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Author(s)	Ebihara, Yuma; Kurashima, Yo; Tanaka, Kimitaka; Nakanishi, Yoshitsugu; Asano, Toshimichi; Noji, Takehiro; Nakamura, Toru; Murakami, Soichi; Tsuchikawa, Takahiro; Okamura, Keisuke; Murakami, Yoshihiro; Murakawa, Katsuhiko; Nakamura, Fumitaka; Morita, Takayuki; Okushiba, Shunichi; Shichinohe, Toshiaki; Hirano, Satoshi
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1 A multicenter retrospective study comparing surgical outcomes between the overlap method and
2 functional method for esophagojejunostomy in laparoscopic total gastrectomy: Analysis using
3 propensity score matching

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5 Yuma Ebihara, PhD^{1,2}), Yo Kurashima, PhD¹), Kimitaka Tanaka, PhD¹), Yoshitsugu Nakanishi,
6 PhD¹), Toshimichi Asano, PhD¹), Takehiro Noji, PhD¹), Toru Nakamura, PhD¹), Soichi Murakami,
7 PhD¹), Takahiro Tsuchikawa, PhD¹), Keisuke Okamura, PhD¹), Yoshihiro Murakami, PhD³),
8 Katsuhiko Murakawa, PhD⁴), Fumitaka Nakamura, PhD⁵), Takayuki Morita, PhD⁶), Shunichi
9 Okushiba, PhD⁷), Toshiaki Shichinohe, PhD¹), Satoshi Hirano, PhD¹)

10
11 1)Department of Gastroenterological Surgery II, Faculty of Medicine, Hokkaido University, Sapporo,
12 Japan;

13 2)Division of Minimally Invasive Surgery, Hokkaido University Hospital, Sapporo, Japan;

14 3)Department of Surgery, Asahikawa City Hospital, Asahikawa, Japan;

15 4)Department of Surgery, Obihiro-Kosei General Hospital, Obihiro, Japan;

16 5)Department of Surgery, Teine Keijinkai Hospital, Sapporo, Japan;

17 6)Department of Surgery, Hokkaido Gastroenterology Hospital, Sapporo, Japan;

18 7)Department of Surgery, Tonan Hospital, Sapporo, Japan

19
20 Corresponding author: Yuma Ebihara, Department of Gastroenterological Surgery II, Hokkaido
21 University Faculty of Medicine, Kita 15 Nishi 7, Kita-ku, Sapporo City, 060-8638, Japan

22 Tel: +81 11 706 7714 Fax: +81 11 706 7158

23 Email: yuma-ebi@wc4.so-net.ne.jp

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25 Running head: Overlap and functional methods for EJS using LTG

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30 Author Contributions:

31 Study conception and design: Yuma Ebihara and Yo Kurashima

32 Acquisition of data: Yuma Ebihara

33 Analysis and interpretation of data: Yuma Ebihara and Yo Kurashima

34 Drafting of manuscript: Yuma Ebihara.

35 Critical revision of the manuscript: Yuma Ebihara, Yo Kurashima, Kimitaka Tanaka, Yoshitsugu
36 Nakanishi, Toshimichi Asano, Takehiro Noji, Toru Nakamura, Soichi Murakami, Takahiro Tsuchikawa,

1 Keisuke Okamura, Yoshihiro Murakami, Katsuhiko Murakawa, Fumitaka Nakamura, Takayuki Morita,

2 Shunichi Okushiba, Toshiaki Shichinohe, and Satoshi Hirano.

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4

1 **Abstract**

2 Background

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

6 Methods

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

14 Results

15 We identified 69 propensity score-matched pairs among 440 patients who underwent LTG. There
16 was no significant between-group difference in the median operative time, intraoperative blood, or
17 number of lymph nodes resected. In terms of postoperative outcomes, the rates of all complications
18 (Clavien-Dindo [CD] classification \geq II; OG 13.0 vs. FG 24.6%, respectively; $p=0.082$), complications
19 more severe than CD grade III (OG 8.7 vs. FG 18.8%, respectively; $p=0.084$), and the occurrence of
20 EJS leakage and stenosis more severe than CD grade III (OG 7.3% vs. FG 2.9%, $p=0.245$; OG 1.5 vs.
21 FG 8.7%, $p=0.115$, respectively) were comparable. The median follow-up period was 830 days (range,
22 18–3376), and there were no differences in overall survival between the two groups.

