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ORIGINAL ARTICLE

Pancreatic cancer in the remnant pancreas following primary pancreatic resection

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Abstract
Purpose To clarify the clinical features of cancer in the pancreatic remnant.
Methods We retrospectively reviewed the clinical and pathological findings of 10 patients who developed remnant pancreatic cancer in our hospital between 2002 and 2012. The KRAS sequences in both the initial pancreatic tumor and remnant pancreatic cancer were examined in two patients.
Results Eight patients underwent a second pancreatectomy for remnant pancreatic cancer (resected group), while two patients were not operated on and underwent chemotherapy (unresected group). The remnant pancreatic cancer developed at the cut end of the pancreas (pancreaticogastrostomy site) in four patients. In the resected group, four patients died 17 months after the emergence of the remnant pancreatic cancer and four patients survived during the median 40.5-month observation period. The median survival of the unresected group after the emergence of the remnant pancreatic cancer was 10 months. The findings of the KRAS sequencing and immunohistological staining of the remnant pancreatic cancer for MUC1 and MUC2 in the two patients were consistent with those of the initial pancreatic tumor in one patient, and not consistent in the other.
Conclusions Our results suggest that both local recurrence and a new primary cancer can develop in the pancreatic remnant, and repeated pancreatectomy can prolong survival.

Keywords Pancreatic cancer · Local recurrence · Operation

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Introduction

Pancreatic cancer remains difficult to cure; however, the surgical mortality rates have fallen to well below 5 % for pancreatic surgery at major centers because of the recent progress in diagnostic imaging modalities, surgical procedures, other systemic therapies and perioperative care [1–7]. Pancreatic cancer is now the fifth leading cause of cancer-related deaths in Japan, the incidence rate almost equals the mortality rate and the five-year survival rate of resected cases remains at only 15–20 % [8]. The poor prognosis is mainly because of the presence of systemic occult disease at the time of surgery in many patients, leading to distant metastasis to the liver (50 % of resected patients) and peritoneum (25 %) [9–11]. Even with macroscopic R0 surgery, cancer cells can still be present on the cut end of the pancreas [9], and this R1-like situation may lead to local recurrence in the pancreatic remnant [9]. To our knowledge, there have been only a few series that have studied the outcomes of recurrent pancreatic cancer [12]. Kleff et al. [13] evaluated the survival of 30 patients with recurrent pancreatic ductal adenocarcinoma and found a

trend toward an increased median survival in patients undergoing resection (17.0 months) compared with bypass/exploration (9.4 months), although this difference was not statistically significant [13].

New primary pancreatic cancer can also develop in the pancreatic remnant following resection for other pancreatic tumors, such as intraductal papillary mucinous neoplasia (IPMN) [14]. The morbidity rates after pancreatic resection range from 30 to 40 % [1–3, 15, 16], and are higher for repeated pancreatectomy because of adhesions and anatomical complexities [13]. The clinical features and the efficacy of repeated pancreatectomy for these situations are unclear because of the limited number of cases, and there are no established therapeutic strategies for pancreatic cancer in the pancreatic remnant.

The aims of this study were to clarify the clinical features of cancer in the pancreatic remnant and to assess the therapeutic strategies that can be used following primary pancreatic resection.

Patients and methods

Between April 2002 and November 2012, 241 patients underwent pancreatoduodenectomy (PD) and 98 patients underwent distal pancreatectomy (DP) at the Department of Gastroenterological Surgery, Kumamoto University Hospital and the Department of Surgery, Kumamoto Regional Medical Center. These 339 pancreatic resections were performed for 227 pancreatic cancers and for 112 other diseases. The PD cases included stomach-preserving pancreaticoduodenectomy (SSPPD) and pylorus-preserving pancreaticoduodenectomy (PPPD); 97 patients were reconstructed with pancreaticogastrostomy (PG) and 164 with pancreaticojejunostomy (PJ). Following the primary pancreatic resection, 10 patients eligible for this study developed pancreatic cancer in the pancreatic remnant (five male and five female; average age, 68.5 years (range 55–80 years) at the initial surgery). Table 1 shows the patient demographics.

