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ORIGINAL ARTICLE

Isolated Roux-en-Y anastomosis of the pancreatic stump in a duct-to-mucosa fashion in patients with distal pancreatectomy with en-bloc celiac axis resection

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Abstract
Background A pancreatic fistula is one of the most serious complications in distal pancreatectomy with *en bloc* celiac axis resection (DP-CAR), because the pancreatic transection is performed on the right side of the portal vein, which results in a large cross-section surface, and because post-pancreatectomy hemorrhage is hard to treat by interventional radiology. Therefore, a procedure to decrease the incidence of postoperative pancreatic fistula is urgently needed.
Methods Twenty-six consecutive patients who underwent DP-CAR between April 2008 and August 2012 were reviewed retrospectively. The first 13 consecutive patients underwent DP-CAR with no anastomosis, and the subsequent 13 consecutive patients were treated with Roux-en-Y pancreaticojejunostomy (PJ) in a duct-to-mucosa fashion.
Results Extremely high amylase levels (>4000 IU/l) of all drainage fluid specimens on postoperative day (POD) 1, 3 and 4 were detected more frequently in cases with no anastomosis ($n = 7$) compared to those with PJ ($n = 1$) ($P = 0.056$).
Conclusion The incidence of grade B/C pancreatic fistulas was 15.4% in cases with isolated Roux-en-Y anastomosis of the pancreatic stump performed in a duct-to-mucosa fashion, and we are currently examining whether this anastomosis method reduces the pancreatic fistula rate in a multicenter, randomized controlled trial for distal pancreatectomy patients (ClinicalTrials.gov NCT01384617).

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Keywords Distal pancreatectomy · Duct-to-mucosa anastomosis · Pancreatic fistula · Pancreaticojejunostomy

Introduction

The overall incidence of pancreatic fistula [1, 2] in patients undergoing distal pancreatectomy is 10% to 30% in the literature [3–5]. Recently, distal pancreatectomy with *en bloc* celiac axis resection (DP-CAR) has been performed to improve survival by achieving an R0 resection in patients with advanced pancreatic body/tail carcinoma [6]. Pancreatic fistulas sometimes cause an intra-abdominal hemorrhage [7], and can become a directly fatal complication, because transarterial embolization via pancreaticoduodenal arcade is difficult to perform by interventional radiology (IVR) in patients who have undergone DP-CAR. Therefore, a procedure that decreases the incidence of postoperative pancreatic fistulas is urgently needed for distal pancreatectomy including DP-CAR. Moreover, the tumors indicated for DP-CAR often require the pancreatic transection to be performed on the right side of the portal vein. However, it is technically difficult to transect the pancreas using a stapler device on the right side of the portal vein, further complicating the procedure and increasing the risk.

A large number of investigations have been performed to avoid fistula formation, such as hand-sewn suturing of the cut end, stapler closure [3, 5, 8, 9], pancreaticoenteric anastomosis [3, 10], seromuscular patches [11–13], fibrin glue sealing [14, 15] and mesh reinforcement [16]. In a randomized controlled trial (DISPACT), the stapler closure after distal pancreatectomy did not decrease the incidence of pancreatic fistula compared to hand-sewn suturing [5]. The appropriate management of the pancreatic stump following distal pancreatectomy remains controversial. Among the various studies of the management of the pancreatic stump, the most attractive results with a low incidence of pancreatic fistula were reported for pancreaticoenteric anastomosis [3, 10]. We hypothesized that pancreaticojejunostomy (PJ) performed in a duct-to-mucosa fashion would provide a favorable outcome by decreasing the back pressure not only in the main pancreatic duct, but also in the branch ducts. We selected the jejunum to anastomose to the pancreatic stump because it is easy to manipulate.

In this study, 13 consecutive patients with pancreatic body/tail carcinoma prospectively underwent DP-CAR with PJ. The collected data were compared to those of the previous 13 consecutive patients who underwent DP-CAR with no anastomosis.

Patients and methods

Patients

We prospectively assigned the 26 consecutive patients between April 2008 and August 2012 into two groups based on the time period of the treatment to assess the effect of pancreaticojejunostomy (PJ) at the pancreatic stump; 13 patients with no anastomosis (until February 2011) and 13 patients with Roux-en-Y PJ performed in a duct-to-mucosa fashion (after February 2011) who expected to undergo DP-CAR for pancreatic body/tail carcinoma at Wakayama Medical University Hospital (WMUH) were included. During the period between May 2010 and December 2011, the patients with borderline resectable [17] pancreatic body/tail carcinoma were planned to receive S-1 standard-dose chemotherapy for 9 weeks and multi-field radiotherapy focused on retropancreatic tissue for a total of 50 Gy over a 5-week period. After 3 weeks of rest for both therapies, the patients without progression of disease and new distant metastasis underwent DP-CAR. We reviewed the postoperative clinical data registered prospectively for 26 patients who underwent DP-CAR with no anastomosis (n = 13) and who underwent Roux-en-Y PJ in a duct-to-mucosa fashion (n = 13).

