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A multi-center, prospective, clinical study to evaluate the anti-reflux efficacy of laparoscopic double-flap technique (ID-FLAP Study)

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Abstract

Background: Double-flap technique (DFT) is a reconstruction procedure after proximal gastrectomy (PG). We previously reported a multi-center, retrospective study in which the incidence of reflux esophagitis (RE) (Los Angeles Classification ≥Grade B [LA-B]) 1 year after surgery was 6.0%. There have been many reports, but all of them were retrospective. Thus, a multi-center, prospective study was conducted.

Methods: Laparoscopic PG + DFT was performed for cT1N0 upper gastric cancer patients. The primary endpoint was the incidence of RE (≥LA-B) 1 year after surgery. The planned sample size was 40, based on an estimated incidence of 6.0% and an upper threshold of 20%.

Results: Forty patients were recruited, and 39, excluding one with conversion to total gastrectomy, received protocol treatment. Anastomotic leakage (Clavien–Dindo ≥Grade III) was observed in one patient (2.6%). In 38 patients, excluding one case of postoperative mortality, RE (≥LA-B) was observed in two patients (5.3%) 1 year after surgery, and the upper limit of the 95% confidence interval was 17.3%, lower than the 20% threshold. Anastomotic stricture requiring dilatation was observed in two patients (5.3%). One year after surgery, body weight change was 88.9 ± 7.0%, and PNI <40 and CONUT ≥5, indicating malnutrition, were observed in only one patient (2.6%) each. In the quality of life survey using the PGSAS-45 questionnaire, the esophageal reflux subscale score was 1.4 ± 0.6, significantly better than the public data (2.0 ± 1.0; $p = 0.001$).

Conclusion: Laparoscopic DFT showed anti-reflux efficacy. Taken together with the acceptable incidence of anastomotic stricture, DFT can be an option for reconstruction procedure after PG.

KEYWORDS
anti-reflux surgery, double-flap technique, gastric cancer, Kamikawa procedure, proximal gastrectomy

1 | INTRODUCTION

Among cancers, gastric cancer (GC) has the fifth highest incidence and the fourth highest mortality worldwide, and its incidence, especially that of early GC, has recently been increasing thanks to improvements in diagnostic technology in Eastern Asia and Eastern Europe.[1] Proximal gastrectomy (PG) is commonly selected for early GC without distinct lymph node metastasis, mainly located in the upper third of the stomach, according to the Japanese gastric cancer treatment guidelines.[2] The safety of laparoscopy-assisted PG was confirmed in the study of the Japan Clinical Oncology Group (JCOG) (JCOG1401),[3] and PG has been increasingly performed laparoscopically for early GC located in the upper third of the stomach. However, the reconstruction methods tested in JCOG1401 were only those that included esophagojejunal anastomosis, such as double-tract (DT) and jejunal interposition (JI). Consequently, esophagogastrostomy (EG), one of the major reconstruction methods after PG, was not included in JCOG1401.

Since gastroesophageal reflux is a serious problem in EG, an additional procedure to prevent reflux is required in EG.[4] The double-flap technique (DFT), also known as the Kamikawa procedure, is one of the EGs, first reported in 1998, and characterized by producing anti-reflux potential by a one-way valve created by the distal esophagus and anastomosis embedded in the submucosal layer of the gastric remnant and covered by the seromuscular double-flap.[5,6] We previously showed the efficacy of the DFT as an anti-reflux procedure in a multi-center, retrospective study (rD-FLAP Study), in which the incidence of reflux esophagitis (RE) of all grades of the Los Angeles classification (LA) at 1 year after surgery was 10.6% and that of LA grade B or higher was 6.0%.[7] This is considered acceptable as real-world data that includes the very first case performed by Kamikawa in 1997. We also reported the accurate and safe performance of DFT under laparoscopy, all steps of which are basically performed by hand-sewn techniques, following a standardized procedure performed by a surgeon proficient in laparoscopic suturing and ligation techniques.[8,9] Although the efficacy of DFT has been reported from other institutions as well,[10,11] all reports, including ours, described retrospective studies, with no prospective study to date.

This paper reports a multi-center, prospective study to evaluate the efficacy and safety of laparoscopic DFT after PG for early GC located in the upper third of the stomach (ID-FLAP Study). This study will provide higher-level evidence regarding DFT, which is expected to facilitate further spread of DFT as a standard reconstruction procedure after PG.

2 | METHODS

2.1 | Study design and participants

This study was designed as a single-arm, non-comparative, open-label, multi-center (five institutions), prospective, clinical trial. This study conformed to the provisions of the Declaration of Helsinki, and the protocol was approved by the Okayama University Hospital Institutional Review Board (Approval no. 1904-002) and the institutional review boards of each participating institution. The UMIN clinical trial registration number was 000036191.

