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Retrocolic or Antecolic Roux-en-Y Reconstruction after Distal Gastrectomy: Which Is More Effective in the Prevention of Postoperative Gastroesophageal Reflux Disease?

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Key Words
Postoperative reflux esophagitis · Postoperative hiatal hernia · Distal gastrectomy

Abstract
Background: It is unclear which reconstructive route (retrocolic or antecolic) is more effective in preventing postoperative gastroesophageal reflux disease (GERD) in Roux-en-Y reconstruction following distal gastrectomy. ***Methods:*** Eighty-one eligible patients (retrocolic, n = 39; antecolic, n = 42) underwent endoscopies before surgery and 1 year after surgery to evaluate reflux esophagitis according to the Los Angeles classifications. The relative anatomical position of gastrojejunostomy to the cardia was measured by CT imaging. ***Results:*** The proportion of patients with reflux esophagitis was also significantly higher in the antecolic group than in the retrocolic group (38.1 vs. 10.3%, p = 0.005). Multivariate analysis revealed that antecolic reconstruction and body mass index (BMI) were independent risk factors for reflux esophagitis. The relative position of gastrojejunostomy to the cardia in the antecolic group was shifted to the left laterally (59.0 vs. 28.8 degree, p < 0.001) and ventrally (65.4 vs. 39.8 degree, p < 0.001) than in the retrocolic group. There was a positive correlation between BMI and left lateral and ventral shifts of gastrojejunostomy in the antecolic group. ***Conclusion:*** Retrocolic reconstruction may be superior to antecolic reconstruction in preventing postoperative GERD, especially in obese patients. The left lateral and ventral shifts of gastrojejunostomy after antecolic reconstruction may aggravate the occurrence of GERD.

Introduction

Roux-en-Y (R-Y) reconstruction after distal gastrectomy has been shown in numerous reports to be superior to Billroth-I reconstruction in preventing postoperative gastroesophageal reflux disease (GERD) [1–5]. A gastrojejunostomy in R-Y reconstruction can be performed through either the retrocolic or the antecolic route [6]. In general, retrocolic route reconstruction has been conventionally and commonly performed in open distal gastrectomies [7]. In retrocolic route reconstruction, the jejunal loop should be brought up through the transverse mesocolon, and fixation of the gastric remnant to the transverse mesocolon is recommended. Recently, laparosco-

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py-assisted distal gastrectomy (LADG) has been increasingly used for the treatment of gastric cancer [8]. In the laparoscopic procedure, retrocolic reconstruction is sometimes difficult to perform, and the antecolic route of reconstruction is favoured. At present, there is no report that has compared the incidence of postoperative GERD between the retrocolic and antecolic routes of R-Y reconstruction after distal gastrectomies.

This study retrospectively compared the incidence of hiatal hernias as evaluated by changes in the esophagogastric junction morphology, the extent of reflux esophagitis, the incidence of postoperative complications, and the relative anatomical position of the gastrojejunostomy to the cardia in antecolic and retrocolic R-Y reconstruction patients who underwent distal gastrectomies for gastric cancer.

Patients and Methods

From January 2003 to August 2008 at the Nagoya University Hospital, all patients with preoperative hiatal hernia, preoperative esophagitis, Barrett's esophagus, or small remnant stomach underwent R-Y reconstruction after distal gastrectomy. The choice of reconstructive method depended on the surgeon's preference in the other patients. Since September 2008, all patients after distal gastrectomy underwent R-Y reconstruction. Of 141 patients who underwent distal gastrectomies with R-Y reconstruction between January 2003 and December 2011, 81 eligible patients who had no recurrence 1 year after surgery and were followed up in our hospital were included in the analysis. There were 39 patients who underwent retrocolic route reconstructions (the retrocolic group) and 42 patients who underwent antecolic route reconstructions (the antecolic group). In the laparoscopic surgeries, the antecolic route was generally selected, whereas, in the open surgeries, the reconstructive route was selected, depending on the surgeon's preference. The following parameters were recorded: age, gender, tumor characteristics, surgical approach, operative time, intraoperative blood loss, length of postoperative hospital stay, incidence of postoperative complications, and postoperative use of gastric antacids such as H2 blockers and proton pomp inhibitors due to reflux symptoms. Postoperative complications were defined as any event requiring specific medical or surgical treatment, which were assessed by the Clavien–Dindo classifications [9, 10]. Postoperative pancreatic fistulas and delayed gastric emptying were classified according to the criteria of the International Study Group of Pancreatic Surgery [11, 12].

Endoscopic Examinations

All of the patients underwent a gastrointestinal endoscopy before surgery and approximately 1 year after surgery to evaluate the presence of hiatal hernias and reflux oesophagitis. Hiatal hernias were classified by their esophagogastric junction morphology using the Hill's grading system [13]. Instances of esophagitis were evaluated using the Los Angeles classifications [14]. The extent of bile reflux to the remnant stomach, residual food, and remnant gastritis was also evaluated according to the residue, gastritis, bile (RGB) classification, which was proposed by Kubo et al. [15].

