The patients were admitted at least 1 week before surgery and underwent mechanical preparation, including the oral intake of 2 L of polyethylene glycol electorolyte lavage solution (Niflec; Ajinomoto). Preoperative cultures were performed using nasal and throat swabs from all the patients to test for methicillin-resistant *Staphylococcus aureus* (MRSA). As a preventative antibiotic, 1 g of cefmetazole sodium (CMZ) (Cefmetazone; Daiichi Sankyo, Tokyo, Japan) was administered intravenously via a drip infusion immediately after the induction of anesthesia. A second dose was given 3 h later, followed by doses every 12 h for 2 days after the surgery. Oral feeding was initiated 5 days after the surgery.

Second, we attempted to evaluate the early postoperative outcome after PD by comparing the Impact group, which consisted of patients who fully complied with the ingestion of Impact for 5 days preoperatively, with a control group, which consisted of patients with a similar clinical background and condition who had undergone the same operative procedure in our hospital in 2004 but who had not ingested an immune-enhanced formula preoperatively. The age, sex, body mass index (BMI), serum albumin level, prognostic nutrition index (PNI) [31], preoperative biliary drainage, operative methods, operation times, and intraoperative blood loss of the two groups were compared. Regarding the postoperative course, the surgical morbidity and mortality and the duration of the hospital stay were investigated. The presence of postoperative complications, such as pancreatic fistula and incisional wound infection, and the infection status were described in the medical records. Incisional wound infection was defined based on the evidence of purulent exudate in the wound and the isolation of pathogenic organisms in culture. Surgical site infection (SSI) was diagnosed according to the Centers for Disease Control (CDC) definitions of SSI [32].

During the perioperative period, laboratory blood tests were performed. The white blood cell (WBC) count and the C-reactive protein (CRP), total protein (TP), serum albumin (Alb), total bilirubin (T-Bil), serum amylase (AMY), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), blood urea nitrogen (BUN), and serum creatinine (Cr) levels were routinely measured at 1, 3, and 7 days after surgery. Changes in body weight (BW), and in the acute physiology and chronic health evaluation (APACHE)II scores [33], and the duration of systemic inflammatory response syndrome (SIRS) in the postoperative course were also investigated. The APACHE-II classification includes twelve physiological measures (temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, WBC count, and Glasgow Coma Scale score), age, and the presence of severe chronic health problems. The worst value in each patient was used as the physiological score. This index enables the prediction of perioperative events in patients undergoing various surgical procedures [34–39]. The definition of SIRS was adopted from the report by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [40]. SIRS was defined as the presentation of two or more of the following criteria: (1) temperature >38°C or <36°C; (2) heart rate >90 beats/min; (3) respiration >20/min or $PaCO_2$ <32 mmHg; (4) leukocyte count >12,000/mm^3, <4000/mm^3, or >10% band cells.

Statistical analysis of the data was performed using an unpaired Student's *t*-test, the χ^2 test, and the Mann–Whitney *U*-test. Variations in some parameters over time and comparisons among the two groups were studied using a repeated measure analysis of variance (ANOVA). Data are shown as means (standard deviation). All statistical analyses were performed using StatView-J 5.0 (Abacus Concepts, Berkeley, CA, USA); all two-sided p values <0.05 were considered statistically significant.

Operation procedures

Five staff surgeons performed all the operations. The operative procedure was a standardized substomach-preserving PD. Reconstruction was achieved using a retrocolic jejunal Roux-en-Y limb with an end-to-side pancreaticojejunostomy, an end-to-side hepaticojejunostomy, and a gastrojejunostomy, according to the child procedure. In all patients, a pancreatic stenting tube was placed in the pancreatic duct and fixed with 2 absorbable suture ligations. The main duct was anchored to the adjacent serosa. A 3-0 polypropylene monofilament thread with curved needle was prepared with a straightened needle at each end. The suture was passed from the ventral to the dorsal surface of the pancreas from the cut end and the serosal surface of the jejunum. All end-to-side pancreaticojejunostomies were performed in two layers. The inner layer comprised the opposition of the pancreatic duct and adjacent pancreatic tissue to a small opening in the jejunum (full thickness), which was made by puncturing the tissues with a thick needle connected to the pancreatic stenting tube and utilizing interrupted stitches of 5-0 monofilament polyglyconate. All pancreaticojejunal anastomoses were stented (decompressed) through 6- or 7.5-F polyvinyl chloride tubes, according to the diameter of the main pancreatic duct, and the tubes were guided externally through the jejunal loop. The pancreatic juice was completely drained via the tube, and the tube was removed 3 weeks or more after the surgery.

Hepaticojejunostomy was performed using interrupted polyglyconate sutures. A stenting tube was not inserted through the anastomosis in any of the patients. Penrose drains were routinely placed on the anterior and posterior

Table 1 List of patients with preoperative Impact consumption

Patient	Age (years)	Sex	Disease	Procedure	Duration of oral intake of Impact (days)	Reasons for discontinuation of Impact
1	79	Female	BDC	SSpPD	5	None
2	57	Female	PIDC	SSpPD	5	None
3	58	Male	IPMN	SSpPD	5	None
4	68	Male	VC	SSpPD	5	None
5	77	Male	BDC	SSpPD	5	None
6	68	Male	DC	SSpPD	1	Diarrhea
7	52	Male	BDC	SSpPD	5	None
8	56	Male	IPMN	SSpPD	5	None
9	62	Female	IPMN	SSpPD	5	None
10	77	Male	VC	SSpPD	2	Nausea
11	57	Male	BDC	EBDR	5	None
12	75	Male	BDC	Not resected	3	Diarrhea
13	64	Female	PIDC	SSpPD	5	None
14	48	Male	IPMN	SSpPD	4	Pancreatitis and cholangitis
15	62	Male	IPMN	SSpPD	5	None
16	57	Female	VC	SSpPD	5	None
17	67	Male	DC	SSpPD	5	None
18	59	Male	SPT	SSpPD	5	None
19	64	Male	PIDC	SSpPD	5	None
20	62	Female	DC	SSpPD	5	None
21	72	Male	BDC	SSpPD	5	None
22	67	Male	PIDC	SSpPD	5	None
23	44	Female	SCT	SSpPD	5	None
24	58	Male	IPMN	SSpPD	3	Changed operation date
25	64	Male	PIDC	Not resected (GJB)	1	Changed operation date

BDC bile duct carcinoma, *PIDC* pancreatic invasive ductal carcinoma, *IPMN* intraductal papillary mucinous neoplasm, *VC* papilla of Vater carcinoma, *DC* duodenal carcinoma, *SPT* solid and pseudo-papillary tumor of pancreas, *SCT* serous cystic tumor of pancreas, *SSpPD* substomach-preserving pancreaticoduodenectomy, *EBDR* extra bile duct resection, *GJB* gastrojejunal bypass

surfaces of the pancreaticojejunal anastomosis and the dorsal side of the hepaticojejunostomy.

Reconstruction was completed before suturing the abdominal wall. Immediately after the opening of the abdomen, the surgical wound was protected by the placement of a drape. Before closing the abdomen, the abdominal cavity was washed using 3000 mL of warm saline, and the drape was removed. The surgeon and assistant changed gloves, and the abdominal muscle and fascia layers were closed using monofilament absorbable sutures. After washing the skin and subcutaneous fat layer with 500 mL of warm saline, the wound was closed using a skin stapler. Postoperatively, the wound was covered using a transparent protective film and was monitored without sterilization until suture removal.

Results

Compliance with preoperative administration of Impact

The amount of the immunonutrition preparation consumed preoperatively was monitored by the doctor in charge of each patient. A total of 25 patients were enrolled in the study (see Table 1). As the scheduled operation date was moved forward for two patients, these 2 patients had to discontinue Impact consumption. Treatment compliance and other reasons for discontinuation are summarized in Table 2. Nineteen patients (82.6%) fully complied with Impact consumption. The mean period of preoperative oral intake was 4.6 ± 1.1 days. The reasons for the discontinuation of Impact consumption were diarrhea in 2 patients, nausea in 1 patient, and pancreatitis and cholangitis caused by the primary disease in 1 patient. The nausea and diarrhea symptoms occurred 3 days after the start of Impact consumption.

Comparison of early postoperative outcome after PD between the Impact and control groups

Of the 25 patients, 18 were able to complete the Impact consumption protocol. These patients (Impact group) were retrospectively compared with a control group consisting of patients treated at our institution in 2004 who had undergone the same surgical procedure for the treatment of

similar conditions but who had not ingested an immune-enhanced formula preoperatively.

The preoperative and intraoperative clinical background characteristics of the two groups of patients are summarized in Table 3. No significant difference was observed in the total numbers of calories served in the daily hospital meals given for 5 days before surgery and until postoperative day (POD) 7 between the two groups (data not shown). In both the Impact and control groups, peripheral parenteral nutritional infusion was used, without using total parenteral nutrition. Moreover, no differences in age, sex, preoperative nutritional status, operative time, or intraoperative blood loss were observed between the groups.

Table 2 Compliance with oral intake of Impact

Duration of oral intake of immunonutrition (days)	4.6 ± 1.1
No. of patients who completed oral intake	19/23[a] (82.6%)
No. of patients who discontinued treatment	4/23[a] (17.4%)
Reasons for discontinuation	
Diarrhea	2 (8.7%)
Nausea	1 (4.3%)
Pancreatitis and cholangitis caused by primary disease	1 (4.3%)

[a] Not including 2 patients (out of a total of 25 patients in this study) who discontinued preoperative Impact consumption because of changed operation dates

Postoperative SIRS duration and complications

The duration and complications associated with postoperative SIRS in each group are shown in Table 4. The duration of postoperative SIRS and the hospital stay were not significantly different between the groups. The incidences of individual complications were also comparable between the groups. The incidence of incisional wound infection was significantly lower in the Impact group than in the control group (0 vs. 30.8%; $p = 0.012$), but no significant differences in the incidences of other postoperative complications were seen between the groups. The operative mortality rate was 0% for each group.

