Case report

A Case of Early Gastric Cancer with Intraductal Papillary Mucinous Carcinoma (IPMC) Recurrence Developing at the Site of Pancreaticogastrostomy (PG) After Pancreaticoduodenectomy (PD) for IPMC of the Pancreatic Head

Momoko Sakaki [*1], Hiroki Taniguchi[1] and Takeshi Yamano[2]

[1]*Department of Surgery, Kyoto Second Red Cross Hospital, Kyoto, Japan*
[2]*Department of Pathology, Kyoto Second Red Cross Hospital, Kyoto, Japan*

Abstract: A 60-year-old man underwent PD with PG for IPMC of the pancreatic head. Seven years later, gastroscopy detected a poorly differentiated adenocarcinoma at the site of the PG. Partial gastrectomy, total residual pancreatectomy, and splenectomy were performed. The histologic diagnosis was both early gastric cancer and IPMC recurrence, which were distinguished immunohistologically. This is the first case report of early gastric cancer clearly developed from PG anastomosis, and also the first report of gastric cancer with IPMC recurrence after PD with PG.

The mortality rate of PD is decreasing, which leads to the problem of a second cancer. Including the present case, eight cases of gastric cancer developing after PD with PG have been reported. To detect any second disease on both the remnant stomach and pancreas in the early stage and treat minimally invasively, post-operative observation is important. PG enables endoscopic and histological examinations of the remnant pancreas, whereas endoscopy reaches the anastomosis of pancreaticojejunostomy (PJ) with difficulty. Our case suggests PG is superior to PJ for observation of the remnant pancreas, and the remnant stomach has to be observed for a longer time after PD with PG.

Key Words: Pancreaticogastrostomy, Gastric cancer, IPMC.

Case report

In 2004, a 60-year-old man undergoing treatment for diabetes for five years exhibited a markedly

Received: November 13, 2014. Accepted: March 5, 2015
*Correspondence to Momoko Sakaki 355-5, Haruobi-cho, Kamigyo-ku, Kyoto-shi, Kyoto, 602-8026, Japan
sakakim@kyoto2.jrc.or.jp

increased the blood glucose level, and slightly increased AST/ALT levels. Abdominal ultrasound and computed tomography revealed both common bile duct dilation and main pancreatic duct (MPD) dilation. Gastroscopy showed a swollen papilla of Vater, which was histologically diagnosed as a well-differentiated adenocarcinoma by the biopsy. Endoscopic retrograde cholangiopancreatography (ERCP) revealed a dilation of both the biliary tree and main pancreatic duct for almost their entire length, and there were neither malignant cells in bile cytology nor in pancreatic juice. Celiac angiography and portogram showed no vascular invasion.

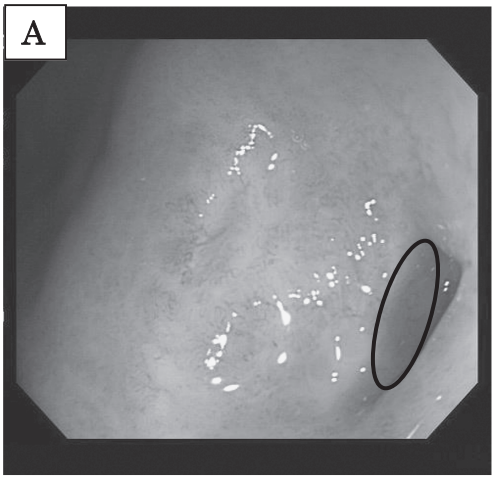
He underwent PD with PG on suspicion of adenocarcinoma of the papilla Vater, and the histologic diagnosis was IPMC with no metastasis in any lymph node. There were no malignant cells, but there was intraductal papillary mucinous adenoma (IPMA) at the surgical margin of the fixed specimens.

In 2011, seven years after the operation, he requested an examination of the remnant stomach without any symptoms. Gastroscopy showed redness and erosion at the site of the PG (Fig. A), which was histologically diagnosed as a poorly differentiated adenocarcinoma. No discharge from the PG detected. Endoscopic ultrasonography on the tumor showed an unseparated submucosal layer, so the tumor was thought to be intramucosal cancer.

Fluoroscopy of the stomach (Fig. B) and ERP from the stomach (Fig. C) showed MPD dilation and no features consistent with IPMC in the histology of the remnant pancreatic duct opening, or cytology of the pancreatic juice. He underwent partial gastrectomy, total residual pancreatectomy and splenectomy.