Surgical procedures and postoperative management

The procedure used for DP-CAR was similar in the 26 patients, and was reported previously [6]. In the no anastomosis group, the pancreatic parenchyma was resected by bipolar scissors (Ethicon Endo-Surgery, Cincinnati, OH, USA) (n = 6), an ultrasonic dissector (HARMONIC FOCUS (r) (Ethicon Endo-Surgery, LLC, Guaynabo, Puerto Rico)) with main pancreatic duct ligation (n = 1), or with a stapler device (Echelon 60 with a gold cartridge (compressible thickness to 1.8 mm; Ethicon Endo-Surgery) (n = 6), according to the status of the pancreatic transection site.

In the PJ group, the pancreatic parenchyma was resected using an ultrasonic dissector (n = 13) and the main pancreatic duct was resected using a scalpel to avoid the sealing of the main pancreatic duct. After achievement of distal pancreatectomy with *en bloc* celiac axis resection, a pancreaticojejunostomy end-to-side anastomosis by a Roux-en-Y limb was carried out in a retrocolic route with a length of at least 30 cm [10, 18]. The anastomosis was performed in a non-stented duct-to-mucosa fashion using a single layer of interrupted 5-0 PDS stitches (Ethicon Endo-Surgery). A seromuscular-parenchymal anastomosis was placed in one or two [18] layers according to the thickness of the pancreas on both sides of the transaction line to the jejunum to cover the cut end of the pancreas using interrupted 4-0 VASCUFIL stitches (Covidien, Mansfield, MA, USA). A tube stent was not inserted for the duct-to-mucosa anastomosis to avoid having it migrate into the duodenal side. A drain (BLAKE Silicone Drains 24Fr) was placed via the pancreatic stump terminating in the left infraphrenic space. No patients received prophylactic subcutaneous octreotide. All patients received postoperative epidural anesthesia.

Data collection

The peritoneal drainage volume was registered daily, and the amylase level in the drainage fluid was measured and recorded on postoperative day (POD) 1, 3, and 4. The drain tube was usually removed on POD 4. The patient characteristics, duration of hospital stay, incidence of pancreatic fistula and perioperative morbidity were recorded prospectively. A pancreatic fistula was defined by the International Study Group of Pancreatic Fistula (ISGPF) guidelines as: any measurable output on or after POD 3 from an operatively positioned drain displaying pancreatic amylase more than three times the upper serum reference value, and was graded according to the previously proposed definition [1, 2]. Delayed gastric emptying (DGE) was defined according to a consensus definition and clinical grading of postoperative DGE proposed by the International Study Group of Pancreatic Surgery (ISGPS) [19]. The patients were discharged only when they fulfilled the criteria as follows: were able to return to preoperative activities of daily living, had no deep-site infections, normal laboratory data, no drains and were able to take in oral nutrition above the basal metabolic requirement.

Statistical analysis

The data are expressed as medians. Statistical comparisons between two groups were made using the χ^2 statistic, Fisher's exact test or the Mann–Whitney U-test, as appropriate. A value of $P < 0.05$ was considered to indicate statistical significance. All the analyses were performed using the statistical software package, SPSS II (version 20.0; SPSS, Chicago, IL, USA).

Results

Patient characteristics and surgical outcomes

Table 1 shows the characteristics of the 26 consecutive patients with pancreatic body/tail cancer. These patients included 18 cases of invasive ductal carcinoma, five of invasive ductal carcinoma derived from intraductal papillary mucinous neoplasm, one acinar cell carcinoma, one anaplastic carcinoma, and one mucinous carcinoma. Combined resections of the portal vein were performed in four patients. The remnant pancreatic parenchyma was soft in 20 patients (76.9%). The median length of the operation for DP-CAR with PJ was 382 min (range, 267–513 min) compared to 366 min (range, 136–846 min) for DP-CAR with no anastomosis ($P = 0.840$). In the PJ group, a seromuscular-parenchymal anastomosis was placed in one layer in eight patients, and two layers in five patients, according to the thickness of the pancreas.

Postoperative complications

Table 2 shows the surgical results and postoperative complications recorded in this study. A clinically significant pancreatic fistula (ISGPF classification Grade B/C) occurred in two patients (15.4%) with PJ and five patients (38.5%) with no anastomosis ($P = 0.189$). There were no significant differences in the incidence of each complication (Table 2). A death associated with surgery was present in each group; an acute myocardial infarction occurred 10 days postoperatively in one patient in the PJ group, and intra-abdominal hemorrhage occurred 28 days postoperatively in

