



# Linear or circular stapler? A propensity score-matched, multicenter analysis of intracorporeal esophagojejunostomy following totally laparoscopic total gastrectomy

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## Abstract

**Background** Presently, there is no consensus as to what procedure of intracorporeal esophagojejunostomy (EJS) in totally laparoscopic total gastrectomy (TLTG) is best to reduce postoperative complications. The aim of this study was to demonstrate the superiority of linear stapled reconstruction in terms of anastomotic-related complications for EJS in TLTG.

**Methods** We collected data on 829 consecutive gastric cancer patients who underwent TLTG reconstructed by the Roux-en-Y method with radical lymphadenectomy between January 2010 and December 2016 in 13 hospitals. The patients were divided into two groups according to reconstruction method and matched by propensity score. Postoperative EJS-related complications were compared between the linear stapler (LS) and the circular stapler (CS) groups.

**Results** After matching, data from 196 patients in each group were analyzed. The overall incidence of EJS-related complications was significantly lower in the LS group than in the CS group (4.1% vs. 11.7%,  $p=0.008$ ). The incidence of EJS anastomotic stenosis during the first year after surgery was significantly lower in the LS group than in the CS group (1.5% vs. 7.1%,  $p=0.011$ ). The incidence of EJS bleeding did not differ significantly between the groups, although no bleeding was observed in the LS group (0% vs. 2.0%,  $p=0.123$ ). The incidence of EJS leakage did not differ significantly between the groups (2.6% vs. 3.6%,  $p=0.771$ ).

**Conclusion** The use of linear stapled reconstruction is safer than the use of circular stapled reconstruction for intracorporeal EJS in TLTG because of its lower risks of stenosis.

**Keywords** Totally laparoscopic total gastrectomy · Linear stapler · Circular stapler · Esophagojejunostomy · Anastomotic stenosis

Gastric cancer is one of the most common malignancies and is the second leading cause of cancer death worldwide [1]. Laparoscopic surgery has become an option for the treatment of gastric cancer with remarkable advances in laparoscopic instruments and improved surgical techniques. The use of laparoscopic gastrectomy has been spreading

globally because of its minimum invasiveness, followed by early recovery of the patient, and its laparoscopic magnified view, which enables surgeons to perform meticulous operations [2–6]. Several studies have reported the feasibility and oncologic safety of laparoscopic total gastrectomy (LTG) in comparison with open total gastrectomy [7–11]. However, LTG has technical difficulties because of its limited operative view and restrictions on the movement of laparoscopic forceps and devices. Esophagojejunostomy (EJS) after removal of the stomach is one of the most difficult procedures in LTG and can be associated with postoperative anastomotic leakage, bleeding, and stenosis in the EJS [12, 13].

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Totally laparoscopic total gastrectomy (TLTG), in which an additional small incision is not made for anastomosis to complete laparoscopic intracorporeal reconstruction, has been developed, as we reported previously [14, 15]. In TLTG, there are currently various types of EJS, including linear stapled and circular stapled reconstruction methods. The linear stapled reconstruction methods include an overlap method [16, 17] and a functional end-to-end anastomosis (FEEA) [14, 18], and the circular stapled reconstruction methods include a single staple technique (SST) [19, 20], a hemi-double staple technique (HDST) [21, 22], and a double staple technique (DST) [23, 24]. Previous studies have suggested that EJS in TLTG should be selected according to the location of the tumor and the experience of the surgeon [25, 26]. However, no large-scale study comparing the linear stapled and the circular stapled reconstruction methods for EJS has been reported, and there is no consensus at present as to what kind of intracorporeal EJS procedure is more feasible and safer to reduce the risk of postoperative complications.

In this multicenter, large-scale, retrospective study, we compared the postoperative complications of the linear stapled and the circular stapled reconstruction methods to demonstrate the superiority of linear stapled reconstruction for EJS in TLTG. In addition, we performed this comparison using a propensity score-matched cohort to reduce bias.