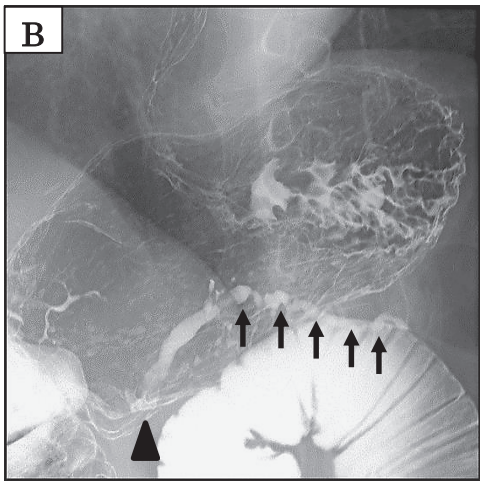
Macroscopically, an ill-defined lesion with a flat surface and brownish discoloration, 0.4 cm in maximum diameter, was found in the gastric mucosa near the main pancreatic duct opening of the pancreaticogastrostomy junction (Fig. D). On cut sections of the remnant pancreas, the main pancreatic duct was dilated from the anastomotic site to the pancreatic tail (Fig. E).

Histologically, the gastric lesion was a poorly differentiated adenocarcinoma with trabecular and tubular structures, and infiltrated into the submucosa (Fig. F-A). The dilated main pancreatic duct was lined by a tall mucous columnar epithelium with papillary proliferation into the duct lumen. The

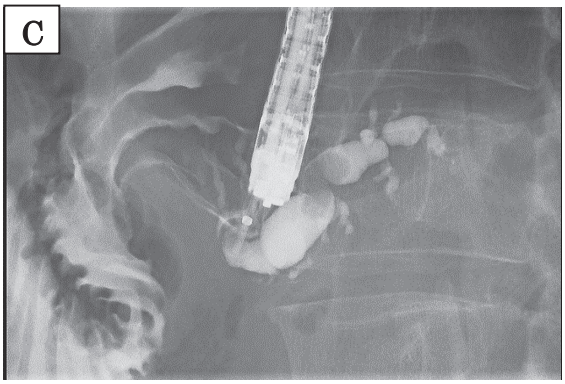


A. Gastroscopy shows irregular membranes with redness around the MPD opening (circle).

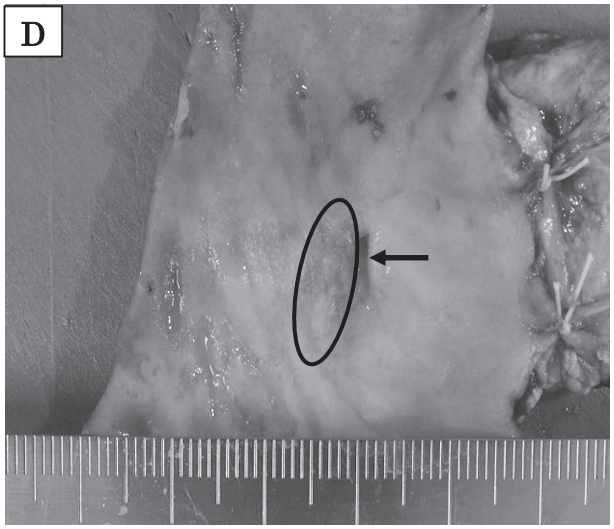
papillary structures lacked fibrovascular stalks and showed loss of nuclear polarity (Fig. F-B). Stromal invasion was not obvious, so we regarded the lesion as non-invasive type of IPMC. Although the primary resected tumor had been mainly growing in the main pancreatic duct of the pancreatic head, the first tumor was a non-invasive adenocarcinoma, which was histologically similar to the remnant pancreatic cancer (Fig. G). Intraductal spread of the IPMA in the first tumor had reached the end margin of the pancreatic cut (Fig. H). From these findings, we diagnosed the remnant pancreatic cancer as recurrent IPMC, non-invasive type. The gastric adenocarcinoma histologically differed from the pancreatic IPMC, and there was no transition between the two carcinomas. Immunohistochemically, gastric adenocarcinoma was Cytokeratin7−/Cytokeratin20+, whereas IPMC was Cytokeratin7+/Cytokeratin20+ (Figs. F-A, F-B). From these findings, we diagnosed the gastric cancer as a primary, poorly differentiated adenocarcinoma, which arose near the site of the pancreaticogastrostomy. There



