

ORIGINAL ARTICLE

Prospective randomized clinical trial of a change in gastric emptying and nutritional status after a pylorus-preserving pancreaticoduodenectomy: comparison between an antecolic and a vertical retrocolic duodenojejunostomy

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Abstract

Background: Although an antecolic duodenojejunostomy was reported to reduce post-operative delayed gastric emptying (DGE) compared with a retrocolic duodenojejunostomy after a pylorus-preserving pancreaticoduodenectomy (PPPD), the long-term effects of these procedures have rarely been studied. The aim of this prospective, randomized, clinical trial was to investigate the influence of the reconstruction route on post-operative gastric emptying and nutrition.

Methods: Reconstruction was performed in 116 patients with an antecolic duodenojejunostomy (A group, $n = 58$) or a vertical retrocolic duodenojejunostomy (VR group, $n = 58$). Post-operative complications, including DGE, gastric emptying variables assessed by ^{13}C -acetate breath test and nutrition, were compared between the two groups for 1 year post-operatively.

Results: The incidence of DGE was not significantly different between the procedures (A group: 12.1%; VR group: 20.7%, $P = 0.316$). At post-operative month 1, gastric emptying was prolonged in the VR versus the A group but not significantly so. At post-operative month 6, gastric emptying was accelerated significantly in the A versus the VR group. Post-operative weight recovery was significantly better in the VR versus the A group at post-operative month 12 (percentage of pre-operative weight, A group: $93.8 \pm 1.2\%$; VR group: $98.5 \pm 1.3\%$, $P = 0.015$).

Conclusions: A vertical retrocolic duodenojejunostomy was an acceptable procedure for the lower incidence of DGE and may contribute to better weight gain affected by moderate gastric emptying.

Received 12 April 2013; accepted 29 May 2013

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Introduction

A pylorus-preserving pancreaticoduodenectomy (PPPD) is the standard operation for peri-ampullary disease. Although operative mortality of PPPD has been reduced to less than 5%,¹⁻⁴ post-operative morbidity remains high, at 30% to 60%.²⁻⁴ Delayed gastric emptying (DGE) is one of the most specific and frustrating complications after PPPD, with an incidence ranging from 5–60%.^{4,5} DGE is self-limiting and can be treated conservatively; however, this complication leads to a prolonged hospital stay and worsens the patient's quality of life.

Two reconstruction methods after PPPD are associated with the transverse colon: an antecolic duodenojejunostomy and a retro-

colic duodenojejunostomy. An antecolic duodenojejunostomy is reported to offer equal or superior outcomes for the prevention of DGE compared with the retrocolic route.⁶⁻¹¹ The reported incidence of DGE with the antecolic route is below 15%, whereas that with the retrocolic route is above 30%. The incidence of DGE reported by these studies for reconstruction by the retrocolic route was considered to be high compared with the authors' experience. The authors reported previously that a vertical retrocolic duodenojejunostomy, by which the stomach and duodenum are brought down the left side of the transverse mesocolon in a straight, vertical manner, reduces the incidence of DGE.^{12,13} However, the number of the patients was small and the period after PPPD was short in these two studies.

The aim of the present study was to perform a prospective, randomized, clinical trial to compare the incidence of DGE assessed according to the definition of the International Study Groups of Pancreatic Surgery (ISGPS)¹⁴ in 116 patients undergoing either an antecolic duodenojejunostomy or a vertical retrocolic duodenojejunostomy. Although some studies reported to notice an association between DGE and reconstruction route, the post-operative effects on gastric emptying function and nutritional status have rarely been compared between the two reconstruction methods. Therefore, in this study, nutritional status and gastric emptying variables assessed by the ¹³C-acetate breath test^{15–17} were compared before and at 1, 3, 6, 9 and 12 months during the first year after surgery between the two reconstruction methods.

Methods

The study protocol was approved by the ethics committee of Miyazaki University, Miyazaki, Japan, and was registered with the National Clinical Database (University Hospital Medical Information Network Clinical Trials Registry as UMIN000001712). From March 2005 until July 2011, 129 patients underwent a PPPD at the Department of Surgical Oncology and Regulation of Organ Function, Miyazaki University School of Medicine. The patients who underwent a pancreaticoduodenectomy with gastric resection, subtotal stomach-preserving PD (SSPPD), additional hepatic resection and a total pancreatectomy were excluded from the study. The patients underwent standard pretreatment evaluation, randomization to an antecolic or a vertical retrocolic duodenojejunostomy, and assessment of the results, DGE, gastric emptying and nutritional status for 1 year after surgery. Patients were recruited into the study before surgery, and informed consent was obtained from all participants. The study flow chart is shown in Fig. 1. Because of their pre-operative condition, four patients who did not give their informed consent and five patients with severe comorbidity were excluded. The remaining 120 patients underwent randomization; however, four patients with post-operative severe sepsis (two undergoing each reconstruction method) were excluded. A re-operation was performed in one patient (0.8%) in the antecolic group for ischaemic perforation of the duodenojejunostomy. Post-operative mortality occurred in two patients (1.7%), one patient in the antecolic group as a result of sepsis from an intravenous catheter infection, and one patient in the vertical retrocolic group owing to liver failure associated with a vascular problem. Thus, the remaining 116 patients were divided into two groups: the antecolic group (A group, *n* = 58) and the vertical retrocolic group (VR group, *n* = 58).

All patients underwent detailed pre-operative physical examination with haematological and biochemical assessment including measurement of tumour markers. The indication for surgery for all patients was suspected peri-ampullary lesion on the basis of computed tomography and additional imaging studies. Patients with distant metastases or locally far advanced tumours were

judged to be inoperable. Patients with jaundice underwent pre-operative endoscopic or percutaneous transhepatic biliary drainage to decrease their serum bilirubin level. Pre-operative diabetes mellitus was assessed by the serum haemoglobin A1c level, fasting plasma glucose level, random glucose level and the oral glucose tolerance test. All patients except those with established diabetes mellitus were referred for oral glucose tolerance testing.