Surgical Procedure

A distal gastrectomy and regional lymph node dissection with R-Y reconstruction were performed according to the guidelines for clinical studies in the 13th edition of the Japanese classification of gastric carcinoma [16]. The distal gastrectomy in this study included a normal distal gastrectomy (resection of two-thirds of stomach) and subtotal gastrectomy (resection of more than two-thirds but not total of stomach). The jejunum was divided at 30 cm distal to the Treitz ligament, and the oral portion of the jejunum was anastomosed to the mid-jejunum at 40 cm distal to the gastrojejunostomy. The gastrojejunostomy was performed by antiperistaltic hand-sewn anastomosis using 4-0 PDS-II (Ethicon, Cincinnati, Ohio, USA) in the retrocolic route, and isoperistaltic mechanical anastomosis was performed using ECHELON FLEX™ 60 mm (Ethicon End-Surgery, Cincinnati, Ohio, USA) in the antecolic route. In the retrocolic route, the jejunal loop was brought up through the transverse mesocolon on the left side of the middle colic artery, and then the distal gastric remnant was fixed to the transverse mesocolon. In the antecolic route, Petersen's space was not closed, and no fixation to the mesocolon was performed.

Evaluation of the Relative Anatomical Position of the Gastrojejunostomy to the Cardia

The relative anatomical position of the gastrojejunostomy to the cardia was measured using axial and multi-planar reconstruction CT scan images obtained approximately 3 months after surgery (fig. 1). Every patient underwent CT scan imaging after at least 4 h of fasting. The cardia was defined as point O on slice X. The position of the gastrojejunostomy was identified by tracing the distal end of the staple line on the stomach by CT imaging, and the distal end of the staple line was defined as point C on slice Y. The orthogonal intersection point where the line from point O crossed slice Y was defined as point A. An intersection point of the horizontal line through point C and the perpendicular line through point A was defined as point D, whereas the intersection point of the horizontal line through point A and the perpendicular line through point C was defined as point B on the Y slice. The lengths of OA, AB, and AD were measured using CT imaging. From these measurements, ∠AOB and ∠AOD were calculated and defined as the lateral cardio-anastomotic angle (LCAA) and ventral cardio-anastomotic angle (VCAA), respectively (fig. 1).

Statistical Analysis

The results are expressed as the median (range). Fisher's exact test and the Mann–Whitney U test were used for the analysis, where appropriate, to assess the differences between the 2 groups. Univariate and multivariate analyses were performed using a logistic regression model to identify the independent factors that were associated with the postoperative incidence of hiatal hernia or reflux esophagitis. In the multivariate analysis, the factors that showed a p value <0.200 in the univariate analysis were selected and subjected to a stepwise logistic regression analysis. All of the statistical analyses were performed with SPSS software version 20.0 J. Two-sided p values were calculated and presented. A p value of <0.05 was considered to indicate statistical significance.