## Methods

### Patients

We collected data on 842 consecutive gastric cancer patients who underwent LTG with radical lymphadenectomy reconstructed by the Roux-en-Y method between January 2010 and December 2016 in 13 hospitals that participated in the

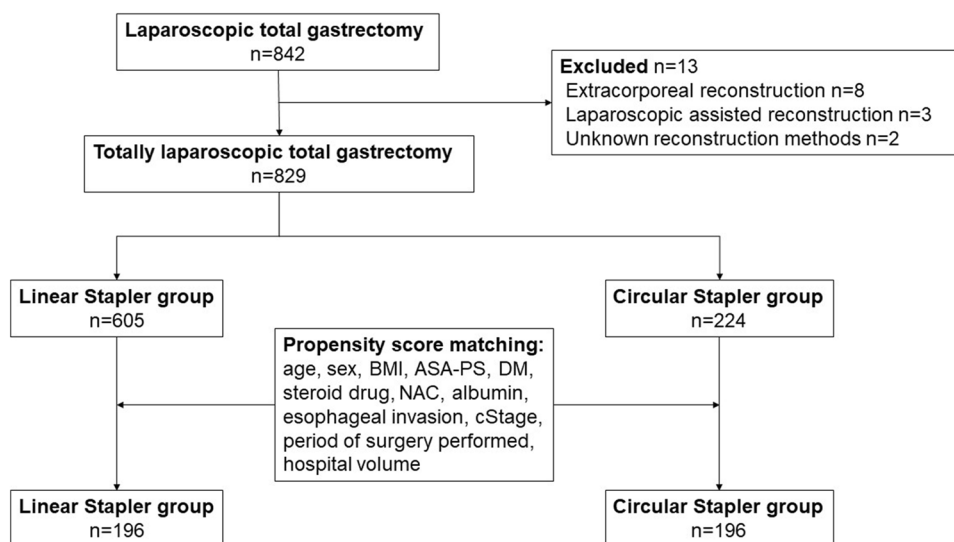
Kyoto Esophageal and Gastric Surgery Study Group. All participating institutions had over 500 cases performed gastrectomy in 10 years. Among them, 829 patients who underwent intracorporeal reconstruction with the linear stapled or the circular stapled reconstruction for EJS were included in the study (Fig. 1). The inclusion criteria were as follows: gastric adenocarcinoma histologically diagnosed preoperatively, clinical stage I to III according to the Japanese Classification of Gastric Carcinoma [27], and TLTG with Roux-en-Y reconstruction. The exclusion criteria were as follows: patients who received a small incision for EJS in the upper abdomen, hand-sewn reconstruction, emergency operation, patients who had gastric cancer with 3 cm or more esophageal invasion, and remnant gastric cancer.

### Surgical technique

The patients were placed in the supine reverse Trendelenburg position with their legs spread apart. The first port was inserted transumbilically for the laparoscope, and four operating ports were placed in the upper abdomen. Total gastrectomy was performed with D1+ or D2 lymph node dissection with the addition of splenectomy or pancreatic tail resection when required according to the Japanese Gastric Cancer Treatment Guidelines [28]. The detailed procedures of lymphadenectomy during LTG are described elsewhere [29–31]. To make a Roux limb, a jejunal loop was transected approximately 20 cm distal to the ligament of Treitz. After that, side-to-side jejunojunctionostomy was performed using a linear stapler and creation of a 40- to 50-cm length of Roux limb was completed.

