Meta-analysis of laparoscopy-assisted distal gastrectomy and conventional open distal gastrectomy for early gastric cancer


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[Abstract] Background and Objective: With the application of laparoscopy, laparoscopic gastrectomy for the treatment of patients with early gastric cancer has been performed, but the safety and effectiveness of this method need to be explored. This study evaluated the safety and effectiveness of laparoscopy-assisted and conventional open distal gastrectomy for patients with early gastric cancer.

Methods: A search of MEDLINE, EMBASE, the Chinese Biomedical Database (CBM), and Cochrane Central Register of Controlled Trials (CENTRAL) identified all the randomized clinical trials that compared laparoscopy-assisted gastrectomy with open distal gastrectomy for patients with early gastric cancer published in the last 10 years. Quality assessment was done on each trial and relevant data were extracted from qualified trials. Meta-analysis was performed using RevMan 4.2.2 software (Cochrane).

Results: Six randomized controlled trials (RCTs) involving 218 patients were included. Comparing laparoscopic resection with open resection, results showed less estimated blood loss (WMD (weighted mean difference): –121.86; 95% CI (confidence interval): –145.61, –98.11; P < 0.001), earlier postoperative first flatus (WMD: –0.95; 95% CI: –1.08, –0.81; P < 0.001), and shorter durations of hospital stays (WMD: –2.27; 95% CI: –3.47, –1.06; P = 0.0002), but longer surgery times (WMD: 58.71; 95% CI: 52.69, 64.74; P < 0.001) and fewer lymph nodes dissected (WMD: –3.64; 95% CI: –5.80, –1.47; P = 0.001). There was no significant difference between the two groups in postoperative complications (OR (odds ratio): 0.57; 95% CI: 0.31, 1.03; P = 0.08).

Conclusions: The short-term outcome of laparoscopy-assisted distal gastrectomy for patients with early gastric cancer is superior to the open procedure, but its long-term outcome should be proven by further outcomes of RCTs.

Key words: Early gastric cancer, laparoscopy-assisted distal gastrectomy, conventional open distal gastrectomy, meta-analysis

Gastric cancer is one of the common digestive tract malignancies in our country. The disease is rarely caught early, and 90% of patients are diagnosed at advanced stages. Although significant progress has been made in the surgical treatment of gastric cancer, currently the 5-year survival rate after surgery for patients with advanced-stage gastric cancer is about 40%, while the number for early-stage gastric cancer has been up to 90%. With the improvement of laparoscopic instruments and the full development of the technique, laparoscopy-assisted distal gastrectomy (LADG) has gradually gained more clinical application in treating early stage gastric cancer. The clinical efficacy and safety of LADG and conventional open distal gastrectomy (ODG) have been reported by many studies. However, sample size is small in each individual randomized control trial (RCT) and the conclusions obtained therein are thus less robust. Herein, we performed a meta-analysis on the clinical efficacy and safety of laparoscopy-assisted surgery and open surgery, to provide an evidence basis for clinical decision-making.

Materials and Methods

Inclusion criteria

The inclusion criteria included: (1) study design: RCT, regardless of the language in which the trial was reported; (2) study subjects: patients with early-stage gastric cancer; (3) interventions: LADG in the test group and ODG in the control group; and (4) measured markers: safety markers, including surgery duration, blood loss, and incidence of complications, and efficacy markers, including time to restoration of bowel function (as time to first flatus or defecation after surgery), hospitalization duration, and the number of dissected lymph nodes.
Data retrieval and databases

Reports listed in MEDLINE, EMBASE, the Chinese Biomedical Database (CBM), and the Cochrane Central Register of Controlled Trials (CENTRAL) between July 1999 and June 2009 were retrieved, regardless of their languages and sample sizes of the study. In English-based databases, reports were retrieved using “early gastric cancer”, “laparoscopy-assisted distal gastrectomy”, “open resection”, and “randomized control trial” as the key words. In Chinese-based databases, “早期胃癌 (early-stage gastric cancer)”, “腹腔镜远端胃切除 (laparoscopy-assisted distal gastrectomy)”, “开腹手术 (open surgery)”, and “随机对照试验 (randomized control trial)” were used as key words for retrieval. Based on the reports obtained, the retrieval was broadened to ensure that no relevant reports were left out.

