Comparison of Delta-Shape Anastomosis and Extracorporeal Billroth I Anastomosis after Laparoscopic Distal Gastrectomy for Gastric Cancer: A Systematic Review with Meta-Analysis of Short-Term Outcomes

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Abstract

Objective
The aim of this systematic review and meta-analysis is to evaluate the safety and relative benefits of delta-shape anastomosis (DA) by comparing to conventional laparoscopy-assisted distal gastrectomy with Billroth I gastroduodenostomy (LADG BI).

Methods
Studies and relevant literature regarding DA versus LADG BI were searched in the electronic databases. Operation time, postoperative complications, estimated blood loss, number of retrieved lymph nodes, time to first flatus, time to oral intake, length of postoperative hospitalization in DA and LADG BI were pooled and compared using meta-analysis. Weighted mean differences (WMDs) and odds ratios (ORs) were calculated with 95% confidence intervals (CIs) to evaluate the effect of DA.

Results
Eight studies of 1739 patients were included in the meta-analysis. Compared with LADG BI, DA had shorter postoperative hospitalization (WMD = -0.47, 95%CI: -0.69 to -0.25, P < 0.01), less blood loss (WMD = -25.90, 95%CI: -43.11 to -8.70, P < 0.01), shorter time to oral intake (WMD = -0.25, 95%CI: -0.49 to -0.01, P = 0.04), and more retrieved lymph nodes (WMD = 1.36, 95%CI: 0.30 to 2.43, P = 0.01). Operation time (WMD = -0.07, 95%CI -15.58 to 15.43, P = 0.99), overall postoperative complication rate (OR = 1.05, 95%CI: 0.74 to 1.49, P = 0.63), surgical complication rate (OR = 1.02, 95%CI: 0.70 to 1.49, P = 0.90), nonsurgical complication rate (OR = 1.21, 95%CI: 0.54 to 2.72, P = 0.64), leakage rate (OR = 2.54, 95%CI: 0.92 to 7.01, P = 0.07), stricture rate (OR = 0.36, 95%CI: 0.09 to 1.44, P = 0.15), wound complication rate (OR = 0.71, 95%CI: 0.33 to 1.55, P = 0.39), time to first flatus (WMD =
-0.10, 95%CI: -0.27 to 0.07, P = 0.26), and proximal surgical margin (WMD = -0.25, 95%CI: -1.14 to 0.65, P = 0.59) was not statistically different.

Conclusion
Compared with LADG BI, DA is a safe and feasible procedure, with significantly reduced blood loss, time to oral intake, and postoperative hospitalization.

Introduction
Radical gastrectomy remains the main management of gastric cancer. Three methods of gastrointestinal tract reconstruction, including the Billroth I (BI) gastroduodenostomy, Billroth II (BII) gastrojejunostomy and Roux-en-Y (R-Y) gastrojejunostomy, are commonly used after distal gastrectomy. Among these methods, the BI anastomosis is especially preferred due to technical simpleness and physiological advantages of allowing food to pass through the duodenum. Besides, postoperative endoscopic examination for biliary tract disorders after BI anastomosis is thought to be easier when compared with that after Billroth II or R-Y anastomosis.

Laparoscopic gastrectomy (LG) has gradually matured and been accepted as a notable alternative to open surgery in the management of gastric cancer [1–3]. More than 90% of patients with early gastric cancer can survive following laparoscopic radical gastrectomy [4–6]. For this population, more comfortable perioperative experience and better postoperative quality of life (QoL) are important goals as well. Usually, surgeons completed the lymph node dissection with laparoscopic techniques and performed gastrointestinal tract reconstruction through the mini-laparotomy, namely laparoscopy-assisted gastrectomy. Advancements in less invasive techniques are ongoing, and many surgeons are attempting to perform totally laparoscopic gastrectomy, which is expected to achieve less invasiveness and better postoperative QoL [7–9]. However, challenges lie in the intracorporeal hand-sewn technique. In 2002, Kanaya et al. described a novel technique named the delta-shaped anastomosis (DA) [10], which was derived from the application of the functional end-to-end technique[11]. The DA completes BI anastomosis just with laparoscopic linear staplers and greatly facilitates intracorporeal BI anastomosis, which gradually gained popularity in Japan, Korea and China [12–14]. Given the critical roles of anastomosis procedure on surgical outcomes, which were still unsettled in DA, we conducted this meta-analysis to clarify the safety and relative benefits of DA by comparing to LADG with Billroth I gastroduodenostomy (LADG BI).

Methods
Literature search
A systematic search was made using PubMed, ISI web of knowledge, Scopus and Embase, from January 2002 to March 2016, to retrieve all published articles comparing DA and LADG BI. The search term was (“delta-shaped anastomosis” or “intracorporeal Billroth I anastomosis”) and (“laparoscopic gastrectomy” or “minimally invasive gastrectomy”) and (“gastric cancer” or “gastric adenocarcinoma” or “gastric neoplasms”). The “related articles”, “similar articles” was also reviewed to broaden the search. The language of publications was restricted in English and Chinese.

Eligibility criteria
All the publications retrieved were included if they were 1) comparing DA with LADG BI; 2) reporting at least 20 patients in each study group; 3) investigating all the primary outcomes in
our standardized questionnaires; and 4) in the event that duplication of data was observed, more recent studies or those with larger sample sizes were preferentially considered. A manual search of the references of all retrieved articles was also carried out to identify publications for possible inclusion.

Exclusion criteria
The following studies or data were excluded: 1) Abstracts, letters, editorials, expert opinions, reviews without original data and case reports; 2) the outcomes and parameters of patients were not clearly reported; 3) it was impossible to extract the appropriate data of the primary outcomes from the published results; and 4) there was an overlap between authors or centers in the published literature.

Data extraction and synthesis
Two reviewers independently undertook literature searches, screened abstracts, and assessed articles met eligibility criteria. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Studies achieving six or more scores were considered to be of high quality and were included in the meta-analysis. Reviewers extracted the following parameters from each study: (1) author and study period; (2) study population characteristics, study design; (3) number of patients operated on with each technique; and (4) preoperative data, intraoperative data and postoperative data. Discrepancies between the two reviewers were resolved by discussion with all co-authors and consensus was reached.

