Efficacy Evaluation of Subtotal and Total Gastrectomies in Robotic Surgery for Gastric Cancer Compared with that in Open and Laparoscopic Resections: A Meta-Analysis



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Abstract

Purposes: Robotic gastrectomy (RG), as an innovation of minimally invasive surgical method, is developing rapidly for gastric cancer. But there is still no consensus on its comparative merit in either subtotal or total gastrectomy compared with laparoscopic and open resections.

Methods: Literature searches of PubMed, Embase and Cochrane Library were performed. We combined the data of four studies for RG *versus* open gastrectomy (OG), and 11 studies for robotic RG *versus* laparoscopic gastrectomy (LG). Moreover, subgroup analyses of subtotal and total gastrectomies were performed in both RG *vs.* OG and RG *vs.* LG.

Results: Totally 12 studies involving 8493 patients met the criteria. RG, similar with LG, significantly reduced the intraoperative blood loss than OG. But the duration of surgery is longer in RG than in both OG and LG. The number of lymph nodes retrieved in RG was close to that in OG and LG (WMD = -0.78 and 95% CI, -2.15-0.59; WMD = 0.63 and 95% CI, -2.24-3.51). And RG did not increase morbidity and mortality in comparison with OG and LG (OR = 0.92 and 95% CI, 0.69-1.23; OR = 0.72 and 95% CI, 0.25-2.06) and (OR = 1.06 and 95% CI, 0.84-1.34; OR = 1.55 and 95% CI, 0.49-4.94). Moreover, subgroup analysis of subtotal and total gastrectomies in both RG vs. OG and RG vs. LG revealed that the scope of surgical dissection was not a positive factor to influence the comparative results of RG vs. OG or LG in surgery time, blood loss, hospital stay, lymph node harvest, morbidity, and mortality.

Conclusions: This meta-analysis highlights that robotic gastrectomy may be a technically feasible alternative for gastric cancer because of its affirmative role in both subtotal and total gastrectomies compared with laparoscopic and open resections.

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• These authors contributed equally to this work.

Introduction

Gastric cancer is the fourth most common malignancy and second leading cause of cancer death in the world [1]. Surgical resection remains the only curative treatment option and open gastrectomy with lymphadenectomy took a leading position in the treatment of gastric cancer for a long time. Kitano *et al.* firstly reported the laparoscopy-assisted distal gastrectomy for gastric cancer in 1994 [2]. Since then, LG has been gradually spread worldwide [3–5].

Minimally invasive surgery represents a developing trend for its unique characteristics. However, conventional laparoscopic surgery itself, accompanied by some limitations such as instrument movement, amplification of hand tremor, two-dimensional imaging, and ergonomic discomfort for the surgeons. Robotic surgery, an emerging technology, was invented to overcome the disadvantages of conventional laparoscopic surgery in 1997 [6]. For robotic surgery, several robotic devices have been developed, but only the Da Vinci Surgical System was widely used [7]. To date, robotic surgery has been maturely adopted in many fields of advanced surgical procedures worldwide, especially for prostate cancer [8]. In the field of gastric cancer, robotic gastrectomy (RG) has been reported to be beneficial for patients, with less injury and also with compatible short-term oncologic outcomes to open gastrectomy (OG) or laparoscopic gastrectomy (LG) [9–20]. However, sample size, a single institution design and different appraise system of complications limited these studies to conclude objective result. To overcome these limitations, a meta-analysis of RG vs. OG or LG for gastric cancer was performed to determine the relative merits of RG for gastric cancer.

Methods

Publication Search

Three electronic databases (PubMed, EMBASE, and Cochrane Library) were searched (last search was updated on 01 June 2013, using the search terms: robotics OR robot PLUS gastrectomy PLUS cancer OR carcinoma OR adenocarcinoma OR malignancy PLUS open OR laparoscope). Article language was limited to English. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand-searched to identify additional eligible studies. Only published studies with full-text articles were included. When the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

Inclusion Criteria

The inclusion criteria were as follows: (a) controlled studies of RG vs. LG or RG vs. OG for gastric cancer; (b) report on at least one of the outcome measures mentioned below; and (c) sufficient published data to estimate an odds ratio (OR) with 95% confidence interval (CI).

Exclusion criteria

Abstracts, letters, editorials and expert opinions, reviews without original data, case reports and studies lacking control groups were excluded. The following studies or data were also excluded: (1) they reported on gastric surgery for benign lesions and gastrointestinal stromal tumor (GIST) and did not contain a distinct group of patients with gastric cancer, (2) the outcomes and parameters of patients were not clearly reported; (3) it was impossible to extract the appropriate data from the published results; and (4) there was overlap between authors or centers in the published literature.

Quality Assessment

The methodological quality of the studies included was assessed. Jadad Scale and MINORS were usually used to assess the quality of RCTs and non-RCTs, respectively [21,22].

Data Extraction

Information was carefully extracted from all eligible studies by two of the authors (Zong L and Seto Y), according to the inclusion criteria listed above. The following information were collected from each study: first author's surname, publication date, district, resection extent, reconstruction method, BMI index, TNM stage, study type, and total number of patients in RG group and OG group or LG group, respectively. We did not define a minimum number of patients for inclusion in our meta-analysis.

Statistical Analysis

Odd ratios with 95% CI were used for the comparisons of dichotomous variables (e.g., morbidity, and mortality) between surgical methods according to the method of Woolf. Heterogeneity assumption was confirmed by the X^2 -based Q-test. A P-value greater than 0.10 for the Q-test indicated a lack of heterogeneity among the studies, therefore, the OR estimate for each study was calculated by the fixed-effects model (the Mantel-Haenszel

method). Otherwise, the random-effects model (the DerSimonian and Laird method) was used. The significance of the pooled OR was determined by the Z-test and P>0.05 was considered statistically significant. Weighted mean difference (WMD) with 95% confidence intervals (95% CI) was calculated for continuous variables (e.g., operation time, and blood loss). WMD was pooled by using the inverse variance model. Sensitivity analyses were carried out to determine if modification of the inclusion criteria for this meta-analysis affected the final results. An estimate of potential publication bias was carried out using the funnel plot, in which the OR for each study was plotted against its log (OR). An asymmetric plot suggested possible publication bias. Funnel plot asymmetry was assessed using Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by the t-test, as suggested by Egger (P<0.05 was considered representative of statistically significant publication bias). All statistical tests were performed with Review Manager Version 5.0 (The Cochrane Collaboration, Oxford, England).

Results

Study Characteristics

Of the 14 published pieces of literature [9–20,23], 12 studies were eligible in this meta-analysis. Two studies published by the same team from the same institute within the same study interval were regarded as 1 trial, but both studies were included and shared the same study number because some separately published data was complementary [17,23]. Hence, a total of 12 studies including 8493 patients were used in the pooled analyses. Table 1 lists the studies identified and their main characteristics. Of the 12 groups, sample size ranged from 39 to 5839 (Figure 1).

Robotic gastrectomy versus open gastrectomy

The mean operation time of RG was 68.47 minutes longer than OG, but intraoperative blood loss and hospital stay were significantly reduced by RG (WMD = 68.47 and 95% CI, 63.40-73.54; WMD = -106.63 and 95% CI, -163.13--50.13; WMD = -2.49 and 95% CI, -3.72--1.27). The difference of lymph node harvest between RG and OG was not statistically significant (WMD = -0.78 and 95% CI, -2.15-0.59). Moreover, Meta-analyses on morbidity and mortality indicated that there was no significant differences between RG and OG (OR = 0.92 and 95% CI, 0.69-1.23; OR = 0.72 and 95% CI, 0.25-2.06). Also, specifically for anastomotic leakage, no difference was observed between two groups (OR = 1.72 and 95% CI, 0.97-3.07). Subgroup analysis of subtotal gastrectomy, and subtotal and total gastrectomies for above parameters all showed a similar trend with the combined results (Table 2) (Figure 2).

