ORIGINAL ARTICLE

Intracorporeal versus extracorporeal anastomosis after laparoscopic gastrectomy for gastric cancer. A systematic review with meta-analysis

suppl. Informations

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Summary
Aim: To perform a systematic review and meta-analyses of studies comparing the totally laparoscopic procedures with intracorporeal anastomosis (IA) to laparoscopic-assisted surgery with extracorporeal anastomosis (EA) in gastric resections.
Methods: We performed a systematic search in the electronic databases. Outcomes analysed were: intraoperative (operative time and intraoperative blood loss), oncologic (harvested nodes, distance of the tumour from proximal and distal margin), postoperative complications (gastric stasis, intraluminal and extraluminal bleeding, leakage and wound infection) recovery (time to first flatus, time to first oral intake and hospital stay). We performed meta-regression analyses after implementing a regression model with the analysed outcomes as dependent variables (y) and the demographic and pathologic covariates as independent variables (x).
Results: A total of 26 studies (20 on distal gastrectomy and 6 on total gastrectomy) were included in the final analysis. Regarding distal gastrectomy, there was no statistical difference between the two groups in the above-mentioned outcomes, except for intraoperative blood loss (less in IA group, $P = 0.003$), number of harvested nodes (better in the IA group, $P = 0.022$) and

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length of hospital stay (shorter in the IA group, $P = 0.037$). Regarding total gastrectomy, there was no statistical difference for all outcomes, except for the distal margin (further in the EA group, $P = 0.040$). Meta-regression analysis showed that a lot of variables influenced results in distal gastric resections, but not in total gastric resections.

Conclusion: We can state laparoscopic gastric resections with IA are safe and feasible when performed by expert surgeons. However, new well-designed studies comparing the two techniques are needed to confirm the benefits of laparoscopic IA.

Introduction

Gastric cancer represents worldwide the third cause of cancer-related death for men and the fifth for women [1].

The most effective treatment for resectable gastric cancer is represented by surgery.

Since its introduction in the 90s, laparoscopy has gained a lot of consent among surgeons, being connected to less postoperative pain, shorter hospital stays and better cosmetic outcome. These benefits, of course, apply also on gastric surgery. Laparoscopic approach for the treatment of early gastric cancer has been demonstrated to be equivalent to the open approach, and became widely accepted and worldwide performed [2,3].

In opposition, the role of laparoscopy in the treatment of advanced gastric cancer is still an open issue, lacking strong evidence-based data about the equivalence between minimal invasive techniques and the traditional approach in terms of oncologic and long-term outcomes.

Moreover, it is important to underline how doubts do not only focus on the approach itself but also on the type of anastomosis to avoid short and long-term complications, even if a totally laparoscopic approach is often associated with faster recovery and a shorter length of hospital stay.

To better understand the role of laparoscopy in advanced gastric cancer treatment, we performed a meta-analysis of the most recent studies comparing the totally laparoscopic procedures (with intracorporeal anastomosis, IA) to laparoscopic-assisted surgery (with extracorporeal anastomosis, EA) in gastric resections.

Materials and Methods

A protocol for this review and meta-analysis was prospectively developed, detailing specific objectives, criteria for study selection, approach to assess study quality, outcomes, and statistical methods.

Selection criteria were defined using the PICO (Problem/Population, Intervention, Comparison and Outcome) framework. Participants included adult population affected by histologically proven gastric cancer. Two types of surgical techniques of laparoscopic distal or total gastrectomy were included, totally laparoscopic gastrectomy with IA and laparoscopic-assisted gastrectomy with EA. No restrictions were placed about the fashion of anastomosis and the anastomosis' technique, stapled or handsewn. In all included studies, we analysed intraoperative outcomes, short-term outcomes, distinguishing oncologic outcomes, postoperative complications and postoperative recovery outcomes.

Primary outcome measures were postoperative complications that included gastric stasis, intra- and extraluminal bleedings, anastomotic leakage and wound infections. Secondary outcomes were intraoperative outcomes (operating time and intraoperative blood loss), oncologic outcomes (number of harvested nodes and distance of the tumour from the proximal and distal resection margins), and postoperative recovery outcomes, including time to first flatus and length of hospital stay.

Literature search

A detailed search was conducted according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [4]. We performed a systematic search in the electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the search strings: (intracorporeal or totally laparoscopic) and gastric and cancer. All the studies since 1990 to 2017 were analysed. The last search was performed on 30th November 2017. In the search strategy only English speaking studies were included. No trial duration or inclusion period limitation was applied. In addition, the reference lists of all retrieved articles were manually reviewed. In case of missing data, study authors were contacted by e-mail to try to retrieve original data.

Study selection

Two independent authors analysed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted. Discrepancies were resolved by consensus. Selection results showed a high inter-reader agreement ($\kappa = 1$) and have been reported according to PRISMA flowchart (Supplementary data).

Data extraction and quality assessment

According to the pre-specified protocol, all studies comparing totally laparoscopic or laparoscopic-assisted anastomosis after distal or total gastrectomy for gastric cancer were included. Case-reports, case-series without a control group, reviews, animal studies and non-English speaking studies were excluded. To be included in the analysis, the retrieved study had to provide a detailed technique description and a clear case selection criterion. In case of overlap between centres or authors, the most recent study or the one with higher quality was selected.

Data regarding sample size, major clinical and demographic variables, oncologic outcomes and postoperative recovery and complications were extracted.

Given the characteristics of the included studies, the evaluation of methodological quality of each study was performed with the Newcastle-Ottawa Scale (NOS), which is specifically developed to assess quality of non-randomized observational studies [5]. The scoring system encompasses three domains (selection, comparability, exposure) and a resulting score range between 0 and 9, a higher score representing a better methodological quality. Results of the NOS quality assessment are reported in Supplementary data [6—31].

Statistical analysis and risk of bias assessment

Statistical analysis and risk of bias assessment was carried out using Comprehensive Meta-Analysis [Version 2.2, Biostat Inc, Englewood, NJ, USA, 2005] provided by Biostat Inc.

Differences among cases and controls were expressed as mean difference (MD) with pertinent 95% confidence intervals (95%CI) for continuous variables, and as Risk Difference (RD) with pertinent 95%CI for dichotomous variables. The overall effect was tested using Z scores and significance was set at $P < 0.05$. Statistical heterogeneity between studies was assessed with chi-square Cochran's Q test and with I^2 statistic, which measures the inconsistency across study results and describes the proportion of total variation in study estimates, that is due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25—50% moderate, and 50% high heterogeneity [32].

Publication bias was assessed by the Egger's test and represented graphically by funnel plots of the standard difference in means versus the standard error. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect. A $P < 0.10$ was considered statistically significant [33]. In case of a significant publication bias, the Duval and Tweedie's trim and fill method was used to allow for the estimation of an adjusted effect size [34].

In order to be as conservative as possible, the random-effect method was used for all analyses to take into account the variability among included studies.

Meta-regression analyses

We hypothesized that differences among included studies may be affected by demographic and clinical variables (mean age, male gender, BMI, ASA Score, previous abdominal surgery) and clinical data related to disease activity (tumoral stage). To assess the possible effect of such variables in explaining different results observed across studies, we planned to perform meta-regression analyses after implementing a regression model with the analysed outcomes (operating time, intraoperative blood loss, lymph nodes retrieved, proximal and distal margin of resection, flatus, return to oral intake, hospital stay, gastric stasis, postoperative bleedings, anastomotic leak and wound infection) as dependent variables (y) and the above-mentioned covariates as independent variables (x). We also performed a meta-regression analysis after implementing a regression model with these mentioned outcomes as dependent variables (y) and the difference of the above-mentioned covariates between the two groups (IA and EA) as independent variables (x), to exclude potential risk of patients' allocation. This analysis was performed with Comprehensive Meta-Analysis [Version 2.2, Biostat Inc, Englewood NJ, USA (2005)].