The inclusion criteria were as follows: (1) histologically diagnosed with gastric cancer; (2) diagnosed with clinical T1N0 according to the Japanese classification of gastric carcinoma[12]; (3) tumor located mainly in the upper third of the stomach, and proximal gastrectomy (PG) considered oncologically appropriate; (4) no obvious esophageal invasion (added after a severe adverse event [SAE] of postoperative death); (5) age ≥20 years; and (6) written, informed consent. The exclusion criteria were as follows: (1) pregnant or possibly pregnant; and (2) judged by the investigator as unsuitable for enrollment. Patients who met the above-mentioned inclusion criteria and none of the exclusion criteria were enrolled, and they underwent laparoscopic PG with lymphadenectomy followed by DFT reconstruction.

2.2 | Intervention (laparoscopic DFT)

The detailed step-by-step procedure and technique of DFT have been described in a previous report.[9] Briefly, an H-shaped seromuscular flap ($2.5 \times 3.5\,cm^2$) is first created on the anterior wall of the gastric remnant. The posterior side of the esophagus is fixed by four-point sutures to the gastric remnant at the upper edge of the flap. Anastomosis of the posterior wall is carried out by a single-layer suture between all layers of the esophagus and mucosa of the stomach, and anastomosis of the anterior wall is carried out by layer-to-layer suturing. DFT reconstruction is completed by closing the double flap in a Y-shape with interrupted or continuous sutures to cover the anastomosis.

Certified surgeons who were qualified by the Endoscopic Surgical Skill Qualification System[13] in the Japan Society of Endoscopic Surgery and had performed ≥5 laparoscopic DFT procedures as an operator performed the operation or acted as the first assistant surgeon in this study for quality control.

2.3 | Endpoints

The primary endpoint was the incidence of RE (LA grade B or higher [≥LA-B]) 1 year after surgery on endoscopic examination, which was assessed by independent central review, as well as by local investigator review.[14] Local investigator review was performed by a surgeon or endoscopist at each institution, and independent central review was performed by a gastrointestinal surgeon qualified as a Board Certified Trainer of the Japan Gastroenterological Endoscopy Society in Okayama University Hospital, who was not involved in this study. The secondary endpoints were the incidence of anastomosis-related complications (leakage, stricture, and bleeding), conversion rate to open surgery, change of body weight (BW), change of nutritional status evaluated with the prognostic nutritional index (PNI),[15] controlling nutritional status (CONUT) score, modified Glasgow prognostic score (mGPS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR),[16] rate of oral intake of proton-pump inhibitors (PPIs), and

quality of life (QOL) 1 year after surgery evaluated by the postgastrectomy syndrome assessment scale (PGSAS)-45 questionnaire.[17] The CONUT score was divided into three categories of 0–1 (normal), 2–4 (mild malnutrition), and 5–12 (moderate/severe malnutrition). The mGPS was divided into two categories of 0 (normal) and 1–2 (malnutrition). The QOL scores were compared with the public data obtained from the PGSAS Study (the PGSAS Statistic Kit), including 193 PG cases consisting of 115 EG, 34 JI, and 44 jejunal pouch interposition (JPI) reconstruction procedures.[18]

Patients were followed-up regularly 1 month, 6 months, and 1 year after surgery. Adverse events were recorded according to the Clavien–Dindo (CD) classification. Information regarding each patient's background, surgery, pathology, and preoperative and postoperative laboratory data were also obtained from medical records.

2.4 | Sample size calculations

The estimated incidence rate of RE ≥LA-B 1 year after surgery was set at 6.0%, based on the rD-FLAP Study, a previous multi-center, retrospective study, and the upper threshold of the incidence rate was first set at 15%, based on a previous review article.[4] When the sample size was calculated based on the estimated rate and the upper limit with an alpha of 0.05 and a beta of 0.2, this design called for 77 evaluable patients, in which ≤5 occurrences of RE ≥LA-B indicated that laparoscopic DFT showed effective anti-reflux potential.

Although the study first started with the planned sample size of 80 patients, the study design was changed after new evidence was reported in 2020, mentioning that the pooled incidence of RE in several types of EG was 19.3%.[19] Based on this new evidence, the upper threshold in this study was raised to 20% from 15%. The sample size was re-calculated based on the estimated incidence rate of RE ≥LA-B of 6.0% and the upper threshold of the incidence rate of 20% with alpha of 0.05 and beta of 0.2, and the new planned sample size was changed to 40 patients. In this study design, ≤2 occurrences of RE ≥LA-B indicated that laparoscopic DFT showed effective anti-reflux potential, because the 95% upper limit of the confidence interval (CI) was less than 20%. This change was also approved by the Ethics Review Committee.

