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Short-term Outcomes of Totally Laparoscopic Versus Laparoscopy-assisted Total Gastrectomy for Gastric Cancer: a Systematic Review and Meta-analysis

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Abstract

Background Totally laparoscopic total gastrectomy (TLTG) has not been generalized because of its technical difficulty during the procedure of digestive tract reconstruction and lack of short-term results. This meta-analysis aimed to evaluate the feasibility and safety of TLTG for gastric cancer.

Methods A systematic literature search in various databases from January 1994 to November 2020 was performed. Eligible studies in comparing TLTG and laparoscopy-assisted total gastrectomy (LATG) for gastric cancer were included in this meta-analysis. The results were analyzed according to predefined criteria.

Results In the present meta-analysis, the outcomes of 8 non-randomized controlled studies enrolling 1503 patients (819 in the TLTG group and 684 in the LATG group) were pooled. The operation time was significantly shorter in the TLTG group than those in the LATG group ($P < 0.01$). Estimated blood loss was significantly less in TLTG than that in LATG ($P = 0.01$). The TLTG group was associated with earlier time to first flatus ($P < 0.01$) and oral intake ($P = 0.02$). The pooled analysis showed no significant difference in postoperative hospital stay, postoperative complications, number of retrieved lymph nodes, and the proximal margin between TLTG and LATG groups (all $P > 0.05$).

Conclusions TLTG can be a safe and feasible procedure concerning short-term surgical outcomes and complications.

Background

Laparoscopy-assisted gastrectomy (LAG) has been increasingly performed since it was first reported in 1994 by Kitano et al[1]. Recently, several multicenter randomized controlled trials (RCTs) have reported laparoscopy-assisted distal gastrectomy (LADG) is a safe and feasible surgical procedure for advanced gastric cancer (AGC) in terms of short-term outcomes [2–4]. The incidence of gastric cancer in the upper stomach has been increasing in both Western and Asian countries [5–7]. Several large retrospective studies reported that laparoscopy-assisted total gastrectomy (LATG) is a safe and feasible procedure with acceptable surgical and long-term oncological outcomes for gastric cancer patients [8–11]. During the procedure of LAG, resection of the stomach and anastomosis is performed via a small incision in the middle-upper abdomen. However, the inclusion of the auxiliary incision in LAG makes it divergent from the minimally invasive treatment concept pursued in minimally invasive surgery. With the accumulation of experience and advancements in laparoscopic surgical instruments, some surgeons in high-volume centers have applied totally laparoscopic distal gastrectomy (TLDG) for gastric cancer [12–16]. A recent meta-analysis demonstrated that TLDG was a technically safe, feasible, and favorable procedure in terms of better cosmesis, less blood loss, and faster recovery compared with LADG[17]. Compared with TLDG, Totally laparoscopic total gastrectomy (TLTG) has not been generalized because of its technical difficulty during the procedure of digestive tract reconstruction and lack of short-term results. A series of reports on TLTG versus LATG for the treatment of gastric cancer have been published in recent years. This study aims to perform a comprehensive evaluation of all the available high-quality published nonrandomized studies to evaluate the feasibility and safety of TLTG for gastric cancer.

Methods

Literature search

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines[18]. A systematic literature was searched from PubMed, MEDLINE, EMBASE, the Cochrane Library, and Web of Science from January 1994 to September 2020 to identify published articles that compared TLTG and LATG. Search terms “gastric carcinoma”, “gastric cancer”, “laparoscopic”, “laparoscopy”, “total gastrectomy”, “entirely”, “totally”, “intracorporeal”, and “endocorporeal” were used in combination with the Boolean operators AND or OR. The reference lists of articles obtained were also reviewed to find relevant literature. Two authors individually conducted the literature search and cross-checked their search results.

Inclusion and exclusion criteria

Included criteria for this meta-analysis were as follows: (1) all patients were confirmed gastric cancer; (2) published studies comparing TLTG with LATG for gastric cancer; (3) studies that reported at least one of the following outcomes, including surgical outcome, postoperative complication, or the postoperative recovery outcomes. The excluded criteria were: (1) studies such as reviews, comments, letters, case reports, or cohort studies including fewer than ten patients; (2) studies published in a language other than English.