Robotic gastrectomy versus Laparoscopic gastrectomy

Operation time was significantly longer in RG compared with LG (WMD = 57.15 and 95% CI, 42.26-72.05). Both as the minimally invasive surgery, RG did not showed a priority in intraoperative blood loss (WMD = -28.59 and 95% CI, -56.57--0.62). As for postoperative hospital stay, there was no significant difference (WMD = -0.16 and 95% CI, -0.87-0.55). In analysis of lymph node harvest, it did not attain statistical significance between RG and LG (WMD = 0.63 and 95% CI, -2.24-3.51). Further analysis revealed that RG did not carry additional postoperative morbidity, as well as anastomotic leakage, and mortality when compared with LG (OR = 1.06 and 95% CI, 0.84-1.34; OR = 1.10 and 95% CI, 0.66-1.82; OR = 1.55 and 95% CI, 0.49-4.94) (Table 3) (Figure 3). However, Meta-analysis

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| Table |

| Study | Study Period | District | Size | Study Group | Resection extent | Reconstruction method | BMI | Stage | Study type |
|-----------------------|-----------------|----------|------|----------------|-------------------------------------------------|--------------------------|------------------------------------------|-------------|---------------|
| Caruso <i>et al</i> | 2011 | Italy | 149 | RG/OG | Total/Subtotal 12/17;37/83 | NA | 27±3/28±4 | NA | Controlled |
| Eom <i>et al</i> | 2012 | Korea | 92 | RG/LG | Subtotal 30;62 | NA | 24.2/24.1 | 81/9/2 | Controlled |
| Huang <i>et al</i> | 2012 | Taiwan | 689 | RG/LG/OG | Total/Subtotal 7/32;7/57; 179/407 | B-l/B-ll/Roux-en-Y | 24.2±3.7/24. ±3.3/23±3.6 | 282/122/285 | Controlled |
| Hyun <i>et al</i> | 2012 | Korea | 121 | RG/LG | Total/Subtotal 9/29; 18/65 | B-I/B-II/Roux-en-Y | 23.8±2.6/23.8±2.9 | 97/14/10 | Controlled |
| Kang <i>et al</i> | 2012 | Korea | 382 | RG/LG | Total/Subtotal 16/84;37/245 | B-I/B-II/Roux-en-Y | 23.7±3.7/23.6±3.5 | NA | Controlled |
| Kim <i>et al</i> | 2010 | Korea | 39 | RG/LG/OG | Subtotal 12;11;16 | NA | $21.3 \pm 3.4/25.3 \pm 2.5/25.2 \pm 1.9$ | 27/9/3 | Controlled |
| Kim <i>et al</i> | 2012 | Korea | 5839 | RG/LG/OG | Total/Subtotal 109/158/1232; 327/703/3309 | B-l/B-ll/Roux-en-Y | 23.6±3.1/23.5±2.8/23.3±8.0 | AN | Controlled |
| Park <i>et al</i> | 2012 | Korea | 150 | RG/LG | Subtotal 30;120 | NA | NA | NA | Controlled |
| Pugliese <i>et al</i> | 2010 | Italy | 64 | RG/LG | Subtotal 16;48 | NA | NA | NA | Controlled |
| Song <i>et al</i> | 2009 | Korea | 40 | RG/LG | Subtotal 20;20 | NA | $23.4 \pm 2.1/22.4 \pm 2.1$ | 39/1/0 | Controlled |
| Woo et al | 2011 | Korea | 827 | RG/LG | Total/Subtotal 62/172; 108/481 | B-I/B-II/Roux-en-Y | 23.5±3/23.5±3 | NA | Controlled |
| Yoon et al | 2012 | Korea | 101 | RG/LG | Total 36;65 | NA | 23.2±2.5/23.6±3.4 | 84/14/3 | Controlled |
| doi:10.1371/jour | rnal.pone.01033 | 12.t001 | | | | | | | |



Figure 1. Flow chart of literature selection. doi:10.1371/journal.pone.0103312.g001

on another surgical outcome evaluation system with Clavien-Dindo grades also did not show significant differences in any subdivided grade. Subgroup analysis of subtotal gastrectomy, total gastrectomy, and subtotal and total gastrectomies was also performed for above parameters and no single subgroup showed a heterogeneous result with the combined one (Table 3) (Figure 4).

Publication Bias

Begg's funnel plot was performed to assess publication bias. The heterogeneity tests for comparing the 12 combined studies showed heterogeneity in some analyses such as operation time, blood loss and so on; however, when significant heterogeneity occurred among the studies, random-effects model was used.

Discussion

Radical gastrectomy with lymphadenectomy has been widely applied in open surgery as standard surgical treatment for gastric cancer. Although minimally invasive surgery improves quality of life, it should be ensured that this technique does not increase morbidity and mortality [24]. With the developing of technique, minimally invasive surgery has gained a revolutionized application in general surgery from last century. But for gastric cancer, minimally invasive surgery experienced a controversy focusing on morbidity and mortality for a long time. Laparoscopic gastrectomy with limited lymphadenectomy is rapidly increasing and quickly admitted in early gastric cancer because of the mass and individual screening in Japan [25]. But the data was still incomplete to support the widespread use of laparoscopic gastrectomy for advanced gastric cancer in last decade [26].

Open gastrectomy with D2 lymphadenectomy is a technically demanding operation for advanced gastric cancer compared with D1, although there is the potential for appreciable morbidity and mortality [27,28]. Therefore, the assessment in favor of D2 lymphadenectomy makes it an integral part of laparoscopic surgery for advanced gastric cancer. Recently strong evidence from a multi-center retrospective study of laparoscopic surgery over open surgery confirmed the therapeutic role of Laparoscopic gastrectomy in advanced gastric cancer [29].

Robotic surgery, as an innovation of laparoscopic surgery, might be a simpler way to expand the indications of minimally invasive surgery for gastric cancer. However, controlled prospective studies are needed to evaluate the role of robotics in the management of gastric cancer. Some studies have demonstrated that robotic total and subtotal gastrectomies with D2-lymphade-nectomy are technically feasible and safe, with acceptable surgical and oncological short-term results [15,30–32]. It is particularly notable that only a few reports have examined the technical feasibility of robotic surgery for gastric cancer till 2011 [9,14,17–19], and the number of patients included in these studies was too

| Parameters | Studies | Sample Size | | Heterogeneity | OR or WMD | Effect 95% Cl | ٩ |
|---------------------------|---------|----------------|------|----------------------------|--------------|------------------|------------|
| Operation time | m | 481 | 4674 | $P = 0.74$, $I^2 = 0\%$ | 68.47 | 63.40-73.54 | P<0.00001 |
| Subgroup of SG | - | 16 | 12 | NA | 77.20 | 54.75-99.65 | P<0.00001 |
| Subgroup of SG and TG | 2 | 465 | 4662 | $P = 1.00, 1^2 = 0\%$ | 68.00 | 62.79-73.21 | P<0.00001 |
| Intraoperative blood loss | 3 | 481 | 4674 | $P = 0.003$, $I^2 = 83\%$ | - 106.63 | -163.13 - 50.13 | P = 0.0002 |
| Subgroup of SG | - | 16 | 12 | NA | -48.50 | -91.07 - 5.93 | P = 0.03 |
| Subgroup of SG and TG | 2 | 465 | 4662 | $P = 0.04$, $ ^2 = 77\%$ | -139.05 | -217.08 - 61.02 | P = 0.0005 |
| Hospital stay | £ | 481 | 4674 | $P = 0.06$, $I^2 = 64\%$ | -2.49 | -3.721.27 | P<0.0001 |
| Subgroup of SG | - | 16 | 12 | NA | - 1.60 | -2.410.79 | P<0.0001 |
| Subgroup of SG and TG | 2 | 465 | 4662 | $P = 0.34$, $I^2 = 0\%$ | -3.07 | -4.142.01 | P<0.00001 |
| Lymph node harvest | 4 | 520 | 5260 | $P = 0.55$, $I^2 = 0\%$ | -0.78 | -2.15-0.59 | P = 0.27 |
| Subgroup of SG | - | 16 | 12 | NA | -2.20 | -10.15 - 5.75 | P = 0.59 |
| Subgroup of SG and TG | S | 504 | 5248 | $P = 0.37$, $I^2 = 0\%$ | -0.73 | -2.13 - 0.66 | P = 0.30 |
| Anastomotic leakage | 4 | 520 | 5260 | $P = 0.53$, $I^2 = 0\%$ | 1.72 | 0.97 - 3.07 | P = 0.06 |
| Subgroup of SG | - | 16 | 12 | NA | NE | NE | NA |
| Subgroup of SG and TG | £ | 504 | 5248 | $P = 0.53$, $I^2 = 0\%$ | 1.72 | 0.97 - 3.07 | P = 0.06 |
| Morbidity | 4 | 520 | 5260 | $P = 0.65$, $I^2 = 0\%$ | 0.92 | 0.69-1.23 | P = 0.59 |
| Subgroup of SG | 1 | 16 | 12 | NA | 0.13 | 0.01 - 2.92 | P = 0.20 |
| Subgroup of SG and TG | ĸ | 504 | 5248 | $P = 0.97$, $I^2 = 0\%$ | 0.95 | 0.71 – 1.27 | P = 0.72 |
| Mortality | 4 | 520 | 5260 | $P = 0.52$, $I^2 = 0\%$ | 0.72 | 0.25-2.06 | P = 0.54 |
| Subgroup of SG | 1 | 16 | 12 | NA | 0.13 | 0.01 - 2.92 | P = 0.20 |
| Subgroup of SG and TG | З | 504 | 5248 | $P = 0.72$, $I^2 = 0\%$ | 0.98 | 0.32-2.96 | P = 0.97 |

Table 2. Meta-analyses results for robotic gastrectomy vs. open gastrectomy.