Eight patients underwent a second pancreatectomy for cancer in the pancreatic remnant (resected group), while two patients were not operated on and underwent chemotherapy because of the presence of multiple liver metastases (unresected group). Pancreatic resection was performed with D2 lymph node dissection [17, 18]. If the tumor invaded the superior mesenteric and portal veins (SMV-PV), the involved SMV-PV were resected and reconstructed. Patients were evaluated every 1–2 months after the operation by physical examination, and every 3 months by computed tomography scanning. In patients without evidence of disease after 2 years of follow-up, evaluations were reduced to 3–4 month intervals. The histological findings, surgical procedure, clinical course and long-term outcomes were analyzed retrospectively.

Table 1 Patient characteristics and the reason for the initial pancreatic resection

Case No.	Age/gender at initial surgery	Diagnosis at initial surgery	Location	AJCC stage	Histology	PanIN	Surgical procedure	Reconstruction	Degree of residual tumor	Adjuvant chemotherapy
Resected group										
1	55/F	PC	Head	T1N0M0	Anaplastic	1B-2	SSPPD PV	PJ	R0	–
2	69/F	PC	Head	T1N0M0	Pap	(–)	SSPPD	PG	R0	GEM S-1
3	80/M	PC	Head	T3N0M0	Mod	1B	PPPD	PG	R0	–
4	60/M	PC	Tail	T2N1M0	Pap	(–)	DP	–	R0	–
5	75/F	PC	Tail	T3N1M0	Wel	(–)	DP	–	R0	GEM
6	76/M	PC	Body	T1N0M0	Mod	2	DP	–	R0	GEM
7	71/F	AC	Head	T2N0M0	Wel	(–)	PPPD	PG	R0	–
8	68/M	IPMN	Head, tail	–	IPMA (adenoma)	1A-1B	PP DP	–	–	–
Unresected group										
9	56/M	PC	Head	T3N0M0	Mod	(–)	PPPD PV	PG	R1	GEM
10	62/F	PC	Head	T3N1M0	Wel	3	PPPD PV	PG	R0	GEM

The resected group underwent repeat pancreatectomy for cancer in the pancreatic remnant. The unresected group did not receive surgery for cancer in the pancreatic remnant and underwent chemotherapy alone because of multiple liver metastases

AC ampullary cancer, *AJCC* American Joint Committee on Cancer, *DP* distal pancreatectomy, *GEM* gemcitabine, *IPMA* intraductal papillary mucinous adenoma, *IPMN* intraductal papillary mucinous neoplasm; mod, moderately differenciated adenocarcinoma, *PanIN* pancreatic intraepithelial lesion, *pap* papillary adenocarcinoma, *PC* pancreatic cancer, *PG* pancreaticogastrostomy, *PJ* pancreaticojejunostomy, *PP* partial pancreatectomy, *PPPD* pylorus-preserving pancreaticoduodenectomy, *PV* resection and reconstruction of the portal vein, *SSPPD* subtotal stomach-preserving pancreaticoduodenectomy, *wel* well differenciated adenocarcinoma

