Am J Transl Res 2020;12(5):2225-2233
www.ajtr.org /ISSN:1943-8141/AJTR0106075

Original Article

Comparison of short- and long-term outcomes following laparoscopy and open total gastrectomy for gastric cancer: a propensity score-matched analysis

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Received August 4, 2019; Accepted May 5, 2020; Epub May 15, 2020; Published May 30, 2020

Abstract: Background: The aim of this study was to compare the short- and long-term outcomes of laparoscopic total gastrectomy (LTG) with those of open total gastrectomy (OTG) for the upper part of clinical Stage I gastric cancer. Methods: Between 2000 and 2015, 122 and 96 consecutive gastric cancer patients who had undergone curative LTG and OTG with lymphadenectomy were enrolled in the study. We performed the simple intracorporeal techniqueof esophagojejunostomy using a circular stapler in LTG. This technique comprised of laparoscopic trans-abdominal anvil insertion into the esophagus, which was assisted by lifting up the nasogastric tube connected to the anvil head. Results: By the Clavien-Dindo classification defined as grade II or high, the rate of postoperative complications was 14.8% (14/112: Grade II (7), IIIa (4), and IIIb (3)) in LTG and 15.6% (15/96) in OTG. There was no anastomotic leakage (0% (0/122)) and only 3.3% (4/122) of anastomotic stenosis in LTG. There was no significant difference in the short-term outcomes between both groups in all enrolled and propensity score-matched patients (LTG vs. OTG: 15.4% (10/65) vs. 16.9% (11/65)). Regarding the long-term outcomes, there was no significant difference in overall survival between both groups in all enrolled (P = 0.190) and propensity score-matched patients (P = 0.643). Conclusions: LTG for the upper part of clinical Stage I gastric cancer is a safe and reliable procedure and could have similar short- and long-term outcomes as OTG.

Keywords: Laparoscopic total gastrectomy, esophagojejunostomy, complication, prognosis, gastric cancer

Introduction

Laparoscopic gastrectomy for gastric cancer has recently grown in popularity [1-4] because of various merits including less invasiveness [5]. Consequently, there is a trend toward an increasing number of patients undergoing laparoscopic total gastrectomy (LTG). However, LTG has still not gained widespread acceptance due to its technical demands and high morbidity rate, especially in performing esophagojejunostomy and lymphadenectomy along the splenic artery and splenic hilar area [6-8]. Therefore, the standardization of surgical procedures for LTG is an important clinical issue.

Esophagogejunostomy for LTG is the most challenging part for surgeons, even for skilled surgeons. To simplify the technique for intracorporeal esophagojejunostomy, many surgeons have invented various techniques to make esophagojejunostomy safe using a linear stapler [9-12] or a circular stapler system [13-18]. Regarding open total gastrectomy (OTG), esophagojejunostomy using a circular stapling device has been commonly performed as a standard and safe reconstruction procedure. Because of its familiarity, we have preferred a circular stapling device for LTG using a laparoscopic trans-abdominal and lift-up anvil insertion technique for esophagojejunostomy, which was originally developed by Hiki and his colleagues [13, 19].

In this study, we compared short- and long-term outcomes following LTG and OTG for the upper

part of clinical Stage I gastric cancer in all enrolled patients and propensity score-matched patients between 2000 and 2015. The results of our study may provide evidence that our technique using a circular stapling device is one of safest procedures for esophagojejunostomy in LTG as well as in OTG.

Methods

Patients and surgical procedures

Between 2000 and 2015, 122 and 96 consecutive gastric cancer patients underwent curative laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) with lymphadenectomy, respectively. The patients enrolled in this study had histologically confirmed gastric cancer, were diagnosed as clinical Stage I (T1N0, T2N0, or T1N1) [20], and had undergone total gastrectomy for the upper part of gastric cancer. The exclusion criteria included carcinoma in the presence of another primary malignancy, and a history of chemotherapy or chemo-radiotherapy. Patients underwent preoperative assessments including gastric endoscopy, computed tomography (CT) scans, and laboratory tests.

