Laparoscopic Total Gastrectomy for Gastric Cancer

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Laparoscopic total gastrectomy (LTG) has been more widely performed in the last decade because of improvements in the techniques and safety of laparoscopic distal gastrectomy. However, due to its technical difficulty, there are still concerns regarding the safety of LTG. Meta-analyses have shown that LTG is technically feasible, safe, and may offer advantages over open total gastrectomy for treatment of gastric cancer. Various methods of performing esophagojejunostomy have been developed in an effort to decrease the rate of anastomosis-related complications, and have ultimately improved the safety and acceptance of LTG. However, there is still a lack of level-one evidence in support of LTG. Conduct of large-scale, randomized clinical trials will be needed in order to verify the safety and efficacy of LTG. Therefore, we reviewed the current status and some of the controversies surrounding LTG.

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INTRODUCTION

Laparoscopic distal gastrectomy (LDG) for gastric cancer has been widely accepted in clinical practice since it was first performed by Kitano in 1994.¹ Since that first report, several large-scale cohort studies and meta-analyses have demonstrated the technical feasibility, surgical benefits, and safety of LDG.²⁻⁵ Large-scale randomized clinical trials (RCTs) comparing the long-term oncological outcomes between LDG and open distal gastrectomy are now underway.^{6,7} These RCTs will provide more concrete evidence regarding the efficacy and safety of LDG.

Laparoscopic total gastrectomy (LTG) is not yet widely accepted as a treatment option for gastric cancer because of concerns regarding its technical difficulty and safety. In addition, there are no established standard procedures for

esophagojejunostomy (E-J stomy) in LTG, even though many methods have been reported in the literature. Nevertheless, LTG is increasingly being performed because of the recent developments in technologies, especially laparoscopic instruments, and the surgeons' accumulating experience of this procedure. The number of studies evaluating the technical feasibility and safety of LTG is also increasing annually, with several meta-analysis, prospective observatory studies, and RCTs, being underway or recently published.

The purpose of this article is to review the current status of LTG, focusing on its safety, technical feasibility, and surgical usefulness. It is also important that surgeons have a broad knowledge of the controversial issues regarding the use of LTG for the treatment of gastric cancer. Therefore, we reviewed the current status and some of the controversies surrounding LTG.

COMPARISON BETWEEN LTG AND OPEN TOTAL GASTRECTOMY (OTG)

Many published articles have compared LTG with OTG in order to validate the feasibility and safety of LTG. Haverkamp et al.⁸ conducted a meta-analysis comparing LTG with OTG, and concluded that LTG had better short-term outcomes; reduced blood loss, shorter hospital stay, and reduced post-operative complications. However, only eight studies were included in this meta-analysis, and most of the included studies involved relatively small sample sizes and did not evaluate the long-term outcomes.

Since the report by Haverkamp et al, several updated meta-analyses have been published (Table 1) and showed that LTG was associated with several benefits, including reduced blood loss, less postoperative pain, quicker recovery of bowel function, earlier oral intake, shorter hospital stay, and reduced postoperative morbidity.⁹⁻¹³ LTG and OTG were similar in terms of the number of harvested lymph nodes (LNs), resection margin, hospital mortality, and long-term outcomes. The only disadvantage of LTG was a longer operative time. The authors concluded that LTG is technically feasible, safe, and may offer some advantages over OTG in the treatment of gastric cancer.

Unfortunately, most of the studies included in these meta-analyses had small sample sizes. Therefore, further large-scale cohort studies analyzing long-term survival or RCTs are required to validate the feasibility, safety, and long-term oncological outcomes of LTG. The Korean Laparoscopic Gastrointestinal Surgery Study (KLASS)-03 trial (NCT01584336) is an ongoing phase II prospective observatory study to compare LTG and OTG in patients with clinical stage I gastric cancer with a planned sample size of 168 patients.

RECONSTRUCTION METHODS

Meta-analyses have shown that the rates of anastomosis-related complications were not significantly different between LTG and OTG.⁸⁻¹³ However, there are many reconstruction methods of E-J stomy for LTG. Generally, the E-J stomy methods can be divided into two main types depending on whether a circular stapling,¹⁴⁻²¹ or linear stapling²²⁻²⁹ approach was used. Four circular stapling approaches have been used: extracorporeal, OrVil[®], endo-purse-string instrument (Endo-PSI II, Lap-Jack), and laparoscopic sutures (including Endostitch). Two linear stapling approaches have been used: overlapping and functional end-to-end stapling. Modified methods are included in the subtype to which they originally belonged.