Pyrosequencing assay for KRAS mutations

Activated KRAS mutations are often the first genetic changes in pancreatic cancer [19]. KRAS mutations increase in frequency with disease progression, and are found in nearly 100 % of pancreatic adenocarcinomas [20–23]. We examined the KRAS sequences in both the initial pancreatic tumor and remnant pancreatic cancer in two of our patients. Pyrosequencing is a non-electrophoretic nucleotide extension sequencing technology used for various applications, including mutation tests in tumors [24–26]. This technology has several advantages, including higher sensitivity and cost effectiveness than other methods, and the method has been described in detail in previous studies [24, 25]. The tumor margins were marked on hematoxylin-eosin-stained slides. Genomic DNA was extracted from the tumor lesions using the RNeasy formalin-fixed paraffin-embedded (FFPE) kit (Qiagen, Valencia, CA. USA). The polymerase chain reaction (PCR) amplification primers for pyrosequencing targeted for KRAS (codons 12) were as follows: KRAS-F, forward, 5′-NN NGGCCTGCTGAAAATGACTGAA-3′ and KRAS-R, reverse biotinylated primer, 5′-TTAGCTGTATCGTCAAG GCACTCT-3′. Each PCR mix contained the forward and reverse primers (each, 20 pmol), 1.0 nmol each of dNTPs with dUTP, 2 mmol/L $MgCl_2$, 1 × PCR buffer, 1.25 U of AmpliTaq Gold 360, 0.5 U of AmpErase UNG and 5 µl of template in a total volume of 50 µl. The PCR conditions consisted of initial denaturing at 50 °C (10 min) for AmpErase UNG or initial denaturing at 94 °C (10 min) for AmpliTaq Gold 360 then 50 cycles of 95 °C (30 s), 57 °C annealing (30 s) and 72 °C (30 s) with a final extension at 72 °C (7 min). KRAS pyrosequencing was performed using the PyroMark Q24 System (Qiagen, Valencia, CA, USA) and all forward sequencing results were confirmed by reverse sequencing. During the KRAS pyrosequencing assay, we routinely confirmed the presence of a mutation using three different sequencing primers and by the creation of frameshift mutants relative to a wild-type sequence in a program. The primer KRAS-PF1 (5′-TGTGGTAGTTGGA GCTG-3′; nucleotide dispensation order, ACTGATCG AT CGATCGATCGATCGATCG) detected the c.35G > T (codon 12 GTT) and c.35G > A (codon 12 GAT) mutations. The primer KRAS-PF2 (5′-TGTGGTAGTTGGAG CT-3′; nucleotide dispensation order, ATCGATCGATCG ATCGATCGATCATCG) detected the c.34G > T (codon 12 TGT) mutation.

Immunohistochemistry

Immunohistochemistry was performed using primary antibodies against MUC1 (diluted 1:100) and MUC2 (diluted 1:100) (Leica Biosystems, Singapore). A subsequent reaction was performed using the biotin-free horseradish peroxidase enzyme-labeled polymer of the EnVision Plus detection system (Dako, Tokyo, Japan). A positive reaction was visualized with a diaminobenzidine (DAB) solution.

Results

Initial pancreatic resection

The surgical findings and adjuvant chemotherapy are summarized in Table 1. Six patients underwent primary pancreatectomy for pancreatic cancer and one patient each was treated for ampullary cancer and IPMN. Both patients in the unresected group underwent primary pancreatectomy for the pancreatic cancer. In the resected group, the tumor was located in the pancreatic head in four patients (including the ampullary cancer), the pancreatic body in one and the tail in two; whereas one case had two IPMNs, one in the head and one in the tail. The tumor was located in the head in both cases in the unresected group.

The surgical procedures were SSPPD in two patients (combined with resection and reconstruction of the portal vein in one), PPPD in two, DP in three and a combination of partial pancreatectomy and DP in the patient with IPMN in the resected group. PPPD combined with resection and reconstruction of the portal vein was performed in both patients in the unresected group. Interestingly, the reconstruction procedures were PG in five cases and PJ in only one case in our study. For the pancreatic cancer, R0 resection (with no tumor within 1 mm of the margin) was achieved for all cases in the resected group. In contrast, in the unresected group, the residual tumor was R0 in one patient and R1 in the other.

The postoperative histological diagnosis was papillary adenocarcinoma in two patients, well-differentiated adenocarcinoma in two, moderately differentiated adenocarcinoma in two, anaplastic carcinoma in one and intraductal papillary mucinous adenoma in one patient in the resected group; with well-differentiated adenocarcinoma in one patient and moderately differentiated adenocarcinoma in the other patient in the unresected group. Lymph node metastasis occurred in two cases in the resected group, and in one in the unresected group. A pancreatic intra-epithelial lesion (PanIN) was detected in four cases in the resected group, and in one case in the unresected group.

The patients with pancreatic cancer in the resected group received adjuvant chemotherapy with gemcitabine ($n = 2$) or a combination of gemcitabine and S-1 ($n = 1$). Both cases in the unresected group received adjuvant chemotherapy with gemcitabine.