Prior to the surgeries, equal numbers of envelopes for an antecolic or a vertical retrocolic duodenojejunostomy were sequentially prepared in a blinded fashion to rule out any influence of bias in the choice of reconstruction technique during surgery.

The same team of surgeons performed all operations. The area resected during the PPPD included the gallbladder, common hepatic duct, pancreas head, duodenum (except the first portion) and 10 cm of the proximal jejunum. Lymph nodes in the hepatoduodenal ligament and those surrounding the common hepatic artery, peripancreatic tissue and the right side of the superior mesenteric artery were dissected. If necessary, combined portal vein resection or dissection of paraaortic lymph nodes was performed to accomplish a complete tumour resection. The duodenum was freed from the surrounding tissue and transected approximately 2–4 cm distal to the pyloric ring. The right gastric artery was divided at its origin in all patients. The lesser omentum close to the liver was dissected while preserving the vagus nerve to allow free movement of the stomach. These procedures allowed the stomach and the duodenum to be mobilized to the left in a straight, vertical manner. In reconstruction, the proximal jejunum was brought through the right side of the transverse mesocolon via the retrocolic route. An end-to-side pancreaticojejunostomy was performed with duct-to-mucosa anastomosis. A hepaticojejunostomy was performed 5–10 cm distal to the pancreaticojejunostomy. Then, an end-to-side duodenojejunostomy was performed about 50 cm distal to the hepaticojejunostomy based on randomization to either the antecolic or vertical retrocolic route. For vertical retrocolic duodenojejunostomy, the left side of the transverse mesocolon (to the left of the middle colic vessels) was opened, and the stomach and duodenum were brought down in a straight, vertical manner. The retrocolic duodenojejunostomy was performed at the caudal side of the transverse mesocolon, and the gastric antrum was fixed to the transverse mesocolon with several sutures. A Braun anastomosis was added in both reconstruction procedures. A schema of the reconstruction techniques used for both procedures is shown in Fig. 2. Two (or three) closed drains were placed around the pancreatic and biliary anastomoses. A pancreatic drainage tube and a biliary drainage tube were placed at the pancreatic duct and hepatic duct, respectively, and were exteriorized through the jejunal limb. A feeding tube was not placed in any of the patients.

All patients received prophylactic antibiotics for 2 to 3 days post-operatively. The patients were given epidural anaesthesia for 4–5 days post-operatively and/or adequate analgesia, and early ambulation was encouraged. The general protocol for patient care

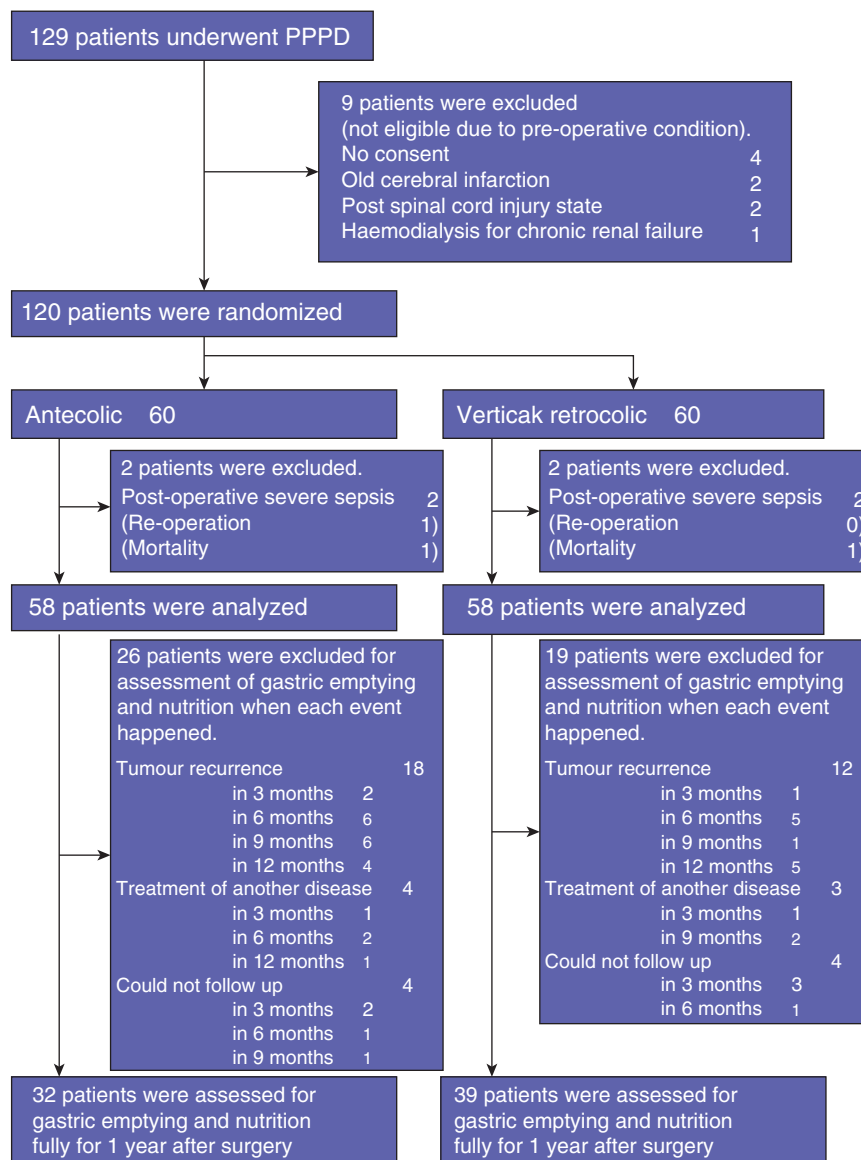


Figure 1 Participant flow chart

was to remove the nasogastric tube (NGT) routinely on postoperative day (POD) 1 if the gastric amount was below 500 ml after the first post-operative night. If the patients vomited persistently after removal of the NGT, it was reinserted. The drinking of water was started from POD 3, and a liquid diet was commenced on POD 4, with progression to a soft diet as tolerated. The drains were checked for amylase every day from POD 1 to POD 5 and were removed if there was no evidence of any pancreatic or biliary leakage. A proton pump inhibitor was administered intravenously after surgery and converted to an oral dose once a diet was tolerated. Pancreatic enzyme supplements were prescribed once a soft diet was commenced. No patient was given prokinetic drugs such as erythromycin or octreotide. Parenteral nutrition was used in

the patients with insufficient dietary intake owing to postoperative complications and was discontinued if the patients could tolerate more than half of their oral diet.