2.5 | Statistical methods

Descriptive statistics were calculated for the participants' background information. Means and standard deviations were calculated for continuous quantities, and frequencies and proportions were calculated for categorical variables. The percentage of postoperative complications at the time of initial admission was calculated, and 95% CIs based on a binomial distribution were calculated.

The incidence of RE 1 year after surgery was evaluated separately for independent central review and local investigator review, and the percentages were calculated. Point estimates and 95% CIs were calculated for the percentage of patients who had RE ≥LA-B.

The QOL survey performed using the PGSAS-45 questionnaire was compared with the results of the PGSAS Study by calculating means and standard deviations. Significance was tested by Student's *t*-test.

Nutritional status after surgery was illustrated with a time series using means, median, or percentages.

A $p < 0.05$ was considered significant, and JMP software (SAS Institute Japan, Tokyo, Japan) was used for statistical analysis.

3 | RESULTS

A total of 40 patients were registered in this study based on the inclusion and exclusion criteria (Figure 1). Thirty-nine patients received the protocol treatment; one patient underwent conversion to total gastrectomy (TG) from the oncological standpoint. Table 1 shows the details of the patients' characteristics. The average age was 72.3 years, the male-to-female ratio was approximately 7:3, and the average body mass index (BMI) was 23.0 kg/m^2. Performance status (PS) was 0, and the American Society of Anesthesiologists physical status (ASA-PS) was 1 or 2 in 90% of patients. No patient was converted to open surgery. D1+ lymph node dissection was performed for all patients, and concurrent cholecystectomy was performed for four patients (10%). The anastomotic location was intra-abdomen in 38 patients (97%) and mediastinum in one patient (3%). The size of the stomach remnant was ≥2/3 in 27 patients (69%) and ≥1/2 and <2/3 in 12 patients (31%). The celiac and hepatic branches of the vagus nerve were preserved in seven patients (18%) and 35 patients (90%), respectively. The median operation time was 331 min, and the median reconstruction time from flap creation to flap closure was 88 min. A total of 34 patients (87%) were classified as pathological T1 (pT1) and 35 patients (90%) as pathological N0 (pN0); in total, 37 patients (95%) were diagnosed with pathological stage I (pStage I).

Table 2 shows the postoperative complications during the first hospitalization. A total of six patients (15.4%) had postoperative complications (CD any grade), including anastomotic leakage in two

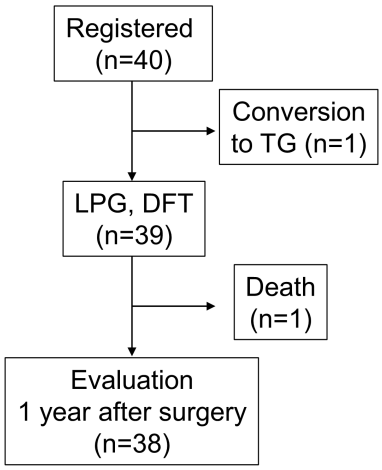

FIGURE 1 CONSORT diagram.

TABLE 1 Patients' characteristics.

	(*n* = 39)
Background	
Age, years, average ± SD	72.3 ± 8.0
Sex, male/female	28/11 (72%/28%)
BMI, kg/m^2, average ± SD	23.0 ± 3.4
Performance status, 0/1	35/4 (90%/10%)
ASA-PS, 1/2/3	8/27/4 (21%/69%/10%)
Surgical factors	
Open conversion	0 (0%)
Lymph node dissection, D1/D1+/D2	0/39/0 (0%/100%/0%)
Concurrent cholecystectomy	4 (10%)
Location of anastomosis	
Intra-abdomen/Mediastinum	38/1 (97%/3%)
Size of the stomach remnant	
≥2/3/1/2≤, <2/3/<1/2	27/12/0 (69%/31%/0%)
Nerve preservation	
Celiac branch	7 (18%)
Hepatic branch	35 (90%)
Operation time, min, median (range)	331 (184–463)
Reconstruction time, min, median (range)	88 (54–146)
Blood loss, mL, median (range)	50 (0–315)
Intra-operative complication	0 (0%)
Histological findings	
Histologic type, Dif/Undif/Other	25/10/4 (64%/26%/10%)
pT, 1/2/3/4	34/4/1/0 (87%/10%/3%/0%)
pN, 0/1/2/3	35/2/2/0 (90%/5%/5%/0%)
pM, 0/1	39/0 (100%/0%)
pStage, I/II/III/IV	37/1/1/0 (95%/3%/3%/0%)

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; Dif, differentiated; Undif, undifferentiated.

TABLE 2 Postoperative complications (during the first hospitalization).

