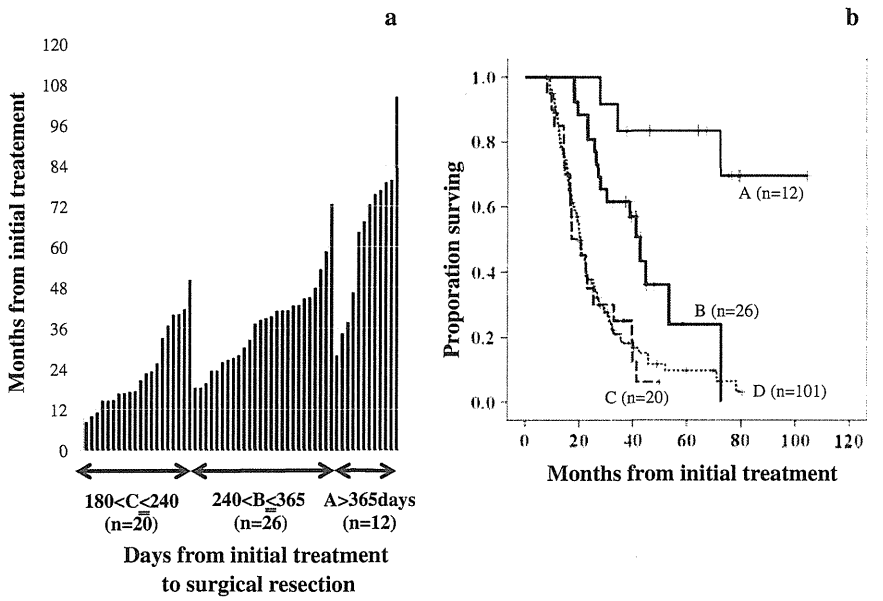


**Fig. 2** Survival time and curves according to time from initial treatment to surgical resection. **a** Survival time in each patient. Group A, 12 patients who underwent adjuvant surgery more than 365 days after initial treatment; Group B, 26 patients who underwent adjuvant surgery between 241 and 365 days; Group C, 20 patients who underwent adjuvant surgery between 180 and 240 days. **b** Comparisons of the survival curves of adjuvant surgery more than 365 days after the initial treatment [$n = 12$, group A, median survival time (MST) not reached], between 241 and 365 days ($n = 26$, group B, MST 43 months), between 180 and 240 days after initial treatment ($n = 20$, group C, MST 17 months), and the control group ($n = 101$, group D, MST 20 months). Although there was no difference in the survival curves between groups C and D ($p = 0.795$), significant differences were found in the survival curve between groups B and C or D ($p < 0.0001$), and between groups A and B, C, or D ($p < 0.005$). The overall survival rate in group A + B was significantly better than in group C ($p < 0.0001$). The dose of gemcitabine and S-1, and the tumor diameter, in group A + B were significantly greater than those in group C ($p < 0.05$) but there were no significant differences in other clinical parameters

that the criteria used to select patients who were eligible for surgical exploration during non-surgical anticancer treatments differed among institutions. The 58 patients in the adjuvant surgery group were collected from 39 hospitals over 8 years, and thus the average number was 1.2 cases per hospital. Moreover, it should be noted that a significantly higher rate of peritoneal metastasis was found in the control group.

Donahue et al. [25] reported that patients with initially unresectable pancreaticobiliary malignant tumors should be selected for surgery on the basis of lack of disease progression, good functional status, and a decrease in the CA19-9 level rather than of evidence that vessel involvement has disappeared on computed tomography or magnetic resonance imaging. The third clinical question is the optimal time for adjuvant surgery in this patient population. When should the shrunken tumor be removed in the process of maintaining chemotherapy and/or radiation therapy? The sub-group analysis according to the time from the initial treatment to surgical resection showed significant favorable differences in the overall survival rates in patients who were able to undergo adjuvant surgery more than 240 days after initial treatment. Therefore, the recommended optimal time for adjuvant surgery is at least 240 days after the initial treatment. A longer duration of non-surgical anti-cancer treatment may be associated with better patient selection, greater doses of chemotherapy, a higher rate of PR/CR, and lower levels of tumor markers, thus resulting in a better prognosis of patients, since a certain period of observation time allows for the identification of progressive disease or poor surgical candidates. The primary findings of this study indicate the importance of finding the appropriate non-surgical anticancer treatments for effective tumor downsizing over at least 240 days after the initial treatment.

The adjuvant surgery group underwent major pancreatic resection with concomitant other organ and/or vascular resection in 69 % of patients. It is technically possible to perform extensive resections with vein and/or arterial reconstruction, but concomitant arterial resection remains controversial because it is associated with a high morbidity [26–28]. Laurence et al. [28] reported that an increased risk of perioperative death appears to be associated with resection performed in patients with initially designated

unresectable tumors prior to neoadjuvant chemoradiation therapy. Nakao et al. [29] reported that pancreatectomy with portal vein resection can be performed safely, and long-term survival is observed in selected patients. The current study found no significant difference in overall survival or morbidity and mortality between those receiving concomitant resection or not. Therefore, the results from this study demonstrated that concomitant resections of other organs and vessels were safely performed with special caution.

In conclusion, adjuvant surgery for initially unresectable pancreatic cancer patients with a long-term favorable response to non-surgical anticancer treatments is considered to be a safe and effective treatment. The overall survival rate from the initial treatment was extremely high, especially in patients who received non-surgical anti-cancer treatment for more than 240 days. Adjuvant surgery can occupy an important position in multimodal therapy for patients with initially unresectable pancreatic cancer.

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**Conflicts of interest** The authors have no commercial affiliations that might pose any conflicts of interest in connection with this study.

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# Pylorus-Resecting Pancreaticoduodenectomy Offers Long-Term Outcomes Similar to Those of Pylorus-Preserving Pancreaticoduodenectomy: Results of a Prospective Study

**Manabu Kawai · Masaji Tani · Seiko Hirono · Ken-ichi Okada · Motoki Miyazawa · Hiroki Yamaue**



**Abstract**

*Background* We showed in a previous study that pylorus-resecting pancreaticoduodenectomy (PrPD), which divides the stomach adjacent to the pylorus ring, preserves more than 95 % of the stomach and significantly reduced the incidence of delayed gastric emptying (DGE) compared with pylorus-preserving pancreaticoduodenectomy (PpPD). However, long-term outcomes of PrPD and the adverse effect of early postoperative DGE on long-term outcomes remain unclear.

*Methods* A total of 130 patients enrolled in a previous study were followed for 24 months after surgery. Primary endpoint was whether PrPD is a better surgical procedure than PpPD regarding long-term outcomes.

*Results* Weight loss > grade 2 (Common Terminology Criteria for Adverse Events, Version 4.03) at 24 months after surgery was significantly better in group PrPD (16.2 %) than in group PpPD (42.2 %) ($p = 0.011$). Nutritional status and late postoperative complications were similar for the two groups. The incidence of weight loss > grade 2 at 24 months was 63.6 % in DGE patients with DGE and 25.3 % in non-DGE patients ($p = 0.010$). $T_{max}$ (time to peak $^{13}CO_2$ content in $^{13}$C-acetate breath test) at 24 months in DGE patients was significantly delayed compared with that in non-DGE patients (27.9 ± 22.7 vs. 16.5 ± 10.1 min, $p = 0.023$). Serum albumin level at 24 months was higher in non-DGE patients than in those with DGE (3.7 ± 0.6 vs. 4.1 ± 0.4 g/dl, $p = 0.013$).

*Conclusions* PrPD offers long-term outcomes similar to those of PpPD. DGE may be associated with weight loss and poor nutritional status in patients with long-term outcomes.

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## Introduction

We designed pylorus-resecting pancreaticoduodenectomy (PrPD) as a new procedure for periampullary neoplasms [1]. With PrPD, the stomach was divided adjacent to the pylorus ring. Although the pylorus ring was resected, more than 95 % of the stomach was preserved. Our previous randomized controlled trial (RCT), which compared pylorus-preserving pancreaticoduodenectomy (PpPD) and PrPD, demonstrated that PrPD is associated with a significantly lower incidence of delayed gastric emptying (DGE) than is PpPD (4.5 vs. 17.2 %, respectively) in the short term [1]. However, the superiority of PrPD compared with PpPD for long-term outcomes remains unknown. Long-term outcomes after PD have become increasingly important because advances in surgical techniques and perioperative management have led to a low mortality rate and long post-PD survival [2–5]. Therefore, it is important to assess nutritional status, body weight change, and late postoperative complications such as dumping syndrome, diarrhea, and marginal ulcers, which affect quality of life (QOL). To our knowledge, there have been no reports evaluating the long-term outcomes of PrPD.