Written informed consent was obtained from all patients, and each patient selected to undergo LTG or OTG. LTG was performed by mainly three surgeons (S.K., D.I., T.K.) and other surgeons who were completely under the guidance of these three surgeons. Other surgeons, who had performed open gastrectomy on at least 30 patients, performed LTG under complete guidance during the operation. OTG was performed during the same period. All enrolled patients underwent D1+ or D2 lymphadenectomy. In D2 lymphadenectomy, the peri-gastric lymph nodes and all second-tier lymph nodes were completely retrieved according to the Japanese guidelines for the treatment of gastric cancer [21].

All enrolled patients underwent macroscopic and pathologically curative resection (R0). Histological types were classified as differentiated (papillary adenocarcinoma or moderately or well-differentiated adenocarcinoma) or undifferentiated (poorly differentiated or undifferentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous adenocarcinoma) based on the 14th JCGC [20]. Our basic surgical procedures for LTG were previously described elsewhere [22]. Regarding suprapancreatic lymphadenectomy, a left-side approach or medial approach was safely performed depending on each surgeon [23, 24].

Surgical procedures for reconstruction

Esophagojejunostomy was performed intracorporeally. After lymphadenectomy around the esophago-gastric junction (EGJ), the anterior wall of the abdominal esophagus near the EGJ area was incised using laparoscopic coagulating shears (LCS). The nasogastric tube was pulled out through the incision into the abdominal cavity. The left upper port was extended vertically to a length of 4.0 cm. A wound retractor was placed into the incision, and then the nasogastric tube was pulled out through the mini-laparotomy. The anvil head of a 25-mm circular stapler (CDH; Ethicon Endosurgery, Cincinnati, OH, USA) was prepared with 4-0 PDS sutures and the anvil tip capped with an 8-cm length of 10-Fr nasogastric tube using 3-0 nylon (**Figure 1A**). Then, the anvil 4-0 PDS sutures were tied to the nasogastric tube (**Figure 1B**), and the anvil head was introduced into the abdominal cavity. By the assistance of lifting-up the nasogastric tube, the anvil head was easily inserted into the esophageal lumen by the operator. Then, the 8-cm length of 10-Fr nasogastric tube connected with the tip of the anvil was positioned in the middle of the esophageal incision, and the entry hole was grasped by the assistant and tightly closed by a linear stapler (**Figure 2A**, **2B**). The anvil shaft was introduced into abdominal cavity by pulling the 10-Fr nasogastric tube. If the closure around anvil shaft seemed insufficient, an additional pre-tied loop suture was placed for reinforcement. The plastic anvil tip was removed. The resected stomach was removed from the abdominal cavity.

Reconstruction was performed by the Roux-en-Y method. The jejunum point for esophagojejunostomy was carefully decided upon to avoid anastomotic tension. A jejuno-jejunal anastomosis was performed with side-to-side jejunojejunostomy using a linear stapler to create a 35-cm Roux-en-Y limb. The Roux limb was positioned in an ante-colic manner. The circular stapler was combined with the anvil head under laparoscopic vision. When adapting, the lifted-up jejunum was placed at the

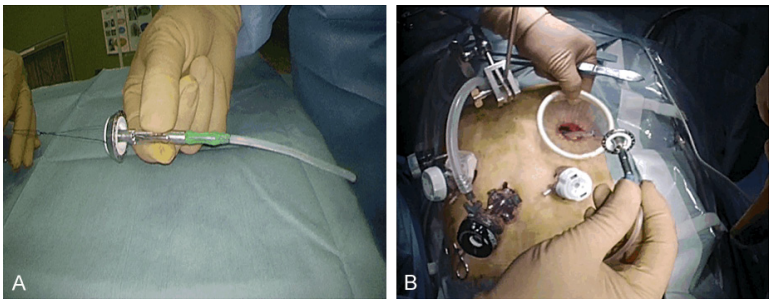

Figure 1. The anvil head of a 25-mm circular stapler (CDH; Ethicon Endosurgery, Cincinnati, OH, USA) was prepared with 4-0 PDS sutures and the anvil tip capped with an 8-cm length of 10-Fr nasogastric tube using 3-0 nylon (A). Then, the anvil 4-0 PDS sutures were tied to the nasogastric tube (B).