Post-operative complications

All resected specimens underwent definitive histological study after surgery. All patients with malignant disease underwent a gross complete (R0 or R1) resection. Post-operative complications were evaluated in all 116 patients (58 in each group). According to the ISGPS consensus criteria, DGE was defined by the need for maintenance or reinsertion of the NGT after POD 3 or inability to tolerate a solid diet after POD 7. The severity of DGE was classified into grades A, B, and C by the length of need for the NGT or

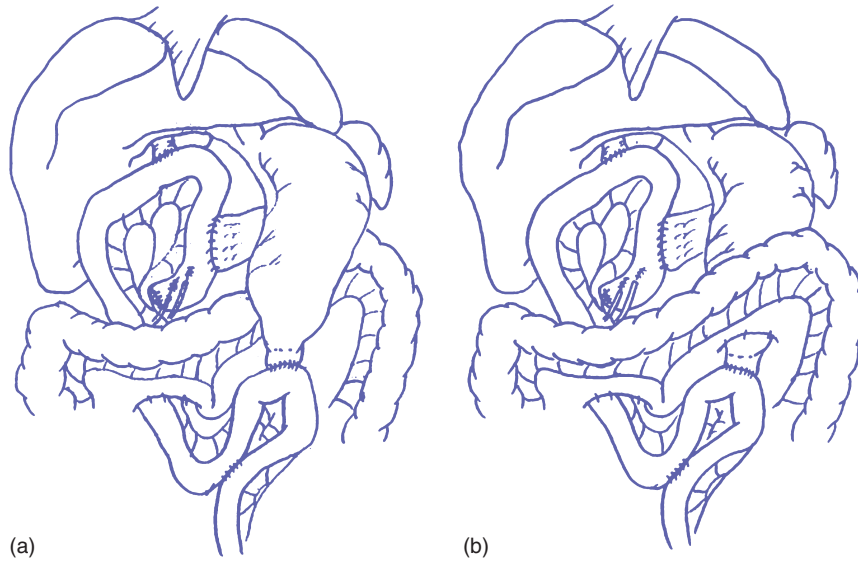


Figure 2 Schema showing reconstruction techniques after a pylorus-preserving pancreaticoduodenectomy. (a) Antecolic duodenojejunostomy. (b) Vertical retrocolic duodenojejunostomy

inability to tolerate a solid diet, and clinical impact.¹⁴ A pancreatic fistula was defined and graded according to the International Study Groups on Pancreatic Fistula (ISGPF) definition, and clinically relevant a pancreatic fistula was defined as grade B or C.¹⁸ A post-pancreatic surgery haemorrhage was defined according to the ISGPS definition.¹⁹ An intra-abdominal abscess was defined as culture-positive purulent drainage or findings of intra-abdominal fluid collection by computed tomography accompanied with fever elevation or leukocytosis. Mortality was defined as the patient death occurring until POD 30.

Gastric emptying and nutritional status for 1 year after surgery

Gastric emptying function was evaluated pre-operatively and at months 1, 3, 6, 9, and 12 post-operatively using the ¹³C-acetate breath test.^{15–17} A proton pump inhibitor was not given for 3 days before the test. All patients ingested a liquid meal (200 Kcal/200 ml, RACOL; Ohtsuka Pharmaceutical Co., Tokyo, Japan) labelled with 100 mg sodium ¹³C-acetate (Cambridge Isotope Laboratories, Inc., Andover, MA, USA) in the morning of the test day after an overnight fast. Breath samples were collected in the collection bag before and after ingestion of the test meal, i.e. before and at 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, 150 and 180 min after ingestion of the ¹³C-acetate. The recovery of ¹³C in the breath samples was analyzed by isotope-selective infrared spectrometry (UBiT-IR300; Otsuka Electronics Co., Ltd, Osaka, Japan). Gastric emptying was estimated by the values of the time when ¹³CO₂ reaches maximum excretion (T max), half-emptying time (T 1/2) and total % excretion of ¹³CO₂ in 2 h (%dose/2 h). These values were calculated with analysis software (Microsoft Office Excel; Microsoft Japan, Tokyo, Japan) from a calculated ¹³CO₂ breath excretion curve.

Follow-up at intervals of least every 3 months comprised a physical examination, laboratory tests including tumour markers, computed tomography, estimation of tumour recurrence and survival. All 58 patients in each group received ¹³C-acetate breath test as the measure of gastric emptying function, but patients with tumour recurrence were excluded at that point as subjects for assessment of nutritional status and ¹³C-acetate breath test. In addition, any patients whose treatment required hospital admission or a laparotomy for another disease and those who could not be followed up at the study institution because they had moved to a different location were excluded at the follow-up evaluation. The number of the patients excluded and the reasons for exclusion are shown in Fig. 1.

Data collection and study end points

The patients' clinicopathological and follow-up data were collected prospectively. The primary end point was the incidence of DGE. Secondary end points were post-operative complications except DGE, evaluation of gastric emptying and nutritional status for 1 year after surgery.

Statistical analysis

For statistical analysis of post-operative complications, especially DGE, a power calculation indicated that 58 patients needed to be enrolled for each procedure to test the premise of improving the rate of DGE from 30% to 10% at the two-tailed significance level of 5% with a power of 80%. Results are reported as median (range) or mean \pm standard error (SE). In comparisons between the A and VR groups, categorical variables were compared with chi-square test or Fisher's exact test, quantitative variables with the Student *t*-test, and non-parametric variables with the

Mann–Whitney U-test. In addition, Dunnett's post hoc test was used to compare change from the baseline (preoperative) value for the post-operative parameters of gastric emptying and nutritional status for 1 year after surgery. The level of significance was set at $P < 0.05$.