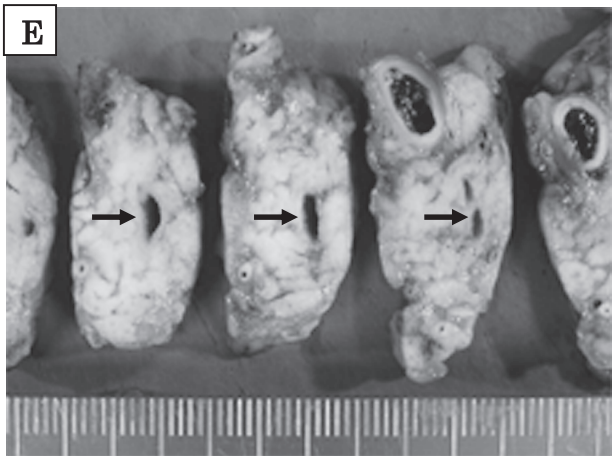
B. The remnant MPD (arrows) is drawn through a pool with a converging fold (PG: arrow head) by fluoroscopy of the stomach.



C. MPD is expansive and winding in ERCP.



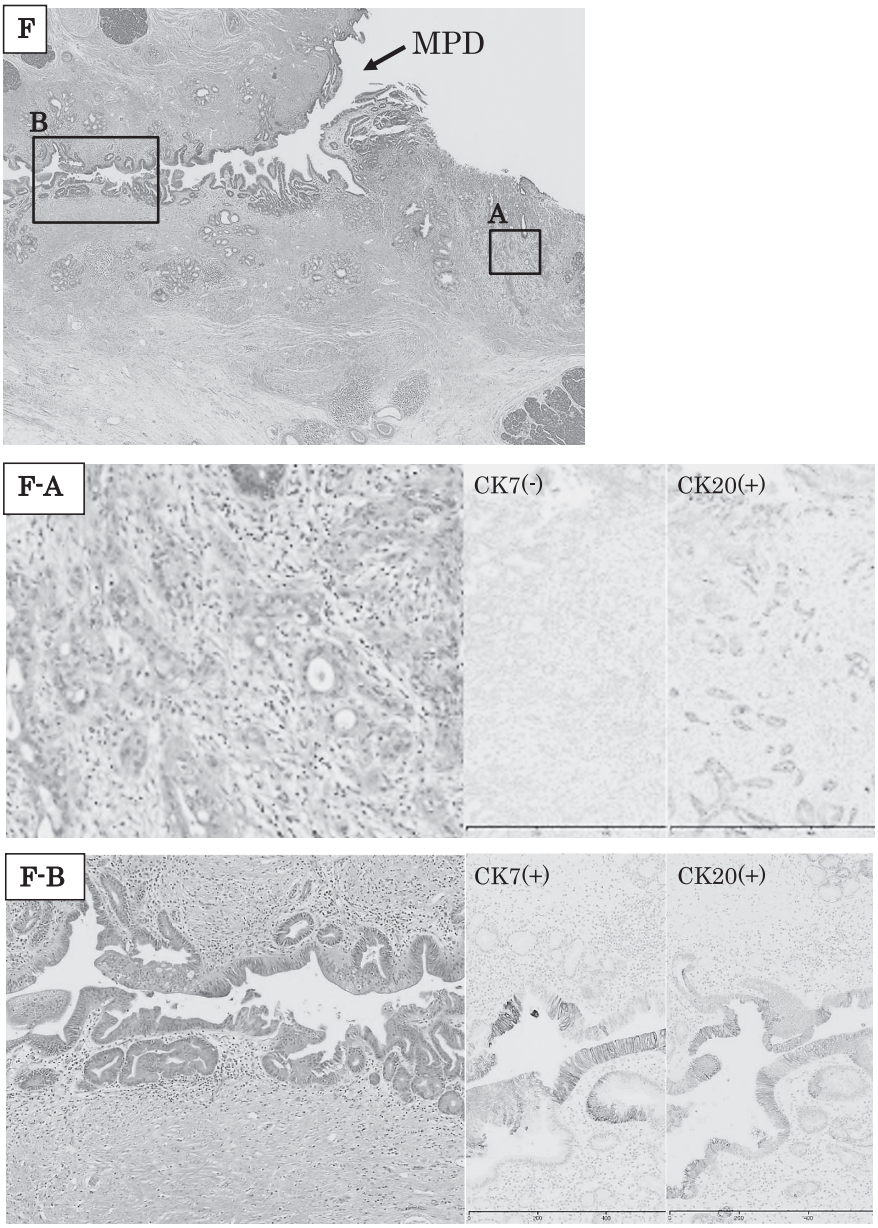
D. Resected specimen at the second operation. A brownish discolored lesion with flat surface (circle) was seen in the gastric mucosa near the main pancreatic duct opening of the anastomotic site (arrow).