Data extraction and quality assessment

Data were extracted independently by two reviewers using predefined standards and cross-checked, and discrepancies were adjudicated by a third reviewer. The following data were extracted from each study: first author, publication year, country, study period, sample size, gender, mean age, level of lymphadenectomy, operation time, anastomotic time, estimated blood loss, time to first flatus, time to first oral intake, postoperative hospital stay, overall complications, anastomosis leakage, anastomosis stricture, number of retrieved lymph nodes, proximal margin. All included studies were methodologically assessed using the Newcastle–Ottawa Scale (NOS), which has been widely used for the assessment of the quality of non-randomized studies in meta-analyses[19]. The high-quality trials should score ≥ 6 of a maximum score of 9.

Statistical analysis

The odds ratio (OR) was used to calculated dichotomous variables. Weighted mean difference (WMD) was used to calculate continuous variables, and both were reported with 95% confidence intervals (CIs). I^2 statistics were used to quantify the heterogeneity among studies. If data was not significantly heterogeneous ($P > 0.05$ or $I^2 < 50$ %), the pooled effects were calculated using a fixed model. Otherwise, the random-effects analysis would be performed. Data analyses were performed with the Review Manager software (RevMan Version 5.3; Cochrane Collaboration). The results were regarded as statistically significant at two-sided $P < 0.05$.

Results

Study selection

Finally, 8 non-randomized controlled studies were eligibly included in the pooled analysis [20–27]. The detailed search steps are presented in Fig. 1.

The characteristics and quality of the studies

Table 1 summarizes the characteristics of the included studies, which were published from 2013 to 2017. These articles are from Japan, Korea, and China. A total of 1503 patients were included in the meta-analysis, among which 819 cases in the TLTG group and 684 in the LATG group. The quality assessment outcomes of non-randomized studies are summarized in Table 2.

Table 1
Characteristics of included studies

Study	Year	Country	Study period	Sample size		Gender (M/F)		Mean age (y)		Level of Lymphadenectomy
				TLTG	LATG	TLTG	LATG	TLTG	LATG	
Jung et al	2013	Korea	2004–2012	40	47	31/9	37/10	63.4	61.2	D1+/D2
Ito et al	2014	Japan	2001–2012	117	46	NA	NA	NA	NA	D1+/D2
Chen et al	2016	China	2006–2015	108	145	73/35	98/47	59.4	57.3	D2
Kim EY et al	2016	Korea	2009–2014	27	29	22/5	20/9	60.8	59.3	D1+/D2
Kim HB et al	2016	Korea	2013–2015	30	24	16/14	14/10	51	53	D1+/D2
Lu et al et al	2016	China	2011–2014	25	25	22/3	21/4	59.0	58.4	D1+/D2
Gong et al	2017	China	2008–2014	421	266	273/148	167/99	57.8	55.7	D1+/D2
Huang et al	2017	China	2014–2016	51	102	34/17	68/34	55.5	55.9	D2

NR, no reported.

Table 2
Newcastle-Ottawa Scale assessment of non-randomized studies

Study	Selection				Comparability	Outcome			Total
	1	2	3	4	5	6	7	8	
Jung et al	*	*	*	*	*	*	*	—	7
Ito et al	*	*	*	*	*	*	—	—	6
Chen et al	*	*	*	*	**	*	*	—	8
Kim EY et al	*	*	*	*	*	*	*	—	7
Kim HB et al	*	*	*	*	*	*	*	—	7
Lu et al et al	*	*	*	*	**	*	*	—	8
Gong et al	*	*	*	*	*	*	*	—	7
Huang et al	*	*	*	*	**	*	*	—	8

1. Representativeness of exposed cohort; 2. Selection of non-exposed cohort; 3.Ascertainment of exposure; 4. Outcome of interest was not present at start of study; 5. Comparability of cohorts on the basis of the design or analysis; 6. Assessment of outcomes;7. Follow-up long enough for outcomes to occur; 8. Adequacy of follow-up.