Results

Clinical characteristics and operative findings of the enrolled patients are shown in Table 1. There were no statistically signifi-

cant differences between the two groups with regards to age, gender ratio, body mass index, pre-operative body weight, the presence of diabetes mellitus, pre-operative nutritional biochemical parameters, pancreatic endocrine and exocrine function, pre-operative biliary drainage and type of disease (benign or malignant). The duration from presentation of disease to operation was also not significantly different between the two groups. Operative findings including operation time, operative blood loss, soft pancreas and portal vein resection were similar between the two groups (Table 1).

Table 1 Characteristics of patients and operative findings

	Antecolic (A) group (n = 58)	Vertical retrocolic (VR) group (n = 58)	P-value
Age (years) ^a	70.0 (36–86)	69.0 (46–86)	0.540
Gender (male/ female)	36 (62.1%)/ 22 (37.9%)	32 (55.2%)/ 26 (44.8%)	0.451
Body mass index (kg/m ²) ^a	21.8 (15.7–29.0)	21.3 (14.7–29.3)	0.463
Pre-operative body weight (kg) ^a	53.9 (35.6–78.8)	51.9 (30.5–75.8)	0.338
Diabetes mellitus	21 (36.2%)	21 (36.2%)	1.000
Pre-existing on admission	11 (19.0%)	7 (12.1%)	0.442
Newly diagnosed	10 (17.2%)	14 (24.1%)	0.359
Insulin dependant	4 (6.9%)	5 (8.6%)	0.729
Oral administration	9 (15.5%)	5 (8.6%)	0.393
Pre-operative albumin (g/dl) ^a	3.75 (2.94–4.78)	3.66 (2.69–4.48)	0.542
Pre-operative total cholesterol (mg/dl) ^a	177 (92–381)	181 (115–372)	0.204
Pre-operative haemoglobin-A1c (%) ^a	5.3 (3.6–11.0)	5.2 (3.9–10.9)	0.968
Pre-operative BT-PABA test (%) ^a	56.6 (10.6–82)	53.0 (12.9–87.4)	0.506
Pre-operative biliary drainage	38 (65.5%)	43 (74.1%)	0.312
Length of time from presentation of disease to operation (weeks) ^a	8 (3–36)	8 (4–21)	0.349
Pathology			
Benign/ malignancy	12 (20.7%)/ 46 (79.3%)	9 (15.5%)/ 49 (84.5%)	0.425
Pancreatic cancer	17 (29.3%)	16 (27.6%)	
Bile duct cancer	17 (29.3%)	20 (34.5%)	
Ampullary carcinoma	4 (6.9%)	9 (15.5%)	
Duodenal cancer	2 (3.4%)	0	
Cystic tumour (IPMN, MCN)	11 (19.0%)	6 (10.3%)	
Chronic pancreatitis	2 (3.4%)	3 (5.2%)	
Benign bile duct disease	2 (3.4%)	2 (3.4%)	
Others	3 (5.2%)	2 (3.4%)	
Operative findings			
Operating time (minutes) ^a	558.0 (427–967)	571.5 (422–769)	0.712
Operative blood loss (ml) ^a	1380 (360–6870)	1295 (230–3980)	0.440
Blood transfusion	36 (62.1%)	30 (51.7%)	0.261
Soft pancreas	32 (55.2%)	35 (60.3%)	0.573
Main pancreatic duct diameter (mm) ^a	4 (2–10)	3 (2–10)	0.467
Resected duodenum (cm) ^a	4 (2–4)	4 (3–4)	0.064
Portal vein resection	8 (13.8%)	4 (6.9%)	0.223

^aResults are expressed as median (range).

BT-PABA, N-benzoyl-L-tyrosyl-para-aminobenzoic acid; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm.

Post-operative complications

Post-operative complications before discharge from the hospital are shown in Table 2. Surgical morbidity between the two groups was not significantly different: 50.0% in the A group and 44.8% in the VR group. The overall incidence of clinically relevant pancreatic fistula (ISGPF grade B or C) occurred in 19 patients (16.4%). The incidence of all-grade pancreatic fistula was 37.9% in the A group and 29.3% in the VR group, and clinically relevant pancreatic fistula (ISGPF grade B or C) was 15.5% in the A group and 17.2% in the VR group, both without a statistically significant difference between the two groups. An intra-abdominal abscess occurred in 29 patients (25.0%), and the difference between the two groups was not statistically significant.

Delayed gastric emptying

The overall incidence of DGE was 16.4% (19 of 116 patients) (Table 2). The DGE grades of these patients were A in 10, B in 1 and C in 8 patients. In A group, the incidence of DGE was 12.1% (7 of 58 patients), and the grades were A in 4, B in 1 and C in 2 patients. In the VR group, the incidence of DGE was 20.7% (12 of 58 patients), and the grades were A in 6, B in 0 and C in 6 patients. Although the incidence of DGE tended to be higher in the VR versus the A group, the difference was not statistically significant ($P = 0.316$). The incidence of clinically relevant DGE (grades B and C) was 5.2% (3 patients) in the A group and 10.3% (6 patients) in the VR group, and the difference was still not statistically significant ($P = 0.298$). Clinical parameters related to DGE are shown in Table 2. The day of NGT removal was similar, on

Table 2 Post-operative complications, including clinical parameters related to delayed gastric emptying (DGE), and post-operative course