The surgical outcomes of E-J stomy studies that enrolled

Table 1. Meta-analyses of laparoscopic and open total gastrectomy for gastric cancer

Authors	Year	Studies (n)	LTG Cases (n)	OTG Cases (n)	Total Cases (n)	Op. Time (min) [†]	EBL (mL) [†]	RLNs (n) [†]	PRM (cm) [†]	Analgesics [†]	Flatus (POD) [†]	Oral intake (POD) [†]	Hospital stay (POD) [†]	Cx. [‡]	Wound Cx. [‡]	Mortality [‡]	5 year OS [‡]	DFS [‡]
Haverkamp L ⁸	2013	8	314	384	698	55.50*	-227.61*	-2.47	NA	NA	-0.80*	-1.2*	-3.96*	0.51	NA	0.68	n=2	
Shen H ⁹	2013	8	409	752	1,161	41.06*	-253.17*	-2.14	NA	-2.55*	-0.90*	NA	-4.08*	0.79	0.53	0.83	n=2	
Chen K ¹⁰	2013	9	436	785	1,221	57.68*	-1.71*	-1.41	-0.40	-0.86*	-0.76*	-0.81*	-2.67*	0.79	NA	0.72	n=3	
Xiong JJ ¹¹	2013	15	811	1,211	2,022	48.25*	-201.19*	-2.49*	-0.26	-0.09	-0.82*	-1.30*	-3.55*	0.73*	0.39*	0.74	n=7	
Wang W ¹²	2014	17	955	1,358	2,313	22.86*	-179.6*	2.33	0.06	-2.46*	-0.80*	-1.11*	-3.37*	0.78*	0.35*	0.94	0.81	0.62

LTG = laparoscopic total gastrectomy; OTG = open total gastrectomy; Op. = operation; EBL = estimated blood loss; RLNs = retrieved lymph nodes; PRM = proximal resection margin; POD = postoperative days; Cx. = complications; OS = overall survival; DFS = disease free survival; NA = not available; SM = Standard mean difference; * $p < 0.05$; † Weighted mean difference; ‡ Odds ratio.

Table 2. Surgical outcomes according to various reconstruction methods after LTG

Author	Country	Year	N	Stapler	Method	Time (min)	EBL (ml)	Morbidity (%)	E-J leak (%)	Duodenal stump leak (%)	E-J Stricture (%)	Luminal Bleeding (%)	Stasis (%)	Mortality (%)	Hospital stay (POD)
Jeong GA ¹⁴	Korea	2009	131	Circular	Extracorporeal	269.0	NA	19.1	2.3	0	0	2.3	1.5	0	11.3
Lee SE ¹⁵	Korea	2009	67	Circular	Extracorporeal	305.4	190.7	26.9	1.5	0	9.0	0	0	0	13.6
Kim MG ¹⁶	Korea	2011	63	Circular	Extracorporeal	150.8	179.7	12.7	1.6	0	0	1.6	0	NA	9.6
Eom BW ¹⁷	Korea	2012	100	Circular	Extracorporeal	283.7	NA	27.0	4.0	0	5.0	0	1.0	1.0	12.6
Jeong O ¹⁸	Korea	2013	122	Circular	Extracorporeal & Orvil	289.0	249.0	23.8	7.4	1.6	1.6	7.4	0.8	1.6	11.8
Lee JH ^{19*}	Korea	2012	94	Circular	Endo-P & Extracorporeal	230.0	150.0	18.1	5.3	0	0	0	1.1	0	7.4
Lee MS ^{20†}	Korea	2013	120	Circular	Endo-P & Extracorporeal	250.0	215.0	18.3	4.2	0	2.5	1.7	3.3	0	9.6
Wada N ²¹	Japan	2014	100	Circular	L-suture	249.0	182.0	18.0	5.0	1.0	0	4.0	0	0	NA
Bracale U ²²	Italy	2010	67	Linear	Oeverlap	249.0	NA	NA	6.0	3.0	3.0	1.5	0	1.5	12.4
Inaba K ²³	Japan	2010	53	Linear	Oeverlap	373.4	146.5	24.5	3.8	1.9	0	0	3.8	0	14.4
Nagai E ²⁴	Japan	2013	94	Linear	Overlap	358.0	76.0	NA	2.1	1.1	0	0	2.1	0	15.2
Shinohara T ²⁵	Japan	2009	55	Linear	FETE	406.0	102.0	33.0	4.0	0	0	0	5.0	0	17.0
Kim HS ²⁶	Korea	2012	124	Linear	FETE	171.0	NA	26.6	2.4	0.8	4.8	1.6	4.8	0	11.0
Kim HS ²⁷	Korea	2013	139	Linear	FETE	144.0	NA	10.0	0	0.7	1.4	0.7	2.1	0	7.0
Ebihara Y ²⁸	Japan	2013	65	Linear	FETE	272.0	85.0	15.4	1.5	1.5	4.6	0	1.5	1.5	21.4
Okabe H ^{29†}	Japan	2014	102	Linear	FETE	377.0	165.0	23.5	2.0	1.0	0	1.0	2.9	1.9	14.0

