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Stomach

Long-term oncologic outcomes of a randomized controlled trial comparing laparoscopic versus open gastrectomy with D2 lymph node dissection for advanced gastric cancer

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ABSTRACT

Background: Laparoscopy-assisted gastrectomy is a feasible and safe procedure for treating advanced gastric cancer in terms of short-term outcomes. However, concern about long-term oncologic outcomes has limited the adoption of laparoscopy-assisted gastrectomy for advanced gastric cancer.
Methods: We launched a prospective randomized controlled trial comparing laparoscopic and open gastrectomy with D2 lymph node dissection for locally advanced gastric cancer to evaluate long-term oncologic feasibility. The 5-year overall survival, disease-free survival, and tumor recurrences have been determined on an intention-to-treat basis.
Results: Between January 2010 and June 2012, a total of 328 patients with preoperative clinical stage $T_{2\text{-}4a}N_{0\text{-}3}M_0$ gastric cancer were enrolled in the trial. We excluded 6 patients with unresected tumor, and the remaining 322 patients were randomized to the laparoscopic group (162 patients) or the open group (160 patients) for radical surgery. One patient in laparoscopy-assisted gastrectomy and 4 patients in open gastrectomy were lost to follow-up immediately after discharge, leaving 317 patients (161 in laparoscopy-assisted gastrectomy and 156 in open gastrectomy) eligible for long-term analysis. The 5-year overall survival rate was 49.0% in the laparoscopic group and 50.7% in the open group, and the 5-year disease-free survival rate was 47.2% and 49.6% in the 2 groups, respectively. Kaplan–Meier curves for overall survival and disease-free survival showed no differences between the 2 groups. There was no difference in the 5-year tumor recurrence rate between the 2 procedures.
Conclusion: Laparoscopy-assisted gastrectomy can provide comparable long-term survival without an increase in recurrence and metastasis in treating advanced gastric cancer.

Introduction

Laparoscopy-assisted gastrectomy (LAG) as an option for treating gastric cancer (GC) has been accepted by surgeons and patients. The latest Japanese gastric cancer treatment guideline[1] recommends LAG as an optional treatment for cStage I GC. According to the short-term results of two multicenter randomized controlled trials (RCTs),[2,3] LAG is a feasible and safe procedure treating advanced GC and maintaining minimally invasive nature. Although the results of two large-scale retrospective studies[4,5] have confirmed that LAG for advanced GC can provide comparable long-term outcomes compared with open surgery, the long-term results of the RCTs have not been reported. Concern about oncologic radicality and long-term outcomes has limited the adoption of LAG for advanced GC.

We began a single-center noninferiority RCT in China to assess the efficacy of LAG with D2 lymphadenectomy for the treatment of patients with advanced GC. The short-term results from this trial have been published, which have confirmed the technical feasibility and safety.[6] Presented here are the long-term oncologic results of this trial.

Patients and Methods

Study design

This is a single-center noninferiority RCT comparing LAG and open gastrectomy (OG) with D2 lymphadenectomy for locally

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advanced GC patients. The study protocol was approved by the Ethics Committee of Southwest Hospital (KY200908; Chongqing, China) before conducting the study. We included patients 18-80 years of age with histologically proven adenocarcinoma through endoscopic biopsy. The preoperative findings of computed tomography (CT) or endoscopic ultrasonography screened patients with $T_{2\text{-}4a}N0_{\text{-}3}M_0$ stage cancer, according to the American Joint Committee on Cancer ([AJCC] 7th ed) staging criteria. We excluded patients who were pregnant or demonstrated one or more of the following: an American Society of Anesthesiologists (ASA) score >3, severe mental disorders, having had an upper abdominal surgery except laparoscopic cholecystectomy, the presence of other malignancies, a history of chemotherapy or radiation therapy, unstable angina or myocardial infarction within the past 6 months, a severe respiratory disease (forced expiratory volume in 1 s, FEV1 < 50%), an abdominal wall hernia, a diaphragmatic hernia, a coagulation disorder, and portal hypertension. After the confirmation of inclusion and exclusion criteria and the acquisition of informed consents, patients underwent laparoscopic exploration. If suitable for curative surgery, patients were randomly assigned to open surgery or laparoscopic surgery, and the surgeon then began a standard radical gastrectomy with D2 lymphadenectomy, according to the Japanese Classification of Gastric Carcinoma (13th ed). Adjuvant chemotherapy was started from 4 to 6 weeks postoperatively. We routinely administered six cycles of 5-fluorouracil and oxaliplatin intravenous chemotherapy for stages II–III. Details of eligibility criteria, treatment protocol, quality control procedures, and randomization have been reported elsewhere.[6]

