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A multicenter retrospective study comparing surgical outcomes between the overlap method and functional method for esophagojejunostomy in laparoscopic total gastrectomy: Analysis using propensity score matching

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Running head: Overlap and functional methods for EJS using LTG

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Abstract

Background

This study aimed to compare the postoperative outcomes after laparoscopic total gastrectomy (LTG) with esophagojejunostomy (EJS) performed using the overlap method or the functional method in a multicenter retrospective study with propensity score matching.

Methods

We retrospectively enrolled all patients who underwent curative LTG for gastric cancer at six institutions between January 2004 and December 2018. Patients were categorized into the overlap group (OG) or functional group (FG) based on the type of anastomosis used in EJS. Patients in the groups were matched using the following propensity score covariates: age, sex, body mass index, American Society of Anesthesiologists physical status, extent of lymph node dissection, and Japanese Classification of Gastric Carcinoma stage. The surgical results and postoperative outcomes were compared.

Results

We identified 69 propensity score-matched pairs among 440 patients who underwent LTG. There was no significant between-group difference in the median operative time, intraoperative blood, or number of lymph nodes resected. In terms of postoperative outcomes, the rates of all complications (Clavien-Dindo [CD] classification ≥II; OG 13.0 vs. FG 24.6%, respectively; p=0.082), complications more severe than CD grade III (OG 8.7 vs. FG 18.8%, respectively; p=0.084), and the occurrence of EJS leakage and stenosis more severe than CD grade III (OG 7.3% vs. FG 2.9%, p=0.245; OG 1.5 vs. FG 8.7%, p=0.115, respectively) were comparable. The median follow-up period was 830 days (range, 18–3376), and there were no differences in overall survival between the two groups.

Conclusions

There was no difference in surgical outcomes and overall survival based on the type of anastomosis used for EJS after LTG. Therefore, selection of anastomosis in EJS should be based on each surgeon's preference and experience.

Keywords: laparoscopic total gastrectomy, gastric cancer, esophagojejunostomy, propensity matching score

Introduction

Since the first laparoscopy-assisted distal gastrectomy for early gastric cancer (GC) was performed in 1991 (1), development of dedicated instruments and surgical techniques led to the use of laparoscopic distal gastrectomy (LDG) to treat GC. However, laparoscopic total gastrectomy (LTG) requires a high degree of skill in performing gastrectomy with systematic lymphadenectomy, as well as postresection reconstruction; indeed, these are difficult procedures even for experienced laparoscopic surgeons (2,3). Esophagojejunostomy (EJS) is one of the most important surgical techniques in LTG, since it is associated with risk of anastomotic leakage and stenosis (4,5). Various EJS methods have been reported, including single stapling (6), double stapling (7), hemi-double stapling (8), functional end-to-end anastomosis (2), overlap (3), and the hand-sewn method (9), all of which are selected on the basis of the preference of each individual surgeon. In our multicenter retrospective study, the short- and long-term outcomes of LTG for GC were satisfactory, and no difference was observed in the postoperative complication rate related to the type of stapler (circular vs. liner stapler) used for EJS after LTG (10, 11). The use of circular staplers in LTG is a technique that is difficult to perform in obese patients (5). There is no consensus on EJS using a linear stapler, which is considered particularly advantageous for LTG. However, it is unclear which technique has the lowest incidence of EJS-related complications after LTG, since there are few comparative studies on these methods. In our affiliated hospitals, anastomosis using linear staplers is typically performed using either a functional end-to-end anastomosis or an overlap method using linear staplers in LTG. The purpose of this study was to compare the functional and overlap methods in LTG in terms of the feasibility and safety of EJS using a linear stapler. A propensity score matching (PSM) method was used to compare the incidence of complications after EJS in a multicenter setting. This is the first multicenter retrospective study to compare the functional and overlap methods in LTG using a PSM method.