Quality evaluation of and data extraction from the literature

In accordance to the quality evaluation system for RCT from the Cochrane Reviewer Handbook[2], randomized controlled clinical trials included in this analysis underwent quality evaluation in terms of randomization, double-blinding, and controls. Data were then extracted using predesigned forms.

Methods for statistical analyses

Table 1 Characteristics of the randomized controlled trials (RCTs) included in this study

<table>
<thead>
<tr>
<th>Reference</th>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Number of LADG</th>
<th>Number of ODG</th>
<th>Level of lymph nodes dissection</th>
<th>Reconstruction of gastrointestinal tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5]</td>
<td>Huscher CG</td>
<td>2005</td>
<td>Italy</td>
<td>30</td>
<td>29</td>
<td>D1, D2</td>
<td>Roux-en-Y, Billroth II</td>
</tr>
</tbody>
</table>

Safety evaluation

Surgery duration Surgery duration was longer for the laparoscopy-assisted group compared to the open surgery group as reported in 5 studies[3-7], but was comparable between the 2 groups in one study[8]. The results of the meta-analysis showed that surgery duration was significantly longer in the laparoscopy-assisted groups than in the open surgery groups (WMD: 58.71; 95% CI: 52.69: 64.74; P < 0.001) (Figure 1).

Results

Retrieved data

In the primary retrieval, a total of 441 English reports and 8 Chinese reports were identified. Among these reports, 435 reports of nonrandomized trials and nonclinical trials or repeatedly published reports were excluded. As a result, a total of 6 English RCT reports and 0 Chinese reports were included. The sample sizes of included studies ranged from 20 to 59 patients (Table 1).
Blood loss In 4 study reports, blood loss was less in the laparoscopy-assisted groups than in the open surgery groups \[3,4,7,8\], but in another 2 studies, the difference was not significant\[5,6\]. The meta-analysis suggested that blood loss in the laparoscopy-assisted groups was significantly less than in the open surgery groups (WMD: -121.86; 95% CI: -145.61, -98.11; P < 0.001) (Figure 2).

![Figure 2](image)

Figure 2 Analysis of the operative blood loss (mL)

Complications Post-surgical complication profiles were described in the 6 study reports. All of the studies revealed insignificant differences between the two groups, except one study suggesting that the LADG group had fewer complications than the ODG group. Results of the meta-analysis showed that the differences in complications were not significant between the laparoscopy-assisted groups and the open surgery groups (OR: 0.57; 95% CI: 0.31, 1.03; P = 0.066) (Figure 3).

![Figure 3](image)

Figure 3 Analysis of overall complications

Efficacy of surgeries

Time to restoration of bowel function Time to first flatus via the anus after surgery was reported in 3 studies\[3,5,6\]. In one study report, time to first flatus was shorter in the laparoscopy-assisted group than in the open surgery group\[3\], while in the other 2 studies, the difference was not significant\[5,6\]. The results of the meta-analysis suggested that time to first flatus was shorter for the laparoscopy-assisted group compared to the open surgery group (WMD: -0.95; 95% CI: -1.09, -0.81; P < 0.001) (Figure 4).

Hospitalization duration Hospitalization duration was reported in 5 of the studies\[3,5-8\]. In 2 studies, hospitalization duration was shorter for the laparoscopy-assisted group compared to the open surgery group\[7,8\], whereas the other 3 studies reported insignificant differences between the two groups\[3,5,8\]. Meta-analysis showed that hospitalization duration for the laparoscopy-assisted group was shorter than for the open surgery group (WMD: -2.27; 95% CI: -3.47, -1.06; P < 0.001) (Figure 5).