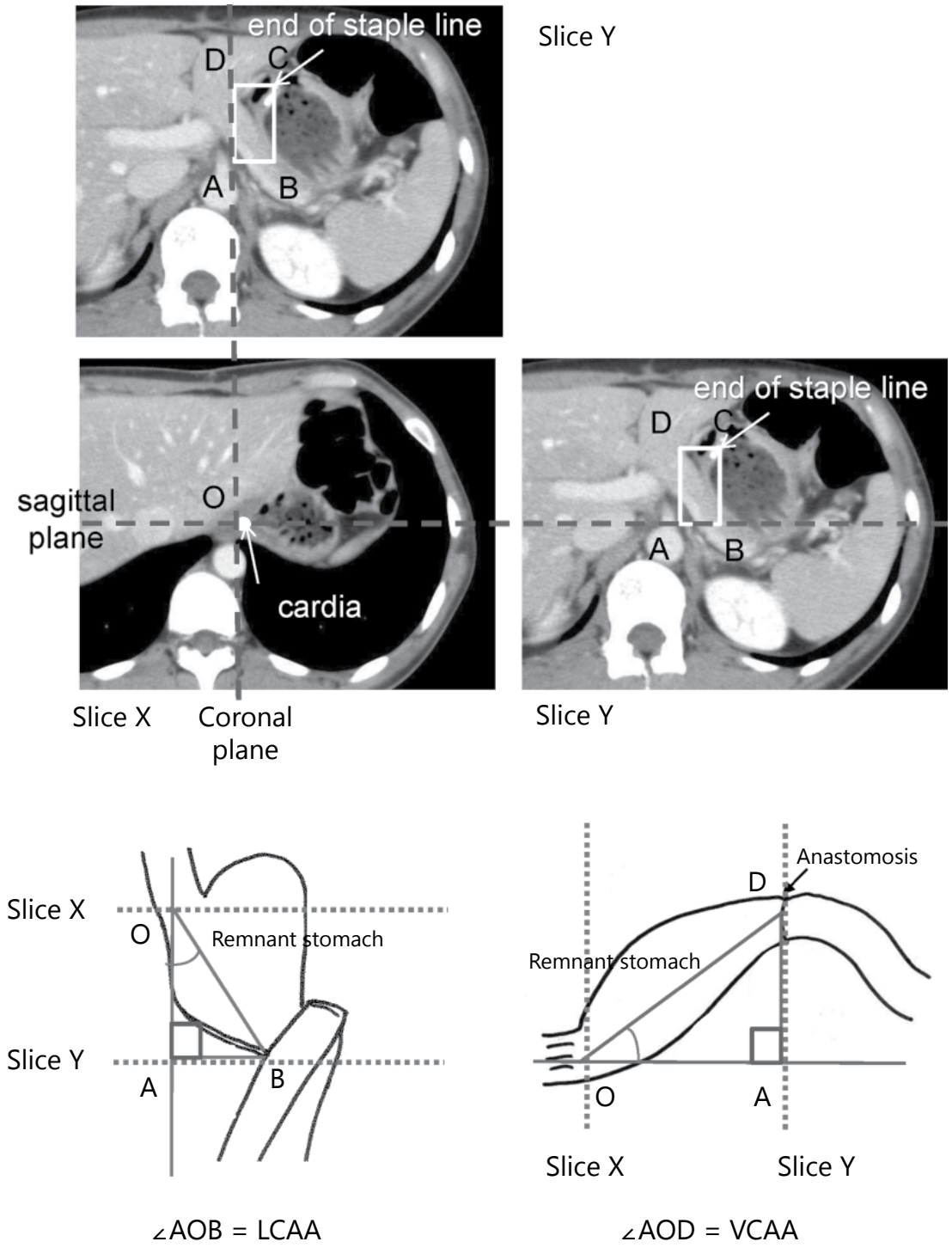

Fig. 1. Measurement of the relative anatomical position of the gastrojejunostomy to the cardia. The centre of the cardia was defined as point O (slice X). The position of the gastrojejunostomy was identified by tracing the distal end of the staple line of the stomach, and this point was defined as point C (slice Y). The location of the gastrojejunostomy was projected on the sagittal plane through point O, and this point was defined as point B. The location of the gastrojejunostomy was projected on the coronal plane through point O, and this point was defined as point D. ∠AOB was defined as the LCAA. ∠AOD was defined as the VCAA.

Table 1. Patient characteristics, the pathological features, and short outcomes

Variables	Reconstruction method		p value
	retrocolic (n = 39)	antecolic (n = 42)	
Age, years	65 (38–86)	66 (41–86)	0.977
Gender, male/female	25/14	32/10	0.330
BMI, kg/m^2	23.6 (16.7–29.4)	22.2 (16.9–26.9)	0.192
Depth of invasion, n (%)			0.348
Tis, T1,	29 (74.4)	27 (64.3)	
T2, T3, T4	10 (25.6)	15 (35.7)	
Stage (UICC 7th), n (%)			
0, I	30 (76.9)	27 (64.3)	0.234
II, III, IV	9 (23.1)	15 (35.7)	
Surgical approach			
Open/laparoscopy	39/0	21/21	<0.001
Extent of gastrectomy			
Subtotal/normal distal	7/32	5/37	0.538
Lymph node dissection D1+/D2*	28/11	24/18	0.246
Operation time, min	255 (157–485)	293 (196–731)	0.021
Blood loss, ml	295 (40–2,165)	189 (4–2,164)	0.103
Postoperative complications, n (%)			
Delayed gastric emptying	3 (7.7)	5 (11.9)	0.714
R-Y stasis syndrome	0	1 (2.4)	1.000
Anastomotic leakage			
Gastrojejunal	0	1 (2.4)	1.000
Duodenal stump	0	1 (2.4)	1.000
Pancreatic fistula	3 (7.7)	7 (16.7)	0.315
Intra-abdominal abscess	0	2 (4.8)	0.494
Any complication (CD** ≥3a)	4 (10.3)	10 (23.8)	0.145
Postoperative hospital stay, days	14 (8–75)	13 (8–103)	0.281
Medication of gastric antacids, n (%)	7 (17.9)	18 (42.9)	0.018

* D1+/D2, according to [18]; ** CD, Clavien–Dindo classification.

Results

The patient characteristics and the pathological features of the gastric cancers are summarized in table 1. No significant differences were observed between the retrocolic and antecolic groups in age, gender, body mass index (BMI), depth of tumor invasion, pathological stages, and the extent of gastrectomy. All of the patients in the retrocolic group underwent an open distal gastrectomy, whereas 50% of the patients (21/42) in the antecolic group underwent LADG. The operation times were significantly longer in the antecolic group than in the retrocolic group (p = 0.021) because the laparoscopic surgery required a significantly longer operation time than the open surgery (open, 256 (157–659) min; laparoscopic, 365 (223–731) min; p < 0.001). No significant differences in the postoperative complications were observed between the 2 groups. There were no surgery-related deaths in either group. The length of the postoperative hospital stays was not significantly different between the 2 groups. The proportion of patients with postoperative medication of gastric antacids 1 year after surgery was significantly higher in the antecolic group than in the retrocolic group (p = 0.018).

