Totally laparoscopic total gastrectomy with linear anastomosis versus laparoscopic-assisted total gastrectomy in gastric cancer：a single-center experience with meta-analysis

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Research Article

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Abstract

Objective

Laparoscopic-assisted total gastrectomy (LATG) is the most common methods of gastrectomy for gastric cancer (GC). However, totally laparoscopic total gastrectomy (TLTG) is uncommon because reconstruction is difficult, especially for the intracorporeal esophagojejunostomy. In this study, we compared short-term oncologic outcomes in TLTG group with linear anastomosis and LATG group.

Methods

The retrospective cross-sectional study was conducted. The clinic-pathological data of 108 patients underwent TLTG and 153 patients underwent LATG who were admitted to the First Affiliated Hospital of Nanjing Medical University between May 2016 and October 2019 were collected. The clinicopathological characteristics and surgical outcomes before and after propensity score matching (PSM) were compared between the two groups. Furthermore, a systematic review and meta-analysis were conducted.

Results

Besides the estimated blood loss($P < 0.001$) and the length of incision($P < 0.001$) in TLTG group was less than those in LATG group, no other differences were found between the two groups in operative time ($P = 0.993$), the number of harvested lymph nodes ($P = 0.181$), the time of first flatus($P = 0.076$), start of liquid diet ($P = 0.240$), start of soft diet ($P = 0.147$), the time of removing drainage ($P = 0.725$), postoperative hospital stay ($P = 0.688$)and postoperative morbidity ($P = 1.000$) after PSM. The meta-analysis also demonstrated no significant differences in above surgical outcomes among the groups, although the number of harvested lymph nodes was higher and estimated blood loss was lower in the TLTG group than that in the LATG group.

Conclusions

TLTG for GC is feasible and safe. However, the further validation of high-quality randomized controlled trial is still needed.

Introduction

Gastric cancer (GC) is the one of the most common cancers worldwide[1]. According to the data of International Agency for Research on Cancer (IARC), the morbidity of GC is the fifth highest among all malignant tumors and the mortality is the fourth highest[2]. Among the GC, esophagogastric junction cancer (EJC) has attracted considerable attention because of the marked increase in its incidence globally[3, 4]. The data from USA revealed that the morbidity of EJC had increased by about 2.5 times in

the past 35 years, about 2/100000[5]. Furthermore, the data from China demonstrated that the morbidity of EJC had increased from 22.3% in period 1992–1998 to 35.3% in period 2008–2012[6].

Although advances in treatments in GC, the surgical resection remains the preferred treatment for GC[7]. Since Kitano reported the first operation of laparoscopy-assisted gastrectomy in 1994[8], the laparoscopic gastrectomy has been widely performed. More and more prospective randomized controlled studies including JCOG0912, KLASS-02 and CLASS-01 demonstrated that laparoscopic gastrectomy is not inferior to open gastrectomy because of its safety and feasibility[9–11]. Moreover, the safety and feasibility of laparoscopic total gastrectomy (LTG) for early EJC has been confirmed (JCOG1401, KLASS-03 and CLASS-02)[12–14]. Nowadays, more and more surgeons prefer to totally laparoscopic total gastrectomy (TLTG) instead of laparoscopic-assisted total gastrectomy (LATG) for decreasing the risk of wounding and pain. TLTG was established as a procedure with intracorporeal resection and anastomosis.

However, TLTG is not widely performed due to its difficulty of techniques, especially for intracorporeal esophagojejunostomy anastomosis. There are several anastomosis methods and all of them can been divided into two categories according to the type of stapler (circular stapler or linear stapler). The circular stapler was primarily used in open surgery and laparoscopic surgery because the circular anastomosis was technically feasible and did not require a long abdominal esophagus[15]. However, there were some technical difficulties need to be resolved in laparoscopic procedure, like the insertion of purse-string suture and anvil[16]. Conversely, more surgeons prefer to use the linear stapler under laparoscopy due to the easier insertion and handing. However, few clinical evidences were reported to demonstrate the advantages of TLTG with linear stapler.

Therefore, we retrospectively enrolled patients received laparoscopic gastrectomy and used the propensity score-matching method to reduce bias. This study compared the short-term outcomes of patients who experience TLTG with linear stapler and LATG in our center. And meta-analysis combined the results in our center were also conducted to further prove the feasibility and safety of TLTG with linear stapler because of the argument in anastomosis method of TLTG.

Materials And Methods

Patients and clinical data

This was a retrospective study of 261 patients who were diagnosed with gastric cancer by endoscopy and biopsy and accepted LTG from May 2016 to October 2019 in the Department of General Surgery, the First Affiliated Hospital of Nanjing Medical University. Inside of them, 108 patients underwent TLTG and other 153 patients underwent LATG. The inclusion criteria were defined as follows: gastric carcinoma proved by histopathology, no distant metastasis, tumors located in the upper two-thirds of the stomach or throughout the stomach, gastric cancer patients who were treated with LTG and an R0 resection. The exclusion criteria were defined as follows: distant metastasis, remnant gastric cancer, receiving

preoperative chemotherapy or radiotherapy, lack of pathological diagnosis, palliative gastrectomy or an emergency operation with bleeding or perforation. All 261 patients were preoperatively examined by gastroscopy (with biopsy), basic blood testing, electrocardiography, abdominal computed tomography (CT), and chest radiography. All operations were performed by an identical team with surgeons who acquire expertly in laparoscopic gastrectomy. All clinical data of each patient were collected and recorded.