The EJS reconstruction method was determined according to the experience and preference of each surgeon. Several surgeons performed both methods. In the linear stapler (LS) group, an overlap method or an FEEA was performed

**Fig. 1** Flow diagram of patient selection in this study. *BMI* body mass index, *ASA-PS* American Society of Anesthesiologists physical status, *DM* diabetes mellitus, *NAC* neoadjuvant chemotherapy



using linear staplers. The details of the overlap method were as follows: A small hole was made on the left edge of the esophageal stump. Another hole was made on the antimesenteric side 5 cm anally from the jejunal stump. The anvil fork or the cartridge fork of the linear stapler was inserted into the small hole of the Roux limb toward the oral side, and the Roux limb was pulled up antecolically to the left side of the esophagus. The fork of the opposite side was inserted into the hole of the esophageal stump, guided by a nasogastric tube. Then, the linear stapler was approximated and fired to create side-to-side EJS. The entry hole was closed by hand-sewn interrupted or continuous suture using 3-0 absorbable thread. The detailed procedures of the FEEA method were as follows: The abdominal esophagus was transected using a linear stapler, with 45° counterclockwise rotation of the esophagus, as reported previously [14]. Small holes were made on the dorsal edge of the esophageal stump and the antimesenteric edge of the jejunal stump. The anvil fork or the cartridge fork of the linear stapler was inserted into the small hole made in the jejunal stump. The esophageal and the jejunal stumps were placed side-by-side. The fork of the opposite side was inserted into the small hole of the esophageal stump, guided by a nasogastric tube. Then, a linear stapler was approximated and fired to create an anastomosis. The entry hole was roughly closed by several sutures, and, then, a linear stapler was applied for proper closure [14].

In the circular stapler (CS) group, SST, HDST, or DST was performed using a circular stapler. The umbilical wound or the trocar-site wound of the left upper abdomen was extended so that an anvil and the circular stapler were inserted into the abdominal cavity through the extended wound. Then, the anvil was introduced into the esophageal stump and fixed using a purse string suture. When OrVil™ (Covidien, New Haven, CT, USA) was employed according to the surgeon's preference, the anvil head of OrVil™ was inserted transorally into the esophagus. The circular stapler was inserted into the jejunum via the jejunal stump and temporarily fixed with a rubber band. The circular stapler was inserted into the abdominal cavity through the extended wound for retrieving the specimen and was fired to create end-to-side EJS. A linear stapler was used to close the jejunal stump.

## Outcomes

The primary end point was the incidence of EJS-related complications that were Grade III or more according to the Clavien–Dindo (CD) classification, including anastomotic leakage within 30 days, postoperative anastomotic bleeding within 30 days, and anastomotic stenosis within 1 year. We have defined anastomotic stenosis of CD grade III as a stenosis that requires surgical or endoscopic intervention. Patients who had a follow-up period of less than 1 year and

had no EJS-related complications were regarded as having no complications. The secondary end points were the incidence of non-EJS-related complications of CD Grade III or more within 30 days, death within 30 days, reoperation within 30 days, and length of postoperative hospital stay.

## Statistical analysis

Based on previous studies, the sample size was determined to detect differences between the LS and CS groups in the incidence of EJS-related complications [32, 33]. The incidences of anastomotic complications in the LS and CS groups were expected to be 5% and 15%, respectively. The sample size after matching was estimated as 150 patients in each group, assuming a two-sided alpha level of 0.05 and a power of 80%. Based on the existing report, we expected the propensity score matching rate to be 70% at maximum. The matching rate was reported to be 70% to 80% in previous studies, and we expected that the attrition of patients who were unmatched, had missing data, or were ineligible would be at most 40% [34, 35]. The sample size before matching was estimated to be 250 patients in each group.

To minimize selection bias, we calculated a propensity score regarding the reconstruction methods and performed a 1:1 matching based on the score. We selected the patient's age, sex, body mass index (BMI), American Society of Anesthesiologists physical status (ASA-PS), diabetes mellitus, use of steroid drugs, neoadjuvant chemotherapy (NAC), preoperative serum albumin, esophageal invasion, and clinical stage as variables. Furthermore, we divided the period from the introduction of TLTG to the end of the research period into the early and the late periods at each hospital, and included this variable in the propensity score matching to adjust the bias of operation period. In addition, we defined hospital volume as the number of patients who underwent TLTG per year and divided it into three groups (< 5, 5–9, ≥ 10 cases per year). Then, we adjusted the disparities between hospitals using the hospital volume as a variable. After matching, continuous variables were compared between the LS and CS groups using an unpaired *t* test, and categorical variables were compared using Fisher's exact test. All *p* values were two-sided, and *p* values less than 0.05 were considered to indicate statistical significance. JMP Statistical Software Version 13 (SAS Institute, Cary, NC, USA) was used to perform all the statistical analyses.