Results

Study selection

After excluding duplicate results, the search retrieved 438 articles. Of these studies, 201 were excluded because they were off the topic after scanning the title and/or the abstract, 34 for language, 5 because regarding animals, 34 because they were case reports-case series (26 and 8 respectively), 41 because they were review. Of 28 studies the on-line full-length version was not available, and it was not possible to extract data from the on-line abstract. All data were retrieved within articles, and no e-mail was sent to the authors to obtain adjunctive data. Other 69 studies were excluded after full-length paper evaluation: 40 were non-comparative studies, 29 for lack of data. Thus, 26 studies [6—31], whereof 20 on distal gastrectomy [6—25] and 6 on total gastrectomy [26—31], were included in the final analysis (Supplementary data).

Distal Gastrectomy

Studies characteristics

Twenty studies on distal gastrectomy were included, involving 3818 patients: 1424 with IA and 2394 with EA [6—25]. All studies were retrospective, except for the studies by Woo et al. and Song et al., that were a randomized controlled trial and a prospective observational study, respectively [11,21]. Major characteristics of studies are shown in Table 1. Number of patients varied from 27 to 642, the mean age from 55 to 72 years, and the prevalence of male gender from 36.36% to 69.6%. Mean body mass index (BMI) varied from $21 \, kg/m^2$ to $27.8 \, kg/m^2$. Prevalence of patients with AJCC stage I varied from 45.4 to 100%, with stage II from 1.6 to 25.3%, with stage III from 0 to 33% and with stage IV from 0.4 to 1.4%. Only one study included patients with stage IV cancer [17]. Technical aspects of each surgical technique are summarized in Table S1, Supplementary data. In all studies, anastomosis was performed using linear or circular stapler, except for the study by Lee et al., Ikeda et al. and Song et al. [19,21,22], who performed handsewn anastomosis in extracorporeal group. There is a large variation among the studies regarding the type of anastomosis. Regarding site extraction, all authors performed a median periumbilical ora supraumbilical incision.

Intraoperative outcomes

Intraoperative outcomes are shown in Fig. 1. Operative time was reported by 19 authors [6—9,11—25], involving 3791 patients, 1408 IA and 2383 EA, with no statistically significant difference between the two groups (MD = −4.231, $P = 0.327$, 95% CI −12.695,4.232) and a statistically significant heterogeneity (I2 = 92.032%; $P < 0.001$). Intraoperative blood loss was analysed by 15 authors [6—9,11—13,15,17,18,20—23,25], involving 2815 patients, 1060 IA and 1755 EA, with a statistically significant difference between the two groups in favour of the IA (MD = −51,257, $P = 0.003$, 95% CI −85.579, −16.935) and a statistically significant heterogeneity (I2 = 97.976%; $P < 0.001$).

Table 1 Characteristics of the included studies about distal gastrectomy.

Author	Year	Type of analysis	Number of patients	Fashion of anastomosis	Number of patients
Lee et al.	2015	Retrospective	132	Intracorporeal	33
				Extracorporeal	99
Choi et al.	2013	Retrospective	72	Intracorporeal	37
				Extracorporeal	35
Ahn et al.	2013	Retrospective	301	Intracorporeal	71
				Extracorporeal	230
Kim et al.	2013	Retrospective	247	Intracorporeal	111
				Extracorporeal	136
Lee J et al.	2012	Retrospective	399	Intracorporeal	130
				Extracorporeal	269
Shinohara et al.	2015	Retrospective	100	Intracorporeal	57
				Extracorporeal	43
Lin et al.	2016	Retrospective	642	Intracorporeal	158
				Extracorporeal	484
Woo et al.	2014	RCT	110	Intracorporeal	55
				Extracorporeal	55
Jeong et al.	2014	Retrospective	221	Intracorporeal	42
				Extracorporeal	179
Zhang C et al.	2015	Retrospective	36	Intracorporeal	11
				Extracorporeal	25
Han et al.	2014	Retrospective	211	Intracorporeal	134
				Extracorporeal	77
Kanaji et al.	2014	Retrospective	114	Intracorporeal	40
				Extracorporeal	74
Kim BS et al.	2011	Retrospective	448	Intracorporeal	180
				Extracorporeal	268
Ichikawa et al.	2009	Retrospective	27	Intracorporeal	16
				Extracorporeal	11
Zhang et al.	2015	Prospective	69	Intracorporeal	24
				Extracorporeal	45
Chen et al.	2014	Retrospective	240	Intracorporeal	147
				Extracorporeal	93
Kim DG et al.	2013	Retrospective	166	Intracorporeal	60
				Extracorporeal	106
Kinoshita et al.	2011	Retrospective	83	Intracorporeal	42
				Extracorporeal	41
Ikeda et al.	2009	Retrospective	80	Intracorporeal	56
				Extracorporeal	24
Song et al.	2008	Prospective	40	Intracorporeal	20
				Extracorporeal	20

Oncologic outcomes

Oncologic outcomes are shown in Fig. 2. Number of retrieved lymph nodes was reported by 17 authors [7,8,10—14,16—25], involving 3140 patients, 1159 IA and 1981 EA, with a statistically significant difference between the two groups in favour of the IA (MD = −1.878, $P = 0.022$, 95% CI −0.277, −3.478) and a statistically significant heterogeneity (I2 = 86.622%; $P < 0.001$).

Proximal margin was analysed by 10 authors [7—9,11,12,16,18,21—23], involving 1720 patients, 789 IA and 931 EA. No statistical difference was assessed between the two groups (MD = 0.464, $P = 0.176$, 95% CI −0.208, 1.136). Heterogeneity among these studies was statistically significant (I2 = 92.558%; $P < 0.001$).

Distal margin was reported by 6 authors [7,16,18,21—23], involving 1136 patients (520 IA and 616 EA), with no statistically significant difference between the two groups (MD = 0.372, $P = 0.272$, 95% CI −0.291, 1.035) and with a significant heterogeneity (I2 = 71.432%; $P = 0.004$).

Postoperative complications

Postoperative complications are shown in Fig. 3. Gastric stasis was analysed by 11 authors [7,12—15,18,20—23,25], involving patients (951 IA and 1646 EA), with no significant difference between the two groups (RD = 0.001, $P = 0.840$, 95% CI −0.008, 0.010) and no heterogeneity (I^2 = 0.000%; $P = 0.902$).

Postoperative intraluminal bleeding was reported by 10 authors [11—13,17,18,20—23,25], involving 1825 patients (611 IA and 1214 EA), with no significant difference between the two groups (RD = −0.004, $P = 0.400$, 95% CI −0.014, 0.005) and no heterogeneity (I2 = 0.000%; $P = 0.789$).

Postoperative extraluminal bleeding was analysed by 13 authors [7—9,12,13,16,18,20—23,25], involving 2880 patients (1122 IA and 1758 EA), with no significant difference between the two groups (RD = 0.001, $P = 0.814$, 95% CI −0.007, 0.009) and no heterogeneity (I2 = 0.000%; $P = 0.925$).