The effects of immune-enhanced nutrition on laboratory and physical data (WBC count, CRP level, TP, Alb, T-Bil, AMY, GOT, GPT, BUN, Cr, BW, and APACHE-II score) during the perioperative period are shown in Fig. 1. No significant differences in the WBC counts, CRP levels, TP, Alb, T-Bil, AMY, GOT, BUN, and Cr results were seen between the two groups. However, the GPT level was significantly higher in the Impact group (Fig. 1h). While the change in BW during the perioperative period also did

Table 3 Baseline patient characteristics

	Impact ($n = 18$)	Control ($n = 13$)	p
Age (years)	62.6 ± 8.5	65.1 ± 10.0	0.466
Sex (male/female)	11/7	7/6	0.686
BMI	21.9 ± 2.1	22.1 ± 3.2	0.821
Serum albumin (g/dL)	3.9 ± 0.3	3.7 ± 0.5	0.296
PNI	46.5 ± 5.8	43.7 ± 5.0	0.176
Biliary drainage	7	8	0.213
PTBD	5 (71.4%)	5 (62.5%)	0.714
ENBD	2 (28.6%)	3 (27.5%)	
Duration of oral intake of Impact (days)	5	None	None
Resection procedure	SSpPD		
Reconstruction method	Modified child method		
Operation time (min)	329 ± 79	308 ± 88	0.488
Intraoperative blood loss (mL)	921 ± 566	947 ± 654	0.905
Pathological diagnosis			
PIDC	4 (22.2%)	2 (15.4%)	
IPMN			
IPMA	3 (16.7%)	1 (7.7%)	
IPMC	0	1 (7.7%)	
SPT	1 (5.6%)	0	
SCA	1 (5.6%)	0	
BDC	5 (27.8%)	3 (23.1%)	
VC	2 (11.1%)	4 (30.8%)	
DC	2 (11.1%)	2 (15.4%)	

BMI body mass index, *PNI* prognostic nutrition index = (10 × serum albumin) + [0.005 × total lymphocyte count (/mm^3)], *PTBD* percutaneous transhepatic biliary drainage, *ENBD* endoscopic naso-biliary drainage, *SSpPD* substomach-preserving pancreaticoduodenectomy, *PIDC* pancreatic invasive ductal carcinoma, *IPMN* intraductal papillary mucinous neoplasm, *IPMA* intraductal papillary mucinous adenoma, *IPMC* intraductal papillary mucinous carcinoma, *SPT* solid and pseudo-papillary tumor, *SCT* serous cystic adenoma, *BDC* bile duct carcinoma, *VC* papilla of Vater carcinoma, *DC* duodenal carcinoma

Table 4 Early postoperative outcome and complications

	Impact ($n = 18$)	Control ($n = 13$)	p
Duration of postoperative SIRS (days)	0.8 ± 1.0	0.9 ± 0.8	0.664
Duration of postoperative hospital stay (days)	29 ± 13	26 ± 12	0.516
Morbidity and mortality			
Pancreatic fistula	12 (66.7%)	8 (61.5%)	0.768
Delayed gastric emptying	2 (11.1%)	1 (5.9%)	0.751
Cholangitis	0	1 (5.9%)	0.232
Wound infection	0	4 (30.8%)	0.012
Perioperative death	0	0	

SIRS systemic inflammatory response syndrome

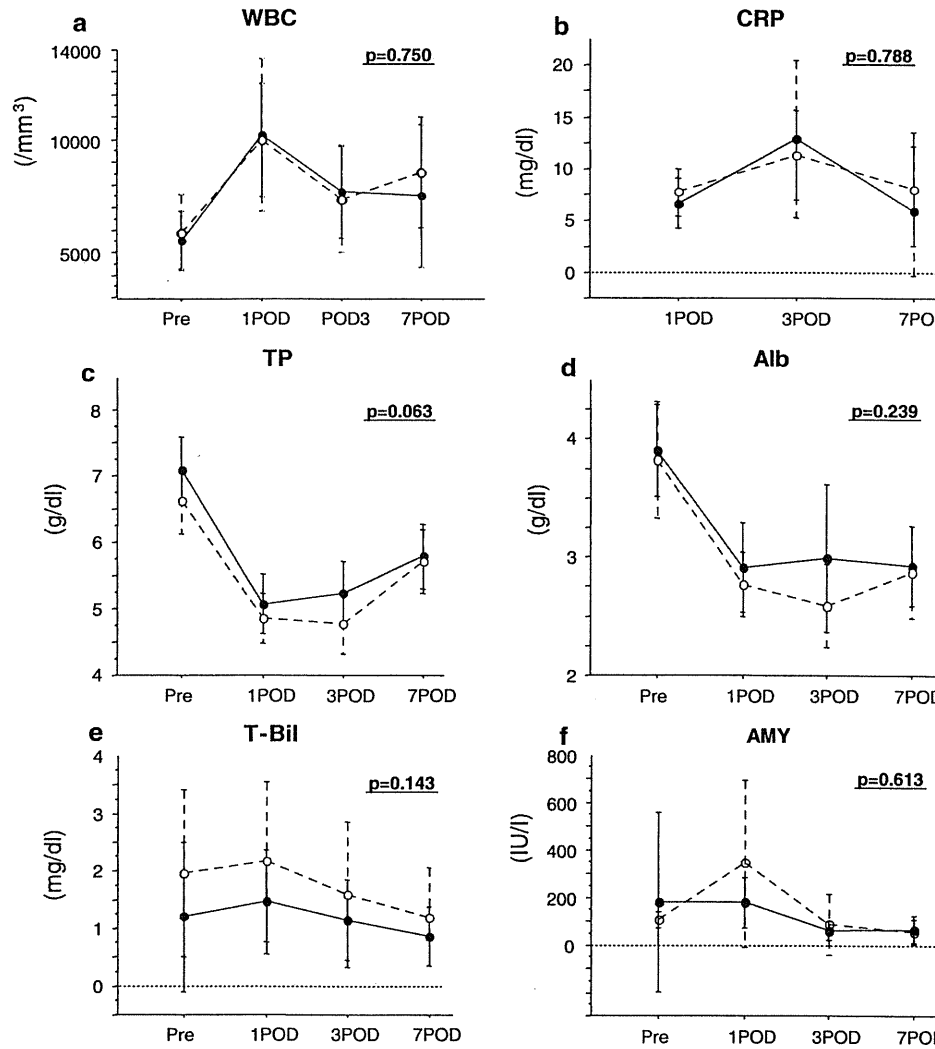
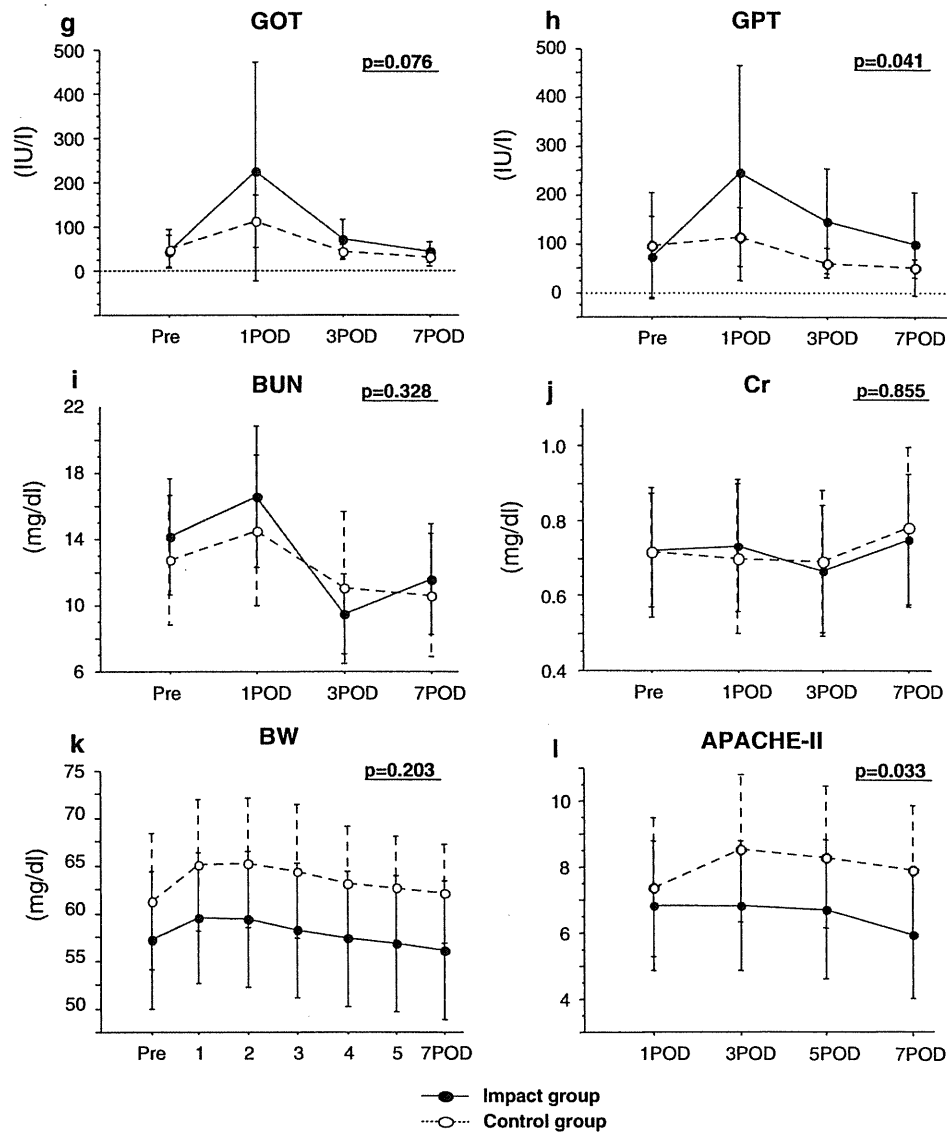


Fig. 1 Laboratory blood test results. *Filled circles* Impact group, *open circles* control group. **a** White blood cell count (*WBC*), **b** C-reactive protein (*CRP*), **c** total protein (*TP*), **d** serum albumin (*Alb*), **e** total bilirubin (*T-Bil*), **f** serum amylase (*AMY*), **g** glutamic oxaloacetic transaminase (*GOT*), **h** glutamic pyruvic transaminase (*GPT*), **i** blood urea nitrogen (*BUN*), **j** serum creatinine (*Cr*), **k** body weight (*BW*), **l** acute physiology and chronic health evaluation score II (*APACHE-II*)

not differ significantly between the two groups, the improvements in the gain or loss of BW after surgery showed a better course in the Impact group than in the control group. To evaluate the systemic severity of patients after surgery, we utilized the APACHE-II classification. A high postoperative APACHE-II score predicts an increased

Fig. 1 continued



risk of a complicated postoperative course [33]. The change in the total APACHE-II score after PD was significantly lower in the Impact group than in the control group ($p = 0.033$). Among the factors measured for the APACHE-II scores, the following factors showed significantly lower scores in the Impact group than in the control group: temperature on POD 1 ($p = 0.008$), mean arterial pressure on POD 1 ($p = 0.048$), heart rate on POD 5 ($p = 0.019$) and POD 7 ($p = 0.049$), and hematocrit on POD 7 ($p = 0.006$).