Between January 2010 and June 2012, a total of 328 patients were enrolled in the trial. During laparoscopic exploration, 6 patients were excluded because of unresectable tumor, and the remaining 322 patients were randomly assigned to the laparoscopic surgery group (162 patients) or the open surgery group (160 patients). Of the patients in the LAG group, 6 were converted to open surgery. All patients underwent R0 resection. The average number of retrieved lymph nodes was 31.6 ± 5.9 in the LAG group and 32.2 ± 6.1 in the OG group ($P = .377$, Table I). The morbidity was not significantly different between the LAG (11.7%) and OG groups (14.4%, $P = .512$). No mortality occurred after radical surgery in either group. This study is to report the 5-year follow-up results of this trial, which was registered at ClinicalTrials.gov (NCT01043835) before conducting the trial.

Table I
Patient demographics and baseline characteristics

Variables	LAG ($n = 161$)	OG ($n = 156$)	P value
Sex, number (%)			
Male	120 (74.5)	101 (64.7)	.067
Female	41 (25.5)	55 (35.3)	
Age, mean (SD) in years	55.2 ± 11.0	54.8 ± 10.8	.738
BMI, mean (SD), kg/m^2	20.7 ± 3.1	20.2 ± 3.0	.109
ASA score, number (%)			
1	79 (49.1)	80 (51.3)	.652
2	68 (42.2)	59 (37.8)	
3	14 (8.7)	17 (10.9)	
Tumor size, mean (SD) in cm	4.3 ± 1.9	4.4 ± 2.0	.501
Retrieved LN, mean (SD)	31.6 ± 5.9	32.2 ± 6.1	.377
Tumor location, number (%)			
Upper	35 (21.7)	34 (21.8)	.753
Middle	46 (28.6)	39 (25.0)	
Lower	80 (49.7)	83 (53.2)	
Extent of resection, number (%)			
Proximal gastrectomy	7 (4.3)	11 (7.1)	.252
Distal gastrectomy	93 (57.8)	98 (62.8)	
Total gastrectomy	61 (37.9)	47 (30.1)	
pT-stage, number (%)			
T2-3	30 (18.6)	35 (22.4)	.408
T4a	131 (81.4)	121 (77.6)	
pN-stage, number (%)			
N0	47 (29.2)	32 (20.5)	.435
N1 (1–2)	33 (20.5)	31 (19.9)	
N2 (3–6)	27 (16.8)	33 (21.2)	
N3a (7–15)	35 (21.7)	40 (25.6)	
N3b (>15)	19 (11.8)	20 (12.8)	
pStage, number (%)			
IB	16 (9.9)	10 (6.4)	.776
IIA	6 (3.7)	9 (5.8)	
IIB	36 (22.4)	34 (21.8)	
IIIA	30 (18.6)	26 (16.7)	
IIIB	22 (13.7)	21 (13.5)	
IIIC	51 (31.7)	56 (35.9)	
Histologic grade, number (%)			
Moderately differentiated	44 (27.3)	36 (23.1)	.222
Poorly differentiated	100 (62.1)	110 (70.5)	
Others	17 (10.6)	10 (6.4)	

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *LN*, lymph node; *OG*, open gastrectomy.
Note: Tumor stage according to the American Joint Committee on Cancer, seventh ed.

Follow-up

All patients were regularly followed up at 3-month intervals in the first year, 6-month intervals for the next 2 years, and annually thereafter. Abdominopelvic CT, upper gastrointestinal endoscopy, and blood test—including serum carcinoembryonic antigen—were performed for regular follow-up and detection of recurrence, which was confirmed by cytology or histology if necessary.