| 1.1.1 Subtotal group Kim 2010 | Mean SD | Total | Mean | SD To | otal Weight | Mean Difference IV, Fixed, 95% | Mean Difference |
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| Subtotal (95% Cl) Heterogeneity: Not ap Test for overall effect: | 203.9 36.4 plicable Z = 6.74 (P < 0 | 16 16 0.00001) | 126.7 2 | 24.1 | 12 5.1% 12 5.1% | 77.20 (54.75, 99. 77.20 (54.75, 99.) | 65] |
| 1.1.2 Subtotal and to Caruso 2011 Kim 2012 Subtotal (95% CI) Heterogeneity: Chi [≠] = Test for overall effect: | tal group 290 67 226 54 0.00, df = 1 (P Z = 25.60 (P < | 29 436 465 = 1.00); 0.0000 | 222 158 1 ² = 0% | 94 1 52 45 46 | 120 2.9% 542 92.0% 562 94.9% | 68.00 [38.38, 97. 68.00 [62.71, 73. 68.00 [62.79, 73. | 62) 29] 21] |
| Total (95% Cl) Heterogeneity: Chi [≢] = Test for overall effect: Test for subgroup diff | 0.61, df = 2 (P Z = 26.46 (P < 'erences: Chi ² | 481 = 0.74); 0.0000 = 0.61, 0 | ; I≊ = 0% 1) 3f = 1 (P = | 46 = 0.43), | 674 100.0% | 68.47 [63.40, 73. | 54] + -100 -50 0 50 100 Favours experimental Favours control |
| в | Robotic tea | m | Open te | eam | | Mean Difference | Mean Difference |
| Study or Subgroup 1.2.1 Subtotal group Kim 2010 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 | Mean SD 30.3 15.1 blicable 2 = 2.23 (P = 0.0) | Total M 16 16 03) | 78.8 74 | 5D Tota 1 1 1 | al Weight 2 34.4% 2 34.4% | IV, Random, 9 -48.50 [-91.07, - -48.50 [-91.07, - | 5% Cl IV, Random, 95% Cl 5.93] |
| 1.2.2 Subtotal and tota Caruso 2011 Kim 2012 Subtotal (95% CI) Heterogeneity: Tau ^a = 1 Test for overall effect: 2 | al group 197.6 202.1 85 160 2545.45; Chi ^a = Z = 3.49 (P = 0.0 | 29 3 436 465 4.28, df 0005) | 386.1 95 192 19 = 1 (P = 0 | .5 12 33 454 466 0.04); ⊫ | 0 24.2% 2 41.3% 2 65.6% = 77% | -188.50 [-264.01, -11 -107.00 [-123.03, -9 - 139.05 [-217.08 , -6 | 2.99] ◀ 0.97] ← 1.02] ━ |
| Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: 2 | 1943.25; Chi ^a = Z = 3.70 (P = 0.0 | 481 11.46, c 0002) | if= 2 (P = | 467 0.003); | 4 100.0% I ^a = 83% | -106.63 [-163.13, -5 | -100 -50 0 50 100 Favours experimental Favours control |
| C Study or Subgroup | Robotic te Mean SD | am Total | Open Mean | team SD To | tal Weight | Mean Difference IV, Random, 95% | Mean Difference CI IV, Random, 95% CI |
| 1.3.1 Subtotal group Kim 2010 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect: | 5.1 0.3 oplicable Z = 3.89 (P < 1 | 16 16 0.0001) | 6.7 | 1.4 | 12 42.9% 12 42.9% | -1.60 [-2.41, -0.7 - 1.60 [-2.41, -0.7 | '9] 9] I |
| 1.3.2 Subtotal and to Caruso 2011 Kim 2012 Subtotal (95% CI) Heterogeneity: Tau ^s = Test for overall effect: | tal group 9.6 2.8 7.5 13.7 0.00; Chi ² = 0 Z = 5.65 (P < 0 | 29 436 465 92, df = 0.00001 | 13.4 10.2 1 (P = 0 | 8.5 1 8.5 45 46 .34);I [≥] = | 20 24.2% 542 32.9% 562 57.1% = 0% | -3.80 [-5.63, -1.9 -2.70 [-4.01, -1.3 - 3.07 [-4.14, -2.0 | 97] 99] 11] (|
| Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: – | 0.74; Chi ² = 5 Z = 4.00 (P < 0 | 481 59, df= 0.0001) | 2 (P = 0 | 46 .06); I ² = | 674 100.0% ⊧64% | -2.49 [-3.72, -1.2 | 77 -100 -50 0 50 100 Favours experimental Favours control |
| D Study or Subgroup | Robotic te Mean SD | am <u>Total</u> | Open <u>Mean</u> | team SD To | otal Weigh | Mean Difference t IV, Fixed, 95% | Mean Difference CI IV, Fixed, 95% CI |
| 1.4.1 Subtotal group Kim 2010 Subtotal (95% Cl) Heterogeneity: Not ap Test for overall effect: | 41.1 10.9 oplicable Z = 0.54 (P = 0 | 16 16 0.59) | 43.3 1 | 10.4 | 12 3.09 12 3.09 | 6 -2.20 [-10.15, 5.7 5 -2.20 [-10.15, 5.7 | 5) 5) |
| 1.4.2 Subtotal and to Caruso 2011 Huang 2012 Kim 2012 Subtotal (95% Cl) Heterogeneity: Chi ² = Test for overall effect: | tal group 28 11.2 32 13.7 40.2 15.5 2.00, df = 2 (P Z = 1.04 (P = 1 | 29 39 436 504 = 0.37); 0.30) | 31.7 1 34 1 40.5 1 ; l ^a = 0% | 15.6 14.8 16.6 4 5 | 120 7.7% 586 9.4% 542 79.9% 2 48 97.0 % | 6 -3.70 [-8.64, 1.2 6 -2.00 [-6.46, 2.4 6 -0.30 [-1.83, 1.2 6 - 0.73 [-2.13, 0.6 | 24] |
| Total (95% CI) Heterogeneity: Chi [≥] = Test for overall effect: Test for subgroup diff | 2.13, df = 3 (P Z = 1.11 (P = (erences: Chi ² | 520 = 0.55); 0.27) = 0.13, 0 | ; I ² = 0% df = 1 (P : | 52 = 0.72). | 260 100.0% | 6 - 0.78 [-2.15, 0.5 | 9] -100 -50 0 50 100 Favours experimental Favours control |
| E | Robotic te | am | Open te | am | Mainles B | Odds Ratio | Odds Ratio |
| 1.5.1 Subtal group Kim 2010 Subtotal (95% CI) Total events Heterogeneity: Not a | 0 0 opplicable | 16 16 16 | 0 | 12 12 12 | overgrit in | Not estimable Not estimable | M-H, FIZEL, 55% CI |
| Test for overall effec | t: Not applical | ble | | | | | |
| Caruso 2011 Huang 2012 Kim 2012 Subtotal (95% CI) Total events Heterogeneity: Chi ^p : | 1 3 10 14 = 1.28, df = 2 t 7 = 1.85 (P = | 29 39 436 504 (P = 0.5 | 7 27 51 | 120 586 4542 5248 | 18.2% 21.5% 60.3% 100.0 % | 0.58 [0.07, 4.88] 1.73 [0.50, 5.96] 2.07 [1.04, 4.10] 1.72 [0.97, 3.07] | |
| | | = 0.06 | i3); I ² = 0 | % | | | |
| Total (95% CI) Total events Heterogeneity: Chi ² Test for overall effec Test for subgroup di | 14 = 1.28, df = 2 t: Z = 1.85 (P ifferences: No | = 0.06) 520 (P = 0.5 = 0.06) t applic | 63); I ² = 0 85 63); I ² = 0 able | % 5260 % | 100.0% | 1.72 (0.97, 3.07) F | 0.001 0.1 10 1000 avours experimental Favours control |
| Total (95% CI) Total events Heterogeneity: Chi≭ Test for overall effec Test for subgroup di | 14 = 1.28, df = 2 t: Z = 1.85 (P fferences: No Robotic te | = 0.06) 520 (P = 0.5 = 0.06) it applic am | 33); I ² = 0 85 33); I ² = 0 able Opente | % 5260 % am | 100.0% | 1.72 [0.97, 3.07] F | 0.001 0.1 10 1000 avours experimental Favours control Odds Ratio |