Table 1 Patient characteristics and outcomes of surgery

Parameters	No anastomosis ($n = 13$)	With pancreaticojejunostomy ($n = 13$)	P-value
Age at surgery	63	68	0.695
Gender			
Male	10	7	0.411
Female	3	6	
NACRT	4	10	0.047[a]
Portal vein resection	1	3	0.593
Histopathology			
IDC	6	12	
Invasive ductal carcinoma derived from IPMN	5	0	
Acinar cell carcinoma	1	1	
Anaplastic carcinoma	0	0	
Mucinous carcinoma	1	0	
Hardness of the pancreas			
Soft	9	11	0.645
Hard	4	2	
Transect position			
Midline of the portal vein	6	7	0.999
Right side of the portal vein	7	6	
Thickness of the pancreas at the transection position (mm)	12.3 ± 1.7	10.9 ± 2.7	0.113
Length of operation (min)	366 (136–846)	382 (267–513)	0.840
EBL (ml)	1,860 (280–9,900)	460 (30–1,250)	0.006[a]
Hospital days after surgery	24 (10–51)	21 (11–192)	0.724

EBL estimated blood loss, *IDC* invasive ductal carcinoma of the pancreas, *IPMN* intraductal papillary-mucinous neoplasm, *n* number of cases, *NACRT* neoadjuvant chemoradiation therapy

All results are shown as medians (range)

[a] $P < 0.05$

Table 2 Postoperative complications and postoperative outcomes

Postoperative complications	No anastomosis (n = 13)	With pancreaticojejunostomy (n = 13)	P-value
Pancreatic fistula[a]			
Grade A	0	1 (7.7%)	0.999
Grade B	4 (30.8%)	1 (7.7%)	0.322
Grade C	1 (7.7%)	1 (7.7%)	0.999
Grade B/C	5 (38.5%)	2 (15.4%)	0.185
Delayed gastric emptying[b]			
Grade A	3 (23.1%)	1 (7.7%)	0.593
Grade B	0	1 (7.7%)	0.999
Grade C	1 (7.7%)	1 (7.7%)	0.999
Necrosis of the gallbladder	0	1 (7.7%)	0.999
Gastroduodenal perforation	2 (15.4%)	0	0.480
Surgical site infection			
Wound infection	1 (7.7%)	0	0.999
Intra-abdominal abscess	3 (23.1%)	1 (7.7%)	0.593
Intra-abdominal hemorrhage[c]			
Grade A	0	0	
Grade B	0	0	
Grade C	3 (23.1%)	3 (23.1%)	0.999
Pulmonary complications	0	0	
Cardiac complications[d]	0	1 (7.7%)	0.999
Percutaneous drainage	2 (15.4%)	3 (23.1%)	0.999
Reoperation	3 (23.1%)	1 (7.7%)	0.593
Mortality	1 (7.7%)	1 (7.7%)	0.999

n number of cases

[a,b,c] Pancreatic fistula, delayed gastric emptying, and intra-abdominal hemorrhage were defined according to the International Study Group of Pancreatic Surgeons

[d] A patient died from an acute myocardial infarction

one patient in the no anastomosis group. An ischemic cholecystitis presumably from temporary decreased flow of the proper hepatic artery occurred 7 days postoperatively in one patient after DP-CAR. This complication was treated successfully by cholecystectomy. The patients combined with grade C pancreatic fistula after this operation and it takes a longer period (192 days) to heal (Table 1). Otherwise, there were no significant differences in regard to the mortality and morbidity rates between the groups.

The amylase level in the drainage fluid

Extremely high amylase levels (>4000 IU/l) of all drainage fluid specimens on POD 1, 3 and 4 were detected more frequently in cases with no anastomosis (n = 7, 17.9%) compared to those with PJ (n = 1, 2.6%) (P = 0.056) (Fig. 1). The median amylase level in the drainage fluid of patients with PJ/no anastomosis were 315/589 (IU/l) on POD 1, 121/286 (IU/l) on POD 3 and 52/247 on POD 4, respectively.

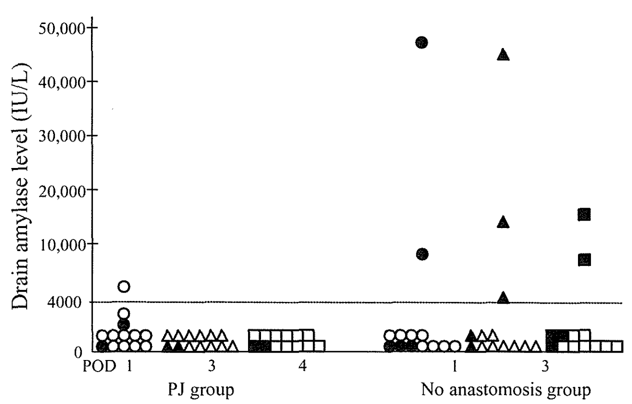

Fig. 1 Extremely high amylase levels (>4000 IU/l) of all drainage fluid specimens on postoperative day (POD) 1, 3 and 4 were detected more frequently in cases with no anastomosis (n = 7, 17.9%) compared to those with pancreaticojejunostomy (n = 1, 2.6%) (P = 0.056). The black dots represent the amylase levels (IU/l) of patients with grade B/C pancreatic fistulas, and white dots represent those of patients with no pancreatic fistula or a grade A pancreatic fistula (circular dot: postoperative day 1, triangular dot: postoperative day 3, tetragonal dot: postoperative day 4). PJ: pancreaticojejunostomy

Discussion

The presence of postoperative hemorrhage from the resected stump of the common hepatic artery due to a pancreatic fistula after DP-CAR is difficult to rescue by IVR techniques because of the resection of the common hepatic artery. Therefore, a novel procedure to reduce the risk of pancreatic fistula formation is urgently needed for DP-CAR, in which the pancreatic transection with a large cross-section surface is usually located on the right side of the portal vein.

