Prospective Randomized Clinical Trial of Change in Gastric Emptying and Nutritional Status After Pylorus-Preserving Pancreaticoduodenectomy: Comparison Between Antecolic and Vertical Retrocolic Duodenojejunostomy

Naoya Imamura, MD, Kazuo Chijiiwa, MD, PhD, FACS, AGAF, Jiro Ohuchida, MD
Masahide Hiyoshi, MD, Motoaki Nagano, MD, Kazuhiro Otani, MD, Kazuhiro Kondo, MD

Department of Surgical Oncology and Regulation of Organ Function, Miyazaki University School of Medicine, Miyazaki, Japan

Corresponding author and reprint requests to:

Kazuo Chijiiwa, MD, PhD, FACS, AGAF

Department of Surgical Oncology and Regulation of Organ Function, Miyazaki University School of Medicine, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan

Tel: +81-985-85-2905

Fax: +81-985-85-2808

E-mail: kazuochi@med.miyazaki-u.ac.jp

Sources of funding for research: Grant-in-aid (No.17591417, No.20591635) from the Japanese Ministry of Education, Culture, Sports, Science and Technology

Category of the manuscript: Randomized clinical trial

Previous communication to a society or meeting: None

Abstract

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

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

Results: Incidence of DGE was not significantly different between procedures (A group: 12.1%; VR group: 20.7%, P=0.316). At postoperative month 1, gastric emptying was prolonged in the VR versus A group but not significantly so. At postoperative month 6, gastric emptying was accelerated significantly in the A versus VR group. Postoperative weight recovery was significantly better in the VR versus A group at postoperative month 12 (percentage of preoperative weight, A group: 93.8±1.2%; VR group: 98.5±1.3%, P=0.015).

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

Clinical trial registration number: (Japanese) University Hospital Medical Information Network Clinical Trials Registry as UMIN000001712

INTRODUCTION

Pylorus-preserving pancreaticoduodenectomy (PPPD) is the standard operation for periampullary disease. Although operative mortality of PPPD has been reduced to less than 5% [1-4], postoperative 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 patient quality of life.

Two reconstruction methods after PPPD are associated with the transverse colon: antecolic duodenojejunostomy and retrocolic duodenojejunostomy. Antecolic duodenojejunostomy is reported to offer equal or superior outcomes for 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 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 antecolic duodenojejunostomy or vertical retrocolic duodenojejunostomy. Although some studies reported to notice an association between DGE and reconstruction route, postoperative 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 ^{13}C-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 PPPD at the Department of Surgical Oncology and Regulation of Organ Function, Miyazaki University School of Medicine. The patients who underwent pancreaticoduodenectomy with gastric resection, subtotal stomach-preserving PD (SSPPD), additional hepatic resection, and total pancreatectomy were excluded from the study. The patients underwent a standard pretreatment evaluation, randomization to antecolic or vertical retrocolic duodenojejunostomy, and assessment of 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 Figure 1. Because of their preoperative condition, 4 patients who did not give their informed consent and 5 patients with severe comorbidity were excluded. The remaining 120 patients underwent randomization; however, 4 patients with postoperative severe sepsis (2 undergoing each reconstruction method) were excluded. Re-operation was performed in 1 patient (0.8%) in the antecolic group for ischemic perforation of the duodenojejunostomy. Postoperative mortality occurred in 2 patients (1.7%), 1 patient in the antecolic group due to sepsis from intravenous catheter infection, and 1 patient in the vertical retrocolic group due to liver failure associated with a vascular problem.

Thus, the remaining 116 patients were divided into two groups: antecolic group (A group, *n* = 58), and the vertical retrocolic group (VR group, *n* = 58).

All patients underwent detailed preoperative physical examination with hematological and biochemical assessment including measurement of tumor markers. The indication for surgery for all patients was suspected periampullary lesion on the basis of computed tomography and additional imaging studies. Patients with distant metastases or locally far advanced tumors were judged to be inoperable. Patients with jaundice underwent preoperative endoscopic or percutaneous transhepatic biliary drainage to decrease their serum bilirubin level. Preoperative diabetes mellitus was assessed by serum hemoglobin A1c level, fasting plasma glucose level, random glucose level, and 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 antecolic or 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 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 complete tumor 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 Figure 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 postoperatively. The patients were given epidural anesthesia for 4-5 days postoperatively and/or adequate analgesia, and early ambulation was encouraged. The general protocol for patient care was to remove the nasogastric tube (NGT) routinely on postoperative day (POD) 1 if the gastric amount was below 500 ml after the first postoperative 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 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 following 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 due to postoperative complications and was discontinued if the patients could tolerate more than half of their oral diet.

Postoperative Complications

All resected specimens underwent definitive histological study after surgery. All patients with malignant disease underwent gross complete (R0 or R1) resection. Postoperative 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 inability to tolerate solid diet, and clinical impact [14]. Pancreatic fistula was defined and graded according to the International Study Groups on Pancreatic Fistula (ISGPF) definition, and clinically relevant pancreatic fistula was defined as grade B or C [18]. Post-pancreatic surgery hemorrhage was defined according to the ISGPS definition [19]. 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 patient death occurring until POD 30.

Gastric Emptying and Nutritional Status for 1 Year After Surgery

Gastric emptying function was evaluated preoperatively and at months 1, 3, 6, 9, and 12 postoperatively by ^{13}C-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) labeled with 100 mg sodium ^{13}C-acetate (Cambridge Isotope Laboratories, Inc., Andover, MA) 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 minutes after ingestion of the ^{13}C-acetate. The recovery of ^{13}C 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 $^{13}CO_2$ reaches maximum excretion (T max), half-emptying time (T 1/2), and total % excretion of $^{13}CO_2$ in 2 hours (%dose/2h). These values were calculated with analysis software (Microsoft Office Excel; Microsoft Japan, Tokyo, Japan) from a calculated $^{13}CO_2$ breath excretion curve.