Surgical Procedures

All the patients were placed in the supine position with legs spread apart after general anesthesia. The pneumoperitoneum was established by trocar which located 1 cm below the umbilicus, and the pressure intra-abdominal cavity was maintained at 12 to 15mmHg (1.6 to 2.0 kPa). Conventional 'Five ports' method were performed in patients. An assistant who stood between two legs of patient manipulated the laparoscope stood via trocar which located 1 cm below the umbilicus. Two 12 mm and two 5 mm trocars were routinely inserted at the both sides of patient's midline. The operator and assistant respectively stood at the left and right side, and all the surgical procedures were performed via these four operating trocars.

Liver, peritoneum and pelvic cavity were routinely examined to exclude distant metastasis and implantation metastasis. The dissection of esophagus and duodenum, lymph node dissection and alimentary tract reconstruction were performed for laparoscopic total gastrectomy by following the Japanese gastric cancer treatment guidelines 2018 (ver. 5) [7].

Reconstruction

LATG:

Roux-en-Y anastomosis of esophagojejunal anastomosis was performed under direct vision in vitro using a circular stapler.

TLTG: π-shaped method:

After about 8–10 cm esophagus was fully mobilized and separated, a band was used to constrict the esophagogastric junction for preventing the esophagus retraction. Then, a long enough incision was made at the distal esophagus above the blocking band. The jejunum 20 to 30 cm distal from the Treitz ligament was lifted under the distal esophagus through the front of the transverse colon and the mesenteric pressure was evaluated and adjusted. After confirming the mesojejunum without apparent pressure, an enterotomy was made on the antimesenteric side of the jejunum, and a functional side to side esophagojejunostomy was made by using a 60 mm liner stapler which was placed into the enterotomy from the proximal to distal jejunum. The site with excessive tension at the anastomosis was reinforced with 2 to 3 reinforcement sutures. After completing the esophagojejunostomy, another 60 mm liner stapler was inserted into the mesojejunum to close esophageal and jejunal common entry hole.

TLTG: overlap method:

The jejunum 20 cm distal from the Treitz ligament will be intracorporeally transected using a 60-mm linear stapler.

Approximately 55 cm from the location where the esophagojejunostomy is planned to be performed, a 60 mm linear stapler will be used to perform the side-by-side jejunojejunostomy. Make a small hole 6 cm at the distal end of the staple line on the antimesenteric side of the jejunal limb, and make another small hole on the left wall of the esophageal stump. Using the nasogastric tube as a guide, insert one limb of the 45mm linear stapler into the esophageal stump, and place the other limb of the linear stapler in the jejunum branch. The forks of the stapler will be closed and fired to complete the Roux-en-Y side-to-side esophagojejunostomy. After confirming that there is no bleeding at the anastomosis, a 3 – 0 barbed wire will be used to reinforce the anastomosis.

Follow-up

Dedicated researchers used outpatient records, telephone calls, WeChat and letters to follow up with patients after their operation. All patients were followed up every 3 months for 1 years. Survival time was defined as the time from surgery to either death or the final follow-up date of June 2022.

Systematic review and meta-analysis

We searched three major electronic databases (PubMed, EMBASE, and Cochrane Library) to compare LATG and TLTG published between January 1995 and October 2020. The following keywords were used: "laparoscopy", "laparoscopic", "minimally invasive", "gastric cancer" and "gastrectomy." These terms were combined using the Boolean operators "AND" and "OR." The language of the article was limited to English. Commentary articles, opinions, and articles without a control group were all excluded. Two investigators reviewed the title and abstract of the article, assessed the full text to determine its eligibility, and resolved the differences through discussion. The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of observational studies. A threshold of six stars or above has been considered an indicator of high quality. The level of evidence was assessed by GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach, and the evidence profile was created by GRADEprofiler 3.6 software.

Statistical Analysis

All statistical analyses were performed by using SPSS22.0 software. The Student's t test was used to compare the differences in the measurement data, and the $\chi 2$ test or Fisher's exact probability test was used to test the comparisons between the groups. For the meta-analysis, Stata16 software was used. Dichotomous variables were analyzed using the risk ratio (RR), and continuous variables were assessed using weighted mean difference (WMD). According to the degree of heterogeneity, random effects model or fixed effects model were choosing for analysis. An informal visual inspection of the funnel chart is used to determine potential publication bias. $P < 0.05$ was considered statistically significant.

Ethic Statement

This study was approved by Ethic Committee of the First Affiliated Hospital of Nanjing Medical University. The informed consents were obtained from each GC patient included in the study.

Results

General information

As Table 1 shown, the clinicopathological characteristics of each patient were summarized. All the operations were performed successfully under laparoscopy. Of all 261 patients, 108 patients underwent TLTG, while LATG was performed on the other 153 patients. Two groups were comparable to each other. Among all patients, these differences of age, gender, tumor size, pT stage, pN stage, TNM stage, Lauren type between TLTG group and LATG group were not significant ($P > 0.05$). Besides, body mass index (BMI) and tumor location significantly differed between two groups ($P < 0.05$). All the tumor size were measured and the pathologic stages were diagnosed according to the 8th edition of the American Joint Committee on Cancer (AJCC).