Anastomotic leak was reported by 17 authors [7,8,10—18,20—25], involving 3094 procedures (1186
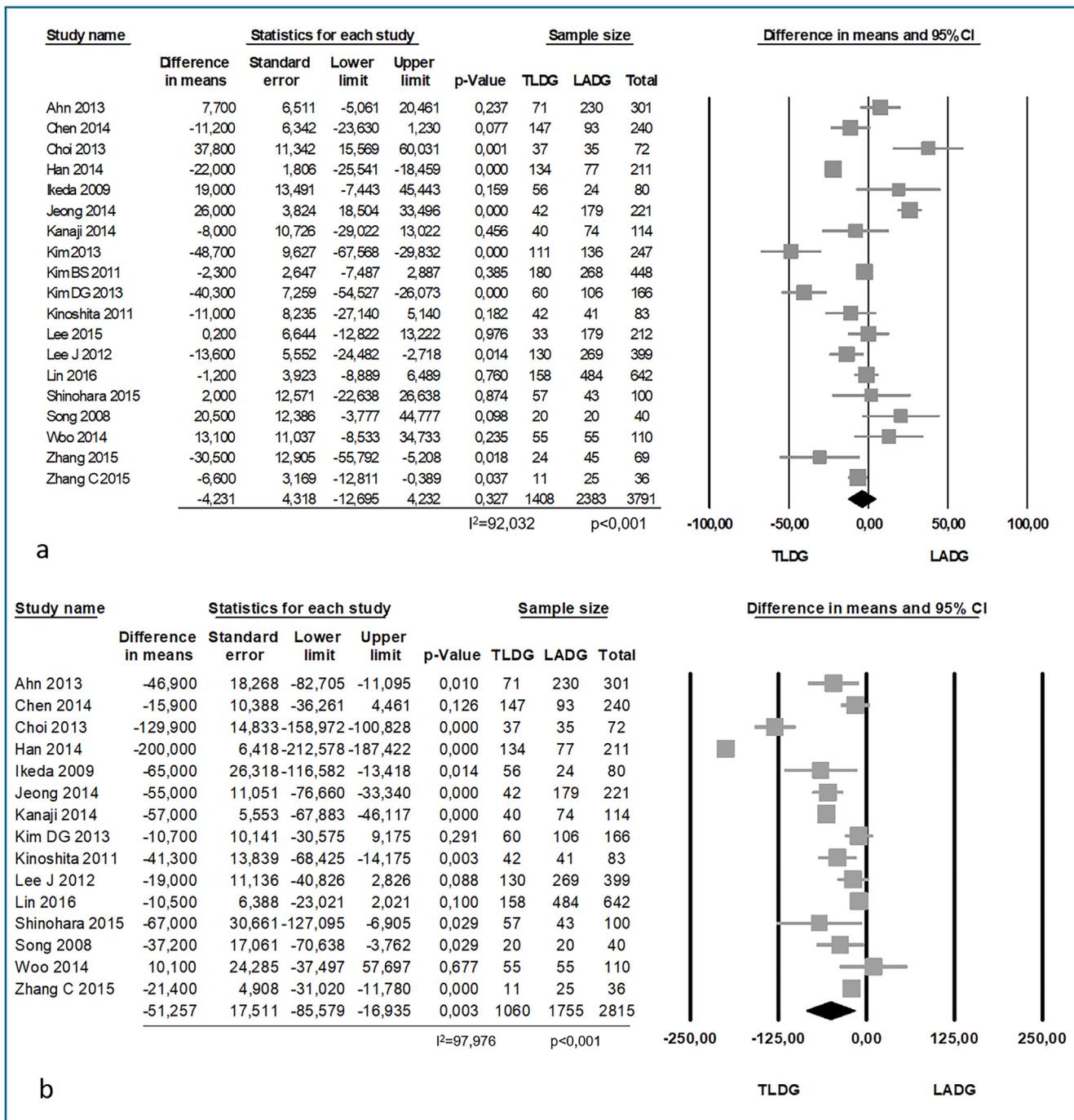
Figure 1. Intraoperative outcomes in distal gastrectomies. a: operative time; b: intraoperative blood loss.

IA and 1908 EA), assessing no significant difference between the two groups (RD = 0.002, $P = 0.651$, 95% CI −0.006, 0.010), with no heterogeneity (I2 = 0.000%; $P = 0.988$).

Wound infection was analysed by 11 authors [9,11−13,16,17,20−23,25], involving 1884 patients (726 IA and 1158 EA), reporting no statistically significant difference between the groups (RD = −0.005, $P = 0.324$, 95% CI −0.014, 0.005), with no heterogeneity (I2 = 0.000%; $P = 0.906$).

Postoperative recovery outcomes

Postoperative recovery outcomes are shown in Fig. 4. Time to first flatus was analysed by 16 authors [7,8,11−17,19−25],

involving 2880 (1073 IA and 1807 EA), with no significant difference between the groups (MD = −0.221, $P = 0.139$, 95% CI −0.513, 0.071). Heterogeneity among the studies was significant (I2 = 94.966%; $P < 0.001$).

Time to first oral intake was reported by 8 authors [7,11−13,19,21,23,25], involving 1033 patients, 441 IA and 592 EA, with no statistical difference between the two groups (MD = −0.313, $P = 0.076$, 95% CI −0.659, 0.033) and no significant heterogeneity (I2 = 88.282%; $P < 0.001$).

Length of stay was reported by 19 authors [6−17,19−25], involving 3419 patients (1294 IA and 2125 EA). Significant difference was observed in favour of the IA (MD = −0.569, $P = 0.037$, 95% CI −1.106, −0.033), with a significant heterogeneity among the studies (I2 = 84.791%; $P < 0.001$).

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value	TLDG	LADG	Total	Difference in means and 95% CI
Chen 2014	-1,400	1,146	-3,646	0,846	0,222	147	93	240	
Choi 2013	-3,000	2,888	-8,661	2,661	0,299	37	35	72	
Ichikawa 2009	1,000	0,152	0,702	1,298	0,000	16	11	27	
Ikeda 2009	-2,100	3,261	-8,491	4,291	0,520	56	24	80	
Jeong 2014	-2,000	2,026	-5,972	1,972	0,324	42	179	221	
Kanaji 2014	-1,000	3,478	-7,817	5,817	0,774	40	74	114	
Kim 2013	-2,600	1,299	-5,146	-0,054	0,045	111	136	247	
Kim BS 2011	-8,800	1,129	-11,012	-6,588	0,000	180	268	448	
Kinoshita 2011	-1,800	2,865	-7,415	3,815	0,530	42	41	83	
Lee 2015	-2,500	2,501	-7,401	2,401	0,317	33	179	212	
Lee J 2012	-1,000	1,175	-3,304	1,304	0,395	130	269	399	
Lin 2016	-3,800	0,969	-5,700	-1,900	0,000	158	484	642	
Shinohara 2015	-4,000	3,337	-10,541	2,541	0,231	57	43	100	
Song 2008	-3,200	4,713	-12,437	6,037	0,497	20	20	40	
Woo 2014	-0,900	2,250	-5,310	3,510	0,689	55	55	110	
Zhang 2015	5,700	3,689	-1,530	12,930	0,122	24	45	69	
Zhang C 2015	1,030	0,582	-0,111	2,171	0,077	11	25	36	
	-1,878	0,817	-3,478	-0,277	0,022	1159	1981	3140	

I²=86,622 p<0,001

a   TLDG   LADG

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value	TLDG	LADG	Total	Difference in means and 95% CI
Chen 2014	0,500	0,176	0,156	0,844	0,004	147	93	240	
Choi 2013	0,800	0,708	-0,589	2,189	0,259	37	35	72	
Han 2014	1,700	0,076	1,551	1,849	0,000	134	77	211	
Ikeda 2009	0,500	0,616	-0,707	1,707	0,417	56	24	80	
Jeong 2014	-1,900	0,776	-3,422	-0,378	0,014	42	179	221	
Kim 2013	0,100	0,316	-0,519	0,719	0,752	111	136	247	
Lee J 2012	-0,400	0,285	-0,959	0,159	0,160	130	269	399	
Shinohara 2015	0,500	0,440	-0,362	1,362	0,255	57	43	100	
Song 2008	1,000	0,636	-0,246	2,246	0,116	20	20	40	
Woo 2014	1,300	0,515	0,290	2,310	0,012	55	55	110	
	0,464	0,343	-0,208	1,136	0,176	789	931	1720	

I²=92,558 p<0,001

b   TLDG   LADG

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value	TLDG	LADG	Total	Difference in means and 95% CI
Chen 2014	0,200	0,196	-0,184	0,584	0,308	147	93	240	
Kim 2013	1,000	0,344	0,326	1,674	0,004	111	136	247	
Lee J 2012	0,800	0,353	0,108	1,492	0,024	130	269	399	
Shinohara 2015	-1,200	0,610	-2,395	-0,005	0,049	57	43	100	
Song 2008	1,600	0,720	0,189	3,011	0,026	20	20	40	
Woo 2014	-1,800	1,400	-4,544	0,944	0,199	55	55	110	
	0,372	0,338	-0,291	1,035	0,272	520	616	1136	