Follow-up at intervals of least every 3 months comprised physical examination, laboratory tests including tumor markers, computed tomography, estimation of tumor recurrence, and survival. All 58 patients in each group received ^{13}C-acetate breath test as the measure of gastric emptying function, but patients with tumor recurrence were excluded at that point as subjects for assessment of nutritional status and ^{13}C-acetate breath test. In addition, any patients whose treatment required hospital admission or 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 Figure 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 postoperative complication except DGE, evaluation of gastric emptying, and nutritional status for 1 year after surgery.

Statistics

For statistical analysis of postoperative 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 ± 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, the Dunnett post hoc test was used to compare change from baseline (preoperative) value for the postoperative 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 significant differences between the two groups in age, sex ratio, body mass index, preoperative body weight, presence of diabetes mellitus, preoperative nutritional biochemical parameters, pancreatic endocrine and exocrine function, preoperative 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).

Postoperative Complications

Postoperative complications before discharge from 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. 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 statistically significant difference between the two groups. 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 the 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 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 median POD 1 in both groups. Only 1 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 start of liquid and solid diets, 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 ^{13}C-acetate breath test for 1 year after surgery are shown in Figure 3. An increase in T max (the time when $^{13}CO_2$ reaches maximum excretion) and in T 1/2 (half-emptying time) indicates prolonged gastric emptying, and an increase in %dose/2h (total % excretion of $^{13}CO_2$ in 2 hours) indicates accelerated gastric emptying.

The value of T max was significantly prolonged at postoperative month 1 in comparison with the preoperative value in both groups. The value of T max in the VR group was greater than that in the A group at postoperative month 1, but it was not significantly different (A group: 1.50 ± 0.14 hours, VR group: 1.79 ± 0.23 hours, P = 0.593). The values of T max at postoperative months 3, 6, 9, and 12 were equal to or shorter than the preoperative values in both groups, and there were no significant differences between the two groups. Similarly, the value of T 1/2 was significantly prolonged at postoperative month 1 in comparison with the preoperative value in both groups. The value of T 1/2 in the VR group was greater than that in the A group at postoperative month 1, but the difference was not statistically significant (A group: 3.37 ± 0.37 hours, VR group: 5.55 ± 1.10 hours, $P = 0.164$). Postoperative 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 postoperative time points and was significantly higher at postoperative month 6 (A group: 42.9 ± 1.0%, VR group: 38.7 ± 1.1%, $P = 0.001$). Collectively, the VR group showed prolonged gastric emptying without a significant difference in the short term postoperatively (postoperative month 1). Both groups showed prolonged gastric emptying at postoperative month 1, but gastric emptying was not prolonged after postoperative month 3 compared with the preoperative value. The A group continued accelerated gastric emptying after postoperative month 3, whereas the VR group values were essentially close to their own preoperative values.

Nutritional Parameters for 1 Year After Surgery

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

The results of changes in postoperative nutritional parameters are shown in Figure 4. Comparisons of the nutritional biochemical parameters including serum albumin, total cholesterol, hemoglobin-A1c, and N-benzoyl-L-tyrosyl-para-aminobenzoic acid (BT-PABA) test were almost similar (Fig. 4a, b, c, and d, respectively). The values of serum albumin returned to the preoperative level at postoperative month 3, but the values of total cholesterol and pancreatic functions continued to remain below the preoperative level during the first postoperative 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 A group vs. -1.36 ± 0.3 kg in VR group; $P = 0.969$). The results of changes in postoperative patient weight are shown in Figure 5. Postoperative weight in both groups decreased at postoperative month 1 compared with preoperative weight, and both groups gradually regained weight as time passed. Postoperative weight loss in the A group was prolonged compared with that in the VR group, and this tendency was observed at all postoperative time points. Postoperative body weight recovered to nearly the preoperative weight in the VR group at 1 year after surgery. The percentage of preoperative weight in the VR group was significantly greater than that in the A group at postoperative month 12 (A group: 93.8 ± 1.2%, VR group: 98.5 ± 1.3%, $P = 0.015$).

DISCUSSION

The results from the present prospective, randomized, clinical trial were that 1) the incidence of DGE was lower in antecolic duodenojejunostomy versus vertical retrocolic duodenojejunostomy, but the difference was not significant, 2) gastric emptying was more accelerated in the patients reconstructed with the antecolic route for 1 year after surgery, and 3) body weight gain during the first year after surgery was superior in patients reconstructed with the vertical retrocolic route.

The PPPD procedure was first described by Watson in 1944 [20] and reintroduced by Traverso and Longmire in 1978 [21] with the intent to improve postoperative 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 ischemia, 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 perioperative use of prokinetic agents or different operative techniques has been tested [4,5,27-30]. These perioperative 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 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 antecolic duodenojejunostomy because it may decrease the risk of mechanical problems due to angulation or torsion of the relatively fixed stomach [4-10]. However, one randomized control trial [11] 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 of DGE incidences in this study may be underestimated by 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 1) the duodenojejunostomy and stomach were separate from the excisions and anastomotic field in the right upper quadrant and thus were spared expected inflammation, and 2) 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.