EBL = estimated blood loss; E-J = esophagojejunostomy; POD = postoperative days; NA = not available; Endo-P = endo-purse-string; L-suture = laparoscopic suture; FETE = functional end to end anastomosis. * Including 6 side to side anastomosis; † Including 21 side to side anastomosis; ‡ Including 10 overlap method.

more than 50 patients are summarized in Table 2.¹⁴⁻²⁹ The surgical outcomes included operative time, estimated blood loss (EBL), overall morbidity, E-J leakage, duodenal stump leakage, E-J stricture, intraluminal bleeding, stasis (including ileus), mortality, and hospital stay.

Extracorporeal E-J stomy was performed by direct vision through a mini-laparotomy in the epigastrium.¹⁴⁻¹⁷ The surgical outcomes of extracorporeal E-J stomy were not significantly different from those of the other E-J stomy subgroups. However, several authors have reported some technical difficulties of this technique. For example, the purse-string clamp and straight needles were too large to be manipulated easily in a deep narrow space and the esophagus could not be adequately extracted.^{16,18} Two phase II prospective studies are ongoing in Korea (a secondary endpoint of KLASS-03) and China (NCT02085031) in order to compare the surgical outcomes between extracorporeal E-J stomy and intracorporeal E-J stomy. This is the secondary endpoint of the KLASS-03 trial and is also being evaluated by Guoxin Li et al in a Chinese RCT (planned sample size=136; NCT02085031).

Because of the technical difficulty of extracorporeal E-J stomy, many types of intracorporeal E-J stomy have been tested.¹⁹⁻²⁹ However, there were no differences in the surgical outcomes between extracorporeal and intracorporeal E-J stomy or between circular and linear stapling. The rate of E-J leakage ranged from 0% to 7.4% overall, from 1.5% to 7.4% for circular stapling,¹⁴⁻²¹ and from 0% to 6% for linear stapling.²²⁻²⁹ The rate of E-J stricture ranged from 0% to 9% overall, from 0% to 9.0% for circular stapling, and from 0% to 4.8% for linear stapling. The rate of stasis ranged from 0% to 3.8% overall, from 0% to 3.3% for circular stapling, and from 0% to 3.8% for linear stapling.

All E-J stomy methods for LTG showed excellent surgical outcomes with low rates of anastomosis-related complications. However, no meta-analysis has compared the surgical

outcomes among the different reconstruction methods used in LTG. The results of the phase II RCTs have not yet been published. Therefore, further well-designed studies are required to validate the safety and feasibility of different types of E-J stomy.

LTG WITHOUT SPLENECTOMY VERSUS LTG WITH SPLENECTOMY FOR ADVANCED GASTRIC CANCER (AGC)

As surgeons gain experience of LTG, its use has expanded from early gastric cancer (EGC) to AGC. Station 10 lymphadenectomy is an important but difficult procedure for LTG in AGC. Several authors have reported the surgical outcomes of spleen-preserving splenic hilar lymphadenectomy using LTG (Table 3).^{30,31} They showed that the procedure was technically feasible with a mean operative time of 169~359 min, EBL of 46~187 ml, morbidity rate of 12.0%~18.9%, and a mortality rate of 0%. They also reported on the safety of this procedure. The number of retrieved LNs ranged from 44.4 to 50.8, the number of retrieved station 10 LNs ranged from 2.6 to 3.0, and the number of metastatic station 10 LNs ranged from 0 to 2.8. However, Li et al reported that the most important factors for achieving successful station 10 lymphadenectomy are a skillful laparoscopic technique, familiarity with the vascular anatomy of the splenic hilum area, and a cooperative surgical team. They recommended that routine station 10 lymphadenectomy may be unnecessary for AGC without serosal invasion, unless T3 tumors are located in the greater curvature of the stomach.