In previous studies, the incidence of DGE after PD was reported to range from 12 to 42 % [6–10]. Although DGE is not a life-threatening complication, it results in a prolonged length of stay, which contributes to increased hospital costs and decreased QOL [6–10]. How DGE influences long-term outcomes such as nutrition status and

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body weight change remains unclear despite DGE being a common complication after PD.

In this study, 130 patients enrolled in our previous RCT were carefully followed for 2 years, and long-term outcomes were compared between two operative procedures. The primary endpoint was whether PrPD is a better surgical procedure than PpPD regarding long-term outcomes. The secondary endpoint was to determine how DGE that occurred during the early period after PD affects long-term outcomes by comparing patients with and without DGE.

## Patients and methods

Between October 2005 and March 2009, 139 patients with periampullary tumors were registered [1]. Among them, 130 patients were enrolled in this study, with 64 randomized to PpPD and 66 to PrPD. The Ethics Committee on Clinical Investigation of Wakayama Medical University Hospital (WMUH) approved this study. Informed consent was obtained preoperatively from all participating patients with pancreatic or periampullary lesions at WMUH. Participants also agreed to follow-up for 24 months after surgery. The follow-up was based on clinical, radiologic, and laboratory assessments to evaluate cancer recurrence every 1–3 months after surgery. Subsequent data after tumor recurrence or metastasis were excluded from this analysis.

### Surgical procedure

The right gastric artery and vagal nerve were transected at the same levels during both PpPD and PrPD. The right gastric artery was dissected by the root, and the first pyloric branch was dissected along the lesser curvature of the stomach. The first pyloric branch of the right gastroepiploic artery was also dissected along the greater curvature of the stomach. The pyloric branch of the vagal nerve was dissected along with lymph nodes around the pylorus ring. In PpPD the proximal duodenum was divided 3–4 cm distal to the pylorus ring. In PrPD the stomach was divided adjacent to the pylorus ring, with more than 95 % of the stomach being preserved [1] although the pylorus ring was resected. In patients with malignant disease, the following areas of lymph nodes were removed in two procedures: hepatoduodenal ligament, circumferentially around the common hepatic artery, and the right half circumference of the superior mesenteric artery.

All patients underwent PD with the following reconstruction [11]. Pancreaticojejunostomy after PpPD and PrPD was performed by duct-to-mucosa, end-to-side pancreaticojejunostomy in all patients [12]. External suture rows were performed as a single suture between the remnant pancreatic capsule, parenchyma, and jejunal seromuscular area using an interrupted suture with 4-0 Novafil (polybutester; Tyco Healthcare Japan, Tokyo, Japan). Internal suture rows, duct to mucosa, were performed between the pancreatic ductal and jejunal mucosa using eight interrupted sutures with 5-0 PDS-II (polydioxanone; Johnson & Johnson, Tokyo, Japan). Then, an end-to-side hepaticojejunostomy was performed by a one-layer anastomosis (5-0 PDS-II) 10–15 cm distal to the pancreaticojejunostomy. Duodenojejunostomy in PpPD or gastrojejunostomy in PrPD was performed by a two-layer anastomosis (4-0PDS-II and 3-0 silk) via an antecolic route based on the results of our RCT [13] from May 2003 onward.

### Postoperative management

A nasogastric tube was inserted prior to surgery and removed from all patients on postoperative day (POD) 1. Oral intake was routinely started on POD 3 or 4. One drain was routinely placed anterior to the pancreaticojejunostomy. If bile leakage and bacterial contamination were absent, this drain was removed on POD 4 in all patients [14]. All patients received an intravenous $H_2$-blocker (famotidine; Astellas Pharma, Tokyo, Japan) for 2 weeks postoperatively and prophylactic antibiotics every 3 h during surgery. To prevent pancreatic fistula formation or DGE, we did not administer prophylactic octreotide or prokinetic agents such as erythromycin postoperatively. Unless contraindicated by a patient's condition, adjuvant chemotherapy was provided to patients with periampullary or pancreatic carcinoma using the regimen in accord with our protocol based on gemcitabine. $H_2$-receptor antagonists or proton pump inhibitors were administrated as oral medication for patients with gastrointestinal symptoms such as heartburn or abdominal discomfort.

### Follow-up and data collection

Data were collected prospectively for all patients. Assessment of nutritional status by body weight change and serum nutritional parameters was performed before surgery and at 6, 12, 18, and 24 months after surgery. Albumin, prealbumin, transferrin, and retinol-binding protein were measured as serum nutritional parameters. $^{13}$C-acetate breath tests at 6, 12, and 24 months after surgery were performed to compare gastric emptying between PpPD and PrPD. Gastric emptying was evaluated by the time to peak $^{13}CO_2$ content ($T_{max}$) [15–17]. We performed the $^{13}$C-labeled mixed triglyceride breath test beyond 24 months after surgery to compare exocrine function between PpPD and PrPD [18].

The QOL was assessed at 6, 12, and 24 months after surgery using the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) questionnaire. The FACT-Ga questionnaire consists of the 27-item FACT-Ga, which assesses physical, social, emotional, and functional well-being using a series of subscale scores, and a newly validated 19-item portion, which assesses gastric cancer-specific domains of postoperative gastrointestinal symptoms including dumping syndrome, gastric fullness, appetite loss, weight loss, diarrhea, and bile reflux gastritis [19].

### Late postoperative complications

Late postoperative complications such as weight loss, dumping syndrome, peptic ulcer, and diarrhea were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [20]. Weight loss is defined by CTCAE version 4.03 as follows: grade 1, weight reduction of 5 to <10 % from baseline, intervention not indicated; grade 2, weight reduction of 10 to <20 % from baseline, nutritional support indicated; grade 3, weight reduction of >20 % from baseline, tube feeding and total parenteral nutrition (TPN) indicated [20]. Symptoms of dumping syndrome included abdominal pain, nausea, dizziness, exhaustion, flushing, diarrhea, or sweating, with onset within 30 min to 1 h of eating or within 2–3 h of eating [21, 22]. Dumping syndrome and peptic ulcer were defined by CTCAE version 4.03 as follows: grade 1, clinical or diagnostic observation only; grade 2, medical intervention indicated; grade 3, TPN indicated, elected operative or endoscopic intervention indicated; grade 4, urgent operative intervention indicated; and grade 5, death [20]. Diarrhea was defined by CTCAE version 4.03 as follows: grade 1, increase of fewer than four stools per day over baseline; grade 2, increase of four to six stools per day over baseline; grade 3, increase of seven or more stools per day over baseline; grade 4, urgent intervention indicated; and grade 5, death [20]. Diabetes associated with endocrine insufficiency was defined as either new diabetes (requiring new medical treatment such as dietary treatment, oral drugs, or insulin) or worsening diabetes (requiring a modification of the medical treatment for deterioration of previously diagnosed diabetes).

### Statistical analysis

Data are expressed as mean ± SD. Patient characteristics and perioperative and postoperative factors between the two groups were compared using $\chi^2$ statistics, Fisher's exact test, and the Mann–Whitney *U*-test. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed with SPSS software, version 20 (SPSS, Chicago, IL, USA).

**Table 1** Demographic characteristics of 130 enrolled patients

| | PpPD ($n = 64$) | PrPD ($n = 66$) | $p$ |
|---|---|---|---|
| Age (years) | 68 ± 9 | 67 ± 9 | 0.5776 |
| Sex (male/female) | 33/31 | 38/28 | 0.6084 |
| Diabetes (yes/no) | 18/46 | 19/47 | 0.9999 |
| Preoperative biliary drainage (yes/no) | 34/30 | 26/40 | 0.1161 |
| Serum hemoglobin level (g/dl)[a] | 13.0 ± 1.5 | 12.5 ± 1.3 | 0.2184 |
| Serum creatinine (mg/dl)[b] | 0.68 ± 0.2 | 0.72 ± 0.2 | 0.1903 |
| Serum total bilirubin level (mg/dl)[c] | 3.8 ± 4.0 | 4.0 ± 6.0 | 0.7965 |
| Serum amylase level (IU/L)[d] | 124 ± 134 | 111 ± 104 | 0.5232 |
| Benign/malignant tumors | 12/52 | 14/52 | 0.8953 |
| Pancreatic adenocarcinoma | 17 | 23 | |
| Bile duct carcinoma | 18 | 15 | |
| Ampullary adenocarcinoma | 6 | 3 | |
| Duodenal adenocarcinoma | 0 | 1 | |
| Intraductal papillary neoplasms | 15 | 15 | |
| Pancreatic endocrine tumor | 1 | 2 | |
| Tumor-forming pancreatitis | 3 | 5 | |
| Other disease | 4 | 2 | |

*PpPD* pylorus-preserving pancreaticoduodenectomy; *PrPD* pylorus-resecting pancreaticoduodenectomy

[a] Normal range 12–17.5 g/dl

[b] Normal range 0.53–1.02 mg/dl

[c] Normal range 0.2–1.2 mg/dl

[d] Normal range 15–150 IU/L

## Results

### Follow-up

Median follow-up for patients in this study was 37.5 months (3–78 months) in the PpPD group and 41.5 months (1–76 months) in the PrPD group. During follow-up, 45 of 130 enrolled patients died due to cancer recurrence (19 after PpPD versus 26 after PrPD). Complete data for body weight and nutritional assessment at the 2-year follow-up were obtained from 85 of the 130 eligible patients (52.7 %).