Discussion

Preoperative oral supplementation with Impact (750 mL/day for 5 days) was well tolerated by patients scheduled to undergo PD. The compliance rate was more than 80%, and the duration and dose of Impact used in this study were suitable. This encouraging result suggests that Impact could also be ingested by outpatients prior to elective PD.

In the present series, one patient with IPMN could not tolerate Impact because of pancreatitis and cholangitis. This patient complained of epigastralgia, fever, and jaundice after beginning to consume Impact. The patient's laboratory data showed elevated serum amylase and bilirubin levels. We suspect that this patient's pancreatitis and cholangitis might have originated from an obstruction caused by a mucinous secretion from the primary tumor, because the pancreatitis and cholangitis occurred simultaneously and progressed synchronously. Actually, the elevated serum bilirubin level consisted predominantly of

direct bilirubin. The patient's condition improved immediately after percutaneous transhepatic biliary drainage.

In the second part of this study, we retrospectively compared the outcomes of patients with and without (control group) the preoperative ingestion of an immune-enhanced formula prior to undergoing PD. In patients without hyperbilirubinemia, laboratory data showed that the postoperative GOT and GPT levels were higher in the Impact group than in the control group; in particular, GPT was significantly higher in the Impact group. In a study examining patients with esophageal cancer who ingested Impact immediately before undergoing a transthoracic esophagectomy with lymph node dissection, Takeuchi et al. [24] also reported an immediate postoperative elevation of transaminases. Although the mechanism remains unclear, a preoperative immune-enhanced diet may impose a load on hepatocytes after invasive surgery such as PD. Immune-enhanced formulas have been suggested to possibly cause a high postoperative BUN level as a result of an overload in nitrogen intake [41]. However, in the present series, we did not observe a marked change in the BUN level, and nitrogen overloading did not appear to be excessive.

Regarding the systemic severity of the patients in this study, the APACHE-II score tended to be lower in the Impact group than in the control group. When measured during the immediate postoperative phase, a high APACHE-II score is thought to be linked to mortality, and the APACHE-II score can be regarded as a summary indicator of an individual's response to surgical injury. The patients who received preoperative immunonutrition had a lower systemic severity score, so it appears that Impact consumption might reduce the severity of systemic damage. Several studies have reported that a supplementary diet rich in omega-3 fatty acids is related to a decrease in PGE2, which is a key fever mediator [42–44]. Our results suggest that the preoperative consumption of an immune-enhanced formula may reduce excess postoperative pro-inflammatory cytokine production (such excess production may result in serious complications or lethal multiple organ dysfunctions in patients who have undergone PD). Additional investigations of the detailed changes in some indicators, such as inflammatory cytokines, are needed.

In the present study, incisional wound infection was significantly less frequent in the Impact group than in the control group. SSI including incisional wound infection is a serious complication following surgery, requiring a prolonged hospitalization period, increased medical costs, and decreased patient satisfaction [45, 46]. SSI is primarily caused by surgical procedures, and performing surgery while minimizing the risk of SSI is important. The preoperative oral intake of immune-enhanced formulas, such as Impact, might also be important for preventing incisional wound infection.

The duration of postoperative SIRS and the length of the hospital stay were not significantly different between the two groups in our study. Thus, the effects of the preoperative ingestion of an immune-enhanced formula on the duration of the hospital stay among patients undergoing PD remain unclear. In this study, pancreatic fistula was the most common and important complication, not wound infection. The length of the hospital stay is likely to be affected by the severity of this complication, as it is regarded as a major unfavorable complication after PD. During this study, an end-to-side dunking anastomosis was used for the anastomosis between the pancreatic stump and the jejunum; however, since 2007 (after the completion of the present study), we have adopted a duct-to-mucosa anastomosis with 5-0 absorbable monofilament using a vinyl tube as a lost stent in pancreaticojejunostomy procedures. As a result, the incidence of pancreatic fistula after PD has decreased (data not shown). This concept has also successfully enabled the duration of the hospital stay after PD to be shortened.

To our knowledge, this is the one of few reports to suggest the feasibility and benefit of using an immune-enhanced formula, Impact, as part of the preoperative management of patients scheduled to undergo PD. To date, several groups have reported on immunonutrition in gastrointestinal cancer surgery patients [11, 12, 15, 47]. Most of these reports have demonstrated that patients receiving immunonutrition before and/or after surgery tended to have fewer postoperative complications. Gianotti et al. [22] reported that patients receiving immunonutrition with an enteral formula after PD had a significantly lower incidence of infectious complications than patients in the standard and parenteral groups. Di Carlo et al. [48] also reported similar results for postoperative enteral feeding in patients with pancreatic head cancer. However, no other reports have described patient compliance with preoperative oral intake, or the clinical significance of the preoperative ingestion of immune-enhanced formulas for patients undergoing PD.

In conclusion, a high rate of compliance with the preoperative oral administration of Impact Japanese version (750 mL/day, for 5 days) was observed in Japanese patients without malnutrition who were scheduled to undergo PD. This treatment appeared to be effective for preventing incisional wound infection and reducing systemic severity. To confirm the clinical benefits of preoperative Impact, a randomized control study including the use of a control group receiving a regular diet alone is needed. Of note, the composition of the commercially available Impact in Japan differs slightly from the original Impact used in Western countries, so we approve the

suggestion from Tsujinaka et al. [29] that such a randomized study should be performed exclusively in Japan. In addition, such a study would require a similar quality of operative procedures and perioperative management in both patient groups.

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J Gastrointest Surg
DOI 10.1007/s11605-011-1782-5

ORIGINAL ARTICLE

Predictive Factors for Anastomotic Leakage after Simultaneous Resection of Synchronous Colorectal Liver Metastasis

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Received: 15 September 2011 / Accepted: 11 November 2011

Abstract
Background The optimal surgical strategy for resectable, synchronous, colorectal liver metastases remains unclear. The objective of this study was to determine which patients could benefit from staged resections instead of simultaneous resection by identifying predictive factors for postoperative morbidity and anastomotic leakage after simultaneous resection of synchronous, colorectal liver metastases and the primary colorectal tumor.
Methods This study involved 86 patients with synchronous colorectal liver metastases who underwent simultaneous resection of the primary colorectal tumor and the hepatic tumor. Postoperative mortality, morbidity, and other surgical outcomes, including survival and hospitalization, were assessed. Predictive factors for postoperative morbidity and for anastomotic leakage were evaluated.
Results Postoperative morbidity and anastomotic leakage were found in 55 (64%) and 18 (21%) patients. Predictive factors for postoperative morbidity and for anastomotic leakage were intraoperative blood loss and operation time >8 h, respectively. The overall 5-year survival rate was 45%.
Conclusions The frequency of morbidity and that of anastomotic leakage seemed to be high after simultaneous resection for synchronous colorectal liver metastases, especially when intraoperative blood loss or operation time increased greatly. Staged resections should be considered in cases in which excessive surgical stress from simultaneous resection of synchronous colorectal liver metastases would be expected.

Keywords Colorectal cancer · Hepatic metastasis · Liver metastasis · Morbidity · Anastomotic leakage

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Introduction

For patients with synchronous colorectal liver metastases (SCLM), hepatic resection is considered the best treatment, with reported 5-year survival rates between 23% and 37%.[1–4] Resections of both the primary colorectal lesion and the hepatic metastases are needed for patients with SCLM when they are resectable. However, the optimal surgical strategy for resectable SCLM still remains controversial.

From the perspectives of less operation with less mental stress and simplifying perioperative treatment, simultaneous resection of the primary colorectal and liver tumors is a favorable strategy for patients with SCLM.[5–8] However, several papers reported that the morbidity rate after simultaneous resection of primary and liver tumors was high because of greater surgical stress and a longer

Published online: 29 November 2011

operation time than for single-organ surgery. Staged resection with initial operation for the primary lesion followed by resection of hepatic tumors is regarded as an alternative strategy to avoid excessive surgical stress for patients with SCLM, though the efficacy of this strategy and the patients who could benefit from this strategy are unknown.[4–6,9,10]

Thus, this study was conducted to determine which patients could benefit from staged resections instead of simultaneous resection by identifying predictive factors for postoperative morbidity and anastomotic leakage after simultaneous resection of SCLM.

Patients and Methods

Patient Population

The medical records of all consecutive patients who underwent liver resections for colorectal liver metastases from January 1992 to January 2004 at our institution were analyzed retrospectively, with institutional review board approval. Eighty-six patients had SCLM. During this period, all SCLM patients received simultaneous resection of primary colorectal and hepatic tumors irrespective of the patient's or the tumor's characteristics. Lateral lymph node dissection was routinely performed in patients with advanced lower rectal cancer. All 86 patients underwent contrast enhanced computed tomography (CT) of the chest, abdomen, and pelvis, as well as hepatic MRI, preoperatively.