Material and Methods

Patients

We retrospectively reviewed patients who underwent LTG for GC at six institutions (Hokkaido University Hospital, Teine Keijinkai Hospital, Obihiro-Kosei General Hospital, Hokkaido Gastroenterology Hospital, Tonan Hospital, and Asahikawa City Hospital) between January 2004 and December 2018. All patients who underwent curative LTG were included in the analysis. All patients were diagnosed with GC using endoscopy, computed tomography (CT), or endoscopic ultrasound. The Japanese Classification of Gastric Carcinoma (JCGC) was used for tumor staging (12). The primary indication for LTG was decided as stage I GC based on the Japanese Society of Endoscopic Surgery (JSES) guidelines (13); however, over time, we expanded the indication to include cases of advanced GC that could be curatively resected. Clinicopathological data, including age, sex, BMI, American

Society of Anesthesiologists physical status (ASA-PS), clinical stage, combined resection of other organs, lymph node dissection, and anastomosis method, were collected. Surgical outcomes, including operative time, estimated blood loss, postoperative complications, and length of postoperative hospital stay, were recorded. Follow-up was defined as the period between surgery and death from GC or other causes. All patients provided informed consent, and the Hokkaido University Hospital Institutional Review Board approved the data collection and analysis (No. 016-0151). This study was performed in accordance with the principles of the Declaration of Helsinki.

Surgical procedure

Gastric procedure type (resection and reconstruction) was determined based on the experience and preference of a surgeon who was accredited through the Endoscopic Surgical Skill Qualification System of the JSES (13). In cases where the operating surgeon did not possess this qualification, a qualified surgeon supervised the surgery. The extent of lymph node dissection was determined based on the JGCA guidelines (12). Patients who underwent D2 lymph node dissection with splenectomy and patients who underwent D2–No.10 lymph node dissection were included in D1+. Patients were categorized into two groups based on whether EJS was performed using an overlap or functional method. Representative examples of EJS are shown in Figs. 1 and 2. We performed intracorporeal EJS using the overlap or functional method, in which the jejunum was transected 20-30 cm below the ligament of Treitz using a linear stapler. In the overlap method, the left end of the stapled line on the cut-off stump of the esophagus was transected by 10 mm, and a small hole was made at the esophagus. A small enterotomy was performed on the anti-mesenteric side of the efferent jejunum, 50 mm from the stump of the jejunum. Both jaws of a 60 mm linear stapler were inserted into holes and fired. Single-ligation full-thickness suture was performed using 3-0 absorbable suture, with 11–13 stitches or running sutures using the extracorporeal slip knot technique or intracorporeal suture for closure. In the functional method, the abdominal esophagus was exposed and transected using a 60-mm linear stapler in the horizontal direction. Subsequently, 10 mm transverse incisions were created at the edges of the tip of the anti-mesenteric border between the jejunum and the right lateral wall of the abdominal esophagus. Both jaws of a 45 mm linear stapler were inserted into holes and fired. The entry hole for the 60 mm linear stapler was closed with one application of the stapler perpendicular to the first suture line.

Patients were divided into three groups based on the Clavien-Dindo (CD) postoperative complication classification grade (14-15). EJS leakage more severe than CD grade III was defined as leakage requiring drainage under radiological guidance or re-operation under general anesthesia. EJS stenosis more severe than CD grade III was defined as stenosis requiring endoscopic dilatation.

Postoperative follow-up

All patients were observed every 3 months after surgery. Hematological analysis (including tumor marker analysis for carcinoembryonic antigen and carbohydrate antigen 19-9) was performed at each visit. Abdominal CT scans were performed every 6 months or when clinical recurrence was suspected. Gastrointestinal endoscopy was performed at 1, 3, and 5 years postoperatively.

Statistical analysis

PSM was performed using a logistic regression model to mitigate the selection bias in the present study. The parameters used for PSM were age, sex, BMI, American Society of Anesthesiologists physical status, splenectomy, clinical stage, surgical method, and lymph node dissection. We matched the logit of the propensity score within the caliper with 0.2 standard deviation of the value based on the recommendations by Austin (16). Categorical variables were analyzed using the chi-square test before propensity score matching and the McNemar and Wilcoxon signed rank tests after PSM. Continuous variables were examined using the unpaired t-test before PSM and the paired t-test or Wilcoxon signed-rank test after propensity score matching. Survival curves were constructed using the Kaplan-Meier method. Group differences in overall survival (OS) were evaluated using log-rank tests. Statistical significance was set at $p<0.05$. Statistical analysis was performed using the JMP® 15 software (SAS Institute Inc., Cary, NC, USA).