The most appropriate treatment of the stump closure following DP remains controversial. A recent randomized controlled trial revealed that stapler closure did not reduce the rate of pancreatic fistula formation compared to hand-sewn closure for standard distal pancreatectomy. Two reasons for the formation of a pancreatic fistula after DP are the development of increased back pressure in the main pancreatic duct [20] and the autolysis of the pancreatic stump [11–13]. Some investigators have reported favorable outcomes with regard to pancreatic fistula by pancreaticoenterostomy [3, 10]. It has been reported that covering the stapled pancreatic remnants with a seromuscular patch can decrease the overall pancreas-related complications, such as fistula formation [11]. On the other hand, prophylactic transpapillary pancreatic stenting did not reduce clinically significant pancreatic fistula formation in a recent randomized controlled trial of distal pancreatectomy [21]. Therefore, in this study, we performed the pancreaticoenterostomy and included a duct-to-mucosa anastomosis to decrease the incidence of pancreatic fistula by decreasing the back pressure of the pancreatic duct and creating a tight seal around the pancreatic stump.

Several studies have reported that a high amylase level in drainage fluid was a predictive risk factor for a pancreatic fistula [22]. In this study, extremely high amylase levels (>4000 IU/l) [22] of all drainage fluid specimens were detected more frequently in cases with no anastomosis compared to those with PJ. The degree of autolysis for the tissues, such as arteries around the pancreatic stump, would be correlated to the amylase level. Therefore, the lower amylase levels of the PJ group in this study suggested that the procedure may have decreased the incidence of clinically significant pancreatic fistulas after DP-CAR. A randomized controlled trial should be performed for patients with distal pancreatectomy to determine the optimal procedure for the pancreatic stump.

We should take an extra caution with the complication of the intestinal side compared to simple closure of the pancreatic stump. However, there were no differences of clinical course in patients with Grade C pancreatic fistula compared to simple closure of pancreatic stump. The patients were able to continue oral intake even in the period with clinically relevant pancreatic fistula because of isolated Roux-en Y anastomosis. With regard to other specific complications, the additional procedure, including jejuno-jejunostomy or closure of the mesentery, did not cause paralytic ileus or small bowel obstruction in the early/later postoperative period so far in this series. A longer-term follow-up will be needed to confirm that this procedure does not result in additional complications.

In conclusion, the greatest advantage of isolated Roux-en-Y anastomosis of the pancreatic stump in a duct-to-mucosa fashion is to suppress the leakage with extremely high amylase level, which could reduce the incidence of clinically significant pancreatic fistula after DP-CAR. However, the groups are not comparable in the use of neoadjuvant chemoradiation and the way of pancreatic transection. Therefore, a valid conclusion could be obtained if we experienced a greater number of patients. We are proceeding to examine whether this anastomosis method reduces the pancreatic fistula formation in a multicenter, randomized controlled trial for distal pancreatectomy patients (ClinicalTrials.gov NCT01384617).

Conflict of interest None declared.

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

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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 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 χ^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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Clinical Science

Preoperative cholangitis during biliary drainage increases the incidence of postoperative severe complications after pancreaticoduodenectomy

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KEYWORDS:
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Delayed gastric emptying;
Wound infection

Abstract

BACKGROUND: It remains controversial how preoperative biliary drainage affects occurrence of severe complications after pancreaticoduodenectomy (PD).

METHODS: One hundred twenty-seven patients (60 external drainage and 67 internal drainage) required biliary drainage before PD were retrospectively reviewed.

RESULTS: Preoperative cholangitis in internal drainage group (22.4%) occurred significantly more often than in external drainage group (1.7%; $P < .001$). The incidence of severe complications (grade III or more) was significantly higher in patients with cholangitis (62.5%) than in those without it (25.2%; $P = .002$). The incidence of delayed gastric emptying was significantly higher in patients with cholangitis (31.2%) than in those without it (5.4%; $P = .001$). A multivariate logistic regression analysis revealed that preoperative cholangitis (odds ratio 4.61, 95% confidence interval 1.3 to 16.5; $P = .019$) was the independent risk factor for severe complications after PD.

CONCLUSIONS: Preoperative cholangitis during biliary drainage significantly increases incidence of severe complications after PD.

Previous retrospective studies have reported benefits of preoperative biliary drainage.[1,2] In contrast, some retrospective studies have reported that preoperative biliary drainage increased the risk for morbidity or mortality.[3–5] A recent randomized controlled trial reported that routine preoperative biliary drainage for patients with pancreaticoduodenectomy (PD) increased the incidence of all complications including cholangitis, stent dysfunction, and the need for repeated stent exchange.[6] One of the major problems is that preoperative biliary drainage may lead to biliary drainage–related complications such as cholangitis, pancreatitis, hemorrhage, or perforation. Moreover, biliary drainage–related complications may introduce postoperative complications. However, it remains unclear what factors in preoperative biliary drainage affect the occurrence of postoperative complications after PD. Moreover, biliary

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drainage–related complications may introduce postoperative complications.