End points

The primary long-term end point was 5-year overall survival (OS). The secondary long-term end points were 5-year disease-free survival (DFS) and tumor recurrences.

Outcome Measurements

OS was calculated from the date of operation to the date of death for any cause. Patients alive or lost to follow-up were censored at the date last known to be alive. DFS was calculated from the date of operation to the date of recurrence or death. Patients alive without recurrent disease or lost to follow-up were censored at the date last known to be alive and recurrence free. Follow-up after 5 years of operation was censored in all analyses. Recurrence patterns were classified into four groups: peritoneum, local site, distant metastasis, and port-site/wound metastasis. Patients' recurrence patterns were defined by the first detected recurrence site.

Sample size and statistical analysis

The primary objective of this RCT was designed to demonstrate that LAG is noninferior to OG in terms of OS. Therefore, the size of the study was calculated on the basis of the effect of LAG and OG on the 5-year OS. The sample size calculation assumed a one-sided error of 0.05, a statistical power of 80%, and a noninferiority margin of 15% in terms of 5-year OS rate.[6] As a result, a total of 328 patients (164 patients per group) were required when we consider a 20% dropout rate.

Continuous variables were displayed by mean ± standard deviation, and categorical variables were expressed as percentage differences. The comparisons among groups were tested with the Fisher exact test, Student t test, or χ^2 test.

The 5-year OS, DFS, and tumor recurrences were evaluated using the intention-to-treat analysis. Differences in OS, DFS, and tumor recurrences between groups were compared using Kaplan-Meier curves and tested using the log-rank test. Multivariate analyses, with backward variable selection, were conducted using the Cox

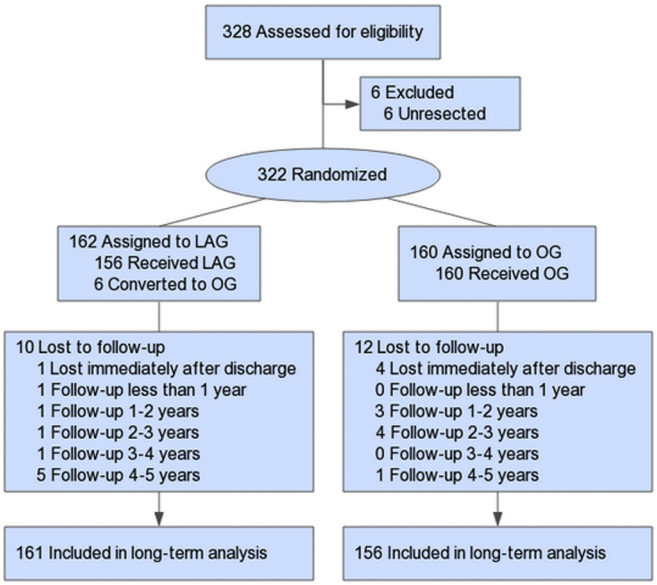

Fig 1. CONSORT flow diagram. *LAG*, laparoscopy-assisted gastrectomy; *OG*, open gastrectomy.

proportional hazards regression model. The predefined baseline variables for the univariate analysis were sex, age, body mass index (BMI), American Society of Anesthesiologists score, tumor size and location, depth of invasion, metastasis of lymph nodes, and degree of tumor differentiation. Variables at the 0.10 level in univariate analysis were included in the multivariate model. $P < .05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY).

Results

Patient characteristics

One patient in the LAG group and 4 patients in the OG group were lost to follow-up immediately after discharge, leaving 317 patients (161 in LAG and 156 in OG) eligible for long-term analysis (Fig. 1). Patient demographics and baseline characteristics were well balanced between the 2 groups (Table I).

Follow-up

A total of 10 patients in the LAG group and 12 patients in the OG group were lost to follow-up during a period of 5 years after surgery (Fig. 1). All remaining patients were compliant with the proposed postoperative surveillance protocol. The median follow-up was 49 months (range, 2–87) in the whole series, 45 months (range, 3–85) in the LAG group, and 54 months (range, 2–87) in the OG group ($P = .752$).