I²=71,432 p=0,004

c   TLDG   LADG

Figure 2. Oncologic outcome after distal gastrectomies. a: harvested lymph nodes; b: distance to proximal margin; c: distance to distal margin.
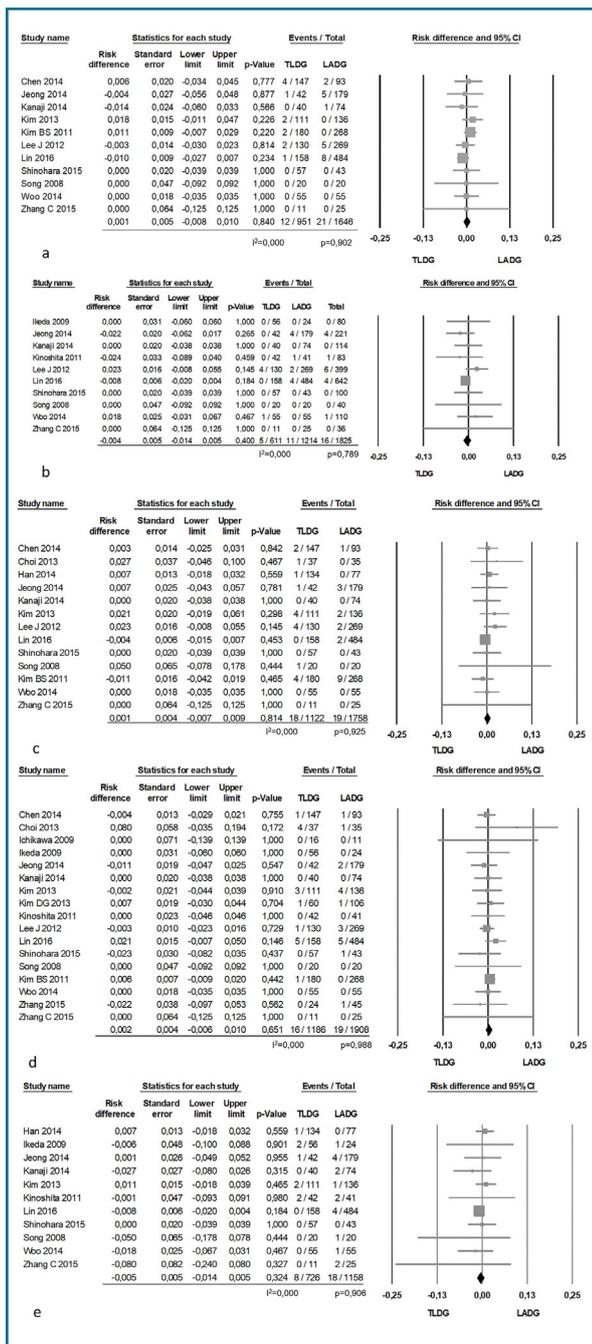
Publication bias

The distribution of studies evaluating all the analysed outcomes was symmetrical and no publication bias was found by the Egger's test, except for harvested lymph nodes, the distance of the tumour from the proximal of the specimen and time to first oral intake, in which visual inspection suggested an asymmetric distribution of studies around the mean and the Egger's test confirmed a significant publication bias (Supplementary data, Figs. S1 to S4).

Meta-regression analysis

Regression models showed that different patients' and tumours' characteristics influenced various of analysed outcomes. A list of significant results is shown in Table S2, Supplementary data.

Regarding oncologic outcomes, the number of harvested nodes was influenced by gender, BMI, previous abdominal surgery and AJCC Stage of the tumour (Stage I, II, III). Proximal margin was influenced by age, gender, BMI, ASA Score,

a

Study name	Risk difference	Standard error	Lower limit	Upper limit	p-Value	TLDG	LADG
Chen 2014	0,006	0,020	-0,034	0,045	0,777	4/147	2/93
Jeong 2014	-0,004	0,027	-0,056	0,048	0,877	1/42	5/179
Kanaji 2014	-0,014	0,024	-0,060	0,033	0,566	0/40	1/74
Kim 2013	0,018	0,015	-0,011	0,047	0,226	2/111	0/136
Kim BS 2011	0,011	0,009	-0,007	0,029	0,220	2/180	0/268
Lee J 2012	-0,003	0,014	-0,030	0,023	0,814	2/130	5/269
Lin 2016	-0,010	0,009	-0,027	0,007	0,234	1/158	8/484
Shinohara 2015	0,000	0,020	-0,039	0,039	1,000	0/57	0/43
Song 2008	0,000	0,047	-0,092	0,092	1,000	0/20	0/20
Woo 2014	0,000	0,018	-0,035	0,035	1,000	0/55	0/55
Zhang C 2015	0,000	0,064	-0,125	0,125	1,000	0/11	0/25
	0,001	0,005	-0,008	0,010	0,840	12/951	21/1646

I2=0,000 p=0,902

b

Study name	Risk difference	Standard error	Lower limit	Upper limit	p-Value	TLDG	LADG	Total
Ileda 2009	0,000	0,031	-0,060	0,060	1,000	0/56	0/24	0/80
Jeong 2014	-0,022	0,020	-0,062	0,017	0,265	0/42	4/179	4/221
Kanaji 2014	0,000	0,020	-0,038	0,038	1,000	0/40	0/74	0/114
Kinoshita 2011	-0,024	0,033	-0,089	0,040	0,459	0/42	1/41	1/83
Lee J 2012	0,023	0,016	-0,008	0,055	0,145	4/130	2/269	6/399
Lin 2016	-0,008	0,006	-0,020	0,004	0,184	0/158	4/484	4/642
Shinohara 2015	0,000	0,020	-0,039	0,039	1,000	0/57	0/43	0/100
Song 2008	0,000	0,047	-0,092	0,092	1,000	0/20	0/20	0/40
Woo 2014	0,018	0,025	-0,031	0,067	0,467	1/55	0/55	1/110
Zhang C 2015	0,000	0,064	-0,125	0,125	1,000	0/11	0/25	0/36
	-0,004	0,005	-0,014	0,005	0,400	5/611	11/1214	16/1825

I2=0,000 p=0,789

c

Study name	Risk difference	Standard error	Lower limit	Upper limit	p-Value	TLDG	LADG
Chen 2014	0,003	0,014	-0,025	0,031	0,842	2/147	1/93
Choi 2013	0,027	0,037	-0,046	0,100	0,487	1/37	0/35
Han 2014	0,007	0,013	-0,018	0,032	0,559	1/134	0/77
Jeong 2014	0,007	0,025	-0,043	0,057	0,781	1/42	3/179
Kanaji 2014	0,000	0,020	-0,038	0,038	1,000	0/40	0/74
Kim 2013	0,021	0,020	-0,019	0,061	0,298	4/111	2/136
Lee J 2012	0,023	0,016	-0,008	0,055	0,145	4/130	2/269
Lin 2016	-0,004	0,006	-0,015	0,007	0,453	0/158	2/484
Shinohara 2015	0,000	0,020	-0,039	0,039	1,000	0/57	0/43
Song 2008	0,050	0,065	-0,078	0,178	0,444	1/20	0/20
Kim BS 2011	-0,011	0,016	-0,042	0,019	0,465	4/180	9/268
Woo 2014	0,000	0,018	-0,035	0,035	1,000	0/55	0/55
Zhang C 2015	0,000	0,064	-0,125	0,125	1,000	0/11	0/25
	0,001	0,004	-0,007	0,009	0,814	18/1122	19/1758