There was no significant difference between groups regarding the number of malignant (PpPD: $n = 52$, PrPD: $n = 52$) and benign (PpPD: $n = 12$, PrPD: $n = 14$) tumors (Table 1).

### Late postoperative complications and long-term outcomes

Table 2 compares late postoperative complications of PpPD and PrPD. Dumping syndrome, which was classified as grade 2 assessed by CTCAE 4.03, was diagnosed in one

**Table 2** Late postoperative complications and long-term follow up

| | PpPD ($n = 64$) | PrPD ($n = 66$) | $p$ |
|---|---|---|---|
| Follow-up (months) | 37.5 (3–78) | 41.5 (1–76) | 0.992 |
| Late postop. complications[a] | | | |
| Dumping syndrome (grade 2) | 0 | 1 (1.6 %) | 0.999 |
| Peptic ulcer (grade 2) | 1 (1.6 %) | 3 (4.5 %) | 0.619 |
| Diarrhea (grade 2) | 0 | 1 (1.6 %) | 0.999 |
| New-onset or worsening diabetes[b] | 3 (4.7 %) | 2 (3.0 %) | 0.678 |
| New diabetes | 2 | 1 | |
| Worsening diabetes | 1 | 1 | |
| Use of pancreatic enzyme supplement | 24 (37.5 %) | 28 (42.4 %) | 0.567 |
| Use of antiulcer agent | 16 (25.0 %) | 13 (19.7 %) | 0.468 |
| Postop. adjuvant chemotherapy | 43 (67.1 %) | 41 (62.1 %) | 0.546 |
| Nutritional status | | | |
| Albumin[c] (g/dl) | | | |
| Preoperation | 4.1 ± 0.5 | 4.0 ± 0.5 | 0.649 |
| 6 months postop. | 4.0 ± 0.4[e] | 3.9 ± 0.4[e] | 0.415 |
| 12 months postop. | 4.1 ± 0.5[e] | 4.0 ± 0.5[e] | 0.645 |
| 18 months postop. | 4.0 ± 0.5[e] | 4.1 ± 0.4[e] | 0.339 |
| 24 months postop. | 4.0 ± 0.5[e] | 4.2 ± 0.3[e] | 0.105 |
| Prealbumin[d] (g/dl) | | | |
| Preoperation | 22.2 ± 7.1 | 21.0 ± 6.3 | 0.319 |
| 6 months postop. | 21.0 ± 5.0[e] | 19.4 ± 5.7[e] | 0.094 |
| 12 months postop. | 21.6 ± 5.9[e] | 22.3 ± 4.6[e] | 0.167 |
| 18 months postop. | 21.2 ± 5.0[e] | 22.6 ± 3.5[e] | 0.238 |
| 24 months postop. | 22.3 ± 5.6[e] | 23.5 ± 4.4[e] | 0.293 |

*PpPD* pylorus-preserving pancreaticoduodenectomy, *PrPD* pylorus-resecting pancreaticoduodenectomy, *Postop.* postoperatively

Results are expressed as the median and range, the number and percent, or the median ± SD

[a] Dumping syndrome, peptic ulcer, and diarrhea were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Dumping syndrome has onset of symptoms with feeling unwell, such as stomach pain, nausea, dizziness, exhaustion, flushing, diarrhea, or sweating within 30 min–1 h of eating or within 2–3 h of eating

[b] New diabetes is defined as diabetes that requires new medical treatment, such as dietary treatment, oral drug(s), or insulin. Worsening diabetes is defined as diabetes that requires modification of the medical treatment because of deterioration of previously diagnosed diabetes

[c] Normal range 3.8–5.1 g/dl

[d] Normal range 22–40 mg/dl

[e] Recovery to baseline or higher than the preoperative level

patient after PrPD—resolved by dietary treatment alone (altered meal size and meal frequency). Dumping did not occur at all after PpPD. Four patients had endoscopically documented peptic ulcer with symptoms of new-onset epigastric pain or tarry stool. Although peptic ulcer classified as grade 2 based on CTCAE 4.03 was diagnosed in one patient after PpPD and three patients after PrPD, there was no significant difference in the incidence between the two procedures. Peptic ulcers in the four patients was completely cured with proton pump inhibitors without requiring an interventional approach. There were no significant differences between the two procedures with regard to diarrhea. The frequency of administration of pancreatic enzyme supplement was similar between the two procedures; 37.5 % for PpPD and 42.4 % for PrPD.

There were no significant differences between the two procedures concerning the incidence of new-onset or worsening diabetes. Serum rapid turnover proteins, such as albumin and prealbumin, at 6, 12, 18, and 24 months after each procedure recovered to preoperative levels. The two procedures were also shown to be equivalent with regard to nutritional status.

## Long-term outcomes of body weight after PpPD and PrPD

Long-term outcomes of body weight change during 24 months after surgery are shown in Table 3. Mean body weight preoperatively and 24 months postoperatively were not significantly different between the PpPD and PrPD groups. The incidences of weight loss > grade 2 at 6 and 12 months after surgery were 41.1 and 43.0 % in the PpPD patients and 45.3 and 27.3 % in the PrPD patients, respectively. There was no significant difference between PpPD and PrPD regarding the incidence of weight loss > grade 2 at 6 and 12 months after surgery. However, the incidences of weight loss > grade 2 at 18 and 24 months after surgery were 39.1 and 42.2 % in the PpPD group and 15.8 and 16.2 % in the PrPD group. Weight loss > grade 2 at 18 and 24 months after surgery improved significantly in the PrPD group compared with that in the PpPD group ($p = 0.018$ and 0.011, respectively).

## Long-term outcomes of gastric emptying and quality of life

The results of $T_{max}$ are shown in Table 4. $T_{max}$ at 6, 12, and 24 months after surgery in the PpPD group was significantly delayed compared with that in the PrPD group: 27.8 ± 19.8 versus 15.2 ± 6.3 min, 23.4 ± 16.9 versus 14.2 ± 4.5 min, 20.9 ± 15.6 versus 14.0 ± 5.5 min, respectively.

Of the 130 patients in this study, those available for QOL assessment at 6, 12, 18, and 24 months numbered 109 (83.0 %), 95 (73.0 %), 84 (63.9 %), and 82 (63.1 %), respectively. The return rate for questionnaires at each time point was 100 %. The overall QOL scores based on the FACT-Ga scales are presented in Table 4. The highest possible total FACT-Ga score is 184. The highest possible score for the 19-item FACT-Ga subscale assessing gastric cancer-specific domains of postoperative gastrointestinal symptoms is 76. There were no significant differences

**Table 3** Long-term outcomes regarding body weight between PpPD and PrPD

| Outcome | PpPD | PrPD | *p* |
|---|---|---|---|
| Change in BW (kg) | | | |
| Preoperative BW (kg) | 54.9 ± 10 | 55.0 ± 9 | 0.934 |
| Change in BW 6 months postop. | | | |
| Available for follow-up | 56 | 53 | |
| Body weight (kg) | 50.9 ± 11 | 50.0 ± 8 | 0.471 |
| Weight loss > grade 2[a], *n* (%) | 23 (41.1 %) | 24 (45.3 %) | 0.657 |
| Change in BW 12 months postop. | | | |
| Available for follow-up | 51 | 44 | |
| Body weight (kg) | 51.0 ± 11 | 50.7 ± 8.9 | 0.891 |
| Weight loss > grade 2[a], *n* (%) | 22 (43.0 %) | 12 (27.3 %) | 0.108 |
| Change in BW 18 months postop. | | | |
| Available for follow-up | 46 | 38 | |
| Body weight (kg) | 51.2 ± 11 | 52.0 ± 9.1 | 0.700 |
| Weight loss > grade 2[a], *n* (%) | 18 (39.1 %) | 6 (15.8 %) | 0.018 |
| Change in BW 24 months postop. | | | |
| Available for follow-up | 45 | 37 | |
| Body weight (kg) | 51.1 ± 11 | 53.0 ± 9.5 | 0.417 |
| Weight loss > grade 2[a], *n* (%) | 19 (42.2 %) | 6 (16.2 %) | 0.011 |