	(*n* = 39)
Postoperative complications, CD any grade	6 (15.4%)
Anastomotic leakage	2 (5.1%)
Abdominal abscess	1 (2.6%)
Pneumonia	1 (2.6%)
Pleural effusion	1 (2.6%)
Cholecystitis	1 (2.6%)
CD grade III or higher	1 (2.6%) Anastomotic leakage

Abbreviation: CD, Clavien–Dindo classification.

patients (5.1%) and abdominal abscess in one patient (2.6%). One patient (2.6%), who had esophageal invasion, died postoperatively (CD grade V) due to adrenal crisis following anastomotic leakage at 3 days after surgery, and "no obvious esophageal invasion" was added to the inclusion criteria after this SAE. The median length of hospital stay was 11 days. Anastomotic stricture requiring endoscopic balloon dilatation was observed in two patients (5.3%, 95% CI: 1.5–17.3%) (Figure 2), one of whom required endoscopic balloon dilatation twice, and the other required it three times.

One year after surgery, 38 patients were evaluated for reflux esophagitis by endoscopic examination, excluding a patient who died postoperatively. RE of LA-A, B, C, and D was observed in three (7.9%), zero, one (2.6%), and one (2.6%) patients, respectively, on independent central review, whereas it was two (5.3%), zero, zero, and zero, respectively, on local investigator review (Table 3). According to the outcome of independent central review, RE ≥LA-B, the primary endpoint, was observed in two patients (5.3%, 95% CI: 1.5–17.3%) (Table 3). The 95% upper CI was 17.3%, which was lower than the 20% threshold, which was set as the upper limit, meaning that laparoscopic DFT showed significantly effective anti-reflux potential and was feasible as a reconstruction procedure after PG. The number of patients who took oral PPIs 1, 6, and 12 months after surgery was one (2.6%), two (5.3%), and three (7.9%), respectively, all of which were considered very small numbers. The collection rate for the

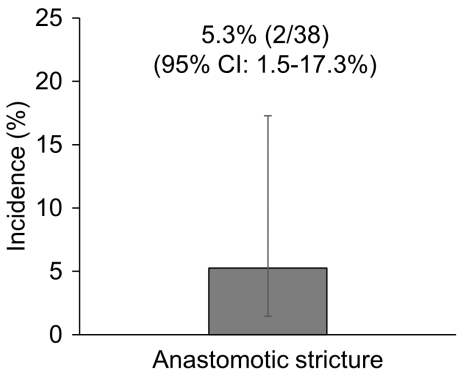

FIGURE 2 Incidence of anastomotic stricture requiring endoscopic balloon dilatation.

TABLE 3 Reflux esophagitis 1 year after surgery.

	Independent central review (*n* = 38)	Local investigator review (*n* = 38)
Reflux esophagitis, LA grade		
A	3 (7.9%)	2 (5.3%)
B	0 (0%)	0
C	1 (2.6%)	0
D	1 (2.6%)	0
≥B	2 (5.3%)	0 (0%)
(primary endpoint)	(95% CI: 1.5–17.3%)	(95% CI: 0–9.2%)

Abbreviations: CI, confidence interval; LA, Los Angeles classification.

QOL survey performed using the PGSAS-45 questionnaire 1 year after surgery was 87% (33/38). In this QOL assessment, the esophageal reflux subscale (SS) score in the present study was 1.4±0.6, which was significantly better than the public data obtained from the PGSAS Study (2.0±1.0; $p=0.001$) (Table 4). The dumping SS, the total symptom score, the necessity for additional meals, dissatisfaction with symptoms, dissatisfaction with daily life SS, and the mental component summary of this study were also significantly better than the public data.

Nutritional status after surgery was evaluated with the CONUT, mGPS, PNI, NLR, and PLR, in addition to BW change. BW change 1, 6, and 12 months after surgery was 93.1%, 89.3%, and 88.9%, respectively (Figure 3A). BW change tended to have a correlation with the size of the stomach remnant, and BW was better maintained in patients with a bigger stomach remnant 1, 6, and 12 months after surgery, although the difference was not significant at any time point (Figure S1). The number of CONUT 5–12 (moderate/severe malnutrition) cases before surgery and 1, 6, and 12 months after surgery was zero (0%), three (7.9%), one (2.6%), and one (2.6%), respectively (Figure 3B). The number of mGPS 1–2 (malnutrition) cases before surgery and 1, 6, and 12 months after surgery was seven (18.4%), nine (23.7%), three (7.9%), and four (10.5%), respectively (Figure 3C). The median PNI before surgery and 1, 6, and 12 months after surgery was 50.8, 48.2, 50.8, and 49.4, respectively, and the number of PNI <40 (malnutrition) cases before surgery and 1, 6, and 12 months after surgery was one (2.6%), four (10.5%), one (2.6%), and one (2.6%), respectively (Figure 3D). The median NLR before surgery and 1, 6, and 12 months after surgery was 2.2, 1.7, 1.8, and 1.7, respectively (Figure 3E), and the median PLR before surgery and 1, 6, and 12 months after surgery was 139, 118, 132, and 124, respectively (Figure 3F). These nutritional findings showed that nutritional status was relatively well-maintained after laparoscopic PG with DFT.

