Comparison between total laparoscopy and laparoscopy-assisted distal gastrectomy for gastric cancer

A meta-analysis based on Japanese and Korean articles

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ABSTRACT

الأهداف: تقييم سلامة و فعالية استئصال المعدة الكلي بمساعدة تنظير المعدة (TLDG).

الطريقة: أجرينا هذا التحليل التلوي خلال الفترة من أبريل حتى يوليو 2013م في مستشفى السرطان في سيتشوان، تشينغ دو، الصين. وبالبحث في قاعدة المكتبة الأمريكية PubMed و EMBASE وقاعدة البيانات الصينية المتكاملة لمصادر المعرفة المحدثة حتى مايو 2013م والتي احتوت على 8 دراسات استرجاعية ودراسة واحدة استطلاعية متضمنة 2,046 مريض.

النتائج: أظهرت النتائج أن TLDGمرتبط مع انخفاض فقدان الدم (متوسط الفرق=-22.39,0.04=*p*)، وعدد أكبر من انحصار الغدد اللمفاوية (متوسط الفرق= 2.74،0.02=*p*). لم يكن هناك اختلاف كبير بين المجموعتين في وقت الجراحة، والوقت للريح الأول، وطول الإقامة في المستشفى بعد العملية، والمضاعفات بعد العملية الجراحية.

الخاتمة: بالمقارنة مع استئصال المعدة باستخدام المنظار للمعدة، يؤدي TLDG إلى التقليل من فقدان الدم، وعدد أكبر من العقد اللمفاوية المحصودة. كما أنه آمن و فعّال لسرطان المعدة.

Objectives: To assess the safety and feasibility of total laparoscopy distal gastrectomy (TLDG).

Methods: This meta-analysis was conducted between April and July 2013 in Sichuan Cancer Hospital, Chengdu, China. We searched PubMed, EMBASE and China Knowledge Resource Integrated Database updated until May 2013. Eight retrospective studies and one prospective study involving 2,046 total patients were included.

Results: The results showed that TLDG was associated with lower blood loss (mean difference=-22.39, *p*=0.04). and a greater number of harvested lymph nodes (mean difference=2.74, *p*=0.02). There was no significant difference between the 2 groups in operation time, time to first flatus, length of postoperative hospital stay, and postoperative complications.

Conclusion: Compared with laparoscopy-assisted distal gastrectomy, TLDG resulted in reduced blood loss, and a greater number of harvested lymph nodes. Total laparoscopy distal gastrectomy is safe and feasible for gastric cancer.

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Laparoscopic surgery has been favored by surgeons. Compared with the conventional open surgery, laparoscopy-assisted distal gastrectomy (LADG) is acknowledged as having many advantages, such as lower blood loss, faster recovery, and shorter hospital stays.[1,2] The LADG has not only been widely used in early gastric cancers and gastrointestinal stromal tumors, but has also been used in advanced gastric cancers.[3,4] As surgery

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techniques advanced and the endoscopic linear stapler was developed, total laparoscopy distal gastrectomy (TLDG) was gradually applied.[5] For TLDG, tumor location determination, specimen removal, and anastomotic reconstruction are different from LADG. Intracorporeal gastrointestinal anastomosis is the major difference between LADG and TLDG.[6] A side-to-side anastomosis using a linear stapler, called "delta-shaped anastomosis," is widely performed by gastrointestinal surgeons. Although there are difficulties associated with intracorporeal anastomosis, TLDG is considered to be less invasive, and results in smaller wounds, and is accepted by most surgeons.[7,8] Many studies have been performed to compare the short-term clinical outcomes of TLDG and LADG, but there were many differences in the data in these studies. Therefore, we performed this meta-analysis to compare the immediate postoperative outcomes of TLDG, and LADG for gastric cancer, and to further assess the safety and feasibility of TLDG.