Outcomes of interest
The following outcomes were used to compare the two operative techniques: (1) primary outcomes, which referred to operation time, postoperative stay, overall postoperative complication rate, surgical complication rate, nonsurgical complication rate, anastomotic leakage rate, anastomotic stricture rate, wound complications rate; (2) secondary outcomes, which included estimated blood loss (EBL), time to first flatus, time to oral intake earlier, number of retrieved lymph nodes and proximal surgical margins. The surgical and nonsurgical complication was defined as Jung et al. [15].

Statistical analysis
The meta-analysis was performed using the Review Manager software, version 5.3, provided by the Cochrane Collaboration (http://tech.cochrane.org/revman/download). We analyzed dichotomous variables using the estimation of odds ratios (ORs) with 95% confidence interval (95% CI) and continuous variables using weighted mean differences (WMDs) with a 95% CI. According to the Higgins I² statistic, heterogeneities <25%, 25% to 50%, and >50% were defined as low, moderate, and high, respectively [16]. A fixed-effects model was used for studies with low or moderate statistical heterogeneity [17]. Otherwise, a random-effects model was used for studies with high statistical heterogeneity [18]. A subgroup analysis of studies more than 50 cases in both DA and LADG BI was conducted. An estimate of potential publication bias was carried out using the funnel plot. P < 0.05 was considered statistically significant.

Result
Selected studies characteristics
After selection, eight studies were eventually included in our research [13,19–25] (Fig 1). In total, 755 patients treated with DA and 984 patients treated with LADG BI were included in the
analyses (Table 1). All the patients were from Eastern Asia, including Korea, Japan and China. The majority of patients underwent DA were with early gastric cancer (520 out of 755). All of the eight studies were retrospective, nonrandomized. All eight studies were considered to be of adequate quality for the meta-analysis according to NOS assessment (score > 5 points) (Table 2).

**Primary outcomes**

As showed in Fig 2, there was no significant difference between DA and LADG BI regarding the operation time (WMD = -0.07, 95%CI -15.58 to 15.43, P = 0.99). Patients underwent DA
had a shorter postoperative stay than those underwent LADG BI (WMD = -0.47, 95% CI: -0.69 to -0.25, \( P < 0.01 \)) (Fig 3). Sixty-seven out of 755 patients in the DA group and 86 out of 984 patients in LADG BI group had postoperative morbidities (Table 3). There was no significant difference between two groups (OR = 1.05, 95% CI: 0.74 to 1.49, \( P = 0.63 \)) (Fig 4A). The pooled effect showed no significant difference between DA and LADG BI in surgical complication.

### Table 1. Main characteristics of all studies included in the meta-analysis.

| Study            | Study period | Country | Study design | Group     | Case number | Mean age | Gender (M/F) | BMI | EGC/AGC  | Matching criteria |
|------------------|--------------|---------|--------------|-----------|-------------|----------|--------------|-----|----------|-------------------|
| Kinoshita et al. | 2007–2009    | Japan   | R            | DA        | 42          | 64.7     | 25/17        | 23.1 | 38/4     | abcdgh            |
|                  |              |         |              | LADG BI   | 41          | 68.4     | 30/11        | 22.8 | 37/4     |
| Kim MG et al.    | 2009–2010    | Korea   | R            | DA        | 239         | 56.6     | 155/84       | 24   | 204/35   | abfe              |
|                  |              |         |              | LADG BI   | 328         | 55.4     | 198/130      | 23.1 | 312/16   |
| Kim DG et al.    | 2009–2012    | Korea   | R            | DA        | 60          | 58.3     | 37/23        | 23.4 | 49/11    | abceg             |
|                  |              |         |              | LADG BI   | 106         | 55.8     | 69/37        | 23.1 | 90/16    |
| Wang et al.      | 2013–2014    | China   | R            | DA        | 50          | 64       | 34/16        | 23   | 9/41     | abceh             |
|                  |              |         |              | LADG BI   | 43          | 61.2     | 28/15        | 22.3 | 5/38     |
| Lee et al.       | 2004–2011    | Korea   | R            | DA        | 138         | 62.4     | 87/51        | 24.2 | 94/6     | dfgh              |
|                  |              |         |              | LADG BI   | 100         | 56       | 47/53        | 22.6 | 127/11   |
| Jeong et al.     | 2013–2014    | Korea   | R            | DA        | 42          | 58.4     | 22/20        | 24.8 | 42/0     | bcdfggh           |
|                  |              |         |              | LADG BI   | 179         | 62.7     | 114/65       | 24.1 | 167/12   |
| Lin et al.       | 2011–2014    | China   | R            | DA        | 143         | 60.1     | 100/43       | 22.3 | 48/95    | abcg              |
|                  |              |         |              | LADG BI   | 143         | 59.4     | 102/41       | 23.5 | 53/90    |
| Park et al.      | 2013–2014    | Korea   | R            | DA        | 41          | 61.7     | 23/18        | 24.3 | 36/5     | abcdfggh          |
|                  |              |         |              | LADG BI   | 44          | 62.2     | 24/20        | 23.4 | 42/2     |

M, male; F, female; EGC, early gastric cancer; AGC, advanced gastric cancer; R, retrospective; a, age; b, gender; c, BMI; d, comorbidity; e, ASA; f, tumor size; g, tumor stage; h, extend of lymph node dissection.