## Ethical approval

This multicenter, retrospective, comparative study was approved by the ethics committees of Kyoto University (R1276) and all the hospitals and was conducted in accordance with the Declaration of Helsinki.

## Results

### Patient characteristics

Table 1 shows patient characteristics. After matching, the data from 196 patients in each group were analyzed. Before propensity score matching, there were significant differences between the LS and the CS groups in BMI, NAC, preoperative serum albumin, and esophageal invasion. After matching, there were no significant differences between the groups.

For EJS reconstruction, 46 patients in the LS group underwent an overlap procedure and 150 patients underwent FEEA. In the CS group, SST was performed in 15 patients, HDST in 68 patients, and DST in 113 patients.

### Postoperative outcomes

#### EJS-related complications

The incidence of overall complications related to EJS was significantly lower in the LS group than in the CS group (4.1% vs. 11.7%,  $p=0.008$ ) (Table 2). The incidence of anastomotic stenosis in the EJS during the 1 year after surgery was significantly lower in the LS group than in the CS group (1.5% vs. 7.1%,  $p=0.011$ ). The incidence of postoperative anastomotic bleeding in the EJS during the 30 days after surgery did not differ significantly between the groups (0% vs. 2.0%,  $p=0.123$ ), although no postoperative anastomotic bleeding was observed in the LS group. The incidence of anastomotic leakage of the EJS did not differ significantly between the groups (2.6% vs. 3.6%,  $p=0.771$ ).

Before propensity score matching, we performed univariate analysis on patients before propensity score matching.

**Table 1** Clinicopathological characteristics of all TLTG patients and propensity score-matched patients

	All TLTG patients ( $n=829$ )			Propensity score-matched patients ( $n=392$ )		
	LS group ( $n=605$ )	CS group ( $n=224$ )	$p$ value	LS group ( $n=196$ )	CS group ( $n=196$ )	$p$ value
Age (years)	70 (27–89) <sup>a</sup>	69 (38–95) <sup>a</sup>	0.527	69 (39–89) <sup>a</sup>	68 (38–86) <sup>a</sup>	0.447
Sex			0.440			0.270
Male	433 (71.6%)	154 (68.8%)		143 (73.0%)	132 (67.3%)	
Female	172 (28.4%)	70 (31.2%)		53 (27.0%)	64 (32.7%)	
BMI (kg/m <sup>2</sup> )	22.2 (14.0–37.1) <sup>b</sup>	21.7 (14.4–30) <sup>b</sup>	0.048	21.7 (14.9–33.9) <sup>b</sup>	22.0 (14.4–30) <sup>b</sup>	0.974
ASA-PS			0.415			0.800
1	157 (25.9%)	67 (29.9%)		52 (26.5%)	58 (29.6%)	
2	402 (66.5%)	144 (64.3%)		133 (67.9%)	128 (65.3%)	
3	46 (7.6%)	13 (5.8%)		11 (5.6%)	10 (5.1%)	
DM	105 (17.4%)	31 (13.8%)	0.077	30 (15.3%)	28 (14.3%)	0.885
Steroid drugs	15 (2.5%)	5 (2.2%)	0.706	7 (3.6%)	5 (2.6%)	0.771
NAC	47 (7.8%)	8 (3.6%)	0.016	9 (4.6%)	7 (3.6%)	0.800
Albumin (g/dl)	4.2 (1.7–5.5) <sup>b</sup>	4 (2–4.9) <sup>b</sup>	< 0.001	4 (1.7–5.1) <sup>b</sup>	4 (2.4–4.9) <sup>b</sup>	0.801
Esophageal invasion	30 (5.0%)	2 (0.9%)	0.004	3 (1.5%)	2 (1.0%)	1.000
cStage			0.147			0.685
I	366 (60.5%)	139 (62.1%)		122 (62.3%)	127 (64.8%)	
II	133 (22.0%)	37 (16.5%)		31 (16.3%)	34 (17.3%)	
III	106 (17.5%)	48 (21.4%)		42 (21.4%)	35 (17.9%)	
Period of surgery			< 0.001			0.539
Early	200 (33.1%)	130 (58.0%)		118 (60.2%)	111 (56.6%)	
Late	405 (66.9%)	94 (42.0%)		78 (39.8%)	85 (43.4%)	
Hospital volume			0.444			0.723
< 5	66 (10.9%)	20 (8.9%)		23 (11.7%)	18 (9.2%)	
5–9	155 (25.6%)	51 (22.8%)		47 (24.0%)	49 (25.0%)	
≥ 10	384 (63.5%)	153 (68.3%)		126 (64.3%)	129 (65.8%)	