The patients with a Hill's grade of 4 were considered to have hiatal hernias. The preoperative proportion of patients with a Hill's grade of 4 was not significantly different between the 2 groups (fig. 2a). No significant difference was observed between the preoperative and postoperative proportion of the patients with a Hill's grade of 4 in the retrocolic group (15.4 vs. 28.2%, p = 0.273), whereas the postoperative proportion of the patients with a Hill's grade of 4 was significantly higher than the preoperative proportion in the antecolic (61.9 vs. 7.1%, p < 0.001) group. Moreover, the postoperative proportion of the patients with a Hill's grade of 4 was significantly higher in the antecolic group than in the retrocolic group (61.9 vs. 28.2%, p = 0.004).

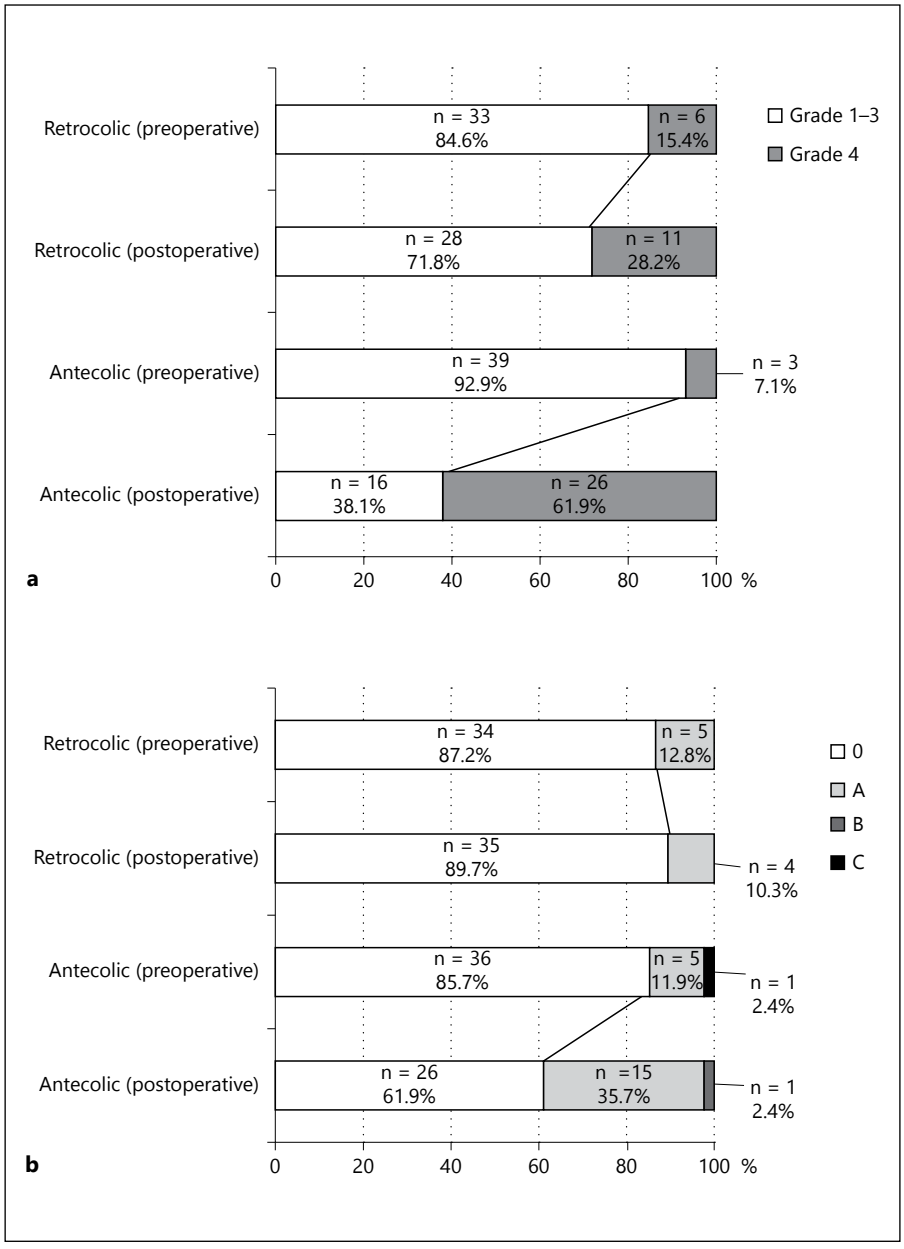

Fig. 2. The incidence of hiatal hernias evaluated by Hill's grades for esophagogastric junction morphology (**a**) and reflux esophagitis evaluated according to the Los Angeles classifications (**b**).

The preoperative proportion of the patients with reflux esophagitis was similar in the retrocolic and antecolic groups (fig. 2b). Although the postoperative proportion of the patients with reflux esophagitis was not significantly different from the preoperative proportion in the retrocolic group (10.3 vs. 12.8%, p = 1.000), it was significantly higher than in the antecolic group (38.1 vs. 14.3%, p = 0.024). The postoperative proportion of the patients with reflux esophagitis was significantly higher in the antecolic group than in the retrocolic group (38.1 vs. 10.3%, p = 0.005).