| Total (95% CI) Total events Heterogeneity: Chi ² - Test for overall effec Test for subaroup di F <u>Study or Subgroup</u> 1.6.1 Subtal group Kim 2010 Subtotal (95% CI) Total events | 14 = 1.28, df = 2 t: Z = 1.85 (P = fferences: No Robotic te Events 0 0 | = 0.06) 520 (P = 0.5 = 0.06) it applic am <u>Total 1</u> 16 16 | 33; I ² = 0 85 33; I ² = 0 able Open te <u>Events</u> 2 2 | % 5260 % am <u>Total</u> 12 12 | 100.0% Weight N 2.8% 2.8% | 1.72 [0.97, 3.07] F Odds Ratio 1.H, Fixed, 95% CI 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] | 0.001 0.1 10 1000 avours experimental Favours control Odds Ratio M-H, Fixed, 95% Cl |
| Total events Total events Heterogeneity: Chi ¹¹ Test for overall effec Test for subgroup di F Study or Subgroup 1.6.1 Subtal group Kim 2010 Subtotal (95% CD) Total events Heterogeneity: Nota Test for overall effec | 14 = 1.28, df = 2 t Z = 1.85 (P + fiferences: No Robotic te Events 0 0 o ppplicable t Z = 1.29 (P + al group | = 0.06) 520 (P = 0.5 = 0.06) it applic am <u>Total 1</u> 16 16 16 = 0.20) | 85 (3); ² = 0 (3); ² = 0 (3); ² = 0 (3); ² = 0 (3); ² = 0 (4);]]]]]]]]]]]]] | % 5260 % am <u>Total</u> 12 12 | 100.0% Weight M 2.8% 2.8% | 1.72 [0.97, 3.07] F Odds Ratio 1-H, Fixed, 95% CI 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] | 0.001 0.1 1 10 1000 avours experimental Favours control Odds Ratio M-H, Fixed, 95% CI |
| Total events Total events Heterogeneity: Chi ² Testfor overall effec Testfor subaroup di F Study or Subgroup Aim 2010 Subtotal (95% Ch) Total events Heterogeneity: Nota Test for overall effec Total events Heterogeneity: Chi ² Total events Heterogeneity: Chi ² | $\begin{array}{c} 14\\ = 1.28, df = 2\\ t, Z = 1.85 (P)\\ merences: No\\ merences: No\\ \hline Robotic te \\ \hline Events\\ 0\\ 0\\ 0\\ pplicable\\ t, Z = 1.29 (P)\\ al group\\ 12\\ 6\\ 42\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\$ | = 0.06) 520 (P = 0.5 = 0.06) it applic am Total 1 16 16 = 0.20) 29 39 436 504 (P = 0.9 | 33); ² = 0 85 (33); ² = 0 able Open te <u>Events</u> 2 2 2 51 86 466 466 77); ² = 0 | % 5260 % <u>Total</u> 12 12 12 120 5862 5248 % | 100.0% <u>Weight N</u> 2.8% 2.8% 12.0% 9.3% 75.9% 97.2% | 1.72 [0.97, 3.07] F Odds Ratio 1.H, Fixed, 95% CI 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 1.06 [0.42, 2.17] 1.06 [0.43, 2.60] 0.93 [0.67, 1.30] 0.95 [0.71, 1.27] | 0.001 0 ¹ 1 10 1000 avours experimental Favours control Odds Ratio M-H, Fixed, 95% CI |
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| Total events Heterogeneity: Chi ² Test for vsubaroup di F Study or Subgroup Heterogeneity: Chi ² Test for vsubaroup di F Study or Subgroup Heterogeneity: Not a Test for vsubarou Caruso 2011 Huang 2012 Stitutoal (05% C) Total events Heterogeneity: Chi ² Test for vsubarouf Heterogeneity: Chi ² Test for vsubarouf Co Subtotal (05% C) Total events Heterogeneity: Not a Test for vsubarouf Co Subtotal (05% C) Total events Heterogeneity: Not a Test for vsubarouf Subtotal (05% C) Total events Heterogeneity: Chi ² | $\begin{array}{c} 14\\ = 1.28, df = 2\\ tZ = 1.82 (0, ff = 2\\ tZ = 1.82 (0, ff = 2\\ tZ = 1.23 (0, ff = 2\\ tZ = 1.23 (0, ff = 2\\ tZ = 1.23 (0, ff = 2\\ tZ = 0.37, df = 2\\ tZ = 0.37, df = 2\\ tZ = 0.37, df = 2\\ tZ = 0.57, df = 2\\ tZ = 0.57$ | $ \begin{array}{l} = 0.060 \\ 520 \\ 520 \\ = 0.060 \\ amm \\ \hline 16 \\ 16 \\ = 0.200 \\ 16 \\ 504 \\ 504 \\ 504 \\ 504 \\ 504 \\ 504 \\ 504 \\ 504 \\ 504 \\ 504 \\ 16 \\ 16 \\ 16 \\ 16 \\ 16 \\ 16 \\ 504 \\ 6 \\ 504 \\ 6 \\ 504 \\ 16 \\ 16 \\ 16 \\ 504 \\ 16 \\ 16 \\ 504 \\ 16 \\ 16 \\ 16 \\ 16 \\ 16 \\ 16 \\ 16 \\ 1$ | (3), $F = 0$ (3), $F = 0$ (3), $F = 0$ (4) (5), $F = 0$ (5), $F = 0$ (6) (6), $F = 0$ (7), | % 5260 % 121 121 120 5862 55248 % 5260 % 30 120 120 586 45428 5248 % | 100.0% Veight t 2.8% 2.8% 9.3% 9.3% 9.7.2% 100.0% 100.0% 100.0% 10.0% 10.5% 40.1% 69.9% | 1.72 [0.97, 3.07] F Ordds Ratio 1.14, Fixed, 95% CI 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.93 [0.67, 1.30] 0.99 [0.71, 1.27] 0.92 [0.69, 1.23] F Ordds Ratio 1.14, Fixed, 95% CI 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.14 [0.02, 8.30] 0.99 [0.23, 4.26] 0.98 [0.32, 2.96] | Odds Ratio M-H, Fixed, 95% CI |
| Total events Heterogeneils: Chi ² Test for vsubaroup di F Study or Subgroup I.1.5 Subtal group Subtotal (95% C)) Total events Heterogeneils: Chi ² Test for vsubaroup di Subtotal (95% C)) Total events Heterogeneils: Chi ² Test for vsubaroup di Reformanti effect Total events Heterogeneils: Chi ² Test for subaroup di Caruso 2011 Ruang 2012 Subtotal (95% C)) Total events Heterogeneils: Chi ² Test for subaroup di Caruso 2011 Ruang 2012 Subtotal (95% C)) Total events Heterogeneils: Chi ² Test for subaroup di Caruso 2011 Ruang 2012 Subtotal (95% C)) Total events Heterogeneils: Not a Test for vsubaroup di Caruso 2011 Ruang 2012 Subtotal (95% C)) Total events Heterogeneils: Not a Test for vsubaroup di Caruso 2011 Ruang 2012 Subtotal (95% C)) | $\begin{array}{c} 14\\ = 1.28, df = 2\\ tZ = 1.85 (r)\\ fferences: No \\ \hline \\ \begin{tabular}{lllllllllllllllllllllllllllllllllll$ | | (3), $r^{2} = 0$ (3), $r^{2} = 0$ able Open te Second (4) (5) (4) (5) (5) (7), $r^{2} = 0$ (6) (7) (7) (7) (7) (7) (7) (7) (7 | % 5260 % am Total 12 12 120 5248 % 6260 % am Total 12 12 120 5260 % am 122 5248 % 5260 % | 100.0% Veight A 2.8% 2.8% 12.0% 9.3% 97.2% 100.0% Veight A 30.1% 30.1% 10.5% 40.1% 69.9% 100.0% | 1.72 [0.97, 3.07] P Oridis Ratio 1.14, Fixed, 95% CI 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.33 [0.61, 2.92] 0.39 [0.71, 30] 0.95 [0.71, 1.27] 0.95 [0.71, 1.27] 0.92 [0.69, 1.23] 0.92 [0.69, 1.23] 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.13 [0.01, 2.92] 0.44 [0.02, 8.38] 0.99 [0.23, 4.26] 0.99 [0.32, 2.96] | Odds Ratio M-H, Fixed, 95% Cl |