The necessity of splenectomy for station 10 lymphadenectomy was not supported by the Japanese Clinical Oncology Group (JCOG) 0110 trial, an RCT in which OTG with splenectomy was compared with OTG without splenectomy (NCT00112099).³² In particular, the morbidity rate was significantly greater for OTG with splenectomy than for OTG

Table 3. Surgical outcomes of laparoscopic total gastrectomy without splenectomy vs. with splenectomy

Author	Country	Year	Splenectomy (%)	N	Op. time (min)	EBL (ml)	Hospital stay (POD)	RLNs (n)	Morbidity (%)	Mortality (%)	RLNs of No. 10 (n)	MLNs of No. 10 (%)
Li P ³¹	China	2014	0 (SP)	108	169	46	11.9	44.4	12.0	0	3.0	2.8
Okabe H ³⁰	Japan	2010	0 (SP)	53	359	187	13.0	50.8	18.9	0	2.6	0
Nakata K ³³	Japan	2014	100 (SR)	18	388	45	12.0	51.0	27.8	0	NA	NA
Shinohara T ²⁵	Japan	2009	56	55	406	102	17.0	46.0	33.0	0	NA	NA
Lee JH ¹⁹	Korea	2012	51	94	230	150	7.4	60.5	18.1*	0	NA	NA

Op. = operation; EBL = estimated blood loss; RLNs = retrieved lymph nodes; MLNs = metastatic lymph nodes; POD = postoperative days; SP = spleen preserving; SR = splenectomy; NA = not available. *Morbidity requiring medical or surgical interventions (grade II or higher of Clavien-Dindo classification) were regarded as an event.

without splenectomy (30.3% vs. 16.7%, respectively).³² In a study of LTG with splenectomy, Nakata et al.³³ reported that the morbidity rate was 27.8%, which was greater than that of LTG without splenectomy, for which the morbidity rate ranged from 12% to 18.9%.^{30,31} The study by Shinohara et al.,²⁵ which included a large proportion of patients who underwent splenectomy, reported a high rate of complications (33%). However, Lee et al.¹⁹ reported that the rate of complications in their study (18.1%) was similar to the rate reported in other studies of LTG without splenectomy (12%~18.9%).^{30,31} The experience of the surgeon, the level of cooperation of the surgical team, and advances in laparoscopic instruments help to reduce the morbidity rate of LTG with splenectomy. Because LTG was associated with lower morbidity than OTG in two updated meta-analyses,^{11,12} the JCOG 0110 OTG trials do not allow conclusions to be made on the safety LTG. More studies comparing LTG with and without splenectomy are therefore necessary.

LAPAROSCOPIC-COMPLETED TOTAL GASTRECTOMY FOR REMNANT GASTRIC CANCER

As the indication for LTG has expanded from EGC to AGC, reflecting the advances made in laparoscopic instruments and techniques, more and more completion total gastrectomies have been performed laparoscopically. Three studies have compared laparoscopic completion total gastrectomy and open completion total gastrectomy (Table 4).³⁴⁻³⁶ Laparoscopic completion total gastrectomy had similar surgical outcomes to open completion total gastrectomy, except the former had a significantly longer operative time. Laparoscopic completion total gastrectomy was technically feasible and reliable, but offered no definitive clinical advantage over open completion

total gastrectomy.³⁶

LEARNING CURVE OF LTG

Jeong et al. reported that the postoperative morbidity rate reached a plateau after around 45 patients.³⁷ By contrast, Jung et al reported that the first generation of surgeons needed to conduct approximately 100 LTG cases to overcome the learning curve.³⁸ The first generation of surgeons who performed the technique did not have a standardized procedure or an established training system. Several other studies showed that about 50~60 LDG cases were required to overcome the learning curve in the first generation of surgeons.^{39,40} However, several recent studies have reported that the learning curve for LDG could be decreased by standardizing the surgical technique and by establishing a training system.^{41,42} Therefore, it is predicted that the LTG learning curve will be much shorter for the second generation of surgeons.