TLTG totally laparoscopic total gastrectomy, LS linear stapler, CS circular stapler, BMI body mass index, ASA-PS American Society of Anesthesiologists physical status, DM diabetes mellitus, NAC neoadjuvant chemotherapy, cStage clinical stage

<sup>a</sup>Median (minimum–maximum)

<sup>b</sup>Average (minimum–maximum)

**Table 2** Esophagojejunostomy-related complications of TLTG patients in propensity score-matched cohort

	LS group (n = 196)	CS group (n = 196)	p value
All EJS-related complications	8 (4.1%)	23 (11.7%)*	0.008
Leakage	5 (2.6%)	7 (3.6%)	0.771
Bleeding	0 (0%)	4 (2.0%)	0.123
Stenosis	3 (1.5%)	14 (7.1%)	0.011

TLTG totally laparoscopic total gastrectomy, LS linear stapler, CS circular stapler, EJS esophagojejunostomy

\*Numbers do not add up because of overlapping elements

The incidence of EJS-related complications was lower in the LS group than in the CS group (3.6% vs. 12.5%,  $p \leq 0.001$ ) (Supplement 1).

### Non-EJS-related complications

There were no significant differences between the LS and the CS groups in the incidence of non-EJS complications, including postoperative ileus, small bowel obstruction, duodenal stump leakage, pancreatic fistula, and intra-abdominal abscess. The incidences of mortality (1.5% vs. 0.5%,  $p = 0.623$ ), reoperation (1.5% vs. 4.1%,  $p = 0.220$ ) within 30 days, and the length of postoperative hospital stay (median; 15 vs. 15 days,  $p = 0.109$ ) did not differ significantly between the groups (Table 3).

## Discussion

In this study, the incidence of EJS stenosis after TLTG was significantly lower in the LS group than in the CS group. The incidence of EJS bleeding and other complications,

including anastomotic leakage of the EJS, did not differ significantly between the LS and the CS groups.

A shorter diameter of the anastomosis was reported to be a cause of anastomotic stenosis in a gastrojejunostomy of Roux-en-Y gastric bypass operation [36, 37]. A linear stapled reconstruction method could create a larger anastomosis than a circular stapled reconstruction method, which might lead to a lower incidence of anastomotic stenosis [13]. Theoretically, when a 45-mm linear stapler is used to make a stoma and a 60-mm linear stapler is applied for closure of the entry hole, the circumference of the anastomosis would be 150 mm (45 + 45 + 60 mm) and the diameter would be 49 mm. In reality, the actual diameter of an anastomosis made with linear staplers could be shorter than the calculated value of 49 mm because of resected esophageal and jejunal tissues at the entry hole. When linear stapling closure of the entry hole would need approximately 10 mm from the edge of the staple line, the circumference and the diameter of the created lumen would be 110 mm and 35 mm, which might be longer than those of an anastomosis created by the use of a circular stapler, with a diameter of 25 mm that is usually adopted for EJS.