Results

Clinical features and surgical outcomes of the study population before matching

Table 1 shows the clinical characteristics and surgical outcomes of the study population. A total of 440 patients were included, comprising 305 men (69.3%) and 135 women (30.7%) [average age, 66.3±11.1 years; D2 lymphadenectomy, 68 patients (15.5%); laparoscopic-assisted total gastrectomy (LATG), 130 patients; total laparoscopic total gastrectomy (TLTG), 310 patients; and postoperative complications, 66 patients (15.0%)]. The method of anastomosis was circular in 170 (38.9%) patients and linear in 267 (61.1%) patients. The average surgery duration was 332.8±83.6 minutes, average operative blood loss was 107.4±187.9 ml, and median duration of postoperative hospital stay was 18±16.6 days.

After applying our exclusion criteria (① Circular stapler; ② Neoadjuvant therapy; ③ Resection of other organs, combined gastric and pancreas or lower esophagus resection; ④ Unknown), 223 patients were included in the subgroup we evaluated for PSM. In all, 69 patients in the overlap group (OG) were individually matched to 69 patients in the functional group (FG) (Fig. 3).

Clinicopathological characteristics

The clinicopathological characteristics of 223 patients who underwent curative LTG and 138 propensity score-matched patients are shown in Table 2. In the propensity score-matched patients, as

determined by the study design, sex, age, BMI, ASA-PS, splenectomy, and clinical JCGC stage distributions between the OG and FG groups were comparable. All patients who underwent LTG at Hokkaido Gastroenterology Hospital were excluded from the study, since they had jejunal pouch reconstruction.

Surgical results and postoperative outcomes

The surgical outcomes and postoperative complications of the 223 patients who underwent curative LTG and propensity score-matched patients are shown in Table3. In the propensity score-matched group of patients, there was no significant difference in the median operative time, blood loss, and number of resected lymph nodes between the two groups. Furthermore, there was no difference in the rate of postoperative complications between the two groups. The incidence of EJS leakage and stenosis was more severe than that of CD grade III, which did not differ between the two groups. The median postoperative hospital stay was significantly shorter in OG than in FG (OG vs. FG; 11 days [range 7–210] vs. 14 days [range 7–79], $p < 0.001$). The median follow-up period was 830 days (range, 18–3376); there were no differences in the 5-year OS rate between the two groups (OG vs. FG: 77.8% vs. 82.1%, $p = 0.272$).

Discussion

This is the first PSM study to compare the surgical outcomes of overlap and functional methods of EJS in LTG for GC in a multicenter study. The results of this study showed that both anastomotic methods were comparable in terms of surgical outcomes, EJS-related complications, and 5-year OS rates.

The advantages of laparoscopic surgery include the following: faster recovery; fewer complications; less blood loss and, therefore, less need for blood transfusion; smaller incisions; less pain; less chance of intestinal obstruction; and lower risk of scarring. Since the introduction of laparoscopic surgery in 1994 (1), LDG for GC has become a common procedure due to the development of specialized equipment and surgical techniques. However, LTG is not performed as often as LDG, partly because EJS is a difficult technique to perform (2,10). Many surgeons have described their experiences with TLTG and acknowledge its safety and feasibility (17-20). TLTG provides a wider field of view than LATG, reduced operative duration, decreased time from surgery to initiation of soft diet, and shorter postoperative hospital stay (21-25). During LATG, extracorporeal anastomosis performed through an incision may result in increased tension and damage to the structures surrounding the anastomosis due to the narrow field of view, especially in obese patients (18,26). TLTG allows a clear view of the entire EJS, thus preventing tension and damage. The subjects in this study had undergone TLTG and LATG. In all cases of LATG, anastomosis of the Y limb was performed intracorporeally, and EJS was performed extracorporeally. We initially performed LATG with mini laparotomy, followed by a