Intraoperative outcomes

All 8 studies reported operation time [20–27]. The present analysis showed TLTG group had shorter operation time compared to LATG (WMD=-11.41 min; 95% CI, − 19.90 to -2.92; $P < 0.01$) (Fig. 2A). Based on the analysis of our studies reporting anastomotic time, our result revealed that TLTG and LATG groups had similar result (WMD = 2.02 min; 95% CI, − 5.74 to 9.79; $P = 0.61$) (Fig. 2B). 6 studies reported estimated blood loss [21–25, 27]. Estimated blood loss was significantly lower in the TLTG group compared with the LATG group (WMD=-42.35 ml; 95% CI, -74.61 to -10.10; $P = 0.01$) (Fig. 2C). All outcomes are summarized in Table 3.

Table 3
Pooled short-term outcomes of meta-analysis

Outcomes	No. of studies	Sample size		Heterogeneity	Overall effect size	95% *CI*	*P* value
		TLTG	LATG	(P, I^2)			
Operation time (min)	8	819	684	0.03, 56%	WMD =-11.4	-19.90 to -2.92	< 0.01
Anastomotic time(min)	4	200	246	< 0.01, 94%	WMD = 2.02	-5.74 to 9.79	0.61
Estimated blood loss(ml)	6	358	371	< 0.01, 78%	WMD = -42.35	-74.61 to -10.10	0.01
Time to first flatus (d)	6	672	614	0.14, 40%	WMD = -0.16	-0.27 to -0.05	< 0.01
Time to first oral intake (d)	7	702	638	0.21, 29%	WMD = -0.28	-0.50 to -0.05	0.02
Postoperative hospital stay (d)	6	281	372	0.22, 29%	WMD = -0.47	-1.05 to 0.12	0.12
Overall complications	6	662	591	0.49, 0%	OR = 1.03	0.78 to 1.36	0.82
Anastomosis leakage	7	794	659	0.65, 0%	OR = 1.58	0.50 to 1.59	0.71
Anastomosis stricture	7	794	659	0.62, 0%	OR = 0.83	0.38 to 1.83	0.65
Retrieved lymph nodes	6	677	613	0.03, 60%	WMD = 2.22	-0.54 to 4.98	0.11
Proximal margin (cm)	6	651	536	< 0.01, 85%	WMD = -0.50	-1.18 to 0.17	0.14

Postoperative outcome

Regarding the time to first flatus, TLTG group showed earlier time compared with that in LATG group (WMD = -0.16 d; 95%CI: -0.27 to -0.05; $P < 0.01$) (Fig. 3A). The time to first oral intake was 0.28 day earlier for TLTG group with a significant difference (WMD= -0.28 d; 95% CI, -0.50 to -0.05; $P = 0.02$) (Fig. 3B). No significant difference between the two groups was observed in terms of postoperative hospital stay (WMD = -0.47 d; 95%CI: -1.05 to 0.12; $P = 0.12$) (Fig. 3C). Morbidity was mentioned in 6 studies, and there was no significant difference in postoperative morbidity (OR, 1.03; 95% CI, 0.78 to 1.36; $P = 0.82$) (Fig. 3D). Regarding to anastomotic-related complications, there was no difference between TLTG and LATG groups in terms of anastomotic leakage (OR, 0.90; 95% CI, 0.50 to 1.59; $P = 0.71$) (Fig. 3E) and anastomotic stricture (OR, 0.83; 95% CI, 0.38 to 1.83; $P = 0.65$) (Fig. 3F).

Oncological outcomes

In terms of oncological outcomes, the mean number of retrieved lymph nodes was similar between the two groups (WMD = 2.22; 95%CI: -0.54 to 4.98; *P* = 0.11) (Fig. 4A). The proximal margin for the TLTG group did not significantly differ from that of the LATG group (WMD = -0.50; 95%CI: -1.18 to 0.17; *P* = 0.14) (Fig. 4B).

Discussion

Laparoscopy-assisted total gastrectomy has been increasingly performed even though it is always considered technically demanding [28]. In LATG, the digestive tract reconstruction is performed through a 5–7 cm small incision in the middle-upper abdomen [29–31]. It has been reported that TLTG has the advantages of less invasive than LATG [32, 33]. However, totally laparoscopic total gastrectomy (TLTG) for gastric cancer has not been generalized because of its technical difficulties and lack of short-term results. So, we performed this meta-analysis to compare the feasibility and safety of TLTG with LATG for gastric cancer.

