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ORIGINAL ARTICLE

Short- and long-term oncological outcomes of totally laparoscopic gastrectomy versus laparoscopy-assisted gastrectomy for clinical stage I gastric cancer

Yusuke Muneoka[1] · Manabu Ohashi[1] · Nozomi Kurihara[2] · Junko Fujisaki[3] · Rie Makuuchi[1] · Satoshi Ida[1] · Koshi Kumagai[1] · Takeshi Sano[1] · Souya Nunobe[1]

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Abstract

Background Totally laparoscopic gastrectomy (TLG), which involves a complete intracorporeal gastric transection and the creation of an anastomosis, has been gradually adopted. However, a potential limitation of intracorporeal transection is the lack of tactile feedback, and whether this limitation influences oncological outcomes is unclear. The aim of this study is to evaluate the short- and long-term oncological safety of TLG using endoscopy-guided intracorporeal gastric transection for clinical stage (cStage) I gastric cancer.

Methods A total of 1875 consecutive patients who underwent laparoscopic gastrectomy for cStage I gastric cancer between January 2007 and March 2015 were enrolled in this study. Marking clips were preoperatively placed and a transection line was determined by perceiving it tactually in laparoscopy-assisted gastrectomy (LAG) or endoscopically in TLG. After propensity score matching, 1366 patients (683 each for LAG and TLG groups) were selected to primarily test the non-inferiority of TLG to that of LAG for relapse-free survival (RFS).

Results In the propensity-matched population, the 5-year RFS rates of the LAG and TLG groups were 94.3% (95% confidence interval (CI) 92.2–95.8%), and 95.6% (95% CI 93.8–96.9%), respectively. The hazard ratio (TLG/LAG) was 0.77 (95% CI 0.48–1.24, P for non-inferiority < 0.01). There were no significant differences in the recurrence profiles. The incidence of the remnant of marking clips or tumor tissue did not differ (LAG: 1.0% vs. TLG: 1.9%, $P = 0.177$).

Conclusions TLG using preoperative markings and intraoperative endoscopic guidance provides cStage I gastric cancer patients with comparable oncological outcomes to the conventional method.

Keywords Totally laparoscopic gastrectomy · Intracorporeal gastric transection · Marking clips

Introduction

Until recently, gastric transection for gastric cancer fully depended on the tactile sensation of surgeons. A transection line was determined according to the tactile feedback that there was no tumor. Even in laparoscopic gastrectomy (LG), laparoscopy-assisted gastrectomy (LAG), in which the stomach is dissected under a laparoscopic view and is pulled out through a mini-laparotomy and transected according to the information gained by touching the tumor, has been adopted. However, as endosurgical devices and techniques rapidly advance, LG tends to be performed completely under a laparoscopic view, including the transection of the stomach and its reconstruction, in a process called totally laparoscopic gastrectomy (TLG) [1–3]. TLG is less invasive, but this approach confers several challenges, including the

✉ Manabu Ohashi
manabu.ohashi@jfcr.or.jp

1 Department of Gastroenterological Surgery, Gastroenterological Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan

2 Department of Clinical Trial Planning and Management, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

3 Department of Gastroenterology, Gastroenterological Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

requirement for intracorporeal gastric transection and the creation of an anastomosis. Especially, limited tactile feedback during gastric transection is the most critical oncological problem of TLG. Transection failure (TF), in which surgeons fail to transect the stomach at an intended line or the resection margin contains cancer tissue despite successful transection at an intended line, may frequently occur because the tumor is missed or because of difficult intracorporeal manipulations under laparoscopic conditions.

We previously reported that the combination of preoperative placement of marking clips and intraoperative endoscopy was helpful in maintaining a safe resection margin to overcome the possibility of TF in TLG [4]. In this previous report, the success rate of obtaining pathologically negative resection margins by the initial transection was 98.9% (550 of 556 margins); this technique may be equivalent to the conventional approach of gastric transection for cancer in LAG or open gastrectomy. However, this is the only study to evaluate the systematical use of preoperative marking clips and intraoperative endoscopy in TLG, and short- and long-term oncological outcomes, such as the incidence of TF, recurrence profiles, and survival outcomes in TLG compared with LAG, remain unclear.