As a control, the morbidity of 167 patients who underwent hepatectomy for metachronous liver metastasis from colorectal cancer from January 1992 to January 2004 and that of 1,728 patients who underwent only resection for colorectal cancer with colorectal reconstruction during the same period were also reviewed. Of the 1,728 colorectal cancer patients, 1,319 had colon cancer and 409 had rectal cancer.

Postoperative Morbidity

Incidences of the following postoperative complications were analyzed: anastomotic leak, rectovaginal fistula, intraperitoneal or pelvic abscess, wound infection, wound dehiscence, ileus, enteroparesis, postoperative delirium, urinary tract infection, dysuria, empyema thoracis, pleural effusion, atelectasis, cholecystitis, perihepatic or subphrenic abscess, bile leak, liver failure, and others. Anastomotic leakage was defined as follows: peritonitis and a dehiscence in the anastomosis, discharge of pus from the anus, vaginal fistula, or feces from the abdominal drain. Leakage was confirmed by CT scan, contrast enema, re-operation, or digital rectal examination. All complications were graded according to the classification proposed by Clavien et al.[11] Postoperative mortality was defined to include any death during postoperative hospitalization or within 30 days.

Assessment of Predictive Factors for Postoperative Morbidity

Correlations between postoperative morbidity and the following patient, tumor, and surgical factors were analyzed: age, sex, body mass index (BMI), preoperative comorbidity, site of primary tumor, intestinal obstruction by tumor, size of primary tumor, differentiation of tumor, distribution of hepatic tumors, number of hepatic tumors, hepatic tumor size, operative methods, operation time, intraoperative blood loss, and blood transfusion.

Survival

Patients were followed regularly at 3-month intervals with blood testing and CT. Survival and follow-up were calculated from the time of the operation to the date of death or last available follow-up. The survivors' median follow-up time after surgery was 73 months.

Statistical Analysis

Statistical comparisons of baseline data were performed using the chi-square test. Continuous variables were compared with the independent t test. Multivariate analyses to evaluate the independent predictive factors for postoperative complications or anastomotic leakage were done by multiple logistic regression analysis. The survival rate was calculated by the Kaplan–Meier method.[12] A difference was considered significant when p was less than 0.05.

Results

Patients and Operative Details

From 1992 to 2004, 86 patients were treated with simultaneous resection of primary and hepatic tumors for SCLM. There were 37 female and 49 male patients, with a median age of 59 years (range, 40 to 85 years). The site of the primary tumor was colon in 48 and rectum in 38. The primary tumor was staged as T3 in 54 (63%) and T4 in 32 (37%) according to the TNM classification. Metastatic lymph nodes were found in 65 patients (76%). The mean diameter of the primary tumor was 55 mm (range, 26–140 mm).

Liver metastases were solitary in 29 patients and multiple in 57 patients. In 47 patients (55%), the hepatic

tumor showed a unilobar distribution, while a bilobar tumor distribution was observed in 39 (45%). The mean diameter of the hepatic tumor was about 43 mm (range, 5–200 mm). The mean resected liver volume was 380 g (range, 10–1,660 g).

The operation for primary colorectal cancer was right (hemi) colectomy in 17 patients, transverse colectomy in 1, left (hemi) colectomy in 4, sigmoidectomy in 24, high anterior resection in 7, low anterior resection in 20, very low anterior resection in 6, inter-sphincteric resection in 2, Hartmann's operation in 1, and abdomino-perineal resection in 4 (Table 4). A diverting stoma to prevent anastomotic leakage was made in 22 (26%) patients at the surgeon's discretion, and lateral lymph node dissection was performed in 20 (23%). In terms of liver tumor resection, lobectomy was performed in 11 patients, segmentectomy in 22, bisegmentectomy in 1, trisegmentectomy in 2, subsegmentectomy in 3, and partial resection in 47.

Adjuvant therapy was given to only 17 patients (19.8%) because adjuvant chemotherapy for colorectal cancer in stage III or more was performed since January 2003. Neoadjuvant chemoradiation targeting for rectal cancer was given to three patients (3.5%).

Morbidity

No patients died within 30 days of the operation, but 55 (64%) patients developed complications (Table 1). Eighteen patients (21%) experienced leakage, of whom 6 needed urgent re-operation with ileostomy and drainage of an intra-abdominal collection caused by leakage. Postoperative bleeding, wound dehiscence, and ileus were the reasons for the three other re-operation cases. The most frequent complication was wound infection.

The morbidity rate of the 167 patients who underwent hepatectomy for metachronous colorectal liver metastasis during the same period was 19.8%, and that of 1,728 patients who underwent only resection for colorectal cancer was 32.1%. Anastomotic leakage occurred in 123 (7.1%) of the aforementioned 1,728 patients.

Factors Affecting Complications, Especially Anastomotic Leakage

Postoperative complications were significantly correlated with presence of diverting stoma ($p<0.01$), duration of operation greater than 8 h ($p<0.01$), amount of intraoperative blood loss ($p<0.01$), and intraoperative blood transfusion ($p<0.01$). The aforementioned factors were entered into multivariate analysis. Only a greater amount of blood loss had a predictive value for increased occurrence of postoperative complications.

Then, the correlations between anastomotic leakage and clinicopathological factors were examined to identify risk factors for anastomotic leakage after simultaneous resection for SCLM. Patients who underwent abdomino-perineal

Table 1 Postoperative complications after simultaneous resection for SCLM according to Clavien grade

Complications	No. of patients	Gr I	Gr II	Gr IIIa	Gr IIIb	Gr IVa
Colon and rectum						
Anastomotic leakage	18 (21%)		12		6	
Intrapelvic abscess	6 (7%)	1	4		1	
Intraperitoneal abscess	5 (6%)	1	0	3	1	
Rectovaginal fistula	4 (5%)		1		3	
Liver						
Bile leakage	7 (8%)	6	1			
Hepatic abscess	7 (8%)		5	1	1	
Liver failure	3 (3%)	1	1			1
Postoperative bleeding	1 (1%)				1	
Other organs						
Wound infection	25 (29%)	23	2			
Pleural effusion	12 (14%)	1		11		
Wound dehiscence	6 (7%)	3	2		1	
Enteroparesis	5 (6%)	5				
Postoperative delirium	4 (5%)	1	3			
Dysuria	4 (5%)		4			
Urinary tract infection	3 (3%)		3			
Pneumonia	2 (2%)		2			
Others	7 (8%)	1	4		2	

resection (n=4) or Hartmann's operation (n=1) were excluded from the analysis. Anastomotic leakage was significantly correlated with lateral lymph node dissection (p<0.01), primary site of rectum (p=0.01), duration of operation greater than 8 h (p<0.01), and amount of intraoperative blood loss (p=0.02). Neither serum levels of TP and ALB, steroid usage, nor neoadjuvant therapy showed correlation with occurrence of anastomotic leakage (data not shown). Multivariate analyses revealed operation time greater than 8 h (p<0.01) as the only independent predictive factor for anastomotic leakage after simultaneous resection of SCLM (Table 2). Extent of hepatectomy, timing of anastomosis and hepatectomy, and usage of Pringle maneuver did not correlate with occurrence of complication or anastomotic leakage.

Table 3 showed the rates of complication ≥ IIIa and anastomotic leakage according to operative procedures of the primary and hepatic resections which were performed in the same patient. Complication ≥ IIIa and anastomotic leakage were more frequently observed in patients with rectal resection; however, extent of hepatectomy did not seem to affect occurrence of complication ≥ IIIa or anastomotic leakage.

Hospitalization was significantly longer in the 55 patients with postoperative morbidity (32.2 days) than in the 31 patients without postoperative morbidity (17.6 days) (p<0.01). In addition, hospitalization was significantly longer in the 18 patients with anastomotic leakage (43.5 days) than in the 63 patients without anastomotic leakage (22.2 days) (p<0.01).

Survival

The overall survival rate after simultaneous resection for SCLM of the 86 patients was 61% at 3 years and 45% at 5 years, with MST of 47 months.

Discussion

For patients with resectable SCLM, both primary tumor resection and hepatectomy for liver metastasis could lead to long-term survival, with a 5-year survival rate of 23–37%. However, the optimal strategy, including surgical resection and perioperative treatment, remains controversial for resectable SCLM. In terms of surgical resection for SCLM, it has not been resolved whether simultaneous resection or staged resections would be preferable.

There are several rationales for simultaneous resection of SCLM. In simultaneous resection, the treatment strategy would become simpler. In the staged resections, a series of neoadjuvant chemotherapy or chemoradiotherapy, resection of primary tumor, chemotherapy between two operations, hepatectomy, and adjuvant chemotherapy could be the maximal total treatment for SCLM, while simultaneous resection could simplify and shorten the treatment schedule by eliminating one operation. Completion of the two resections and initiation of adjuvant chemotherapy occur earlier with simultaneous resection than with staged resections. Considering survival, comparable survival for simultaneous resection was shown in comparison with that for staged resections.[13] Furthermore, simultaneous resection could relieve patients from a considerable degree of mental and physical stress and decrease total treatment cost by preventing a second resection for hepatic metastases. Recent advances in colorectal and hepatic surgery have enabled simultaneous resection to be performed more safely. Martin et al. reported the safety and efficacy of simultaneous resection. By avoiding a second laparotomy, the overall complication rate was reduced, and length of hospital stay was shortened, with no change in operative mortality.[7,8]

However, at present, staged resections with initial resection of the primary tumor followed by hepatic resection have been frequently performed in patients with SCLM for several reasons.[4,5,9,10] First, the perioperative risk of staged resections has been thought to be less than that of simultaneous resection.[4,13,14] Sheele et al. reported 13 anastomotic leakages of 90 simultaneous procedures in their series, and two of them led to death.[4] Thelen et al. proposed the criteria for simultaneous liver resection according to the age and extent of liver resection, because death after simultaneous liver resection (n=4) occurred after major hepatectomies, and three of these four patients were 70 years of age or older.[15] Second, staged resections might offer a chance to evaluate liver or extrahepatic metastases between the two operations. Lambert et al. reported that staged resections of synchronous hepatic metastases with an interval of 3 to 6 months might allow occult disease to become clinically detectable and could potentially identify patients for whom a hepatic resection would offer no survival benefit.[10] Fujita recommended an interval resection to assess the metastatic status of the regional lymph nodes, because the presence of six or more lymph node metastases was an independent poor prognostic factor in patients with resected SCLM and a relative contraindication for hepatic resection.[9] Some authors proposed chemotherapy between primary tumor resection and liver resection to select patients that could benefit from hepatectomy.[13,16] Alternatively, a liver-first approach of doing liver resection first and primary resection second was newly proposed as a strategy for SCLM.[17,18] The liver-first approach might avoid needless radical colorectal surgery by confirming curability of hepatic metastases first and also might increase resectability compared with the ordinary staged resections especially in patients with progressive hepatic metastases.