	Antecolic (A) group (n = 58)	Vertical retrocolic (VR) group (n = 58)	P-value
Morbidity	29 (50.0%)	26 (44.8%)	0.577
Pancreatic fistula (PF)	22 (37.9%)	17 (29.3%)	0.326
ISGPF grading (A/B/C)	13/6/3	7/8/2	
ISGPF grade B/C	9 (15.5%)	10 (17.2%)	0.802
Intra-abdominal abscess	16 (27.6%)	13 (22.4%)	0.520
Post-operative haemorrhage ^a	3 (5.2%)	3 (5.2%)	1.000
Biliary leakage	1 (1.7%)	0	0.315
Wound infection	9 (15.5%)	9 (15.5%)	1.000
Peptic ulcer	2 (3.4%)	1 (1.7%)	0.559
Cholangitis	5 (8.6%)	3 (5.2%)	0.464
DGE	7 (12.1%)	12 (20.7%)	0.316
ISGPS grading (A/B/C)	4/1/2	6/0/6	
ISGPS grade B/C	3 (5.2%)	6 (10.3%)	0.298
Clinical parameters related to DGE			
Removal of NGT (day) ^b	1 (0–2)	1 (0–20)	0.729
Removal of NGT as per protocol	55 (94.8%)	55 (94.8%)	1.000
Reinsertion of NGT	0	1 (1.7%)	0.315
Start of water drinking (day) ^b	3 (3–17)	3 (2–21)	0.833
Start of liquid diet (day) ^b	4 (4–37)	4 (4–28)	0.633
Start of solid diet (day) ^b	5 (5–38)	5.5 (5–29)	0.258
Start and progression of diet as per protocol	44 (75.9%)	42 (72.4%)	0.672
Duration of parenteral nutrition (days) ^b	11 (5–43)	14 (7–35)	0.097
Parenteral nutrition over 2 weeks	19 (32.8%)	21 (36.2%)	0.696
Post-operative course			
Hospital stay (days) ^p	36 (27–116)	36 (23–75)	0.910
Adjuvant chemotherapy	30 (51.7%)	29 (50.0%)	0.851
Tumour recurrence in 1st postoperative year	18 (31.0%)	12 (20.7%)	0.203

^aPost-pancreatic surgery haemorrhage was defined according to the ISGPS definition.

^bResults are expressed as median (range).

DGE, delayed gastric emptying; ISGPF, International Study Groups on Pancreatic Fistula; ISGPS, International Study Groups of Pancreatic Surgery; NGT, nasogastric tube.

median POD 1 in both groups. Only one patient in the VR group required reinsertion of the NGT, and the patient improved with conservative treatment and without additional interventions. The number of days to the start of liquid and solid diets, the duration of parenteral nutrition, and length of hospital stay were not significantly different between the two groups.

Changes in gastric emptying variables for 1 year after surgery

Results of the gastric emptying variables from the ¹³C-acetate breath test for 1 year after surgery are shown in Fig. 3. An increase in T max (the time when ¹³CO₂ reaches maximum excretion) and

in T 1/2 (half-emptying time) indicates prolonged gastric emptying, and an increase in %dose/2h (total % excretion of ¹³CO₂ in 2 h) indicates accelerated gastric emptying.

The value of T max was significantly prolonged at post-operative month 1 in comparison with the pre-operative value in both groups. The value of T max in the VR group was greater than that in the A group at post-operative month 1, but it was not significantly different (A group: 1.50 ± 0.14 h, VR group: 1.79 ± 0.23 h, *P* = 0.593). The values of T max at post-operative months 3, 6, 9, and 12 were equal to or shorter than the pre-operative values in both groups, and there were no significant differences between the two groups. Similarly, the value of T 1/2 was