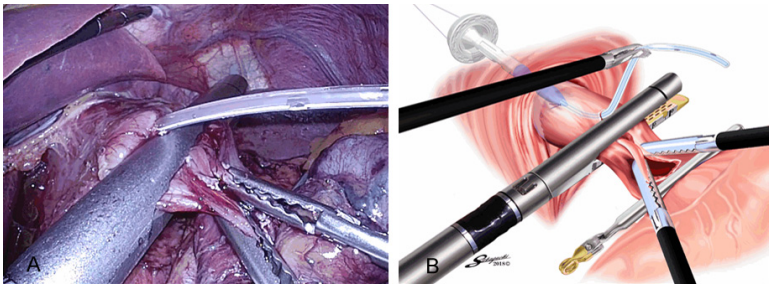

Figure 2. The 8-cm length of 10-Fr nasogastric tube, which was connected with the tip of the anvil, was positioned in the middle of the esophageal incision, and the entry hole was grasped by the assistant and tightly closed by a linear stapler (A). Schema (B).

right side without torsion, the left-side rotation of the jejunum edge was placed along the axis of the body of the circular stapler to keep the straightness of the jejunum mesentery and the right angle of the anastomotic axis was kept without tension. These techniques are very important to prevent the involvement of the mucosa and stricture and are similar to those performed in open esophagojejunostomy. A complete laparoscopic esophagojejunostomy was performed. The connecting thread was cut, and the nasogastric tube was disconnected from the anvil and taken out of the esophagus. Finally, the jejunum stump was closed by a linear stapler.

Definitions of postoperative morbidity and mortality

Postoperative morbidity and mortality were defined as complications or death within 30 days of surgery or during hospitalization. Complications were classified according to the Clavien-Dindo classification system reported by Dindo et al. [25]. In this system, Grade I or II complications were considered minor, and complications of Grade IIIa or greater were considered major complications. In this study, we presented the results of patients with complications of Grade II or greater.

Follow-up and adjuvant treatment

All of the patients were regularly followed for at least 5 years after surgery. Follow-up investigations were scheduled at 3-month intervals for the first 2 years, at 6-month intervals for the next 3 years. Patients with pathological Stage II or greater received adjuvant chemotherapy using S-1 for one year.

Propensity score matching and statistical analysis

The propensity score approach attempts to construct a randomized experiment-like situation in which the treatment groups being contrasted are comparable for the observed prognostic factors [26]. We performed a one-to-one matching analysis between the LTG and OTG groups based on the estimated propensity scores of each patient [27]. The propensity scores were estimated using a logistic regression model and the following covariates: age, gender, BMI, tumor location, tumor size, histological grade, T-stage, and N-stage. The x^2 test and Fisher's exact probability test were performed for categorical variables, whereas the Mann-Whitney *U*-test for unpaired data of continuous variables was performed to compare the clinicopathological characteristics between the two groups. Survival curves were estimated using the Kaplan-Meier method, and statistical differences were examined using the log-rank test. $P < 0.05$ was considered statistically significant.

Results

Baseline patient characteristics

Table 1 summarizes the unmatched patient characteristics of the two groups. In the LTG

Table 1. Comparison of clinicopathological factors between LTG and OTG in unmatched patients and propensity score-matched patients