Figure 2. RG *vs.* OG: a) Operation time; b) Intraoperative blood loss; c) Hospital stay; d) Lymph node harvest; e) Anastomotic leakage; f) Morbidity; g) Mortality. doi:10.1371/journal.pone.0103312.g002

| arameters | Studies | Sample Size | | Heterogeneity | OR or WMD | Effect 95% Cl | ٩ |
|-------------------------|---------|----------------|------|--------------------------------|--------------|------------------|------------|
| peration time | 8 | 898 | 1961 | P<0.00001, I ²⁼ 88% | 57.15 | 42.26-72.05 | P<0.00001 |
| Subgroup of SG | £ | 52 | 79 | $P = 0.03$, $l^2 = 72\%$ | 86.73 | 56.61-116.84 | P<0.00001 |
| Subgroup of TG | 1 | 36 | 65 | NA | 95.60 | 55.26-135.94 | P<0.00001 |
| Subgroup of SG and TG | 4 | 810 | 1817 | $P = 0.0002$, $I^2 = 85\%$ | 38.09 | 25.44-50.74 | P<0.00001 |
| traoperative blood loss | 7 | 862 | 1896 | P<0.00001, l ²⁼ 92% | -28.59 | -56.570.62 | P = 0.05 |
| Subgroup of SG | £ | 52 | 79 | $P = 0.0007$, $I^2 = 86\%$ | -11.00 | -61.25-39.26 | P=0.67 |
| Subgroup of SG and TG | 4 | 810 | 1817 | P<0.00001, I ²⁼ 95% | - 39.54 | - 79.71 - 0.63 | P = 0.05 |
| ospital stay | 7 | 882 | 1950 | $P = 0.59$, $I^2 = 0\%$ | -0.16 | -0.87 - 0.55 | P = 0.65 |
| Subgroup of SG | 2 | 36 | 68 | $P = 0.65, I^2 = 0\%$ | -0.29 | -1.36-0.79 | P = 0.60 |
| Subgroup of TG | - | 36 | 65 | NA | -1.50 | -4.34-1.34 | P = 0.30 |
| Subgroup of SG and TG | 4 | 810 | 1817 | $P = 0.35$, $I^2 = 8\%$ | -0.11 | -0.89-1.11 | P = 0.83 |
| mph node harvest | 8 | 837 | 1743 | P<0.0001, I ^{2 =} 78% | 0.63 | -2.24-3.51 | P = 0.67 |
| Subgroup of SG | £ | 52 | 79 | $P = 0.07$, $I^2 = 62\%$ | -3.77 | -9.63-2.09 | P = 0.21 |
| Subgroup of TG | L | 36 | 65 | NA | 3.40 | -1.87 - 8.67 | P = 0.21 |
| Subgroup of SG and TG | 4 | 749 | 1599 | $P = 0.39$, $l^2 = 0\%$ | 2.33 | 1.05-3.62 | P = 0.0004 |
| lastomotic leakage | 11 | 266 | 2207 | $P = 0.96$, $l^2 = 0\%$ | 1.10 | 0.66-1.82 | P = 0.71 |
| Subgroup of SG | 5 | 112 | 261 | NA | 2.03 | 0.18-23.22 | P = 0.57 |
| Subgroup of TG | - | 36 | 65 | NA | 0.24 | 0.01-4.87 | P = 0.36 |
| Subgroup of SG and TG | 5 | 849 | 1881 | $P = 0.99$, $l^2 = 0\%$ | 1.16 | 0.68-1.96 | P = 0.59 |
| orbidity | 11 | 266 | 2207 | $P = 0.65$, $l^2 = 0\%$ | 1.06 | 0.84-1.34 | P = 0.60 |
| Subgroup of SG | S | 112 | 261 | $P = 0.37$, $I^2 = 7\%$ | 1.29 | 0.61 - 2.72 | P = 0.51 |
| Subgroup of TG | - | 36 | 65 | NA | 1.10 | 0.36-3.32 | P = 0.87 |
| Subgroup of SG and TG | 5 | 849 | 1881 | $P = 0.57$, $I^2 = 0\%$ | 1.04 | 0.81 - 1.34 | P = 0.76 |
| ortality | 11 | 266 | 2207 | $P = 0.96$, $I^2 = 0\%$ | 1.55 | 0.49-4.94 | P = 0.45 |
| Subgroup of SG | S | 112 | 261 | NA | 3.13 | 0.18-53.21 | P = 0.43 |
| Subgroup of TG | - | 36 | 65 | NA | NE | NE | NA |
| Subgroup of SG and TG | 5 | 849 | 1881 | $P = 0.99, I^2 = 0\%$ | 1.36 | 0.38-4.88 | P = 0.63 |
| avien-Dindo grade | | | | | | | |
| | 6 | 965 | 2148 | $P = 0.22$, $I^2 = 26\%$ | 1.15 | 0.86-1.53 | P = 0.35 |
| Subgroup of SG | £ | 80 | 202 | $P = 0.50$, $I^2 = 0\%$ | 1.77 | 0.69-4.54 | P = 0.23 |
| Subgroup of TG | - | 36 | 65 | NA | 2.46 | 0.62-9.82 | P = 0.20 |
| Subgroup of SG and TG | 5 | 849 | 1881 | $P = 0.13$, $l^2 = 43\%$ | 1.06 | 0.77-1.44 | P = 0.73 |
| | 6 | 965 | 2148 | $P = 0.82$, $I^2 = 0\%$ | 1.07 | 0.72-1.60 | P = 0.73 |
| Subgroup of SG | 3 | 80 | 202 | $P = 0.99$, $I^2 = 0\%$ | 2.07 | 0.33-13.01 | P = 0.44 |
| Subgroup of TG | - | 36 | 65 | NA | 0.28 | 0.03 - 2.43 | P = 0.25 |

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| Table 3. Cont. | | | | | | | |
|----------------------------------------------|-------------------------|-------------------|------------------|--------------------------------------|--------------------------|------------------|----------|
| Parameters | Studies | Sample Size | | Heterogeneity | OR or WMD | Effect 95% Cl | ۵. |
| Subgroup of SG and TG | 5 | 849 | 1881 | $P = 0.81$, $I^2 = 0\%$ | 1.12 | 0.74-1.70 | P = 0.60 |
| 2 | 6 | 965 | 2148 | $P = 0.85$, $I^2 = 0\%$ | 0.70 | 0.34-1.43 | P = 0.32 |
| Subgroup of SG | З | 80 | 202 | NA | NE | NE | NA |
| Subgroup of TG | 1 | 36 | 65 | NA | NE | NE | NA |
| Subgroup of SG and TG | 5 | 849 | 1881 | $P = 0.85$, $I^2 = 0\%$ | 0.70 | 0.34-1.43 | P = 0.32 |
| > | 6 | 965 | 2148 | $P = 0.99$, $I^2 = 0\%$ | 1.36 | 0.38-4.88 | P = 0.63 |
| Subgroup of SG | c | 80 | 202 | NA | NE | NE | NA |
| Subgroup of TG | 1 | 36 | 65 | NA | NE | NE | NA |
| Subgroup of SG and TG | 5 | 849 | 1881 | $P = 0.99$, $I^2 = 0\%$ | 1.36 | 0.38-4.88 | P = 0.63 |
| SG, subtotal gastrectomy; TG, total gastrect | tomy; NA, not applicabl | e; NE, not estima | able; OR, odds r | atio; WED, weighted mean difference; | Cl, confidence interval. | | |

Robotic Gastrectomy in Gastric Cancer

small to generalize its application for gastric cancer [14,17,18]. Recently some large sized studies have been conducted to evaluate the efficacy and safety of robotic gastrectomy for gastric cancer [11,13,15,19]. But single comparison and conflict results limited them to conclude persuasible conclusions. However, those examined in the present study allowed meta-analyses to be performed, providing a better view of the safety and efficacy of RG in gastric cancer. In reality, it is difficult to conduct a high-quality RCT to evaluate a new surgical intervention because of some obstacles such as learning curve effects, ethical and culture resistance, and urgent or unexpected conditions during operation in surgical treatment. For these reasons, to include non-RCTs is an appropriate strategy to extend the source of evidence [33].

In the first part of RG versus OG, our analyses highlighted the advantage of RG in minimal injury because less intraoperative blood loss and shorter postoperative hospital stay were observed. But its complication in technique correspondently brought RG significantly longer operation time than OG. Further analyses of lymph node harvest, anastomotic leakage, morbidity, and mortality between RG and OG did not show significant differences. Although no controlled study for single total gastrectomy was included in subgroup analysis, we deduced that RG was feasible and safe in either subtotal gastrectomy or total gastrectomy compared with OG by similar evidences in subtotal and total mixed group and subtotal single group.

Continually, in comparison of RG and LG, we found it was similar in surgical injury for these two methods because of no significant difference in intraoperative blood loss. The disadvantage of longer surgical duration was also observed in RG, although significant heterogeneity existed. The heterogeneity might be caused by surgeons' experience. However, it is important to stress that surgeons had got considerable experience of LG before RG, which helped them adapt quickly to the robotic procedure. Therefore, the effect of learning curve was limited in RG. Also, higher BMI might be another important factor to increase operation time and several reports described the association between gender and BMI as increased operation time [34,35]. But Park *et al* thought that this factor could be overcome by surgeon's expertise [36]. To explore the influence of BMI to our study, we made comparisons of BMI among three groups and no significant difference was observed (data not shown). Importantly, for analyses of lymph node harvest, anastomotic leakage, morbidity, and mortality, similar results were achieved between RG and LG in either subtotal gastrectomy or total gastrectomy. We also make a pooled analyses using Clavien-Dindo (C-D) classification. Still, no significant difference was observed. What's far more important to limit the application of RG is the higher cost compared with LG. Due to the limited published study, meta-analysis for cost evaluation was not performed. But nevertheless, recent study by Park et al showed the total cost for RG was significantly higher than LG with a difference of \in 3189 [16].