Overall survival

The 5-year OS rate for all patients was 49.8%. The 5-year OS rate was 49.0% in the laparoscopic surgery and 50.7% in the open surgery. Kaplan–Meier curves for OS showed no survival differences between the 2 groups (log-rank test, $P = .767$; Fig. 2). Furthermore, there was no difference in OS for patients with IB, II, or III stage of GC between the 2 techniques, although a nonsignificant difference was observed for worse 5-year OS after laparoscopic surgery in patients with stage III tumor ($P = .273$; Fig. 2).

Disease-free survival

The 5-year DFS rate for all patients was 48.3%. The 5-year DFS rate was 47.2% in the laparoscopic surgery and 49.6% in the open surgery. Kaplan-Meier curves for DFS showed no differences between the 2 groups (log-rank test, $P = .654$; Fig. 3). Also, there was no difference in DFS for patients with IB, II, or III stage of GC between the two techniques, though a nonsignificant difference was observed for worse 5-year DFS after laparoscopic surgery in patients with stage III tumor ($P = 0.224$; Fig. 3).

Multivariable analysis of OS and DFS

In multivariable analysis of OS and DFS (Table II), OS and DFS were closely related to tumor size, depth of invasion, and metastasis of lymph nodes. The treatment effect did not significantly differ between the 2 groups ($P = .386$ and $P = .230$ for OS and DFS, respectively).

Recurrence

Peritoneal recurrence was the most frequent recurrence pattern. The 5-year overall peritoneal recurrence rate was 27.4%: 28.6% in the LAG group and 26.0% in the OG group. No difference was observed between the 2 groups ($P = .705$). The 5-year overall local site recurrence rate was 12.9%: 13.3% in the LAG group and 12.4% in the OG group. No difference was observed in local site recurrence between the laparoscopic and open surgeries ($P = .732$). The 5-year overall distant recurrence rate was 19.3%: 20.4% in the LAG group and 18.0% in the OG group without significant difference between the 2 techniques ($P = .599$). Notably, there was no port site or wound recurrence in either group.

Stratified analysis for patients with T4a tumor

In the T4a group, the 5-year OS rate was 43.1% in the laparoscopic surgery and 42.4% in the open surgery. The 5-year DFS rate was 40.8% in the laparoscopic surgery and 41.9% in the open surgery. Kaplan-Meier curves for OS and DFS showed no differences between the 2 groups (log-rank test, $P = 1.000$ and $P = .822$, respectively; Fig. 4). In multivariable analysis (Table II), OS and DFS were closely related to tumor size and metastasis of lymph nodes. The treatment effect did not significantly differ between the 2 groups ($P = .594$ and $P = .351$ for OS and DFS, respectively). For patients with T4a tumor, the 5-year overall peritoneal recurrence rate was 32.8%: 32.8% in the LAG group and 32.7% in the OG group. No difference was observed between the 2 groups ($P = .967$). The 5-year local site recurrence rate in the laparoscopic group (16.3%) was similar to that in the open group (14.4%, $P = .523$). The 5-year distant recurrence rate was similar between the laparoscopic and open surgeries (24.0% vs 20.4%, $P = .690$).

Discussion

Since Kitano et al[7] performed LAG for early GC in 1991 for the first time, the role of LAG in treating early GC has been introduced and widely accepted, especially in East Asia. Despite initial concerns with oncologic safety, laparoscopic surgery has been used for treating locally advanced GC, owing to improved surgical outcomes of early bowel recovery, better quality of life, and shorter hospital stay. The results of two large-scale retrospective studies[4,5] revealed that compared with open surgery, laparoscopic surgery for locally advanced GC can lead to better short-term outcomes and comparable long-term oncologic results. The recent multicenter RCTs[2,3] have demonstrated that LAG for locally advanced GC is a feasible