In the present study, to evaluate the oncological safety of TLG using non-touched and endoscopy-guided intracorporeal gastric transection, we retrospectively compared the surgical outcomes of LAG and TLG for clinical stage I (cStage) I gastric cancer. We attempted to verify our hypothesis that TLG for cStage I gastric cancer was not inferior to LAG using tactile-guided extracorporeal gastric transection in terms of relapse-free survival (RFS), although the higher incidence of TF in TLG is of concern. Furthermore, we adopted propensity score matching (PSM) to exclude confounding factors influencing survival outcomes and the maintenance of resection margins. The information obtained from this study will establish the oncological safety of TLG and assist the development of fully intracorporeal manipulation in laparoscopic and robotic gastrectomy for cancer.

Methods

Patients

Consecutive patients with histologically proven gastric adenocarcinoma who underwent LG at the Department of Gastroenterological Surgery, Cancer Institute Hospital, Tokyo, Japan, between January 2007 and March 2015 were enrolled in this study. Among these patients, we excluded those who met any of the following criteria: patients who underwent intended total gastrectomy, patients who were converted to open surgery before harvesting of specimens or patients without cStage I gastric cancer. Tumor location and gastric circumference were ascertained by upper gastrointestinal endoscopy, and clinical depth of tumor was determined by endoscopy, upper gastrointestinal series, and computed tomography findings. Endoscopic ultrasonography was performed in some cases. Tumors were classified according to the third English edition of the Japanese Classification of Gastric Carcinoma [5]. Differentiated types included papillary and tubular adenocarcinomas; undifferentiated types included poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma. This study was approved by the institutional review board of the Cancer Institute Hospital (2019–1139).

Surgical procedure

Indication of each procedure

LAG and TLG had common indications for each procedure. LAG was exclusively performed from 2007 to 2009. TLG was gradually adopted from 2010 and performed for most patients in 2015. Laparoscopic or laparoscopy-assisted distal gastrectomy (L or LADG) was performed for cStage I gastric cancer located in the middle or lower third of the stomach. Laparoscopic or laparoscopy-assisted pylorus-preserving gastrectomy (L or LAPPG) was applied to cT1N0M0 disease located in the middle to lower a third of the stomach, of which the distal boundary was more than 4–5 cm from the pylorus. Laparoscopic or laparoscopy-assisted subtotal gastrectomy (L or LASTG) was defined as laparoscopic distal gastrectomy for tumors located in the upper third of the stomach or tumors invading the area. L or LASTG was conducted for cT1 disease for which the proximal boundary was more than 2 cm from the esophagogastric junction. Laparoscopic or laparoscopy-assisted proximal gastrectomy (L or LAPG) was performed for cT1N0M0 disease located in the upper third of the stomach. The extent of lymph node dissection was determined according to the Japanese Gastric Cancer Association (JGCA) treatment guidelines [6].

Preoperative management and gastric transection methods

At the initial preoperative endoscopy, biopsies were taken from the tumor and from the proximal and/or distal mucosa of normal appearance. Several days before surgery, marking clips were placed at two proximal and/or two distal biopsy sites on the pathologically confirmed normal mucosa [4]. In LAG, the dissected stomach was pulled out through a mini-laparotomy, and a transection line was determined to be approximately 2 cm from the proximal or distal tumor boundary, which corresponded to the location of intraluminal marking clips. In TLG, the gastric transection line was designated using intraoperative endoscopy, as described previously [4]. The dissected stomach was divided intracorporeally at the designated transection line using an endoscopic linear stapler. The gross proximal or distal margin length was roughly measured on the back table by surgeons other than the operator and assistants based on the information obtained during preoperative examinations, including marking clips and inspected and palpated findings of the resected specimen obtained immediately after the specimen was removed from the surgical field. If the gross margin length was too short to be confirmed as negative or suspicious for cancer, intraoperative frozen section (IFS) analysis of the cutting edge was conducted. However, some surgeons routinely submitted the cutting edge to IFS analysis.

Outcome measurements

RFS was the primary endpoint, which was defined as the time from the date of gastrectomy to the date of relapse or death from any cause, whichever came first. After patients underwent surgery, follow-up examinations, including computed tomography, abdominal ultrasonography, and endoscopy, were conducted every 6 months during the initial 5 years according to the JGCA treatment guidelines [6]. Secondary endpoints included a pattern of recurrence and incidence of TF. TF was classified into two types: a harvested specimen did not include all marking clips (remnant marking clips) or a resection margin contained tumor tissue even though a specimen included all marking clips (remnant tumor tissue).