In this study, EJS bleeding did not occur in the LS group. This could be an advantage of linear stapled reconstruction, because intraluminal bleeding after the first firing of the linear stapler could be easily checked from the intraluminal side through the entry hole during the operation. Furthermore, the linear stapler has three rows of staples compared with two rows in the circular stapler, which might also contribute to the reduction of the occurrence rate of EJS bleeding, both intraluminal and extraluminal [38].

The length of the abdominal esophagus after resection of the specimen is crucial when the surgeon adopts a linear stapled reconstruction for EJS, because a sufficient length of the mobilized esophagus is necessary for making a stoma using

**Table 3** Non-esophagojejunostomy-related complications and postoperative course of TLTG patients in propensity score-matched cohort

	LS group (n = 196)	CS group (n = 196)	p value
Non-EJS-related complications	8 (4.1%)*	9 (4.6%)	1.000
Ileus	2 (1.0%)	1 (0.5%)	
Small bowel obstruction	2 (1.0%)	2 (1.0%)	
Duodenal Stump leakage	1 (0.5%)	1 (0.5%)	
Pancreatic fistula	2 (1.0%)	3 (1.6%)	
Intra-abdominal abscess	1 (0.5%)	2 (1.0%)	
Cardiac arrest	1 (0.5%)	0 (0%)	
Death within 30 days	3 (1.5%)	1 (0.5%)	0.623
Reoperation within 30 days	3 (1.5%)	8 (4.1%)	0.220
Postoperative hospital stay (days)	15 (3–113) <sup>a</sup>	15 (5–153) <sup>a</sup>	0.109

TLTG totally laparoscopic total gastrectomy, LS linear stapler, CS circular stapler, EJS esophagojejunostomy

\*Numbers do not add up because of overlapping elements

<sup>a</sup>Median (minimum – maximum)

a linear stapler. When the proximal margin of the tumor has invaded beyond the esophagogastric junction toward the abdominal esophagus, the surgeon sometimes has to dissect the esophagus even in the lower mediastinum transhiatally to ensure a secure surgical margin of the tumor. Therefore, the factor “esophageal invasion” was considered one of the most influential confounding factors when we compared the LS and CS groups. In the current study, “esophageal invasion (less than 3 cm)” was used as a variable for propensity score matching so that we could reduce the risk of bias of esophageal invasion. Even after propensity score matching, the incidence of EJS-related complications in the LS group was significantly lower than that in the CS group. This result suggested that, regardless of the existence of esophageal invasion of less than 3 cm, a linear stapled reconstruction can be performed safely.

There are some studies comparing reconstruction methods in terms of short-term outcomes in EJS of TLTG [25, 26, 32, 33, 39, 40]. In a recent multicenter retrospective study, Kyogoku et al., comparing 66 cases in each group, reported that there were no significant differences in the incidence of postoperative complications between the LS and the CS groups. Even though these two groups in their study did not differ significantly in postoperative complications, including EJS stenosis and leakage, these negative results might be attributable to the small number of patients for analysis. Moreover, their study included patients who underwent either laparoscopic-assisted total gastrectomy (LATG) or TLTG, and most of the LATG cases were in the CS group [39]. Therefore, it would be necessary to include more patients for sufficient statistical power to detect differences in EJS-related complications between the LS and the CS groups in TLTG. In the present study, we performed propensity score-matched analysis using as many as 196 patients in each group and successfully detected the significantly better short-term outcomes, especially for EJS stenosis.