Methods. This meta-analysis was conducted from April to July 2013 in Sichuan Cancer Hospital, Chengdu, China. We searched PubMed, EMBASE, and the China Knowledge Resource Integrated Database (CNKI), and no restrictions were applied. The following key words were used: 'gastric' or 'stomach,' 'cancer' or 'tumor' or 'carcinoma,' 'laparoscopy,' or 'laparoscopic,' 'laparoscopy-assisted' or 'laparoscopic-assisted,' and 'gastrectomy.' The last search was conducted in May 2013. A total of 1,169 articles were selected (**Figure 1**). The collected studies for this meta-analysis met all of the following inclusion criteria: (1) contained both TLDG and LADG for gastric cancer; (2) study designs were retrospective case-control and prospective, non-random studies; and (3) sufficient data were provided. The main exclusion criteria included: (1) contained either TLDG or LADG alone for gastric cancer; (2) no sufficient data; (3) contained cases of total and proximal gastrectomy. According to the pre-specified inclusion and exclusion criteria, all data were extracted independently. Crosschecking was used to discover differences, and disagreements were resolved through discussion. The following data from each study were extracted: the name of the first author, year of publication, nationality of the corresponding author, study period, numbers of TLDG and LADG procedures, characteristics of patients, operation time, blood loss, postoperative hospital stay, lymph nodes, time to first flatus, and postoperative complications. When duplicate articles and data were discovered, the article that was published most recently, or contained more study subjects was included.

The RevMan 5.2 statistical package (The Cochrane Collaboration, www.cochrane.org) was used to perform statistical analysis of the data. Heterogeneity was assessed using the chi-squared test with significance set at $p<0.10$, and measured using the I^2 index. When $p>0.10$, the fixed effects model was used. When $p<0.10$, the random effect model was used. For qualitative variables (surgical complications), the odds ratio (OR) was used to assess the outcomes of these studies. For quantitative variables (operation time, blood loss, hospitalization days, lymph nodes, time to first flatus) the mean difference (MD) with 95% confidence interval (CI) was used to assess the outcomes of these studies. $P<0.05$ was considered as statistically significant. The study was approved by the Institution Review Board.

Results. In the process of searching the literature, only one prospective, multicenter study was found. We included both retrospective and prospective studies that were of high quality. A total of 9 studies were included in our meta-analysis, comprising 2,046 patients; 846 of these patients underwent TLDG and 1,200 underwent LADG.[6,9-16] The main characteristics of the 9 studies were not statistically different, this information is listed in **Table 1**.

Operation time. Operation time was measured in all 9 studies. The meta-analysis results had shown that there was no significant difference for TLDG and LADG for gastric cancer in operation time. The heterogeneity test for operation time was: $I^2=95\%$, $p<0.00001$, and the test for overall effect was: $Z=0.28$, $p=0.78$ (**Table 2**).

Blood loss. There were 6 studies that provided data on blood loss (784 patients). Our results revealed that blood loss of TLDG was less than that of LADG. Meanwhile, a significant difference was displayed. The heterogeneity test for blood loss was: $I^2=61\%$, $p=0.02$, and the test for overall effect was: $Z=2.07$, $p=0.04$ (**Figure 2**).

Number of harvested lymph nodes. All studies (2,046 patients) provided data on the number of harvested lymph nodes. The MD of harvested lymph nodes came from TLDG minus LADG. Moreover, the result displayed the harvested lymph nodes was greater of TLDG than of LADG. Forest plot revealed that there was a significant difference between TLDG and LADG in the dissected lymph nodes. The heterogeneity test for the number of harvested lymph nodes was: $I^2=75\%$, $p=0.0001$, and the test for overall effect was: $Z=2.26$, $p=0.02$ (**Figure 3**).

Time to first flatus. Eight studies (1647 patients) provided data on the time to first flatus. The Forest plot results revealed there was no significant difference in the time to first flatus between TLDG and LADG. The heterogeneity test for time to first flatus was: I^2=77%, p<0.0001, and the test for overall effect was: Z=1.88, p=0.06 (**Table 2**).