doi:10.1371/journal.pone.0162720.t001

### Table 2. Newcastle-Ottawa Scale assessment of pooled studies.

| Study     | Selection | Comparability | Outcomes | Total | Representativeness of exposed cohort | Selection of nonexposed cohort | Ascertainment of exposure | Outcome not present at the start of the study | Assessment of outcomes | Length of follow-up | Adequacy of follow-up |
|-----------|-----------|----------------|----------|-------|-------------------------------------|-------------------------------|---------------------------|-----------------------------------------------|------------------------|---------------------|-----------------------|
| Kinoshita et al. | *         | *              | *        | *     | *                                  | *                             | *                         | *                                             | *                      | *                   | *                     |
| Kim MG et al.   | *         | *              | *        | *     | *                                  | *                             | *                         | *                                             | *                      | *                   | *                     |
| Kim DG et al.   | *         | *              | *        | *     | *                                  | *                             | *                         | *                                             | *                      | *                   | *                     |
| Wang et al.     | *         | *              | *        | *     | *                                  | *                             | *                         | *                                             | *                      | *                   | *                     |
| Lee et al.      | *         | *              | *        | *     | *                                  | *                             | *                         | *                                             | *                      | *                   | *                     |
| Jeong et al.    | *         | *              | *        | *     | *                                  | *                             | *                         | *                                             | *                      | *                   | *                     |
| Lin et al.      | *         | *              | *        | *     | *                                  | *                             | *                         | *                                             | *                      | *                   | *                     |
| Park et al.     | *         | *              | *        | *     | *                                  | *                             | *                         | *                                             | *                      | *                   | *                     |

*, one score.

doi:10.1371/journal.pone.0162720.t002
rate (OR = 1.02, 95%CI: 0.70 to 1.49, P = 0.90) (Fig 4B) and nonsurgical complication rate (OR = 1.21, 95%CI: 0.54 to 2.72, P = 0.64) (Fig 4C). Regarding the anastomotic leakage, no statistically significant difference was observed (DA vs. LADG 10/755 vs. 5/984; OR = 2.54, 95%CI: 0.92 to 7.01, P = 0.07) (Fig 4D). Two out of 755 patients in the DA group and 6 out of 984 patients in the LADG BI group suffered anastomotic stricture with no significant difference between two groups (OR = 0.36, 95%CI: 0.09 to 1.44, P = 0.15) (Fig 4E). DA had similar wound complications rate compared with LADG BI (OR = 0.71, 95%CI: 0.33 to 1.55, P = 0.39) (Fig 4F).

Secondary outcomes

Secondary outcomes were summarized in Table 4 and Fig 5. Six out of the included studies reported EBL in both groups [13,19,21–24]. A significant reduction in blood loss was observed in the DA compared to LADG BI (WMD = -25.90, 95%CI: -43.11 to -8.70, P < 0.01).

As for the postoperative recovery, DA groups had similar time to first flatus (WMD = -0.10, 95%CI: -0.27 to 0.07, P = 0.26). Patients in the DA group started oral intake earlier than those in LADG BI group (WMD = -0.25, 95%CI: -0.49 to -0.01, P = 0.04).

DA retrieved more lymph nodes as compared with LADG BI (WMD = 1.36, 95%CI: 0.30 to 2.43, P = 0.01). Proximal surgical margins were equivalent between two groups (WMD = -0.25, 95%CI: -1.14 to 0.65, P = 0.59).

Nutritional status and postgastrectomy symptoms

Four pooled studies reported the postoperative nutritional status and postgastrectomy symptoms [13,19,22,25], as showed in Table 5. Lee et al. reported DA group had more food intake...
22]. Park et al. reported DA group maintained higher albumin postoperatively [25]. Kim et al. and Park et al. found more patients in the DA group suffered reflux [13,25]. No difference was revealed between the DA group and LADG BI group regarding nausea, dyspepsia, diarrhea and dumping syndrome.

**Subgroup analysis**

Subgroup analysis of the pooled studies was performed to evaluate whether the pooled primary outcomes and secondary outcomes altered in different case volume subgroup. Subgroup analysis regarding the surgical outcomes had similar results as above (Table 6).

**Publication bias**

A funnel plot was constructed for the overall postoperative complications and showed symmetry, suggesting that publication bias was acceptable and was unlikely to drive conclusions (Fig 6).

**Discussion**

Totally laparoscopic gastrectomy is increasingly used since its debut in 1992 [26]. Several meta-analyses hinted totally laparoscopic distal gastrectomy (TLDG), pooling miscellaneous intracorporeal anastomosis including DA, BII and R-Y, has equivalent feasibility and safety as LADG [27–29]. More importantly, TLDG is seemingly less invasive and more suitable for the obese than LADG. Potential heterogeneity arises from different intracorporeal anastomosis in

| Study               | Group | Case number | Complication                                                |
|---------------------|-------|-------------|-------------------------------------------------------------|
| Kinoshita et al     | DA    | 42          | Intra-abdominal abscess×2, Wound complications×2, Others×2 |
| LADG BI             |       |             | Anastomotic stenosis×1, Bleeding×1, Intra-abdominal abscess×1, Wound complications×2, Others×1 |
| Kim MG et al        | DA    | 239         | Anastomotic leakage×1, Bleeding×2, Intra-abdominal abscess×3 Wound complications×2, Others×1 |
| LADG BI             |       | 328         | Anastomotic leakage×2, Anastomotic stenosis×1, Bleeding×3, Intra-abdominal abscess×4, Wound complications×11 |
| Kim DG et al        | DA    | 60          | Anastomotic leakage×1, Delayed gastric emptying×2, Intra-abdominal abscess×2, Wound complications×2, Others×1 |
| LADG BI             |       | 106         | Anastomotic leakage×1, Intra-abdominal abscess×4, Others×1 |
| Wang et al          | DA    | 50          | Delayed gastric emptying×1, Others×2                         |
| LADG BI             |       | 43          | Bleeding×1, Others×3                                        |
| Lee et al           | DA    | 138         | Anastomotic leakage×2, Anastomotic stenosis×2, Bleeding×1, Wound complications×1, Others×4 |
| LADG BI             |       | 100         | Anastomotic stenosis×4, Wound complications×2, Others×1     |
| Jeong et al         | DA    | 42          | Bleeding×1, Delayed gastric emptying×1, Wound complications×1 |
| LADG BI             |       | 179         | Anastomotic leakage×2, Anastomotic stenosis×1, Bleeding×3, Intra-abdominal abscess×4, Wound complications×11 |
| Lin et al           | DA    | 143         | Anastomotic leakage×5, Bleeding×1, Delayed gastric emptying×1, Intra-abdominal abscess×3, Others×12 |
| LADG BI             |       | 143         | Bleeding×2, Delayed gastric emptying×1, Intra-abdominal abscess×3, Others×8 |
| Park et al          | DA    | 41          | Anastomotic leakage×1, Wound complications×1, Others×3      |
| LADG BI             |       | 44          | Anastomotic leakage×1, Intra-abdominal abscess×1, Others×2 |

doi:10.1371/journal.pone.0162720.t003
### A Meta-Analysis Comparing Delta-Shape Anastomosis and Extracorporeal Billroth I Anastomosis

| Study/Year | Events | Total | Weight | Odds Ratio | % 95% CI |
|------------|--------|-------|--------|------------|---------|
| Overall    |        |       |        |            |         |
|            |        |       |        |            |         |