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 postoperative 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 postoperative 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 preoperative values. In contrast, gastric emptying as indicated by the %dose/2h results was more accelerated in the A group than VR group patients, and the difference was significant at postoperative month 6. In addition, the %dose/2h results in the VR group were essentially close to their own preoperative values, whereas those in the A group were higher than the preoperative values until postoperative month 12. These results imply that the vertical retrocolic reconstruction may maintain more physiological gastric emptying after surgery compared to the antecolic reconstruction.

With regard to nutritional status in the present study, the values of serum albumin returned to the preoperative level at postoperative month 3, but the values of total cholesterol continued to remain below the preoperative level during the first postoperative year in both groups. These results were similar to those 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 prolonged body weight loss compared with those in the VR group. The factors relating to postoperative weight gain after PPPD have been reported to be pancreatic endocrine and exocrine function, disease, operative procedure, intra- or postoperative chemoradiation therapy, and tumor recurrence [33-36]. The nutritional parameters and tumor 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 are considered, gastric emptying may be highlighted. In a series of gastric surgeries, pylorus-preserving gastrectomy was reported to lead to slower gastric emptying and better postoperative weight gain compared with 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 due 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 postoperative weight loss affected by accelerated gastric emptying. However, postoperative 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, postoperative patient eating habits and status of health including quality of life were not evaluated. Further analysis focusing on postoperative 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 vertical retrocolic duodenojejunostomy was an acceptable procedure for lower incidence of DGE. In addition, vertical retrocolic duodenojejunostomy may result in better body weight recovery by maintaining moderate (not too accelerated) gastric emptying compared with that of antecolic duodenojejunostomy. Although further studies are awaited, vertical retrocolic duodenojejunostomy is proposed as a potential choice of reconstruction method in patients undergoing PPPD.

Acknowledgment

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.

REFERENCES

1. McPhee JT, Hill JS, Whalen GF, Zayaruzny M, Litwin DE, Sullivan ME, et al. (2007) Perioperative mortality for pancreatectomy: a national perspective. *Ann Surg* 246:246–253.
2. Schäfer M, Müllhaupt B, Clavien PA. (2002) Evidence-based pancreatic head resection for pancreatic cancer and chronic pancreatitis. *Ann Surg* 236:137–148.
3. Cameron JL, Riall TS, Coleman J, Belcher KA. (2006) One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 244:10–15.
4. Lytras D, Paraskevas KI, Avgerinos C, Manes C, Touloumis Z, Paraskeva KD, et al. (2007) Therapeutic strategies for the management of delayed gastric emptying after pancreatic resection. *Langenbecks Arch Surg* 392:1–12.
5. Traverso LW, Hashimoto Y. (2008) Delayed gastric emptying: the state of the highest level of evidence. *J Hepatobiliary Pancreat Surg* 15:262–269.
6. Tani M, Terasawa H, Kawai M, Ina S, Hirono S, Uchiyama K, et al. (2006) Improvement of delayed gastric emptying in pylorus-preserving pancreaticoduodenectomy: results of a prospective, randomized, controlled trial. *Ann Surg* 243:316–320.
7. Horstmann O, Markus PM, Ghadimi MB, Becker H. (2004) Pylorus preservation has no impact on delayed gastric emptying after pancreatic head resection. *Pancreas* 28:69–74.
8. Hartel M, Wente MN, Hinz U, Kleeff J, Wagner M, Müller MW, et al. (2005) Effect of antecolic reconstruction on delayed gastric emptying after the pylorus-preserving Whipple procedure. *Arch Surg* 140:1094–1099.
9. Sugiyama M, Abe N, Ueki H, Masaki T, Mori T, Atomi Y. (2004) A new reconstruction method for preventing delayed gastric emptying after pylorus-preserving pancreatoduodenectomy. *Am J Surg* 187:743–746.

10. Kurosaki I, Hatakeyama K. (2005) Preservation of the left gastric vein in delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy. *J Gastrointest Surg* 9:846–852.

11. Gangavatiker R, Pal S, Javed A, Dash NR, Sahni P, Chattopadhyay TK. (2011) Effect of antecolic or retrocolic reconstruction of the gastro/duodenojejunostomy on delayed gastric emptying after pancreaticoduodenectomy: a randomized controlled trial. *J Gastrointest Surg* 15:843–52.

12. Chijiiwa K, Imamura N, Ohuchida J, Hiyoshi M, Nagano M, Otani K, et al. (2009) Prospective randomized controlled study of gastric emptying assessed by (13)C-acetate breath test after pylorus preserving pancreaticoduodenectomy: comparison between antecolic and vertical retrocolic duodenojejunostomy. *J Hepatobiliary Pancreat Surg* 16:49–55.

13. Chijiiwa K, Ohuchida J, Hiyoshi M, Nagano M, Kai M, Kondo K. (2007) Vertical retrocolic duodenojejunostomy decreases delayed gastric emptying after pylorus-preserving pancreatoduodenectomy. *Hepatogastroenterology* 54:1874–1877.

14. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 142:761–768.

15. Braden B, Adams S, Duan LP, Orth KH, Maul FD, Lembcke B, et al. (1995) The [13C]acetate breath test accurately reflects gastric emptying of liquids in both liquid and semisolid test meals. Gastroenterology 108:1048–1055.

16. Nakata K, Aoyama N, Nakagawa M, Kawasaki S, Shirasaka D, Zai H, et al. (2002) The present and the future in gastric emptying study assessed by 13C-acetate breath test-with special reference to the standardization of the method- [in Japanese]. *J Smooth Muscle Res* 6:J75–J91.

17. Takahashi Y, Amano Y, Yuki T, Ose T, Miyake T, Kushiyama Y, et al. (2006) Influence of

acid suppressants on gastric emptying: cross-over analysis in healthy volunteers. *J Gastroenterol Hepatol* 21:1664–1668.

18. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 138:8–13.
19. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. (2007) Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 142:20–25.
20. Watson K. (1944) Carcinoma of the ampulla of Vater. Successful radical resection. *Br J Surg* 31:368–373.
21. Traverso LW, Longmire WP Jr. (1978) Preservation of the pylorus in pancreaticoduodenectomy. *Surg Gynecol Obstet* 146:959–962.
22. Welsch T, Borm M, Degrate L, Hinz U, Büchler MW, Wente MN. (2010) Evaluation of the International Study Group of Pancreatic Surgery definition of delayed gastric emptying after pancreatoduodenectomy in a high-volume centre. *Br J Surg* 97:1043–1050.
23. Malleo G, Crippa S, Butturini G, Salvia R, Partelli S, Rossini R, et al. (2010) Delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy: validation of International Study Group of Pancreatic Surgery classification and analysis of risk factors. *HPB* 12:610–618.
24. Akizuki E, Kimura Y, Nobuoka T, Imamura M, Nagayama M, Sonoda T, et al. (2009) Reconsideration of postoperative oral intake tolerance after pancreaticoduodenectomy: prospective consecutive analysis of delayed gastric emptying according to the ISGPS definition and the amount of dietary intake. *Ann Surg* 249:986–994.
25. Park JS, Hwang HK, Kim JK, Cho SI, Yoon DS, Lee WJ, et al. (2009) Clinical validation and risk factors for delayed gastric emptying based on the International Study Group of

Pancreatic Surgery (ISGPS) Classification. *Surgery* 146:882–887.

26. Qu H, Sun GR, Zhou SQ, He QS. (2013) Clinical risk factors of delayed gastric emptying in patients after pancreaticoduodenectomy: a systematic review and meta-analysis. *Eur J Surg Oncol.* 39:213–223.
27. Hochwald SN, Grobmyer SR, Hemming AW, Curran E, Bloom DA, Delano M, et al. (2010) Braun enteroenterostomy is associated with reduced delayed gastric emptying and early resumption of oral feeding following pancreaticoduodenectomy. *J Surg Oncol* 101:351–355.
28. Sakamoto Y, Yamamoto Y, Hata S, Nara S, Esaki M, Sano T, et al. (2011) Analysis of risk factors for delayed gastric emptying (DGE) after 387 pancreaticoduodenectomies with usage of 70 stapled reconstructions. *J Gastrointest Surg* 15:1789–1797.
29. Kollmar O, Sperling J, Moussavian MR, Kubulus D, Richter S, Schilling MK. (2011) Delayed gastric emptying after pancreaticoduodenectomy: influence of the orthotopic technique of reconstruction and intestinal motilin receptor expression. *J Gastrointest Surg* 15:1158–1167.
30. Balzano G, Zerbi A, Braga M, Rocchetti S, Beneduce AA, Di Carlo V. (2008) Fast-track recovery programme after pancreatico- duodenectomy reduces delayed gastric emptying. *Br J Surg* 95:1387–1393.
31. Kawai M, Tani M, Hirono S, Miyazawa M, Shimizu A, Uchiyama K, et al. (2011) Pylorus ring resection reduces delayed gastric emptying in patients undergoing pancreatoduodenectomy: a prospective, randomized, controlled trial of pylorus-resecting versus pylorus-preserving pancreatoduodenectomy. *Ann Surg* 253:495–501.
32. Fujii T, Kanda M, Kodera Y, Nagai S, Sahin TT, Hayashi M, et al. (2012) Preservation of the pyloric ring has little value in surgery for pancreatic head cancer: a comparative study comparing three surgical procedures. *Ann Surg Oncol* 19:176–183.

33. Niedergethmann M, Shang E, Farag Soliman M, Saar J, Berisha S, Willeke F, et al. (2006) Early and enduring nutritional and functional results of pylorus preservation vs classic Whipple procedure for pancreatic cancer. *Langenbecks Arch Surg* 391:195–202.

34. van Berge Henegouwen MI, Moojen TM, van Gulik TM, Rauws EA, Obertop H, Gouma DJ. (1998) Postoperative weight gain after standard Whipple's procedure versus pylorus-preserving pancreatoduodenectomy: the influence of tumour status. *Br J Surg* 85:922–926.

35. Ohtsuka T, Yamaguchi K, Chijiiwa K, Tanaka M. (2001) Postoperative pancreatic exocrine function influences body weight maintenance after pylorus-preserving pancreatoduodenectomy. *Am J Surg* 182:524–529.

36. Ohuchida J, Chijiiwa K, Ohtsuka T, Konomi H, Tanaka M. (2007) Pylorus-preserving pancreatoduodenectomy: preoperative pancreatic function and outcome. *Hepatogastroenterology* 54:913–916.

37. Nunobe S, Sasako M, Saka M, Fukagawa T, Katai H, Sano T. (2007) Symptom evaluation of long-term postoperative outcomes after pylorus-preserving gastrectomy for early gastric cancer. *Gastric Cancer* 10:167–172.

38. Park do J, Lee HJ, Jung HC, Kim WH, Lee KU, Yang HK. (2008) Clinical outcome of pylorus-preserving gastrectomy in gastric cancer in comparison with conventional distal gastrectomy with Billroth I anastomosis. *World J Surg* 32:1029–1036.

39. Horner KM, Byrne NM, Cleghorn GJ, Näslund E, King NA. (2011) The effects of weight loss strategies on gastric emptying and appetite control. *Obes Rev* 12:935–951.