Postoperative hospital stay. All studies provided data on hospital stay, however, Kim et al[9] provided only mean hospital stay, not postoperative hospital stay, and so this study was excluded. Eight studies (1699 patients) were included for the analysis of postoperative hospital stay. The results showed that there was no significant difference in postoperative hospital stay between TLDG and LADG. The heterogeneity test for postoperative hospital stay was: I^2=80%, p<0.00001,and the test for overall effect was: Z=0.93, p=0.35 (**Table 2**).

Postoperative complications. Not all studies provided intact data regarding postoperative complications. One study only analyzed the anastomosis-related complications, and one study did not provide any data on postoperative complications. We collected data on

Table 1 - Characteristics of studies of total laparoscopy distal gastrectomy (TLDG) and laparoscopy-assisted distal gastrectomy (LADG) for gastric cancer.

Study	Country	Study period	TLDG	LADG	Male to female ratio		Age, years		Body mass index (kg/m^2)	
			n		TLDG	LADG	TLDG	LADG	TLDG	LADG
Choi et al,[15] 2013	Korea	2007-2012	37	35	23:14	22:13	65.2±10.9	67.9±10.1	24.7±3.2	24.2±3.1
Kim et al,[6] 2013	Korea	2005-2012	111	136	77:44	91:45	61.0±11.2	60.1±11.7	23.5±4.5	23.5±2.8
Lee et al,[14] 2012	Korea	2004-2011	130	269	76:54	161:108	61.0±11.8	62.5±12.0		
Kinoshita et al,[13] 2011	Japan	2007-2009	42	41	25:17	30:11	64.7±10.8	68.4±10.3	23.1±3.1	22.8±3.3
Kim et al,[12] 2011	Korea	2006-2009	180	268	115:65	184:84	55.8±11.7	56.7±11.5	24.2±2.9	24.2±4.0
Kim et al,[9] 2011	Korea	2009-2010	31	79	23:8	42:37	59.5±11.7	55.4±11.1	24.0±3.4	23.0±1.7
Kim et al,[10] 2011	Korea	2009-2010	239	328	155:84	198:130	56.6±12	55.4±11.2	24±3.2	23.1±2.7
Ikeda et al,[11] 2009	Japan	2005-2007	56	24	28:28	16:8	63.5±11.2	64.5±11.9	21.9±3.5	22.4±3.1
Song et al,[16] 2008	Korea	2005-2006	20	20	13:7	12:8	58.7±7.1	58.5±10.1	23.0±3.1	22.8±2.8

Table 2 - Meta-analysis results of operation time, time to first flatus, postoperative hospital stay. Mean difference are shown with 95% confidence intervals (CIs).

Variables	No. of studies	No. of patients	Z	Mean difference inverse variance, random, 95% CI	*P*-value	I^2	*P*-value
						Heterogeneity test	
Operation time	9	2046	0.28	2.15 (-12.67, 16.97)	0.78	95%	0.00001
Time to first flatus	9	2046	1088	-0.17 (-0.35, 0.01)	0.06	77%	0.00001
Postoperative hospital stay	9	2014	0.93	-0.30 (-0.93,0.33)	0.35	80%	0.00001