23 Conclusions

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

27
28 **Keywords:** laparoscopic total gastrectomy, gastric cancer, esophagojejunostomy, propensity matching
29 score

1 **Introduction**

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

26 **Material and Methods**

27 **Patients**

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

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

8 9 **Surgical procedure**

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

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

35 36 **Postoperative follow-up**

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

5 6 **Statistical analysis**

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

18 19 **Results**

20 **Clinical features and surgical outcomes of the study population before matching**

21 Table 1 shows the clinical characteristics and surgical outcomes of the study population. A total of
22 440 patients were included, comprising 305 men (69.3%) and 135 women (30.7%) [average age,
23 66.3 ± 11.1 years; D2 lymphadenectomy, 68 patients (15.5%); laparoscopic-assisted total gastrectomy
24 (LATG), 130 patients; total laparoscopic total gastrectomy (TLTG), 310 patients; and postoperative
25 complications, 66 patients (15.0%)]. The method of anastomosis was circular in 170 (38.9%) patients
26 and linear in 267 (61.1%) patients. The average surgery duration was 332.8 ± 83.6 minutes, average
27 operative blood loss was 107.4 ± 187.9 ml, and median duration of postoperative hospital stay was
28 18 ± 16.6 days.

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

33 34 **Clinicopathological characteristics**

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

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

6 **Surgical results and postoperative outcomes**

7 The surgical outcomes and postoperative complications of the 223 patients who underwent curative
8 LTG and propensity score-matched patients are shown in Table 3. In the propensity score-matched
9 group of patients, there was no significant difference in the median operative time, blood loss, and
10 number of resected lymph nodes between the two groups. Furthermore, there was no difference in the
11 rate of postoperative complications between the two groups. The incidence of EJS leakage and stenosis
12 was more severe than that of CD grade III, which did not differ between the two groups. The median
13 postoperative hospital stay was significantly shorter in OG than in FG (OG vs. FG; 11 days [range 7–
14 210] vs. 14 days [range 7–79], $p < 0.001$). The median follow-up period was 830 days (range, 18–
15 3376); there were no differences in the 5-year OS rate between the two groups (OG vs. FG: 77.8% vs.
16 82.1%, $p = 0.272$).

18 **Discussion**

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

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

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

1 prognosis of patients with GC (38,39). In our previous multicenter retrospective study on the long-
2 term prognosis of laparoscopic surgery for GC, postoperative complications were also shown to be
3 associated with survival (40). Therefore, ensuring the safety of LG may be important for the short-
4 and long-term outcomes of patients with GC. The same was true in the present study for the occurrence
5 of severe complications of CD grade III or higher after LTG (8.7 vs. 18.8%, respectively, $p = 0.084$)
6 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%,
7 $p = 0.115$, respectively). The results were similar for both reconstruction methods. There was no
8 difference in long-term prognosis between the two groups ($p = 0.272$), which may be due in part to
9 the similarity of complications.