Other postoperative endoscopic findings for the remnant stomach (the RGB classification) are summarized in table 2. There was no significant difference between the 2 groups regarding the incidence of residual food and remnant gastritis. There was only 1 patient with bile reflux in each group.

The risk factors for the development of postoperative hiatal hernia were analysed using univariate and multivariate logistic regression analyses (table 3). The patients who already had hiatal hernia before gastrectomy were excluded (n = 9) because all patients with preoperative

Table 2. Postoperative endoscopic findings (RGB classification)

	Reconstruction method		p value
	retrocolic (n = 39)	antecolic (n = 42)	
Residual food, n (%)			0.125
Grade 0	31 (79.5)	26 (61.9)	
Grade 1	3 (7.7)	10 (23.8)	
Grade 2	5 (12.8)	6 (14.3)	
Remnant gastritis, n (%)			0.518
Grade 0	35 (89.7)	35 (83.3)	
Grade 1	2 (5.1)	6 (14.3)	
Grade 2	1 (2.6)	1 (2.4)	
Grade 3	1 (2.6)	0	
Bile reflux, n (%)	1 (2.6)	1 (2.4)	0.863

Table 3. Risk factors related to postoperative hiatal hernia

Variables	n	Hiatal hernia (+), n (%)	Univariate, p value	Multivariate	
				Hazard ratio (95% CI)	p value
Age, years			0.026		0.009
>70	49	16 (32.7)		1	
>70	23	14 (60.9)		5.469 (1.543–19.390)	
Gender			0.105		
Male	50	24 (27.3)			
Female	22	6 (48.0)			
BMI, kg/m^2			0.699		
>25	61	26 (42.8)			
>25	11	4 (36.4)			
Preoperative reflux esophagitis			0.159		
Absent	64	25 (39.1)			
Present	8	5 (62.5)			
Reconstructive route			0.002		0.001
Retrocolic	33	7 (21.2)		1	
Antecolic	39	23 (59.0)		8.051 (2.350–27.584)	
Approach			0.091		
Open	51	18 (35.3)			
Laparoscopic	21	12 (57.1)			
Extent of gastrectomy			0.782		
Subtotal	11	5 (45.5)			
Normal distal	61	25 (41.0)			
Lymph node dissection			0.197		
D1	47	17 (36.2)			
D2	25	13 (52.0)			
Postoperative reflux esophagtis			0.445		
Absent	56	22 (39.3)			
Present	16	8 (50.0)			
Postoperative complication*			0.329		
Absent	59	23 (39.0)			
Present	13	7 (53.9)			

* ≥3a by Clavien–Dindo classification.

Table 4. Risk factors related to postoperative reflux esophagitis

Variables	n	Reflux esophagitis (+), n (%)	Univariate, p value	Multivariate	
				Hazard ratio (95% CI)	p value
Age, years			0.817		
>70	55	14 (25.5)			
≥70	26	6 (23.1)			
Gender			0.110		
Male	57	17 (29.8)			
Female	24	3 (12.5)			
BMI, kg/m^2			0.001		0.001
>25	66	11 (16.7)		1	
≥25	15	9 (60.0)		16.328 (3.097–86.097)	
Preoperative esophagitis			0.096		
Absent	70	15 (21.4)			
Present	11	5 (45.5)			
Reconstructive route			0.006		0.004
Retrocolic	39	4 (10.3)		1	
Antecolic	42	16 (38.1)		11.162 (2.207–56.450)	
Approach			0.632		
Open	60	14 (23.3)			
Laparoscopic	21	6 (28.6)			
Extent of gastrectomy			0.979		
Subtotal	12	3 (25.0)			
Normal distal	69	17 (24.8)			
Lymph node dissection			0.325		
D1	52	11 (21.2)			
D2	29	9 (31.0)			
Postoperative hiatal hernia			0.337		
Absent	44	9 (20.5)			
Present	37	11 (29.7)			
Postoperative complication*			0.127		
Absent	67	19 (28.4)			
Present	14	1 (7.1)			

* ≥3a by Clavien–Dindo classification.

hiatal hernia had postoperative hiatal hernia. The 10 possible risk factors were included in the analysis. Among these potential risk factors, elderly patients and antecolic reconstruction were the significant risk factors for postoperative reflux oesophagitis in the multivariate analysis.

The risk factors for the development of postoperative reflux esophagitis were also analysed using univariate and multivariate logistic regression analyses (table 4). The 10 possible risk factors were included in the analysis. Among these potential risk factors, antecolic reconstruction and BMI (≥25) were identified as independent risk factors by the multivariate analysis.