I2=0,000 p=0,925

d

Study name	Risk difference	Standard error	Lower limit	Upper limit	p-Value	TLDG	LADG
Chen 2014	-0,004	0,013	-0,029	0,021	0,755	1/147	1/93
Choi 2013	0,080	0,058	-0,035	0,194	0,172	4/37	1/35
Ichikawa 2009	0,000	0,071	-0,139	0,139	1,000	0/16	0/11
Ikeda 2009	0,000	0,031	-0,060	0,060	1,000	0/56	0/24
Jeong 2014	-0,011	0,019	-0,047	0,025	0,547	0/42	2/179
Kanaji 2014	0,000	0,020	-0,038	0,038	1,000	0/40	0/74
Kim 2013	-0,002	0,021	-0,044	0,039	0,910	3/111	4/136
Kim DG 2013	0,007	0,019	-0,030	0,044	0,704	1/60	1/106
Kinoshita 2011	0,000	0,023	-0,046	0,046	1,000	0/42	0/41
Lee J 2012	-0,003	0,010	-0,023	0,016	0,729	1/130	3/269
Lin 2016	0,021	0,015	-0,007	0,050	0,146	5/158	5/484
Shinohara 2015	-0,023	0,030	-0,082	0,035	0,437	0/57	1/43
Song 2008	0,000	0,047	-0,092	0,092	1,000	0/20	0/20
Kim BS 2011	0,006	0,007	-0,009	0,020	0,442	1/180	0/268
Woo 2014	0,000	0,018	-0,035	0,035	1,000	0/55	0/55
Zhang 2015	-0,022	0,038	-0,097	0,053	0,562	0/24	1/45
Zhang C 2015	0,000	0,064	-0,125	0,125	1,000	0/11	0/25
	0,002	0,004	-0,006	0,010	0,651	16/1186	19/1908

I2=0,000 p=0,988

e

Study name	Risk difference	Standard error	Lower limit	Upper limit	p-Value	TLDG	LADG
Han 2014	0,007	0,013	-0,018	0,032	0,559	1/134	0/77
Ikeda 2009	-0,006	0,048	-0,100	0,088	0,901	2/56	1/24
Jeong 2014	0,001	0,026	-0,049	0,052	0,955	1/42	4/179
Kanaji 2014	-0,027	0,027	-0,080	0,026	0,315	0/40	2/74
Kim 2013	0,011	0,015	-0,018	0,039	0,465	2/111	1/136
Kinoshita 2011	-0,001	0,047	-0,093	0,091	0,980	2/42	2/41
Lin 2016	-0,008	0,006	-0,020	0,004	0,184	0/158	4/484
Shinohara 2015	0,000	0,020	-0,039	0,039	1,000	0/57	0/43
Song 2008	-0,050	0,065	-0,178	0,078	0,444	0/20	1/20
Woo 2014	-0,018	0,025	-0,067	0,031	0,467	0/55	1/55
Zhang C 2015	-0,080	0,082	-0,240	0,080	0,327	0/11	2/25
	-0,005	0,005	-0,014	0,005	0,324	8/726	18/1158

I2=0,000 p=0,906

Figure 3. Postoperative complications after distal gastrectomies. a: gastric stasis; b: postoperative intraluminal bleeding; c: postoperative extraluminal bleeding; d: anastomotic leak; e: wound infection.

previous abdominal surgery and AJCC Stage I and II of the tumour. Distal margin was influenced by age, BMI, tumour's AJCC Stage I, II, III.

Regarding recovery outcomes, time to first flatus was influenced by age, gender, BMI, mean ASA Score and previous abdominal surgery. Length of hospital stay was influenced by gender, BMI, tumoral stage I, II, III, IV.

Interestingly, none of patients' and tumours' characteristics (age, gender, BMI, mean ASA Score, previous abdominal surgery, AJCC stage) influenced postoperative complications, i.e. gastric stasis, postoperative intraluminal and extraluminal bleeding, anastomotic leak and wound infection.

Patient allocation bias in each study was also assessed. Number of harvested nodes was influenced by the difference in age, prevalence of male patient, BMI, prevalence of tumoral Stage I, II and III between the two groups. Proximal margin was influenced by the difference in age, prevalence of male gender, BMI, mean ASA Score, prevalence of previous abdominal surgery, tumoral Stage I and II between the two groups. Distal margin was influenced by difference in age and prevalence of male gender between the two groups. Among recovery outcomes, difference in age, prevalence of male patients, BMI impacted on time to first flatus, while difference in age, prevalence of male patients, BMI, tumoral stage I, II, III, IV between the two groups significantly impacted on length of hospital stay. Interestingly, none of these differences influenced postoperative complications.

Total gastrectomy

Studies characteristics

Six studies were included, involving 722 patients: 407 with IA and 315 with EA [26–31]. All studies were retrospective, except for the studies by Ito et al. [27] and Kim et al. [30]. Major studies' characteristics are shown in Table 2. Number of patients varied from 50 to 253, mean age from 56.8 to 63.4 years, and the prevalence of male gender from 67.58% to 88%. Mean body mass index (BMI) varied from 22.2 kg/m² to 24 kg/m². Prevalence of patients with AJCC stage I cancer varied from 16 to 92.59%, with stage II from 3.7 to 25%, with stage III from 3.7 to 68% and with stage IV from 0 to 12% stage IV cancer. Technical aspects of each surgical technique are summarized in Table S3, Supplementary data. In all studies, anastomosis was performed using linear or circular stapler. Regarding the type of the anastomosis, all authors performed the Roux-en-Y anastomosis. Regarding site extraction, there was a large variation among authors, but no one used a Pfannenstiel incision in the IA group.

Intraoperative outcomes

Intraoperative outcomes are shown in Fig. 5. Operative time was reported by all authors [26–31], involving 722 patients, 407 IA and 315 EA, with no statistically significant difference between the two groups (MD = −9.243, P = 0.051, 95% CI −18.525, 0.038), and no statistically significant heterogeneity (I2 = 33.796%; P = 0.183). Intraoperative blood loss was analysed by 3 authors [26,27,29], involving 472 patients, 252 IA and 220 EA, with no statistically significant difference between the two groups (MD = −46,381, P = 0.080, 95% CI −98.365, 5.604) and a statistically significant heterogeneity (I2 = 85.512%; P = 0.001).

Oncologic outcomes

Oncologic outcomes are summarized in Fig. 6. Number of harvested nodes was analysed by 4 authors [26,28,30], involving 509 procedures (265 IA and 244 EA), with no significant differences between the two groups (MD = 1.484, P = 0.439, 95% CI −2.276, 5.243) and no significant heterogeneity (I2 = 35.907%; P = 0.197).