Characteristics		All patients				*P*-value	Propensity score-matched patients				*P*-value
		LTG (n=122)		OTG (n=96)			LTG (n=65)		OTG (n=65)		
		n	%	n	%		n	%	n	%	
Age*	years (mean)	67		66		0.313	68		67		0.176
Sex*	Male	97	79.5	72	75.0	0.429	50	73.5	51	75.0	0.833
	Female	25	20.5	24	25.0		15	26.5	14	25.0	
BMI*	kg/m^2 (mean)	23		22		0.186	22		22		0.401
Tumor location*	U, UM	84	68.9	60	62.5	0.325	39	57.4	39	57.4	1.000
	MU	38	31.1	36	37.5		26	42.6	26	42.6	
Tumor size*	mm (mean)	42		47		0.236	44		41		0.241
Histology*	Diff.	69	56.6	55	57.3	0.913	34	50.0	39	57.4	0.377
	Undiff.	53	43.4	41	42.7		31	50.0	26	42.6	
Retrieved LNs	number (mean)	37		36		0.393	38		34		0.127
Operation time	min (mean)	410		317		<0.001	405		323		<0.001
Blood loss	ml (mean)	98		306		<0.001	150		526		<0.001
pT-stage*	T1	92	75.4	48	50.0	0.002	44	67.7	44	67.7	0.747
	T2	16	13.1	19	19.8		9	13.8	14	21.5	
	T3	11	9.0	19	19.8		9	13.8	6	9.2	
	T4	3	2.5	10	10.4		3	4.6	1	1.5	
pN-stage*	N0	103	84.4	69	71.9	0.256	51	78.5	54	83.1	0.943
	N1	9	7.4	15	15.6		6	9.2	4	6.2	
	N2	7	5.7	7	7.3		6	9.2	5	7.7	
	N3	3	2.5	5	5.2		2	3.1	2	3.1	

*Factors used for propensity score matching.

group, there were 89 males and 33 females, with a mean age of 67 years. The mean BMI was 23 kg/m^2. In the OTG group, there were 72 males and 24 females, with a mean age of 66 years. The mean BMI was 22 kg/m^2. There was no significant difference of distributions between two groups in age, sex, BMI, tumor location, tumor size, histology, retrieved lymph nodes, and pN-stage, excluding pT-stage.

Both groups were balanced for the variables such as age, sex, BMI, tumor location, tumor size, histological type, pT-stage, and pN-stage that were considered in the propensity score derivation model. Using one-to-one propensity score matching, 65 pairs of LTG and OTG patients were selected (**Table 1**). After propensity score matching, the patient distributions were carefully balanced between the LTG and OTG groups.

Short-term surgical outcomes

Tables 1 and **2** provide details of the short-term surgical outcomes for the two groups in all and the propensity score-matched patients. The LTG group had a significantly longer operating time ($P < 0.001$) in all and the propensity score-matched patients. Also, estimated blood loss in the LTG group was significantly less than in the OTG group ($P < 0.001$) in all and the propensity score-matched patients. There was no significant difference in retrieved lymph nodes between both groups in all and the propensity score-matched patients (**Table 1**). Regarding postoperative complications in all patients, 14.8% (18/122) of the LTG group and 15.6% (15/96) of the OTG group were defined by the Clavien-Dindo classification as having complications of Grade II or greater. Whereas in propensity score-matched patients, 15.4% (10/65) of the LTG group and 16.9% (11/65) of the OTG group were defined, which was almost equivalent to all patients. There was no difference between both groups in postoperative early and late complications (**Table 2**).

Long-term survival outcomes

The survival data were obtained until December 2016, with a median follow-up of 28.2

Table 2. Comparison of short-term surgical outcomes between LTG and OTG in unmatched patients and propensity-matched patients