#### Results
- **Total events:** 97
- **Heterogeneity:** Chi² = 7.80, df = 7 (P = 0.33), I² = 9%  
- **Test for overall effect:** Z = 2.39, P = 0.01

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### Table B

| Study/Year | Events | Total | Weight | Odds Ratio | % 95% CI |
|------------|--------|-------|--------|------------|---------|
| Overall    |        |       |        |            |         |
|            |        |       |        |            |         |

#### Results
- **Total events:** 50
- **Heterogeneity:** Chi² = 7.00, df = 7 (P = 0.33), I² = 9%  
- **Test for overall effect:** Z = 2.39, P = 0.01

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### Table C

| Study/Year | Events | Total | Weight | Odds Ratio | % 95% CI |
|------------|--------|-------|--------|------------|---------|
| Overall    |        |       |        |            |         |
|            |        |       |        |            |         |

#### Results
- **Total events:** 12
- **Heterogeneity:** Chi² = 7.00, df = 7 (P = 0.33), I² = 9%  
- **Test for overall effect:** Z = 2.39, P = 0.01

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### Table D

| Study/Year | Events | Total | Weight | Odds Ratio | % 95% CI |
|------------|--------|-------|--------|------------|---------|
| Overall    |        |       |        |            |         |
|            |        |       |        |            |         |

#### Results
- **Total events:** 10
- **Heterogeneity:** Chi² = 7.00, df = 7 (P = 0.33), I² = 9%  
- **Test for overall effect:** Z = 2.39, P = 0.01

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### Table E

| Study/Year | Events | Total | Weight | Odds Ratio | % 95% CI |
|------------|--------|-------|--------|------------|---------|
| Overall    |        |       |        |            |         |
|            |        |       |        |            |         |

#### Results
- **Total events:** 2
- **Heterogeneity:** Chi² = 7.00, df = 7 (P = 0.33), I² = 9%  
- **Test for overall effect:** Z = 2.39, P = 0.01

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### Table F

| Study/Year | Events | Total | Weight | Odds Ratio | % 95% CI |
|------------|--------|-------|--------|------------|---------|
| Overall    |        |       |        |            |         |
|            |        |       |        |            |         |

#### Results
- **Total events:** 10
- **Heterogeneity:** Chi² = 7.00, df = 7 (P = 0.33), I² = 9%  
- **Test for overall effect:** Z = 2.39, P = 0.01

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PLOS ONE | DOI:10.1371/journal.pone.0162720 September 15, 2016 8 / 16
these studies and obscures the veritable efficacy of each method. To obtain a more reliable comparison on the feasible and safety of DA, we conducted this systematic review and meta-analysis of published articles that directly compared the DA with LADG BI.

There is no consensus on the indications of DA yet. The decision of DA usually resides with surgeons’ or patients’ preferences [13,20,23]. DA was mostly applied in early gastric cancer (EGC) located in the low third stomach, which combined indications of LG and conventional BI anastomosis [23,25]. Indications were also expanded to locally advanced gastric cancers (AGC) along with the accumulating surgeons’ experiences [20,21,24]. Remarkably, radical treatment of AGC usually requires longer surgical margin than EGC, which increases the anastomosis tension and results in related complications. Lin et al. reported patients with AGC underwent DA had a higher risk of anastomotic leakage [24]. Identifying the lesion precisely during the operation and achievement of enough surgical margin is crucial in deciding the methods of anastomosis. Distinguishing from LADG BI, DA is deficient with tactility in detecting the lesion of EGC merely by the laparoscopic grasper. Preoperative or intraoperative endoscopy is quite practical to mark the lesion as recommended by quite a few of surgeons [19,20].

Prolonged operation time is a common concern of laparoscopic surgery. Our meta-analysis revealed DA wasn’t inferior to LADG BI in this outcome. By using the liner stapler, DA has much saved the anastomosis time as well as the total operation time. In experienced hands, the operation time of LG with DA can be shorter than open gastrectomy and laparoscopy-assisted gastrectomy [13,20,23,24,30]. But this doesn’t mean the DA is easy. Conversely, coordination between the surgeon and assistants is especially technically demanding. During joining the posterior walls of duodenum and stomach together, appropriate traction by the assistant is of great importance. Given the majority of studies included in our meta-analysis were conducted by surgeons well-trained in LG, or even in DA, outcomes may be discrepant in the non-specially trained surgeons. Kanaya et al. and Jeong et al. revealed the learning curve of DA was quite steep for laparoscopic surgeons [23,30]. After around 10~15 cases, time of completing DA would reach a plateau and maintain in 10~25 min.