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

16

17 **Conclusions**

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

21

22

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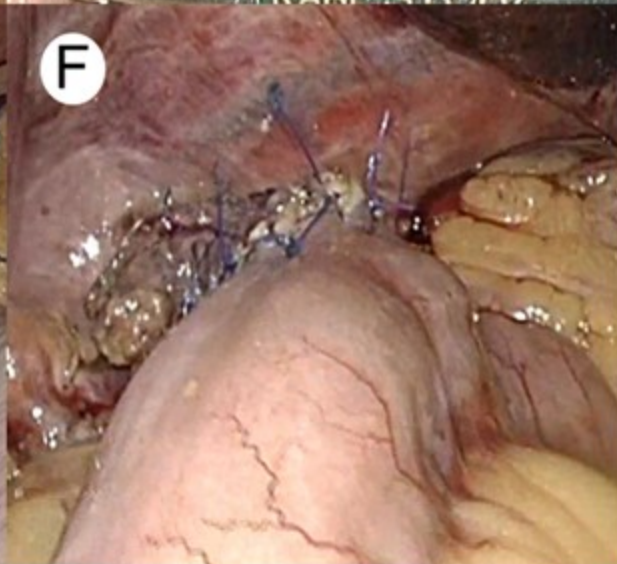
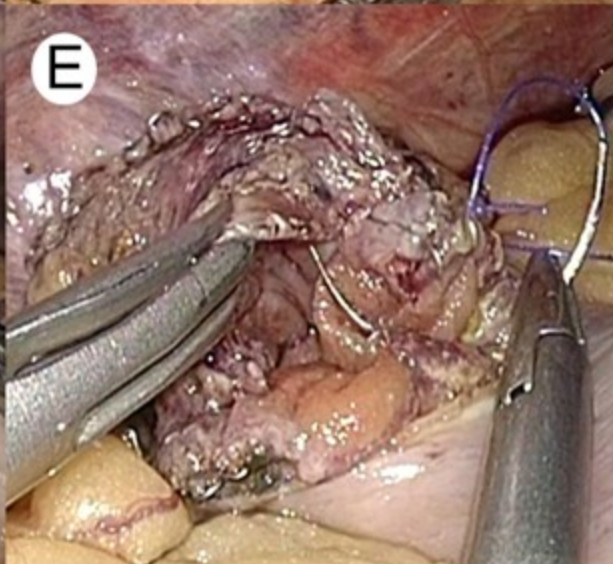
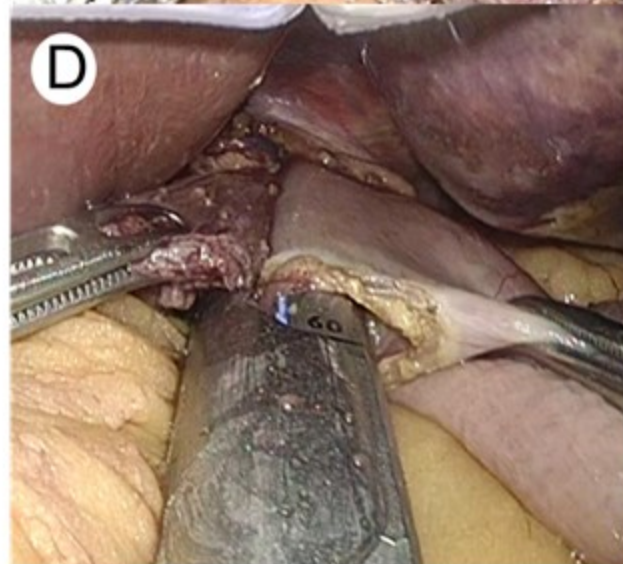
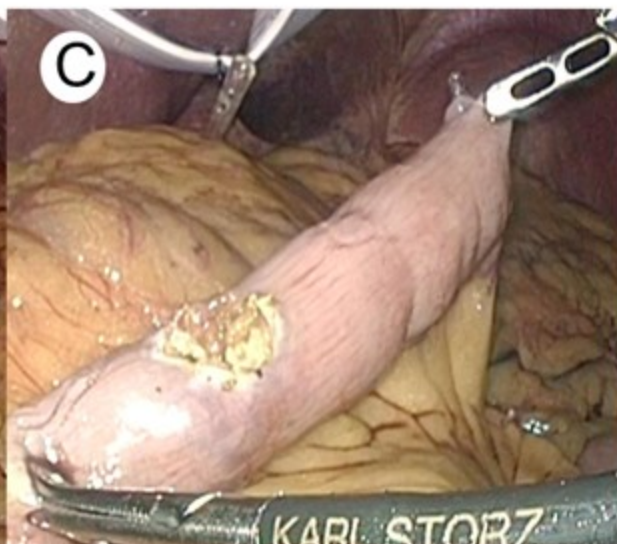
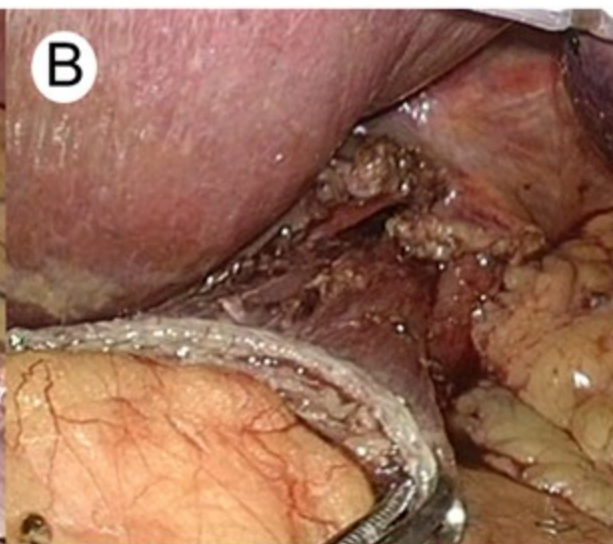
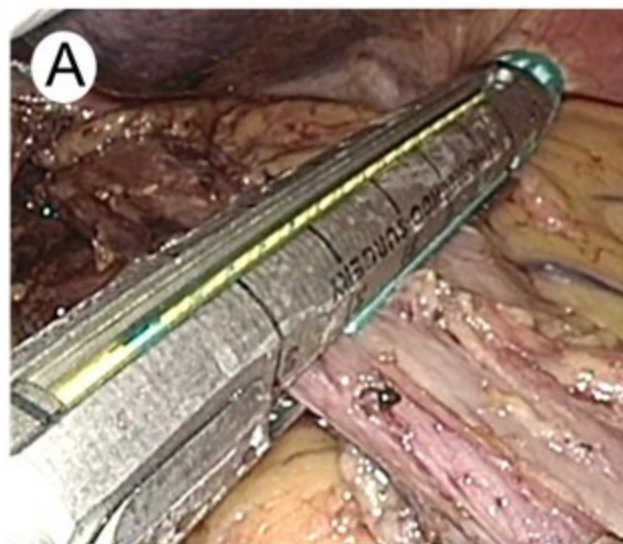
1 **Figure legends**