	Unmatched patients				*P*-value	Propensity score-matched patients				*P*-value
	LTG n=122		OTG n=96			LTG n=65		OTG n=65		
	All*	Grade IIIa or more	All*	Grade IIIa or more		All*	Grade IIIa or more	All*	Grade IIIa or more	
Early complications										
anastomotic leakage	0 (0%)	0 (0%)	5 (5.2%)	5 (5.2%)	0.036	0 (0%)	0 (0%)	4 (6.1%)	4 (6.1%)	0.127
anastmotic bleeding	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0.904	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	1.000
pancreatic fistula	3 (2.5%)	0 (0%)	2 (2.1%)	0 (0%)	0.336	1 (1.5%)	0 (0%)	1 (1.5%)	0 (0%)	0.476
intrabdominal abscess	3 (2.5%)	0 (0%)	3 (3.1%)	0 (0%)	0.905	2 (3.0%)	0 (0%)	3 (4.6%)	0 (0%)	1.000
acute cholecystitis	1 (0.8%)	0 (0%)	1 (1.0%)	0 (0%)	0.585	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	1.000
blind loop syndrome	1 (0.8%)	1 (0.8%)	0 (0%)	0 (0%)	0.904	1 (1.5%)	1 (1.5%)	0 (0%)	0 (0%)	1.000
pneumonia	1 (0.8%)	0 (0%)	2 (2.1%)	0 (0%)	0.834	1 (1.5%)	0 (0%)	1 (1.5%)	0 (0%)	0.476
Late complications										
anastomotic stenosis	4 (3.3%)	4 (3.3%)	1 (1.0%)	1 (1.0%)	0.522	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)	0.476
internal hernia	2 (1.6%)	2 (1.6%)	0 (0%)	0 (0%)	0.585	1 (1.5%)	1 (1.5%)	0 (0%)	0 (0%)	1.000
ileus	2 (1.6%)	0 (0%)	1 (1.0%)	0 (0%)	0.834	1 (1.5%)	0 (0%)	1 (1.5%)	0 (0%)	0.476
Morbidity	18 (14.8%)	7 (5.7%)	15 (15.6%)	6 (6.3%)	0.858	10 (15.4%)	3 (4.6%)	11 (16.9%)	5 (7.7%)	1.000
Mortality	0 (0%)		0 (0%)		1.000	0 (0%)		0 (0%)		1.000

*Clavien-Dindo classification Grade II complications or greater.

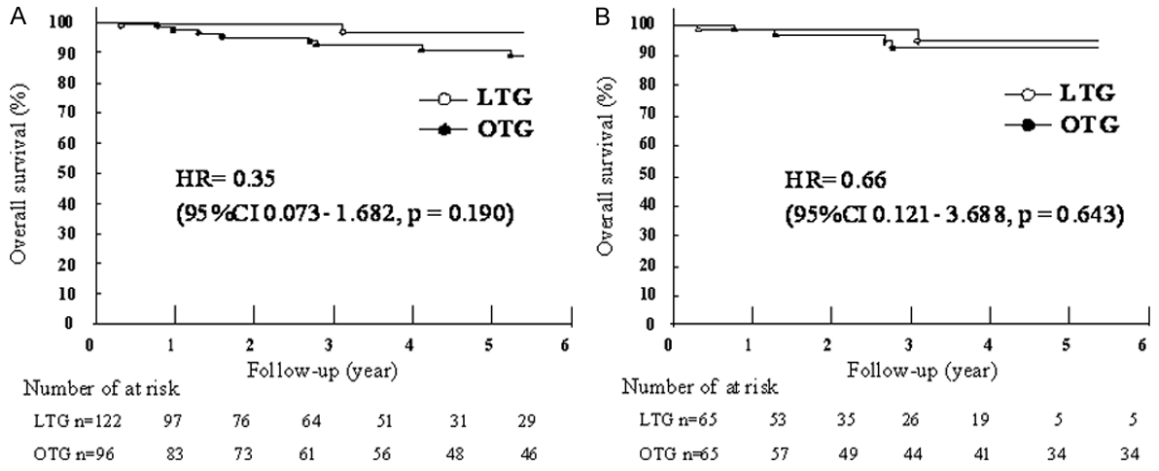

Figure 3. The Kaplan-Meier plots show 5-year overall survival (OS) according to the operative approach. In all patients, OS tended to be better in patients who underwent laparoscopic total gastrectomy (LTG) than in patients who underwent open total gastrectomy (OTG) (A, P = 0.190). In the propensity score-matched cohorts, we found no significant differences between both groups (B, P = 0.643).

months in the LTG group and 82.8 months in the OTG group. The Kaplan-Meier plots show 5-year OS according to the operative approach (**Figure 3**). In all patients, OS tended to be better in patients who underwent LTG than in patients who underwent OTG (**Figure 3A**, P = 0.190). In the propensity score-matched cohorts, we found no significant differences between both groups (**Figure 3B**, P = 0.643).