The postoperative complication is a key index to evaluate the safety and technical feasibility of the surgical procedure. This study demonstrated no significant differences between TLTG and LATG groups in terms of overall postoperative complication rate. The major difference between TLTG and LATG is the methods of digestive tract reconstruction after lymphadenectomy. Therefore, we further analyze the incidence of anastomotic leakage and anastomotic stricture. In this study, the incidence of anastomotic stricture in the TLTG group was ranging from 0 to 10%. Kim et al[34] reported that the use of 45-mm linear staplers during the procedure of side-to-side esophagojejunostomy could create a stoma larger than 30-mm diameter, which therefore reduces anastomotic stricture. Ito et al [21]found there was no significant difference among the TLTG and LATG groups in the incidence of anastomotic stricture. Kim EY et al [23]did not observe anastomotic strictures, even after a long-term follow-up. The present study showed no significant differences between the two groups in terms of anastomosis-related complications. Intracorporeal esophagojejunostomy (IEJ) styles during the procedure of TLTG are various [35–38]. In this study, IEJ styles were liner staple and Orvil™. However, we could not perform subgroup analysis according to IEJ styles due to the limitation of sample size. Because the IEJ can be difficult, some researchers believe that TLTG was associated with longer operation time [27]. In this meta-analysis, the operation time for TLTG was shorter than LATG. Based on the further analysis of anastomotic time, our result showed that IEJ did not shorten the operation time. However, this result was not consistent among the included studies. In this study, the anastomotic time in the TLTG group was ranging from 18.6 to 47.5 min. Lu et al [25] reported that IEJ can shorten the operation time by 6 min when compared with extracorporeal esophagojejunostomy (EEJ). Conversely, Chen et al [22] found that the TLTG would take a longer time by 15 min as compared with LATG. As we all know, operation time was always affected by the learning curve. The skillful surgeons are capable of performing the operation safer and faster than unskilled surgeons. Previous studies have demonstrated that 20 to 40 cases are needed to overcome the initial learning curve of TLDG even for surgeons with sufficient experience in LADG [39, 40]. After completion of the learning for TLDG, the surgeon extended the technique from TLDG to include TLTG. In this study, the included studies did not clearly state the learning stage and experience of surgeons. So, we could not perform subgroup analysis based on different learning stage and surgeon's experience.

This study showed that the estimated blood loss in the TLTG group was significantly lower than that in the LATG group. This might be attributed to TLTG does not need additional mini-laparotomy. Meanwhile, blood vessels in the muscles and mesentery can be more readily identified and are less likely to be transacted during the IEJ [27]. Moreover, the esophageal stump should be pulled out from the abdominal cavity when EEJ is performed. Chen et al [22]stated that the pulling puts great pressure on the esophageal stump and might even cause tearing and bleeding of the spleen envelope. However, we aware that the heterogeneity between studies was high and therefore this result should be interpreted prudently.

In terms of postoperative recovery outcomes, the TLTG group showed the earlier time to first flatus and oral intake. Meanwhile, we also found that the TLTG group was associated with shorter postoperative hospital stay though it failed to reach statistically significant. These results suggest that TLTG might a less invasive surgical procedure than LATG.

Theoretically, long-term survival outcomes are a critical measure to evaluate oncological outcomes. In the present meta-analysis, the number of the retrieved lymph nodes and the proximal resection margin is considered as the major indicators of oncological surgical quality due to limited studies included reported the outcomes of long-term follow-up. Chen et al [22] found that the number of harvested lymph nodes of TLTG was more than that of LATG with a marginal difference ($P = 0.06$). In this meta-analysis, our result also revealed a tendency favoring the TLTG group though it failed to reach statistically significant. Logically, TLTG and LATG were similar in the procedure of lymphadenectomy. The marginal difference might because some surgeons perform LATG during their early period. In clinical practice, TLTG was usually performed by surgeons experienced in LATG. Our result showed that the length of the proximal resection margin was similar between the two groups. But this result was in high heterogeneity among the included studies. Gong et al [26] reported a shorter proximal margin in the TLTG group compared with the LATG group. We argued that such a result may relate to the fact that linear staplers are often placed on either side of the resection line and therefore might hinder the evaluation of the surgical margin. Kim et al[24] also found the length of the proximal margin was shorter in TLTG than in the conventional LATG, but the resection margins were free of tumor. Studies conducted by Chen et al and Lu et al demonstrated no significant difference between TLTG and LATG groups. These results suggest that TLTG can also achieve an adequate resection distance.