Table 2 Correlation between anastomotic leakage and clinicopathological factors in patients who underwent simultaneous resection for SCLM

		Leakage (−) (n=63)	Leakage (+) (n=18)	Univariate analysis p value	Multivariate analysis p value, RR (95%CI)
Patient characteristics					
Median age (range) (years)		59 (40–85)	59 (41–73)	0.81	
Male/female		33/30	12/6	0.42	
BMI (mean±SD)		21.9±2.9	22.5±2.2	0.44	
Preoperative comorbidity					
Absent		44	12	0.78	
Present		19	6		
Primary colorectal tumor					
Site	Colon	42	6	0.01	N.S.
	Rectum	21	12		
Stenosis	Absent	56	0	0.34	
	Present	7	18		
Tumor size, mm		52.0	58.0	0.25	
pT stage	pT3	41	9	0.25	
	pT4	22	9		
pN stage	pN0	17	2	0.22	
	pN+	46	16		
Histology	Well, mod	60	15	0.12	
	Poor	3	3		
Liver metastasis					
Distribution	Unilobar	38	9	0.43	
	Bilobar	25	9		
Number of tumors (range)		2.3 (1–8)	2.6 (1–8)	0.57	
Tumor size, mm		47	33	0.06	
Operative factors					
Lateral lymph node dissection					
Absent		55	10	<0.01	N.S.
Present		8	8		
Diverting stoma					
Absent		48	11	0.24	
Present		15	7		
Liver resection					
Partial Hx, segmentectomy		51	16	0.72	
≥Lobectomy		12	2		
Timing of anastomosis					
Colectomy→anastomosis→Hx		20	4	0.20	
Colectomy→Hx→anastomosis		7	5		
Hx→colectomy→anastomosis		36	9		
Pringle maneuver					
Absent		10	1	0.44	
Present		53	17		
Operation time					
<8 h		53	8	<0.01	<0.01, 6.63 (2.09–20.9)
≥8 h		10	10		
Blood loss, g (range)		1,345 (162–6,000)	2,487 (430–6,560)	0.02	N.S.
Transfusion					
Absent		39	9	0.37	
Present		24	9		
Blood transfusion, ml		343	1,212	0.05	

RR relative risk, *CI* confidence interval, *Hx* hepatectomy, *N.S.* non-significant (p>0.05)

Table 3 Rates of complication ≥ Gr IIIa and anastomotic leakage according to the site of primary colorectal resection and extent of hepatectomy

Primary colorectal resection	Hepatectomy	Complication ≥ Gr IIIa	Anastomotic leakage
Colectomy	<Lobectomy	4/40 (10%)	5/39[a] (13%)
	≥Lobectomy	0/7 (0%)	1/7 (14%)
Rectal resection	<Lobectomy	11/32 (34%)	11/28[b] (39%)
	≥Lobectomy	2/7 (29%)	1/7 (14%)

[a] One patient who underwent Hartmann's operation was excluded from the analysis

[b] Four patients who underwent abdomino-perineal resection were excluded from the analysis

This study evaluated morbidity, especially anastomotic leakage, after simultaneous resection for SCLM in order to assess the safety of simultaneous resection. Anastomotic leakage is sometimes fatal and can cause a difficult situation with physical and mental discomfort or pain. The morbidity rate of patients who underwent simultaneous resection for SCLM seemed to be higher than that of patients with resected metachronous colorectal hepatic metastasis or that of patients who underwent only resection for colorectal primary cancer. Predictive factors for postoperative morbidity and for anastomotic leakage were intraoperative blood loss and operation time greater than 8 h, respectively. The overall morbidity rate and the rate of anastomotic leakage were 91% and 50%, respectively, in patients with operation time greater than 8 h, and 54% and 13%, respectively, in patients with operation time less than or equal to 8 h. Blood loss and operation time usually represent the amount of surgical stress. Excessive surgical stress was possibly correlated with postoperative morbidity. Hospitalization of patients with complications was significantly longer than that of patients without complications. In particular, the average hospitalization of the 18 patients with anastomotic leakage was more than 43 days. Retrospective studies have also indicated that the occurrence of anastomotic leakage is associated with increased morbidity, mortality, and prolonged hospital stay. Additionally, anastomotic leakage may be associated with an increased risk of local recurrence.[19]

Various risk factors for anastomotic leakage have been analyzed by several investigators. Age, sex, obesity, level of anastomosis, smoking, blood transfusion, tumor diameter, preoperative (chemo) radiotherapy, physical status, obstruction, and coronary heart disease have been shown to be significant risk factors for leakage.[20–24] In simultaneous resection for SCLM, not only the factors related to the tumor, the patient, or the colorectal operation, but factors related to the hepatectomy could affect the occurrence of anastomotic leakage. However, the extent of hepatic resection, sequence of colectomy, hepatectomy, anastomosis, use of the Pringle maneuver, and total time of the Pringle maneuver were not predictive factors for anastomotic leakage or postoperative complications in patients with resected SCLM.

Recently, a diverting stoma has been often used to prevent anastomotic leakage in patients who undergo low anterior resection by diverting the fecal stream and keeping the anastomosis free of material.[19,25,26] In this study, the presence of a diverting stoma was not a predictive factor for absence of postoperative anastomotic leakage. However, the analysis estimating efficacy of a diverting stoma in this study was not accurate, because a diverting stoma was basically used in patients whose risk for anastomotic leakage was considered to be high by the surgeons. The site of primary tumor that has been reported as a strong predictive factor in previous studies was not a predictive factor for anastomotic leakage in this series. Use of diverting stoma might affect the result of analyses of predictive factors for anastomotic leakage. A randomized, controlled trial is needed to elucidate the efficacy of a temporary diverting stoma.

Although several rationales for the simultaneous resection for SCLM are clear, staged resections should be selected to prevent anastomotic leakage or serious complications when the scheduled operation would result in considerable surgical stress, i.e., predicted operation time greater than 8 h according to the results of the present study. Predicted operation time should be calculated by considering various factors, such as characteristics of the patient, primary and metastatic tumor, extent of operation, difficulty of the procedure, and so on. Based on the results of this study, we now select staged resections when operation time is expected to be greater than 8 h; otherwise, we select simultaneous resection. A prospective study of SCLM to evaluate the efficacy and safety of the operation time-based decision model is in progress.

Currently, adjuvant chemotherapy is one of the key factors which could affect prognosis. Then, comparison of ratio of patients who could receive adjuvant chemotherapy will be essential when comparing the efficacy of simultaneous resection and that of staged resections in a future study of SCLM. Furthermore, in staged resections, there is a risk that some patients could not undergo a second resection after the first resection due to tumor progression or complication of first surgery. Resection rate of patients who could undergo both primary and hepatic resections

should be assessed when comparing simultaneous resection and staged resections in SCLM.

The limitations of our study are its retrospective design and the relatively small number of patients studied.

Conclusion

The morbidity rate and the frequency of anastomotic leakage were high with simultaneous resection for SCLM, especially in patients with greater intraoperative blood loss or operation time greater than 8 h. For patients with SCLM, staged resections should be considered when simultaneous resection would involve excessive surgical stress.

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Pylorus Ring Resection Reduces Delayed Gastric Emptying in Patients Undergoing Pancreatoduodenectomy

A Prospective, Randomized, Controlled Trial of Pylorus-Resecting Versus Pylorus-Preserving Pancreatoduodenectomy

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Objective: To determine in a prospective randomized controlled trial (RCT) whether pylorus-resecting pancreatoduodenectomy (PrPD) with preservation of nearly the entire stomach reduces the incidence of delayed gastric emptying (DGE) compared with pylorus-preserving pancreatoduodenectomy (PpPD).

Background: Several RCTs have compared PpPD and conventional pancreatoduodenectomy with antrectomy. However, no study has reported the difference between PrPD with preservation of nearly the entire stomach and PpPD.

Methods: One hundred thirty patients were randomized to preservation of the pylorus ring (PpPD) or to resection of the pylorus ring with preservation of nearly the entire stomach (PrPD). This RCT was registered at clinicaltrials.gov NCT00639314.

Results: The incidence of DGE was 4.5% in PrPD and 17.2% in PpPD, a significant difference. Delayed gastric emptying was classified into 3 categories proposed by the International Study Group of Pancreatic Surgery. The proposed clinical grading classified 11 cases of DGE in PpPD into grades A (n = 6), B (n = 5), and C (n = 0) and one case in PrPD into each of the 3 grades. The time to peak $^{13}CO_2$ content in the ^{13}C-acetate breath test at 1, 3, and 6 months postoperatively was significantly delayed in PpPD compared with PrPD (34.3 ± 24.6 minutes versus 18.7 ± 11.8 minutes, 26.5 ± 21.1 minutes versus 17.3 ± 11.7 minutes, 26.7 ± 18.8 minutes versus 17.4 ± 13.2 minutes, respectively). Pylorus-resecting pancreatoduodenectomy and PpPD had comparable outcomes for quality of life, weight loss, and nutritional status during a 6-month follow-up period.