E. Sagittally sectioned remnant pancreas. The main pancreatic duct (arrows) was dilated from the anastomotic site to the tail of the pancreas.

were no lymph node metastases in either carcinoma. The clinical stage of the gastric cancer was stage IA (pT1b,pN0,pM0).

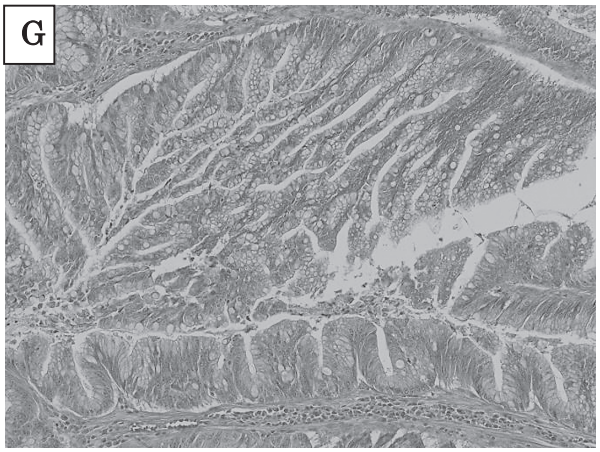
The patient was discharged 17 days after the operation, and his blood sugar level was controlled with insulin. Though neither of the two cancers recurred, he died of pneumonia two years after the second operation.



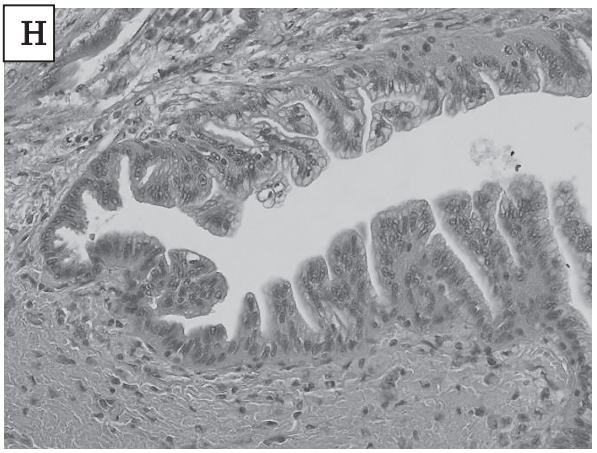
F. The anastomotic site. A: gastric tumor, B: pancreatic tumor, MPD: main pancreatic duct

F-A. The gastric tumor. A poorly differentiated adenocarcinoma with trabecular and tubular structures showed submucosal invasion. Its immunohistochemical staining of cytokeratin 7 was negative and of cytokeratin 20 was positive.

F-B. The main pancreatic duct of the remnant pancreas. The ductal epithelium showed occasional papillary proliferation with a lack of fibrovascular stalks and loss of nuclear polarity. Its immunohistochemical staining of both cytokeratin 7 and cytokeratin 20 was positive.



G. The primary resected tumor. The primary tumor was a non-invasive adenocarcinoma, which was histologically similar to the remnant pancreatic cancer.



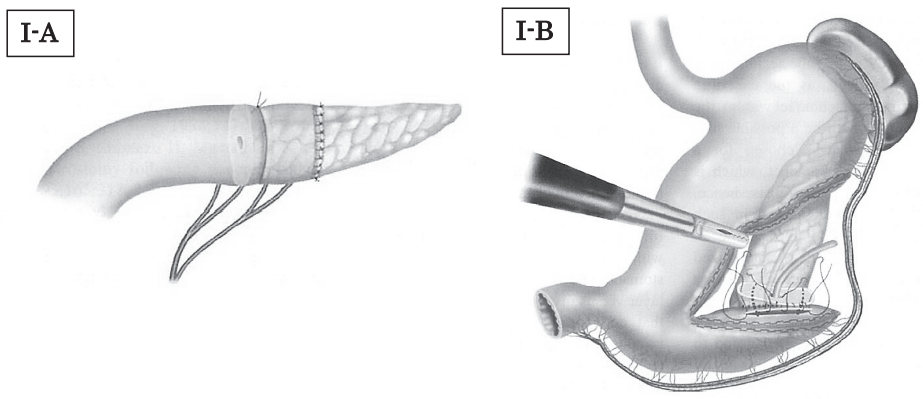
H. The pancreatic cut end margin at first resection. Intraductal spread of IPMA was found.