There are several limitations in the present study. First, all the included studies were retrospective and conducted in single-center from East Asia, which may have a bias in patients selection, surgeons experience, and regional differences, etc. Second, high heterogeneity was observed in some outcomes such as estimated blood loss, operative time, time to first flatus, and postoperative hospital stay. Additionally, limited data were available on long-term survival and quality of life, so we cannot perform further analysis.

Conclusions

In conclusion, the currently available evidence indicated that TLTG is a safe and feasible procedure compared to LATG concerning short-term surgical outcomes and complications. However, Well-designed multicenter RCTs are warranted to reach more definitive conclusions on this topic.

Abbreviations

TLTG: Totally laparoscopic total gastrectomy; LATG: laparoscopy-assisted total gastrectomy; LADG: Laparoscopy-assisted distal gastrectomy; AGC: Advanced gastric cancer; EEJ: Extracorporeal esophagojejunostomy; ASA: American Society of Anesthesiologists; BMI: Body mass index; T: tumor; N: node; M: metastasis ; TNM: Tumor-node-metastases SD standard deviation OR odd ratio; CI Confidence Interval;

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Xijing hospital,

Consent for publication

Not applicable.

Availability of data and material

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Not applicable.

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Authors' contributions

Fengni Xie and Gang Ji conceived the study and drafted the manuscript. Fengni Xie, Zhengyan Li and Shuai Xu identified and screened the search findings for potentially eligible studies of the meta-analysis. Bing Bai and Dan Song independently extracted the data using a unified datasheet, and the Qingchuan Zhao was consulted when controversial issues were presented. Jie Chen and Qingchuan Zhao performed the statistical analyses and gave an interpretation of the results. Fengni Xie and Gang Ji revised and supervised the study. All authors read and approved the final manuscript.

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Not applicable.

Conflict of interests

The authors declare that they have no conflict of interests.

Disclosures

The authors declare that they have no conflict of interest.