In summary, we found that Robotic subtotal and total gastrectomies combined with lymphadenectomy are technically feasible and safe for gastric cancer, and can produce satisfying short-term postoperative outcomes. However, a weakness of present study was lack of randomized controlled studies included and significant heterogeneity was observed in operative time, intraoperative blood loss, length of hospital stay and lymph node harvest. In addition, total and subtotal gastrectomy was pooled together in most of included studies, which limited us to make a more precise conclusion. Also, economic value and long-term survival outcome are the mandatory appraisal index. Importantly, high-quality randomized controlled studies should be conducted to evaluate the role of robotic surgery for gastric cancer in future.

| A Study or Subgroup | Robot Mean | tic team SD | Total | Laparos Mean | copic te SD | ram Total | Weight | Mean Difference IV, Random, 95% | Mean Difference CI IV, Random, 95% CI |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------|-----------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Kim 2010 Fugliese 2009 Song 2009 Subtotal (95% CI) Heterogeneity: Tau* = 5 Test for overall effect: Z | 259.2 344 230 08.84; C = 5.64 (| 38.9 62 34.9 hi# = 7.1 P < 0.000 | 16 16 20 52 6, df = 001) | 203.9 235 134.1 = 2 (P = 0.0 | 36.4 23 40 3); I# = 3 | 11 48 20 79 | 10.3% 9.7% 11.9% 32.0% | 55.30 [26.56, 84 109.00 [77.93, 140 95.90 [72.63, 119 86.73 [56.61, 116. | 04) 07] 17] 184] |
| 2.1.2 Total group Yoon 2012 Subtotal (95% Ch) Heterogeneity: Not app Test for overall effect: 2 | 305.8 licable := 4.64 (l | 115.8 P = 0.001 | 36 36 001) | 210.2 | 67.7 | 65 65 | 7.5% 7.5% | 95.60 (55.26, 135 95.60 (55.26, 135. | |
| 2.1.3 Sutal and total gr Hyun 2012 Kang 2012 Kim 2012 Woo 2011 Subtotal (95% CI) Heterogeneity: Tau ^z = 1 Test for overall effect. 2 | 234.4 202.05 226 219.5 31.67; C = 5.90 0 | 49 52.31 54 46.8 hi [#] = 19. P < 0.000 | 38 100 436 236 810 .46, df | 220 173.45 176 170.7 (P = 0. | 60.6 51.2 63 55.8 0002); I | 83 282 861 591 1817 *= 85% | 12.9% 15.2% 16.3% 16.1% 60.5% | 14.40 [-5.67, 34 28.60 [16.73, 40 50.00 [43.41, 56 48.80 [41.32, 56 30.09 [25.44, 50 | 471 471 501 201 741 |
| Total (95% Cl) Heterogeneity: Tau [#] = 3 Test for overall effect: Z | 43.66; C = 7.52 (| hi# = 58. P < 0.001 | 898 .06, df 001) | f=7 (P ≺ 0. | 00001); | 1961 I*= 88 | 100.0% % | 57.15 [42.26, 72. | Favours experimental Favours control |
| B Sturbe or Subaroun | Robot | ic team | otal | Laparosc | opic te | Total | Mainht | Mean Difference | Mean Difference |
| 2.2.1 Subtotal group Kim 2010 Pugliese 2009 Song 2009 Subtotal (95% Cl) Heterogeneity: Tau ^a = 1 Test for overall effect <i>Z</i> | 30.3 90 94.6 1 637.06; = 0.43 0 | 15.1 48 21.5 Chi ^p = 1 P = 0.67 | 16 16 20 52 4.47, 0 | 44.7 148 39.5 df= 2 (P = 1 | 37.1 63 27.7 0.0007) | 11 48 20 79 1* = 86 | 14.9% 14.3% 10.2% 39.4% | -14.40 [-37.54, 8 -58.00 [-85.89, -30 55.30 [0.68, 109 -11.00 [-61.25, 39. | 741 111 26] |
| 2.2.3 Subtotal and tota Hyun 2012 Kang 2012 Kim 2012 Woo 2011 Subtotal (95% CI) Heterogeneity: Tau ^e = 1 Teet for general effect. | d group 131.3 93.25 85 91.6 1 560.34; | 10.1 14.59 160 52.6 Chi# = 5 | 38 100 436 236 810 9.80, 4 | 130.48 173.45 14 112 147.9 df= 3 (P < 1 | 17.8 15.19 229 269 | 83 282 861 591 1817); I ^e = 9 | 16.5% 14.9% 15.1% 14.1% 60.6% 5% | 0.82 [-4.18, 5 80.20 [-103.91, -56 -27.00 [-48.44, -5 -56.30 [-85.44, -27 -39.54 [-79.71, 0 | 82] 49] 56] 53] 53] |
| Total (95% Cl) Heterogeneity: Tau* = 1 Test for overall effect: Z | 225.24; | Chi# = 7 P = 0.05 | 862 8.55, (| df=6 (P ≺) | 0.00001 | 1896); I* = 9 | 100.0% 2% | -28.59 [-56.57, -0. | 62] -100 -50 0 50 100 Favours experimental Favours control |
| C | Robe | otic tear | | Laparo | scopic | team | | Mean Difference | Mean Difference |
| Study or Subgroup 2.3.1 Subtotal group Pugliese 2009 Song 2009 Subtotal (95% Cl) Heterogeneity: Chi [#] = 1 Toot for overall offect | Mean 10 5.7 0.20, df: | 3 1 = 1 (P = | 16 20 36 0.65) | 10 6.2 | 2.6 3.1 | 4 2 6 | 8 18.7% 0 24.8% 8 43.5% | IV, Fixed, 95% (0.00 [-1.64, 1.6 -0.50 [-1.93, 0.9 -0.29 [-1.36, 0.7) | 1 IV, Fixed, 95% Cl |
| 2.3.2 Total group Yoon 2012 Subtotal (95% Cl) Heterogeneity: Not ap Test for overall effect. | 8.8 plicable Z = 1.04 | 3.3 (P = 0.3 | 36 36 30) | 10.3 | 10.8 | 6 | 5 6.3% 5 6.3% | -1.50 [-4.34, 1.3 -1.50 [-4.34, 1.3 | 8 • |
| 2.3.3 Subtotal and tot Hyun 2012 Kang 2012 Kim 2012 Woo 2011 Subtotal (95% Cb | al group 10.5 9.81 7.5 7.7 | 5.9 12.16 13.7 17.2 | 38 100 436 236 810 | 11.9 8.11 7.8 7 | 10.3 4.1 8.5 5.7 | 8 28 86 59 181 | 3 6.0% 2 8.6% 1 25.6% 1 10.1% 7 50.2% | -1.40 [-4.30, 1.5 1.70 [-0.73, 4.1 -0.30 [-1.71, 1.1 0.70 [-1.54, 2.9 0,11 [-0.89, 1.1' | |
| Heterogeneity: Chi [#] = Test for overall effect : Total (95% Ct) Heterogeneity: Chi [#] = | 3.28, df= Z = 0.21 4.66, df= | = 3 (P = (P = 0.8 | 0.35) 13) 882 0.59) | I* = 8% | | 195 | 0 100.0% | -0.16 [-0.87, 0.5 | |
| Test for overall effect: Test for subgroup diffe | Z = 0.45 erences: Robot | (P = 0.6 Chi ^p = 1 | 1.19, (| df = 2 (P = | 0.55), P :opic te | am | Moight | Mean Difference | Favours experimental Favours control Mean Difference D. D. Bandom 95% Cl |
| 2.4.1 Subtotal group Kim 2010 Publices 2000 | 41.1 | 10.9 | 16 | 37.4 | 10 | 11 | 7.7% | 3.70 (-4.27, 11.6 | 7] |
| Song 2009 Subtotal (95% CI) Heterogeneity: Tau* = Test for overall effect 2 2.4.2 Total group | 35.3 16.72; C Z = 1.26 | 10.5 hi* = 5.3 (P = 0.2 | 20 52 31, df | 42.7 = 2 (P = 0.1 | 14.9 07); I* = | 20 79 62% | 7.7% | -7.40 [-15.39.0.5 -3.77 [-9.63, 2.09 | |