Table 1
Comparison of clinicopathological characteristics between TLTG group and LATG group

Characteristics	All patients (n = 261)		P value	Patient propensity matching(n = 160)		P value
	LATG(n = 153)	TLTG (n = 108)		LATG(n = 80)	TLTG (n = 80)	
Age	62.79 ± 8.704	62.04 ± 10.083	0.519	62.66 ± 8.487	61.68 ± 10.258	0.508
Gender			0.518			0.391
Male	124	84		69	65	
Female	29	24		11	15	
BMI(kg/m^2)	24.10 ± 2.753	22.85 ± 2.579	< 0.001	23.11 ± 2.429	23.20 ± 2.354	0.799
Tumor Location			0.048			0.740
Upper	128	80		63	61	
Middle	24	24		16	19	
Total	1	4		1	0	
Tumor size(cm)	3.74 ± 2.186	3.429 ± 2.105	0.264	3.68 ± 2.290	3.60 ± 2.176	0.816
pT stage			0.070			0.179
T1	39	36		18	23	
T2	19	18		11	13	
T3	67	39		32	31	
T4	28	15		19	13	
pN-stage			0.078			0.387
N0	59	53		31	37	
N1	25	16		13	12	
N2	30	19		16	13	
N3	39	20		20	18	
TNM stage			0.063			0.252
I	47	46		25	32	
II	39	24		17	16	

Characteristics	All patients (n = 261)		P value	Patient propensity matching(n = 160)		P value
	LATG(n = 153)	TLTG (n = 108)		LATG(n = 80)	TLTG (n = 80)	
III	67	38		38	32	
IV	0	0		0	0	
Lauren type			0.705			0.728
Intestinal	66	41		35	37	
Diffuse	16	18		14	14	
Mixed	48	32		31	29	

The propensity scores were calculated using a logistic regression model to balance the following covariates: age, gender, BMI, tumor location. Finally, 160 patients (80 patients who underwent LATG and 80 patients who underwent TLTG) were selected for analysis. After propensity score matching (PSM), age, gender, BMI, tumor location, tumor size, pT stage, pN stage, TNM stage, Lauren type did not differ significantly between the two groups.

Surgical outcomes

Before PSM, the estimated blood loss ($P < 0.001$), the length of incision ($P < 0.001$) and the administration of analgesics ($P = 0.002$) in TLTG group with linear anastomosis were less than those in LATG group. Besides, these differences of operative time, the number of harvested lymph nodes, the time to first flatus, start of liquid diet, start of soft diet, extubation time (the time to remove the abdominal drain) and postoperative hospital stay between two groups were not significant ($P > 0.05$). After PSM, the results above did not change (Table 2).

Table 2
Comparison of short-term outcomes between TLTG group and LATG group

Characteristics	All patients (n = 261)		P value	Patient propensity matching(n = 160)		P value
	LATG(n = 153)	TLTG(n = 108)		LATG(n = 80)	TLTG (n = 80)	
Operative time (min)	203.37 ± 37.944	200.80 ± 45.561	0.620	199.30 ± 39.215	199.36 ± 45.569	0.993
Blood loss (ml)	169.29 ± 45.558	112.49 ± 65.014	< 0.001	169.93 ± 46.802	120.38 ± 66.360	< 0.001
Incision length (cm)	12.27 ± 1.187	5.26 ± 0.604	< 0.001	12.19 ± 1.183	5.29 ± 0.593	< 0.001
Analgesic drugs use	5.29 ± 1.286	4.66 ± 1.725	0.002	5.36 ± 1.214	4.55 ± 1.683	0.001
Number of harvested lymph nodes	44.53 ± 12.662	47.01 ± 11.013	0.102	45.29 ± 12.585	47.73 ± 10.238	0.181
Gas-passing (days)	2.95 ± 0.972	3.13 ± 0.738	0.079	2.98 ± 1.031	3.23 ± 0.711	0.076
Start of liquid diet (days)	4.47 ± 2.230	4.66 ± 3.218	0.596	4.44 ± 2.099	5.00 ± 3.649	0.240
Start of soft diet(days)	5.97 ± 2.987	6.47 ± 4.440	0.305	5.97 ± 2.900	6.93 ± 5.049	0.147
Drainage-tube removing (days)	9.02 ± 6.072	8.87 ± 6.752	0.852	8.96 ± 5.252	9.33 ± 7.549	0.725
Postoperative hospital stay (days)	11.92 ± 7.329	11.15 ± 7.220	0.403	12.14 ± 8.036	11.65 ± 8.038	0.688

As Table 3 shown, the postoperative complications in the two groups were summarized. There was no in-hospital mortality. Complications developed in 11.76% (18/153) of patients in the LATG group and 11.11% (12/108) of patients in the TLTG group (P = 0.871). There were no significant differences in overall postoperative complications and surgical complications between the two groups. After propensity matching, the postoperative complication rates of the LATG group and OTG group were 12.5% and 12.5% (P = 1.000), respectively. No significant intergroup differences were found in complications after PSM.