Statistical analysis

This retrospective study using a PSM approach was performed to show the non-inferiority of TLG versus LAG. RFS at 5 years was selected as the primary endpoint, assuming a RFS of 95% for LAG and no difference between groups [7]. With a non-inferiority margin of 5.0% [7], 61 RFS events are required to reach a power of 80% at a significance level of 2.5% (one-sided) [8]. We clarified the preoperative information related to the decision to choose LAG or TLG. A total of 11 covariates before surgery, comprising patients' characteristics and tumor findings (patient age, sex, body mass index, history of preoperative endoscopic resection, tumor location, tumor size, macroscopic type, histological features, clinical T category, clinical N category and intended type of gastrectomy), were identified.

The propensity score was estimated using a logistic regression model with the 11 items as co-variables. Optimal matching, at a ratio of 1:1 without replacement, with a caliper width of 0.2 of the pooled standard deviation of the estimated logit was performed. The balance of each covariate before and after the matching between the two groups was evaluated by standardized differences [9]. Absolute values of standardized differences less than 10% were considered a relatively small imbalance. A flowchart of patient enrollment is shown in Fig. 1.

RFS was analyzed using the Kaplan–Meier method and compared between the LAG and TLG groups using the log-rank test. To test the non-inferiority of TLG, we calculated

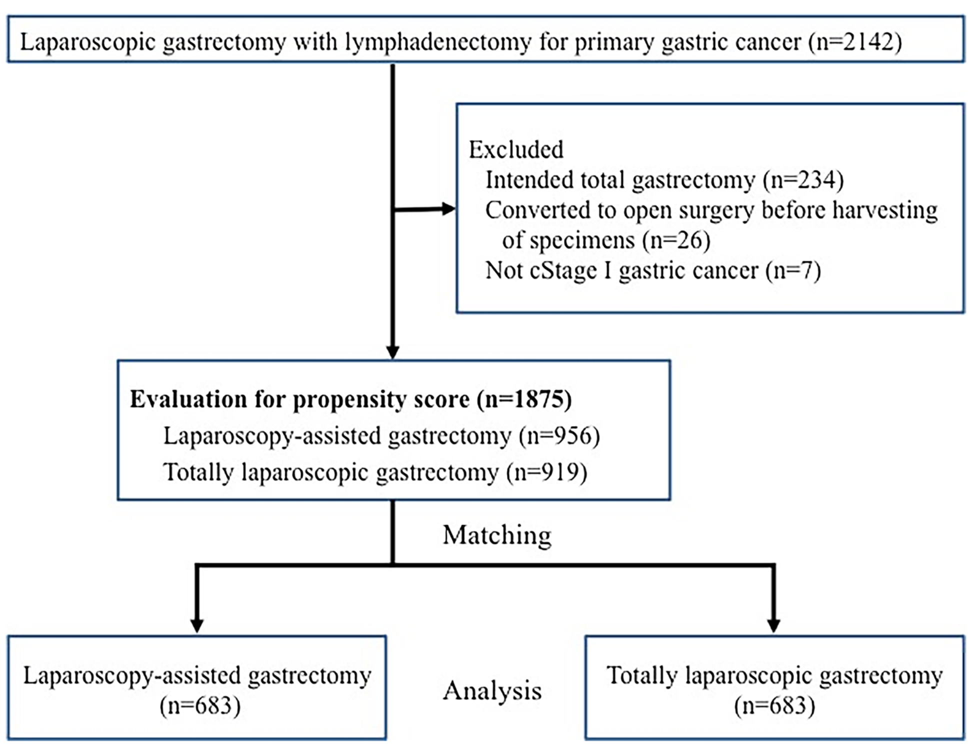

Fig. 1 Flowchart of patient enrollment

hazard ratios (HR) and 95% confidence intervals (CI) using the Cox proportional hazards model and established whether the upper limit of the CI was less than the non-inferiority margin of HR (=2.054). Subgroup analyses for RFS were conducted in which the Cox regression model was used to assess statistically significant interactions between treatment type and seven characteristics.