Discussion

At the first operation, PD was performed for IPMC of the pancreatic head. At that time, IPMN had not yet been defined and the histologic diagnosis was papillary adenocarcinoma of the papilla of Vater. However, histological reexamination immediately before the second operation led to a diagnosis of IPMC of the pancreatic head. In addition, IPMA at the surgical margin was demonstrated, but this did not mean that the pancreas was resected insufficiently. It is generally believed that IPMA on surgical margins does not warrant further resection, because IPMA is a common incidental finding in the general

population[1-5].

PG was performed as a method of reconstruction following PD. PG is a reasonable alternative procedure, which was first reported in 1934, with expectations of less tension on and better blood supply to the anastomosis. Thereafter, many retrospective comparative studies of PG and PJ have been reported. Some studies supported using PG over PJ, showing higher mortality, greater body weight loss, a larger number of bile leaks, and a larger number of infections requiring new CT-guided drainage in the PJ group, compared to the PG group[6-8]. However, the latest clinical analyses of randomized controlled trials concluded that there is no universal agreement as to which reconstruction method is superior[9][10]. A meta-analysis showed the pancreatic fistulae, mortality, reoperation, and length of hospital stay were not statistically different between the PG and PJ groups, and that binding PJ significantly reduced the pancreatic fistula and postoperative complications compared with conventional PJ[9]. Further studies are necessary to define the optimal technique of pancreatic reconstruction after PD in high-volume centers by high-volume surgeons considering new approaches, such as bindng PJ and modified PG[11] (Fig. I-A, I-B). Although no consensus has been reached on the superiority of PG, we support using PG over PJ, based on postoperative observations. PG enables endoscopic and histological examinations of the remnant pancreas, whereas reaching the anastomosis of PJ by endoscopy is difficult. As peroral pancreatoscopy enables more detailed examination[12][13], if it had been performed in our case, the IPMC could have been diagnosed before the second operation. This is especially important for patients with non-invasive IPMNs who have a significant risk of recurrence and need careful evaluation of the remnant pancreas. Therefore, following PD, PG is performed at our institution. Although in patients who underwent PD with PG, exocrine insufficiency was a concern because pancreatic juice is deactivated by gastric acid after PG, several published studies have reported that exocrine pancreatic function after PD depends on the degree of fibrosis in the pancreatic remnant, and that there is no significant difference in pancreatic exocrine insufficiency between PJ and PG[14][15]. Even in a study which concluded that PG was more frequently associated with severe steatorrhea than PJ in cases of nonhistologic obstructive pancreatitis, there was no significant difference in post-operative weight loss between PJ and PG[16]. Our patient, who stood 164 cm tall, had lost very little



I-A. The reconstruction of binding PJ.[11]
I-B. The reconstruction of modified PG.[11]

weight in the seven years after PD, from 53 kg to 52 kg. Anastomosis occlusion is easy to detect in PG. Of course, it doesn't mean that PG produces anastomosis occlusion more frequently than PJ. In PJ, anastomosis occlusion is often overlooked because endoscopic examination is impossible, though CT showed changes of pancreatic duct diameter after PD as frequent as in PG[14].

Seven years after PD, a second disease was detected at the site of the PG as a poorly differentiated adenocarcinoma. Early gastric cancer and IPMC recurrence were possible because of IPMA at the surgical margin of the first operation. A second operation was thought to be sufficient for both cancers, and partial gastrectomy, total residual pancreatectomy, and splenectomy were performed. If non-invasive IPMC is limited, partial pancreatectomy may be considered to preserve a part of the tail of the pancreas and the spleen. In our case, as the main pancreatic duct was dilated and IPMC for almost the entire length was suspected, we carried out total residual pancreatectomy and splenectomy. On the other hand, if gastric cancer had developed, poorly differentiated intramucosal cancer would have been suspected. The standard treatment for that cancer is distal gastrectomy and D1+ lymph-node dissection[17]. However, undifferentiated-type intramucosal early gastric cancer 20 mm or less in size without lymphatic-vascular capillary involvement or ulcerative findings was reported to present a negligible risk of lymph node metastasis[18], so endoscopic resection of these lesions is permitted for clinical study, although indications for endoscopic resection for undifferentiated-type early gastric cancer have not yet been established[17]. The lesion on the PG was less than 20 mm and without ulcers. Although capillary involvement cannot be estimated before resection, if involvement is positive, partial gastrectomy is thought to be sufficient. Of course, endoscopic resection of the PG is also technically difficult.