Proximal margin was analysed by 5 authors [26,28–31], involving 559 patients (290 IA and 289 EA), with no significant difference between the groups (MD = 0.030, P = 0.820, 95% CI −0.231, 0.292) and no heterogeneity among the studies (I2 = 3.974%; P = 0.384). Distal margin of the specimen was analysed by only two authors [29,30] and showed a
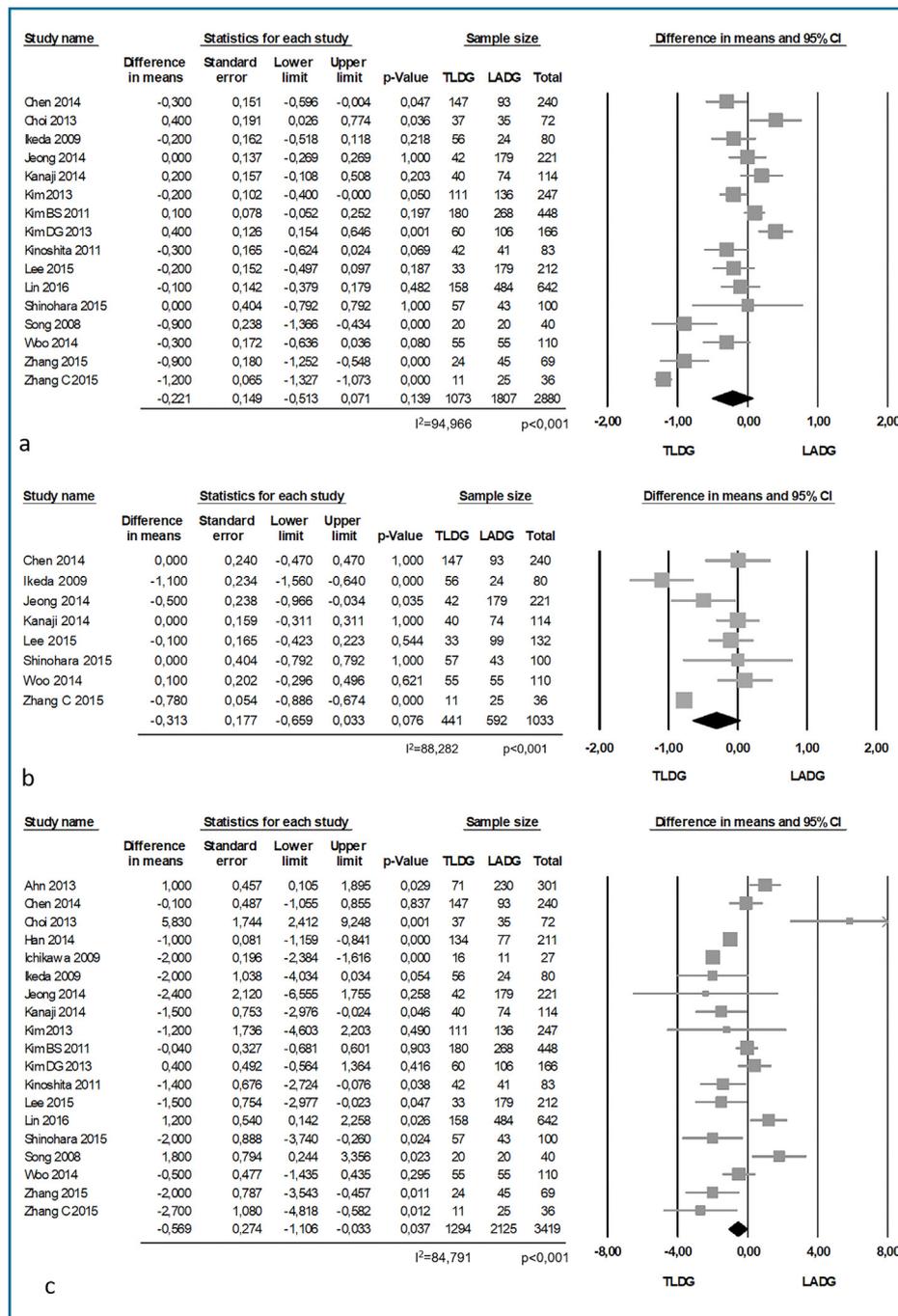
Figure 4. Postoperative recovery outcomes after distal gastrectomies. a: time to first flatus; b: time to first oral intake; c: length of hospital stay.

significant difference between the two groups in favour of EA (MD = 1.623, $P = 0.040$, 95% CI 0.074, 3.173), with no significant difference among the studies ($I^2 = 1.825\%$; $P = 0.384$).

Postoperative complications

Postoperative complications are shown in Fig. 7.

Postoperative intraluminal bleeding was analysed by 2 authors [29,31], involving 106 patients (52 IA and 54 EA), with no significant difference between the two groups (RD = −0.014, $P = 0.644$, 95% CI −0.072, 0.044) and no heterogeneity among the studies ($I2 = 0.000\%$; $P = 0.569$).

Postoperative extraluminal bleeding was reported by 2 authors [29,31], involving 366 patients (198 IA and 168 EA), showing no significant difference between the groups (RD = 0.013, $P = 0.323$, 95% CI −0.013, 0.040), and no heterogeneity among the studies ($I2 = 0.000\%$; $P = 0.774$).

Anastomotic leak was analysed by all the authors [26—32], involving 722 patients (407 IA and 315 EA), with no statistically significant difference between the groups (RD = 0.005, $P = 0.613$, 95% CI −0.013, 0.023), and no heterogeneity among the studies ($I2 = 0.000\%$; $P = 0.498$).

Table 2 Characteristics of the included studies about total gastrectomy.

Author	Year	Type of analysis	Number of patients	Fashion of anastomosis	Number of patients
Kim et al.	2016	Retrospective	56	Intracorporeal	27
				Extracorporeal	29
Chen et al.	2016	Retrospective	253	Intracorporeal	108
				Extracorporeal	145
Lu et al.	2016	Retrospective	50	Intracorporeal	25
				Extracorporeal	25
Kim S et al.	2013	Prospective	113	Intracorporeal	90
				Extracorporeal	23
Ito et al.	2014	Prospective	163	Intracorporeal	117
				Extracorporeal	46
Jung et al.	2013	Retrospective	87	Intracorporeal	40
				Extracorporeal	47
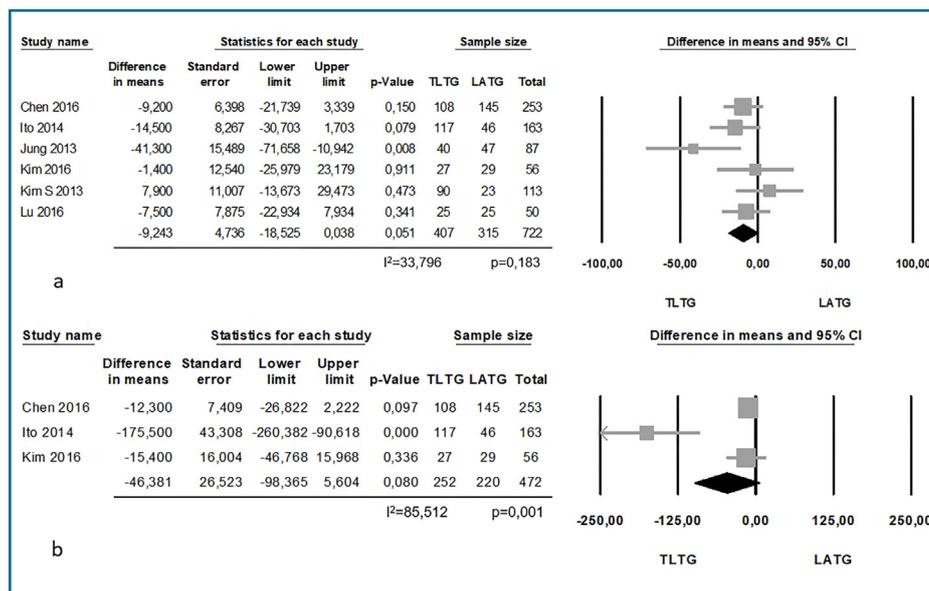
Figure 5. Intraoperative outcomes in total gastrectomies. a: operative time; b: intraoperative blood loss.

Wound infection was reported by 3 authors [26,30,31], involving 392 patients (223 IA and 169 EA), with no significant difference between the groups (RD = −0.007, P = 0.591, 95% CI −0.034, 0.019), with no heterogeneity among the studies (I2 = 0.000%; P = 0.807).

Postoperative recovery outcomes

Postoperative recovery outcomes are shown in Fig. 8. In details, time to first flatus and length of hospital stay were reported by 5 authors [26,28—31], involving 559 patients (290 IA and 269 EA) with no significant difference between the groups (MD = −0.051, P = 0.484, 95% CI −0.195,0.092 and MD = −0.365, P = 0.229, 95% CI −0.960, 0.230 respectively), with no heterogeneity among the studies (I2 = 0.000%; P = 0.622 and I2 = 0.000%; P = 0.512 respectively). Time to first oral intake was reported by 4 authors [26,28,29,31], involving 446 patients (200 IA and 246 EA), with no significant difference between the two groups (MD = −0.268, P = 0.051, 95% CI −1.952, 0.051) and no heterogeneity among the studies (I2 = 0.000%; P = 0.418).

Publication bias

The distribution of studies evaluating all the analysed outcomes was symmetrical and no publication bias was found by the Egger's test, except for distal margin and postoperative intraluminal and extraluminal bleeding, in which it was not possible to perform a funnel plot analyses because these parameters were only analysed by two authors (Supplementary data, Figs. S5 to S7).