We used the Mann–Whitney *U* test to compare the continuous variables and the Chi squared or Fisher's exact test to compare the categorical variables between the two groups. *P* values less than 0.05 were considered to denote statistical significance. All statistical analyses were performed using IBM SPSS statistical software version 22 (IBM, Armonk, NY, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Background characteristics

In total, 1875 patients were enrolled, of whom 956 and 919 underwent LAG and TLG, respectively (Supplemental Table 1). After PSM, 683 patients remained in each group. Table 1 shows the patient characteristics for post-PSM. Demographics and tumor-related characteristics were well balanced between the groups.

Table 2 shows a comparison of the surgical and pathological results between the two groups (Supplemental Table 2 shows that of the pre-matched cohort). The median surgery time was significantly longer in the TLG

Table 1 Baseline characteristics after propensity score matching

	Propensity-matched patients (*n* = 1366)				
Characteristics	LAG (*n* = 683)	%	TLG (*n* = 683)	%	SD
Age, mean	63.0		62.9		−0.01
Sex					
Male	421	61.6	425	62.2	0.01
Female	262	38.4	258	37.8	−0.01
Location of tumor					
Upper	75	11.0	69	10.1	−0.03
Middle	441	64.6	443	64.9	0.01
Lower	167	24.5	171	25.0	0.01
Pretreatment with ESD					
Absent	561	82.1	551	80.7	−0.04
Present	122	17.9	132	19.3	0.04
Size of tumor, mean	31.6		31.6		0
Macroscopic type					
Superficial	675	98.8	672	98.4	−0.03
Advanced	8	1.2	11	1.6	0.03
Histology					
Differentiated	304	44.5	309	45.2	0.01
Undifferentiated	379	55.5	374	54.8	−0.01
Intended procedure					
DG	415	60.8	405	59.3	−0.03
PPG	192	28.1	199	29.1	0.02
STG	33	4.8	36	5.3	0.02
PG	43	6.3	43	6.3	0
cT stage					
cT1a	190	27.8	183	26.8	−0.02
cT1b	468	68.5	473	69.3	0.02
cT2	25	3.7	27	4.0	0.02
cN stage					
cN0	679	99.4	677	99.1	−0.03
cN1	4	0.6	6	0.9	0.03

SD standardized difference; *LAG* laparoscopy-assisted gastrectomy; *TLG* totally laparoscopic gastrectomy; *ESD*, endoscopic submucosal dissection; *DG* distal gastrectomy; *PPG*, pylorus-preserving gastrectomy; *STG*, subtotal gastrectomy; *PG*, proximal gastrectomy

Table 2 Surgical and pathological findings

	LAG group $n=683$ (%)	TLG group $n=683$ (%)	*P* value
Performed procedure			0.959
DG	419 (61.3)	411 (60.2)	
PPG	186 (27.2)	189 (27.7)	
STG	32 (4.7)	35 (5.1)	
PG	42 (6.1)	42 (6.1)	
TG	4 (0.6)	6 (0.9)	
Conversion to other gastrectomy	9 (1.3)	14 (2.0)	0.293
Retrieved lymph nodes[a]	35 (13–82)	41 (10–94)	< 0.001
Operating time[a] (min)	220 (106–602)	275 (153–594)	< 0.001
Blood loss[a] (ml)	30 (0–770)	20 (0–670)	0.005
Pathological T			0.219
T1	604 (88.4)	600 (87.9)	
T2	43 (6.3)	59 (8.6)	
T3	30 (4.4)	18 (2.6)	
T4	6 (0.9)	6 (0.9)	
Pathological N			0.616
N0	607 (88.9)	598 (87.6)	
N1	51 (7.5)	62 (9.1)	
N2	19 (2.8)	20 (2.9)	
N3	6 (0.8)	3 (0.4)	
Pathological stage			0.391
Stage I	619 (90.6)	632 (92.5)	
Stage II	55 (8.1)	42 (6.1)	
Stage III	9 (1.3)	9 (1.3)	

LAG laparoscopy-assisted gastrectomy; *TLG* totally laparoscopic gastrectomy; *DG* distal gastrectomy; *PPG* pylorus-preserving gastrectomy; *STG* subtotal gastrectomy; *PG* proximal gastrectomy; *TG* total gastrectomy.