Table 2 Cancer in the pancreatic remnant and long-term outcomes

Case No.	Location	AJCC stage	Interval	Histology	PanIN	Surgical procedure	Recon -struction	Degree of residual tumor	Adjuvant chemo -therapy	Observation period
Resected group										
1	Tail	T2N0M0	24	Wel	(–)	TP	–	R0	–	68
2	Tail	T1N0M0	38	Wel	3	TP	–	R0	GEM	10
3	Body (cut end)	T3N1M0	21	Mod	(–)	TP	–	R1	–	18+
4	Body	T1N0M0	33	Pap	(–)	TP	–	R0	–	85
5	Head	T1N0M0	39	Wel	1B	TP	–	R0	S-1	13
6	Head	T3N1M0	23	Mod	2	TP	–	R0	GEM	13+
7	Body (cut end)	T3N1M0	86	Mod	1B	MP	PJ	R0	–	16+
8	Head	T3N1M0	103	Wel	(–)	TP PV	–	R0	GEM	26+
Unresected group										
9	Body (cut end)	T4N1M1	23	–	–	–	–	–	S-1	9+
10	Body (cut end)	T3N1M1	17	–	–	–	–	–	S-1	11+

The resected group underwent repeat pancreatectomy for cancer in the pancreatic remnant. The unresected group did not receive surgery for cancer in the pancreatic remnant and underwent chemotherapy alone because of multiple liver metastases. Interval, months from the initial surgery to the emergence of the remnant pancreatic cancer; Observation period, months after the emergence of the remnant pancreatic cancer

AJCC American Joint Committee on Cancer, *GEM* gemcitabine, *mod* moderately differentiated adenocarcinoma, *MP* middle pancreatectomy, *PanIN* pancreatic intra-epithelial lesion, *pap* papillary adenocarcinoma, *PJ* pancreaticojejunostomy, *PV* resection and reconstruction of portal vein, *TP* total pancreatectomy, *wel* well-differentiated adenocarcinoma

+ Dead

Cancer in the pancreatic remnant

The intraoperative and clinicopathological findings of the patients are summarized in Table 2. Remnant pancreatic cancer developed at the cut end (PG anastomosis site) in four patients. The interval from the initial surgery to the emergence of the remnant pancreatic cancer in the resected group was 35.5 months (range 23–103 months), which was longer than that in the unresected group (20 months; range 17–23 months).

Second pancreatectomies were performed immediately after the detection of the remnant pancreatic cancer in all cases in the resected group. The postoperative histological diagnoses were consistent with those of the primary tumors in four cases (case Nos. 3, 4, 5 and 6; the suspected local recurrence group) and the remnant pancreatic cancer was a suspected to be a recurrence of the primary lesion. These results were not seen in the remaining four cases (case Nos. 1, 2, 7, and 8; suspected new primary group). In these four cases, the remnant pancreatic cancer was a suspected new primary lesion. PanIN was detected in two cases in the suspected local recurrence group, and in two cases in the suspected new primary group. The interval from the initial surgery to the operation for the remnant pancreatic cancer was shorter (28 months; range 21–39) in the suspected local recurrence group than in the suspected new primary group (62 months; range 24–103 months), although the difference was not statistically significant. Total (residual) pancreatectomy (Fig. 1a, b) was performed for the remnant pancreatic cancer in all but one of the patients the resected group, and this patient underwent middle pancreatectomy with PJ reconstruction. R0 resection for the remnant pancreatic cancer was performed in almost all of the patients in the resected group, except for one patient with R1 resection. There were no hospital deaths after these operations.

Lymph node metastasis was present in four cases in the resected group, and in two in the unresected group. Four patients in the resected group received adjuvant chemotherapy with gemcitabine ($n = 3$) or S-1 ($n = 1$). Both cases in the unresected group received chemotherapy with S-1 without surgery because of multiple liver metastases.