| Yoon 2012 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect 2 2.4.3 Subtotal and total | 42.8 plicable Z = 1.26 al group | 12.7 (P = 0.2 | 36 36 | 39.4 | 13.4 | 65 | 11.5% | 3.40 [-1.87, 8.6 3.40 [-1.87, 8.6 | |
| Huang 2012 Hyun 2012 Kim 2012 Wioo 2011 Subtotal (95% Cl) Heterogeneity: Tau ^e = Test for overall effect : | 32 32.8 40.2 39 0.00; Ch | 13.7 13.8 15.5 15.2 # = 3.00 | 39 38 436 236 749 0, df = | 26 32.6 37.6 37.4 3 (P = 0.3) | 12.4 13.3 13.9 14.2 $0; I^{\mu} = 0$ | 64 83 861 591 1599 | 11.6% 11.6% 17.7% 16.9% 57.7% | 6.00 [0.74, 11.2 0.20 [-5.04, 5.4 2.60 [0.87, 4.3 1.60 [-0.65, 3.8 2.33 [1.05, 3.6] | |
| Total (95% Cl) Heterogeneity: Tau [#] = Test for overall effect ; | 11.39; C Z = 0.43 | hi [#] = 31 (P = 0.6 | 837 .41, d | f = 7 (P < 0 | .0001); | 1743 I ^a = 78 | 100.0% % | 0.63 [-2.24, 3.5 | n -500 -250 0 250 500 |
| F | Pabat | ic to an | | aparosco | pic to a | | | Odde Patio | Odds Patio |
| Study or Subgroup 2.5.1 Subtotal group 5 cm 2012 | Event | s Tot | 20 | Events | т | otal V | Veight N | I-H, Fixed, 95% CI | M-H, Fixed, 95% Cl |
| Eom 2012 Kim 2010 Park 2012 Pugliese 2009 Song 2009 Subtotal (95% CI) Total events Heterogeneity: Not ap Text for overall effect | oplicable | 0 1 0 1 1 | 16 30 16 20 12 | 00200 2 | | 11 120 48 20 261 | 2.7% 2.7% : | Not estimable 2.03 [0.18, 23.22] Not estimable Not estimable 2.03 [0.18, 23.22] | |
| 2.5.2 Total group Yoon 2012 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: | plicable $Z = 0.93$ | 0 | 36 36 .36) | 3 | | 65 65 | 8.8% 8.8% | 0.24 [0.01, 4.87] 0.24 [0.01, 4.87] | |
| 2.5.3 Subtotal and to Huang 2012 | tal grou | р 3 : | 39 | 3 | | 64 | 7.4% | 1.69 [0.32, 8.84] | |
| Hyun 2012 Kang 2012 Kim 2012 Woo 2011 Subtotal (95% CI) Total events | 1 | 3 10 2 10 4 23 4 23 84 2 | 38 00 36 36 49 | 6 5 18 9 41 | 1 | 83 282 861 591 881 | 12.3% 9.1% 41.8% 17.9% 88.5% | 1.10 [0.26, 4.65] 1.13 [0.22, 5.92] 1.10 [0.50, 2.40] 1.11 [0.34, 3.66] 1.16 [0.68, 1.96] | |
| Heterogeneity: Chi [#] = Test for overall effect: Total (95% Cl) Total events | 0.23, df Z = 0.54 | f = 4 (P = 0. 4 (P = 0. 99 | = 0.99 .59) 97 | 46 | 2 | 207 1 | 100.0% | 1.10 [0.66, 1.82] | |
| Test for overall effect. Test for subgroup diff | Z = 0.33 ferences Robot | 7 (P = 0 s: Not an | .71) pplica | aparosco | pic tea | m | | F Odds Ratio | 0.01 0.1 1 10 100 avours experimental Favours control Odds Ratio |
| 2.6.1 Subtotal group Eom 2012 | Event | <u>s Tot</u> | 30 | Events 4 | т | 62 62 | 1.6% | 2.23 [0.52, 9.62] | M-H, Fixed, 95% Cl |
| Kim 2010 Park 2012 Pugliese 2009 Subtotal (95% CI) Total events Heterogeneity: Chi≇ = Test for overall effect: | 1 4.31, dt Z = 0.6 | 0 5 1 1 f = 4 (P = 6 (P = 0 | 16 30 16 20 12 = 0.37 .51) | 1 9 6 2 7); I ^a = 7% | | 11 120 48 20 261 | 1.2% 2.2% 2.0% 1.4% 8.5% | 0.21 [0.01, 5.71] 2.47 [0.76, 8.00] 0.47 [0.05, 4.20] 0.47 [0.04, 5.69] 1.29 [0.61, 2.72] | • |
| 2.6.2 Total group Yoon 2012 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect | plicable $Z = 0.1$ | 6 6 7 (P = 0 | 36 36 | 10 10 | | 65 65 | 4.3% 4.3% | 1.10 [0.36, 3.32] 1.10 [0.36, 3.32] | - |
| 2.6.3 Subtotal and to Huang 2012 Hyun 2012 Kang 2012 Kim 2012 | tal grou | 10 6 8 4 11 4 4 | 39 38 00 36 | 10 32 29 81 | | 64 83 282 861 | 4.7% 7.7% 9.5% 35.5% | 0.98 [0.33, 2.95] 1.43 [0.66, 3.11] 1.42 [0.72, 2.81] 1.08 [0.73, 1.60] | |
| Woo 2011 Subtotal (95% Cl) Total events Heterogeneity: Chi [#] = Test for overall effect | 2 10 2.95, dt Z = 0.3 | 6 2: 84 6 = 4 (P = 1 (P = 0 | 36 49 = 0.57 .76) | 81 233 7); I [#] = 0% | 1 | 591 881 | 29.9% 87.2% | 0.78 (0.49, 1.25) 1.04 (0.81, 1.34) | - |
| Total (95% Cl) Total events Heterogeneity: Chi ^a = Test for overall effect Test for subgroup diff | 12 7.79, dt Z= 0.5 ferences | 91 5 f = 10 (F 2 (P = 0 s: Not a | 97 P = 0.6 .60) pplics | 265 55); I ^e = 09 able | 6 | 207 | 100.0% | 1.06 [0.84, 1.34] | 0.01 0.1 10 100 avours experimental Favours control |
| G Study or Subgroup | Robot | ic team s Tot | n L tal | aparosco Events | pic tea T | m otal V | Veight N | Odds Ratio 1-H, Fixed, 95% Cl | Odds Ratio M-H, Fixed, 95% Cl |
| Eom 2012 Kim 2010 | | 0 | 30 | 0 | | 62 11 | | Not estimable Not estimable | |
| r-ark 2012 Pugliese 2009 Song 2009 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect | oplicable $Z = 0.7$ | 1 0 1 9 (P = 0 | 16 20 12 | 0 1 0 1 | | 48 20 261 | 10.8% 10.8% | Not estimable 3.13 (0.18, 53.21) Not estimable 3.13 (0.18, 53.21) | |
| 2.7.2 Total group Yoon 2012 Subtotal (95% CI) Total events Heterogeneity: Not ap | oplicable | 0 | 36 36 | 0 0 | | 65 65 | | Not estimable Not estimable | |
| 2.7.3 Subtotal and to | tal grou | plicable p | 20 | | | | 17.07 | 1 00 10 1 | |
| Huang 2012 Hyun 2012 Kang 2012 Kim 2012 Woo 2012 Woo 2012 Subtotal (95% CI) Total events | | 1 0 1 2 4 1 2 8 4 | 39 38 00 36 36 49 | 1 0 3 2 6 | , | 64 83 282 861 591 881 | 17.0% 46.1% 26.1% 89.2% | 1.66 [0.10, 27.29] Not estimable Not estimable 1.32 [0.22, 7.92] 1.25 [0.11, 13.89] 1.36 [0.38, 4.88] | |
| Heterogeneity: Chi*= Test for overall effect: Total (95% CI) Total events Heterogeneity: Chi*= | 0.02, df Z = 0.41 | 5 5 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 | = 0.99 .63) 97 = 0.96 | $r_{1}^{2} = 0\%$ (5); $r_{2}^{2} = 0\%$ | 2 | 207 | 100.0% | 1.65 [0.49, 4.94] | 0.01 0.1 10 100 |
| . est ior overall effect | 2 = 0.71 | - (r- = 0. | nolics | able | | | | | avours experimental Favours control |