Discussion

Despite clinical issues regarding the reconstruction in esophagojejunostomy and lymphadenectomy along the splenic artery and splenic hilar area [6-8], LTG has become popular as one of treatment options in gastric cancer due to the advancement of instruments and surgical techniques for laparoscopic surgery. In this study, we clearly demonstrated that there was no significant difference of short- and long-term outcomes between LTG and OTG patients for the upper part of gastric cancer in both all enrolled patients and the propensity score-matched patients. Our results may also provide evidence that our intracorporeal esophagojejunostomy using a circular stapling device and lymphadenectomy in LTG are feasible procedures, with similar short- and long-term outcomes to those of OTG.

Several recent systematic reviews and meta-analyses comparing LTG with OTG have shown that the short-term outcomes of LTG were better and similar to that of OTG, suggesting that LTG is a safe and feasible option [28-31]. Specifically, Wang et al. investigated 17 studies including a total of 2313 patients with 955 patients in LTG and 1358 patients in OTG. LTG showed longer operative time but less blood loss, fewer analgesic uses, earlier passage of flatus, quicker resumption of oral intake, earlier hospital discharge, and reduced postoperative morbidity. The number of retrieved lymph nodes, hospital mortality, and 5-year overall and disease-free survival rates were similar [32]. Okabe et al. also comprehensibly reviewed the surgical outcomes of all comparative studies of LTG and OTG including more than 30 patients with LTG, and prospective and retrospective series including more than 50 patients with LTG. As a result, the incidence of leakage during the esophagojejunosotomy of LTG ranged from 0.9 to 8.5%. Specifically, the average leakage frequency was 3.5%: 3.9% with a circular stapler and 2.8% with linear stapler. This frequency, which is comparable to the incidence of leakage reported regarding OTG, ranged from 3 to 8% [30]. In our study, the rates of anastomotic leakage and stricture were 0% and 3.3% in LTG using a circular stapler, which were the same as OTG. Thus, overall short-term outcomes of LTG were similar to those of OTG, suggesting that LTG is a safe and feasible procedure.

Recently, the potential surgical merits of LTG have been proved by single-arm confirmatory

trial of LTG or laparoscopic proximal gastrectomy [33] although there have been no well-designed nationwide or randomized controlled phase II or III study. Therefore, we also conducted a propensity score-matched analysis to overcome the biased estimates of treatment effects when comparing LTG with conventional OTG. In our study, the propensity score-matched analysis of the short- and long-term outcomes did not show a significant difference between both groups. Concerning the propensity score-matched analysis comparing LTG with OTG, there have been four previous reports. Lee et al. reported that anastomosis-related complications were significantly higher in LTG (8.0% vs. 4.2% in OTG; $P = 0.015$), and postoperative death was more common in LTG than OTG (1.6% vs. 2.0% in OTG; P = 0.015) [8]. However, the other three reports suggested that LTG is feasible and safe, even in elderly gastric cancer patients [34], with acceptable oncologic outcomes from the viewpoint of an increased number of retrieved lymph nodes [35] and better long-term survival [35, 36]. Thus, implementation of LTG for gastric cancer may be safe and reliable with short- and long-term outcomes similar to those of OTG.

Our study had several limitations. As explained above, first and most importantly, this was not a randomized controlled trial, and the selection biases for selecting LTG or OTG existed, which could be minimized but not completely eliminated even by the propensity score-matching analysis. Second, a small number patients were included in this study. Nevertheless, we believe that our study could serve as a basis for performing future randomized and nationwide clinical trials. In conclusions our results suggest that LTG for the upper part of gastric cancer could be safe and feasible in terms of short- and long-term outcomes. Particularly, our circular stapler technique could be one of the safest and most useful procedures for esophagojejunistomy in LTG.

Acknowledgements

This study was designed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Kyoto Prefectural University of Medicine. All patients received sufficient explanation of the study, and written informed consent was obtained.

Disclosure of conflict of interest

None.

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