Four patients in the resected group (case Nos. 3, 6, 7, and 8) died 17 months (range 13–26 months) after the emergence of the remnant pancreatic cancer and four patients (case Nos. 1, 2, 4, and 5) survived to the end of the 40.5-month (range 10–85 months) median observation period. The median survival of the unresected group after the emergence of the remnant pancreatic cancer was 10 months (range 9–11 months). Therefore, the survival after the emergence of the remnant pancreatic cancer in the resected group was longer than that in the unresected group.

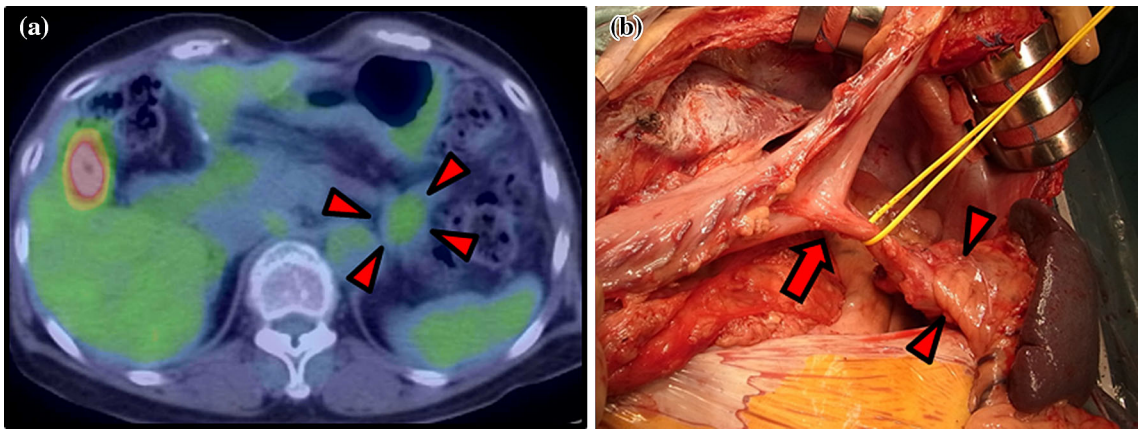

Fig. 1 The total pancreatectomy for remnant pancreatic cancer in case 2. Positron emission tomography-computed tomography **(a)** revealed pancreatic cancer in the tail of the pancreatic remnant, and total pancreatectomy **(b)** was performed. *Arrow*, pancreaticogastrostomy; *arrowheads*, the remnant pancreatic cancer

Table 3 The results of the pyrosequencing assay for KRAS mutations (codon 12), and immunohistochemical staining for MUC1 and MUC2

Case No.	Initial pancreatic tumor			Remnant pancreatic cancer		
	KRAS (codon 12)	MUC1	MUC2	KRAS (codon 12)	MUC1	MUC2
Resected group						
1	GGT (wild-type)	Negative	Negative	GTT	Positive	Negative
2	X	x	x	GGT (wild-type)	Positive	Negative
3	GTT	Positive	Negative	x	x	x
4	X	x	x	x	x	x
5	GTT	Positive	Negative	GTT	Positive	Negative
6	CGT	Positive	Negative	x	x	x
7	X	x	x	x	x	x
8	X	x	x	CGT	Negative	Negative
Unresected group						
9	GAT	Positive	Positive	–	–	–
10	X	x	x	–	–	–

The resected group underwent repeat pancreatectomy for cancer in the pancreatic remnant. The unresected group did not receive surgery for cancer in the pancreatic remnant and underwent chemotherapy alone because of multiple liver metastases

x a suitable sample was not found

Pyrosequencing assay for KRAS mutations and immunohistochemistry for MUC1 and MUC2