Conclusion: Pylorus-resecting pancreatoduodenectomy significantly reduces of the incidence of DGE compared with PpPD.

(*Ann Surg* 2011;253:495–501)

Pylorus-preserving pancreatoduodenectomy (PpPD) with preservation of the entire stomach was popularized for the treatment of chronic pancreatitis as a modification of conventional pancreatoduodenectomy (PD) with antrectomy reported by Traverso and Longmire[1] in the late 1970s. Results of several randomized controlled trials (RCTs) or meta-analyses comparing PpPD and PD have been reported, and the 2 procedures are equivalent in regard to morbidity, mortality, and survival for the treatment of periampullary tumors.[2–7] Moreover, PpPD has been reported to reduce dumping, diarrhea, and bile reflux gastritis after gastrectomy and to afford patients an improved nutritional status compared with PD with antrectomy.[8–12] Therefore, PpPD has been generally accepted as the surgical procedure for periampullary neoplasms such as cancer of the pancreatic head or bile duct.

However, delayed gastric emptying (DGE) after PpPD is a persistent and frustrating complication. Delayed gastric emptying, with an incidence varying from 12% to 42% in previous series, is not a life-threatening complication, but it results in a prolonged length of stay that contributes to increased hospital costs and decreased quality of life (QOL).[12–16]

The pathogenesis of DGE after PpPD remains controversial. Delayed gastric emptying after PpPD has been attributed to denervation and devascularization of the pylorus ring due to pylorospasm caused by operative injuries of the vagus nerves innervating the pyloric ring,[17–19] ischemia of the pylorus ring due to division of the right gastric artery,[20] or congestion around the pylorus ring due to division of the left gastric vein.[21] Therefore, one should consider developing a new PD surgical procedure with resection of only the pylorus ring with preservation of nearly all the stomach. To our knowledge, no report has evaluated whether resection of the pylorus ring in PD lowers the incidence of DGE compared with that in PpPD. We designed this technique to preserve more than 95% of the stomach, calling the procedure pylorus-resecting pancreatoduodenectomy (PrPD). We conducted this RCT to confirm the hypothesis that PrPD reduces the incidence of DGE compared with conventional PpPD.

PATIENTS AND METHODS

Between October 2005 and March 2009, this RCT was performed at Wakayama Medical University Hospital (WMUH) to compare PrPD and PpPD in patients with pancreatic or periampullary lesions. A total of 139 eligible patients were recruited into the study before surgery on the basis of whether preserving the pylorus ring was anticipated. This trial was approved by the Ethical Committee on Clinical Investigation of WMUH and prepared in accordance with clinicaltrials.gov (ID# NCT00639314). Informed consent was obtained from all participating patients preoperatively; they also agreed to a follow-up of at least 6 months postoperatively. Exclusion criteria were (1) tumor infiltration into the stomach and metastasis into lymph nodes of the peripylorus; (2) patients with severe comorbidity such as myocardial infarction, respiratory disorder that required oxygen inhalation, liver cirrhosis, hemodialysis, or cancer of the other organ, which were possible to prolong hospital stay; (3) patients with combined resection of the liver; (4) patients with proven mental illness; and (5) patients without an informed consent.

Assignment

During PD, patients were randomized to the group with preservation of the pylorus ring (PpPD) or resection of the pylorus ring with preservation of more than 95% of the stomach (PrPD). A research physician conducted the randomization using a computer-generated random number pattern in a central registry for the study at WMUH.

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This study was registered at clinicaltrials.gov; ID# NCT00639314.

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ISSN: 0003-4932/11/25303-0495
DOI: 10.1097/SLA.0b013e31820d98f1

Description of the Operations

Figure 1 presents a schematic drawing of the 2 procedures. The root of the right gastric artery and the pyloric branch of the vagal nerve were dissected at the same levels along with lymph nodes around the pylorus ring in both PpPD and PrPD. In PpPD, the proximal duodenum was divided 3 to 4 cm distal to the pylorus ring. In PrPD, the stomach was divided just adjacent to the pylorus ring and more than 95% of the stomach was preserved. In patients with malignant disease, for either procedure, lymph nodes from the following areas were removed: 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.[22] Pancreatojejunostomy after PpPD and PrPD was performed by duct-to-mucosa, end-to-side pancreatojejunostomy in all patients.[23] External suture rows were created as a single suture between the remnant pancreatic capsule, parenchyma, and jejunal seromuscular tissue by using interrupted sutures of 4-0 Novafil (polybutester, Tyco Healthcare Japan Co, Tokyo, Japan). Internal suture rows, duct to mucosa, were performed between the pancreatic duct and jejunal mucosa by using 8 interrupted 5-0 PDS-II (polydioxanone, Johnson and Johnson Co, Tokyo, Japan). The internal drainage catheter, cut to a length of 5 cm of a 5-F polyethylene pancreatic duct drainage catheter (Sumitomo Bakelite Co, Tokyo, Japan) was used as a stent for pancreatojejunostomy in all patients. Then, an end-to-side hepatojejunostomy was performed by a 1-layer anastomosis (5-0 PDS-II) 10 to 15 cm distal to the pancreatojejunostomy. Duodenojejunostomy in PpPD or gastrojejunostomy in PrPD was performed by a 2-layer anastomosis (4-0 PDS-II and 3-0 silk) via an antecolic route.[24] One 10-mm Penrose drain (a silicon, multitubular flat drain) was routinely placed anterior to the pancreatojejunostomy. This drain was connected to a closed drainage system. The drains were to be removed on postoperative day 4 in all patients if bile leakage and bacterial contamination were absent.[25] A 16-F nasogastric catheter was inserted and then removed from all patients on postoperative day 1.

No patient received radiotherapy preoperatively or postoperatively. All patients received an H_2-blocker (famotidine, Astellas Pharma, Inc, Tokyo, Japan) intravenously for 2 weeks postoperatively and prophylactic antibiotics intraoperatively and for 2 days postoperatively. Prophylactic octreotide or prokinetic agents such as erythromycin were not postoperatively administered to prevent pancreatic fistula or DGE.

Data Collection

Data were collected prospectively for all patients and included history, pathologic examination, perioperative clinical information, and complications. Before surgery and at 1, 3, and 6 months after surgery, nutritional status was assessed by serum nutritional parameters such as albumin, prealbumin, transferrin, and retinol-binding protein and body weights were measured. Upper gastrointestinal contrast study by gastrografin was performed on postoperative day 7. Time for the passage of gastrografin from the esophagogastric junction to gastrojejunostomy or duodenojejunostomy was measured.

The ^{13}C-acetate breath tests at 1, 3, and 6 months after surgery were performed to compare gastric emptying between PpPD and PrPD.[26] Patients ingested a liquid meal (200 kcal/200 mL, Racol, Ohtsuka Phama Co Ltd, Tokyo, Japan) labeled with 100-mg sodium ^{13}C-acetate (Cambridge Isotope Laboratories, Inc, Andover, Mass). Breath samples were collected in the collection bag before and at 5, 10, 15, 20, 30, 40, 50, 60, 75, and 90 minutes after ingestion of the test meal.[27] The $^{13}CO_2$ content was measured by infrared spectrophotometry (UBiT IR300, Otsuka Electronics Co Ltd, Osaka, Japan). Gastric emptying was evaluated on the basis of the time of peak $^{13}CO_2$ content.[28]

The QOL was recorded using Functional Assessment of Cancer Therapy–Gastric (FACT-Ga) questionnaire.[29] This questionnaire consists of the 27 items of the FACT-G, which provides a series of subscale scores for physical, social, emotional, and functional well-being and the newly validated 19-item scale, which assesses gastric cancer–specific domains of postoperative gastrointestinal symptoms

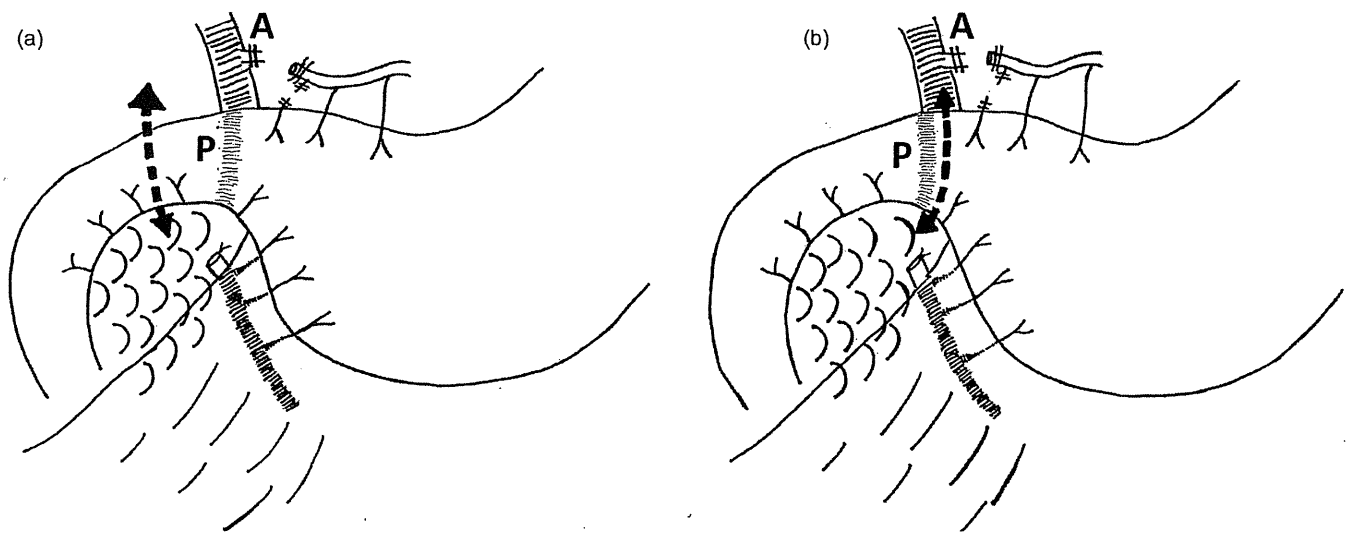

FIGURE 1. The right gastric artery (A) and vagal nerve were transected at the same levels in both PpPD and PrPD. The right gastric artery was dissected by the root, and the first pyloric branch was dissected along the lesser curvature of the stomach. The first pyloric branch of the right gastroepiploic 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 (P). (**a**), In PpPD, the proximal duodenum was divided 3 to 4 cm distal to the pylorus ring. (**b**), In PrPD, the stomach is divided just adjacent to the pylorus ring and more than 95% of the stomach can be preserved.

including dumping syndrome, gastric fullness, appetite loss, weight loss, diarrhea, and bile reflux gastritis. The patient's QOL by the FACT-Ga questionnaire was assessed at 1, 3, and 6 months after surgery.