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Figures

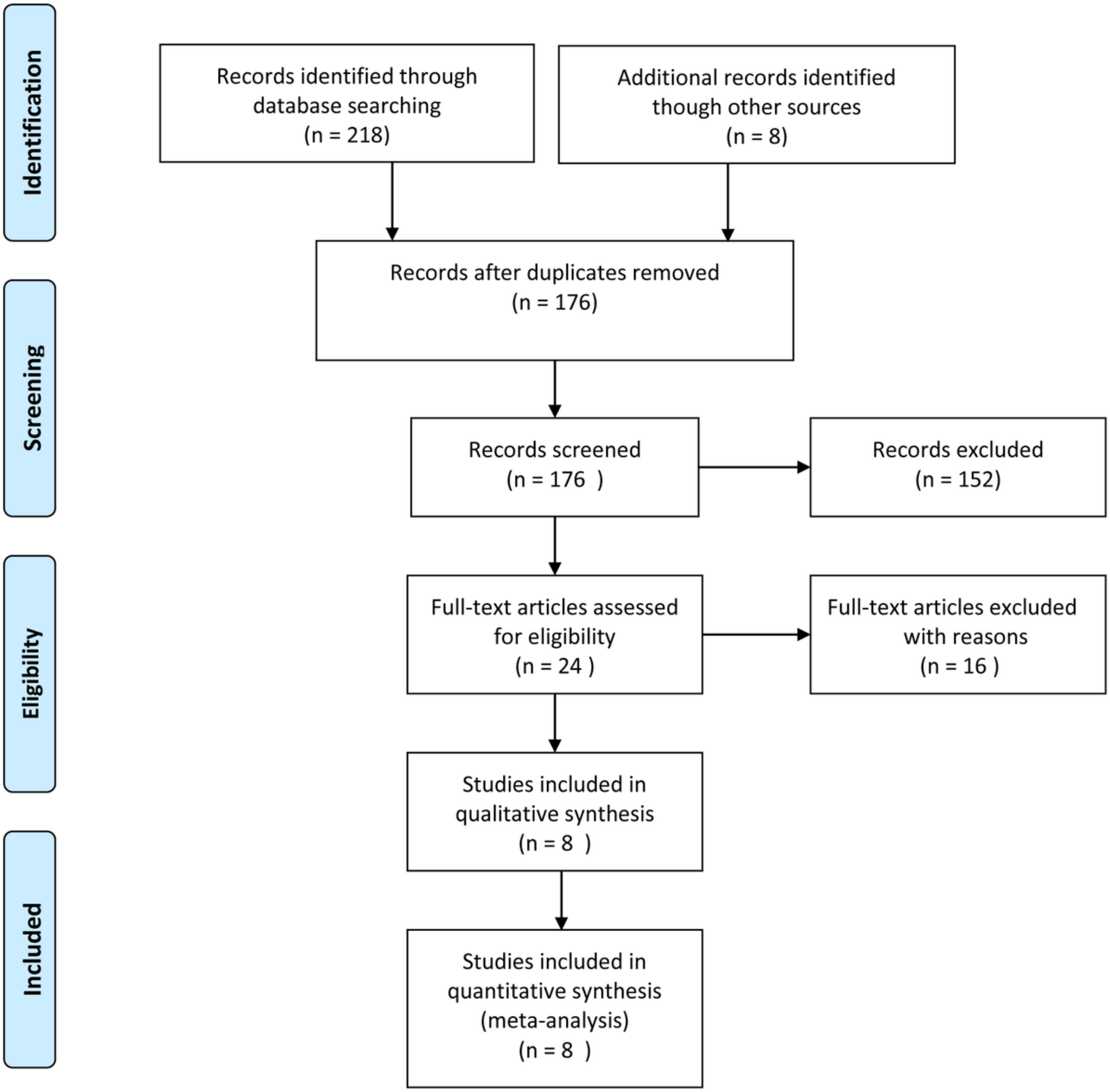

Figure 1

The PRISMA flow diagram of the meta-analysis