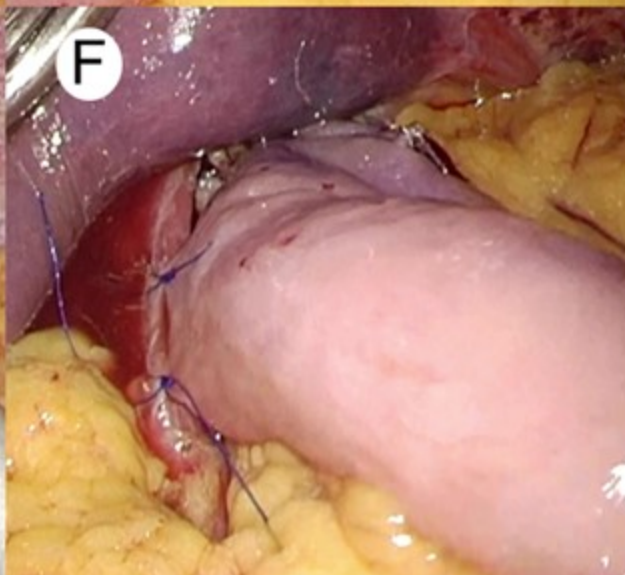
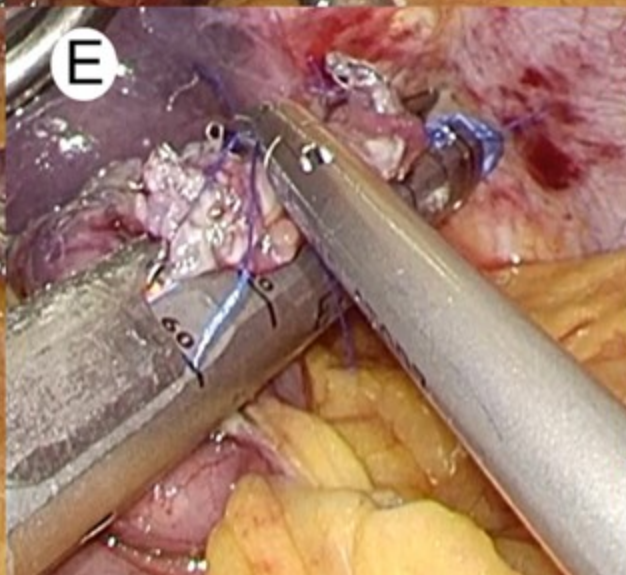
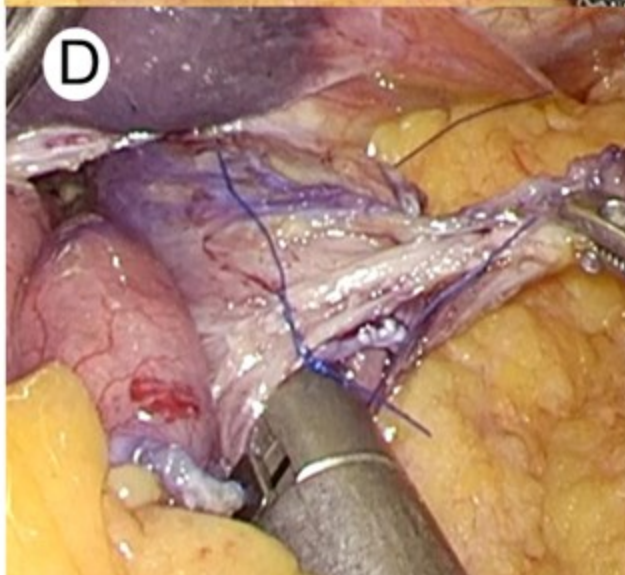
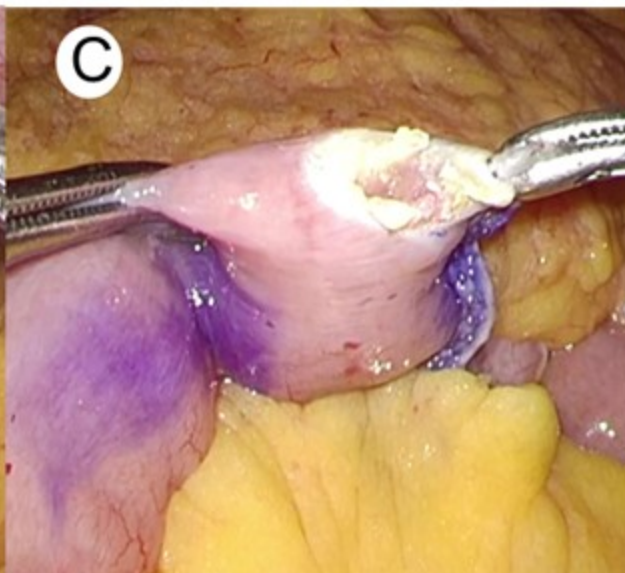
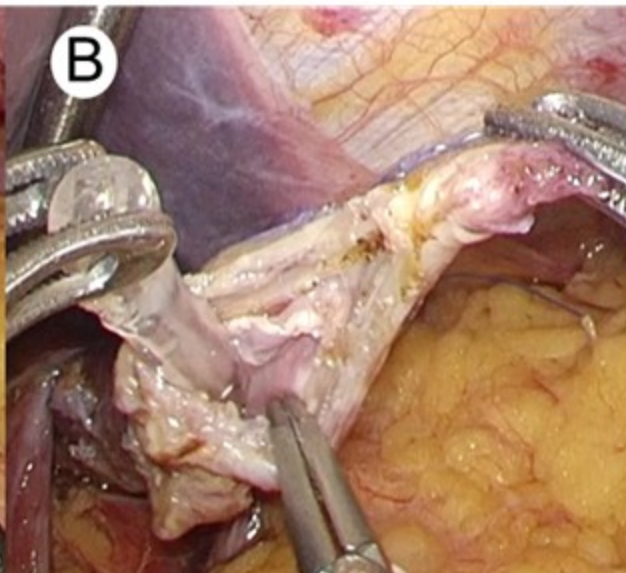
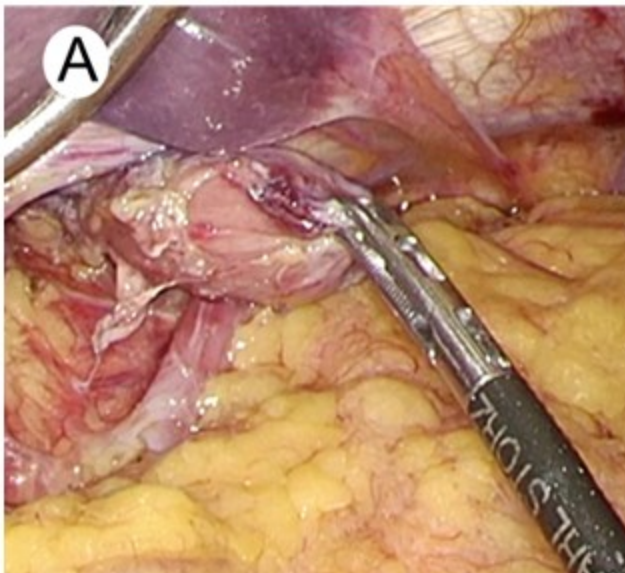
2 Fig. 1. Representative example of the overlap method. A: Transection of the abdominal esophagus
3 using a 60 mm linear stapler. B: Stump of the esophagus. An entry hole is created at the left end of the
4 stapled line on the cut-off stump of the esophagus. C: A small hole at the lifted jejunum (anti-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