The histologic diagnosis proved both IPMC reccurence and poorly differentiated intrasubmucosal (SM1) early gastric cancer without lymphatic-vascular capillary involvement, and these were distinguished immunohistologically. The gastric cancer cells were negative, while the IPMC cells were positive for CK7. There was no lymph node metastasis. This meant that the sphere resected in the second operation was adequate.

The IPMC of the remnant pancreas was a non-invasive carcinoma, and this supports the general impression that cancers developing from IPMNs show slow progression, although it is not clear when the IPMC developed from the IPMA at the surgical margin over the seven years between the first and second operations.

As the mortality rate of PD is decreasing, post-operative patients have good long-term survival rates and this leads to the problem of a second gastric cancer in the preserved stomach. Seven cases of gastric cancer developing after PD with PG have been reported (Table 1), and all of them were in Japan[19-25]. In two cases, gastric cancer involved PG anastomosis[19][20]. However it was not proven that the cancers had developed originally from the anastomosis because both cancers were detected in the advanced stage. In our case, an early gastric cancer of 4 mm was on the anastomosis, so this is the first report of a gastric cancer clearly developed from PG anastomosis. Including the present case, the eight cases are not so high a number, considering the frequency of gastric cancer in Japan. Even so, if similar cases increase in the future, PG should be suspected of leading to gastric cancer. The condition in the gastric cavity certainly changes with PG. Though the influence of pancreatic juice excretion on the development of gastric cancer has not been clarified, in rats, it is indicated that pancreaticoduodenal secretions are associated with gastric carcinoma[26][27]. Incidentally, the influence of gastric juice reflux on

Table 1.

Year Reference	Patient age (yr)-gender	First Diagnosis	Second Diagnosis: Surgical procedure	Period(mo)	Prognosis (after second operation)
1995 [23]	68 M	Pancreatic mucinous cyst adenoma	Early gastric carcinoma: mucosal resection	49	Alive (1 yr)
1996 [22]	65 F	Chronic pancreatitis	Early gastric carcinoma: wedge resection	21	Alive (1 yr 4 mo)
2001 [21]	Not stated	Not stated	Early gastric carcinoma: not stated	Not stated	Not stated
2001 [18]	55 F	Carcinoma of the papilla of Vater	Advanced gastric carcinoma: distal gastrectomy	70	Dead (1 yr 10 mo) due to recurrence
2002 [20]	72 M	Pancreatic carcinoma	Early gastric carcinoma: distal gastrectomy	50	Alive (3 yr 3 mo)
2004 [17]	59 F	Carcinoma of the common bile duct	Advanced gastric carcinoma: total gastrectomy, residual pancreatectomy, and splenectomy	48	Dead (10 mo) due to recurrence
2006 [19]	76 M	Carcinoma of the intrapancreatic bile duct	Early gastric carcinoma: distal gastrectomy	62	Alive (10 mo)
2011 (present case)	67 M	IPMC of the pancreatic head	Early gastric carcinoma: partial gastrectomy, total residual pancreatectomy and splenectomy.	84	Dead (2 yr) due to pneumonia

the occurrence of IPMC has not been reported.

In the eventuality that PG has any relationship with the development of gastric cancer, it is remarkable that the latter developed comparatively long after PD in the eight cases. It developed with a median time of 50.0 months (range: 21-84 months), and in three of the eight patients, after more than 5 years. At that point in time, patients are not under regular observation , even if the original diseases were malignant.

When gastric cancer develops after PD with PG without cancer of the pancreas, the residual pancreas can be preserved. If gastric cancer is revealed in the early stage and separate from the PG, the PG anastomosis and the whole remnant pancreas can be retained[19)20)22)23)]. Even when the anastomosis is occupied by advanced gastric cancer, a part of the distal pancreas can be left by reconstructive pancreaticojejunostomy[20)].