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
Sex (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
Preoperative 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
Preexisting 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
Preoperative albumin (g/dl)[a]	3.75 (2.94-4.78)	3.66 (2.69-4.48)	0.542
Preoperative total cholesterol (mg/dl)[a]	177 (92-381)	181 (115-372)	0.204
Preoperative hemoglobin-A1c (%)[a]	5.3 (3.6-11.0)	5.2 (3.9-10.9)	0.968
Preoperative BT-PABA test (%)[a]	56.6 (10.6-82)	53.0 (12.9-87.4)	0.506
Preoperative 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 tumor (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

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

[a] Results are expressed as median (range).

Table 2. Postoperative Complications, Including Clinical Parameters Related to DGE, and Postoperative 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
Postoperative hemorrhage [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
Postoperative course			
Hospital stay (days)[b]	36 (27-116)	36 (23-75)	0.910
Adjuvant chemotherapy	30 (51.7%)	29 (50.0%)	0.851
Tumor recurrence in 1st postoperative year	18 (31.0%)	12 (20.7%)	0.203

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

[a] Post-pancreatic surgery hemorrhage was defined according to the ISGPS definition.

[b] Results are expressed as median (range).

FIGURE LEGENDS

Fig. 1 Participant flow chart.

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

Fig. 3 Postoperative change in parameters related to the ^{13}C-acetate breath test: (a) the time when $^{13}CO_2$ reaches maximum excretion (T max), (b) half-emptying time (T 1/2), and (c) total % excretion of $^{13}CO_2$ in 2 hours (%dose/2h). Values are mean ± standard error. **P* <0.05 for comparison of each postoperative time point value with the preoperative 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 preoperative value showed the following. (a) The values at postoperative month 1 were significantly greater than the preoperative values for each group. (b) The values at postoperative month 1 were significantly greater than the preoperative values for each group. (c) The value at postoperative month 6 in the A group was significantly greater than the preoperative 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).

Fig. 4 Postoperative changes in nutritional parameters: serum albumin (a), total cholesterol (b), hemoglobin-A1c (c), and BT-PABA (N-benzoyl-L-tyrosyl-para-aminobenzoic acid) test (d).

Values are mean ± standard error. *P <0.05 for comparison of the value of each postoperative time point with the preoperative 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 preoperative value showed the following. (a) The values at postoperative months 1 and 6 were significantly lower than the preoperative value in the A group, and the values at postoperative months 1 and 12 were significantly lower than the preoperative value in the VR group. (b) The values at every postoperative time point were significantly lower than the preoperative values in both groups. (c) There were no significant differences at any time point for both groups. (d) The value at postoperative month 1 was significantly lower than the preoperative value in the A group, whereas the values at postoperative months 1, 6, and 12 were significantly lower than the preoperative value in the VR group.