Table 3
Postoperative complications of LATG and TLTG groups

Characteristics	All patients (n = 261)		P value	Patient propensity matching(n)		P value
	LATG(n = 153)	TLTG(n = 108)		LATG(n = 80)	TLTG(n = 80)	
Overall complications	18 (11.76%)	12(11.11%)	0.871	10(12.5%)	10(12.5%)	1.000
Abdominal infection	3(1.96%)	1(0.93%)	0.644	2(2.50%)	1(1.25%)	1.000
Intra-abdominal bleeding	1(0.65%)	0(0.00%)	1.000	1(1.25%)	0(0.00%)	1.000
Anastomotic leakage	4(2.61%)	5(4.63%)	0.593	1(1.25%)	4(5.00%)	0.367
Anastomotic stenosis	1(0.65%)	1(0.93%)	1.000	1(1.25%)	1(1.25%)	1.000
Intestinal obstruction	2(1.31%)	0(0.00%)	0.513	2(2.50%)	0(0.00%)	0.497
Incision-related complications	4(2.61%)	0(0.00%)	0.237	2(2.50%)	0(0.00%)	0.497
Pneumonia	3(1.96%)	5(4.63%)	0.386	1(1.25%)	4(5.00%)	0.367

Subgroup analysis:

LATG versus TLTG-overlap:

Among 175 patients, these differences of age, gender, tumor size, pT stage, pN stage, TNM stage, Lauren type between TLTG-overlap group and LATG group were not significant (P > 0.05). Besides, BMI and tumor location significantly differed between two groups (P < 0.05). 44 patients (22 patients who underwent LATG and 22 patients who underwent TLTG with overlap method) were selected using PSM for analysis. After PSM, age, gender, BMI, tumor location, tumor size, pT stage, pN stage, TNM stage, Lauren type did not differ significantly between the two groups (Table S1).

As Table S2 shown, before PSM, the TLTG-overlap group exhibited a significantly longer operative time (P < 0.001), less blood loss (P < 0.001), shorter incision length (P < 0.001) and longer time to starting a liquid diet (P = 0.026). After PSM, the results above all did not change. However, the time to starting a liquid diet resembled between two groups (P = 0.061).

Complications developed in 11.76% (18/153) of patients in the LATG group and 18.18% (4/22) of patients in the TLTG-overlap group (P = 0.614). There were no significant differences in overall postoperative complications and surgical complications between the two groups. After PSM, the postoperative complication rates of the LATG group and TLTG-overlap group were 9.90% and 18.18% (P = 0.660), respectively. No significant intergroup differences were found in complications after propensity matching (Table S2).

LATG versus TLTG-π:

Among 239 patients, these differences of age, gender, tumor size, pT stage, pN stage, TNM stage, Lauren type between TLTG-π group and LATG group were not significant (P > 0.05). Besides, BMI and tumor location significantly differed between two groups (P < 0.05). 130 patients (65 patients who underwent LATG and 65 patients who underwent TLTG with π method) were selected using PSM for analysis. After PSM, age, gender, BMI, tumor location, tumor size, pT stage, pN stage, TNM stage, Lauren type did not differ significantly between the two groups (Table S3).

Before PSM, the TLTG-π group exhibited a significantly shorter operative time (P = 0.014), less blood loss (P < 0.001), shorter incision length (P < 0.001), less use of analgesic drugs (P = 0.001), more harvested lymph nodes (P = 0.020), shorter time to starting a liquid diet (P = 0.044). After PSM, the TLTG-π group showed no significant differences on operative time and the time to starting a liquid diet (Table S4).

Complications developed in 11.76% (18/153) of patients in the LATG group and 9.30% (8/86) of patients in the TLTG-π group (P = 0.557). There were no significant differences in overall postoperative complications and surgical complications between the two groups. After PSM, the postoperative complication rates of the LATG group and TLTG-π group were 15.38% and 9.23% (P = 0.286), respectively. No significant intergroup differences were found in complications after propensity matching (Table S4).

TLTG-π versus TLTG-overlap:

After PSM, age, gender, BMI, tumor location, tumor size, pT stage, pN stage, TNM stage, Lauren type did not differ significantly between the two groups (Table S5).

As Table 4 shown, TLTG-π group was found associated with a shorter operative time (P = 0.001), a higher number of retrieved lymph nodes (P = 0.001), a shorter mean time to starting a liquid diet (P = 0.010) and other variates were similar. After PSM, these differences of above and the time to starting of soft diet were statistically significant. No significant intergroup differences were found in complications after propensity matching.

Table 4
Comparison of short-term outcomes and postoperative complications between TLTG-π group and TLTG-overlap group

Characteristics	All patients (n = 108)		P value	Patient propensity matching(n = 44)		P value
	π(n = 86)	overlap(n = 22)		π(n = 22)	overlap(n = 22)	
Operative time (min)	190.99 ± 35.666	239.14 ± 59.110	0.001	186.45 ± 38.737	239.14 ± 59.110	0.001
Blood loss (ml)	112.20 ± 65.756	113.64 ± 63.512	0.927	113.14 ± 69.462	113.64 ± 63.512	0.980
Incision length (cm)	5.29 ± 0.553	5.14 ± 0.775	0.398	5.49 ± 0.499	5.14 ± 0.775	0.083
Analgesic drugs use	4.57 ± 1.746	5.00 ± 1.633	0.299	4.59 ± 1.681	5.00 ± 1.633	0.418
Number of harvested lymph nodes	48.41 ± 11.373	41.55 ± 7.424	0.001	51.14 ± 12.194	41.55 ± 7.424	0.003
Gas-passing (days)	3.11 ± 0.653	3.36 ± 1.049	0.290	3.14 ± 0.560	3.36 ± 1.049	0.377
Start of liquid diet (days)	3.92 ± 1.229	7.55 ± 5.974	0.010	3.77 ± 1.343	7.55 ± 5.974	0.008
Start of soft diet(days)	5.95 ± 3.825	8.50 ± 5.982	0.069	5.14 ± 1.424	8.50 ± 5.982	0.017
Drainage-tube removing (days)	8.17 ± 5.006	11.59 ± 11.005	0.169	7.14 ± 2.253	11.59 ± 11.005	0.076
Postoperative hospital stay (days)	10.47 ± 5.633	13.82 ± 11.304	0.190	9.45 ± 2.632	13.82 ± 11.304	0.091
Overall complications	8(9.30%)	4(18.18%)	0.422	1(4.45%)	4(18.18%)	0.342
Abdominal infection	0(0.00%)	1(4.45%)	0.043	0(0.00%)	1(4.45%)	1.000
Intra-abdominal bleeding	0(0.00%)	0(0.00%)	1.000	0(0.00%)	0(0.00%)	1.000
Anastomotic leakage	2(4.63%)	3(13.63%)	0.092	0(0.00%)	3(13.63%)	0.232
Anastomotic stenosis	1(2.33%)	0(0.00%)	1.000	0(0.00%)	0(0.00%)	1.000
Intestinal obstruction	0(0.00%)	0(0.00%)	1.000	0(0.00%)	0(0.00%)	1.000
Incision-related complications	0(0.00%)	0(0.00%)	1.000	0(0.00%)	0(0.00%)	1.000
Pneumonia	5(5.81%)	0(0.00%)	0.581	1(4.45%)	0(0.00%)	1.000