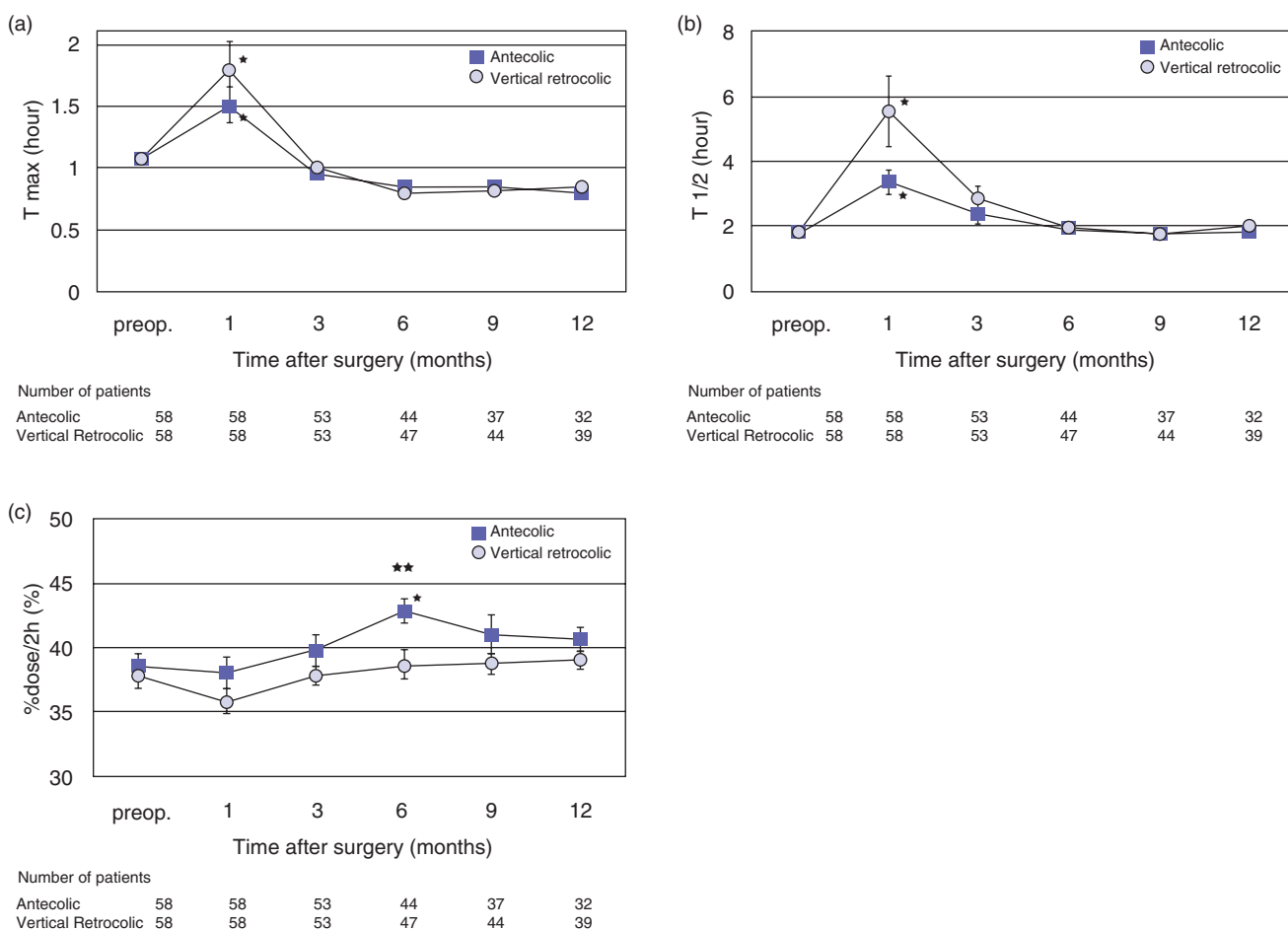


Figure 3 Post-operative change in parameters related to the ¹³C-acetate breath test: (a) the time when ¹³CO₂ reaches maximum excretion (T max), (b) half-emptying time (T 1/2), and (c) total % excretion of ¹³CO₂ in 2 h (%dose/2 h). Values are mean ± standard error. **P* < 0.05 for comparison of each post-operative time point value with the pre-operative value in the same group. ***P* < 0.05 for comparison of the antecolic (A) group with the vertical retrocolic (VR) group. There were no significant differences at any time points compared between the two groups in (a) and (b), except for (c). Comparisons between the values of each time point and the pre-operative value showed the following. (a) The values at post-operative month 1 were significantly greater than the pre-operative values for each group. (b) The values at post-operative month 1 were significantly greater than the pre-operative values for each group. (c) The value at post-operative month 6 in the A group was significantly greater than the pre-operative value. The values were greater in the A group than in the VR group at every time point, and the difference was significant at month 6 after surgery (A group: 42.9 ± 1.0%, VR group: 38.7 ± 1.1%, *P* = 0.001)

significantly prolonged at post-operative month 1 in comparison with the pre-operative value in both groups. The value of T 1/2 in the VR group was greater than that in the A group at post-operative month 1, but the difference was not statistically significant (A group: 3.37 ± 0.37 h, VR group: 5.55 ± 1.10 hours, $P = 0.164$). Post-operative changes in the value of T 1/2 gradually decreased as time passed, but the difference was not significant between the two groups. The value of %dose/2h was higher in the A group than in the VR group at all post-operative time points and was significantly higher at post-operative month 6 (A group: $42.9 \pm 1.0\%$, VR group: $38.7 \pm 1.1\%$, $P = 0.001$). Collectively, the VR group showed prolonged gastric emptying without a significant difference in the short term post-operatively (post-operative month 1). Both groups showed prolonged gastric emptying at post-operative month 1, but gastric emptying was not prolonged after post-operative month 3 compared with the pre-operative value. The A group continued accelerated gastric emptying after post-operative month 3, whereas the VR group values were essentially close to their own pre-operative values.

Nutritional parameters for 1 year after surgery

Post-operative backgrounds of the study subjects, such as undergoing of adjuvant chemotherapy and tumour recurrence within the first postoperative year, were not significantly different between the A and VR groups (Table 2).

The results of changes in post-operative nutritional parameters are shown in Fig. 4. Comparisons of the nutritional biochemical parameters including serum albumin, total cholesterol, haemoglobin-A1c and the N-benzoyl-L-tyrosyl-para-aminobenzoic acid (BT-PABA) test were almost similar (Fig. 4a–d, respectively). The values of serum albumin returned to the pre-operative level at post-operative month 3, but the values of total cholesterol and pancreatic functions continued to remain below the pre-operative level during the first post-operative year in both groups. Weight change in all patients from admission to operation was -1.27 ± 0.2 kg and was without significant difference between the two groups (-1.18 ± 0.3 kg in the A group versus -1.36 ± 0.3 kg in the VR group; $P = 0.969$). The results of changes in post-operative patient weight are shown in Fig. 5. The post-operative weight in both groups decreased at post-operative month 1 compared with the pre-operative weight and in both groups gradually regained weight as time passed. Post-operative weight loss in the A group was prolonged compared with that in the VR group, and this tendency was observed at all post-operative time points. The post-operative body weight recovered to nearly the pre-operative weight in the VR group at 1 year after surgery. The percentage of pre-operative weight in the VR group was significantly greater than that in the A group at post-operative month 12 (A group: $93.8 \pm 1.2\%$, VR group: $98.5 \pm 1.3\%$, $P = 0.015$).

Discussion

The results from the present prospective, randomized, clinical trial were that (i) the incidence of DGE was lower in an antecolic

duodenojejunostomy versus a vertical retrocolic duodenojejunostomy, but the difference was not significant, (ii) gastric emptying was more accelerated in the patients reconstructed with the antecolic route for 1 year after surgery, and (iii) body weight gain during the first year after surgery was superior in patients reconstructed using the vertical retrocolic route.