4 | DISCUSSION

Although DFT is already recognized as a representative reconstruction procedure after PG that has a strong anti-reflux potential, the results of the present prospective study make DFT more

TABLE 4 QOL assessment using the PGSAS-45 questionnaire 1 year after surgery.

	Present study, PG, DFT ($n=33$)		PGSAS study[b], PG ($n=193$)		Cohen's	*t*-test
	Mean	SD	Mean	SD	*d*	*p* value
Symptoms						
Esophageal reflux SS	1.4	0.6	2.0	1.0	0.65	0.001
Abdominal pain SS	1.5	0.6	1.7	0.7	0.31	0.161
Meal-related distress SS	2.4	0.8	2.6	1.1	0.26	0.202
Indigestion SS	2.1	0.9	2.2	0.8	0.08	0.680
Diarrhea SS	1.9	1.1	2.0	1.0	0.04	0.882
Constipation SS	1.9	1.0	2.3	1.1	0.40	0.058
Dumping SS	1.6	0.7	2.0	1.0	0.44	0.036
Total symptom score	1.8	0.6	2.1	0.7	0.41	0.050
Living status						
Change in body weight[a]	−11.1%	7.0%	−10.9%	8.2%	0.01	0.943
Ingested amount of food per meal[a]	6.7	1.3	6.5	1.9	0.11	0.585
Necessity for additional meal	1.7	0.7	2.0	0.8	0.49	0.014
Quality of ingestion SS[a]	3.6	1.0	3.6	1.0	0.02	0.934
Ability for working	2.0	1.0	2.0	0.9	0.12	0.684
QOL						
Dissatisfaction with symptoms	1.7	0.8	2.0	0.9	0.37	0.047
Dissatisfaction with meals	2.5	1.2	2.7	1.1	0.18	0.276
Dissatisfaction with working	1.7	0.8	2.0	1.1	0.35	0.059
Dissatisfaction with daily life SS	1.9	0.7	2.2	0.9	0.36	0.047
Physical component summary[a]	49.1	5.7	49.5	6.1	0.00	0.687
Mental component summary[a]	51.4	5.0	49.0	6.0	0.39	0.034

[a]A higher score is better. For all others, a lower score is better.

[b]PGSAS Statistic Kit ver 1.0 (Nakada K, Oshio A. 2016).

Abbreviations: DFT, double-flap technique; PG, proximal gastrectomy; QOL, quality of life; SS, subscale.