gradual transition to performing TLTG with intracorporeal reconstruction. TLTG requires complete intracorporeal reconstruction, which is an anastomotic technique that uses a linear stapler intended for intracorporeal use. Reports on TLTG have described several methods of intracorporeal EJS, in which the most widely used conventional methods are the percutaneous insertion anvil (Orvil™; Covidien, Mansfield, MA, USA) using a circular stapler, the functional method, and the overlap method using a linear stapler. TLTG has many advantages; however, it is associated with a high incidence of postoperative complications (10 %–40%) (27). EJS-related complications can lead to morbidity and mortality, and the incidence of EJ anastomotic complications, such as stenosis and leakage, was higher with Orvil™ (Covidien, Mansfield, MA, USA) than with a linear stapler (leakage rate 4.1% vs. 0.7%, p=0.106; stenosis rate 4.1% vs. 0%, p=0.017) (28). Conversely, both EJS procedures evaluated had a lower complication rate than the others, and there was no difference in the complication rate of EJS (10). Although many techniques have been reported for EJS after LTG, it is unclear which anastomosis method is the most useful, and no standard technique has been established. In recent years, there have been many reports of robot-assisted total gastrectomy (29,30), and it is expected that EJS using a linear stapler will become more common with the increase in robot-assisted laparoscopic gastrectomies. In order to ensure a safe surgical technique for EJS, it is necessary to clarify the postoperative outcomes of the anastomosis method using a linear stapler, which can also be used for robot-assisted surgery. There are two methods of EJS using a linear stapler: overlap and functional edge-to-edge anastomosis. The overlap method was first reported by Inaba et al. (31) as a new method for EJS in LTG. The entry hole was closed with sutures using Roeder's knot; however, the use of continuous sutures has also been reported, which is reportedly a simple technique and shortens the duration of surgery (3). In contrast, Matsui et al. (32) and Ebihara et al. (2) reported that functional end-to-end esophageal junction after total gastrectomy is convenient, safe, and reliable, as it is not dependent on the depth of the esophagus or esophageal hiatus and does not require complicated suturing techniques. In a comparative report on EJS using linear staplers in TLTG, a single-center PSM of the overlap method and the functional method was reported in Korea (33). In this study, we performed a multicenter retrospective study using PSM to compare surgical outcomes between the overlap and functional methods for EJS in LTG. The six affiliated hospitals that participated in this study are high-volume centers in our prefecture, and each facility has a JSES-certified laparoscopic surgeon who performed the procedure as a surgeon or teaching assistant in this study. Based on our results, both EJS methods evaluated had a low complication rate, and the complication rate associated with EJS was similar. The reason for the difference in the median postoperative hospital stay between the two groups was attributed to the differences in the criteria for discharge among the affiliated hospitals. However, studies on long-term prognosis suggest an association between postoperative complications and long-term survival in several malignancies, including breast cancer, colorectal cancer, and peripancreatic cancer (34-37). Furthermore, several reports have indicated that postoperative complications are associated with the

prognosis of patients with GC (38,39). In our previous multicenter retrospective study on the long-term prognosis of laparoscopic surgery for GC, postoperative complications were also shown to be associated with survival (40). Therefore, ensuring the safety of LG may be important for the short- and long-term outcomes of patients with GC. The same was true in the present study for the occurrence of severe complications of CD grade III or higher after LTG (8.7 vs. 18.8%, respectively, $p = 0.084$) and severe EJS leakage and stenosis of CD grade III or higher (7.3 vs. 2.9%, $p = 0.24$ and 1.5 vs. 8.7%, $p = 0.115$, respectively). The results were similar for both reconstruction methods. There was no difference in long-term prognosis between the two groups ($p = 0.272$), which may be due in part to the similarity of complications.

This study has several limitations. This was a retrospective, observational, and non-experimental study. Additionally, we included patients who underwent either LATG or TLTG; different results may have been obtained in an analysis that excluded patients who underwent LATG. Furthermore, although PSM was performed, selection bias, such as operator bias, cannot be eliminated. In the present study, most LTGs were performed by laparoscopic surgery experts as operators or teaching assistants. A well-designed randomized control trial is required to validate our findings.

Conclusions

There was no difference in surgical outcomes and OS related to the type of anastomosis used for EJS after LTG. Therefore, the decision to perform EJS should be based on the preference and experience of the surgeon.