Figure 3. RG *vs.* LG: a) Operation time; b) Intraoperative blood loss; c) Hospital stay; d) Lymph node harvest; e) Anastomotic leakage; f) Morbidity; g) Mortality. doi:10.1371/journal.pone.0103312.g003

| 1 | A | Robotic | team | Lanarosconi | c team | | Odds Batio | Odds Batio |
|---|-------------------------------------------------------------------------------------------|-------------------------------------------|---------------------------------------|--------------------------------------|-----------------|----------------------|-------------------------------------------------------------|----------------------------------------------------------|
| _ | Study or Subgroup 2.8.1 Subtotal group | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% Cl |
| | Eom 2012 Song 2009 | 3 1 | 30 20 | 3 2 | 62 20 | 2.1% 2.2% | 2.19 [0.41, 11.54] 0.47 [0.04, 5.69] | |
| | Park 2012 Subtotal (95% CI) | 4 | 30 80 | 7 | 120 202 | 2.9% 7.2% | 2.48 [0.68, 9.12] 1.77 [0.69, 4.54] | - |
| | Total events Heterogeneity: Chi ² = Test for overall effect: | 8 1.40,df= Z=1.19 | 2 (P = 0. (P = 0.23) | 12 50); I ² = 0% | | | | |
| | 2.8.2 Total group Yoon 2012 | 5 | 36 | 4 | 65 | 2.9% | 2.46 [0.62, 9.82] | |
| | Subtotal (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: : | 5 plicable Z = 1.27 (| 36 (P = 0.20) | 4 | 65 | 2.9% | 2.46 [0.62, 9.82] | |
| | 2.8.3 Subtotal and tot | al group | 400 | 40 | 202 | 6.70 | 0.07/0.04 0.47 | |
| | Kang 2012 Huang 2012 Hyun 2012 | 8 3 12 | 100 | 10 8 19 | 282 | 5.7% 6.6% | 2.37 [0.91, 6.17] 0.58 [0.15, 2.35] | |
| | Kim 2012 Woo 2011 | 24 | 436 236 | 44 | 861 591 | 32.9% | 1.08 [0.65, 1.80] 0.71 [0.41, 1.25] | |
| | Subtotal (95% CI) Total events | 65 | 849 | 138 | 1881 | 90.0% | 1.06 [0.77, 1.44] | † |
| | Heterogeneity: Chi ² = Test for overall effect: | 7.05, df= Z = 0.34 (| 4 (P = 0. (P = 0.73) | 13); I ^a = 43% | | | | |
| | Total (95% CI) | 70 | 965 | 151 | 2148 | 100.0% | 1.15 [0.86, 1.53] | + |
| | Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe | 78 10.76, df Z = 0.94 (erences: | = 8 (P = ((P = 0.35) Not appli | 154 0.22); I≊ = 26%) cable | | | F | 0.01 0.1 1 10 100 avours experimental Favours control |
| | В | Robotic | team | Laparoscopi | c team | | Odds Ratio | Odds Ratio |
| - | Study or Subgroup 2.9.1 Subtotal group | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% Cl |
| | Eom 2012 Park 2012 Song 2009 | 1 | 30 | 1 2 0 | 120 20 | 1.4% | 2.10 [0.13, 34.83] 2.03 [0.18, 23.22] | |
| | Subtotal (95% CI) Total events | 2 | 80 | 3 | 202 | 3.0% | 2.07 [0.33, 13.01] | |
| | Heterogeneity: Chi ² = Test for overall effect: 2.9.2 Total group | 0.00, df= Z=0.77 | 1 (P = 0.44) | 99); I ² = 0% | | | | |
| | Yoon 2012 Subtotal (95% CI) | 1 | 36 36 | 6 | 65 65 | 9.0% 9.0 % | 0.28 [0.03, 2.43] 0.28 [0.03, 2.43] | |
| | Total events Heterogeneity: Not ap Test for overall effect: | 1 plicable Z = 1.15 | (P = 0.25) | 6 | | | | |
| | 2.9.3 Subtotal and tot Huang 2012 | al group 3 | 39 | 2 | 64 | 3.0% | 2.58 [0.41, 16.20] | |
| | Hyun 2012 Kang 2012 | 5 6 | 38 100 | 12 12 | 83 282 | 14.2% 12.8% | 0.90 [0.29, 2.75] 1.44 [0.52, 3.93] | |
| | Kim 2012 Woo 2011 Subtotal (95% CI) | 17 | 436 | 30 13 | 861 591 | 42.1% | 1.12 [0.61, 2.06] 0.77 [0.25, 2.38] | _ |
| | Total events Heterogeneity: Chi ² = Test for overall effect: | 35 1.61,df= Z=0.52 | 4 (P = 0. (P = 0.60) | 69 81); I² = 0% | 1881 | 87.9% | 1.12 [0.74, 1.70] | T |
| | Total (95% CI) Total events | 20 | 965 | 70 | 2148 | 100.0% | 1.07 [0.72, 1.60] | + |
| | Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffe | 3.63, df = Z = 0.34 erences: | 7 (P = 0. (P = 0.73) Not appli | 82); I ² = 0% cable | | | F | 0.01 0.1 1 10 100 avours experimental Favours control |
| C | Stude of Subaroun | Robotic | team | Laparoscopi | ic team | Mainht | Odds Ratio | Odds Ratio |
| - | 2.10.1 Subtotal group | events | 30 | Events | 62 | weight | Not estimable | M-H, Fixed, 95% Ci |
| | Park 2012 Song 2009 | 0 | 30 20 | 0 | 120 20 | | Not estimable Not estimable | |
| | Subtotal (95% CI) Total events | 0 | 80 | 0 | 202 | | Not estimable | |
| | Heterogeneity: Not ap Test for overall effect: | plicable Not appli | cable | | | | | |
| | 2.10.2 Total group | 0 | 36 | 0 | 65 | | Not estimable | |
| | Subtotal (95% CI) Total events | 0 | 36 | 0 | 65 | | Not estimable | |
| | Heterogeneity: Not ap Test for overall effect: | plicable Not appli | cable | | | | | |
| | 2.10.3 Subtotal and to Huang 2012 | otal group 1 | p 39 | 2 | 64 | 7.6% | 0.82 [0.07, 9.31] | |
| | Hyun 2012 Kang 2012 | 0 | 38 100 | 2 7 | 83 282 | 8.0% 20.1% | 0.42 [0.02, 9.03] 0.18 [0.01, 3.23] | |
| | Kim 2012 Woo 2011 | 1 7 | 436 236 | 3 19 | 861 591 | 10.3% 54.0% | 0.66 [0.07, 6.34] 0.92 [0.38, 2.22] 0.70 [0.34, 1.43] | |
| | Total events Heterogeneity: Chi ² = | 9 1.34,df= | 4 (P = 0. | 33 85); I² = 0% | 1001 | 100.078 | 6.1 0 [0.54, 1.45] | |
| | Test for overall effect: | Z = 0.99 | (P = 0.32) |) | | | | |
| | Total events | 9 1.34 df - | 965 4 (P = 0 | 33 85): I ^z = 0% | 2148 | 100.0% | 0.70 [0.34, 1.43] | |
| | Test for overall effect. Test for subgroup diffi | Z = 0.99 erences | (P = 0.32) Not appli |) cable | | | F | 0.01 0.1 1 10 100 avours experimental Favours control |
| I | D | Det | | | | | 044- 5-4 | p.11- p.4- |
| _ | Study or Subgroup | Robotic Events | Total | Laparoscopio Events | ; team Total | Weight | M-H, Fixed, 95% Cl | Udds Ratio M-H, Fixed, 95% Cl |
| 1 | Eom 2012 Park 2012 | 0 | 30 30 | 0 | 62 120 | | Not estimable | |
| | Song 2009 Subtotal (95% CI) | õ | 20 80 | õ | 20 202 | | Not estimable Not estimable | |
| 1 | Total events Heterogeneity: Not app Test for overall effect: N | 0 Ilicable Jot applic | able | 0 | | | | |
| ; | 2.11.2 Total group Yoon 2012 | 0 | 36 | 0 | 65 | | Not estimable | |
| | suptotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: N | 0 Ilicable Not applic | 36 able | 0 | 65 | | Not estimable | |
| | 2.11.3 Subtotal and to | tal group | 20 | | ~ • | 10.0~ | 1 66 10 40 07 07 | |
| | Hyun 2012 Hyun 2012 Kang 2012 | 0 | 39 38 100 | 0 | 83 292 | 19.0% | Not estimable | |
| 1 | Kim 2012 Woo 2011 | 2 | 436 | 3 | 861 591 | 51.7% 29.3% | 1.32 [0.22, 7.92] 1.25 [0.11, 13.89] | |
| | Subtotal (95% CI) Total events | 4 | 849 | 6 | 1881 | 100.0% | 1.36 [0.38, 4.88] | |
| | Heterogeneity: Chi ² = 0 Test for overall effect: 2 | 1.02, df = 1 = 0.48 (1 | 2 (P = 0.9 P = 0.63) | 99); I ² = 0% | | | | |
| | Total (95% CI) | | 965 | - | 2148 | 100.0% | 1.36 [0.38, 4.88] | - |
| | Heterogeneity: Chi ² = 0 Test for overall effect: 2 | 4 1.02, df = 1 = 0.48 (1 | 2 (P = 0.9 P = 0.63) | 99); I ^z = 0% | | | E | 0.01 0.1 1 10 100 avours experimental Favours control |
| | Test for subaroup diffe | rences: N | lot applic | able | | | | |

Figure 4. RG vs. LG: a) Clavien-Dindo grade I and II; b) Clavien-Dindo grade III; c) Clavien-Dindo grade IV; d) Clavien-Dindo grade V. doi:10.1371/journal.pone.0103312.g004

Supporting Information

Checklist S1 (DOC)

Diagram S1

(DOC)

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Author Contributions

Conceived and designed the experiments: LZ. Performed the experiments: LZ. Analyzed the data: LZ SA. Contributed reagents/materials/analysis tools: LZ TT. Contributed to the writing of the manuscript: LZ YS. Revised the manuscript: LZ YS.

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