Comparing with LADG BI, the potential benefits of DA are better cosmesis, less blood loss and less postoperative pain. Usually, the surgical incision in LADG BI is longer than DA. By hiding the largest surgical incision around the umbilicus, patients undergo DA appears to be scarless. Avoiding the mini-laparotomy for gastrointestinal anastomosis, DA is totally intracorporeal and more tense-free, which reduces the risk of injury around the anastomosis. These characteristics of DA contribute to less intraoperative blood loss, less postoperative pain and more comfortable experience presenting as lower pain score and less administration of

Table 4. Meta-analyses results for DA vs. LADG BI.

| Outcomes                  | Pooled studies | Sample size | Pooled effect | Pooled estimates | 95% CI     | P value | I²     |
|---------------------------|----------------|-------------|---------------|------------------|------------|---------|--------|
| EBL                       | 6              | 1087        | Random        | WMD -25.90       | -43.11, -8.70 | <0.01   | 83%    |
| Time to first flatus      | 7              | 1654        | Random        | WMD -0.10        | -0.27, 0.07  | 0.26    | 71%    |
| Time to first oral taking | 6              | 1561        | Fixed         | WMD -0.25        | -0.49, -0.01 | 0.04    | 60%    |
| Retrieved lymph nodes     | 7              | 1573        | Fixed         | WMD 1.36         | 0.30, 2.43  | 0.01    | 45%    |
| Proximal surgical margin  | 4              | 1111        | Random        | WMD -0.25        | -1.14, 0.65  | 0.59    | 86%    |

EBL, estimated blood loss; WMD, weighted mean difference; OR, odds ratio.

doi:10.1371/journal.pone.0162720.t004
Fig 5. Forest plots of secondary outcomes, DA vs. LADG BI. (A) EBL, (B) time to first flatus, (C) time to first oral taking, (D) number of retrieved lymph nodes, and (E) proximal surgical margin.

doi:10.1371/journal.pone.0162720.g005
analgesics. In the studies by Kim et al. and Wang et al., postoperative pain score was significantly lower in DA than in the LADG BI[20,21]. Kinoshita et al. reported the acute inflammatory response following operation was milder in DA with a placid elevation of C-reactive protein [19]. In the present study, data from pooled studies were insufficient to evaluate the postoperative pain and acute inflammatory response. The evaluation of these parameters after DA will be sufficiently assessed by prospective RCTs only.

Acceptable postoperative complication of DA was observed in the present study, which was equivalent to LADG BI and even lower than open distal gastrectomy as historical reports [31,32]. Anastomosis-related complication such as leakage and stricture can be disastrous. There was a higher leakage rate in DA (DA vs. LADG BI, 10/755 vs.5/984), but it did not achieve a significant statistical difference. Kim et al. proposed mobilization of the duodenum until the gastroduodenal artery exposure to make sufficient duodenal stump, which eased the tension of anastomosis and might reduce the risk of anastomotic leakage [20]. DA contained several cutting edges, which may cause poor blood supply, yield more weak points around the anastomosis and result in leakage. Huang et al. modified the DA by resection the intersection of the duodenal cutting edge and the common closed edge at the same time to lessen the anastomotic weak point [33,34]. In contrast to leakage, DA group has less anastomotic stricture (2/755 vs.6/984). In LADG BI the size of anastomosis ring depends on the diameter of the circular stapler, while a large anastomosis ring can be easily achieved with the 45-mm linear stapler in DA. However, we should also admit the fact that the sample size was still too small to reveal the real benefits and drawbacks of DA because of the low risk of anastomotic leakage and stricture as reported.

Milder surgical trauma and comparable postoperative morbidity brought substantial clinical superiority. Patients in the DA group were able to resume oral intake earlier and have a shorter length of hospitalization, which could counteract the higher expense of DA technique itself. Enhanced recovery program was also applied in some included studies, which emphasized earlier oral intake and might contribute to these advantages of DA in some degrees. Apart from this, LADG BI had more severe complications demanded reoperation or other interventions, which postponed the discharge.

An unexpected result of our study was that the DA retrieved more lymph nodes than LADG BI. It didn’t mean the DA was superior to LADG BI in lymphadenectomy because this

Table 5. details of postoperative nutritional status and postgastrectomy symptoms.

| Study        | Length of follow-up | Nutritional status | Total lymphocyte count | Assessment terms of gastrointestinal symptoms | Postgastrectomy symptoms |
|--------------|---------------------|--------------------|------------------------|-----------------------------------------------|--------------------------|
|              | Food intake | Body weight | Serum albumin | Total cholesterol | Reflux | Nausea | Dyspepsia | Diarrhea | Dumping syndrome |
| Kinoshita et al. | 3 months     | NS               | NS           | NS                   | questionnaire | NS | NS | NS | NS |
| Kim DG et al. | 3 months     | NS               | NS           | NS                   | questionnaire | NS | NS | NS | NS |
| Lee et al.   | 46 months (mean)| NS               | NS           | NS                   | questionnaire and endoscopy examination | NS | NS | NS | NS |
| Park et al.  | 1 year       | NS               | NS           | NS                   | questionnaire | NS | NS | NS | NS |

NS, no significance; †, worse; ††, better.

doi:10.1371/journal.pone.0162720.t005
procedure is supposed to be identical for both approaches. We deemed surgeons’ experience played an important role as the majority of surgeons converted to DA after they had matured LADG BI [13,19]. Both DA and LADG BI achieved proximal resection margins more than 3cm that was believed to improve oncological outcomes[35]. Pooled analysis also demonstrated these two approaches achieved similar proximal surgical margins and overall survival rate.

Table 6. Subgroup analyses results for DA vs. LADG BI.