When the relative anatomical position of the gastrojejunostomy to the cardia was measured, both the LCAA and VCAA were significantly greater in the antecolic group than in the retrocolic group (table 5). The LCAA and VCAA were significantly greater in the patients with postoperative hiatal hernias (a Hill's grade of 4) than in the patients without hiatal hernias. The LCAA and VCAA were significantly greater in the patients with postoperative reflux esophagitis than in the patients without reflux esophagitis.

Finally, the correlation between BMI and the relative position of the gastrojejunostomy to the cardia was analysed in both the retrocolic and antecolic groups. In the retrocolic route reconstruction, there was a weak correlation between the VCAA and BMI ($r = 0.407$, $p = 0.010$). However, there was no correlation between the LCAA and BMI (fig. 3). In contrast, in the antecolic route reconstruction, both the VCAA and the LCAA were significantly correlated with BMI. The correlation was especially strong between the VCAA and BMI ($r = 0.703$, $p < 0.001$).

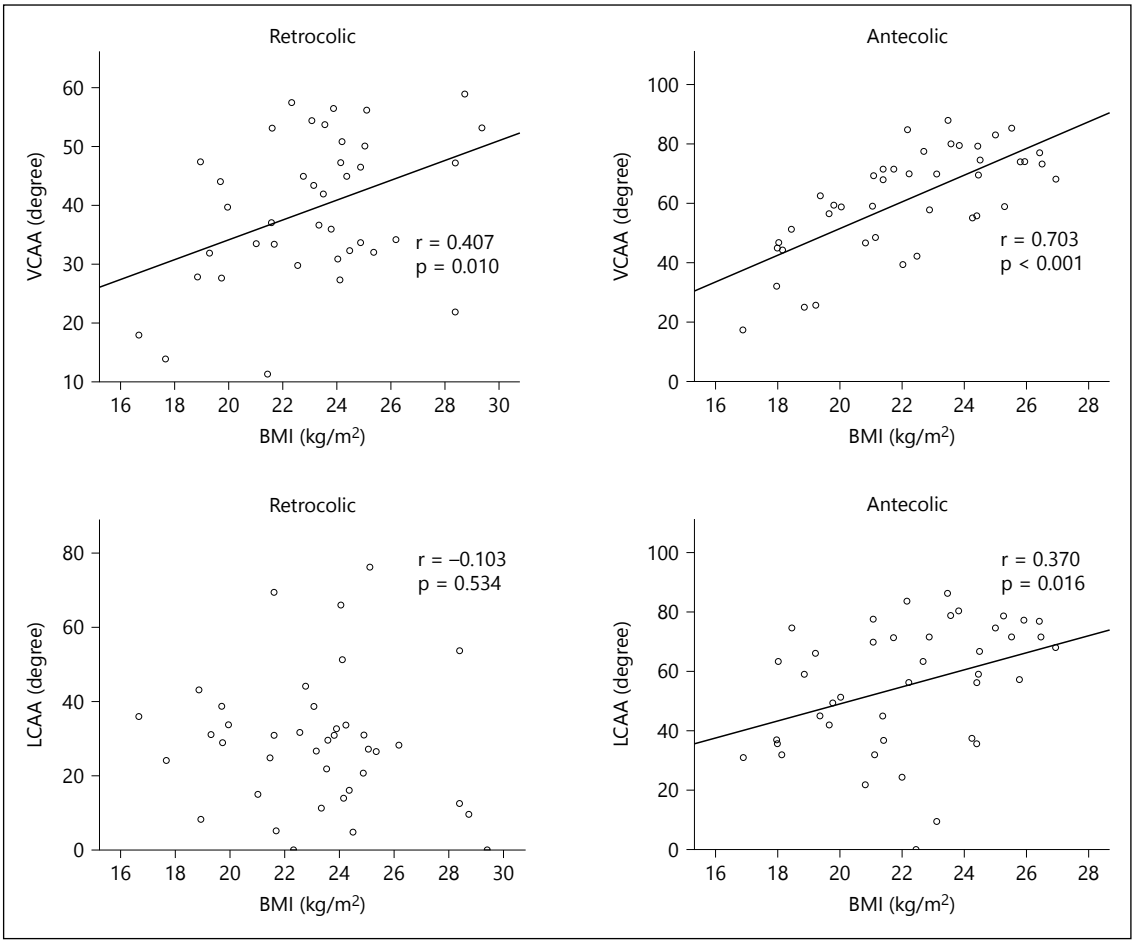

Fig. 3. The correlation between BMI and the relative anatomical position of the gastrojejunostomy to the cardia in the retrocolic and antecolic reconstruction groups.