Obstructive jaundice may be related to hepatic dysfunction, disturbances in coagulation, and the development of cholangitis. Kimmings et al[1] reported that preoperative biliary decompression improves nutritional metabolic and immune function and reduces postoperative complications after PD. Therefore, preoperative biliary drainage may still be required to improve obstructive jaundice, when patients who plan to receive neoadjuvant chemotherapy or chemoradiation therapy have this condition. Therefore, it is important to evaluate how to manage biliary drainage. Another issue in preoperative biliary drainage is which approach to use, internal or external drainage. However, it remains controversial which is the most appropriate approach for preoperative biliary drainage.[7]

The aim of this study was to clarify how biliary drainage–related complications affect postoperative complications after PD and to evaluate the appropriate approach for preoperative biliary drainage after PD by comparing internal and external biliary drainage.

Methods

Patients

Between April 2005 and December 2010, 292 patients underwent PD for periampullary tumors and pancreatic tumors at Wakayama Medical University Hospital. Of these, 127 patients with PD had preoperative biliary drainage for obstructive jaundice or hepatic dysfunction (transaminase >100 IU/mL). We retrospectively reviewed a prospectively maintained database to assess patient demographics, type of preoperative biliary drainage, operative details, perioperative complications, and pathology in the 127 patients with preoperative biliary drainage.

Type of preoperative biliary drainage

A jaundiced patient was defined as patients with symptoms such as cholangitis, serum bilirubin level greater than 5.0 mg/dL, or hepatic dysfunction (transaminase > 100 IU/mL) for tumor-causing obstructive jaundice. When gastroenterologist or surgeon diagnosed the jaundiced patients who required PD, the patients underwent preoperative biliary drainage by percutaneous transhepatic biliary drainage (PTBD), endoscopic nasobiliary drainage (ENBD), or endoscopic retrograde biliary drainage (ERBD) in Japan. Approach for biliary drainage was chosen by the gastroenterologist or surgeon. Because Japanese guideline for preoperative biliary drainage proposed that a method for preoperative biliary drainage should be used that can be safely performed with the equipment and techniques available at each facility for clinical question concerning to appropriate procedures for preoperative biliary drainage.[8] PTBD and ENBD were performed as the types of external drainage, and ERBD was performed as the internal drainage. Plastic stents were used for ERBD. PTBD and ENBD were performed as the types of external drainage, and ERBD was performed as the internal drainage. In the procedure of PTBD, the intrahepatic bile duct was punctured using a hollow needle under ultrasound guidance. A guidewire was inserted into the elastic needle after backflow of bile was confirmed. A 7-French PTBD tube was then passed over the guidewire. The procedure of ENBD was performed using endoscopic retrograde cholangiopancreatography (ERCP) with a conventional side-viewing duodenoscope in a standard manner. A guidewire was passed through the catheter into the bile duct, after an endoscopic catheter was cannulated into the bile duct. The catheter is withdrawn, and a 7-French ENBD tube is passed along the guidewire. The endoscope is then removed while applying pushing pressure on the ENBD tube to keep it in place. Afterward, the tube that exits orally was pulled back out nasally. The procedure of ERBD was performed using ERCP. "Pigtail-type" plastic stent was used as ERBD tube.

Jaundiced patients were given 2 g cefazolin intravenously 30 minutes before biliary drainage. When cholangitis occurred during biliary drainage, levofloxacin, 500 mg/d, was intravenously administrated until fever came down. An additional drainage was performed or a new stent exchange was performed if signs of inadequate bile drainage developed, whether cholangitis or not.

Surgical procedure

All patients underwent PD, pylorus-preserving pancreaticoduodenectomy (PpPD), or pylorus-resecting pancreaticoduodenectomy (PrPD).[9] In PD, 30% to 40% distal gastrectomy was performed. On the other hand, in PrPD, the stomach is divided just adjacent the pylorus ring. Therefore, the nearly total stomach more than 95% was preserved, although the pylorus ring was resected in PrPD. In PpPD, the proximal duodenum was divided 3 to 4 cm distal to the pylorus ring; 20-mm occluding atraumatic bulldog clamp was positioned across the transected common hepatic duct to minimize intraperitoneal contamination of bile until the start of an end-to-side hepaticojejunostomy. All patients underwent PD with the reconstruction, and pancreaticojejunostomy after PD, PpPD, and PrPD were performed by duct-to-mucosa, end-to-side pancreaticojejunostomy in all patients. A 5-Fr polyethylene pancreatic duct drainage tube (Sumitomo Bakelite Co., Tokyo, Japan) was usually used as a stent for pancreaticojejunostomy in all patients except those with a dilated duct size greater than 5 mm. Then an end-to-side hepaticojejunostomy was performed by 1-layer anastomosis (5-0PDS-II) 10 to 15 cm distal to the pancreaticojejunostomy. No stent was used for the biliary anastomosis. Duodenojejunostomy in PpPD or gastrojejunostomy in PD or PrPD was performed by 2-layer anastomosis (4-0PDS-II