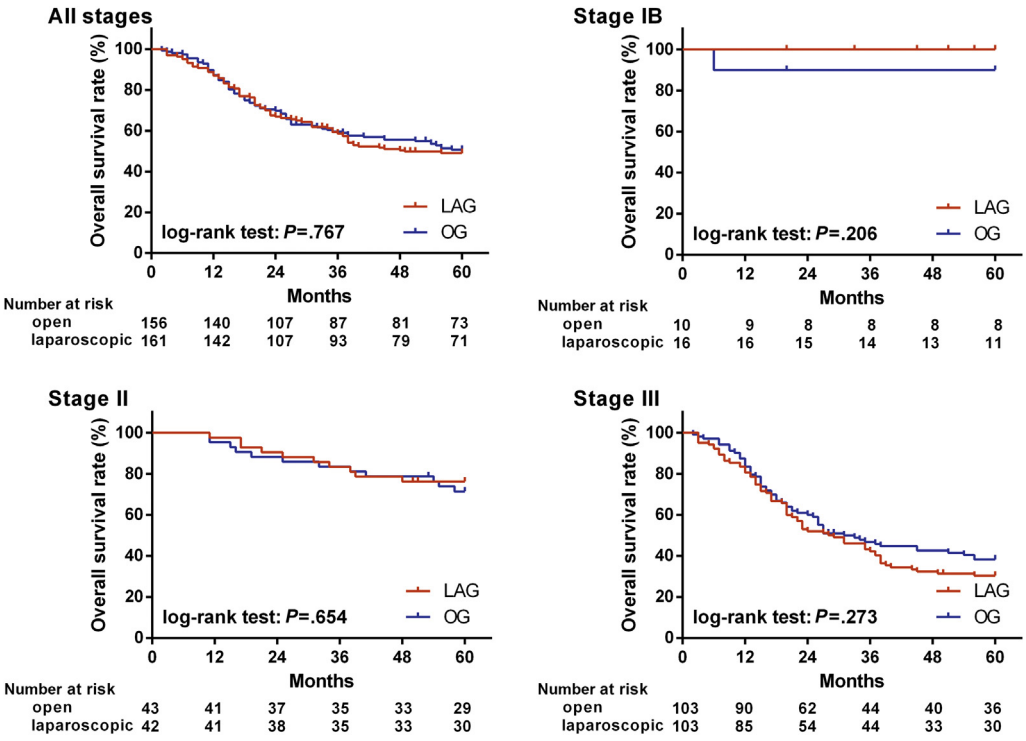

Fig 2. Kaplan-Meier curves for comparison of 5-year overall survival between patients with different tumor stages. *LAG*, laparoscopy-assisted gastrectomy; *OG*, open gastrectomy.