We performed a pyrosequencing assay for KRAS (codon 12) mutations and immunohistochemistry for MUC1 and MUC2 in nine lesions from seven patients (Table 3). No suitable samples were found for the other lesions. The KRAS sequences and the immunohistochemistry results in both the initial pancreatic tumor and the remnant pancreatic cancer were examined in two patients (case Nos. 1 and 5). Wild-type (GGT) and three types of mutations (GTT, CGT, and GAT) in KRAS were detected by the pyrosequencing assay. We found that seven lesions were MUC1 positive and one was MUC2 positive. In case No. 1, KRAS codon 12 of the initial pancreatic cancer was GGT (wild-type) and that of the remnant pancreatic cancer was GTT. MUC1 was negative in the initial pancreatic cancer and positive in the remnant pancreatic cancer (Fig. 2a, b). In case 1, the remnant pancreatic cancer was a suspected new primary lesion. In contrast, KRAS codon 12 in both the initial pancreatic cancer and the remnant pancreatic cancer was GTT in case 5, and MUC1 was positive in both the initial pancreatic cancer and the remnant pancreatic cancer (Fig. 2c, d). The remnant pancreatic cancer in case 5 was therefore a suspected recurrence of the primary pancreatic cancer.

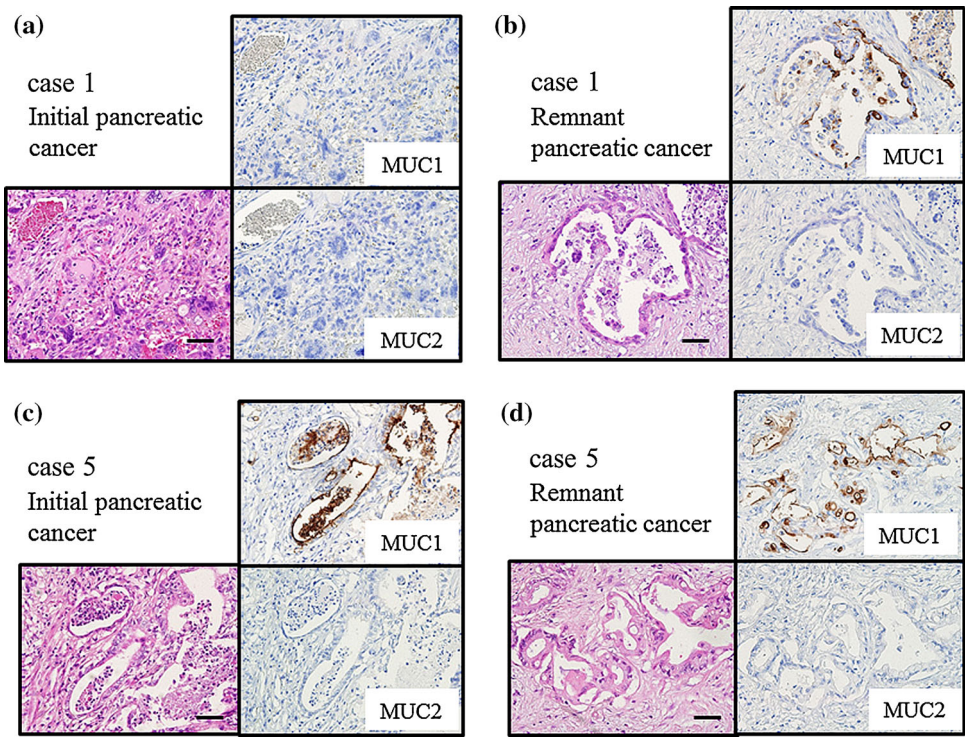

Fig. 2 The histological findings in cases 1 and 5. Hematoxylin-eosin staining (*left lower panel*) and MUC1 (*upper panel*) and MUC2 (*right lower panel*) immunohistological staining were performed. In case 1, the MUC1 staining was negative in the initial pancreatic cancer **(a)** and positive in the remnant pancreatic cancer **(b)**. In contrast, MUC1 was positive in both the initial pancreatic cancer **(c)** and in the remnant pancreatic cancer **(d)** in case 5. MUC2 was negative in these four tumors **(a–d)**. *Bars*: 10 μm

Discussion

Because disease recurrence develops in up to 80 % of patients with resected tumors within 2 years [9, 10], pancreatic cancer remains difficult to cure. As surgery is the only option with the potential to provide a cure, it is logical that resection for localized recurrence might provide a chance for prolonged survival for some patients. Pancreatic cancer can develop in the pancreatic remnant after previous pancreatic resection for various diseases, such as IPMN, ampullary cancer and bile duct cancer. Because surgical procedures and perioperative care have recently progressed [1, 6], resection of pancreatic cancer in the pancreatic remnant is now possible [13, 27, 28]. Therefore, in an attempt to cure patients, we have aggressively treated remnant pancreatic cancer by surgical resection if there is no distant metastasis and if R0 resection can be achieved.