Meta-regression analysis

Regression models showed that none of patients' and tumours' characteristics (see above) influenced outcomes. In addition, patient allocation bias in each study could be excluded because the difference in patients' and tumors' characteristics between totally laparoscopic and laparoscopic-assisted groups did not influence the analysed outcomes.

DISCUSSION

Despite laparoscopy is widespread nowadays and considered as gold standard for a lot of abdominal procedures, its role in gastric resection is still debated, especially for advanced gastric cancer [26].

This can be related to technical difficulties and to the long learning curve. Moreover, two types of anastomosis
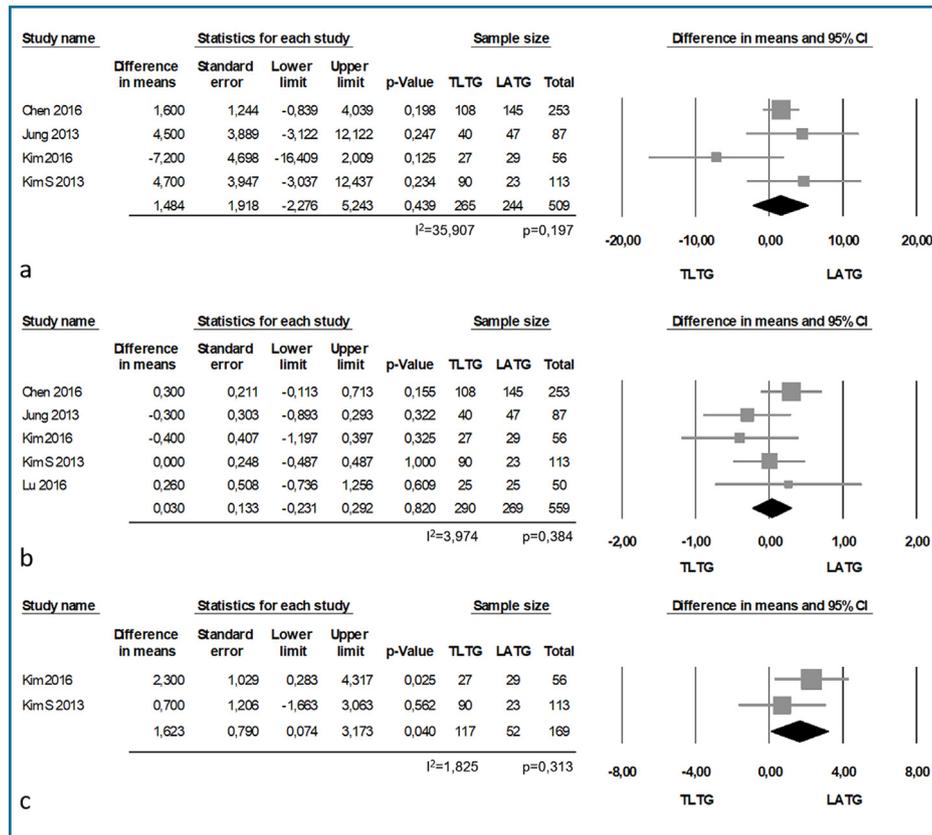
a

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value	TLTG	LATG	Total
Chen 2016	1,600	1,244	-0,839	4,039	0,198	108	145	253
Jung 2013	4,500	3,889	-3,122	12,122	0,247	40	47	87
Kim 2016	-7,200	4,698	-16,409	2,009	0,125	27	29	56
Kim S 2013	4,700	3,947	-3,037	12,437	0,234	90	23	113
	1,484	1,918	-2,276	5,243	0,439	265	244	509

$I^2=35,907$ p=0,197

b

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value	TLTG	LATG	Total
Chen 2016	0,300	0,211	-0,113	0,713	0,155	108	145	253
Jung 2013	-0,300	0,303	-0,893	0,293	0,322	40	47	87
Kim 2016	-0,400	0,407	-1,197	0,397	0,325	27	29	56
Kim S 2013	0,000	0,248	-0,487	0,487	1,000	90	23	113
Lu 2016	0,260	0,508	-0,736	1,256	0,609	25	25	50
	0,030	0,133	-0,231	0,292	0,820	290	269	559

$I^2=3,974$ p=0,384

c

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value	TLTG	LATG	Total
Kim 2016	2,300	1,029	0,283	4,317	0,025	27	29	56
Kim S 2013	0,700	1,206	-1,663	3,063	0,562	90	23	113
	1,623	0,790	0,074	3,173	0,040	117	52	169

$I^2=1,825$ p=0,313

Figure 6. Oncologic outcome after total gastrectomies. a: harvested nodes; b: distance to proximal margin; c: distance to distal margin.

may be performed, which makes difficult to compare the different techniques and to develop strong evidence-based conclusions. The fashioning of the anastomosis is a crucial point during gastrectomy procedure. For comparison, totally laparoscopic procedures are widely studied in colorectal surgery. However, IA was rarely performed after gastric resection, but the improvement of mini-invasive techniques and the simplification of anastomosis fashioning procedures (as Kanaya has proposed) made total laparoscopic gastrectomy possible and more widely performed [35]. Bariatric surgery [36—38] participated in these improvements and in the diffusion of the techniques.

Since its introduction, several studies have compared IA with EA in gastric surgery. Lin et al. [20] recently published a study with 642 patients undergoing distal gastrectomy, comparing Billroth I IA and EA. There was no difference, except for a larger number of dissected lymph nodes in the EA group. However, in locally advanced gastric cancer, there were more dissected lymph nodes and a higher rate of postoperative complications in the IA group [20].

Four other recent studies have reached similar conclusions [19,24,26,29]. In their retrospective study, Chen et al. [26] analysed data from 253 patients undergoing total gastrectomy. There were no significant differences in first flatus, diet resumption, and postoperative hospital stay. The surgical complication rates were 17.2% and 13.9% in the EA and IA groups, respectively. These conclusions were confirmed by two other studies [31,39].

In our best knowledge, only two meta-analyses comparing totally laparoscopic and laparoscopic-assisted for gastric cancer treatment have been performed. Chen et al. [26] analysed data from three studies comparing totally laparoscopic total gastrectomy to laparoscopic-assisted total gastrectomy, in 816 patients. They found no

significant differences in operative time, blood loss, time to first flatus, length of hospital stay and anastomosis-related complications between groups. Surgical complication rates were 17.2% after AE and 13.9% after IA.

Similar conclusions were drawn by Zhang et al. in his meta-analyses, including twelve non-randomized observational clinical studies involving 2255 patients, studying distal gastrectomies [40].

Although these conclusions are encouraging and concordant, the lack of high-level evidence in literature and the limits of current meta-analyses encouraged us to perform a meta-analysis that included a wider number of studies.

Regarding distal gastrectomy, intraoperative outcomes seem to be in favour of IA: less blood loss but with some heterogeneity and no difference in operative time. Oncological results plead also for IA, with a larger lymph nodes dissection in AI, with some heterogeneity. there was no difference in resection margins with a significant heterogeneity. Regarding postoperative results, the meta-analysis does not show any difference regarding time to first flatus and first oral intake, but length of stay was in favour of IA. Postoperative morbidity was not different between groups.

Regarding total gastrectomy, no statistical difference was found in terms of intraoperative outcomes between the two groups. The only difference regarding oncological outcomes favoured AE for distal margin. But this difference was grounded on only two studies among the six studies. There was no difference regarding postoperative morbidity and recovery.