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

Figure 1

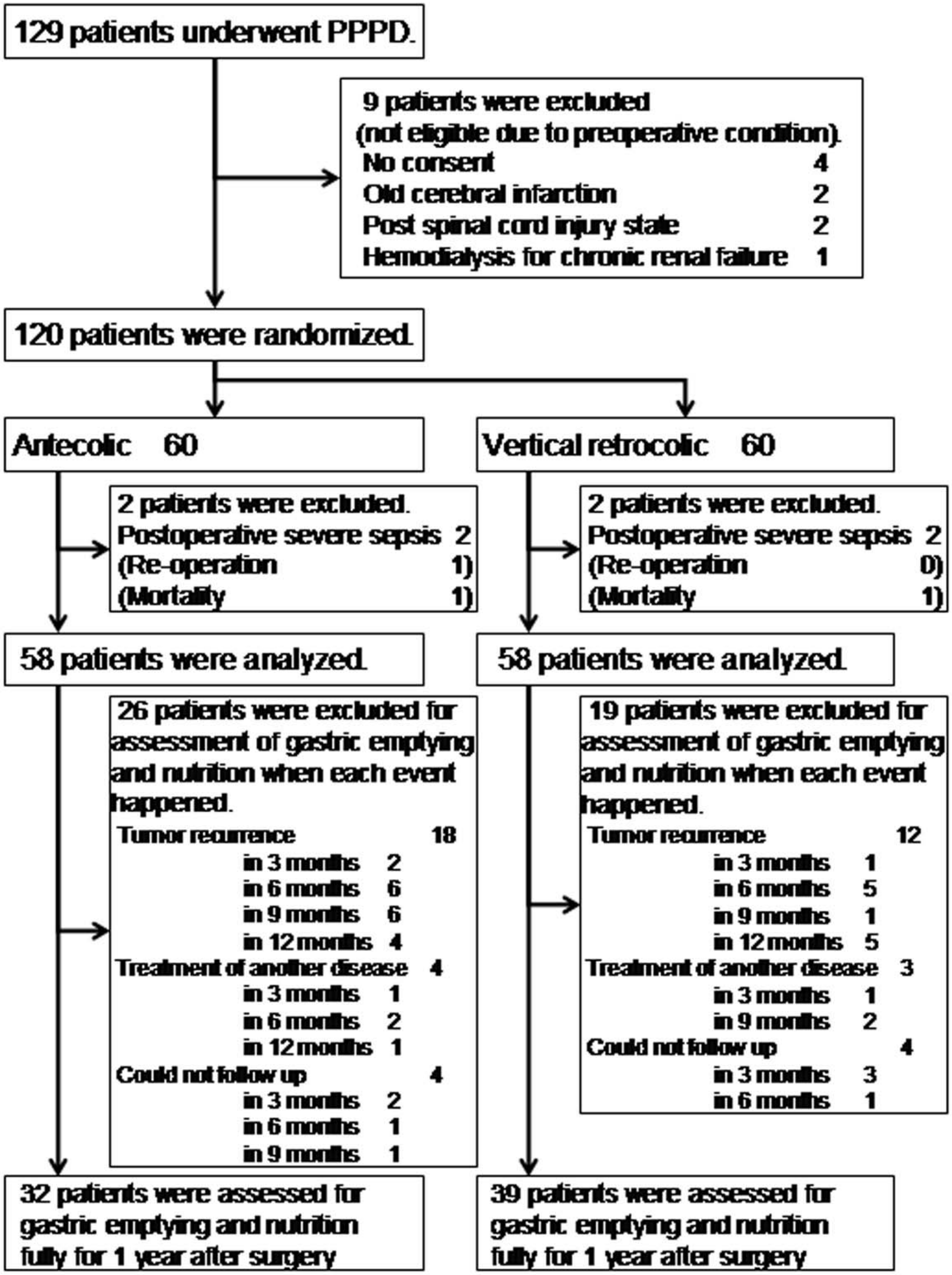

129 patients underwent PPPD.
9 patients were excluded
(not eligible due to preoperative condition).
No consent 4
Old cerebral infarction 2
Post spinal cord injury state 2
Hemodialysis for chronic renal failure 1
120 patients were randomized.
Antecolic 60
Vertical retrocolic 60
2 patients were excluded.
Postoperative severe sepsis 2
(Re-operation 1)
(Mortality 1)
2 patients were excluded.
Postoperative severe sepsis 2
(Re-operation 0)
(Mortality 1)
58 patients were analyzed.
58 patients were analyzed.
26 patients were excluded for assessment of gastric emptying and nutrition when each event happened.
Tumor recurrence 18
in 3 months 2
in 6 months 6
in 9 months 6
in 12 months 4
Treatment of another disease 4
in 3 months 1
in 6 months 2
in 12 months 1
Could not follow up 4
in 3 months 2
in 6 months 1
in 9 months 1
19 patients were excluded for assessment of gastric emptying and nutrition when each event happened.
Tumor recurrence 12
in 3 months 1
in 6 months 5
in 9 months 1
in 12 months 5
Treatment of another disease 3
in 3 months 1
in 9 months 2
Could not follow up 4
in 3 months 3
in 6 months 1
32 patients were assessed for gastric emptying and nutrition fully for 1 year after surgery
39 patients were assessed for gastric emptying and nutrition fully for 1 year after surgery