*BW* body weight, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PrPD* pylorus-resecting pancreaticoduodenectomy

[a] Weight loss greater than grade 2 here is a loss that is >10 % from baseline. Weight loss has been defined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 as follows: grade 1, reduction of 5 % to <10 % from baseline, intervention not indicated; grade 2, reduction of 10 % to <20 % from baseline, nutritional support indicated; grade 3, reduction of >20 % from baseline, tube feeding and total parenteral nutrition indicated

**Table 4** Long-term outcomes of gastric emptying and quality of life after PpPD or PrPD

| | PpPD ($n = 64$) | PrPD ($n = 66$) | *p* |
|---|---|---|---|
| Gastric emptying by $^{13}$C-acetate breath test ($T_{max}$) (min)[a] | | | |
| 6 months postop. | 26.7 ± 18.8 | 17.4 ± 13.2 | 0.020 |
| 12 months postop. | 23.4 ± 16.9 | 14.2 ± 4.5 | 0.011 |
| 24 months postop. | 20.9 ± 15.6 | 14.0 ± 5.5 | 0.036 |
| Quality of life | | | |
| Total FACT-Ga score (range 0–184) | | | |
| 6 months postop. | 139.1 ± 22.9 | 139.6 ± 21.4 | 0.914 |
| 12 months postop. | 144.7 ± 20.0 | 145.9 ± 24.8 | 0.831 |
| 24 months postop. | 149.5 ± 20.1 | 148.8 ± 23.2 | 0.886 |
| FACT-Ga subscale (range 0–76) | | | |
| 6 months postop. | 59.6 ± 11.0 | 60.1 ± 11.3 | 0.814 |
| 12 months postop. | 61.3 ± 10.0 | 60.8 ± 11.6 | 0.812 |
| 24 months postop. | 63.5 ± 10.5 | 62.7 ± 10.9 | 0.766 |

*FACT-Ga* functional assessment of cancer therapy–gastric cancer survey, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PrPD* pylorus-resecting pancreaticoduodenectomy

[a] Gastric emptying was evaluated by $T_{max}$ (the time to peak $^{13}CO_2$ content) using the $^{13}$C-acetate breath test at 1, 3, 6, 12, and 24 months after surgery

between the PpPD and PrPD groups regarding the results of any subscale score or the total FACT-Ga scores at 1, 3, 6, 12, and 24 months after surgery. The QOL scores after PpPD and PrPD increased smoothly.

### Short-term and long-term outcomes after early postoperative DGE

Regarding short-term outcomes, there was no significant difference between patients with and without DGE concerning the incidence of pancreatic fistula: 42.9 and 27.6 % in patients with and without DGE, respectively ($p = 0.381$). Concerning an association between DGE and intraabdominal abscess, there was no significant difference between patients with and without DGE. The incidences of intraabdominal abscess were 21.4 and 10.3 % in patients with and without DGE, respectively ($p = 0.206$). Body weight and nutritional status were assessed between patients with and without early postoperative DGE during the 24 months after surgery (Table 5). The incidence of weight loss > grade 2 at 24 months after surgery was 63.6 % in the patients with DGE and 25.3 % in those without DGE. Body weight at 24 months after surgery improved significantly in patients without DGE compared to that in patients with DGE ($p = 0.010$). Serum albumin at 24 months after surgery was higher in patients without DGE than those with DGE: 3.7 ± 0.6 versus 4.1 ± 0.4 g/dl ($p = 0.013$). $T_{max}$ at 24 months after surgery in patients who had early postoperative DGE was significantly delayed compared to that in patients without early postoperative DGE: 27.9 ± 22.7 versus 16.5 ± 10.1 min ($p = 0.023$). There were no significant differences in the results of any subscale scores or the total FACT-Ga scores at 24 months after surgery for patients with and without DGE.

## Discussion

Recent advances in surgical techniques and perioperative management have led to increased length of survival after PD [21–23]. Therefore, long-term outcomes for survivors have become a great concern. We clearly demonstrated in an RCT that PrPD significantly reduces the incidence of DGE compared with PpPD at the short-term follow-up [1]. However, long-term outcomes after PrPD remained

**Table 5** Short-term and long-term outcomes for patients who had early postoperative DGE

| Parameter | With DGE | Without DGE | *p* |
|---|---|---|---|
| Short-term outcome | | | |
| Available no. | 14 | 116 | |
| Pancreatic fistula[a] | 6 (42.9 %) | 32 (27.6 %) | 0.381 |
| Intraabdominal abscess | 3 (21.4 %) | 12 (10.3 %) | 0.206 |
| Long-term outcome (24 months postop.) | | | |
| Available no. | 11 | 71 | |
| Preoperative BW (kg) | 55.8 ± 9.2 | 55.1 ± 9.2 | 0.804 |
| Change in BW 24 months postop. | | | |
| Body weight (kg) | 49.8 ± 11.4 | 52.3 ± 10.5 | 0.477 |
| Weight loss > grade 2[b] *n* (%) | 7 (63.6 %) | 18 (25.3 %) | 0.010 |
| Nutritional status | | | |
| Albumin[c] (g/dl) | | | |
| Preoperation | 3.9 ± 0.7 | 4.1 ± 0.5 | 0.110 |
| 24 months postop. | 3.7 ± 0.6 | 4.1 ± 0.4 | 0.013 |
| Prealbumin[d] (g/dl) | | | |
| Preoperation | 20.3 ± 7.6 | 21.8 ± 6.7 | 0.454 |
| 24 months postop. | 21.3 ± 5.1 | 23.1 ± 5.0 | 0.272 |
| Gastric emptying by $^{13}$C-acetate breath test ($T_{max}$) (min)[e] | 27.9 ± 22.7 | 16.5 ± 10.1 | 0.023 |
| Quality of life | | | |
| Total FACT-Ga score (range 0–184) | 143.2 ± 25.9 | 150.1 ± 20.7 | 0.886 |
| FACT-Ga subscale (range 0–76) | 58.3 ± 14.8 | 63.8 ± 9.8 | 0.766 |

*DGE* delayed gastric emptying, *FACT-Ga* functional assessment of cancer therapy-gastric cancer survey

[a] Pancreatic fistula was defined by the International Study Group on Pancreatic Fistula (ISGPF)

[b] Weight loss greater than grade 2: weight loss more than 10 % from preoperative body weight

[c] Normal range of albumin level: 3.8–5.1 g/dl

[d] Normal range of prealbumin level: 22–40 mg/dl

[e] Gastric emptying was evaluated by $T_{max}$ (the time to peak $^{13}CO_2$ content) in $^{13}$C-acetate breath test at 1, 3, 6, 12, and 24 months after surgery

unknown. Therefore, this report focused on long-term outcomes after PrPD compared with PpPD.

Some authors have proposed that postoperative body weight change should be assessed as a percentage of preoperative body weight because the assessment by body weight change based on one time point during the postoperative period may be misleading [24, 25]. Our study has shown that patients who underwent PrPD had a more favorable recovery than those with PpPD at 18 and 24 months after surgery concerning weight loss of >10 % from their preoperative weight. One reason for weight loss may be associated with dietary intake based on the gastric emptying function. The $^{13}$C-acetate breath test is a useful marker of gastric emptying [22]. $T_{max}$ in the $^{13}$C-acetate breath test was significantly more delayed in the PpPD patients than in the PrPD patients. After PpPD, pyloric dysfunction caused by denervation may be responsible. It was also reported that there was a significant correlation between the $^{13}$C-acetate breath test and dietary intake [26]. Favorable gastric emptying may have contributed to increased dietary intake and led to subsequent improved body weight in the PrPD patients. Concerning nutritional status, serum albumin and prealbumin after PrPD (which preserves almost the entire stomach) was similar to that after PpPD for a long time after surgery. The serum albumin level is well established as one of the markers for nutritional assessment [27]. Nutritional status is a good indicator when estimating QOL [28].