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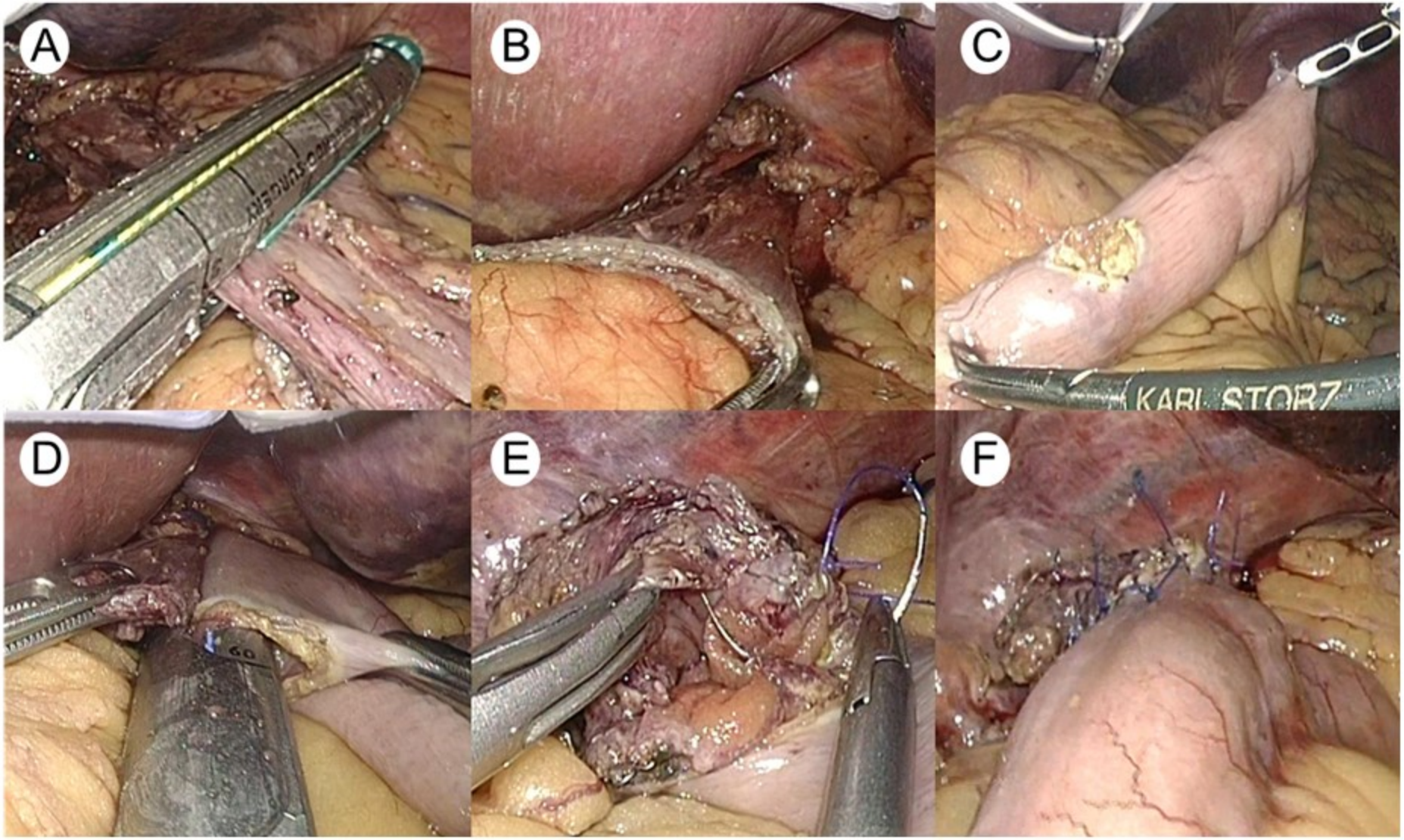
Figure legends

Fig. 1. Representative example of the overlap method. A: Transection of the abdominal esophagus using a 60 mm linear stapler. B: Stump of the esophagus. An entry hole is created at the left end of the stapled line on the cut-off stump of the esophagus. C: A small hole at the lifted jejunum (anti-mesenteric side of 50 mm from the jejunal stump). D: Both jaws of the linear stapler are inserted into a small hole at the lifted jejunum and esophagus and fired. E: The entry hole is closed by single ligation or running suture for a full thickness suture to make a V-shaped staple line in the inner cavity. F: An esophagojejunostomy (overlap method) is performed.

Fig. 2. Representative example of functional end-to-end esophagojejunostomy. A: Stump of the esophagus. B: An entry hole is created at the right end of the stapled line on the cut-off stump of the esophagus and confirming the mucosa using a transnasal gastric tube. C: A small hole at the stump of lifted jejunum (anti-mesenteric side of the jejunum). D: Both jaws of the linear stapler are inserted into a small hole at the lifted jejunum and esophagus and fired. E: The entry hole is closed using a linear stapler. F: An esophagojejunostomy (functional method) is performed.