Figure 2

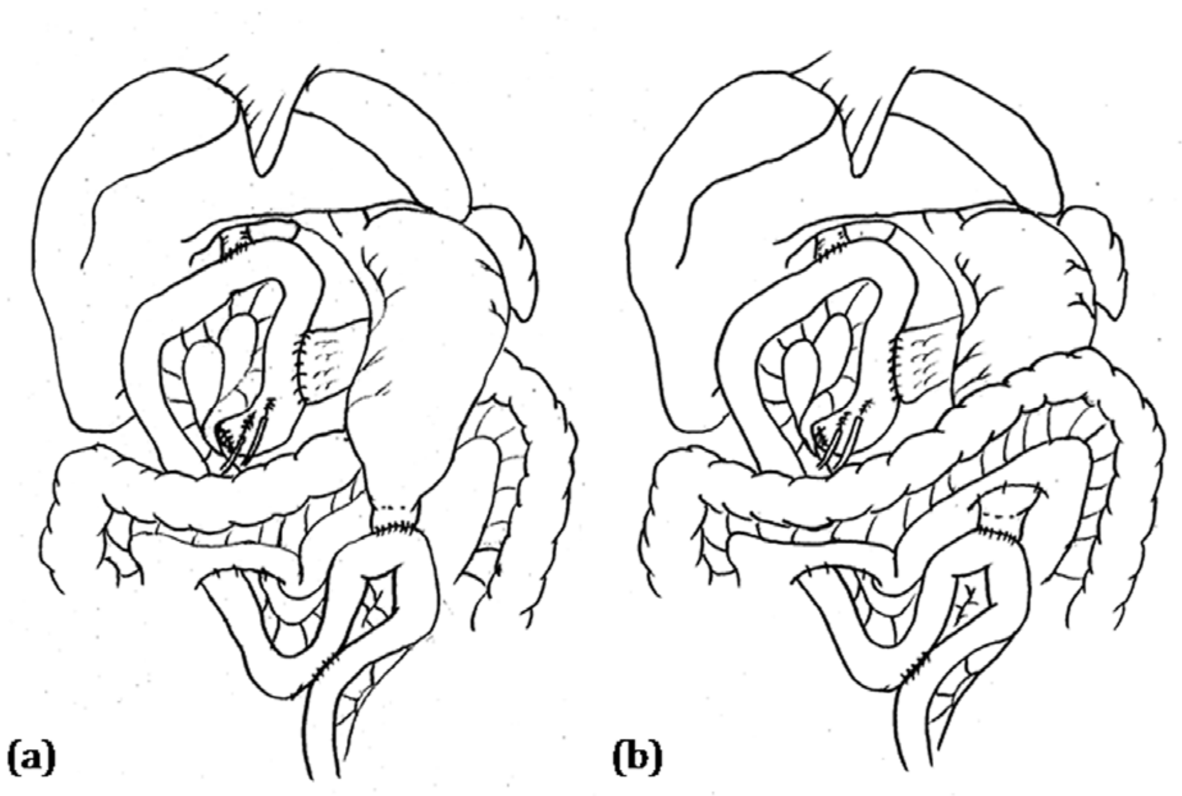


Figure 3

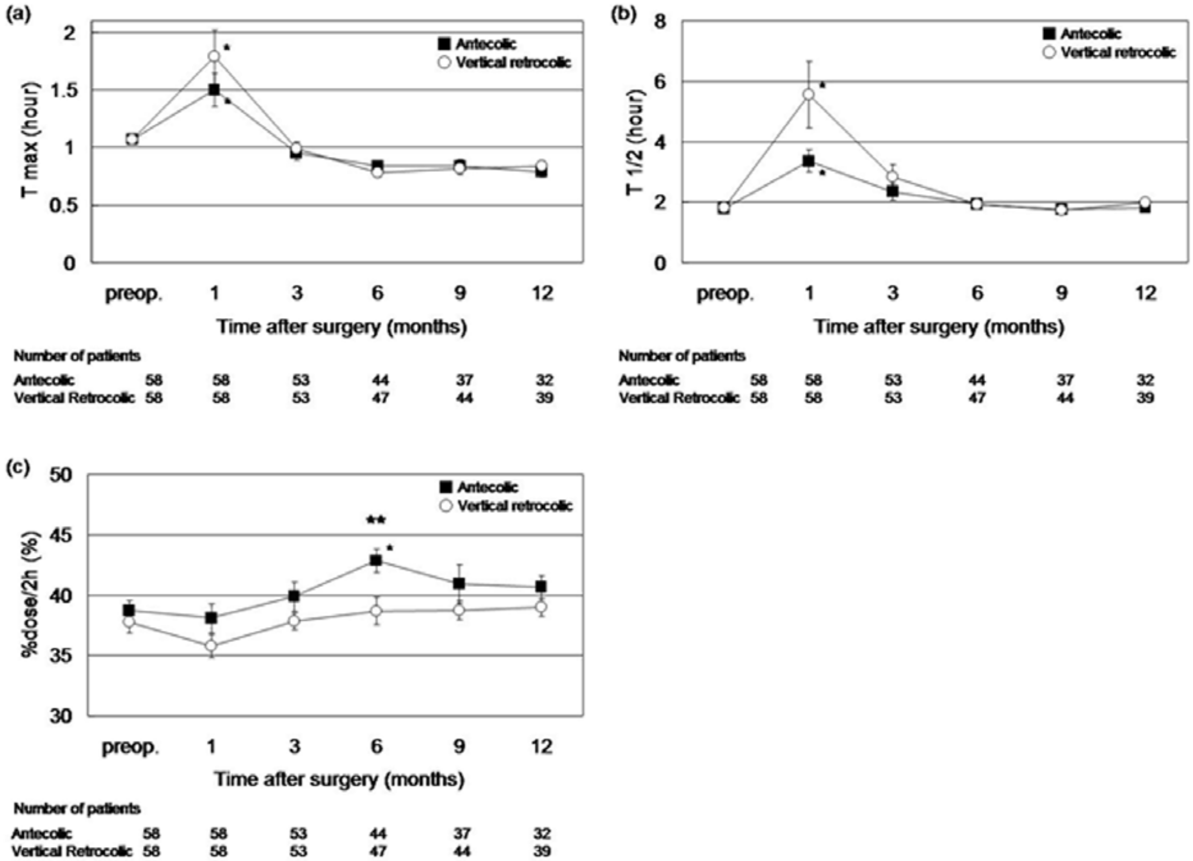
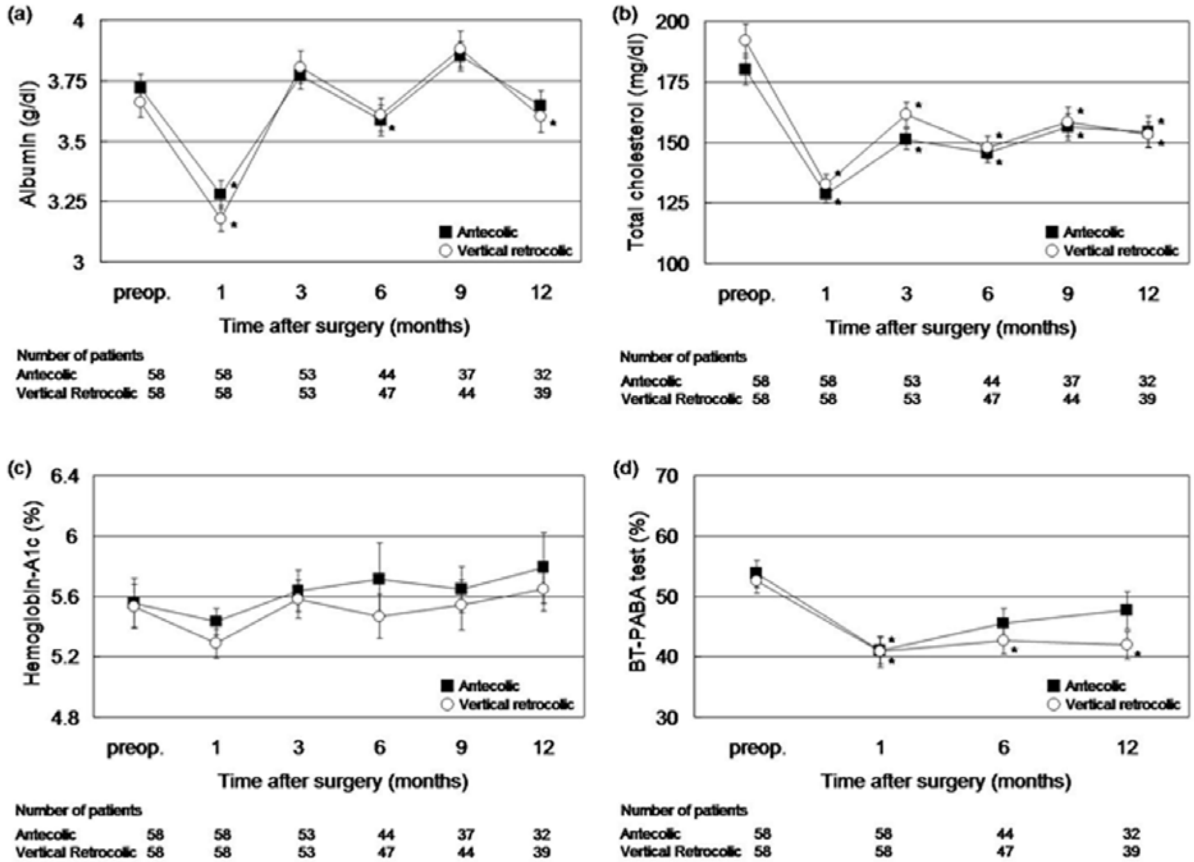
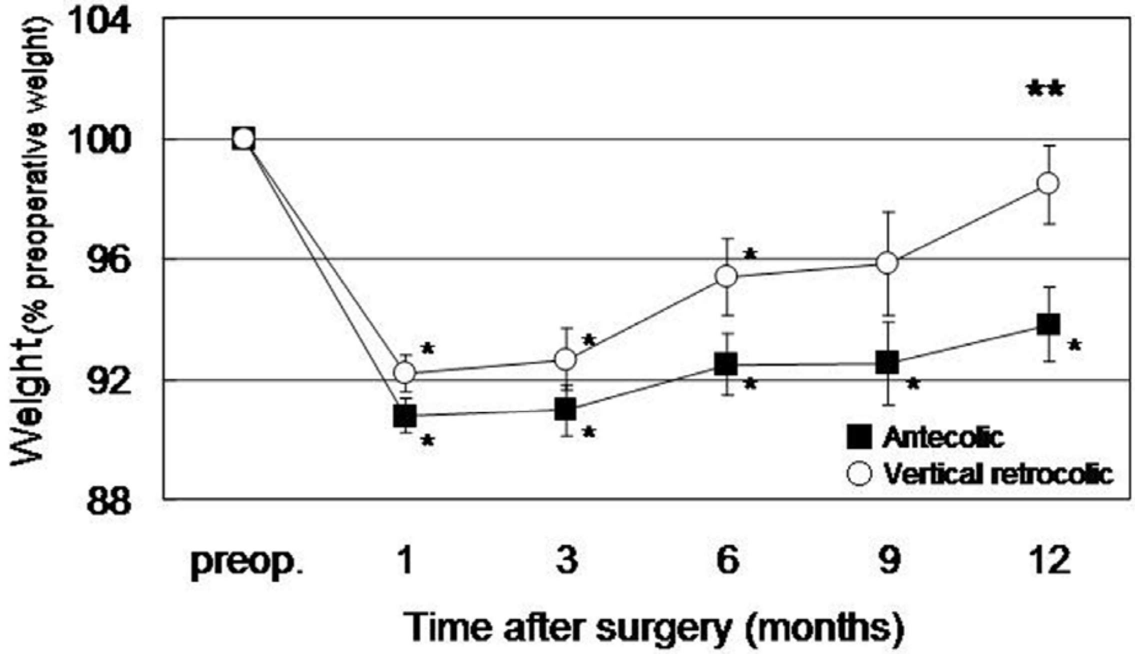