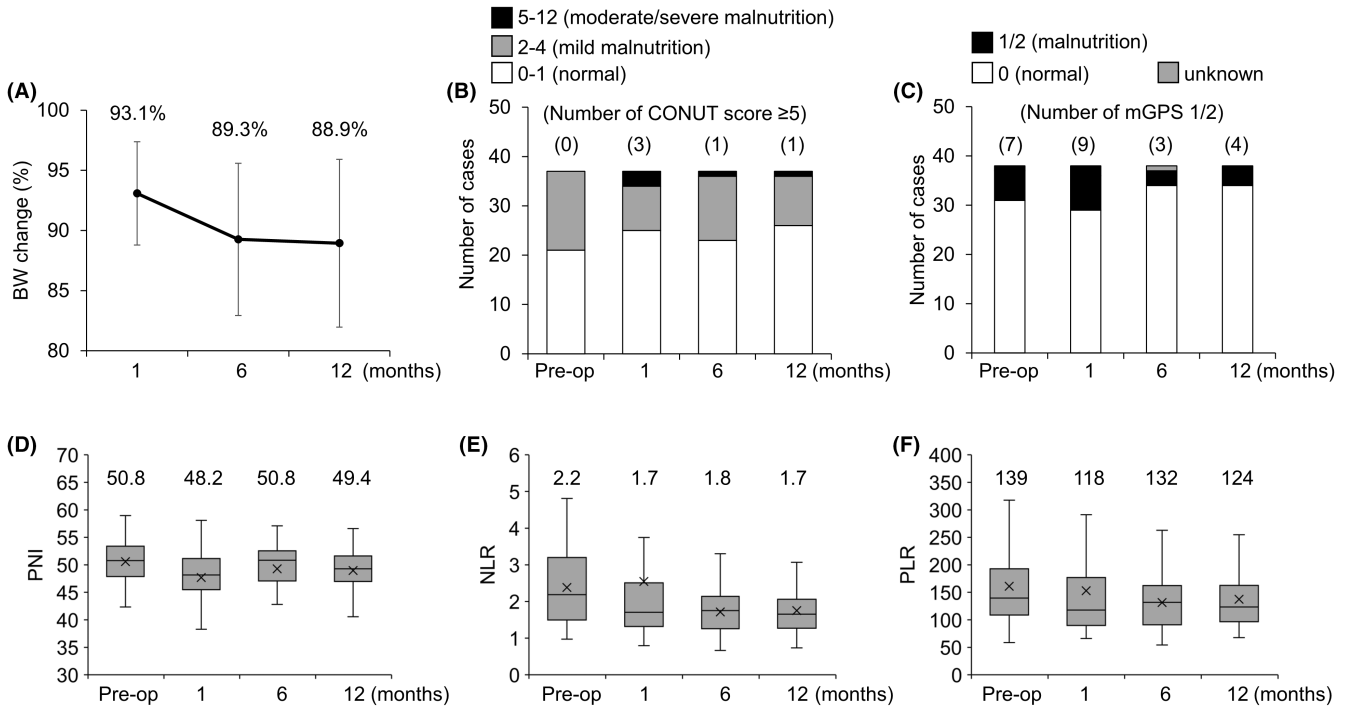

FIGURE 3 Changes in nutritional status after surgery. (A) Body weight change. (B) CONUT score. (C) mGPS. (D) PNI. (E) NLR. (F) PLR.

attractive. The incidences of RE ≥LA-A and ≥LA-B were 13.2% and 5.3%, respectively, on independent central review. These numbers were similar to those in the rD-FLAP Study, a multi-center, retrospective study we previously conducted, in which the incidences of RE ≥LA-A and ≥LA-B were 10.6% and 6.0%, respectively. Yamashita et al. reported in their original article that, in the modified side overlap esophagogastrostomy (mSOFY), which is a recent, commonly used EG, the incidences of RE of LA-A, B, and C were reported to be 7.1%, 7.1%, and 3.6%, respectively, meaning that the incidences of RE ≥LA-A and ≥LA-B were 17.9% and 10.7%, respectively.[20] The incidence of RE in the present study may be comparable even compared to other procedures that interpose the jejunum between the esophagus and the stomach such as DT and JI based on the systematic review in which Shaibu et al. reported that the incidences of RE were 4.3–54.7% (19.3% in total) for EG, 0%–20% (9.6% in total) for DT, and 0%–30% (13.8% in total) for JI.[19] In QOL assessment as well, reflux symptoms were significantly mildly suppressed compared to the public data from the PGSAS Study. It was noteworthy that the rates of regular oral PPI intake 1, 6, and 12 months after surgery were only 2.6%, 5.3%, and 7.9%, respectively, less frequently than in the rD-FLAP Study, in which the rate of PPI or H2-blocker oral intake 1 year after surgery was 19.4%. It is generally considered acceptable if reflux symptoms are controlled by oral PPI intake, and the rate of oral PPI intake after PG with EGs is actually reported to be high. Aburatani et al. reported that the PPI usage rate 1 year after surgery was as high as 72.7% in the EG group and 31.6% even in the DT group.[21] In the mSOFY, the oral PPI intake rate was as high as 80.6%.[20] Based on these previous reports, the evidence of the present study may change common views related to PPI usage after PG.

An anastomotic stricture is a postoperative complication to beware of in DFT. The incidence of anastomotic stricture requiring endoscopic balloon dilatation in the rD-FLAP Study was 5.5%, and if limited in laparoscopic DFT, it was as high as 13.4%. In the present study, the incidence of anastomotic stricture requiring endoscopic balloon dilatation was 5.3%. Shaibu et al. reported that the incidence of anastomotic stricture was 0%–40% (13.0% in total) for EG, 0%–4.65% (3.5% in total) for DT, and 0%–64.3% (11.3% in total) for JI.[19] Yamashita et al. reported that the incidence of anastomotic stricture was 2.8% for mSOFY.[20] According to these reports, the incidence of anastomotic stricture in the present study would be considered acceptable, although more effort to reduce it further is needed. With regard to other anastomosis-related complications, anastomotic leakage was observed in two cases (5.1%) in the present study, one of which was a case with esophageal invasion and resulted in postoperative mortality via adrenal crisis. Shaibu et al. reported that the incidence of anastomotic leakage was 0%–18.2% (4.6% in total) for EG, 0%–10% (3.9% in total) for DT, and 0%–13% (4.1% in total) for JI.[19] Although the incidence of anastomotic leakage was 1.5% in the rD-FLAP Study and DFT was considered a safe reconstruction procedure, the present study showed that we should be careful, especially in cases with esophageal invasion requiring reconstruction in the lower mediastinum.