Rapid gastric emptying caused by resection of the pylorus ring during PrPD may result in more frequent occurrence of dumping syndrome than after PpPD. Dumping syndrome is a serious late postoperative complication affecting QOL, body weight change, and nutritional status [7]. Several studies have reported that PpPD reduces postgastrectomy syndrome, including dumping, compared with its occurrence after PD with antrectomy [6–8, 24]. Previous studies have also reported that dumping syndrome after PpPD is rare, although its incidence after PD is 0–10 % in the literature [6, 7, 29–31]. In our study, only 1 of 66 patients (1.6 %) with PrPD had dumping syndrome (grade 2) during follow-up, and the patients could be treated with dietary management alone. PrPD patients may not have severe dumping syndrome because its pooling ability in the stomach is similar to that after PpPD. FACT-Ga was designed specifically to assess gastrointestinal disorders such as dumping syndrome [19]. Therefore, the FACT-Ga questionnaire was chosen in this study to focus on postgastrectomy syndrome or the postoperative gastric emptying function. FACT-Ga results indicated that PrPD had QOL outcomes similar to those achieved with PpPD.

As another important result of this study, we clarified short- and long-term outcomes in patients with DGE for the first time. DGE is a persistent, frustrating complication and decreases QOL [6–10]. Many pancreatic surgeons believe that DGE after PD is a secondary phenomenon caused by postoperative complications such as pancreatic fistula or intraabdominal abscess. However, our study demonstrated that pancreatic fistula or intraabdominal abscess is not associated with the incidence of DGE. It has been reported that factors such as nutritional status and dehydration related to DGE are the common reasons for readmission

after PD in the short term [32]. However, there have been no reports to evaluate how DGE affects long-term outcomes after PD. In this study, the patients with DGE had significantly lower serum albumin and prealbumin levels than those without DGE at 24 months. Moreover, the patients with DGE had significantly poorer body weight recovery than those without DGE at 24 months after surgery. Interestingly, $T_{max}$ in the $^{13}$C-acetate breath test was significantly more delayed in patients who had early postoperative DGE than those who did not—even 24 months after surgery. In patients who did not have early postoperative DGE, favorable gastric emptying may have contributed to increased dietary intake over the long term, leading to their subsequent recovery of body weight.

Malignant disease, administration of a pancreatic enzyme supplement, or postoperative adjuvant chemotherapy may affect body weight loss after PD over the long term. The frequency of postoperative adjuvant chemotherapy may cause poor oral intake tolerance. Two studies have reported that weight loss after PD is associated with diarrhea or exocrine insufficiency [17, 27]. In the present study, the incidences of DGE were similar for patients with malignant and benign disease (8.7 % in malignant disease patients vs. 19.2 % in benign disease patients, $p = 0.120$). Also, neither malignant disease nor postoperative adjuvant chemotherapy for malignant disease affected the incidence of body weight loss at 24 months after surgery (29.8 % in those with malignant disease vs. 32.0 % in those with benign disease, $p = 0.844$ and 29.5 % in patients with adjuvant chemotherapy vs. 31.6 % in patients without adjuvant chemotherapy, $p = 0.842$).

The present study has an important methodologic limitation arising from missing data due to death or disease progression during follow-up. Missing data may have biased the results and overestimated any positive effect of treatment. Also, follow-up is needed to clarify how the incidence of DGE or type of procedure affects body weight change in the long term.

## Conclusions

Our previous study suggested that PrPD has a significant impact on reducing the incidence of DGE (compared with PpPD) in the short term [1]. In the present study, we clarified that PrPD was associated with more favorable recovery of body weight. Long-term outcomes were shown to be similar with PpPD and PrPD concerning QOL, nutritional status, and gastrointestinal symptoms. Moreover, DGE may be associated with weight loss and poor nutritional status after surgery, affecting long-term outcomes. Therefore, PrPD is one of the procedures that may be recommended for treatment of periampullary neoplasms, including pancreatic adenocarcinoma.

**Conflict of interest** The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

# Impact of anticancer treatment on recurrent obstruction in covered metallic stents for malignant biliary obstruction

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**Abstract**
*Background* In patients with unresectable malignant biliary obstruction (MBO), anticancer treatment is often administered. The impact of anticancer treatment on recurrent biliary obstruction in covered self-expandable metallic stents (SEMS) has not been fully elucidated.
*Methods* Data on 279 patients enrolled in a multicenter prospective cohort study of two different covered SEMS for distal MBO, WATCH study (141 partially covered WallFlex stents and 138 partially covered Wallstents) were retrospectively analyzed. The rates and causes of recurrent biliary obstruction (stent occlusion or migration) were compared between anticancer treatment group ($n = 173$) and best supportive care alone (BSC) group ($n = 106$). Cumulative time and prognostic factors for recurrent biliary obstruction were analyzed, using a proportional hazards model with death without recurrent biliary obstruction as a competing risk.
*Results* The overall rate (43 vs. 25 %, $P = 0.002$) and the cumulative incidence (16.1 vs. 8.2, 27.9 vs. 18.9 and 44.1 vs.

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26.6 % at 3, 6 and 12 months, $P = 0.030$ by Gray's test) of recurrent biliary obstruction were significantly higher in anticancer treatment group compared with BSC group. The multivariate analysis revealed anticancer treatment [sub-distribution hazard ratio (SHR) 1.93, $P = 0.007$) as well as the use of a partially covered WallFlex stent (SHR 0.65, $P = 0.049$) as prognostic factors.

*Conclusions* Anticancer treatment was a risk factor for recurrent biliary obstruction in covered SEMS for distal MBO. The superiority of a partially covered WallFlex stent was again confirmed in this competing risk analysis; UMIN-CTR: UMIN000002293.

**Keywords** Chemotherapy · Competing risk analysis · Covered metallic stents · Obstructive jaundice

## Introduction

Endoscopic biliary stenting [1, 2] is an established palliation for malignant biliary obstruction. Self-expandable metallic stents (SEMSs) were proved to have longer stent patency than plastic stents [3–5]. Covered SEMSs were developed to prevent stent occlusion by tumor ingrowth [6–9], which is the major problem with uncovered SEMSs. However, two randomized controlled trials (RCTs) failed to demonstrate better stent patency due to stent migration in covered SEMSs [10, 11]. Recently, we reported the superiority of a newly developed a partially covered WallFlex stent over a partially covered Wallstent in a multicenter prospective study, the WATCH study [12]. A partially covered WallFlex stent with low axial force and anti-migration system [13, 14] demonstrated less stent migration and longer time to recurrent biliary obstruction.

Recent development of chemotherapy in pancreatic cancer [15, 16] or biliary tract cancer has improved the prognosis, even in patients with distant metastasis. While better local tumor control by anticancer treatment can prevent tumor ingrowth or overgrowth and improve stent patency [17], tumor volume reduction may theoretically increase stent migration due to the resolution of the stricture. In addition, adverse events such as neutropenia can potentially increase cholangitis and/or sludge formation. We previously reported the safety and efficacy of SEMSs in patients with advanced pancreatic cancer receiving gemcitabine [18]. Though a Cox hazard regression analysis [19] was used to adjust the differences in patient characteristics, i.e., performance status (PS) and disease stage, the influence of different survival between patients receiving chemotherapy or best supportive care (BSC) alone, which can potentially affect the analysis of stent outcomes [20], has not been fully elucidated. Generally, conventional methods such as Kaplan–Meier method with the log-rank test and Cox proportional hazard model overestimate a cumulative incidence of recurrent biliary obstruction in the presence of a competing risk, death without recurrent biliary occlusion in this setting. Therefore, the comparison of stent outcomes between patients receiving anticancer treatment versus BSC alone can be biased if death without stent occlusion is not taking into account because of different prognosis in these two groups.

Here we conducted a retrospective analysis of 279 patients with distal malignant biliary obstruction enrolled in WATCH study [12] to clarify the impact of anticancer treatment on recurrent biliary obstruction using a competing risk analysis [21, 22].

## Patients and methods

### Study design

This is a retrospective analysis of WATCH study, a previously reported multicenter prospective consecutive study with a historical cohort in patients with distal malignant biliary obstruction [12]. A total of 279 patients were included in the study; 141 patients received a partially covered WallFlex stent between April 2009 and March 2010, and 138 patients received a partially covered Wallstent between May 2001 and Jan 2007.

### Definitions of complications

Recurrent biliary obstruction was diagnosed if patients have recurrent jaundice with evidence of elevated bilirubin

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along with biliary dilation on CT, MRI or US. When recurrent biliary obstruction was suspected, reintervention was performed to confirm the biliary obstruction and its cause, unless patients were at terminal stage of the disease and could not tolerate the procedure. Recurrent biliary obstruction was defined as stent occlusion or migration. Death without recurrent biliary obstruction was defined as patients' death before any recurrent biliary obstruction was observed.