(a)
T max (hour)
Antecolic
Vertical retrocolic
2
1.5
1
0.5
0
preop.
1
3
6
9
12
Time after surgery (months)
Number of patients
Antecolic 58 58 53 44 37 32
Vertical Retrocolic 58 58 53 47 44 39
(b)
T 1/2 (hour)
Antecolic
Vertical retrocolic
8
6
4
2
0
preop.
1
3
6
9
12
Time after surgery (months)
Number of patients
Antecolic 58 58 53 44 37 32
Vertical Retrocolic 58 58 53 47 44 39
(c)
%dose/2h (%)
Antecolic
Vertical retrocolic
50
45
40
35
30
preop.
1
3
6
9
12
Time after surgery (months)
Number of patients
Antecolic 58 58 53 44 37 32
Vertical Retrocolic 58 58 53 47 44 39

Figure 4



(a)
Albumin (g/dl)
4
3.75
3.5
3.25
3
Antecolic
Vertical retrocolic
preop. 1 3 6 9 12
Time after surgery (months)
Number of patients
Antecolic 58 58 53 44 37 32
Vertical Retrocolic 58 58 53 47 44 39
(b)
Total cholesterol (mg/dl)
200
175
150
125
100
Antecolic
Vertical retrocolic
preop. 1 3 6 9 12
Time after surgery (months)
Number of patients
Antecolic 58 58 53 44 37 32
Vertical Retrocolic 58 58 53 47 44 39
(c)
Hemoglobin-A1c (%)
6.4
6
5.6
5.2
4.8
Antecolic
Vertical retrocolic
preop. 1 3 6 9 12
Time after surgery (months)
Number of patients
Antecolic 58 58 53 44 37 32
Vertical Retrocolic 58 58 53 47 44 39
(d)
BT-PABA test (%)
70
60
50
40
30
Antecolic
Vertical retrocolic
preop. 1 6 12
Time after surgery (months)
Number of patients
Antecolic 58 58 44 32
Vertical Retrocolic 58 58 47 39

Figure 5



Number of patients

Antecolic	58	58	53	44	37	32
Vertical Retrocolic	58	58	53	47	44	39