[a] Values are presented as median (range)

group than in the LAG group. Furthermore, the median intraoperative blood loss was significantly less in the TLG group than in the LAG group. There was no significant difference in the pathological findings.

Long-term outcomes

Non-inferiority of TLG to LAG in RFS

Figure 2 shows that the Kaplan–Meier estimates of the RFS curves stratified by the gastric transection methods. The 5-year RFS rates of the LAG and TLG groups were 94.3% (95% CI 92.2–95.8%) and 95.6% (95% CI 93.8–96.9%), respectively. The HR (TLG/LAG) was 0.77 (95%CI 0.48–1.24, P for non-inferiority < 0.01, P for superiority $= 0.281$). Therefore, the RFS of the TLG group was not inferior to that of the LAG group.

Recurrence profiles

The details of recurrence are listed in Table 3 (Supplemental Table 3 shows that of the pre-matched cohort). The number and type of recurrence were not different between the LAG and TLG groups.

Subgroup analysis of RFS

Forest plots with the HRs for RFS according to demographic and clinicopathological factors are shown in Fig. 3. The results indicate that TLG was significantly better than LAG in patients undergoing pylorus-preserving gastrectomy (HR 0.12, 95% CI 0.02–0.97; $P = 0.047$), although the other subgroups had no significant differences.

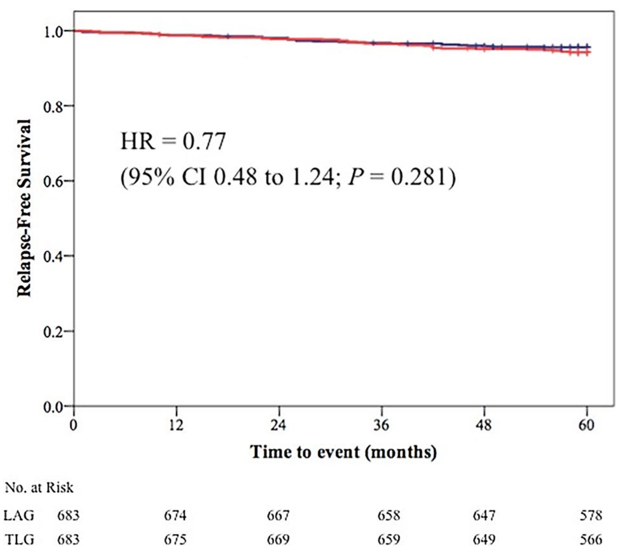

Fig. 2 Relapse-free survival curves demonstrated that statistically significant non-inferiority of totally laparoscopic gastrectomy relative to laparoscopy-assisted gastrectomy was evident (red, laparoscopy-assisted gastrectomy; blue, totally laparoscopic gastrectomy)

Table 3 First recurrence site compared between laparoscopy-assisted gastrectomy and totally laparoscopic gastrectomy

Site	Number of patients (%)		*P* value
	LAG group (n=683)	TLG group (n=683)	
Total number of relapse	13 (1.9)	8 (1.2)	0.272
Peritoneum	4 (0.6)	4 (0.6)	1.000
Hematogenous	4 (0.6)	4 (0.6)	1.000
Lymph nodes	5 (0.7)	1 (0.1)	0.218
Local	1 (0.1)	0	1.000

One patient in each group had a first recurrence at more than one site

LAG laparoscopy-assisted gastrectomy, *TLG* totally laparoscopic gastrectomy

Short-term outcomes

Incidence and details of TF

Table 4 shows the incidence of TF during the initial gastric transection. There was no significant difference in the incidence of overall TF (LAG group: 1.0% vs. TLG group: 1.9%, P=0.177). There was also no difference in the incidence of each type of TF.

Remnant marking clips occurred in six patients, all of whom underwent additional gastric resection to achieve complete removal of the clips. Frozen-section analysis during surgery revealed that 11 patients had pathological remnant tumor tissue, even though the resected specimens contained all marking clips. These patients all underwent additional resection sequentially during the same surgery to obtain R0 resection. Postoperative histopathological analysis of formalin-fixed, paraffin-embedded tissue sections revealed that three additional patients who did not undergo IFS analysis had pathological remnant tumor tissue. All of the three additional patients underwent a second surgery to obtain pathologically negative margins. Eight of fourteen positive resection margins contained undifferentiated type cancer and the remaining six contained differentiated type. Three margins revealed undifferentiated type cancer from the muscle to the subserosal layer without mucosal involvement and the other eleven revealed mucosal or submucosal cancer.