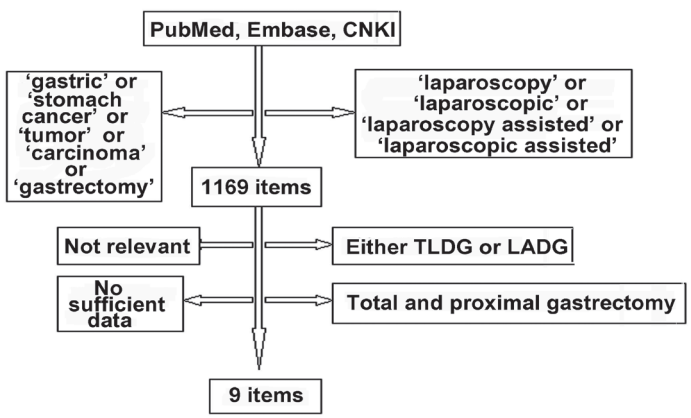

Figure 1 - Flow chart of the selecting process of articles. LADG - laparoscopy-assisted distal gastrectomy, TLDG - total laparoscopy distal gastrectomy. CNKI - China Knowledge Resource Integrated Database.

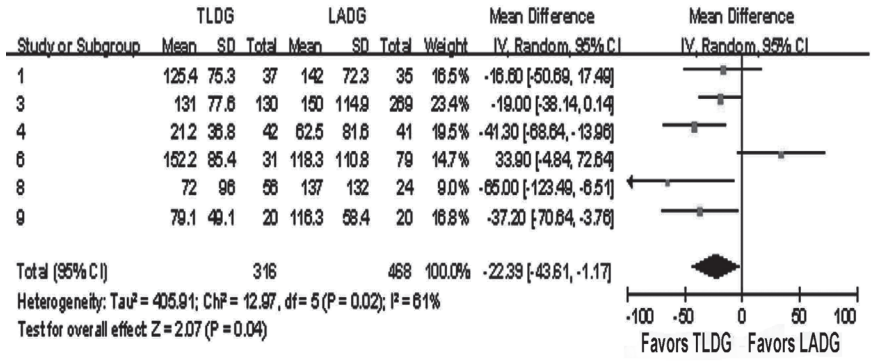

Figure 2 - Forest plot corresponding to blood loss, standardized mean differences (SMDs) are shown with 95% confidence interval (CI). LADG - laparoscopy-assisted distal gastrectomy, TLDG - total laparoscopy distal gastrectomy, IV - inverse variance, df - degrees of freedom

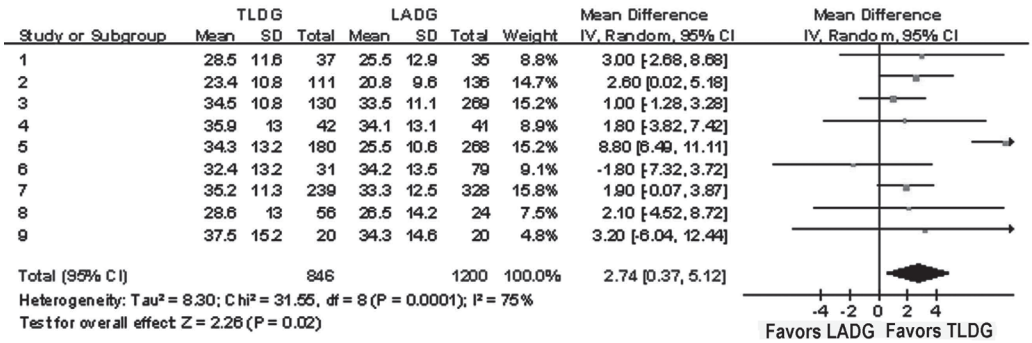

Figure 3 - Forest plot corresponding to number of harvested lymph nodes, mean differences with 95% confidence interval (CI). LADG - laparoscopy-assisted distal gastrectomy, TLDG - total laparoscopy distal gastrectomy, IV - inverse variance, df - degrees of freedom

Table 3 - Meta-analysis results of postoperative complications, and odds ratio (OR) with 95% confidence interval (CI).