| Outcomes                           | Pooled studies | Sample size | Pooled estimates | 95% CI          | P value |
|------------------------------------|----------------|-------------|------------------|-----------------|---------|
| Operation time                     | 8              | 1739        | WMD -0.07        | -15.58, 15.43   | 0.99    |
| <50 cases                          | 4              | 482         | WMD 2.01         | -19.32, 23.34   | 0.85    |
| >50 cases                          | 4              | 1257        | WMD -2.43        | -30.81, 25.96   | 0.87    |
| Length of hospitalization          | 8              | 1739        | WMD -0.47        | -0.69, -0.25    | <0.01   |
| ≤50 cases                          | 4              | 482         | WMD -0.94        | -0.60, -0.10    | <0.01   |
| >50 cases                          | 4              | 1257        | WMD -0.35        | -1.44, -0.44    | <0.01   |
| Overall postoperative complication | 8              | 1739        | OR 1.05          | 0.74, 1.49      | 0.78    |
| ≤50 cases                          | 4              | 482         | OR 1.05          | 0.41, 1.50      | 0.46    |
| >50 cases                          | 4              | 1257        | OR 1.19          | 0.78, 1.81      | 0.41    |
| Surgical complication              | 8              | 1739        | OR 1.21          | 0.54, 2.72      | 0.64    |
| ≤50 cases                          | 4              | 482         | OR 1.01          | 0.24, 4.25      | 0.99    |
| >50 cases                          | 4              | 1257        | OR 1.32          | 0.49, 3.52      | 0.58    |
| Nonsurgical complication           | 8              | 1739        | OR 1.02          | 0.70, 1.49      | 0.90    |
| ≤50 cases                          | 4              | 482         | OR 0.78          | 0.38, 1.57      | 0.48    |
| >50 cases                          | 4              | 1257        | OR 1.15          | 0.73, 1.81      | 0.54    |
| Anastomotic leakage                | 8              | 1739        | OR 2.54          | 0.92, 7.01      | 0.07    |
| ≤50 cases                          | 4              | 482         | OR 1.64          | 0.22, 12.16     | 0.63    |
| >50 cases                          | 4              | 1257        | OR 2.90          | 0.87, 9.66      | 0.08    |
| Anastomotic stricture              | 8              | 1739        | OR 0.36          | 0.09, 1.44      | 0.15    |
| ≤50 cases                          | 4              | 482         | OR 0.32          | 0.01, 0.83      | 0.49    |
| >50 cases                          | 4              | 1257        | OR 0.38          | 0.08, 1.71      | 0.21    |
| Wound complication                 | 8              | 1739        | OR 0.71          | 0.33, 1.55      | 0.39    |
| ≤50 cases                          | 4              | 482         | OR 1.29          | 0.35, 4.77      | 0.70    |
| >50 cases                          | 4              | 1257        | OR 0.53          | 0.20, 1.41      | 0.20    |
| EBL                                | 6              | 1087        | WMD -25.90       | -43.11, -8.70   | <0.01   |
| ≤50 cases                          | 3              | 397         | WMD -34.72       | -67.60, -1.85   | 0.04    |
| >50 cases                          | 3              | 690         | WMD -13.89       | -25.51, -2.27   | 0.02    |
| Time to first flatus               | 7              | 1654        | WMD -0.10        | -0.27, 0.07     | 0.26    |
| ≤50 cases                          | 3              | 397         | WMD -0.20        | -0.45, 0.04     | 0.11    |
| >50 cases                          | 4              | 1257        | WMD -0.03        | -0.28, 0.21     | 0.8     |
| Time to first oral taking          | 6              | 1561        | WMD -0.25        | -0.49, -0.01    | 0.04    |
| ≤50 cases                          | 2              | 304         | WMD -0.48        | -0.75, -0.21    | <0.01   |
| >50 cases                          | 4              | 1257        | WMD -0.12        | -0.47, 0.23     | 0.51    |
| Retrieved lymph nodes              | 7              | 1573        | WMD 1.36         | 0.30, 2.43      | 0.01    |
| ≤50 cases                          | 4              | 482         | WMD -0.13        | -1.74, 1.49     | 0.88    |
| >50 cases                          | 3              | 1091        | WMD 2.50         | 1.09, 3.92      | <0.01   |
| Proximal surgical margin           | 4              | 1111        | WMD -0.25        | -1.14, 0.65     | 0.59    |
| ≤50 cases                          | 2              | 306         | WMD -0.91        | -2.87, 1.05     | 0.37    |
| >50 cases                          | 2              | 805         | WMD 0.26         | -0.71, 1.24     | 0.60    |

EBL, estimated blood loss; WMD, weighted mean difference; OR, odds ratio.

doi:10.1371/journal.pone.0162720.t006
Large anastomotic ring and straightforward passageway from the esophagus to the duodenum allow fast gastric emptying and permit more food intakes. More food intake and better nutritional status was observed in DA group during long-term follow-up [22]. Clinically significant postgastrectomy symptoms will deteriorate postoperative QoL. Without the barrier of the pylorus, large anastomosis ring of DA has the concern of reflux gastritis, which makes patients uncomfortable and increases in risk of gastric remnant cancer [36–38]. Against with this hypothesis, several studies reported the rate of reflux gastritis after DA was acceptable and comparable with conventional LADG BI and R-Y. Both Kanaya et al. and Lee et al. reported DA had a prevalence of bile reflux but was not a clinical problem [22,30]. Other symptoms are also concerned. Twisting duodenum after DA appears to cause gastric stasis and gastroesophageal reflux. On the other hand, twisting duodenum happened to ward off dumping syndrome in some degree. According to the follow-up result, DA had a similar risk of these symptoms as LADG BI as showed in Table 4.

This meta-analysis had several limitations which should be taken into consideration in interpreting the conclusions of this study. First, this meta-analysis pooled eight retrospective studies which may bias the interpretation of their results. Though well-designed randomized clinical trials are suitable for meta-analysis, RCTs on this issue are rarely conducted because of ethical concern or practical difficulty. Nevertheless, all eight pooled studies were of high quality according to the NOS. Abraham et al. have found that meta-analysis of the well-designed non-randomized clinical trial of surgical procedures was probably as accurate as that of RCTs [39]. Second, case volumes of the included studies varied greatly, which may lead to heterogeneity among studies. In such a case, comparisons of surgical results would be influenced by surgeons’ experience. Third, DA and LADG BI were performed in different periods, from 2004–2014. Due to the development of laparoscopic instruments, perioperative management protocol and
surgeons’ surgical techniques, the clinical outcomes varied and may result in biases. Fourth, long-term functional outcomes in terms of nutritional status and postgastrectomy symptoms weren’t directly compared in the present meta-analysis because four pooled studies report using inconsistent assessment scales with different follow-ups. Furthermore, our study was based on studies conducted in East Asia which should extrapolate these data to the Western population prudently, in where the patient population and disease biology may differ [40,41].