We reported the first case of early gastric cancer with IPMC recurrence, both developing at the site of the PG, which suggests that we should follow up carefully both the remnant stomach and the pancreas after PD. This is especially important in patients with IPMNs because of the high prevalence of malignant neoplasms, and care should be taken regarding the possible occurrence of malignant neoplasms in other organs[1)]. Finally, PG is thought to be superior to PJ in terms of observation of the remnant pancreas and to ask for longer observation of the remnant stomach.

The authors indicated no potential conflict of interest.

References

1) International Consensus Guidelines 2012 for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas. Pancreatology 2012; 12: 183-197.

2) Kitagawa Y, Unger TA, Taylor S, Kozarek RA, Traverso LW. Mucus is a predictor of better prognosis and survival in patients with intraductal papillary mucinous tumor of the pancreas. J Gastrointest Surg 2003; 7: 12-19.

3) Sugiyama M, Izumisato Y, Abe N, Masaki T, Mori T, Atomi Y. Predictive factors for malignancy in intraductal papillary-mucinous tumors of the pancreas. Br J Surg 2003; 90: 1244-1249.

4) Salvia R, Fernandez-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, Pederzoli P, Warshaw A L. Main duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Ann Surg 2004; 239: 678-687.

5) Chari S, Yadav D, Smyrk TC, DiMagno EP, Miller LJ, Massimo M, Jonathan E C, Ian A N, Randall K P, Bret T P, Maurits J W, Michael B F,Michael G S. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. Gastroenterology 2002; 123: 1500-1507.

6) Aranha GV, Hodul P, Golts E, Oh D, Pickleman J,Creech S. A comparison of pancreaticogastrostomy and pancreaticojejunostomy following pancreaticoduodenectomy. J Gastrointest Surg 2003; 7: 672-682.

7) Miyagawa S, Makuuchi M, Lygidakis NJ, Noguchi T, Nishimaki K, Hashikura Y, Harada H, Hayashi K, Kakazu T. A retrospective comparative study of reconstructive methods following pancreaticoduodenectomy- pancreaticojejunostomy vs. pancreaticogastrostomy. Hepatogastroenterology 1992; 39: 381-384.

8) Schlitt HJ, Schmidt U, Simunec D,Jager M, Aselman H, Neipp M, Piso P. Morbidity and mortality associated with pancreaticogastrostomy and pancreaticojejunostomy following partial pancreaticoduodenectomy. Br J Surg 2002; 89: 1245-1251.

9) Yang SH, Dou KF, Sharma N, Song WJ. The Methods

of Reconstruction of Pancreatic Digestive Continuity After Pancreaticoduodenectomy: A Meta-Analysis of Randomized Controlled Trials. World J Surg 2011; 35: 2290-2297.

10) Fernandez-Cruz L, Belli A, Acosta M, Chavarria EJ, Adelsdorfer W, Lopez-Boado MA, Joana F. Which Is the Best Technique for Pancreaticoenteric Reconstruction After Pancreaticoduodenectomy? A Critical Analysis. Surg Today 2011; 41: 761-766.

11) Fernandez-Cruz L. Pancreaticojejunostomy versus pancreaticogastroatomy. J Hepatobiliary Pancreat Sci 2011; 18: 762-768.

12) Yamaguchi T, Hara T, Tsuyuguchi T, Ishihara T, Tsuchiya S, Saito M, Saisho H. Peroral pancreatoscopy in the diagnosis of mucin-producing tumors of the pancreas. Gastrointest Endosc 2000; 52: 67-73.

13) Hara T, Yamaguchi T, Ishihara T, Tsuyuguchi T, Kondo F, Kato K, Saisho H. Diagnosis and patient management of intraductal papillary mucinous tumor of the pancreas by using peroral pancreatoscopy and intraductal ultrasonography. Gastroenterology 2002; 122: 34-43.

14) Fang WL, Su CH, Shyr YM, Chen TH, Lee RC, Tai LC, Wu CW, Lui WY. Functional and Morphological Changes in Pancreatic Remnant After Pancreaticoduodenectomy Pancreas 2007; 35: 361-365.

15) Nakamura H, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Ohge H, Sueda T. Predictive Factors for Exocrine Pancreatic Insufficiency After Pancreatoduodenectomy with Pancreaticogastrostomy J Gastrointest Surg 2009; 13: 1321-1327.