Fig. 3. Study enrollment. LTG: laparoscopic total gastrectomy; NAC: Neoadjuvant therapy
*Resection of other organs, combined gastric and pancreatic or lower esophagus resection.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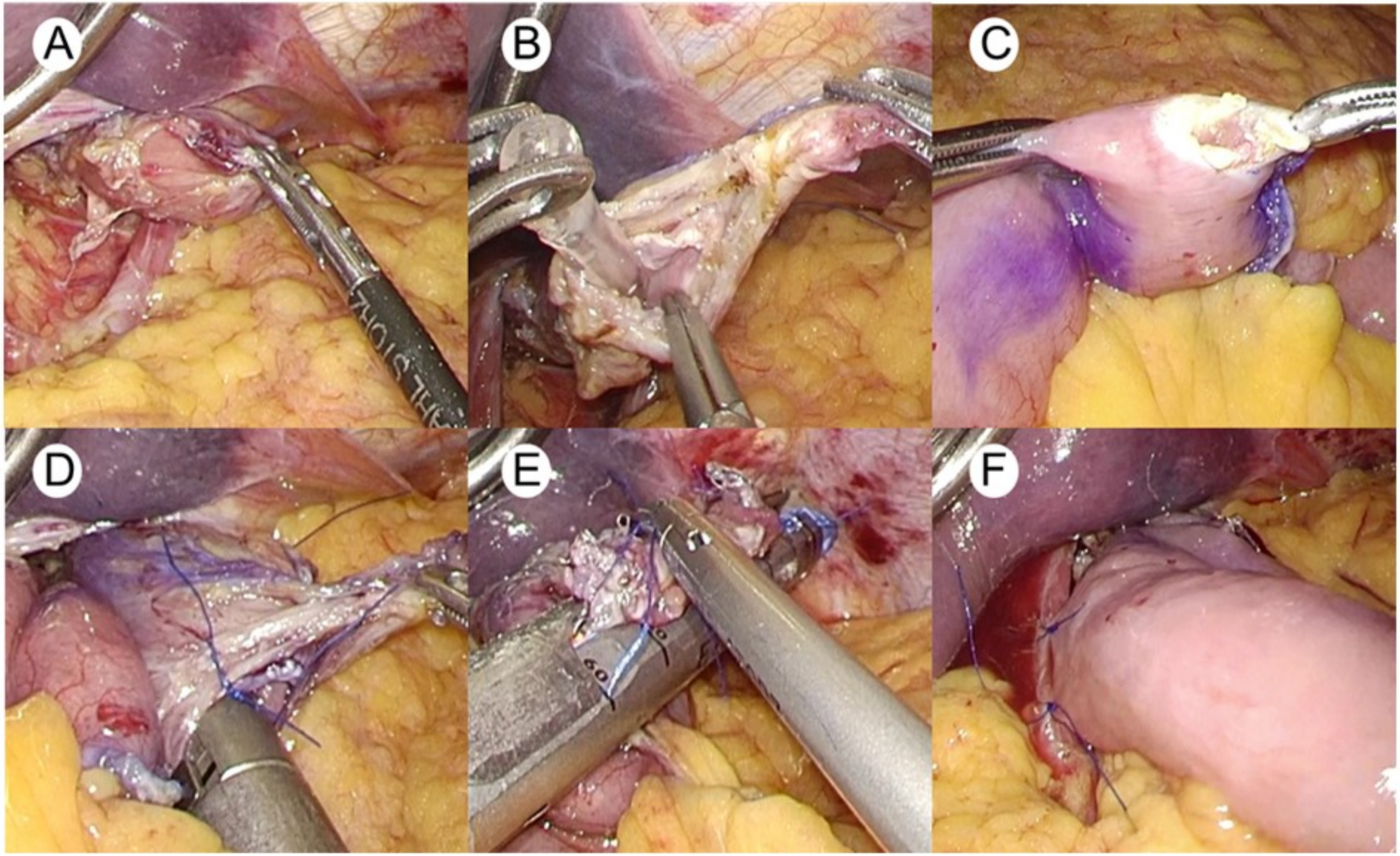
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Enrollment