Table 5
Overall results comparing TLTG with LATG

				Test for Overall Effect		Test for Heterogeneity	
Items	**Type**	**n**[a]	**WMD or RR 95% CI**	Z	P	I²	P
Operative time(min)	NRS	11	10.47 (-4.08, 25.02)	1.41	0.159	90.6%	**< 0.001**
Number of harvested lymph nodes	NRS	9	4.47(3.28, 5.65)	7.39	**< 0.001**	25.3%	0.211
Blood Loss(ml)	NRS	9	-45.78(-59.12, -32.43)	6.72	**< 0.001**	77.9%	**< 0.001**
Gas-passing(days)	NRS	10	0.03 (-0.14, 0.20)	0.33	0.740	72.7%	**< 0.001**
Start of liquid diet(days)	NRS	5	0.18 (-0.03, 0.39)	1.72	0.085	0.00%	0.895
Start of soft diet(days)	NRS	7	-0.03 (-1.48, 1.41)	0.04	0.964	96.4%	**< 0.001**
Postoperative hospital stay(days)	NRS	11	-0.09(-0.84, 0.66)	0.24	0.813	70.5%	**< 0.001**
Overall complications	NRS	10	1.03 (0.88, 1.22)	0.39	0.695	0.00%	0.465
Anastomosis-related complications	NRS	11	0.85(0.59,1.23)	0.85	0.394	47.2%	**0.035**

CI, confidence interval; TLTG, total laparoscopic total gastrectomy; LATG, laparoscopic-assisted total gastrectomy; RR, relative risks; WMD, weighed mean difference; NRS, non-randomized studies; data in bold, significant *P*-value.

[a] Number of comparisons.

Survival after surgery

The median follow-up time of the two groups was 39 months (TLTG) and 44 months (LATG), respectively. Until June 2022, death occurred in 17 of 108 participants (15.74%) in the TLTG group and in 30 of 153 (19.61%) in the LATG group. The 3-years and 5-years survival rates did not significantly differ between two groups before(P = 0.7294) and after PSM (P = 0.4806) (Fig. 1A and 1B). Moreover, the 3-years and 5-years survival rates between three groups also did not significantly differ (P = 0.8833) (Fig. 1C).

Outcomes of a systematic review and meta-analysis:

Aforementioned search strategy identified 165 articles that mentioned TLTG and LATG for gastric cancer from the three major electronic databases. After reviewing the titles and abstracts, we selected 10 articles

based on the inclusion and exclusion criteria and the characteristics were listed in Table S6[15, 17–25]. Including the present data, there were 2315 participants in 11 studies (1028 patients in the TLTG group and 1287 patients in the LATG group). According to the Newcastle-Ottawa Quality Assessment Scale, all 11 studies received at least six stars (Table S7).

The results of meta-analysis are summarized in Table 6. Meta-analysis of the operation time (WMD = 10.47min, 95% confidence interval (CI) -4.08 to 25.02, P = 0.159) showed no significant difference between the two groups (Fig. 2A). Inter-study variability was confirmed by a significant heterogeneity test result. However, the number of harvested lymph nodes of TLTG was more than that of LATG (WMD = 4.47; 95% CI 3.28 to 5.65, P < 0.001) and the blood loss was less than that of LATG with a statistical difference (WMD =-45.78; 95% CI -59.12 to -32.43, P < 0.001) (Fig. 2B-C). There was also no significant difference in gas-passing (WMD = 0.03; 95% CI -0.14 to 0.20, P = 0.740), start of liquid diet (WMD = 0.18; 95% CI -0.03 to 0.39, P = 0.085), start of soft diet (WMD =-0.03; 95% CI -1.48 to 1.41, P = 0.964), postoperative hospital stay (WMD =-0.09; 95% CI -0.84 to 0.66, P = 0.813), overall complications (RR = 1.03; 95% CI 0.88 to 1.22, P = 0.695) and anastomosis-related complications (RR = 0.85; 95% CI 0.59 to 1.23, P = 0.394) between the two groups (Fig. 2D-I).