Postoperative complications have been reported to be associated with the long-term outcomes of patients with gastric cancer. Relapse-free survival and overall survival are lower in gastric cancer patients with complications than in patients without complications [41–43]. Because intracorporeal EJS in LTG is still considered technically demanding, there is a pressing need for endoscopic surgeons to establish an optimal intracorporeal reconstruction method with surgical safety in LTG to decrease complications and ultimately for better long-term outcomes. According to our finding that the incidence of EJS-related complications was significantly lower in the LS group than in the CS group, intracorporeal EJS using linear stapler could be a better option in terms of better long-term outcomes.

There is a learning curve in performance of a new laparoscopic surgical method, and the surgeon’s experience may affect the rate of postoperative complications [44, 45].

Therefore, we performed a sensitivity analysis using the data excluding the initial consecutive 10 patients who underwent a new reconstruction procedure in each hospital to eliminate the influence of learning curve, by a 1:1 matching based on the propensity score. As a result of this sensitivity analysis, the incidence of EJS-related complications was lower in the LS group than in the CS group (4.2% vs. 12.0%,  $p=0.015$ ). This result suggests that a linear stapled reconstruction is better than a circular stapled reconstruction in terms of EJS-related complications, even after taking the learning curve into consideration.

This study has some limitations. First, the study could have unexpected biases due to the retrospective nature of this observational study. Second, the study included patients for whom the follow-up period was less than 1 year because of their death or relocation. There were 25 patients in the LS group and 22 patients in the CS group of such short follow-up patients, respectively, and the median follow-up period of these patients did not differ significantly between the LS and the CS groups (147 vs. 162 days,  $p=0.949$ ). Inclusion of these patients was considered to scarcely affect the comparison of postoperative stenosis of the EJS. Third, it was impossible to evaluate the effect of the type of the linear stapler cartridge (length and staple height) and the width of the circular stapler (diameters of 21 or 25 mm) on postoperative complications, especially on anastomotic stenosis, because we did not collect this information in this study. Application of a circular stapler with a larger diameter might reduce the risk of stenosis of the EJS; however, a separate study may be needed to investigate this issue. Fourth, we could not evaluate the effect of surgeon on postoperative complications, because we could not collect information regarding surgical skills of surgeons at each hospital.

Even though there were several limitations to our study, it is the first that shows the superiority of linear stapled over circular stapled reconstruction methods in a multicenter, comparative study with a substantial sample size. Because endoscopic surgeons usually do not employ both linear stapled and circular stapled reconstruction methods in the same period when performing EJS, it is difficult to conduct randomized, controlled trials comparing linear stapled and circular stapled reconstruction methods. Hence, we designed a propensity score-matched analysis so that we could decrease the risk of biases as much as possible. Considering these viewpoints, this study has produced a high level of evidence as to whether linear stapled or circular stapled reconstruction methods should be applied for EJS in TLTG.

## Conclusion

The use of linear stapled reconstruction is better than the use of circular stapled reconstruction for intracorporeal EJS in TLTG because of its lower risk of stenosis.

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**Author contributions** Katsuhiko Murakami and Kazutaka Obama designed the study, and Katsuhiko Murakami wrote the initial draft of the manuscript. Katsuhiko Murakami, Shigeru Tsunoda, Shigeo Hisamori, Tatsuto Nishigori, Koya Hida, Nobuaki Hoshino, and Shiro Tanaka contributed to analysis and interpretation of data. Kazutaka Obama assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Compliance with ethical standards

**Disclosures** Drs. Katsuhiko Murakami, Kazutaka Obama, Shigeru Tsunoda, Shigeo Hisamori, Tatsuto Nishigori, Koya Hida, Seiichiro Kanaya, Seiji Satoh, Dai Manaka, Michihiro Yamamoto, Yoshio Kadokawa, Atsushi Itami, Hiroshi Okabe, Hiroaki Hata, Eiji Tanaka, Yoshito Yamashita, Masato Kondo, Hisahiro Hosogi, Nobuaki Hoshino, Shiro Tanaka, and Yoshiharu Sakai have no conflicts of interest or financial ties to disclose.


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