Table 5. The relative position of gastrojejunostomy to cardia

Angles, degree	Reconstruction method		p value
	retrocolic (n = 39)	antecolic (n = 42)	
LCAA	28.8 (0–76.3)	59.0 (0–86.5)	<0.001
VCAA	39.8 (11.3–59.0)	65.4 (17.4–88.1)	<0.001
	Postoperative hiatal hernia		
	absent (n = 44)	present (n = 37)	
LCAA	33.2 (5.1–83.8)	56.3 (0–86.5)	0.024
VCAA	45.8 (17.4–85.0)	58.8 (11.3–88.1)	0.015
	Postoperative reflux esophagitis		
	absent (n = 61)	present (n = 20)	
LCAA	33.7 (0–86.5)	65.1 (0–79.1)	0.010
VCAA	45.0 (11.3–88.1)	66.8 (46.6–85.5)	<0.001

Discussion

This study demonstrated that the proportion of patients with hiatal hernias or reflux esophagitis was dramatically increased in the antecolic group compared to the retrocolic group following a distal gastrectomy with R-Y reconstruction. In multivariate analysis, the antecolic route reconstruction was identified as an independent risk factor for the development of postoperative hiatal hernia and reflux esophagitis. Hiatal hernia or reflux esophagitis sometimes leads to heart burn and nausea, and gastric antacids are prescribed for these symptoms in a clinical setting. In this study, there were more patients who were prescribed gastric antacids in the antecolic group (42.9%) than the retrocolic group (17.9%; table 1). This result may be associated with a higher incidence of hiatal hernia and reflux esophagitis in the antecolic group compared to the retrocolic group. To elucidate the patho-

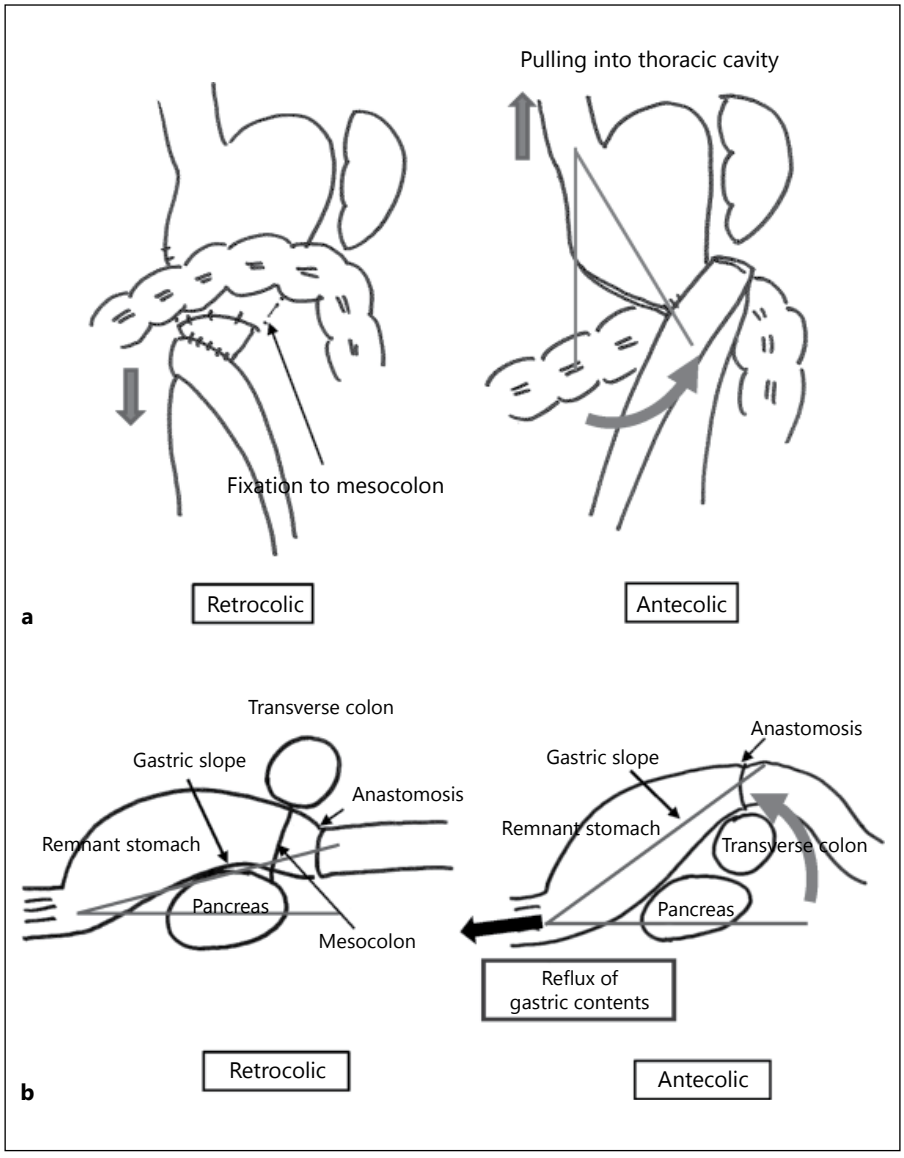

Fig. 4. The schematic images of the front (**a**) and lateral (**b**) views of the remnant stomach after retrocolic and antecolic reconstruction. In retrocolic reconstruction, the remnant stomach is fixed to the mesocolon and is kept in a perpendicular position, which may prevent the gastroesophageal junction from sliding into the thoracic cavity. In contrast, in antecolic reconstruction, the position of the gastrojejunostomy may shift to the left lateral side, and the gastroesophageal junction may easily be pulled into the thoracic cavity. The anatomical location of the gastrojejunostomy is the ventral side of the transverse colon after antecolic reconstruction. Therefore, the gastric slope is steeper than in the retrocolic group, and stasis of gastric contents as well as intestinal fluid reflux to the esophagus may easily occur.