### Study outcomes and statistics

The rates and causes of recurrent biliary obstruction were compared between patients receiving anticancer treatment (anticancer treatment group) and patients receiving no anticancer treatment (BSC group). Cumulative time to recurrent biliary obstruction was first calculated by the Kaplan–Meier method [23] and compared by the log-rank test [24]. Then, it was re-calculated treating death without recurrent biliary obstruction as a competing risk and compared by the Gray's test [21].

Univariate and multivariate analyses of prognostic factors for recurrent biliary obstruction were performed using a proportional hazards model proposed by Fine and Gray [22], with death without recurrent biliary obstruction as a competing risk. We included age (≥70 vs. <70), gender (male vs. female), WHO PS (0 vs. ≥1), primary cancer (pancreatic cancer vs. others), anticancer treatment (yes vs. no), tumor size (≥30 vs. <30 mm), stricture length (≥20 vs. <20 mm), stent length (80 vs. ≤60 mm), liver metastasis (yes vs. no), ascites (yes vs. no), duodenal invasion (yes vs. no), prior drainage (yes vs. no), location of distal stent end (duodenum vs. bile duct), stent type (a partially covered WallFlex stent vs. a partially covered Wallstent) into the model. Age, tumor size and stricture length were divided into two groups by the median value. In the competing risk analysis, death without recurrent biliary obstruction was considered as a competing risk and subdistribution hazard ratios (SHRs), with 95 % confidence intervals (CIs) calculated. Factors with $P < 0.20$ by univariate analysis were considered to be potential risk factors for recurrent biliary obstruction and were further analyzed in a multivariate analysis.

Either the chi square or Fisher's exact test was used to compare the categorical variables, and Student's *t*-test or Wilcoxon nonparametric test was used to compare continuous variables. A $P$ value <0.05 was considered statistically significant. All analyses were performed using R software, version 2.14.0 (R Development Core Team: http://www.r-project.org). We used the *cmprsk* package for a competing risk analysis in R produced by Gray. All authors had access to the study data and had reviewed and approved the final manuscript.

## Results

### Patients

All 279 patients enrolled in WATCH study [12] were included in this retrospective analysis. Patient characteristics are shown in Table 1. Anticancer treatment was administered in 173 patients; chemotherapy alone in 154 (gemcitabine monotherapy in 120, S-1 monotherapy in 12, gemcitabine and S-1 combination therapy in 17 and others in 5), radiation therapy alone in 5, and chemoradiation therapy in 14. Between anticancer treatment group and BSC group, there were significant differences in age, PS and primary tumor. Stent type or length was similar between two groups. Median survival time by Kaplan–Meier method was 251 [interquartile range (IQR) 150–441] days in anticancer treatment group and 170 (IQR 73–301) days in BSC group ($P = 0.001$).

### Recurrent biliary obstruction and stent-related complications

The incidences of recurrent biliary obstruction and stent-related complications are shown in Table 2. The overall rate of recurrent biliary obstruction was significantly higher in anticancer treatment group (43 %) compared with BSC group (25 %). Median time to recurrent biliary obstruction in those patients with recurrent obstruction was 126 (range 7–556) days in anticancer treatment group and 125 (range 3–385) days in BSC group ($P = 0.578$). Among recurrent biliary obstruction, the rate of stent migration was significantly higher in the anticancer treatment group (16 vs. 7 %, $P = 0.038$). Median time to stent migration was 84 (range 7–426) days in anticancer treatment group and 116 (range 4–281) days in BSC group ($P = 0.240$). The rate of pancreatitis or cholecystitis was similar between two groups.

### Risk factors for recurrent biliary obstruction

Cumulative time to recurrent biliary obstruction was calculated with two different methods. Median cumulative time to recurrent biliary obstruction by the Kaplan–Meier method was 291 (IQR 250–373) days in anticancer treatment group and 378 (IQR 281 to unknown) days in BSC group ($P = 0.415$ by the log-rank test, Fig. 1). When death without recurrent biliary obstruction was treated as a competing risk, cumulative incidence of recurrent biliary obstruction was significantly higher in anticancer treatment group compared with BSC group ($P = 0.030$ by Gray's test, Fig. 2). Cumulative incidence of recurrent obstruction at 3, 6 and 12 months was 16.1 versus 8.2 %, 27.9 versus

**Table 1** Patient characteristics

| | Anticancer treatment ($n = 173$) | BSC ($n = 106$) | $P$ value |
|---|---|---|---|
| Age (years) | 69 (41–90) | 77 (32–99) | <0.001 |
| Male/female | 106 (61 %)/67 (39 %) | 60 (57 %)/46 (43 %) | 0.454 |
| WHO PS, 0/1/2– | 75 (43 %)/65 (38 %)/33 (19 %) | 17 (16 %)/26 (25 %)/63 (59 %) | <0.001 |
| Primary tumor | | | <0.001 |
| Pancreatic cancer | 138 (80 %) | 59 (56 %) | |
| Bile duct cancer | 18 (10 %) | 22 (21 %) | |
| Gallbladder cancer | 4 (2 %) | 3 (3 %) | |
| Others | 13 (8 %) | 22 (21 %) | |
| Tumor size | 30 (10–115) | 31 (10–70) | 0.334 |
| Stricture length | 20 (5–65) | 20 (8–55) | 0.790 |
| Liver metastasis | 49 (28 %) | 31 (29 %) | 0.892 |
| Ascites | 20 (12 %) | 18 (17 %) | 0.212 |
| Duodenal invasion | 42 (24 %) | 35 (34 %) | 0.099 |
| Stent type, WallFlex/Wallstent | 92 (53 %)/81 (47 %) | 49 (46 %)/57 (54 %) | 0.270 |
| Stent length (40/60/80 mm) | 44 (25 %)/124 (72 %)/5 (3 %) | 27 (25 %)/74 (70 %)/5 (5 %) | 0.745 |
| Distal end, duodenum/bile duct | 168 (97 %)/5 (3 %) | 100 (94 %)/6 (6 %) | 0.342 |

*PS* performance status

The numbers are expressed in either median (range) or $n$ (%)

**Table 2** Recurrent biliary obstruction and complications

| | Anticancer treatment ($n = 173$) | BSC ($n = 106$) | $P$ value |
|---|---|---|---|
| Recurrent biliary obstruction | 74 (43 %) | 26 (25 %) | 0.002 |
| Stent occlusion | 46 (27 %) | 19 (18 %) | 0.109 |
| Biliary sludge | 24 (14 %) | 9 (8 %) | |
| Food impaction | 11 (6 %) | 4 (4 %) | |
| Tumor overgrowth | 7 (4 %) | 6 (6 %) | |
| Hemobilia | 1 (1 %) | 0 | |
| Unknown | 3 (2 %) | 0 | |
| Stent migration | 28 (16 %) | 7 (7 %) | 0.038 |
| Cholecystitis | 15 (9 %) | 8 (8 %) | 0.825 |
| Pancreatitis | 7 (4 %) | 5 (5 %) | 0.770 |

The numbers are expressed in $n$ (%)

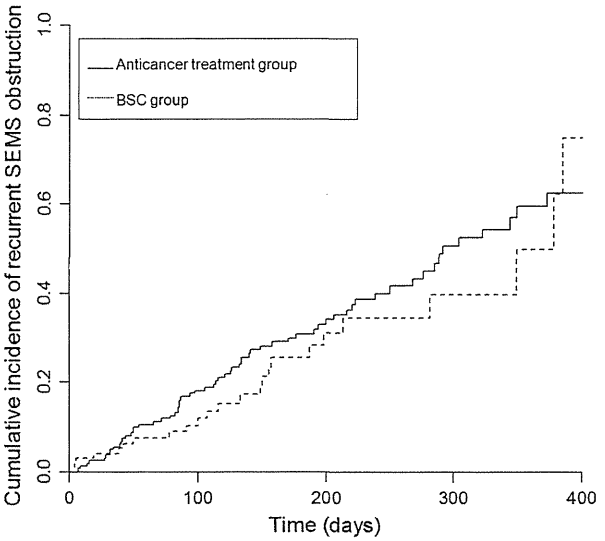


**Fig. 1** Cumulative incidence of recurrent biliary obstruction in anticancer treatment and BSC groups by the Kaplan–Meier method

18.9 % and 44.1 versus 26.6 % in anticancer treatment group versus BSC group.