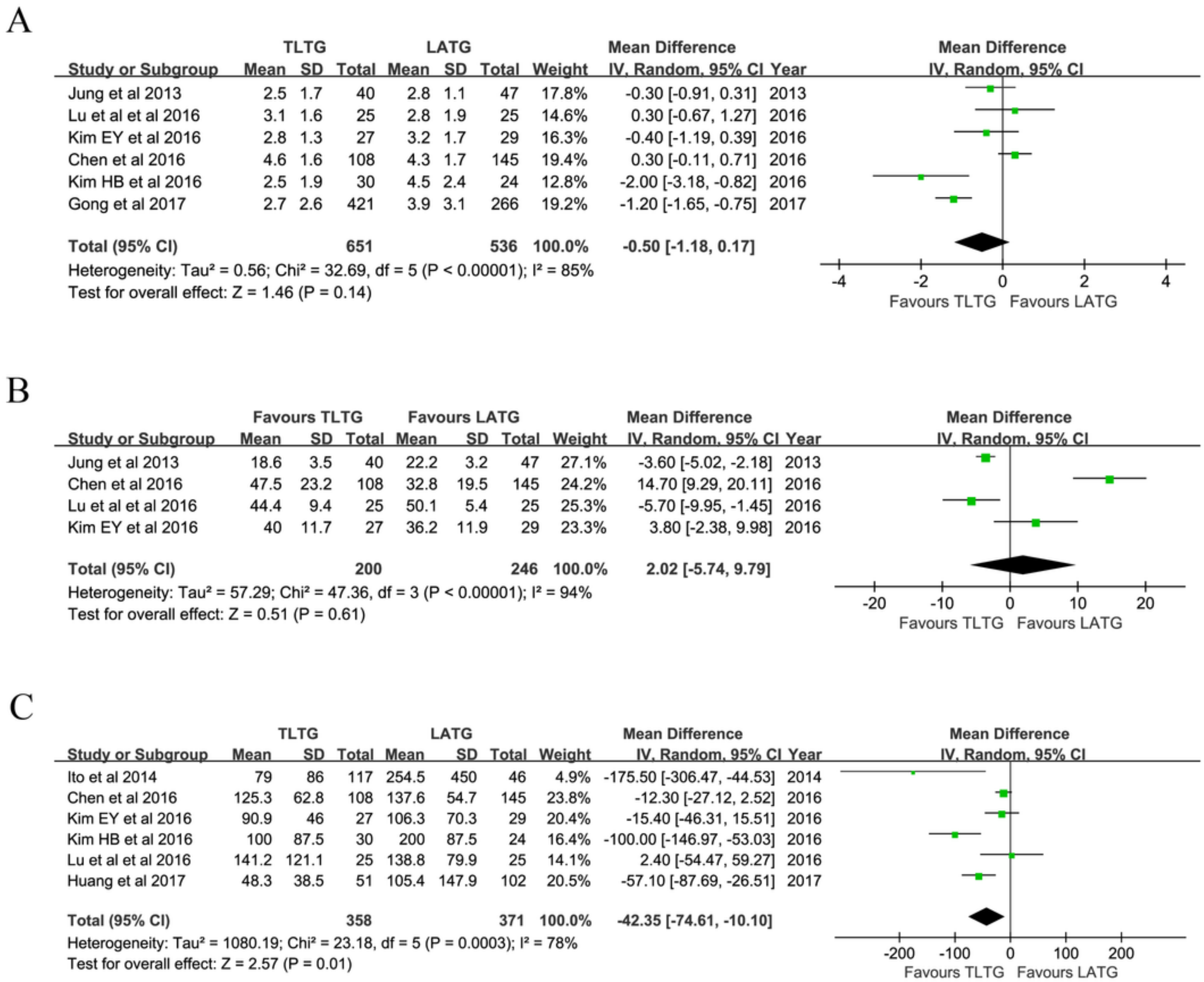

Figure 2

Forest plot of intraoperative outcomes. A operation time; B anastomotic time; C Estimated blood loss.