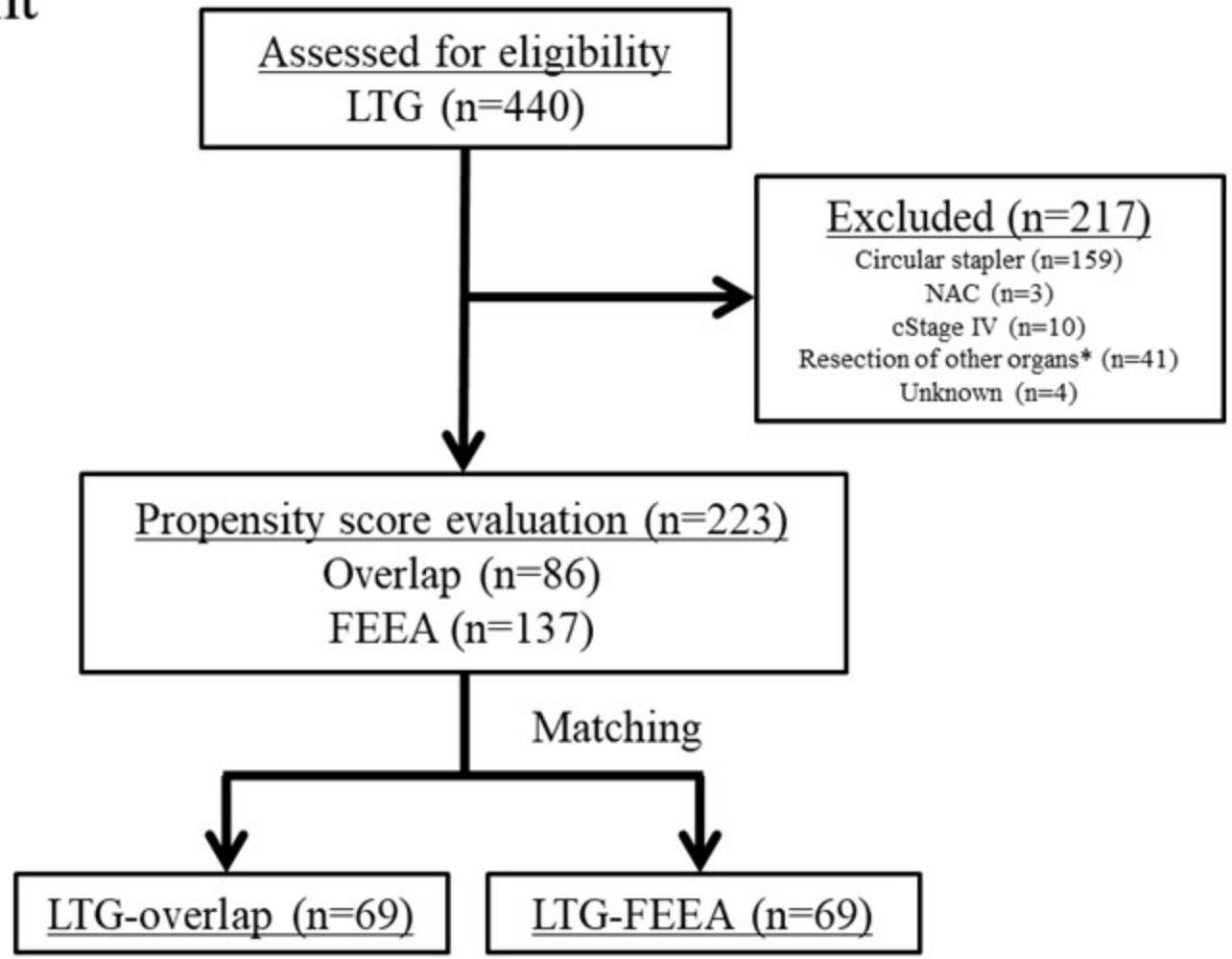
Assessed for eligibility
LTG (n=440)
Excluded (n=217)
Circular stapler (n=159)
NAC (n=3)
cStage IV (n=10)
Resection of other organs* (n=41)
Unknown (n=4)
Propensity score evaluation (n=223)
Overlap (n=86)
FEEA (n=137)
Matching
LTG-overlap (n=69)
LTG-FEEA (n=69)