Cumulative recurrent biliary obstruction in partially covered WallFlex stents and partially covered Wallstents is shown in Fig. 3. Partially covered WallFlex stents showed longer time to recurrent biliary obstruction in a competing risk analysis, which was in line with results of the original analysis using the Kaplan–Meier method [12].

Univariate and multivariate analyses of prognostic factors for recurrent biliary obstruction were performed using a proportional hazard regression model by Fine and Gray [22], treating death without recurrent biliary obstruction as a competing risk (Table 3). The multivariate analysis revealed BSC group as well as the use of a partially covered WallFlex stent as prognostic factors for longer time to recurrent biliary obstructions. The SHRs of anticancer treatment and a partially covered WallFlex stent were 1.93 (95 % CI 1.20–3.10, $P = 0.007$) and 0.65 (95 % CI 0.42–1.00, $P = 0.049$).

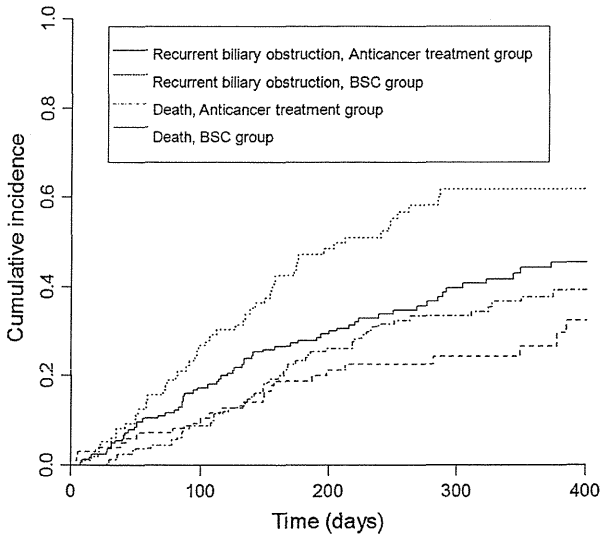


**Fig. 2** Cumulative incidence of recurrent biliary obstruction and death in anticancer treatment and BSC groups, using a competing risk analysis. Death without recurrent obstruction was treated as a competing risk

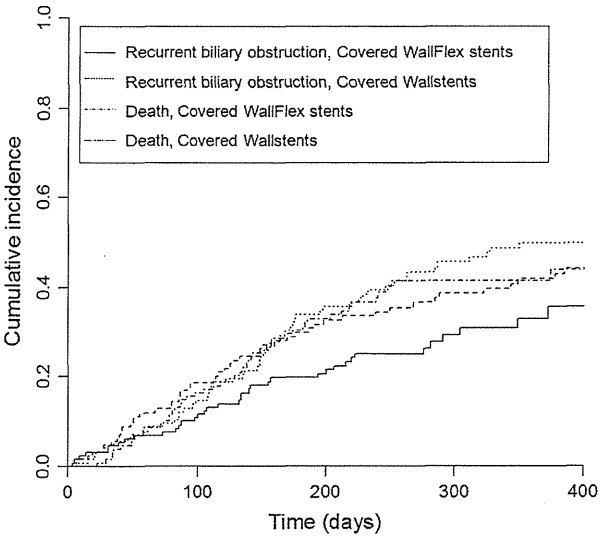


**Fig. 3** Cumulative incidence of recurrent biliary obstruction and death in covered WallFlex stents and covered Wallstents, using a competing risk analysis. Death without recurrent obstruction was treated as a competing risk

## Discussion

In this retrospective analysis of 279 patients with distal malignant biliary obstruction receiving a partially covered WallFlex stent or a partially covered Wallstent enrolled in the WATCH study [12], anticancer treatment was a significant risk factor for recurrent biliary obstruction only when survival difference was accounted for using a competing risk analysis. A partially covered WallFlex stent was proved to be superior to a partially covered Wallstent in this analysis as previously reported [12].

Safety and efficacy of biliary stenting have been reported in patients receiving chemotherapy [17, 18, 25, 26]. The conventional Kaplan–Meier analysis [23] or Cox regression analysis [19] was used and differences in survival were not accounted for in these studies. In these analyses, death without biliary event is usually treated as non-informative censoring, and given the possible overestimation of biliary events in BSC group with poor prognosis using that non-informative censoring, it is possible that the negative impact of anticancer treatment in patients with better survival was relatively underestimated. Therefore, we introduced a competing risk analysis [21, 22] to adjust the differences in survival between two groups. In this analysis, death without recurrent biliary obstruction was considered as a competing risk. In the conventional Kaplan–Meier analysis, anticancer treatment did not appear to affect time to recurrent biliary obstruction, but a competing risk analysis showed anticancer treatment was a significant risk factor for recurrent biliary obstruction both in univariate and multivariate analyses.

The incidences of recurrent biliary obstruction (43 vs. 25 %), especially stent migration (16 vs. 7 %), were significantly higher in the anticancer treatment group, but we can argue that the anticancer treatment group developed biliary events because of their longer survival. However, time to recurrent biliary obstruction or stent migration in patients with recurrent biliary event was similar between anticancer treatment group and BSC group. In addition, the cumulative time to recurrent biliary obstruction was shorter in patients with anticancer treatment, only when death without recurrent obstruction was treated as a competing risk. These results support the hypothesis that anticancer treatment per se, rather than longer survival in the anticancer treatment group, was a risk factor for recurrent biliary obstruction.

There are a few possible causes of shorter cumulative time to recurrent biliary obstruction in patients with anticancer treatment. Chemotherapy is reported to be a risk factor for stent migration of SEMS placement for gastric outlet obstruction [27, 28] due to reduced tumor burden. Similarly, higher migration rate in anticancer treatment group in this study might be caused by local tumor burden reduction, though no data was available about relations between local tumor response and stent migration. Meanwhile, neutropenia induced by anticancer treatment can lead to cholangitis or sludge formation due to bacterial overgrowth. Local tumor control by radiation therapy was reported to prevent tumor ingrowth and to provide longer stent patency in uncovered SEMSs [29], but in this study all patients received covered SEMSs, and tumor ingrowth was successfully prevented by the covering membrane

**Table 3** Univariate and multivariate analyses of risk factors for recurrent biliary obstruction using a proportional hazard model by Fine and Gray [22]

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | SHR (95 % CI) | *P* value | SHR (95 % CI) | *P* value |
| Age ≥70 | 0.88 (0.59–1.32) | 0.542 | | |
| Male | 0.90 (0.60–1.35) | 0.619 | | |
| WHO PS 0 | 0.87 (0.57–1.31) | 0.503 | | |
| Primary tumor, pancreas | 1.00 (0.65–1.54) | 0.990 | | |
| Primary tumor ≥30 mm | 0.73 (049–1.08) | 0.116 | 0.79 (0.52–1.20) | 0.270 |
| Liver metastasis | 0.68 (0.42–1.11) | 0.126 | 0.66 (0.41–1.07) | 0.094 |
| Ascites | 0.40 (0.17–0.94) | 0.036 | 0.49 (0.20–1.17) | 0.110 |
| Duodenal invasion | 0.92 (0.56–1.50) | 0.733 | | |
| Anticancer treatment | 1.79 (1.13–2.86) | 0.014 | 1.93 (1.20–3.10) | 0.007 |
| Stricture length ≥20 mm | 0.87 (0.58–1.31) | 0.508 | | |
| Stent length 8 cm | 1.44 (0.92–2.23) | 0.112 | 1.29 (0.81–2.06) | 0.280 |
| Prior drainage | 0.99 (0.61–1.61) | 0.975 | | |
| Stent end in duodenum | 1.01 (0.41–2.50) | 0.982 | | |
| WallFlex stent | 0.67 (0.45–1.01) | 0.056 | 0.65 (0.42–1.00) | 0.049 |

*SHR* subdistribution hazard ratio, *CI* confidence interval, *PS* performance status

even in patients without anticancer treatment. To draw a more solid conclusion, further studies are needed which focus on local tumor response or neutropenia and recurrent biliary obstruction.

The better outcome of a partially covered WallFlex stent than that of a partially covered Wallstent needs some comments. We reported longer time to recurrent biliary obstruction and less stent migration with a partially covered WallFlex stent because of the low AF profile and antimigration system [12]. The significantly better outcomes of a partially covered WallFlex stent were also confirmed even after the introduction of competing risk analysis. Similar results were obtained in two different analyses because there were no significant differences in survival between patients who received a partially covered WallFlex stent or Wallstent placement.