Table 1 Demographics of 127 patients with preoperative biliary drainage

	Number of patients (%)
Indication for biliary drainage	
Obstructive jaundice	120 (94.4)
Hepatic dysfunction (transaminase > 100 IU/mL)	7 (5.6)
Type of preoperative biliary drainage	
PTBD	50 (39.3)
ENBD	10 (7.9)
ERBD	67 (52.8)
Internal/external drainage*	60 (47.2)/67 (52.8)
Preoperative biliary instrumentation	
ERCP with biliary drainage	77 (60.6)
Primary PTBD	43 (33.8)
PTBD after failed ERCP	7 (5.6)
Number of procedures per patient	
1 procedure	110 (86.6)
2 procedures	17 (13.4)
Biliary drainage-related complications	18 (14.1)
Cholangitis	16 (12.6)
Cholangitis because of stent occlusion	10 (7.8)
Pancreatitis	2 (1.6)

ENBD = endoscopic nasobiliary drainage; ERBD = endoscopic retrograde biliary drainage; PTBD = percutaneous transhepatic biliary drainage.
*Internal drainage was defined as ERBD. External drainage was defined as PTBD or ERBD.

and 3-0 silk) via an antecolic route.[10] One drain was routinely placed anterior to the pancreaticojejunostomy.

Postoperative management

Flomoxef (1 g) as prophylactic antibiotics was administrated before skin incision. Afterward, antibiotics were administrated every 3 hours during the operative procedure. The duration for prophylactic antibiotics was 2 days postoperatively in accordance with the guideline of the Japan Society of Surgical Infection. A nasogastric tube was inserted before surgery and removed from all patients on postoperative day 1. Oral intake was routinely started 3 or 4 days after surgery. If bile leakage and bacterial contamination were absent, this drain was removed on postoperative day 4 in all enrolled patients.[11] All patients received an intravenous H2 blocker (famotidine; Astellas Pharma, Inc., Tokyo, Japan) for 2 weeks postoperatively. Prophylactic octreotide or prokinetic agents, such as erythromycin, were not administered postoperatively. Adjuvant chemotherapy was provided to patients with periampullary carcinoma or pancreatic carcinoma by the regimen in accordance with our protocol based on gemcitabine, S-1, or the others, unless contraindicated by a patient's condition.

Preoperative and postoperative complications

Preoperative cholangitis was defined by the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines 2013.[12] Acute pancreatitis is defined as follows: abdominal pain and a serum concentration of pancreatic enzymes (amylase or lipase) 2 or more times the upper limit of normal that required more than 1 night of hospitalization. Stent occlusion is diagnosed in the case of recurring obstructive jaundice with necessary stent replacement.

Infectious complications were defined as any complication with evidence of associated localized or systemic infection indicated by fever and leukocytosis and confirmed by imaging and/or positive culture. Moreover, any positive cultures, such as positive wound cultures, drain cultures, or blood cultures, required drainage or administration of antibiotics different from those received at the time of surgery. The diagnosis of pancreatic fistula was determined by the International Study Group on Pancreatic Fistula guideline.[13] Delayed gastric emptying (DGE) was defined according to a consensus definition and clinical grading of postoperative DGE proposed by the International Study Group of Pancreatic Surgery (ISGPS).[14] DGE was then classified into 3 categories (grade A, B, or C) by the ISGPS clinical criteria based on the clinical course and postoperative management. Postoperative complications, such as intra-abdominal abscess, intra-abdominal hemorrhage, bile leakage, wound infection, and sepsis in this study, were classified based on the Clavien classification.[15] Severe complications were defined in this study as a condition that was grade III or more based on the Clavien classification. Mortality was defined as death within 30 days after surgery.

Statistical analysis

Data are expressed as mean ± SD or median (range). Patient characteristics and perioperative and postoperative factors between 2 groups were compared using chi-square statistics, Fisher exact test, and Mann–Whitney U test. Variables with P less than .1 were entered into a logistic regression model to determine the independent risk factors of postoperative complications. The independent risk factors of the variables were expressed as odds ratios with their 95% confidence intervals. Statistical significance was defined as P less than .05. All statistical analyses were performed with SPSS software, version 20 (SPSS, Chicago, IL).

Results

Patient characteristics

Table 1 shows demographics of 127 patients with preoperative biliary drainage. In the 127 patients with preoperative biliary drainage, external drainage was performed in 60 patients (PTBD in 50 cases and ENBD in 10 cases) and internal drainage (ERBD) was performed in 67 patients. Drainage was successfully established in all patients who underwent preoperative biliary drainage, although 17 patients (13.4%) had 2 procedures of biliary drainage for PTBD after failed ERCP or plastic stent occlusion. Biliary drainage–related complications occurred in 18 patients (14.1%). Cholangitis occurred in 16 patients (12.6%). In 10 of 16 patients (7.8%) with cholangitis, stent occlusion resulting in stent replacement occurred. There was no biliary drainage–related death.