The funnel plots and Egger's linear regression test were used to detect publication bias for each result. When the number of studies was small, there was a limitation in this test. So the statistics of funnel plots to starting of liquid diet were not showed. Eight funnel plots were constructed for the outcomes of interest (Figure S1). In addition to the number of harvested lymph nodes, symmetry was observed for most of the outcomes and showed no obvious publication bias. We used a Galbraith plot to determine which articles contributed to the heterogeneity (Figure S2). Then, we excluded these articles and analyzed the pooled data from the remaining articles, and demonstrated the similar results (Table S8).

We also assessed the quality of the primary outcomes of these studies. The Table S9 showed the reasons for upgrade and downgrade and the GRADE quality of evidence for the primary outcomes.

Discussion

Laparoscopic gastrectomy has become the common operation for gastric cancer worldwide. For early upper gastric cancer, several random controlled trials (RCTs) including JCOG1401, KLASS-03 and CLASS-02 have demonstrated that LATG is safe and feasible[12–14]. Thus, LATG has been established as one of the standard surgical procedures according to Japanese Gastric Cancer Treatment Guideline 2018 (5th edition)[7]. Since Goh et al. firstly reported the intracorporeal gastrojejunostomy with the linear stapler[26], totally laparoscopic total gastrectomy (TLTG) has been more and more widely accepted. Kanaji et al. believed that TLTG was associated with shorter hospital stay, smaller incision, adequate working space and faster postoperative recovery through a comparative analysis of 114 patients[27]. These results may be due to intraoperative refinement and field enlargement during anastomosis. However, totally laparoscopic esophagojejunostomy is still a big challenge for surgeons.

At present, the circular and linear staplers are used for reconstruction after TLTG. Most previous comparative studies between TLTG and LATG were mainly based on data by using circular stapler[28]. TLTG with circular stapler may cause postoperative anastomotic stenosis. Compared with circular stapler, linear stapler has the advantages of no purse-string suture, larger anastomotic diameter, and no limitation of esophagus and small intestine diameter[21]. In addition, intracorporeal esophagojejunostomy is normally performed in a narrow space, and the reconstruction can be achieved more easily by linear stapler[29, 30]. Nowadays, TLTG with linear anastomosis mainly includes overlap anastomosis, π-shaped anastomosis and functional end-to-end anastomosis (FEEA). Through a retrospective analysis of 113 patients, Kim et al. concluded that totally laparoscopic anastomosis by linear stapler was the best procedure for esophagogastric junction tumors in overweight patients[31]. Similarly, Wang et al. confirmed the safety and feasibility of TLTG (overlap reconstruction) in advanced Siewert III esophagogastric junction cancer and the upper and middle third of gastric cancer by a prospective, single-center, single-blind, two-arm randomized controlled trial[22]. However, few comparative studies between TLTG with linear stapler and LATG have been reported. Therefore, we retrospectively analyzed the results of patients received the TLTG with linear stapler(overlap and π-shaped method)in our center to determine the advantage of this method. For more, we also meta-analyzed all of the available studies that compared LATG and TLTG with linear stapler, which resulted in 6 nonrandomized controlled studies (NRS).

Our results demonstrated the estimated blood loss, the length of incision and the administration of analgesics in TLTG group were less than those in LATG group. The result of less blood loss was also supported by meta-analysis. In LATG group, more blood loss might be caused by the larger skin incision and anastomosis by hand though the incision. The administration of analgesics was used to evaluate the postoperative pain, and less pain in TLTG group is most likely due to the shorter incision. There were no statistically differences among the number of harvested lymph nodes, start of liquid diet, start of soft diet, extubating time and postoperative hospital stay between two groups. However, the result of meta-analysis revealed that TLTG group was associated with more harvested lymph nodes. Because the lymph nodes dissection was performed by laparoscopy in both groups, there should be no difference in number of harvested lymph nodes. Then we checked the data and found that the data from Gong et al. contributed a lot to the result of meta-analysis[21]. The author didn’t explain the reason and also confessed that the lymphadenectomy procedure was the same. The safety of operation is an important factor focused by surgeons. In our research, 12 patients (11.11%) in TLTG group and 18 patients (11.76%) in LATG group suffered from postoperative complications. However, there was still 9 patients experienced anastomotic leakage in our study which was diagnosed by CT examination. Through conservative treatment such as CT-guided puncture and drainage, anti-infection, and enteral nutrition tube placement, the patients recovered uneventfully. There were no significant differences on complications between two groups, which was similar with the results of meta-analysis. Therefore, the rate of the complications related to anastomosis was 6.25% with no significant difference by data of our center or meta-analysis.

In TLTG, Inaba firstly developed a side-to-side anastomosis called “overlap”[32], which has several advantages including a change in the direction of the jejunal limb to alleviate tension at the anastomosis. Huang et al. summarized the clinicopathological data of 507 patients received TLTG with overlap anastomosis or LATG and revealed that overlap anastomosis could reduce blood loss, pain and dysphagia, thus improving postoperative quality of life[23]. Although, the overlap method was reported as a safe and useful technique, there are still technical difficulties in this procedure[33]. It is difficult to insert linear stapler into the short esophageal stump. And it requires advanced suturing skills to close the common incision after anastomosis in a narrow and deep field[34, 35]. In our study, compared with LATG group, the group of TLTG-overlap showed favorable surgical outcomes of less blood loss, shorter incision length and less uses of analgesics. But overlap method was associated with more operative time, which may be due to the difficulty in suturing.