It is also important to underline that regression models have showed that numerous patients' and tumour's characteristics did influence the outcomes of distal gastrectomy, but not of total gastrectomy. An important result of this meta-analysis is that the laparoscopic approach is useful in
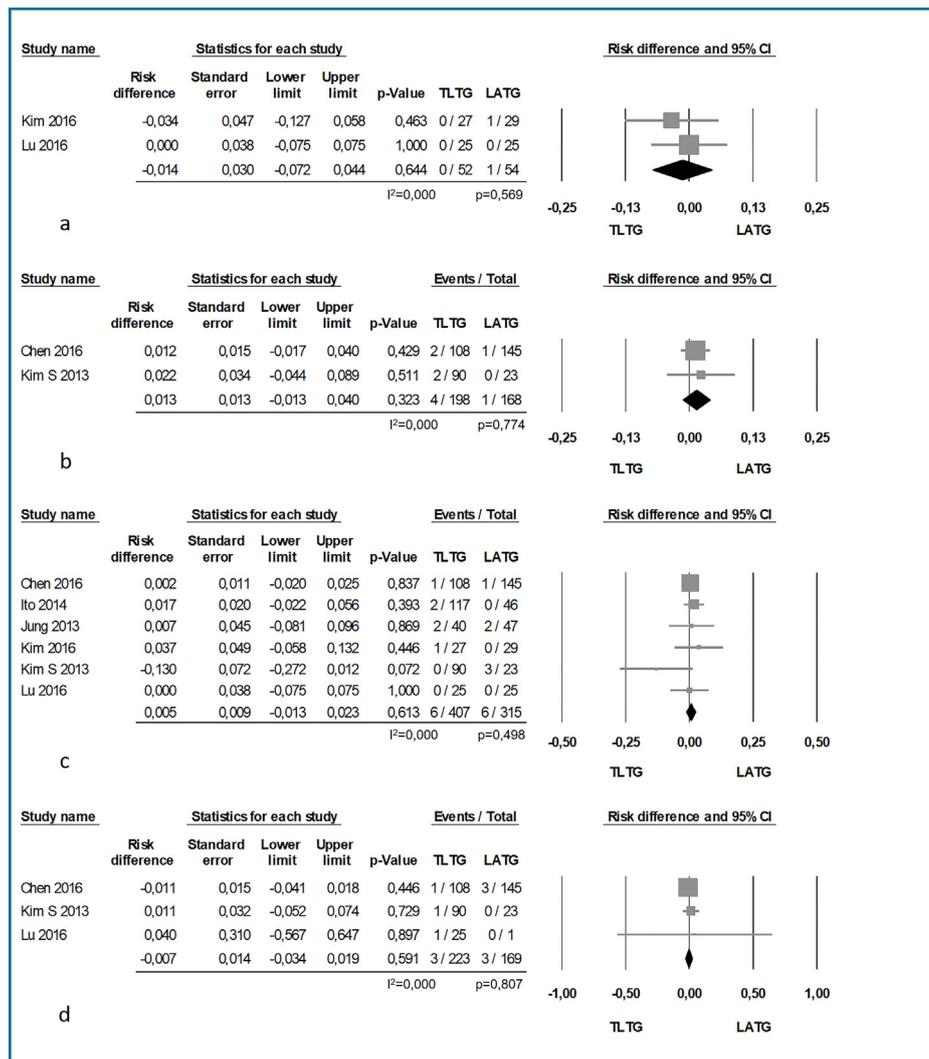
Figure 7. Postoperative complications after total gastrectomies. a: postoperative intraluminal bleeding; b: postoperative extraluminal bleeding; c: anastomotic leak; d: wound infection.

all cancer stages, especially in stage IV cancer where results were not different that those from other stages.

As a matter of fact, meta-analyses itself represents a good way to draw scientific conclusions about controversial subjects or about studies based on narrow sample sizes. However, it must be underlined that meta-analyses are a reflection from the literature and have the same limits. Inthe present meta-analysis, there is a huge lack of high-quality, well-designed randomized studies. Moreover, there is no clear definition of all the necessary outcomes to define advantages and limitations of the two techniques.

Considering the major complications evaluated in the analysed studies, IA seemed safe and feasible, although there was no clear definition of each outcome. For example, no author defined wound infection and only Shinohara et al. [21] defined anastomotic leak. The large heterogeneity frequently observed among studies also impact on results and on their interpretation. No study demonstrated a real benefit of AI comparing to EA in terms of oncological results. In the present meta-analysis, only the number of retrieved lymph nodes showed a statistically significant difference between the two groups in favour of the IA, even if lymphadenectomy is always intracorporeally performed in the two techniques.

Indeed, this meta-regression is a call for a high quality randomized controlled trial.

Another limitation of current literature is that Clavien-Dindo Score is almost never reported. In fact, it can be found in only 5 studies on distal gastrectomy [13,15,20,21,23] and in only two studies on total gastrectomy [29,31]. Even when reported, there is no accurate classification of Clavien-Dindo stages, especially stage I and II, that include nausea and vomiting with a major influence on recovery and hospital stay.

As expected, IA is associated with faster recovery IA, probably because of less traction of the viscera and a minor exposure of bowel to open air that can negatively influence the restart of the bowel function. Other parameters involved in postoperative recovery have been ignored in the studies selected for analysis, such as first mobilization and other perioperative measures that should be taken into account in the studies.

Finally, all the selected studies were from Asian countries, where this kind of surgery is performed in specialized centres, reaching high volumes of patients, making the results truthful only for very expert surgeons.

By pooling together 4540 patients with gastric cancer, we were able to state that IA is safe and feasible. A high
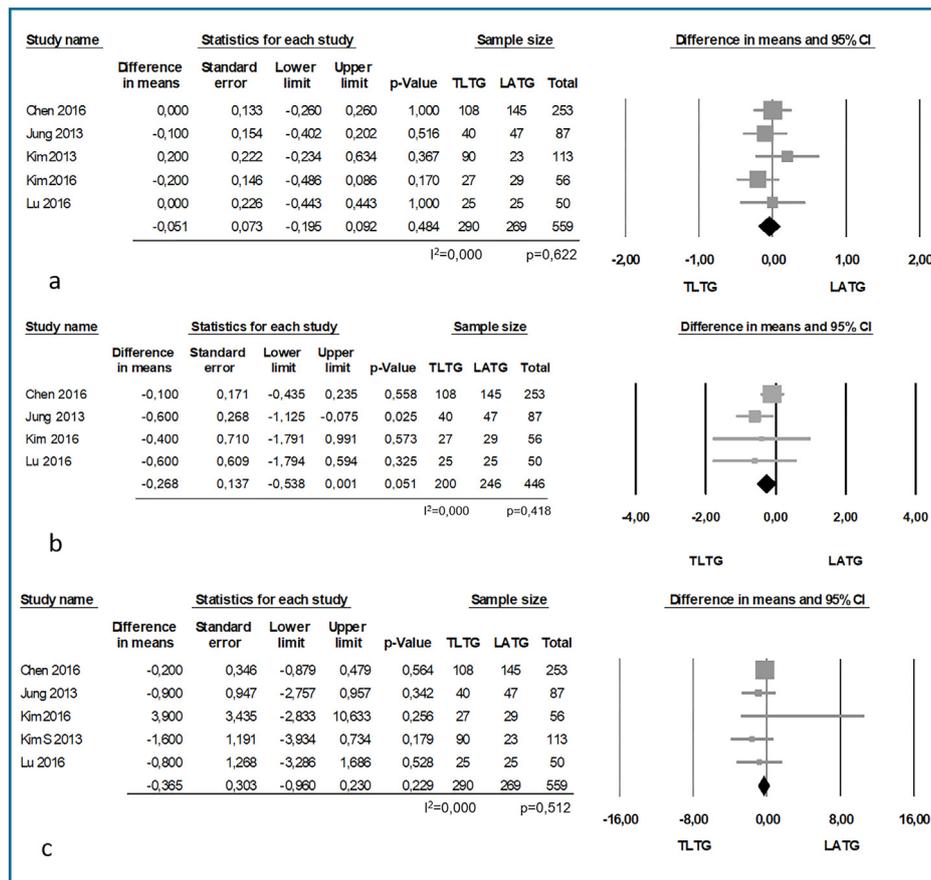
Figure 8. Postoperative recovery outcomes after total gastrectomies. a: time to first flatus; b: time to first oral intake; c: length of hospital stay.

quality randomized controlled trial in non-Asian countries comparing IA and EA is required.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/ j.jviscsurg.2019.01.004.

Disclosure of interest

The authors declare that they have no competing interest.

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