16) Rault A, SaCunha A, Klopfenstein D, Larroude D, Epoy FND, Collet D, Masson B. Pancreaticojejunal Anastomosis Is Preferable to Pancreaticogastrostomy after Pancreaticoduodenectomy for Longterm Outcomes of Pancreatic Exocrine Function J Am Coll Surg vol.201, No. 2, August 2005: 239-244.

17) The Japanese Gastric Cancer Society. Gastric Cancer Treatment Guidelines 2014.

18) Hirasawa T, Gotouda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, Fujisaki J, Sano T, Yamaguchi T. Incidence of lymph node metastasis and feasibility of endoscopic resection for undifferentiated-type early gastric cancer. Gastric Cancer 2009; 12: 148-52.

19) Mihara Y, Kubota K, Nemoto T, K Rokkaku, S Yamamoto, M Tachibana, Sakuma A, Ohkura Y, Fujimori T. Gastric cancer developing in the stomach after pylorus-preserving pancreatoduodenectomy with pancreaticogastrostomy: Case report and review of literature. J Gastrointest Surg 2005; 9: 498-502.

20) Ohasi N, Tamaki H, Sanda T, T Yano, E Matsumoto, A Ishihara. Development of carcinoma of the stomach after pylorus-preserving pancreatoduodenectomy (PPPD) for early carcinoma of the papilla of Vater: case report. J Jpn Panc Soc 2001; 16: 42-47.

21) Tsukahara A, Koyama S, Hatayama S, Tanaka N, Takeda N, Shimoda S. A case of early gastric cancer after pylorus-preserving pancreatoduodenectomy. Operation 2006; 60: 259-262. (in Japanese)

22) Emoto T, Yoshikawa K, Dousei T, Fujikawa M, Fujii M, Yoshioka Y, Naka Y, Komaki T, Yokota T, Oda T. A case of early gastric cancer after pylorus-preserving pancreatoduodenectomy. Jpn J Gastroenterol Surg 2002; 35: 277-281.

23) Taniguchi H, Yoshida K, Mizokami H, Osanai M, Takahashi K. A case of early gastric cancer after pylorus-preserving pancreatoduodenectomy. J Okayama Med Assoc 2001; 113: 51.

24) Kaneda K, Nomura H, Fujiwara H, Kuroda D, Nishimura S, Kawamura M, Kato M, Ohyanagi H. A case of early gastric cancer after pylorus-preserving pancreatoduodenectomy. Acta Med Kinki Univ 1996; 3: 263-268.

25) Tatsuzawa Y, Osari A, Uno K, Tsuchida K, Yagi S, Bandou H, Yamada T, Kitagawa S, Nakagawa M. A case of early gastric cancer after pylorus-preserving pancreatoduodenectomy. J Jpn Surg Assoc 1995; 56: 2089-2093.

26) Mason RC, Taylor PR, Filipe MI. Pancreaticoduodenal secretions and genesis of gastric stump carcinoma in the rat. Gut 1988; 29: 830-834.

27) Mason RC. Duodenogastric reflux in rat gastric carcinoma. Br J Surg 1986; 29: 830-834.

〈和文抄録〉

膵頭十二指腸切除後, 膵胃吻合部に早期胃癌の発生と IPMC 再発を認めた 1 例

坂木　桃子[1]，谷口　弘毅[1]，山野　　剛[2]

[1]京都第二赤十字病院外科
[2]京都第二赤十字病院病理部

症例は 60 歳男性．膵頭部 IPMC に対し膵頭十二指腸切除（PD-IV）を施行され，7 年後に上部内視鏡検査にて胃膵吻合部に発赤とびらんを認め，生検にて poorly differentiated adenocarcinoma と診断された．胃部分切除，残膵全摘，脾臓摘出を施行したところ，病理組織検査にて早期胃癌および主膵管型 IPMC と診断され，両者は免疫組織学的に区別された．本症例は，初めて明確に胃膵吻合部から発生した早期胃癌であり，PD 術後に胃膵吻合部の IPMC 再発に合併した胃癌としても，初の報告となる．

近年，PD は安全に施行される術式となり，長期生存を得られた場合，別の悪性腫瘍発生が問題となる．PD において胃膵吻合は，膵空腸吻合に比し，残膵の内視鏡的観察が可能であるという点で優れた再建術式であると考えられる．また，PD にて胃膵吻合後に，自験例を含め 8 例の胃癌発生が報告されており，より長期にわたる残胃の経過観察が必要である．

キーワード：胃膵吻合，胃癌，IPMC.