**Conclusion**

Our study suggests that the DA is a safe and feasible procedure as compared with LADG BI. DA broadens the options of gastrointestinal reconstruction following laparoscopic distal gastrectomy and might bring more minimally invasive benefits and better postoperative nutritional status. However, well designed large-scaled studies which balance the baseline of each arm are needed for further confirming the real benefits of DA.

**Supporting Information**

S1 Text. PRISMA Checklist. (DOC)

S2 Text. Search Strategy. (DOC)

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**References**

1. Kim HH, Han SU, Kim MC, Hyung WJ, Kim W, Lee HJ, et al. Long-term results of laparoscopic gastrectomy for gastric cancer: a large-scale case-control and case-matched Korean multicenter study. J Clin Oncol. 2014; 32: 627–633. doi: 10.1200/JCO.2013.48.8551 PMID: 24470012

2. Hu Y, Ying M, Huang C, Wei H, Jiang Z, Peng X, et al. Oncologic outcomes of laparoscopy-assisted gastrectomy for advanced gastric cancer: a large-scale multicenter retrospective cohort study from China. Surg Endosc. 2014; 28: 2048–2056. doi: 10.1007/s00464-014-3426-9 PMID: 24651893
1. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011; 14: 101–112. doi: 10.1007/s10120-011-0041-5 PMID: 21573743

2. Park YS, Son SY, Oo AM, Jung DH, Shin DJ, Ahn SH, et al. Eleven-year experience with 3000 cases of laparoscopic gastric cancer surgery in a single institution: analysis of postoperative morbidities and long-term oncologic outcomes. Surg Endosc. 2015:

3. Sugita H, Kojima K, Inokuchi M, Kato K. Long-term outcomes of laparoscopic gastrectomy for gastric cancer. J Surg Res. 2015; 193: 190–195. doi: 10.1016/j.jss.2014.07.040 PMID: 25193579

4. Maruyama K, Kato H. Surgical treatment of gastric cancer in Japan, trend from standardization to individualization. Chirurgia (Bucur). 2014; 109: 722–730.

5. Lee SH, Kim IH, Kim IH, Kwak SG, Chae HD. Comparison of short-term outcomes and acute inflammatory response between laparoscopic-assisted and totally laparoscopic distal gastrectomy for early gastric cancer. Ann Surg Treat Res. 2015; 89: 176–182. doi: 10.4174/asatr.2015.89.4.176 PMID: 26446446

6. Umemura A, Koeda K, Sasaki A, Fujiwara H, Kimura Y, Iwaya T, et al. Totally laparoscopic total gastrectomy for gastric cancer: literature review and comparison of the procedure of esophageojunostomy. Asian J Surg. 2015; 38: 102–112. doi: 10.1016/j.asjsur.2014.09.006 PMID: 25458736

7. Jin Y, Yoon JH, Kim JM, Park J, Song WS, et al. Comparison of the cost and outcomes following totally laparoscopic and laparoscopic-assisted distal gastrectomies for gastric cancer: a single-institution comparison. Surg Endosc. 2015:

8. Kanaya S, Gomi T, Momoi H, Katayama T, et al. Delta-shapped anastomosis in totally laparoscopic Billroth I gastrectomy: new technique of intraabdominal gastroduodenostomy. J Am Coll Surg. 2002; 195: 284–287. PMID: 12168979

9. Steichen FM. The use of staples in anatomical side-to-side and functional end-to-end enterostomies. Surgery. 1968; 64: 948–953. PMID: 5687844

10. Huang C, Lin M, Chen Q, Lin J, Zheng C, Li P, et al. A modified intracorporeal billroth-I anastomosis after laparoscopic distal gastrectomy for gastric cancer: a safe and feasible technique. Annals of surgical oncology. 2015; 22: 247. doi: 10.1245/s10434-014-3862-8 PMID: 24969440

11. Kim DG, Choi YY, An JY, Kwon IG, Cho I, Kim YM, et al. Comparing the short-term outcomes of totally intracorporeal gastroduodenostomy with extracorporeal gastroduodenostomy after laparoscopic distal gastrectomy for gastric cancer: a single surgeon's experience and a rapid systematic review with meta-analysis. Surg Endosc. 2013; 27: 3153–3161. doi: 10.1007/s00464-013-2869-8 PMID: 23494509

12. Kitagami H, Morimoto M, Nozawa M, Nakamura K, Tanimura S, Murakawa K, et al. Evaluation of the delta-shaped anastomosis in laparoscopic distal gastrectomy: midterm results of a comparison with Roux-en-Y anastomosis. Surg Endosc. 2014; 28: 2137–2144. doi: 10.1007/s00464-014-3445-6 PMID: 24515263

13. Jung MR, Park YK, Seon JW, Kim KY, Cheong O, Ryu SY. Definition and classification of complications of gastrectomy for gastric cancer based on the accordion severity grading system. World J Surg. 2012; 36: 2400–2411. doi: 10.1007/s00268-012-1693-y PMID: 22752074

14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557–560. PMID: 12958120

15. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959; 22: 719–748. PMID: 13655060

16. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177–188. PMID: 3802833

17. Kinoshita T, Shibasaki H, Oshiro T, Ooshimi M, Okazumi S, Katoh R. Comparison of laparoscopy-assisted and total laparoscopic Billroth-I gastrectomy for gastric cancer: a report of short-term outcomes. Surg Endosc. 2011; 25: 1395–1401. doi: 10.1007/s00464-010-1402-6 PMID: 20972584

18. Kim MG, Kawada H, Kim BS, Kim TH, Kim KC, Yook JH, et al. A totally laparoscopic distal gastrectomy with gastroduodenostomy (TLDG) for improvement of the early surgical outcomes in high BMI patients. Surg Endosc. 2011; 25: 1076–1082. doi: 10.1007/s00464-010-1319-0 PMID: 20835726

19. Wang N, Qiao Q, Wu T, Bao G, Zheng B, Zhou S, et al. Application study of totally laparoscopic distal gastrectomy with delta-shaped anastomosis. Zhonghua Wei Chang Wai Ke Za Zhi. 2014; 17: 1111–1114. PMID: 25421771