Another novel operative technique called π-shaped method was reported as an easy and effective option for TLTG[36]. In this method, gastric resection, jejunal division and common hole closure were integrated into one procedure. The difficulty of hand-sewn sutures and traction of the esophagus were solved by this method[37]. Through a retrospective analysis of 143 patients, Chen et al. concluded that totally laparoscopic anastomosis with π-shaped anastomosis was safe and feasible[18]. In our study, we found that traction of the esophagus was easier, which could provide the maximum visual operating space, and the 3-in-1 procedure really simplified the anastomosis procedures. Therefore, in our study, the operative time was significantly reduced in TLTG-π group, and the trend was also observed even after PSM. The TLTG-π group also exhibited less blood loss, more harvested lymph nodes, shorter incision length and less administration of analgesics compared with LATG group. However, the surgeons could only check the proximal margin after completion of the anastomosis. If the tumor invaded the margin, it would be a disaster. Therefore, according to our experiences, π-shaped method is recommended for patients with the upper edge of tumor below the Zigzag line. And it’s also very important for the surgeons to identify the location of the tumor by gastroscopy and CT scan before surgery.

In our research, compared π-shaped method with overlap method, we found that πgroup showed shorter operative time, more harvested lymph nodes and faster postoperative diet. After esophagojejunostomy, it’s easier for π-shaped method to close the common incision by a linear stapler, and the operative time is reduced. In this study, more cases in π-shaped group were operated on 3D laparoscopy, and several studies reported that 3D laparoscopy can harvest more lymph nodes than 2D laparoscopy[38–42]. That might be the reason for the difference in number of dissected lymph nodes. Because the number of patients involved in overlap group is relatively small, more cases are still needed to validate the differences between these two methods and the immature technology at that time.

There are several limitations to our studies. First, it was retrospective and the number of cases included was relatively not enough. Some selection biases might exist. Second, it was performed at a single center in China, where the average BMI is lower than a common Western BMI. Thus, our results may not be applicable to Western people. Third, 2D or 3D laparoscopy was used in this study, that might influence the

results. Fourth, although there are several different linear anastomosis methods, our center only included patients with overlap and π-shaped anastomosis.

Conclusion

In general, compared with the LATG, TLTG showed similar surgical and oncological safety. Thus, TLTG with linear stapler is safe and feasible with good clinical application prospects, but it will still require a high quality prospective randomized controlled study for further validation.

Declarations

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Conflict of Interest

The authors declare that they have no competing interests.