DUAL-PORT OR SINGLE-PORT LTG

Kunisaki et al.⁴³ and Kawamura et al.⁴⁴ compared conventional LTG with dual-port LTG (Table 5). Kunisaki et al. reported that the operative time was significantly longer with dual-port LTG (319.0 min) than with conventional LTG (259.0 min). However, the EBL, the number of retrieved LNs, and the morbidity rate were similar in both groups. Meanwhile, Kawamura et al reported that all surgical outcomes, including operative time, were similar between the two groups. Both research groups concluded that dual-port LTG is acceptable for the treatment of gastric cancer requiring total gastrectomy, when performed by surgeons sufficiently experienced in conventional LTG.

Table 4. Comparative studies of laparoscopic and open completion total gastrectomy

Author	Country	Year	Approach	N	Op. time (min)	EBL (mL)	Hospital stay (POD)	RLNs (n)	Morbidity (%)	Mortality (%)	5 year OS (%)	Open conversion (%)
Nagai E ³⁴	Japan	2014	Laparoscopy	12	362.3*	65.8*	11.3*	23.7	0	0	77.8	0
			Open	10	270.5*	746.3*	24.9*	15.9	20.0	0	72.9	NA
Kwon IG ³⁵	Korea	2014	Laparoscopy	18	266.2*	182.0	6.0*	8.0	33.3	0	100	5.6
			Open	58	203.3*	193.0	9.0*	7.0	44.8	0	94.9	NA
Son SY ³⁶	Korea	2015	Laparoscopy	17	234.4*	228.0	9.3	18.8	35.2	0	66.7	47.1
			Open	17	170.0*	184.0	9.3	22.3	29.4	0	60.3	NA

Op. = operation; EBL = estimated blood loss; POD = postoperative days; RLNs = retrieved lymph nodes; OS = overall survival; NA = not applicable.

* $p < 0.05$.

Table 5. Surgical outcomes of dual port and single port laparoscopic total gastrectomy

Author	Country	Year	N	Port (n)	BMI (kg/m ²)	Op. time (min)	EBL (ml)	Hospital stay (POD)	RLNs (n)	Morbidity (%)	Mortality (%)
Kawamura H ⁴⁴	Japan	2013	10	2	23.8	253.0	33.4	11	31.6	0	0
			10	5	23.6	235.5	39.8	NA	40.9	10.0	0
Kunisaki C ⁴³	Japan	2014	45	2	22.7	319.0*	93.7	16.3*	46.3	13.3	0
			45	5	22.3	259.0*	118.9	27.0*	46.6	28.9	0
Ertem M ⁴⁶	Turkey	2013	1	1	22.1	282.0	NA	8	34.0	0	0
Ahn SH ⁴⁵	Korea	2014	2	1	18.95	190.0	55.0	6	76.5	0	0

Op. = operation; EBL = estimated blood loss; POD = postoperative days; RLNs = retrieved lymph nodes; NA = not available. * $p < 0.05$.

Ahn et al.⁴⁵ and Ertem et al.⁴⁶ reported several patients who successfully underwent single-port LTG (Table 5). The surgical outcomes of single-port LTG were not significantly different from those of dual-port LTG or conventional LTG. However, these reports cannot confirm the technical feasibility of single-port LTD because only one or two cases were included in each report.

Although several studies have been reported to date, the feasibility and safety of dual-port or single-port LTG have not yet been confirmed. Nevertheless, the results to date suggest that LTG will develop into a less-invasive procedure, reflecting the advances in laparoscopic instruments and techniques, and the increasing number of experienced surgeons and excellent surgical teams.

CONCLUSION

Multiple meta-analyses have shown that LTG is technically feasible, safe, and may offer some advantages over OTG for the treatment of gastric cancer. All E-J stomy methods for LTG had excellent surgical outcomes with low rates of anastomosis-related complications. The optimal E-J stomy method should be selected based on the individual patient's characteristics (for example, body mass index), tumor characteristics (for example gastroesophageal junctional invasion), and the surgeon's technical abilities. However, there is still no level-one evidence supporting the technical feasibility, surgical usefulness, or safety of LTG. Therefore, large-scale RCTs and meta-analyses of these large-scale RCTs are still necessary.

There has been much debate about whether LTG with or without splenectomy is superior for AGC. It is also debated whether laparoscopic-completed total gastrectomy is better than open-completed total gastrectomy for remnant gastric cancer and whether conventional LTG, or dual-port or single-port LTG is preferable. Advances in laparoscopic instruments, the introduction of high-resolution laparoscopes, continual

improvements in techniques, and further studies will help address these questions. Overall, we believe that these refinements will further improve the safety and reduce the invasiveness of LTG.

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