Variables	No. of studies	No. of patients	Fixed OR	95% CI	*P*-value	I^2 Heterogeneity test	*P*-value
Overall postoperative complications	7	1607	1.02	0.72 ± 1.45	0.92	0%	0.44
Main postoperative complications							
Anastomotic leakage	8	2006	0.91	0.45 ± 1.84	0.80	0%	0.48
Wound problem	6	1159	0.490	0.22 ± 1.10	0.08	0%	0.88
Postoperative bleeding	7	1926	1.40	0.73 ± 2.68	0.31	0%	0.56

the overall postoperative complications from 7 studies including a total of 1,607 patients. Forest plot results revealed there was no significant difference between TLDG and LADG. Moreover, we also analyzed the main postoperative complications, such as anastomotic leakage, wound problems, and postoperative bleeding (**Table 3**). Interestingly, these were no differences between the 2 groups.

Discussion. Laparoscopy gastrectomy (LG) was widely accepted for treating early gastric cancer in Japan and Korea.[17-19] Many studies demonstrated the safety and feasibility of LG, and most surgeons performed LADG as the first step of LG.[20-22] During the process of LADG, when the surrounding omentum is divided and the blood vessels are clipped, surgeons must pull the stomach out of the abdomen through a small

abdominal wall incision. Then, the surgeons cut off the stomach carcinoma, and perform the anastomosis extracorporeally. This process has technical difficulties, especially in cases of obese patients.[6,15] However, compared with open surgery, LADG was less invasive, and was associated with shorter hospital stays and faster recovery time,[1] except for several trocar puncture wounds, LADG only requires a small abdominal incision to complete the surgery. Along with the accumulated surgeon experience and improved anastomotic equipment came the development of TLDG. Compared with LADG with extra-corporeal stomach dissection and gastroenterostomy, the specimen was extracted via a smaller incision, and anastomosis was performed intracorporeally during TLDG. The mini laparotomy was considered to be less invasive and more favorable. Existing research compared the short-term clinical outcomes between TLDG and LADG for gastric cancer, but inconsistent conclusions were reported. For example, some studies reported that TLDG can shorten the postoperative hospital stay, while other researchers do not agree. Therefore, we performed this meta-analysis to compare the clinical outcomes between TLDG and LADG to confirm whether TLDG should be recommended for distal gastrectomy.

In our studies, compared with LADG, TLDG had lower blood loss and more harvested lymph nodes. The smaller abdominal incision of TLDG may be the reason for lower blood loss. We cannot confirm why TLDG resulted in a greater number of harvested lymph nodes, but most studies observed this, and a statistically significant difference was displayed. The D2 lymph node dissection is the standard radical surgery for gastric cancer. Based on this radical surgery, the number of lymph nodes harvested should be the same in both TLDG and LADG. More high quality clinical trials are needed to confirm this inference. Although the mean difference in the operation time between TLDG and LADG was 2.15 in the current study, -there was no significant difference.

Many studies revealed that TLDG can shorten the postoperative recovery time and reduce postoperative complications. Our meta-analysis results revealed that no significant differences existed in the postoperative recovery time and complications between TLDG and LADG. In the studies from our search, only one reported the comparative outcome of total cost.[16] Due to the requirement for more staplers, the cost of TLDG was higher than that of LADG. More studies are needed to compare surgery costs between LADG and TLDG. Due to the heterogeneity of the included studies, the meta-analysis results should be treated with caution.

Several limitations were discussed in our study. First, the sample size was low in some of the studies, and most of the studies included in this meta-analysis were retrospective studies, only one prospective, non-random study was included. Compared with randomized controlled trials, factors in the retrospective studies were not controlled, thereby decreasing the reliability of the results. Second, LADG and TLDG were performed from 2005-2012. Due to the experience of these surgeons and the fact that the learning curve revealed large differences, the clinical outcomes varied greatly. Therefore, it may be better to combine these studies using a random-effect model.

In summary, this meta-analysis provides evidence that TLDG significantly reduces intraoperative bleeding and harvests more lymph nodes. However, long-term follow-up outcome is not clear, especially regarding the recurrence rate and overall survival rate. At the same time, more prospective, random trials are needed to confirm the clinical outcomes of TLDG.

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