Relationship between TF and RFS

Supplemental Table 4 shows uni- and multivariate analysis for RFS. Univariate analysis revealed that TF was a significant prognostic factor (HR 3.04, 95% CI 1.12–8.27). However, multivariate analysis revealed that advanced age, tumor location, macroscopic type, pT and pN were significant prognostic factors, and the presence of TF was not.

Discussion

In this retrospective comparative study using PSM, we identified three new findings concerning the oncological outcomes of TLG for cStage I gastric cancer. First, the RFS of patients who underwent TLG was not inferior to that of patients who underwent LAG. Second, there were no significant differences in the profiles of recurrence between patients undergoing LAG and TLG. Third, the incidence of TF was also not significantly different between LAG and TLG. These new findings show that TLG using endoscopy-guided intracorporeal gastric transection provides patients with cStage I gastric cancer with safe oncological outcomes even if the tactile sensation is not used in transection of the stomach, unlike conventional approaches in LAG.

Katai et al. reported the non-inferiority of LADG compared with open distal gastrectomy for cStage I gastric cancer located in the middle or lower third of the stomach in terms of the RFS (JCOG0912) [10]. In this Japanese multicenter randomized phase III trial, the 5-year RFS rate was 95.1% (95% CI 92.7–96.8%) in the LADG group. In the current study, the 5-year RFS rates of patients in the LAG and TLG groups were 94.3% (95% CI 92.2–95.8%) and 95.6% (95% CI 93.8–96.9%), respectively, which exactly reproduced the results of the JCOG0912 trial. However, our results seemed to represent far better outcomes than these values because ours were obtained from daily practice. The patients enrolled in this study were

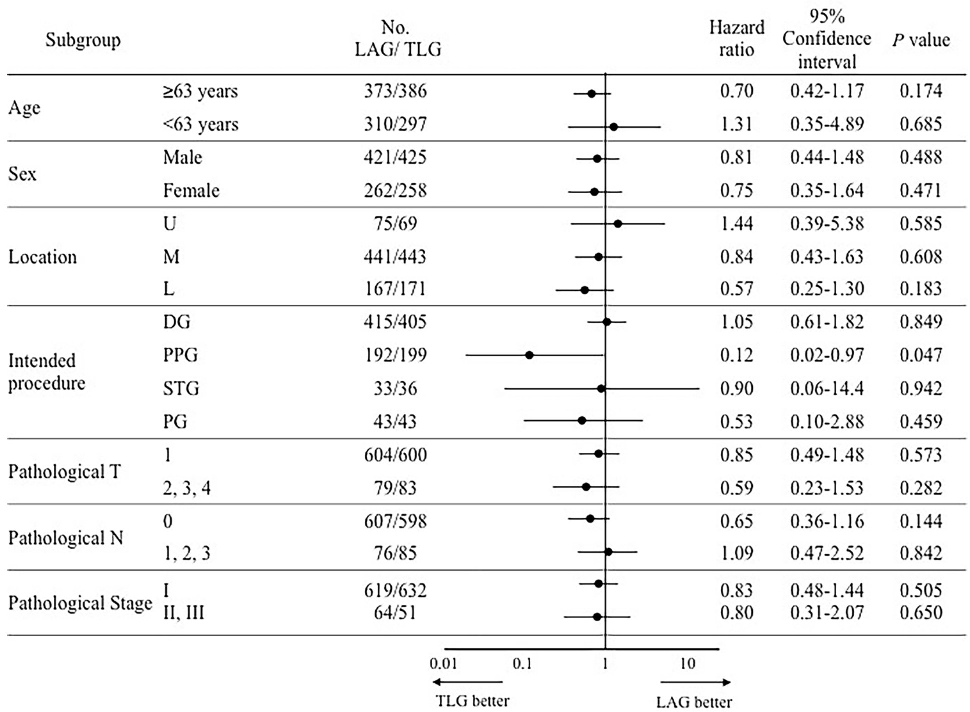

Fig. 3 Forest plot showing hazard ratios for relapse-free survival. A statistically significant interaction was observed in terms of planned procedure; pylorus-preserving gastrectomy (HR 0.12, 95%CI 0.02–0.97; $P=0.047$), although the other subgroups had no significant differences