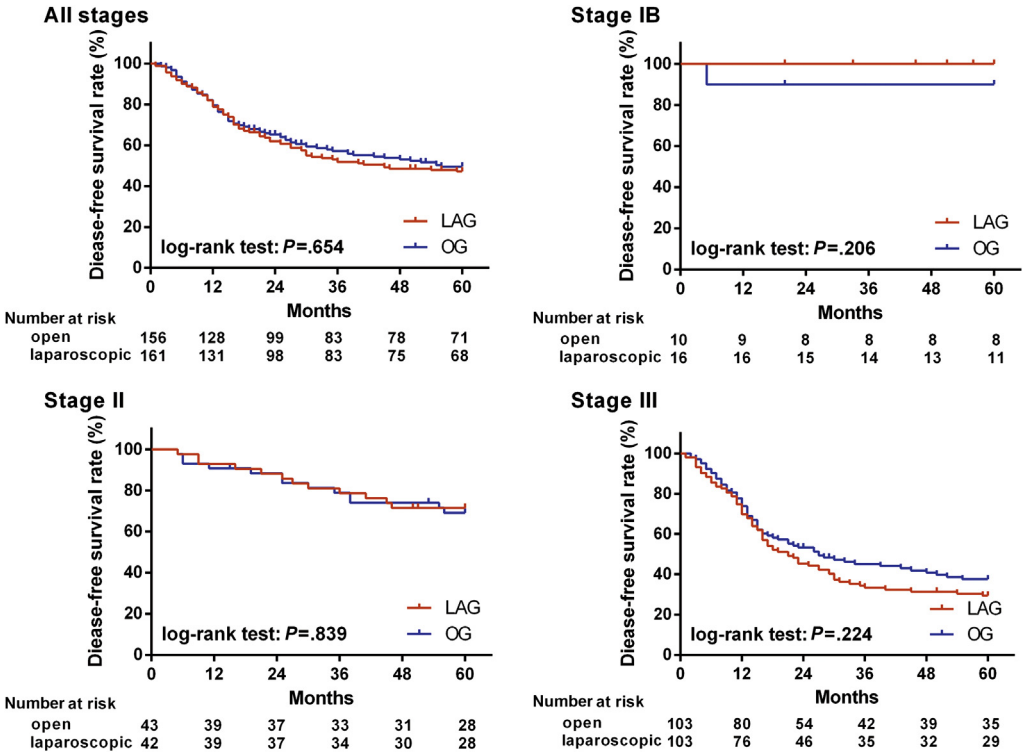

Fig 3. Kaplan-Meier curves for comparison of 5-year disease-free survival between patients with different tumor stages. *LAG*, laparoscopy-assisted gastrectomy; *OG*, open gastrectomy.

and safe procedure in terms of its short-term results. However, the long-term results of the RCTs have not been reported. Thus, the long-term outcomes of treating locally advanced GC by LAG remain unclear. To our knowledge, this is the first report of the long-term results from a prospective RCT to evaluate the efficacy of LAG with D2 lymphadenectomy for locally advanced GC.

Minimal trauma and quick recovery promote the recognition of laparoscopic surgery. Meanwhile debate about laparoscopy

Table II
Multivariable analysis of overall survival and disease-free survival

	OS			DFS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
For all patients						
Tumor size						
< 4 cm/≥ 4 cm	1.764	1.235–2.519	.002	1.766	1.245–2.505	.001
T stage						
T2-3/T4a	2.149	1.195–3.863	.011	2.174	1.234–3.828	.007
N stage						
N0/N1/N2/N3	1.634	1.386–1.927	< .001	1.578	1.345–1.850	< .001
Surgery						
LAG/OG	0.863	0.619–1.203	.386	0.819	0.591–1.135	.230
For patients with T4a tumor						
Tumor size						
< 4 cm/≥ 4 cm	1.626	1.124–2.351	.010	1.664	1.157–2.393	.006
N stage						
N0/N1/N2/N3	1.573	1.328–1.862	< .001	1.508	1.280–1.777	< .001
Surgery						
LAG/OG	0.910	0.643–1.288	.594	0.850	0.603–1.197	.351

CI, confidence interval; *HR*, hazard ratio; *OG*, open gastrectomy.

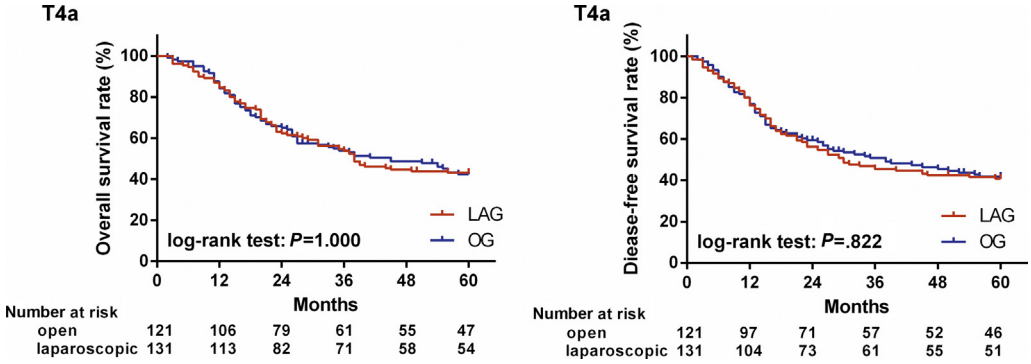

Fig 4. Kaplan-Meier curves for comparison of 5-year overall survival and disease-free survival between patients with T4a tumor. *LAG*, laparoscopy-assisted gastrectomy; *OG*, open gastrectomy.

promoting tumor dissemination continues. In colorectal cancer surgery, the results from the three large, multicenter, prospective RCTs (COST, COLOR, and UK MRC CLASICC)[8–10] have confirmed that laparoscopic surgery has comparable long-term outcomes and shares similar recurrence patterns with open surgery. However, these results cannot alleviate the concern about LAG for GC. Because of the characteristics of tumor biology, gastric cancer, especially the poorly differentiated type or the signet ring cell type, is known to have a much higher tendency to develop peritoneal metastasis than colorectal cancer. Thus, there are general concerns that LAG for advanced GC, especially for T4a tumor (serosa involved), may increase the incidence of peritoneal recurrence and port-site metastasis and even sacrifice long-term survival.