The PPPD procedure was first described by Watson in 1944²⁰ and reintroduced by Traverso and Longmire in 1978²¹ with the intent to improve post-operative nutritional status and avoid postgastrectomy syndromes, and DGE was considered as a specific complication after PPPD attributed to pylorus-sparing resection.⁴ The causative factors of DGE have been widely debated. These include anastomotic ischaemia, nerve damage, altered hormone levels, pylorospasm, gastric dysrhythmia, mechanical torsion and angularity, local inflammation and abdominal complications.^{4,7,10,22–26} To prevent or treat DGE after PPPD, the peri-operative use of prokinetic agents or different operative techniques has been tested.^{4,5,27–30} These peri-operative management or operative procedures were reported as possibly effective, but they have not gained wide acceptance. Several reports support an association between the reconstruction route used with PPPD and the incidence of DGE.^{4–13,26–29} Two reconstruction routes are used for a duodenojejunostomy during PPPD: the antecolic route and the retrocolic route. Many of the previous studies have suggested that the incidence of DGE is lower with an antecolic duodenojejunostomy because it may decrease the risk of mechanical problems as a result of angulation or torsion of the relatively fixed stomach.^{4–10} However, one randomized control trial¹¹ and the authors' preliminary reports^{12,13} showed no significant difference in the incidence of DGE between antecolic and retrocolic reconstruction.

Although DGE occurrence in the VR group was higher than that in the A group in the present study, the difference was not statistically significant. Of note, the difference in DGE incidences in this study may be underestimated by a lack of power (type II error) because the number of patients was set on the basis of the hypothesis that antecolic reconstruction decreases the rate of DGE from 30% to 10%. However, the vertical retrocolic reconstruction showed a lower incidence of DGE than was expected. The 10% incidence of clinically relevant DGE with the authors' vertical retrocolic reconstruction method was much less than the 24%–72% incidence reported with retrocolic reconstruction in previous reports^{6,8,9,11,24,29} and was comparable to the rates of 3–34% reported with antecolic reconstruction.^{6–11,25,27,28,31,32} Two possible reasons for the decreased occurrence of DGE with the authors' vertical retrocolic reconstruction method include (i) the duodenojejunostomy and stomach were separate from the excisions and the anastomotic field in the right upper quadrant and thus were spared expected inflammation, and (ii) the vertical and straight reconstruction avoided flexion and angulation of the stomach and contributed to flow of gastric contents by gravity in the upright position in patients.

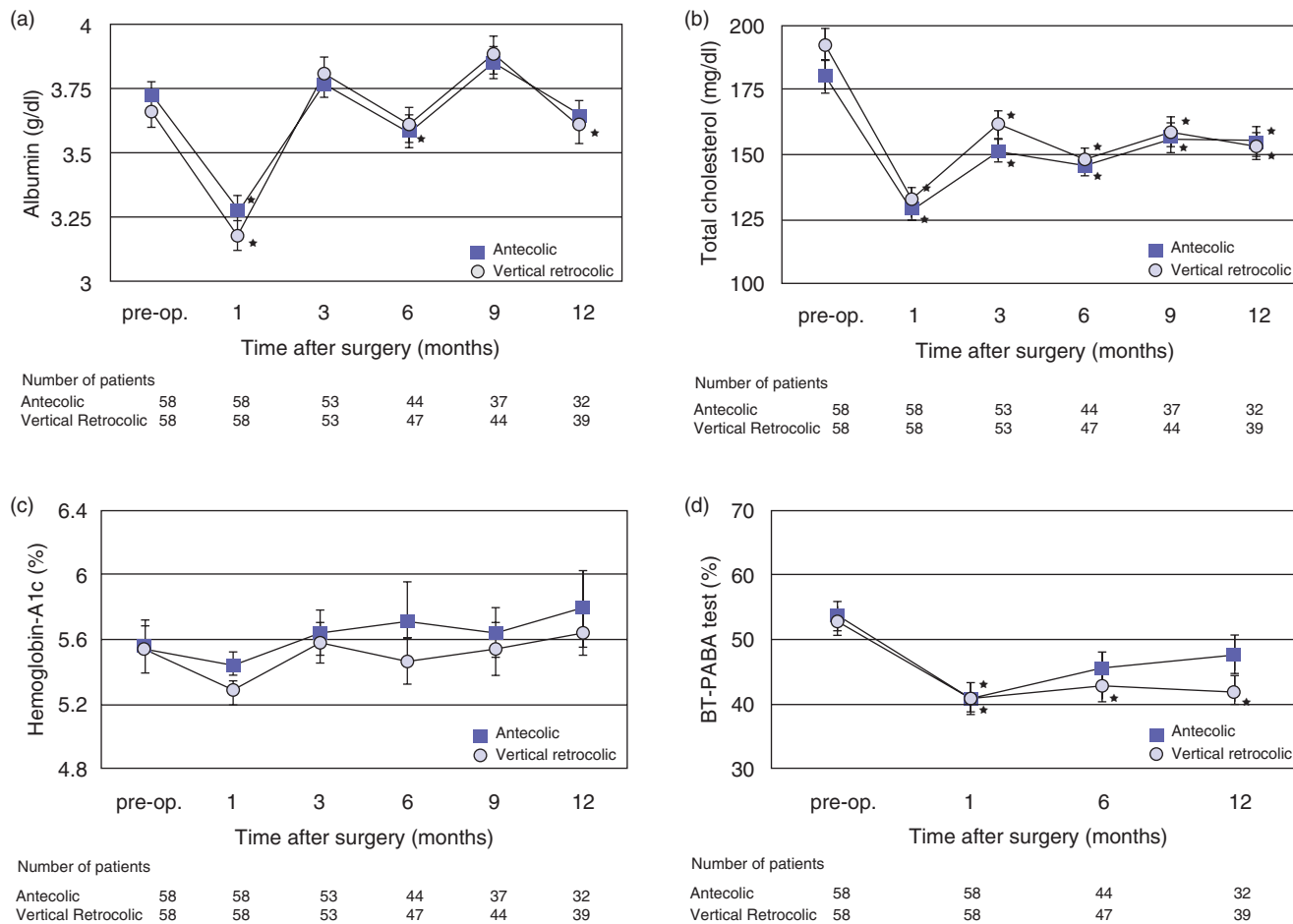
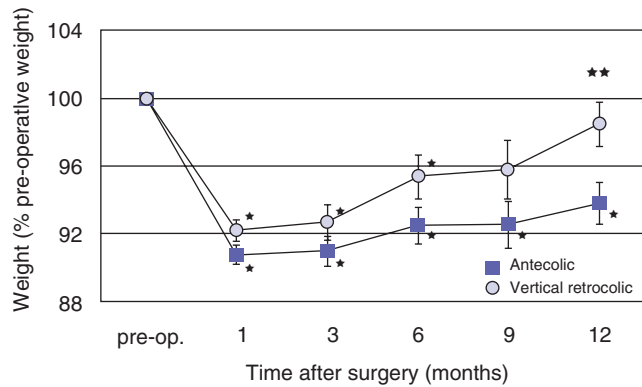