Study End Points

The primary end point was the incidence of DGE. Delayed gastric emptying was defined according to a consensus definition and clinical grading of postoperative DGE proposed by the International Study Group of Pancreatic Surgery (ISGPS),[30] using the Web-based calculator (http://pancreasclub.com/calculator/) to improve the homogeneity of the definition.[16] Delayed gastric emptying is classified into 3 categories (grade A, B, or C) by ISGPS clinical criteria based on the clinical course and postoperative management such as reinsertion of a nasogastric catheter, the period of inability to tolerate a solid diet, presence or absence of vomiting, or use of prokinetics.[30]

Secondary end points were evaluation of QOL, nutritional status, postoperative complications except DGE, and mortality. *Pancreatic fistula* was defined by the ISGPF guideline: amylase level in fluid collection on postoperative day 3 that was more than 3 times the serum amylase level.[31] Pancreatic fistulae are classified into 3 categories (grades A, B, or C) by ISGPF clinical criteria. Intra-abdominal hemorrhage was defined by ISGPS.[32] Intra-abdominal hemorrhage is classified into 3 categories (grades A, B, or C) by ISGPS clinical criteria based on the clinical course. *Biliary fistulae* were defined as the presence of bile in drainage fluid that persisted by postoperative day 4. *Intra-abdominal abscess* was defined as intra-abdominal fluid collection with positive cultures identified by ultrasonography or computed tomography associated with persistent fever and elevations of white blood cell counts. Patients were discharged only when they fulfilled the criteria as follows: a return to preoperative activities of daily living, no deep-site infections, normal laboratory data, no drains, and the possibility for oral nutrition above the basal metabolism. *Mortality* was defined as death within 30 days after surgery.

Statistical Analysis

The study design to predict the number of patients necessary for statistical validity (2-sided) was based on the premise of improving DGE rate from 30% in PpPD to 10% in PrPD, with the α value set at .05 and the β value set at .2, yielding a power of 80%. We calculated that 65 patients were required in each arm of this study, for a total study population of 130 patients. Data were expressed as mean $\pm$ SD. Patient characteristics and perioperative and postoperative factors between the 2 groups were compared using χ^2 tests, the Fisher exact test, and the Mann-Whitney U test. *Statistical significance* was defined as $P < 0.05$.

RESULTS

Between October 2005 and March 2009 at WMUH, 139 patients with periampullary tumors were registered and 130 patients were enrolled in this study, with 64 patients randomized to PpPD and 66 to PrPD. Nine patients were excluded from this study before randomization because of the coexistence of hepatic cell carcinoma (n = 2), renal cell carcinoma (n = 1), severe cirrhosis (n = 1), hemodialysis (n = 1), psychological disorders (n = 1), and absence of informed consent (n = 3). A consort flow diagram of this RCT is shown in Figure 2.

Patient Characteristics

Table 1 shows the results of histologic analysis of the resected specimens, patient characteristics, preoperative status, and perioperative status. The 2 groups did not differ significantly in numbers with malignant (PpPD: n = 52; PrPD: n = 52) or benign tumors (PpPD:

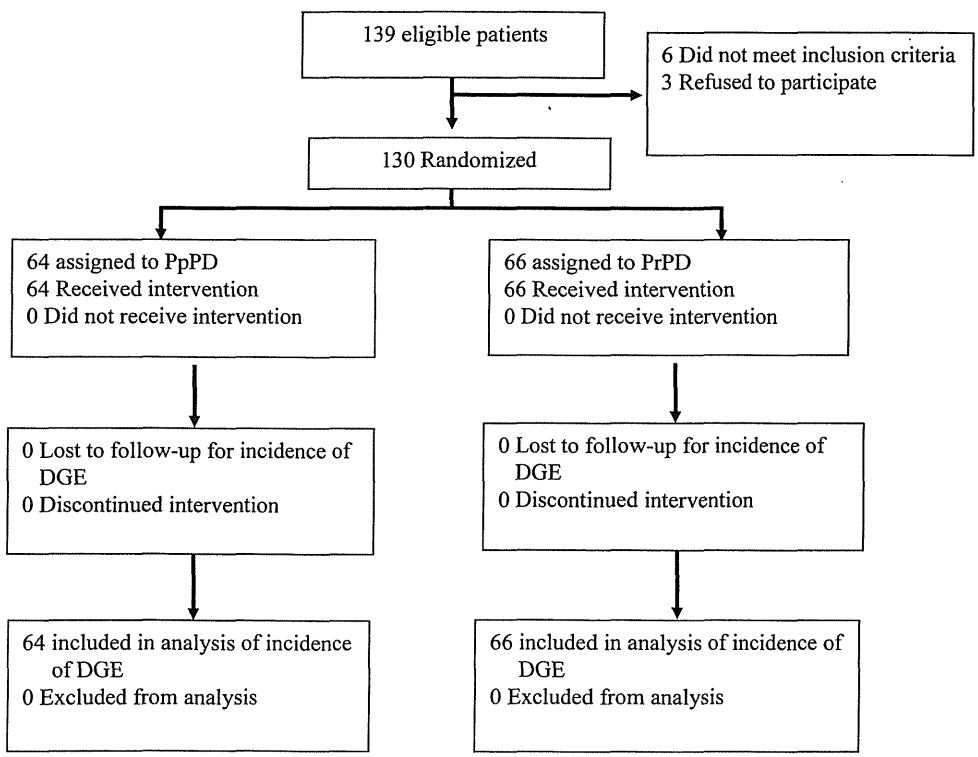

FIGURE 2. Study flow diagram. Nine patients were excluded from this study before randomization as indicated in the text.

TABLE 1. Characteristics of Enrolled Patients

	PpPD (n = 64)	PrPD (n = 66)	P
Age, yrs	68 ± 9	67 ± 9	0.5776
Gender (male/female)	33/31	38/28	0.6084
Diabetes (yes/no)	18/46	19/47	0.9999
Preoperative biliary drainage (yes/no)	34/33	26/40	0.2532
Diabetes (yes/no)	18/46	19/47	0.9999
Serum hemoglobin, g/dL*	13.0 ± 1.5	12.5 ± 1.3	0.2184
Serum creatinine, mg/dL†	0.68 ± 0.2	0.72 ± 0.2	0.1903
Serum total bilirubin, mg/dL‡	3.8 ± 4.0	4.0 ± 6.0	0.7965
Serum amylase, IU/L§	124 ± 134	111 ± 104	0.5232
Benign tumors/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	
Operative time, min	342 ± 71	358 ± 84	0.2631
Intraoperative bleeding, mL	820 ± 987	902 ± 1075	0.6527
Red blood cell transfusion, units	1.1 ± 3.0	1.9 ± 5.0	0.2400
Lymph node dissection (D1/D2)	9/55	9/57	0.9999
Portal vein resection (yes/no)	5/59	10/56	0.3007

*Normal range of hemoglobin: 12–17.5 g/dL.
†Normal range of creatinine: 0.53–1.02 mg/dL.
‡Normal range of total bilirubin: 0.2–1.2 mg/dL.
§Normal range of amylase: 15–150 IU/L.

n = 12; PrPD: n = 14). Background data and perioperative status were similar in the 2 groups.

Incidence of DGE and Postoperative Course Associated With DGE

The overall incidence of DGE in this RCT was 10.8% (14 of the 130 patients); the overall incidence of DGE was 4.5% in PrPD and 17.2% in PpPD, a significant difference ($P = 0.0244$). Delayed gastric emptying was classified into 3 categories by ISGPS.[30] The proposed clinical grading of 11 patients with DGE in PpPD are grade A (n = 6), grade B (n = 5), and grade C (n = 0). In PrPD, 1 patient in each grade classification reported DGE. The 2 groups did not differ significantly in management of the nasogastric catheter, start of solid foods, and postoperative length of hospital stay (Table 2).

Time of passage from esophagogastric junction to gastrojejunostomy or duodenojejunostomy by postoperative upper gastrointestinal gastrografin series on postoperative day 7 was significantly delayed in PpPD compared with PrPD (27.2 ± 31.3 s versus 10.1 ± 9.0 s, $P < 0.0001$). The results of the time of peak $^{13}CO_2$ content are shown in Table 2. The time of peak $^{13}CO_2$ content at 1, 3, and 6 months after surgery in PpPD was significantly delayed compared with PrPD (34.3 ± 24.6 minutes versus 18.7 ± 11.8 minutes, 26.5 ± 21.1 minutes versus 17.3 ± 11.7 minutes, and 26.7 ± 18.8 minutes versus 17.4 ± 13.2 minutes, respectively). Thus, the gastric emptying of ^{13}C-acetate breath test or postoperative upper gastrointestinal gastrografin series was significantly delayed in patients in the PpPD group compared with those undergoing PrPD (Table 3).