Table 2 compares the patient characteristics, preoperative status, and perioperative status between the external drainage and internal drainage groups. Total bilirubin before biliary drainage between the 2 groups was similar (8.3 ± 5.7 mg/dL in external drainage group vs 7.5 ± 5.8 mg/dL in internal drainage group). Moreover, there was no significant difference in the waiting periods for operation from drainage between the 2 groups (20 ± 11 days in external drainage group vs 28 ± 15 days in internal drainage group). Regarding operative factors, median intraoperative bleeding (745 mL in external drainage group vs 550 mL in internal drainage group; $P = .012$) and the rate of transfusion (47% in external drainage group vs 19% in internal drainage group; $P = .001$) were significantly greater in the external drainage group.

Preoperative and postoperative complications between external drainage and internal drainage

Table 3 compares preoperative and postoperative complications between the external drainage and internal drainage groups. Preoperative cholangitis occurred with significantly greater frequency in the internal drainage group (1.7% in external drainage group vs 22.4% in internal drainage group; $P < .001$). In this study, no incidence of hemorrhage and perforation because of biliary drainage occurred in either group.

Table 2 Patient characteristics according to types of preoperative biliary drainage

	External drainage (n = 60)	Internal drainage (n = 67)	*P* value
Age	70 ± 9	68 ± 8	.333
Gender (male/female)	32/28	39/28	.581
Total bilirubin before biliary drainage (mg/dL)*	8.3 ± 5.7	7.5 ± 5.8	.842
Operative procedure (PD/PpPD/PrPD)	8/48/4	2/43/22	.0001
Histology (pancreatic cancer/other)	26/34	29/38	.995
Pancreatic adenocarcinoma	26	29	
Bile duct carcinoma	24	25	
Ampullary adenocarcinoma	5	7	
Duodenal adenocarcinoma	0	1	
Intraductal papillary neoplasms	2	0	
Pancreatic endocrine tumor	1	1	
Tumor-forming pancreatitis	3	3	
Neoadjuvant therapy (yes/no)	0/60	3/64	.144
Operative time (min)			
Median (range)	359 (259–723)	370 (219–584)	.475
Intraoperative bleeding (mL)			
Median (range)	745 (45–6,320)	550 (80–7,335)	.012
Red blood cell transfusion (yes/no)	28/32	13/54	.001
Pancreatic texture (soft/hard)	31/29	35/32	.949
Waiting periods for operation from drainage (d)			
Median (range)	19 (5–74)	26 (5–79)	.066
Postoperative hospital stay (d)			
Median (range)	24 (5–113)	19 (8–223)	.199

PD = pancreaticoduodenectomy; PpPD = pylorus-preserving pancreaticoduodenectomy; PrPD = pylorus-resecting pancreaticoduodenectomy.
*Normal range of total bilirubin level: .2–1.2 mg/dL.

Table 3 Comparison of complications according to the type of biliary drainage

	External drainage (n = 60)	Internal drainage (n = 67)	*P* value
Preoperative cholangitis*	1 (1.7%) 15 (22.4%)	<.001	
All postoperative complications†	14 (23.3%)	28 (41.8%)	.027
0–II	2 (3.4%)	2 (3.0%)	
IIIa	10 (16.7%)	18 (26.9%)	
IIIb	0 (0%)	0 (0%)	
IVa	1 (1.7%)	4 (6.0%)	
IVb	0 (0%)	1 (1.5%)	
V	1 (1.7%)	3 (4.4%)	
Severe complications (grade III or more)	12(20%)	26 (38.8%)	.021
Infectious complications	9 (15%)	16 (23.9%)	.209
Pancreatic fistula‡	13 (21.7%)	26 (38.8%)	.037
Grade A	6 (10%)	12 (17.9%)	
Grade B	7 (11.7%)	9 (13.4%)	
Grade C	0 (0%)	5 (7.5%)	
Delayed gastric emptying§	4 (6.7%)	7 (10.4%)	.449
Grade A	2 (3.3%)	3 (4.5%)	
Grade B	1 (1.7%)	3 (4.5%)	
Grade C	1 (1.7%)	1 (1.4%)	
Bile leakage	1 (1.7%)	1 (1.4%)	.937
0–II	0 (0%)	0 (0%)	
IIIa	1 (1.7%)	1 (1.4%)	
IIIb	0 (0%)	0 (0%)	
IVa	0 (0%)	0 (0%)	
IVb	0 (0%)	0 (0%)	
V	0 (0%)	0 (0%)	
Intra-abdominal abscess	7 (11.7%)	9 (13.4%)	.765
0–II	0 (0%)	0 (0%)	
IIIa	7 (11.7%)	9 (13.4%)	
IIIb	0 (0%)	0 (0%)	
IVa	0 (0%)	0 (0%)	
IVb	0 (0%)	0 (0%)	
V	0 (0%)	0 (0%)	
Intra-abdominal hemorrhage	2 (3.4%)	5 (7.5%)	.309
0–II	0 (0%)	0 (0%)	
IIIa	1 (1.7%)	2 (3.0%)	
IIIb	0 (0%)	0 (0%)	
IVa	0 (0%)	2 (3.0%)	
Vb	0 (0%)	1 (1.5%)	
V	1 (1.7%)	0 (0%)	
Wound infection	2 (3.3%)	7 (10.4%)	.119
0–II	0 (0%)	0 (0%)	
IIIa	2 (3.3%)	7 (10.4%)	
IIIb	0 (0%)	0 (0%)	
IVa	0 (0%)	0 (0%)	
IVb	0 (0%)	0 (0%)	
V	0 (0%)	0 (0%)	
Sepsis	1 (1.7%)	4 (6.0%)	.213
0–II	0 (0%)	0 (0%)	
IIIa	0 (0%)	0 (0%)	
IIIb	0 (0%)	0 (0%)	
IVa	1 (1.7%)	4 (6.0%)	
IVb	0 (0%)	0 (0%)	
V	0 (0%)	0 (0%)	
Reoperation	0 (0%)	0 (0%)	.999
Mortality	1 (1.7%)	3 (4.5%)	.365