Table 4 Incidence and details of transection failure compared between laparoscopy-assisted gastrectomy and totally laparoscopic gastrectomy

	LAG group $n=683$ (%)	TLG group $n=683$ (%)	*P* value
Transection failure			0.177
Absent	676 (99.0)	670 (98.1)	
Present	7 (1.0)	13 (1.9)	
Remnant marking clips			0.218
Absent	682 (99.9)	678 (99.3)	
Present	1 (0.1)	5 (0.7)	
Remnant tumor tissue			0.591
Absent	677 (99.1)	675 (98.8)	
Present	6 (0.9)	8 (1.2)	

LAG laparoscopy-assisted gastrectomy, *TLG* totally laparoscopic gastrectomy

collected consecutively during the study period regardless of age, comorbidities and types of gastrectomy. The HR (TLG/LAG) for RFS was 0.77 (95%CI 0.48–1.24), showing non-inferiority of TLG to LAG because the upper limit of the CI (1.24) was lower than the non-inferiority margin for the HR (2.054), which corresponded to a margin of 5% for the difference in terms of RFS at 5 years. Therefore, TLG was not inferior to LAG in RFS and should be considered an oncologically safe procedure in the long-term view of cStage I gastric cancer. The subgroup analysis of RFS indicated that TLG was significantly better than LAG in patients undergoing pylorus-preserving gastrectomy, while the other subgroups had no significant differences. The differences in pylorus-preserving gastrectomy might be influenced by the incidentally high number of deaths from other diseases, which indicates why the difference in RFS was not due to the difference between the transection methods of the stomach. TLG may be oncologically safe even if the stomach is transected anywhere using the endoscopy-guided method.

In LG for early gastric cancer, several methods, including intraoperative endoscopy [11–13] and endoscopic tattooing [14, 15], have been reported as useful approaches to identify the tumor site and to determine a transection line while maintaining an adequate resection margin. We previously reported the combination of preoperative placement of marking clips and intraoperative endoscopy as helpful in the determination of a safe resection margin in patients undergoing TLG for gastric cancer [4]. However, we were concerned that we may easily overlook the thickness of the stomach wall because of the lack of tactile feedback, that is, we may underestimate the existence of cancer at the intended transection line. Such oversight may lead to an increased incidence of TF in TLG. However, the incidence of TF was not significantly different between the LAG and TLG groups. This result shows that our strategy using endoscopy-guided intracorporeal gastric transection is effective in overcoming the potential limitation of intracorporeal gastric transection due to missing the tactile tumor information and the difficult manipulation of the stomach.

To achieve the long-term oncological safety of TLG for cStage I gastric cancer, securing a pathologically negative resection margin is an indispensable prerequisite. The incidence of pathologically positive resection margins in this series was 0.9% in the LAG group and 1.2% in the TLG group. Other large series have shown that the rate of positive resection margins ranges from 2.8 to 18.2% [16–28]. Most of these studies included patients who underwent open gastrectomy for advanced disease. Furthermore, the locations of the positive resection margins were the esophagus or the duodenum in many patients. When limited to T1 or T2 cases, the incidence of positive resection margins ranges from 0.7 to 5.3% [22–28]. Kelly et al. reported that the laparoscopic approach was associated with a higher incidence of microscopic margin positivity (open group: 1% vs. laparoscopic group: 9%) in their large series of Western gastric cancer patients [29]. When the incidence of the positive margin increases, there is concern about increased recurrence and the specific recurrence pattern, such as peritoneal dissemination in TLG due to cancer cells scattering under a pneumoperitoneal condition. Compared with the aforementioned reports, the incidence of positive gastric resection margins in the present study seemed to be excellent. Moreover, the incidence and pattern of recurrence did not differ between the LAG and TLG groups. These results indicate that our strategy to determine a gastric transection line may replace the conventional method using tactile sensation and the positive resection margin under pneumoperitoneal conditions does not influence cancer relapse.