Figure 4 Post-operative changes in nutritional parameters: serum albumin (a), total cholesterol (b), haemoglobin-A1c (c) and the BT-PABA (N-benzoyl-L-tyrosyl-para-aminobenzoic acid) test (d). Values are mean \pm standard error. * $P < 0.05$ for comparison of the value of each post-operative time point with the pre-operative value in the same group. ** $P < 0.05$ for comparison of the antecolic (A) versus vertical retrocolic (VR) group. There were no significant differences at any time points compared between the two groups in (a)–(d). Comparisons between the values of each time point and the pre-operative value showed the following. (a) The values at post-operative months 1 and 6 were significantly lower than the pre-operative value in the A group, and the values at post-operative months 1 and 12 were significantly lower than the pre-operative value in the VR group. (b) The values at every post-operative time point were significantly lower than the pre-operative values in both groups. (c) There were no significant differences at any time point for both groups. (d) The value at post-operative month 1 was significantly lower than the pre-operative value in the A group, whereas the values at post-operative months 1, 6, and 12 were significantly lower than the pre-operative value in the VR group

Gastric emptying as assessed by the results of T max and T 1/2 was more prolonged in the VR group than the A group at post-operative month 1, but the difference was not significant. Most patients in the VR group did not develop clinical problems including the need for interventional treatment. At post-operative months 3, 6, 9, and 12, the results of T max and T 1/2 were essentially similar between the two groups, recovering close to the pre-operative values. In contrast, gastric emptying as indicated by the %dose/2h results was more accelerated in the A group than in VR group patients, and the difference was significant at post-operative month 6. In addition, the %dose/2 h results in the VR

group were essentially close to their own pre-operative values, whereas those in the A group were higher than the pre-operative values until post-operative month 12. These results imply that the vertical retrocolic reconstruction may maintain more physiological gastric emptying after surgery compared with the antecolic reconstruction.

With regard to nutritional status in the present study, the values of serum albumin returned to the pre-operative level at post-operative month 3, but the values of total cholesterol continued to remain below the pre-operative level during the first post-operative year in both groups. These results were similar to those



Number of patients	pre-op.	1	3	6	9	12
Antecolic	58	58	53	44	37	32
Vertical Retrocolic	58	58	53	47	44	39

Figure 5 Post-operative change in patient weight. Post-operative weight was compared as a percentage of pre-operative weight. Values are mean \pm standard error. * $P < 0.05$ for comparison of the value of each post-operative time point with the pre-operative value in the same group. ** $P < 0.05$ for comparison of the antecolic (A) versus the vertical retrocolic (VR) group. The values at post-operative months 1, 3, 6, 9 and 12 were significantly lower than the pre-operative value in the A group, whereas the values at post-operative months 1, 3 and 6 were significantly lower than the pre-operative value in the VR group. In comparison between the two groups, the values were greater in the VR versus the A group at every time point, and the difference was significant at month 12 after surgery (percentage of preoperative weight, A group: $93.8 \pm 1.2\%$; VR group: $98.5 \pm 1.3\%$, $P = 0.015$)

in previous reports.^{31,32} The changes in biochemical parameters between the two groups were similar. In contrast, the patients in the A group had a prolonged body weight loss compared with those in the VR group. The factors relating to post-operative weight gain after PPPD have been reported to be pancreatic endocrine and exocrine function, disease, operative procedure, intra- or post-operative chemoradiation therapy and tumour recurrence.^{33–36} The nutritional parameters and tumour status were similar between the two groups in the present study. Thus, these results were difficult to explain in terms of the differences in body weight change between the two reconstruction methods. When the reason for the differences in body weight change between the two reconstructions is considered, gastric emptying may be highlighted. In a series of gastric surgeries, a pylorus-preserving gastrectomy was reported to lead to slower gastric emptying and better post-operative weight gain compared with a conventional distal gastrectomy with Billroth I anastomosis.^{37,38} In regard to bariatric surgeries, several reports suggested that operative procedures such as gastric Roux-en-Y bypass or sleeve gastrectomy may reduce weight owing to enhanced endogenous release of anorexigenic gut peptides (cholecystokinin, glucagon-like peptide-1, and polypeptide YY) by changing the acceleration

of gastric emptying and increasing delivery of nutrients to the distal small intestine.³⁹ In the present study, antecolic reconstruction is speculated to be potentially associated with prolonged post-operative weight loss affected by accelerated gastric emptying. However, the post-operative weight change is a result of multiple factors, and it may be difficult to explain weight change only on the basis of the influence of gastric emptying. Furthermore, post-operative patient eating habits and the status of health including quality of life were not evaluated. Further analysis focusing on post-operative nutritional status affected by subsequently changing gastrointestinal function such as gastric emptying and the profile and response of gut peptides may be required.

In conclusion, the results of this prospective, randomized, clinical trial showed that a vertical retrocolic duodenojejunostomy was an acceptable procedure for a lower incidence of DGE. In addition, a vertical retrocolic duodenojejunostomy may result in a better body weight recovery by maintaining moderate (not too accelerated) gastric emptying compared with that of an antecolic duodenojejunostomy. Although further studies are awaited, a vertical retrocolic duodenojejunostomy is proposed as a potential choice of reconstruction method in patients undergoing PPPD.

Acknowledgement

A part of this study was supported by grants-in-aid (Nos. 17591417 and 20591635) from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

Conflicts of interest

None declared.

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