In our study, after 339 pancreatic resections, 10 patients (2.9 %) developed pancreatic cancer in the pancreatic remnant. Unfortunately, multiple liver metastasis was present with the remnant pancreatic cancer in two cases. S-1, an oral fluoropyrimidine, is one of the key drugs used to treat PC in Japan. In the GEST study, a randomized, prospective, three-arm (gemcitabine, S-1, gemcitabine and S-1), phase III trial for unresectable advanced pancreatic cancer, S-1 led to similar overall survival and tolerable toxicity to gemcitabine as the first-line treatment [29, 30]. The unresected group in our study was treated with S-1, however, their prognosis was poor. In contrast, R0 resection for the remnant pancreatic cancer was performed safely and successfully in almost all cases in the resected group. Although our study was limited by the number of cases, the resected group tended to survive much longer than the unresected group, even those whose remnant pancreatic cancer was considered to be local recurrence.

Kleff et al. [13] reported that, in 586 operated cases for pancreatic ductal adenocarcinoma, 30 (5.1 %) patients underwent surgery for recurrent disease. In the 227 patients who underwent initial pancreatic resection for pancreatic cancer in our study, seven cases (3.1 %) developed remnant pancreatic cancer. Although our results were comparable, Kleff et al. did not indicate whether the recurrent lesions were true local recurrences or new primary lesions. We compared the histological diagnosis of the initial tumor and the remnant pancreatic cancer in the resected group to assess this in our study. The results indicated that four cases might have developed local recurrence of the primary lesions (suspected local recurrence group), and the other four cases might have developed new primary lesions (suspected new primary group). These data were confirmed by the pyrosequencing assay for KRAS mutations and immunohistochemistry for MUC1 and MUC2. The initial pancreatic cancer and the remnant pancreatic cancer had the same KRAS mutations and the same histological diagnosis, and both were positive for MUC1 in case 5 (suspected local recurrence group). In contrast, the KRAS sequences, MUC1 immunohistochemistry and histological diagnosis were not similar between the initial and remnant

pancreatic cancers in case 1 (suspected new primary group). Therefore, we hypothesize that pancreatic cancer can develop not only as a local recurrence after a short interval, but also as a new primary lesion after a longer interval.

Because of the retrospective design and limited number of patients, our study failed to find a specific clinical or histological feature discriminating the initial tumors based on whether there would be a tumor that developed in the pancreatic remnant. A recent meta-analysis showed that postoperative complications, such as postoperative pancreatic fistula, biliary fistula, mortality, reoperation and the length of hospital stay, were not significantly different between PG and PJ groups [31]. However, the long-term outcomes of PG and PJ, including carcinogenesis after reconstruction, have not been adequately clarified, and no previous study has reported the location of the cancer within the pancreatic remnant. In our study, six patients developed remnant pancreatic cancer after PD following primary pancreatic resection, and five cases underwent PG. Four of these cases developed remnant pancreatic cancer at the anastomosis site. Unlike the normal physiological condition, pancreatic secretions meet with acidic conditions during PG, and the interaction between pancreatic secretions and the gastric fluid may contribute to carcinogenesis in the pancreatic remnant following PG. Further studies are needed to determine the mechanism(s) underlying local pancreatic recurrence after reconstruction following PD, in addition to prospective follow-up studies focusing on carcinogenesis in the pancreatic remnant.

In conclusion, our results suggest that both local recurrence and new primary cancer can develop in the pancreatic remnant, and repeated pancreatectomy for cancer in the pancreatic remnant can prolong survival. Further studies are required to to elucidate carcinogenesis in the pancreatic remnant.

Conflict of interest The authors declare that they have no conflicts of interest.

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