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

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

19





Enrollment

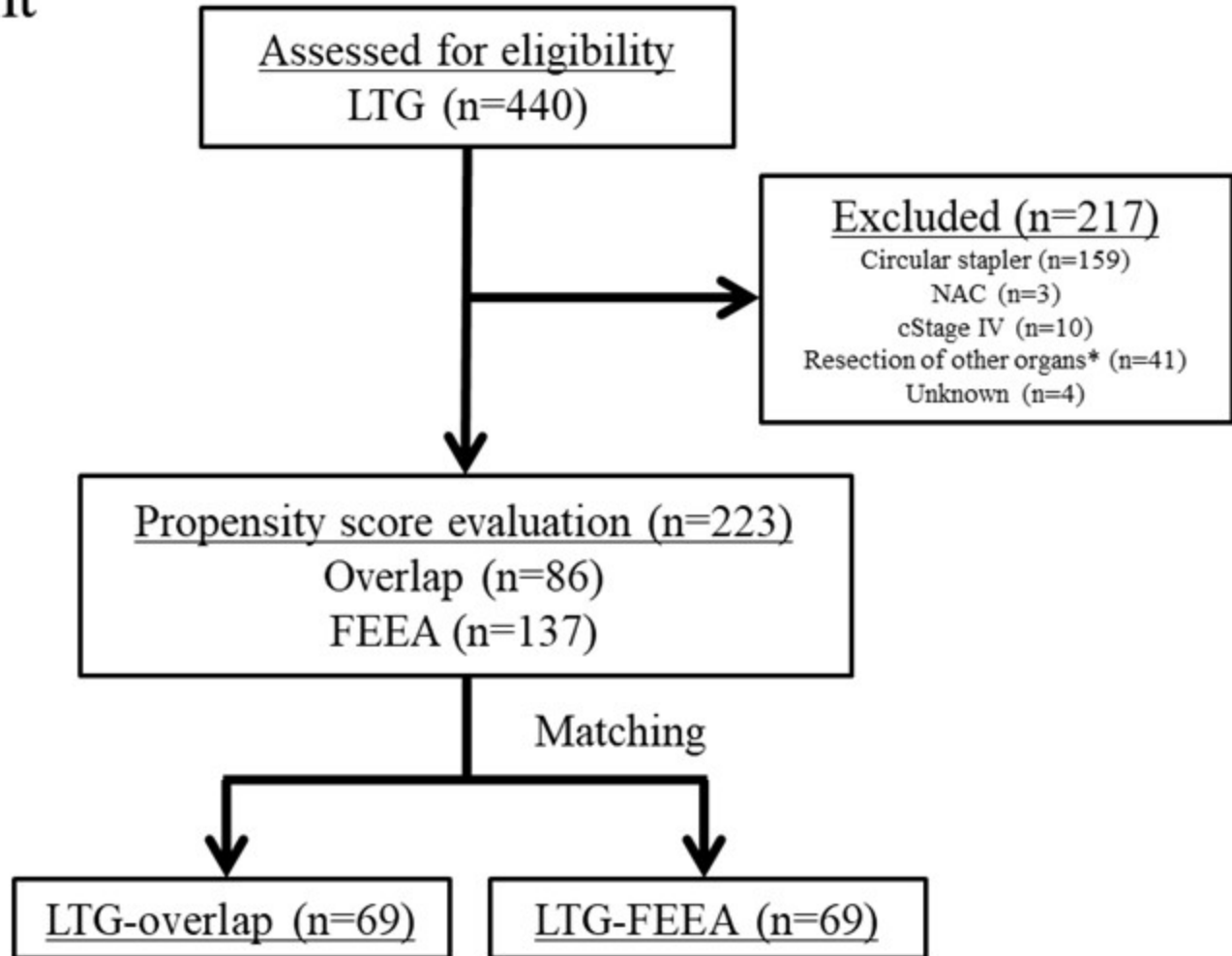


Table 1. Clinical features and surgical outcomes of the study population

Variable	Overall (n=440)
Gender (M/F)	305/135
Age (year, mean \pm SD)	66.3 \pm 11.1
BMI (kg/m ² , mean \pm SD)	22.7 \pm 3.5
ASA-PS* (II \leq)	318 (72.3%)
Clinical stage** (II \leq)	135 (30.7%)
Lymph node dissection (D2 \leq)	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 \pm SD)	332.8 \pm 83.6
Blood loss (ml, mean \pm SD)	107.4 \pm 187.9
Postoperative complication (CD [§] , IIIa \leq)	66 (15.0%)
Postoperative hospital stays (days, mean \pm SD)	18 \pm 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)	<i>p</i> value	Overlap (n=69)	FEEA (n=69)	<i>p</i> 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)	<i>p</i> value	Overlap (n=69)	FEEA (n=69)	<i>p</i> 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