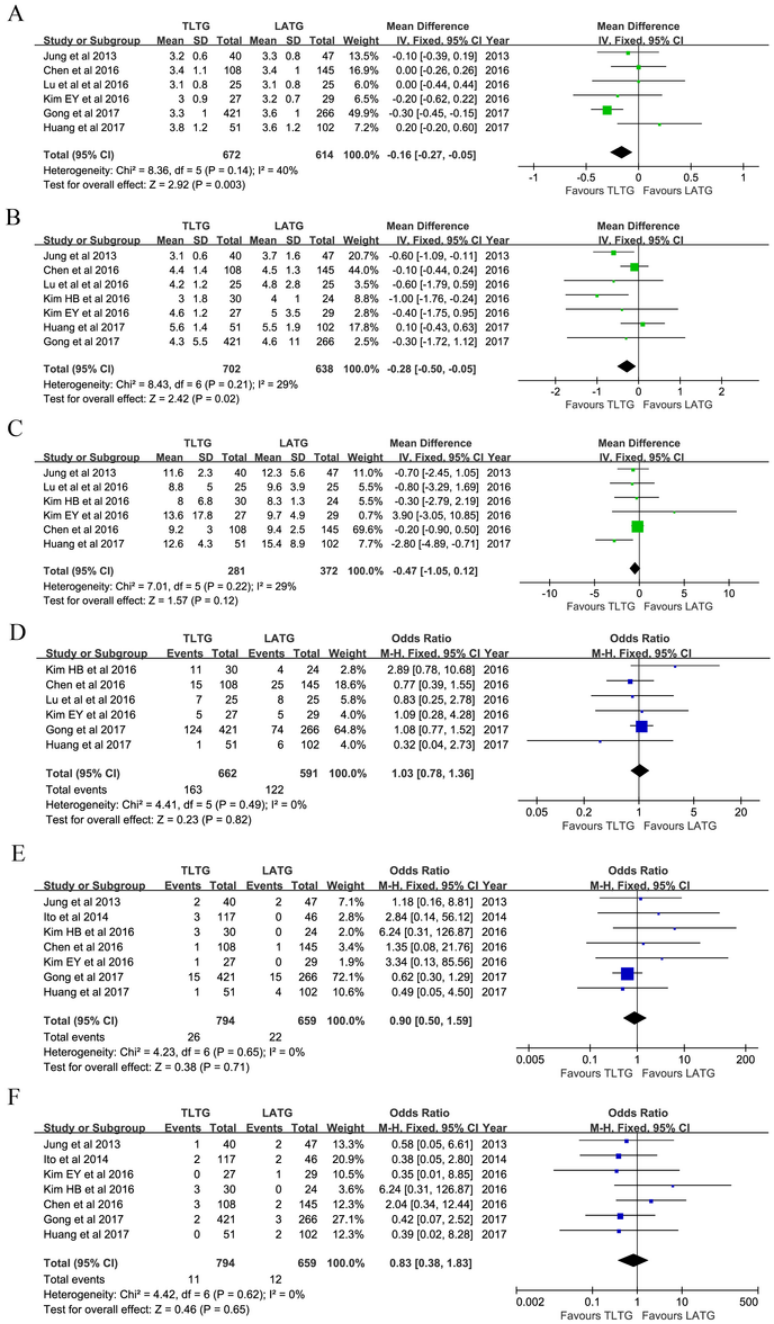

Figure 3

Forest plot of postoperative outcome. A time to first flatus; B time to first oral intake; C postoperative hospital stay; D postoperative morbidity; E anastomotic leakage; F anastomotic stricture.

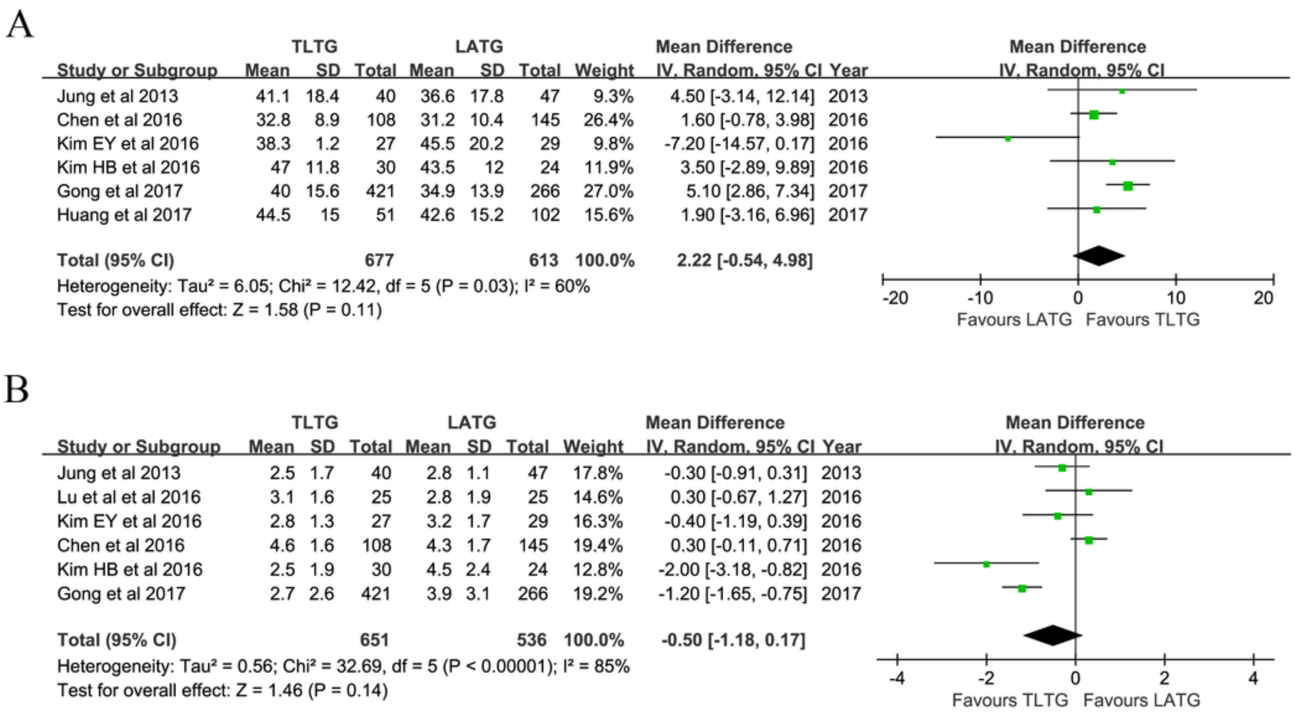

Figure 4

Forest plot of oncological outcomes. A number of retrieved lymph nodes; B proximal margin.