6,7,16,28,30]. Thus, we recommend distal pancreatectomy for pancreatic NETs with enucleations of NETs in the pancreatic head more than 1 cm, as recommended by Thompson[1].

As for optimal surgical resection for sporadic duodenal NET, recently several articles have dealt with the subject relating to the staging of duodenal nonfunctioning NETs. Evans's group have performed a retrospective analysis of patients with duodenal NETs operated at their institute and they proposed a standard strategy for duodenal NETs using a staging based on the depth of tumor invasion and the grading of the development of the distant metastases[31]. Sarr's group also published a similar study[32]. Both groups recommended endoscopic excisions for duodenal NET smaller than 1 cm, and open transduodenal resection with dissection of the regional lymph nodes for duodenal NET between 1 cm and 2 cm, because rate of lymph node metastases cannot be ignored in duodenal NET between 1 and 2 cm in diameter. Both groups recommended PD for duodenal NET more than 2 cm with lymph node metastases[31,32]. However, both groups intentionally excluded duodenal gastrinoma from their retrospective analytical studies, because the natural history of duodenal gastrinoma seemed quite different from other duodenal NETs, which suggested a more aggressive progression of duodenal gastrinoma[31,32].

In our study, 7 of 16 patients had only 1 duodenal gastrinoma, but 3 of the 7 patients had metastatic lymph nodes, and 1 of them (No. 14) had distant metastases resulting in noncurative resection of gastrinoma (Table 3). So, instead of endoscopic excision, local resection with dissection of lymph nodes may be recommended for a few < 1 cm duodenal gastrinomas in MEN 1 patients[1,2]. For substantial numbers of < 1 cm duodenal gastrinomas with multiple pancreatic NETs in MEN 1 patients, we would like to recommend PPTD with distal pancreatectomy and enucleation of > 1 cm NETs in the head of the pancreas, because cure of duodenal gastrinoma is not likely to be achieved for a long time due to both possible residual microgastrinoma and development of de novo gastrinomas in the duodenum[20,29]. PD might be indicated for MEN 1 patients with a substantial number of both duodenal gastrinomas and metastatic regional lymph nodes with a few > 1 cm pancreatic NETs. Of course, curative resection has to be indicated before development of hepatic micrometastases.

In this series, only one patient has died of other diseases and the other patients have been alive and well to date. Overall survival curve of the patients is shown in Figure 3A. Evaluating together with the gastrinoma-free survival curve of these patients (Figure 3B), we would like to conclude that resection surgery was useful for cure of gastrinoma and prolongation of survival of the patients with MEN 1 and gastrinoma.

Given that pancreatic gastrinoma co-existed with duodenal gastrinoma in 12.5% of our patients, caution is advised, because many surgeons and pathologists have believed that pancreatic gastrinoma is rare in MEN 1 patients[33]. To date, total pancreatectomy has rarely been performed for MEN 1 patients, but we think that total pancreatectomy may be indicated for a few MEN 1 patients according to decisions based on the clinicopathological genetic analysis of pancreatic NET in such patients[34].

In conclusion, aggressive resection surgery based on accurate localization was useful for biochemical cure of gastrinoma in patients with MEN 1 and gastrinoma. Given that pancreatic gastrinoma co-existed with duodenal gastrinomas in 2 of 16 patients (13%), we would like to recommend the SASI test for preoperative localization of gastrinoma in MEN 1 patients.

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COMMENTS

Background

Treatment strategy for gastrinoma and pancreatic neuroendocrine tumors (NETs) in patients with multiple endocrine neoplasia type 1 (MEN 1) has been controversial. Most doctors have thought that gastrinomas in MEN 1 cannot be cured because curative resection is rare and recurrence rate is high, and pancreatectomy for pancreatic NETs in MEN 1 does not make sense, since NETs and micro-NETs exist diffusely in the pancreas. On the other hand, recent reports by a few aggressive surgeons show that a high cure rate of gastrinomas and long term prolongation of survival have been achieved by aggressive surgery. For achieving curative resection of gastrinomas in MEN 1, correct localization of gastrinomas is essential for guiding curative surgery, and in order to prolong the life of patients with MEN 1 and duodenopancreatic NETs, surgical resection of these NETs before development of hepatic metastases is essential, because hepatic metastases is the most significant prognostic factor.

Research frontiers

The authors should select an optimal modus of surgery for curing gastrinoma and pancreatic NETs in MEN 1 patients, otherwise surgery may end noncuratively or may become too invasive to ensure quality of life for patients. For the best balance between curability of surgery and postoperative good quality of life, the best modus of surgery should be applied for patients with MEN 1 and gastrinoma by estimating the stage of duodenopancreatic NETs.

Innovations and breakthroughs

The present study shows that cure of gastrinomas in MEN 1 patients can be obtained when you resect gastrinomas guided by localization with the SASI test, and prevention of hepatic metastases can be obtained by resection of > 1 cm pancreatic NETs by pancreatectomy of enucleations. As for the modus of surgery, we are the first to propose pancreas-preserving total duodenectomy (PPTD) for multiple or numerous duodenal gastrinomas in MEN 1 as the optimal extent of aggressive surgery. The authors have also proved that pancreatic gastrinoma co-exists with duodenal gastrinoma in 13% of patients with MEN 1, although recently most surgeons and some pathologists have reported that gastrinomas exist only in the duodenum in MEN 1 patients.

Applications

By understanding the fact that curative surgical resection is possible by correct localization, and by further development of clinicopathological genetic analysis

of the disease, the optimal surgical strategy corresponding to the stage of the disease will be established for gastrinomas and duodenopancreatic NETs in MEN 1 patients in the near future.

Terminology

PPTD is the modus of surgery by which total duodenum is resected without resecting pancreas tissue. Traditionally, for resecting malignant tumors in the duodenum, pancreatoduodenectomy has been used by which one third of the pancreas is resected with the duodenum.

Peer review

The study evaluates the standard surgery for patients with gastrinoma in MEN 1 guided by accurate preoperative localization.

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