Our analysis of long-term oncologic outcomes showed that 5-year OS and DFS in advanced GC patients undergoing LAG with D2 lymphadenectomy are no worse than those undergoing open surgery. Of note, even for patients with T4a tumors, no difference was observed in 5-year OS and DFS between the two procedures. Furthermore, multivariable analysis of OS and DFS showed that the treatment effect did not significantly differ between the laparoscopic and open surgeries. Thus, we demonstrate that LAG with D2 lymphadenectomy for locally advanced GC is a safe procedure with no detriment to long-term survival, which is consistent with published retrospective reports.[4,5,11–13]

Song et al[14] and Nakagawa et al[15] reported that the peritoneal recurrence rate of T4a cases is 17.8% and 35%, respectively, after LAG. A retrospective study[13] showed that the incidence of peritoneal recurrence was 15.6% after LAG for advanced GC, which is comparable with that after the open procedure. Our results presented that the proportion of peritoneal recurrence is 27.4% for all patients and 32.8% for the patients with T4a tumor in the LAG group; moreover, no difference was observed between the two surgical procedures. Therefore, we confirm that laparoscopic surgery for advanced GC does not increase the risk of peritoneal recurrence.

After laparoscopic colectomy for colon cancer, port-site metastasis was reported as 0.5% to 0.94%.[16,17] However, port-site metastasis after LAG remains unclear. Although some reports have been published regarding port-site metastasis after laparoscopic surgery for GC, most cases of port-site metastases occur in patients with peritoneal dissemination undergoing diagnostic laparoscopy.[18,19] The first case of port-site metastasis after LAG for GC was reported in 2007.[20] Later, Sakurai et al[21] reported a case of port-site metastasis after LAG for early gastric cancer. Hwang et al[22] reported a pure port-site recurrence without widespread metastases after LAG for advanced GC. However, in a multicenter retrospective analysis of 1,417 patients who underwent LAG, the results did not show any case with port-site metastasis.[14] Our retrospective study[12] reported that one patient had port-site metastasis after LAG. Moreover, one patient had wound metastasis and one patient had metastasis at the orifice of the abdominal drain after open surgery. No significant difference was found between the two groups. In the present trial, enrolling almost 80% of patients with T4a tumor, there was no incidence of port-site metastasis in laparoscopic surgery. In summary, there is no evidence that LAG for GC

increases the incidence of port-site metastasis. However, we cannot neglect the fact that the indication for LAG is limited to patients with early GC. Thus, after LAG is widely used in treating advanced GC, the effect of pneumoperitoneum on port-site metastasis after LAG needs further evaluation.

In addition to peritoneal recurrence and port-site metastasis, no difference was observed in local site recurrence and distant metastasis between the laparoscopic and open procedures in this study. We demonstrate that, taken together, laparoscopic surgery does not increase the risk of recurrence and metastasis in the treatment of patients with advanced GC.

This study has several limitations. First, this is a single-center clinical trial recruiting a relatively small number of patients. Second, 22 (6.83%) patients were lost during the 5-year follow-up. However, the rate of lost to follow-up is low and acceptable. Thus, this work is a well-designed RCT with a 5-year follow-up period performed in a high-volume center. The selected surgeons participating in the trial have extensive experience in either laparoscopic or open surgery, which leads to low conversion rates and high-qualified operations. More than 65% of patients with stage III GC were recruited into the trial, which is more likely to represent the “real-life” situation in clinical practice.

In conclusion, the results of the trial demonstrate that the long-term outcomes of LAG with D2 lymphadenectomy for locally advanced GC are not inferior to open gastrectomy. Laparoscopic surgery can provide comparable long-term survival without an increase in recurrence and metastasis in treating advanced GC. The solid evidence justifies the implementation of laparoscopic surgery for advanced GC into daily practice. The results of this study need to be further validated by multicenter RCT studies.

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Conflict of interest

There exists no financial interests or potential conflicts of interest in the paper.

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