Table 1. Clinical features and surgical outcomes of the study population

Variable	Overall (n=440)
Gender (M/F)	305/135
Age (year, mean ± SD)	66.3±11.1
BMI (kg/m^2, mean ± SD)	22.7±3.5
ASA-PS* (II≤)	318 (72.3%)
Clinical stage** (II≤)	135 (30.7%)
Lymph node dissection (D2≤)	68 (15.5%)
Method of surgery (LATG†, TLTG‡)	130:310
Method of anastomosis (Circular: Linear)	170:267 (Unknown=3)
Jejunal pouch reconstruction	71 (16.1%)
Operation time (min, mean ± SD)	332.8±83.6
Blood loss (ml, mean ± SD)	107.4±187.9
Postoperative complication (CD§, IIIa≤)	66 (15.0%)
Postoperative hospital stays (days, mean ± SD)	18±16.6

*The American Society of Anaesthesiologist's physical status, **According to the American Joint Committee on Cancer Cancer Staging, Manual 8th edition, † LATG, laparoscopic-assisted total gastrectomy, ‡ TLTG, totally laparoscopic total gastrectomy, § Clavien-Dindo, classification

Table 2. Patient‘s characteristics who underwent LTG before and after propensity score matching

		All patients (n=223)			Propensity-matched patients (n=138)		
		Overlap (n=86)	FEEA (n=137)	*p* value	Overlap (n=69)	FEEA (n=69)	*p* value
		Number	Number		Number	Number	
Sex (%)				0.565			0.708
	Male	61 (70.9)	102 (74.5)		50 (72.5)	48 (69.6)	
	Female	25 (29.1)	35 (25.5)		19 (27.5)	21 (30.4)	
Age (year)*		69 (35-87)	69 (36-88)	0.399	69 (35-87)	70 (36-88)	0.797
BMI (kg/m^2)*		22.8 (13.6-33.4)	22.5 (14.9-34.3)	0.964	23.1 (15.6-33.4)	22.2 (14.9-34.3)	0.603
ASA-PS (%)				0.144			0.682
	1-2	78 (90.7)	132 (96.4)		66 (95.7)	65 (94.2)	
	3-4	8 (9.3)	5 (3.4)		3 (4.3)	4 (5.8)	
Clinical JCGC stage (%)				0.013			0.848
	I	50 (58.2)	103 (75.2)		47 (68.1)	45 (65.2)	
	II	29 (33.7)	23 (16.8)		16 (23.2)	16 (23.2)	
	III	7 (8.1)	11 (8.0)		6 (8.7)	8 (11.6)	
Pathological JCGC stage (%)				0.095			0.920
	I	39 (45.4)	81 (59.1)		36 (52.2)	35 (50.8)	
	II	24 (27.9)	33 (24.1)		18 (26.1)	17 (24.6)	
	III	23 (26.7)	23 (16.8)		15 (21.7)	17 (24.6)	

Table 3 Surgical outcomes and postoperative course in patients who underwent curative LTG before and after propensity score matching

	All patients (n=223)			Propensity-matched patients (n=138)		
	Overlap (n=86)	FEEA (n=137)	*p* value	Overlap (n=69)	FEEA (n=69)	*p* value
	Number	Number		Number	Number	
Operative time (min)	305 (185-485)	290 (171-648)	0.212	305 (185-485)	288 (172-648)	0.496
Blood loss (ml)	0 (0-1070)	0 (0-500)	0.007	20 (0-1070)	40 (0-500)	0.084
Extent of lymph node dissection			0.545			0.478
D1/D1+ (%)	73 (84.9)	112 (81.8)		60 (87.0)	57 (82.6)	
D2 (%)	13 (15.1)	25 (18.2)		9 (13.0)	12 (17.4)	
Number of lymph nodes resected	41 (0-113)	41 (0-106)	0.346	41 (0-113)	43 (1-106)	0.843
Postoperative complication (%)						
CD ≥ II	10 (11.6)	31 (22.6)	0.039	9 (13.0)	17 (24.6)	0.082
CD ≥ III	7 (8.1)	20 (14.6)	0.150	6 (8.7)	13 (18.8)	0.084
EJS leakage	5 (5.8)	3 (2.2)	0.157	5 (7.3)	2 (2.9)	0.245
EJS stenosis	1 (1.2)	8 (5.8)	0.084	1 (1.5)	6 (8.7)	0.115
Postoperative hospital stay (day)	11 (7-210)	15 (6-115)	<0.001	11 (7-210)	14 (7-79)	<0.001