There are limitations in this study. First, this is a retrospective analysis of previously reported prospective study. There are imbalances between patients with and without anticancer treatment. In addition, various types of cancer were included and pancreatic cancer and bile duct cancer might behave differently in terms of biliary stenting. Though multivariate analyses were performed, it is impossible to avoid bias completely, due to the retrospective nature of our study. However, a prospective study randomizing patients to chemotherapy or BSC is clinically and ethically impossible. Since the survival benefit of anticancer treatment has been established in patients with malignant biliary obstruction, anticancer treatment should be given in eligible patients despite the increased risk of recurrent biliary obstruction. Second, data on adverse events including neutropenia by anticancer treatment were not collected and the influence of neutropenia could not be evaluated. Therefore, the cause of increased recurrent biliary obstruction in patients with anticancer treatment was unclear. There are also possibilities that patients with anticancer treatment had clinical visits with shorter intervals and biliary events might be overdiagnosed.

In conclusion, the use of anticancer treatment was a risk factor for recurrent biliary obstruction in patients with distal malignant biliary obstruction who underwent covered SEMS placement. For better management of malignant biliary obstruction in patients receiving anticancer treatment, further evaluation of subgroups at high risk for recurrent biliary obstruction is necessary. And improvement of covered SEMSs such as antimigration system is also essential, given the high rate of stent migration in anticancer treatment group.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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RESEARCH Open Access

# Phase I/II clinical trial using HLA-A24-restricted peptide vaccine derived from KIF20A for patients with advanced pancreatic cancer

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## Abstract

**Background:** We previously developed an immunotherapy treatment utilizing a cancer vaccine reagent KIF20A-66 in order to treat pancreatic cancer. KIF20A-66 is HLA-A24-restricted epitope peptide derived from KIF20A, a member of kinesin super family protein 20A that is significantly transactivated in pancreatic cancer. In this report, we further demonstrated non-randomized, open-label, single centered phase I/II clinical trial of immunotherapy using the KIF20A-66 peptide for the patients with advanced pancreatic cancer.

**Methods:** Vaccination was performed to the patients with metastatic pancreatic cancer, in whom gemcitabine-based therapy had failed. In phase I study, KIF20A-66 peptide was subcutaneously injected weekly in a dose-escalation manner (doses of 1.0 and 3.0 mg/body, 6 patients/1 cohort). After safety was assessed, phase II study was conducted using 3.0 mg of KIF20A-66 peptide.

**Results:** KIF20A-66 peptide vaccination was well tolerated in the doses we examined and tumor responses after 1 month of the treatment were evaluated. Among 29 patients who completed one course of the treatment at least, stable disease (SD) was found in 21 cases, while progressive disease (PD) was found in 8 cases, indicating that the disease control rate was 72%. Objective tumor shrinkage was observed in 8 cases, including 1 case of complete response (CR). The median survival time (MST) and progression free survival time (PFS) were 142 days and 56 days, respectively. These results clearly demonstrate that overall survival of the patients was significantly prolonged, compared to the historical controls of 9 cases with unmatched HLA in the same hospital (MST: 83 days), as well as 81 cases in our and other hospitals (MST: 63 days).

**Conclusion:** The patients vaccinated with KIF20A-66 peptide had better prognosis than the control group with best supportive care (BSC). Thus, we concluded that KIF20A-66 vaccination is significantly effective as an immunotherapy against advanced pancreatic cancer. KIF20A-66 peptide was well tolerable in the dose of either 1.0 mg or 3.0 mg/body, and effectively induced peptide-specific response of cytotoxic T lymphocyte (CTL). Further clinical study using this peptide is a promising approach for advanced pancreatic cancer to achieve high potential benefit for better prognosis.

**Clinical trial registration:** UMIN-CTR, number UMIN000004919

**Keywords:** KIF20A, Peptide vaccine, Pancreatic cancer

## Introduction

Pancreatic cancer remains one of the most challenging conditions to treat, due to extremely poor prognosis with the overall five-year survival of less than 10% [1-3]. During the last decades, gemcitabine has been the standard single-agent chemotherapy for unresectable pancreatic cancer [4,5]. Regarding combination chemotherapy, several phase III trials of gemcitabine-based multi-drug regimens have been attempted, whereas significant improvement in survival has not been observed [6-14]. Although TS-1, a prodrug of 5-FU, has been employed as a major alternative approach in a variety of solid tumors, the single-agent treatment of TS-1 yielded non-inferiority result against the gemcitabine treatment [15]. After all, once pancreatic cancer became

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refractory to gemcitabine, there is virtually no effective treatment for the patients. Hence, novel strategy providing better survival benefit is urgently required, in particular, for the patients with advanced pancreatic cancer.

Cancer immunotherapy is a promising approach to fight against cancer, and thus we have conducted research and development of peptide vaccines targeting tumor-specific antigens [16-19]. Briefly, we identified dozens of cancer-testis or oncofetal proteins from more than 1,000 clinical cancer tissues using cDNA microarray including 32,000 genes or ESTs [20]. Utilizing the result of this genome-wide expression profile analysis, we tried to establish an epitope peptide derived from the tumor-associated antigen mentioned above, which is applicable for cancer peptide vaccination [21,22]. KIF20A, kinesin family member 20A, is one of the candidates of such target antigen, as it was up-regulated in the majority of pancreatic cancer [23]. Therefore, we developed an epitope peptide, namely KIF20A-66, restricted to HLA-A*2402 that is the most common HLA-A allele in a Japanese population [24]. We here report the results of a phase I/II clinical trial using KIF20A-66 mono peptide as cancer immunotherapy for the patients with advanced pancreatic cancer.

## Methods

### Patient eligibility

Patients with unresectable or metastatic pancreatic cancer, who were resistant to gemcitabine and TS-1 treatments or unable to continue the treatment of gemcitabine or TS-1 because of severe adverse events, were enrolled in this trial from March 2009 to February 2010 at Chiba Tokushukai Hospital. The eligibility criteria are as follows: unresectable pancreatic cancer with metastatic, recurrent and/or locally advanced disease based on diagnostic imaging using computed tomography (CT) and histological examinations. Other entry criteria included the HLA-A*2402-positive status, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, age of 20–85 years, life expectancy of at least 2 months, adequate respiratory, and liver and kidney functions for vaccination treatment. The exclusion criteria are as follows: pregnancy or lactation, active infection, other active malignancy, non-recovered injury, and treatment with immunosuppressive agents or steroid. Written informed consent was obtained from each individual patient, and the study was approved by Tokushukai Group Ethical Committee. The study was registered at University Hospital Medical Information Network (UMIN) Center with the Clinical Trial Registration number UMIN000004919.

### Control group

Clinical data used as the control group (BSC, multi-center, n = 81) in this study were obtained from our and other hospitals where written informed consent was obtained at each institution. Clinical information of each patient utilized in our statistical analysis includes age at diagnosis, sex, performance status at the endpoint of the Standard Chemotherapy, treatment status at primary lesion, median survival time, and mean survival time. This study was approved by the institutional review board at each institution.

### Study design and end points

This study is a non-randomized, open-label phase I/II clinical trial with dose escalation of KIF20A-66 peptide mono-therapy. The primary end point of phase I part was safety of peptide vaccination and tolerance for phase II part. The primary end point of phase II part was antitumor effects assessed by CT scan in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1. The secondary end points were overall survival (OS), progression free survival (PFS), immunological responses assessed by CTL induction specific to the KIF20A-66 peptide and the injection site reactions (ISRs). In phase II part, the information of 9 patients with best supportive care in the Chiba Tokushukai Hospital from January 2007 to January 2009 was used as a historical control.

### Treatment protocol

After emulsified with Incomplete Freund's adjuvant (Montanide ISA51VG, SEPPIC, France), KIF20A-66 peptide in the amount of 1.0 or 3.0 mg/body was subcutaneously administered on days 1, 8, 15 and 22 in a 28 days-treatment cycle. After two cycles of the vaccination, the peptide was administrated once in every two weeks until tumor progression was observed in the patient.

### Toxicity assessment

The toxicity was assessed based on the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0).

### Peptides

The KIF20A-66 peptide (KVYLRVRPLL) was synthesized and its quality was analyzed by American Peptide Company Inc. (Sunnyvale, CA). The epitope peptide derived from HIV-Env peptide (RYLRDQQLL), restricted to HLA-A*2402, was used as a control to evaluate CTL response.

### Enzyme-linked immunospot (ELISPOT) assay

To evaluate the peptide-specific CTL response, ELISPOT assay was performed after *in vitro* sensitization [16]. Briefly, frozen Peripheral Blood Mononuclear Cells (PBMC) derived from the same patient were thawed, cultured with respective peptide and IL-2 (Novartis, Emeryville, CA) (IVS), and harvested after two weeks. Followed by