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Figures

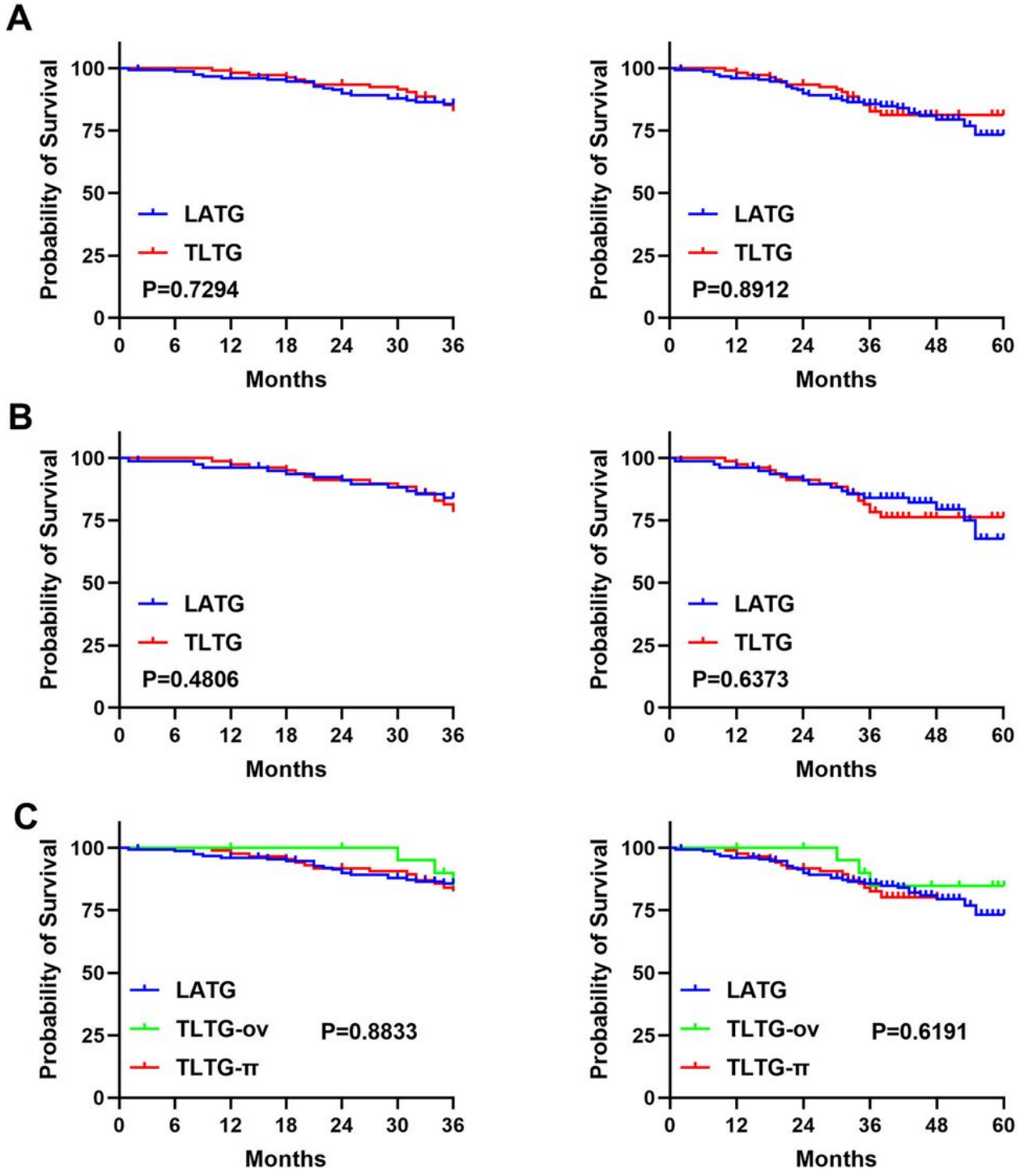

Figure 1

Kaplan-Meier plot of overall survival.

Kaplan–Meier estimates of 3-years and 5-years overall survival in the TLTG and LATG group before and after PSM (Panel A and B) and three groups (Panel C) are shown. LATG: laparoscopic-assisted total gastrectomy; TLTG: totally laparoscopic total gastrectomy.

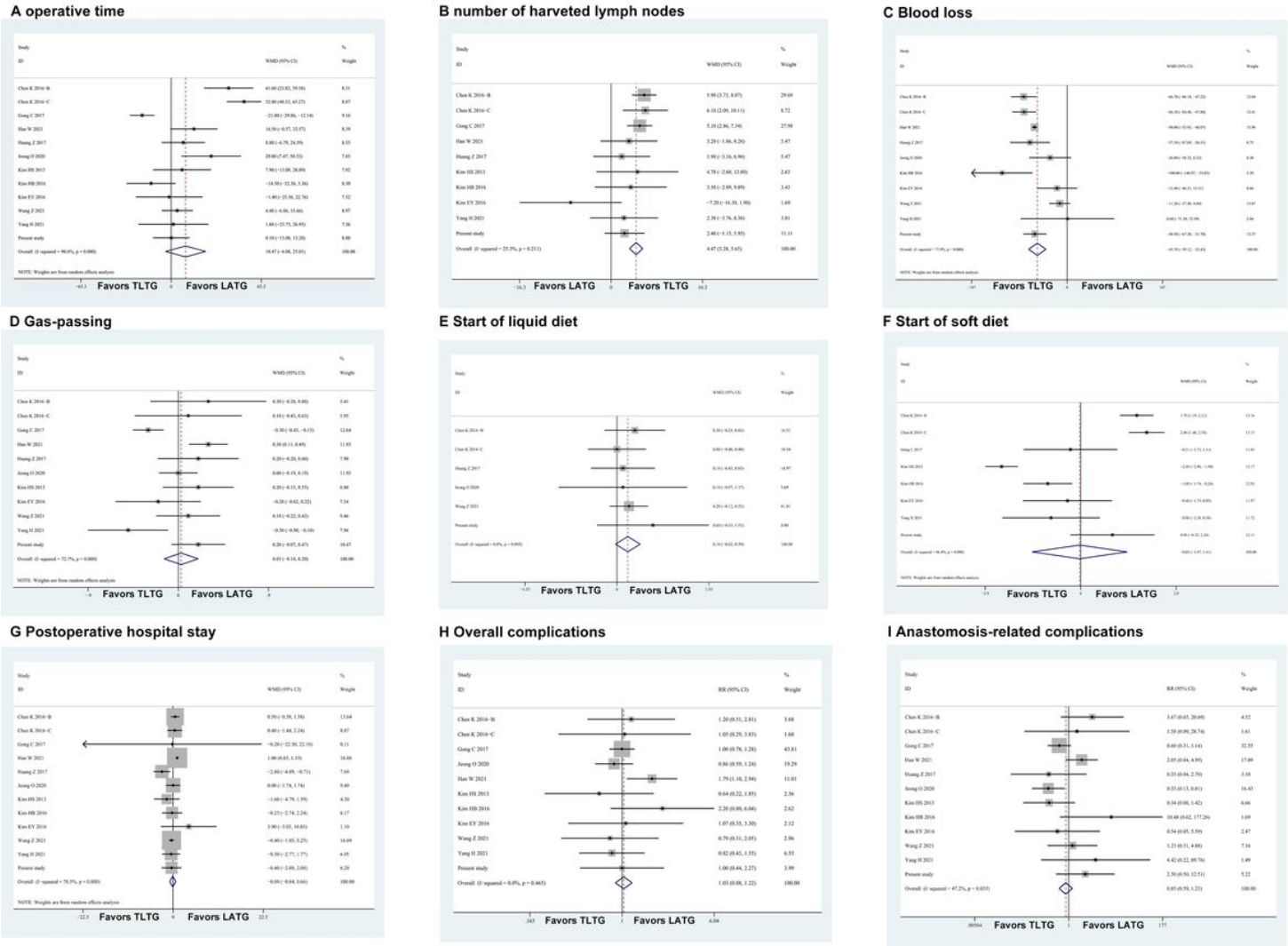

Figure 2

Meta-analysis of the pooled data. (A)Operative time;(B)Number of harvested lymph nodes;(C)Blood loss;(D)Gas-passing;(E)Start of liquid diet;(F)Start of soft diet;(G)Postoperative hospital stay;(H)Overall complications;(I)Anastomosis-related complications.

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