Although the present study provides the above-mentioned interesting evidence, it still has several limitations. First, the sample size of this study was relatively small. Although the study was first started with a planned sample size of 80 patients, it was decided to reduce it from 80 to 40 patients. The main reason for this reduction was delayed patient recruitment due to the COVID-19 pandemic. At the same time, new evidence was reported from a systematic

review article that the incidence of RE in several types of EG was 19.3%. It was then decided to reduce the planned sample size from 80 to 40 patients in parallel with the change in the upper limit of the incidence of RE from 15% to 20% to finish the study in the period that was originally planned. Second, this was a single-arm, non-comparative study. Although comparison with other types of reconstruction procedures such as DT or other types of esophagogastrostomy with some anti-reflux function such as mSOFY will be interesting in clinical practice, it was judged that these comparative studies were not appropriate because we had little experience with reconstruction procedures other than DFT. These comparative, prospective studies are expected to be part of a larger, multicenter study in the future, though there are several retrospective reports comparing reconstruction procedures after PG.[22] Third, cases with esophageal invasion were excluded after an SAE of postoperative death; therefore, the efficacy of laparoscopic DFT for such cases including esophagogastric junction cancer was not confirmed in the present study. Rather, the present study showed that laparoscopic DFT is a technically demanding procedure, and careful attention is required, especially in reconstruction in the lower mediastinum, even by experienced surgeons. However, we believe that DFT would be highly valuable for reconstruction in such a high location if appropriately performed. Robotic surgery would contribute to the broader applicability of the procedure by reducing the level of technical difficulty, although further study is needed in this regard. Fourth, the outcomes of independent central review and local investigator review in the assessment of RE were rather different. Two cases assessed as RE of LA-A on local investigator review were changed to LA-C and D on independent central review, and three cases assessed as no RE were changed to LA-A. However, it is reported that there is evident variability between independent central review and local investigator review in clinical trials, which could potentially change the conclusions of such trials.[23] In the present study, the anti-reflux potential of DFT was statistically proven to be effective on both independent central review and local investigator review, showing the high credibility of this study.

In conclusion, the present ID-FLAP Study, the first prospective study to evaluate the efficacy of DFT, showed that laparoscopic DFT had effective anti-reflux potential both on objective assessment by endoscopic examination and on subjective assessment by a QOL survey. Taken together with the acceptable incidence of anastomotic stricture, DFT can be a favorable option for reconstruction procedure after PG. Robotic surgery has a good fit with DFT, all steps of which are performed by hand-sewn technique, and will contribute to facilitating further spread of DFT by reducing the level of technical difficulty.

AUTHOR CONTRIBUTIONS

Shinji Kuroda conceived and designed the study, collected and analyzed the data, and wrote the manuscript. Michihiro Ishida, Yasuhiro Choda, Atsushi Muraoka, Shinji Hato, Tetsuya Kagawa, and Norimitsu Tanaka collected and interpreted the data. Toshiharu Mitsuhashi contributed to statistical analysis. Yoshihiko Kakiuchi, Satoru Kikuchi, Masahiko Nishizaki, and Shunsuke Kagawa revised the manuscript. Toshiyoshi Fujiwara supervised the study.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

Approval of the research protocol: This study conformed to the provisions of the Declaration of Helsinki, and the protocol was approved by the Okayama University Hospital Institutional Review Board (Approval no. 1904-002) and the institutional review boards of each participating institution.

Informed Consent: N/A.

Registry and the Registration No. of the study: The UMIN clinical trial registration number was 000036191.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

DISCUSSANT

PROFESSOR HIROSHI SAEKI

The outcomes of independent review, central review, and local investigators' review of the assessment of reflux esophagitis were very different. For example, two cases assessed as LA grade A in the local investigators' review were changed to LA grade C or D in the independent central review. Why do you think the outcomes were so different?

I consider endoscopic esophageal reflux to be very important, but I think we also need to assess patients' QOL. Did you compare the outcomes of reflux esophagitis and reflux symptoms in this study?

Unfortunately, cases with esophageal invasion were excluded because postoperative death due to anastomotic leakage occurred in this study. Is it possible that the low incidence of reflux esophagitis was due to the exclusion of cases of esophageal invasion?

What is your opinion on the significance of DFT in cases of esophageal invasion in daily practice?

DR. SHINJI KURODA

That was a very important point in this study, and I was actually very surprised by the difference between these two assessments. I think the difference is due to the investigators' tendency to assess symptoms as less severe. I don't think that's a good approach, but it happens. That's the mindset of investigators. I think that's why an independent central review is recommended for many clinical studies, especially the late stage of clinical studies. I am very happy to receive this comment about the independent central review because we had originally not planned to include such a review.