DGE = delayed gastric emptying.
*Preoperative cholangitis was defined by the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines 2013.
†Other complication except pancreatic fistula and DGE are classified based on Clavien classification.
‡Pancreatic fistula is classified based on the International Study Group on Pancreatic Fistula guideline.
§DGE is classified based on an International Study Group of Pancreatic Surgeons on DGE recommendation.

Table 4 Theassociation between preoperative cholangitis and postoperative complications

	Preoperative cholangitis*		
	+ (n = 16) (%)	− (n = 111) (%)	*P* value
All postoperative complications†	10 (62.5)	32 (28.8)	.007
0–II	0 (0)	4 (3.6)	
IIIa	9 (56.3)	19 (17.1)	
IIIb	0 (0)	0 (0)	
IVa	1 (6.3)	4 (3.6)	
IVb	0 (0)	1 (.9)	
V	0 (0)	4 (3.6)	
Severe complications (grade III or more)	10 (62.5)	28 (25.2)	.002
Infectious complications	5 (31.3)	20 (23.9)	.213
Pancreatic fistula‡	7 (43.8)	32 (28.8)	.226
Grade A	3 (18.7)	15 (13.5)	
Grade B	3 (18.7)	13 (11.7)	
Grade C	1 (6.3)	4 (3.6)	
Delayed gastric emptying§	5 (31.2)	6 (5.4)	.001
Grade A	1 (6.3)	4 (3.6)	
Grade B	3 (18.7)	1 (.9)	
Grade C	1 (6.3)	1 (.9)	
Bile leakage	0 (0)	2 (1.8)	.588
0–II	0 (0)	0 (0)	
IIIa	1 (6.3)	2 (1.8)	
IIIb	0 (0)	0 (0)	
IVa	0 (0)	0 (0)	
IVb	0 (0)	0 (0)	
V	0 (0)	0 (0)	
Intra-abdominal abscess	3 (18.8)	13 (11.7)	.428
0–II	0 (0)	0 (0)	
IIIa	3 (18.8)	13(11)	
IIIb	0 (0)	0 (0)	
IVa	0 (0)	0 (0)	
IVb	0 (0)	0 (0)	
V	0 (0)	0 (0)	
Intra-abdominal hemorrhage	1 (6.3)	6 (5.4)	.890
0–II	0 (0)	0 (0)	
IIIa	1 (6.3)	2 (1.8)	
IIIb	0 (0)	0 (0)	
IVa	0 (0)	2 (1.8)	
IVb	0 (0)	1 (.9)	
V	0 (0)	1 (.9)	
Wound infection	4 (25.0)	5 (4.5)	.003
0–II	0 (0)	0 (0)	
IIIa	4 (25.0)	5 (4.5)	
IIIb	0 (0)	0 (0)	
IVa	0 (0)	0 (0)	
IVb	0 (0)	0 (0)	
V	0 (0)	0 (0)	
Sepsis	1 (6.3)	4 (3.6)	.611
0–II	0 (0)	0 (0)	
IIIa	0 (0)	0 (0)	
IIIb	0 (0)	0 (0)	
IVa	0 (0)	0 (0)	
IVb	1 (6.3)	4 (3.6)	
V	0 (0)	0 (0)	
Reoperation	0 (0)	0 (0)	.999
Mortality	0 (0)	4 (3.6)	.440

DGE = delayed gastric emptying.
*Preoperative cholangitis was defined by the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines 2013.
†Other complication except pancreatic fistula and DGE are classified based on Clavien classification.
‡Pancreatic fistula is classified based on the International Study Group on Pancreatic Fistula guideline.
§DGE is classified based on an international study group of pancreatic surgeons on DGE recommendation.