TABLE 2. Delayed Gastric Emptying and Postoperative Course

	PpPD (n = 64)	PrPD (n = 66)	P
Delayed gastric emptying*	11 (17.2%)	3 (4.5%)	0.0244
Grade A	6 (9.4%)	1 (1.5%)	
Grade B	5 (7.8%)	1 (1.5%)	
Grade C	0 (0%)	1 (1.5%)	
Removal of nasogastric catheter, d	0.6 ± 0.9	0.6 ± 1.0	0.9410
Reinsertion of nasogastric catheter	8 (12.5%)	2 (3.0%)	0.0527
Start of solid diet, d	6.3 ± 3.7	5.6 ± 3.3	0.1138
Postoperative hospital stay, d	24.1 ± 14.8	24.3 ± 15.5	0.9305

*Delayed gastric emptying is defined according to the International Study Group of Pancreatic Surgeons.

TABLE 3. Results of Gastric Emptying Assessed by ^{13}C-Acetate Breath Test

	PpPD (n = 64)	PrPD (n = 66)	P
Postoperative upper gastrointestinal gastrografin series, s*	27.2 ± 31.3	10.1 ± 9.0	0.0001
^{13}C-acetate breath test, min†			
1 mo after surgery	34.0 ± 24.1	18.7 ± 29.7	<0.0001
3 mo after surgery	26.5 ± 21.1	17.3 ± 11.7	0.0136
6 mo after surgery	26.7 ± 18.8	17.4 ± 13.2	0.0197

*Time for the passage of gastrografin from esophagogastric junction to gastrojejunostomy or duodenojejunostomy was measured on postoperative day 7.
†Gastric emptying was evaluated by the time of peak $^{13}CO_2$ content in ^{13}C-acetate breath test at 1, 3, and 6 months after surgery.

Postoperative Complications

Table 4 shows the other postoperative complications in the PpPD and PrPD groups. The groups did not differ significantly in the incidence of other postoperative complications, specifically, clinically relevant pancreatic fistula, intra-abdominal abscess, and intra-abdominal hemorrhage. The overall rate of pancreatic fistula in this RCT was 29.2% (38 of 130 patients). Moreover, pancreatic fistula was classified into 3 categories by ISGPF[31]: grade A in 22 of the 130 patients (16.9%), grade B in 12 patients (9.2%), and grade C in 4 patients (3.1%). Ultrasonography-guided percutaneous drainage was required for intra-abdominal abscess in 14 (10.7%) of the 130 patients. Moreover, there was no significant difference between patients with and without pancreatic fistula concerning to the incidence of DGE (15.8% and 8.7% in patients with and without pancreatic fistula, respectively; $P = 0.3812$). All patients (n = 3) with intra-abdominal hemorrhage in this study were classified as grade B according to the criteria of ISGPS.[32] Although 1 patient in the PpPD group and 2 patients in PrPD group had intra-abdominal bleeding complicated by pancreatic fistula, complete hemostasis was achieved by interventional radiographic techniques. Reoperation rate in this study was 0.8% (1 of the 130 patients), and 1 patient underwent a reoperation requiring drainage on postoperative day (POD) 7 for pancreatic fistula. The postoperative course was uneventful and discharged on POD 40. The mortality rate in this study was 0.8% (1 of the 130 patients). One patient in the PrPD group died because of nonobstructive membrane ischemia.

TABLE 4. Postoperative Complications and Outcomes

	PpPD (n = 64)	PrPD (n = 66)	*P*
Pancreatic fistula*	19 (29.6%)	19 (28.8%)	0.9999
Grade A	11 (17.1%)	11 (16.7%)	
Grade B	7 (10.9%)	5 (7.6%)	
Grade C	1 (1.6%)	3 (4.5%)	
Intra-abdominal abscess	8 (12.5%)	6 (9.1%)	0.7309
Intra-abdominal hemorrhage	1 (1.6%)	2 (3.0%)	0.9999
Intraabdominal hemorrhage	1 (1.6%)	2 (3.0%)	0.9999
Grade A	0 (0%)	0 (0%)	
Grade B	1 (1.6%)	2 (3.0%)	
Grade C	0 (0%)	0 (0%)	
Wound infection	2 (3.1%)	2 (3.0%)	0.9999
Pulmonary complications	1 (1.6%)	2 (3.0%)	0.9999
NOMI	0 (0%)	1 (1.5%)	0.9999
Percutaneous drainage†	8 (12.5%)	6 (9.1%)	0.7309
Reoperation‡	0 (0%)	1 (1.5%)	0.9999
Mortality§	0 (0%)	1 (1.5%)	0.9999

*Pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons.

†Percutaneous drainage done as postoperative management of intra-abdominal abscess related to pancreatic fistula.

‡One patient underwent reoperation requiring drainage for pancreatic fistula.

§One patient died because of nonobstructive membrane ischemia (NOMI).

TABLE 5. Long-Term Outcomes Between PpPD and PrPD

	PpPD (n = 64)	PrPD (n = 66)	*P*
Quality of life			
Total FACT-Ga score, range 0–184			
1 mo after surgery	119.9 ± 24.3	120.4 ± 29.7	0.9205
3 mo after surgery	132.3 ± 21.3	125.4 ± 26.8	0.1630
6 mo after surgery	139.1 ± 22.9	139.6 ± 21.4	0.9140
FACT-Ga subscale, range 0–76			
1 mo after surgery	48.3 ± 12.3	49.2 ± 16.6	0.7479
3 mo after surgery	55.9 ± 10.2	53.9 ± 13.3	0.3935
6 mo after surgery	59.6 ± 11.0	60.1 ± 11.3	0.8137
Change of body weight, kg			
Before operation	54.9 ± 10	55.0 ± 9	0.9335
1 mo after surgery	50.0 ± 10	0.0 ± 8	0.8547
3 mo after surgery	49.8 ± 10	48.8 ± 8	0.5624
6 mo after surgery	50.9 ± 11	50.0 ± 8	0.4712
Endocrine function			
HbA_{1c},* %			
Before operation	5.8 ± 1.3	6.0 ± 1.7	0.4558
3 mo after surgery	5.6 ± 0.7	5.6 ± 0.8	0.9596
6 mo after surgery	5.7 ± 1.0	5.7 ± 1.2	0.8534
New-onset or worsening diabetes†	3/64 (4.7%)	2/66 (3.0%)	0.6777
New diabetes	2	1	
Worsening diabetes	1	1	

*Normal range of HbA_{1c}: 3.8–5.1 g/dL.

†*New-onset diabetes* is defined as diabetes requiring new medical treatment such as diet treatment, oral drug, or insulin. *Worsening diabetes* is defined as diabetes requiring a modification of the medical treatment for deterioration of previously diagnosed diabetes.

Comparison of QOL, Nutritional Status, and Body Weight Change Between PpPD and PrPD

The overall QOL scores from the FACT-Ga scales are presented in Table 5. The highest possible scores for the physical, social, emotional, and functional subscales in FACT-G are 28, 28, 24, and 28, respectively. The highest possible score for the 19-item FACT-Ga subscale is 76. The highest possible score of total FACT-Ga score by combining total FACT-G score and FACT-Ga subscale is 184. No significant differences were found in the results of any subscale score or the total FACT-Ga scores at 1, 3, and 6 months after surgery between PpPD and PrPD.

Moreover, the patients who underwent PpPD and PrPD did not differ significantly in endocrine function or body weight change before surgery and at 1, 3, and 6 months postoperatively (Table 5).

Among serum nutritional parameters as assessment of nutritional status, rapid turnover proteins, such as albumin, prealbumin, transferrin, and retinol-binding protein, were decreased at 1 month after surgery. The levels were gradually restored thereafter and recovered to baseline or higher than the preoperative levels at 6 months after surgery. The changes in those parameters were similar in the 2 groups (Table 6).

DISCUSSION

The reported overall incidence of DGE according to the new definitions from ISGPS is 33% to 47%.[15,16,32] In previous studies, the pathogenesis of DGE after PpPD has been thought to include several factors, such as (1) antroduodenal ischemia,[20,33] (2) gastric atony caused by vagotomy,[34] (3) pylorospasm,[17–19] (4) absence of gastrointestinal hormone,[35] (5) gastric dysrhythmia secondary to other complications such as pancreatic fistula,[12,14,36–39] and (6) antroduodenal congestion.[21] Operative techniques using antecolic reconstruction for duodenojejunostomy[24] and postoperative management using erythromycin[20,35] were reported to reduce the incidence of DGE. However, the relatively high incidence of DGE after PpPD remains unsolved and we should consider ways to improve the surgical technique to decrease the incidence of DGE.

None of the 139 eligible patients in this study had lymph nodes metastasis of the peripylorus region. However, infrapyloric lymph nodes metastasis in pancreatic head carcinoma was reported to be 12%.[40] Therefore, the sampling or dissection of the peripylorus lymph nodes should be needed in patients with pancreatic head carcinoma. In the present study, we hypothesized that preservation of the pylorus ring is a risk factor for DGE and assessed whether resection of the pylorus ring with preservation of nearly the entire stomach (designated as PrPD) would significantly reduce the incidence of DGE compared with that in conventional PpPD. The results confirmed our hypotheses with the DGE rate of 17.2% in PpPD compared with that of 4.5% in PrPD ($P = 0.0244$). This is the first RCT to clarify that PrPD reduces the incidence of DGE compared with PpPD. If such reduced incidence of DGE is achieved by PrPD, one would expect a shorter hospital stay in the PrPD group. However, postoperative hospital stay in both groups may be longer than that observed in the Western countries. The Japanese health care system is different from the Western countries. Therefore, comparing lengths of postoperative hospital stay is difficult between Japan and the Western countries. Several studies proposed that gastric dysrhythmia secondary to other abdominal complications, such as pancreatic fistula or intra-abdominal abscess, induced the incidence of DGE.[12,14,36–39] In the present study, we found no significant differences between PpPD and PrPD in the incidence of clinically relevant pancreatic fistula or intra-abdominal abscess. Therefore, other postoperative complications had no bias or influence on the incidence of DGE in this study evaluating the 2 procedures. Many pancreatic surgeons believe that DGE after PD is