20. Lee HH, Song KY, Lee JS, Park SM, Kim JJ. Delta-shaped anastomosis, a good substitute for conventional Billroth I technique with comparable long-term functional outcome in totally laparoscopic distal gastrectomy. Surg Endosc. 2015; 29: 2545–2552. doi: 10.1007/s00464-014-3966-z PMID: 25427413

21. Jeong O, Jung MR, Park YK, Ryu SY. Safety and feasibility during the initial learning process of intracorporeal Billroth I (delta-shaped) anastomosis for laparoscopic distal gastrectomy. Surg Endosc. 2015; 29: 1522–1529. doi: 10.1007/s00464-014-3836-8 PMID: 25294524
24. Lin M, Zheng CH, Huang CM, Li P, Xie JW, Wang JB, et al. Totally laparoscopic versus laparoscopy-assisted Billroth-I anastomosis for gastric cancer: a case-control and case-matched study. Surg Endosc. 2016.

25. Park KB, Kwon OK, Yu W, Jang BC. Body composition changes after totally laparoscopic distal gastrectomy with delta-shaped anastomosis: a comparison with conventional Billroth I anastomosis. Surg Endosc. 2016.

26. Goh P, Tekant Y, Isaac J, Kum CK, Ngoi SS. The technique of laparoscopic Billroth II gastrectomy. Surg Laparosc Endosc. 1992; 2: 258–260. PMID: 1341542

27. Chen K, Mou YP, Xu XW, Pan Y, Zhou YC, Cai JQ, et al. Comparison of short-term surgical outcomes between totally laparoscopic and laparoscopic-assisted distal gastrectomy for gastric cancer: a 10-year single-center experience with meta-analysis. J Surg Res. 2015; 194: 367–374. doi: 10.1016/j.jsr.2014.10.020 PMID: 25488721

28. Gao J, Li P, Li QG, Chen J, Wang DR, Tang D. Comparison between totally laparoscopic and laparoscopically assisted distal gastrectomy for gastric cancer with a short follow-up: a meta-analysis. J Laparoendosc Adv Surg Tech A. 2013; 23: 693–697. doi: 10.1089/la.p.2012.0580 PMID: 23678885

29. Zhang YX, Wu YJ, Lu GW, Xia MM. Systematic review and meta-analysis of totally laparoscopic versus laparoscopic assisted distal gastrectomy for gastric cancer. World J Surg Oncol. 2015; 13: 116. doi: 10.1186/s12957-015-0532-7 PMID: 25889971

30. Kanaya S, Kawamura Y, Kawada H, Iwasaki H, Gomi T, Satoh S, et al. The delta-shaped anastomosis in laparoscopic distal gastrectomy: analysis of the initial 100 consecutive procedures of intracorporeal gastroduodenostomy. Gastric Cancer. 2011; 14: 365–371. doi: 10.1007/s10120-011-0054-0 PMID: 21573920

31. Kubota T, Hiki N, Sano T, Nomura S, Nunobe S, Kumagai K, et al. Prognostic significance of complications after curative surgery for gastric cancer. Ann Surg. 2014; 260: 429–434. doi: 10.1097/SLA.0b013e31829e8c89

32. Zhou J, Yu P, Shi Y, Tang B, Hao Y, Zhao Y, et al. Evaluation of Clavien-Dindo classification in patients undergoing total gastrectomy for gastric cancer. Ann Surg Oncol. 2014; 21: 891–898. doi: 10.1245/s10434-013-3384-9 PMID: 25788033

33. Huang C, Lin M, Chen Q, Lin J, Zheng C, Li P, et al. A modified delta-shaped gastroduodenostomy in totally laparoscopic distal gastrectomy for gastric cancer: a safe and feasible technique. PLoS One. 2014; 9: e102736. doi: 10.1371/journal.pone.0102736 PMID: 25019646

34. Huang CM, Lin M, Lin JX, Zheng CH, Li P, Xie JW, et al. Comparison of modified and conventional delta-shaped gastroduodenostomy in totally laparoscopic surgery. World J Gastroenterol. 2014; 20: 10478–10485. doi: 10.3748/wjg.v20.i30.10478 PMID: 25132765

35. Postlewait LM, Maithel SK. The importance of surgical margins in gastric cancer. J Surg Oncol. 2016; 113: 277–282. doi: 10.1002/jso.24110 PMID: 26662226

36. Takeno S, Noguchi T, Kimura Y, Fujiwara S, Kubo N, Kawahara K. Early and late gastric cancer arising in the remnant stomach after distal gastrectomy. Eur J Surg Oncol. 2006; 32: 1191–1194. PMID: 16797159

37. Ahn HS, Kim JW, Yoo MW, Park do J, Lee HJ, Lee KU, et al. Clinicopathological features and surgical outcomes of patients with remnant gastric cancer after a distal gastrectomy. Ann Surg Oncol. 2008; 15: 1832–1839. doi: 10.1245/s10434-008-9817-8 PMID: 18379851

38. Sinning C, Schaerfer N, Standop J, Hirner A, Wolff M. Gastric stump carcinoma—epidemiology and current concepts in pathogenesis and treatment. Eur J Surg Oncol. 2007; 33: 133–139. PMID: 17071041

39. Abraham NS, Byrne CJ, Young JM, Solomon MJ. Meta-analysis of well-designed nonrandomized comparative studies of surgical procedures as good as randomized controlled trials. J Clin Epidemiol. 2010; 63: 238–245. doi: 10.1016/j.jclinepi.2009.04.005 PMID: 19716267

40. Strong VE, Song KY, Park CH, Jacks LM, Gonen M, Shah M, et al. Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. Ann Surg. 2010; 251: 640–646. doi: 10.1097/SLA.0b013e3181d3d29b PMID: 20224369

41. Bamboat ZM, Strong VE. Minimally invasive surgery for gastric cancer. J Surg Oncol. 2013; 107: 271–276. doi: 10.1002/jso.23237 PMID: 22903454