Yes, we did. But there was no association between reflux esophagitis and reflux symptoms. However, our results demonstrated the effectiveness of the DFT reconstruction based on objective evaluations using endoscopic findings and also subjective assessments by the QOL survey. There was no correlation between these two assessments in individual patients, but overall, DFT reconstruction is very effective.

Yes, I think it's possible. Actually, in our previous retrospective study, one of the risk factors for reflux esophagitis was anastomosis in the mediastinum. As you noted, the low incidence of reflux

esophagitis in the present study may have been due to the exclusion of esophageal invasion cases.

I believe DFT reconstruction is still effective for higher anastomoses if the procedure is performed accurately. I recognize that it is difficult to perform accurately in higher places, so I think it is necessary to create a clear, wide view. By incising the diaphragm and opening the left thoracic cavity, if necessary, it is possible to create a large view, which allows the procedure to be performed accurately. If it can be performed accurately, I think this DFT reconstruction works well.

PROFESSOR KEISHI YAMASHITA

Kuroda et al. concluded that the laparoscopic double-flap technique showed anti-reflux efficacy with an acceptable incidence of anastomotic stricture, and I agree with this conclusion. However, they claimed that the double-flap technique could be a standard reconstruction procedure after PG. I think this latter conclusion is highly conditional, and depends on the surgical skill. I think that the excellent clinical outcomes obtained in the study may be due to the limited number of surgeons, who are one of the most critical factors for the double-flap technique. How many surgeons were included in this study, and how many inexperienced surgeons instructed by experienced surgeons were included in this study?

The older group had a good surgical protocol and was experienced with the double-flap technique, so excellent clinical outcomes could be obtained. This good protocol should become the standard for the double-flap technique. Please focus on this point for the future.

One more question. I think that postoperative stricture might be affected by the double-flap reconstruction technique and may be associated with the final Y-shaped closure with the interrupted and continuous sutures to cover the anastomosis. How many sutures do you think are appropriate to prevent postoperative stricture, or does your group have fixed suture numbers to close the final flap?

Do you think the stricture is correlated with the flap closure technique?

You have two leakage cases. Were they related to the stricture or not?

I am interested in the low frequency of PPI usage after PG with the double-flap technique in this study. In comparison to your retrospective study, what do you think is the reason for the large difference?

DR. SHINJI KURODA

Seven surgeons performed the operations in this study, including one inexperienced surgeon with an experienced first assistant.

Thank you very much for the question about the anastomotic stricture. That's one of the biggest complications of DFT reconstruction, and one of the important points is closing the double flap. We usually do not decide the exact number of stitches in advance, but we typically put four to five stitches in the middle, at about the midpoint of the flap, and we don't favor interrupted or continuous sutures.

That's one possibility, but the main problem is with the anastomosis process. An inappropriate suturing technique can directly cause an anastomotic stricture.

I don't check the CRF, but it might not be related to the stricture. However, if you have anastomotic leakage, that could lead to anastomotic stricture after correcting the leakage.

In the retrospective study, PPI usage at 1 year after surgery was about 20%, and in the present study, it was 7.9%. I think that clinical practice has changed in each hospital to not use PPI regularly. Yes, in my personal experience at least, no patients regularly use PPI.

PROFESSOR TOSHIMI KAIDO

When performing a clinical trial, the sample size is calculated based on the hypothesis, alpha error, beta error, and other factors. But you reduced your sample size from 80 to 40 before conducting the study. Is it methodological or statistically acceptable to reduce the sample size without changing the hypothesis?

DR. SHINJI KURODA

That's a very important point. The alpha error was 0.05 and the beta error was 0.2, which were similar to those in the previous study design. We simply changed the upper threshold from 15% to 20%.

PROFESSOR NAOKI HIKI

I fully agree with your conclusion concerning reflux symptoms. But, I have one question concerning the anastomotic leakage because, in the case of the double-flap technique, the flap itself makes it very difficult to find anastomotic leakage. Intra-flap leakage is also very difficult to find. Therefore, you selected the complication of higher than grade 3. How about grade 2 or patients with high fever or inflammatory response and so on, because intra-flap leakage is very difficult to find?

DR. SHINJI KURODA

In the present study, we had two cases of anastomotic leakage. One was grade 1 and the other was grade 5, leading to the patient's death. We didn't have a grade 2 case suspected of intra-flap leakage. I personally haven't paid much attention to intra-flap leakage so far, but I think there is a possibility that intra-flap leakage can be a cause of unexplained high fever because it is very difficult to find, as you mentioned.