Number of dissected lymph nodes The number of dissected
lymph nodes during surgery was described in 5 study reports\textsuperscript{[3,5-8]}, one of which suggested that the number of dissected lymph nodes in the laparoscopy-assisted group was smaller than in the open surgery group\textsuperscript{[3]}, while the other 4 studies suggested insignificant differences\textsuperscript{[5-8]}. Meta-analysis revealed that the number of dissected lymph nodes in the laparoscopy-assisted group was significantly smaller compared to the open surgery group (WMD: -3.64; 95% CI: -5.80, -1.47; \( P = 0.001 \)) (Figure 6).

### Discussion

**Limitations of this study**

**Limitations of the included studies** Included in this meta-analysis were 6 foreign study reports of various levels of quality, suggesting selection bias, execution bias, and measurement bias to different extents. The long-term efficacy of the surgical treatment was not thoroughly discussed in the included reports. This has impacted the comprehensiveness of the evaluation on the measured markers in this meta-analysis. Among the included studies, the grading system for disease severity, as well as a staging system, for the two groups of patients was not well defined. In some studies, the number of included patients was small and had thus decreased the power of the test.

**Limitations of this meta-analysis** Methodological quality issues of varying degrees were seen for the reports included in this meta-analysis. Different markers had been selected. This decreases the robustness and comprehensiveness of the results of this meta-analysis. Different gastric resection approaches, resection scopes, and perioperative treatments were used in the included studies and might have given rise to clinical heterogeneity.

**Efficacy**

Ever since 1994 when Kitano \textit{et al.} performed the very first LADG\textsuperscript{[9]}, the procedure has gradually gained more clinical application both at home and abroad because it is associated with less pain for the patients after surgery, shorter times to the restoration of bowel function, shorter hospitalization durations,
less scarring on the abdominal wall, less impact on the immunity of the human body, and a lower incidence of complications. However, LADG is technically more difficult and riskier. Moreover, it is doubtful whether it can achieve as extensive lymph node dissections as open surgery. Therefore, its efficacy is still seriously questioned. In our country, LADG has just made its debut. Surgeons at a small number of centers have performed the procedure, but at the moment it is hard to evaluate the quality of these surgeries. In addition, no relevant clinical RCT has been conducted in our country as yet. In this study, we mainly included foreign RCTs and performed a comparative analysis on the safety and clinical efficacy of LADG and ODG. Although the LADG procedure takes longer, it was associated with less blood loss during surgery than ODG. The incidence of post-surgical complications was comparable between them, but the number of dissected lymph nodes was smaller for LADG than for ODG.

The guidelines by Japanese Gastric Cancer Association recommend that, for early-stage gastric cancer, intramucosal carcinoma, and submucosal carcinoma of less than 1.5 cm in diameter, the dissection should cover the perigastric lymph nodes (D1) and those around the left gastric artery. For node-negative submucosal carcinomas as indicated by presurgical examinations and early-stage gastric cancer of less than 2.0 cm in diameter with positive perigastric lymph nodes, the dissection should cover the perigastric lymph nodes (D1) and those around the left gastric artery and the celiac trunk. As for early-stage gastric cancer of more than 2.0 cm in diameter with lymph node metastasis, the dissection should include perigastric lymph nodes and those around the left gastric artery, the common hepatic artery, the proper hepatic artery, the celiac trunk, and the splenic artery. While in the US and some European countries, extensive lymph node dissection is rarely performed, because two European RCTs suggested that D2 dissection showed no survival advantage over D1 dissection, but was associated with higher surgery-related mortality and more complications than D1 dissection. This study suggested that ODG was superior over LADG in terms of lymph node dissection. This may be related to the learning curve of laparoscopy skills in the included RCTs, indicating that, during learning phase, it is better to use LADG in early-stage gastric cancer without potential metastasis. Extensive lymph node dissection with LADG is more difficult than laparoscopy-assisted cholecystectomy and colectomy, because it has to identify major vessels and accomplish extensive dissection of large numbers of lymph nodes. This has also resulted in a smaller number of dissected lymph nodes in the LADG groups. In most study reports, the scope of lymph node dissection is limited to within the D1 level. Although LADG has reached the plateau of the learning curve, lymph node dissection is still time-consuming. With improvements in laparoscopic instruments and skills, surgery duration will be further shortened, and the number of dissected lymph nodes further increased.