genic mechanism for the development of hiatal hernia and reflux esophagitis, the relative anatomical position of the gastrojejunostomy to the cardia was evaluated using CT scan images. The relative position of the gastrojejunostomy to the cardia was shifted left laterally and ventrally in the antecolic group than in the retrocolic group (fig. 4). Moreover, the lateral and ventral shifts of the gastrojejunostomy were greater in patients with postoperative hiatal hernias or postoperative reflux esophagitis (table 5). These results indicated that the gastric slope produced after an antecolic R-Y reconstruction had a significant impact on the development of postoperative hiatal hernia and reflux esophagitis.

This study revealed that the proportion of patients with hiatal hernias (a Hill's grade of 4) increased after a gastrectomy for gastric cancer with R-Y reconstruction in both the antecolic and retrocolic groups (fig. 2a). Moreover, the proportion was significantly higher in the antecolic group than in the retrocolic group ($p = 0.004$). To perform a right paracardial lymph node dissection in gastric cancer surgery, it is necessary to dissect the attachment between the esophagogastric junction and the crus of the diaphragm. This detachment of the esophagogastric junction may lead to the development of a postoperative hiatal hernia. In retrocolic reconstruction, the remnant stomach is fixed to the mesocolon and is kept in a

perpendicular position, which may prevent the gastroesophageal junction from sliding into the thoracic cavity. In contrast, in antecolic reconstruction, the position of the gastrojejunostomy may shift to the left lateral side because the splenic flexure of the transverse colon is in a lower position than the mid transverse colon (fig. 4a). This shift is greater in patients with a high BMI, most likely due to a mesocolon thickened by fat accumulation. These hypotheses were supported by data obtained from CT scan images on the relative location of the gastrojejunostomy to the cardia.

The postoperative proportion of patients with reflux esophagitis was significantly higher in the antecolic group than in the retrocolic group ($p = 0.005$). When the patient is in a supine position, the anatomical location of the gastrojejunostomy is the ventral side of the transverse colon after an antecolic reconstruction, whereas its location is the dorsal side of the transverse colon after a retrocolic reconstruction. Therefore, in the antecolic group, the gastric slope is steeper than in the retrocolic group, and stasis of the gastric contents as well as intestinal fluid reflux to the esophagus may easily occur (fig. 4b). There was a greater positive correlation between BMI and ventral shift of the gastrojejunostomy in the antecolic group than in the retrocolic group (fig. 3). Therefore, when the antecolic R-Y reconstruction is performed for a patient with a high BMI, the patient may easily develop reflux esophagitis. To further clarify this hypothesis, it is necessary to perform real-time monitoring of gastric motility, comparing patients with high and low BMIs, a thick and thin mesocolon, or high and low VCAAs after an antecolic reconstruction.

A unique finding of this study demonstrated that the incidence of hiatal hernia or reflux esophagitis was associated with the relative anatomical position of the gastrojejunostomy to the cardia (i.e. VCAA and LCAA). To the best of our knowledge, no previous report had investigated the relationship between the incidence of GERD and the anatomical position of the gastrojejunostomy after distal gastrectomy. However, there were several limitations to this study. First, this was a retrospective study that included only a small number of patients. Second, all of the patients in the retrocolic reconstruction group underwent open surgery, and no laparoscopic procedures were performed in this group. The effects of the laparoscopic procedure on the incidence of GERD are unknown. Third, there was a difference in the anastomotic procedure between the 2 groups; an antiperistaltic hand-sewn anastomosis was performed in the retrocolic reconstruction, and an isoperistaltic mechanical anastomosis was performed in the antecolic reconstruction. Fourth, the volume and clearance of the remnant stomach was not assessed. The volume of the remnant stomach may affect the capacity of gastric acid secretion and food storage and may influence the incidence of postoperative hiatal hernia and reflux esophagitis. However, the analysis in this study indicated that the difference between normal gastrectomy and subtotal gastrectomy did not influence the incidence of hiatal hernia and reflux esophagitis. Fifth, data were not available on postoperative nutritional status, clinical symptoms related to either hiatal hernias or reflux esophagitis, and pH and bilirubin concentrations in the remnant stomach and esophagus after gastrectomy. To resolve the above-mentioned issues, a prospective randomized trial is being conducted to compare retrocolic and antecolic reconstructions using 24 h pH and bilirubin concentration monitoring in the stomach and esophagus as well as gastric motility testing (UMIN 000012062).

In conclusion, this study demonstrated that the retrocolic route may be superior to the antecolic route in preventing postoperative hiatal hernia and reflux esophagitis after a distal gastrectomy with R-Y reconstruction for gastric cancer. The retrocolic route of reconstruction is highly recommended, especially in patients with a high BMI.

Disclosure Statement

The authors have no conflicts of interest to declare.

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