When a positive resection margin occurs after transecting the stomach, despite the application of the utmost care and attention, the subsequent management is important. Bickenbach et al. reported that margin status was an independent predictor of survival in patients with T1 or T2 disease and local recurrence occurred in 16% of patients with a positive margin [27]. In the current study, 20 patients had TF and all of them underwent additional resection to achieve complete removal of the clips or R0 resection. As a result, no patients who experienced TF and had pathological T1 or T2 disease died of primary disease, although local recurrence occurred in one patient. Therefore, additional resection in the same or second surgery should be an indispensable management approach for TF, especially in pathological T1 or T2 disease. Of course, additional resection in the same surgery may diminish invasiveness to patients. IFS analysis is recommended to confirm the pathological negativity of the resection margin when the gross margin length is shorter than that recommended in the guidelines [6].

Previously published observational studies and several randomized trials have reported the surgical and oncological safety of LG compared with open gastrectomy for patients with gastric cancer that is more advanced than stage I [30–36]. These results suggest that the indication for LG could be extended to include locally advanced gastric cancer. Based on this situation, another clinical question that arises from this study is whether we can safely determine the resection margin in TLG for advanced gastric cancer such as serosa-invasive tumors. In our strategy, the endoscopic findings and pathological negativity of biopsied specimens taken from normal-appearing mucosa is critical for determining regions negative for cancer or where we should place marking clips. Hence, in patients whose advanced gastric cancer diffusely invades beyond the submucosal layer without mucosal lesions, the value of preoperative and intraoperative endoscopy is limited. Several gastric cancer guidelines recommend different extents of macroscopic tumor-free resection margins. These vary from 3 cm in the JGCA treatment guidelines for advanced gastric cancer with expansive growth pattern to 8 cm for diffuse gastric cancer in the European Society of Medical Oncology Guidelines, but these recommendations do not refer to clear scientific evidence [6, 37, 38]. Recently, we published a study investigating just enough gross proximal margin length to obtain a pathologically negative margin [39]. According to this study, the proper gross proximal margin length are 30 mm for expansive growth type tumors and 50 mm for infiltrative growth type tumors. Therefore, in TLG for advanced gastric cancer, we should place marking clips further away from the gross proximal boundary of the tumor. Based on this strategy, we planned a feasibility study of TLG for advanced gastric cancer (UMIN000029317) which is currently ongoing.

There are several important limitations to our study. First, it was a single institutional and retrospective study. We included 1875 patients, a relatively large number, who underwent LG for cStage I gastric cancer under the same strategy and procedure. However, only 93 RFS and 29 TF events were obtained from the 1875 patients. This number of events was insufficient for multivariate analysis in which all the explanatory variables to be considered were inputted. Therefore, we used PSM in the comparative analysis. These approaches may reduce any potential selection bias arising from differences in patients' backgrounds, preoperative management, tumor status, indication of procedures, surgical techniques, and pre- and postoperative therapies. Nevertheless, there is no guarantee that all confounding factors were included in our database and it might be possible to overlook unmeasurable or unknown but important factors. Second, the selection of the procedure type, LAG or TLG, mainly depended on the period in which the procedure was performed. TLG was adopted after many experiences of LAG. Therefore, the excellent outcomes of TLG may be based on the greater experience of TLG than of LAG. Third, the most concerning problem of TLG, in which tactile sensation cannot be used for gastric transection, is the incidence of TF. However, to obtain a sufficient statistical power in analyzing the incidence of TF, a far higher number of patients than that enrolled in this study were required. Thus, we gave up testing the non-inferiority of the TF. Instead of such a design, we determined that the primary endpoint was RFS and that the incidence of TF was the secondary endpoint. Given these limitations, a prospective study is needed to confirm the feasibility of TLG and the results of an ongoing randomized controlled trial in Korea (KLASS 07) are awaited [40].

In conclusion, the short- and long-term oncological safety of TLG using intracorporeal gastric transection for cStage I gastric cancer was demonstrated. Precise preoperative tumor evaluation and intraoperative endoscopic guidance enable surgeons to make an exact intracorporeal gastric transection without touching the tumor, similar to conventional extracorporeal transection using tactile sensation in LAG. However, surgeons will experience TF once per one hundred transections even if TLG can achieve an accurate gastric transection, and they should not hesitate to perform an immediate additional transection to salvage such patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10120-021-01181-w.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical standards All procedures were conducted in accordance with the ethical standards of institutional and national committees responsible for human experimentation and with the 1964 and later versions of the Declaration of Helsinki.

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