LADG induces less impact and less injury on the gastrointestinal tract, and therefore triggers a milder stress response. As a result, gastrointestinal function will be restored for the patients early after the surgery and the risk of intestinal obstruction is eliminated. On the other hand, earlier adoption of a normal diet after surgery and shorter hospitalization durations are useful in reducing the incidence of nausea, vomiting, and abdominal discomfort after surgery. Therefore, the short-term efficacy of LADG is better than that of ODG. While in a meta-analysis including 951 patients from non-RCTs by Danny et al., it was also suggested that LADG was superior over ODG in terms of blood loss during surgery, adoption of a normal diet after surgery, hospitalization duration, and the restoration of bowel functions. However, no conclusive evidence has been reported for the long-term efficacy of LADG. Among the 6 RCTs included in this meta-analysis, the study by Huscher et al. showed that the 5-year survival and disease-free survival rates were not significantly different between the two groups, but the survival profile was not specified in the other 5 studies. The reason for this may be that laparoscopy-assisted surgery has been used to treat early gastric cancer for a short time, therefore

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>LADG Mean (SD)</th>
<th>N</th>
<th>ODG Mean (SD)</th>
<th>WMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>WMD (fixed) 95% CI</th>
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<td>1</td>
<td>14</td>
<td>20.20 (3.60)</td>
<td>14</td>
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<tr>
<td>2</td>
<td>10</td>
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<td>10</td>
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<tr>
<td>3</td>
<td>24</td>
<td>31.80 (13.50)</td>
<td>23</td>
<td>38.10 (15.90)</td>
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<tr>
<td>4</td>
<td>14</td>
<td>28.00 (14.00)</td>
<td>14</td>
<td>27.00 (10.00)</td>
<td>5.76 [1.00, 10.01]</td>
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<td>5</td>
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<td>21</td>
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<td></td>
<td>100.00</td>
<td>-3.64 [-5.80, -1.47]</td>
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</tbody>
</table>

Test for heterogeneity: chi²=4.35, df=5 (P=0.36), I²=8.1%  
Test for overall effect: Z=3.29 (P<0.0010)

Figure 6 Analysis of the number of lymph nodes dissected
sample sizes are small and systemic randomized controlled trials are rare. A multicenter non-RCT Japanese study\(^n\) showed that mortality during surgery was 0 in 1294 patients with early-stage gastric cancer who underwent laparoscopy-assisted resection. The percent of patients with stage-Ia, -Ib, and -II disease after surgery were 93.7%, 5.8%, and 0.5%, respectively. The median follow-up time was 36 months and recurrence was seen in merely 0.6% of the patients. The 5-year disease-free survival rates for patients with stage-Ia, -Ib, and -II disease were 99.8%, 98.7%, and 85.7%, respectively. The long-term efficacy of LADG was obviously superior to ODG.

In conclusion, LADG for patients with early-stage gastric cancer is associated with less blood loss, shorter times to the restoration of bowel function, as well as shorter hospitalization durations, with superior short-term efficacy compared to ODG. However, the number of published studies included in this analysis is small, resulting in a small sample size. Moreover, follow-up time is short as well. The limitations are obvious in both the included literature and this meta-analysis. Therefore, further and intensive large-sample multicenter RCTs are needed to obtain more robust results about the long-term efficacy of these two surgical procedures.

References