Open vs. laparoscopic surgery for locally advanced gastric cancer after neoadjuvant therapy: Short-term and long-term survival outcomes

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Abstract. The aim of the present study was to compare the short-term and long-term survival outcomes of laparoscopic gastrectomy vs. open gastrectomy in treating locally advanced gastric cancer (LAGC) after neoadjuvant therapy. This study retrospectively reviewed the medical records of 270 patients with LAGC, who underwent laparoscopic (n=49) or conventional open (n=221) surgery following neoadjuvant therapy between January 2007 and December 2016 in China National Cancer Center. Postoperative parameters and survival outcomes including overall survival and disease-free survival were analyzed. Patients who underwent laparoscopic gastrectomy (LP) had significantly shorter postoperative stay and a decreased number of metastatic lymph nodes harvested compared to those who underwent open surgery. The 75% disease-free survival (DFS) time in the laparoscopic surgery group (25.7 months) was higher compared with the open surgery group (15.6 months). However, no significant difference was observed in 5-year overall survival and DFS between the two groups. In conclusion, LG provides non-inferior short- and long-term survival outcomes compared with open surgery, suggesting a laparoscopic approach may be justified for patients with LAGC receiving neoadjuvant therapy. More randomized controlled trials are required to investigate the positive effects of LG for LAGC following neoadjuvant therapy.

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Key words: gastric cancer, laparoscopic surgery, neoadjuvant therapy, short-term outcomes, long-term survival outcomes

Introduction

Gastric cancer is the third leading cause of cancer-associated mortality worldwide (1). Locally advanced gastric cancer (LAGC) is a major treatment challenge and accounts for 80% of total gastric cancer cases in China (2,3). The current therapeutic strategy for LAGC is multidisciplinary with a surgical procedure as the core. Accumulating evidence has revealed that neoadjuvant therapy improves the efficacy of LAGC compared with surgery alone (4-7).

Since the 2014 version of the guidelines of the Japan Society for Endoscopic Surgery, distal gastrectomy by the laparoscopic approach was recommended for stage I gastric cancer (8). For advanced gastric cancer following neoadjuvant therapy, however, the safety and efficacy of laparoscopic approach following were unclear, as oncologic outcomes of currently ongoing randomized trials are unknown (9,10). A number of surgeons are now actively applying laparoscopic gastrectomy (LG) to patients with LAGC receiving neoadjuvant therapy. To the best of our knowledge, a limited number of studies have reported the safety and efficacy of LG following neoadjuvant therapy, particularly in terms of long-time survival.

Therefore, the aim of the present study was to evaluate the postoperative safety and efficacy and the long-time survival of patients who had undergone LG compared with patients who had undergone open gastrectomy (OG) following neoadjuvant therapy.

Patients and methods

Patient selection. This study retrospectively reviewed the medical records of 270 patients with LAGC who underwent LG (n=49) or conventional OG (n=221) surgery following neoadjuvant therapy between January 2007 and December 2016 at the China National Cancer Center (Beijing, China). LAGC was defined as clinical stage II-III according to the eighth edition American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC)

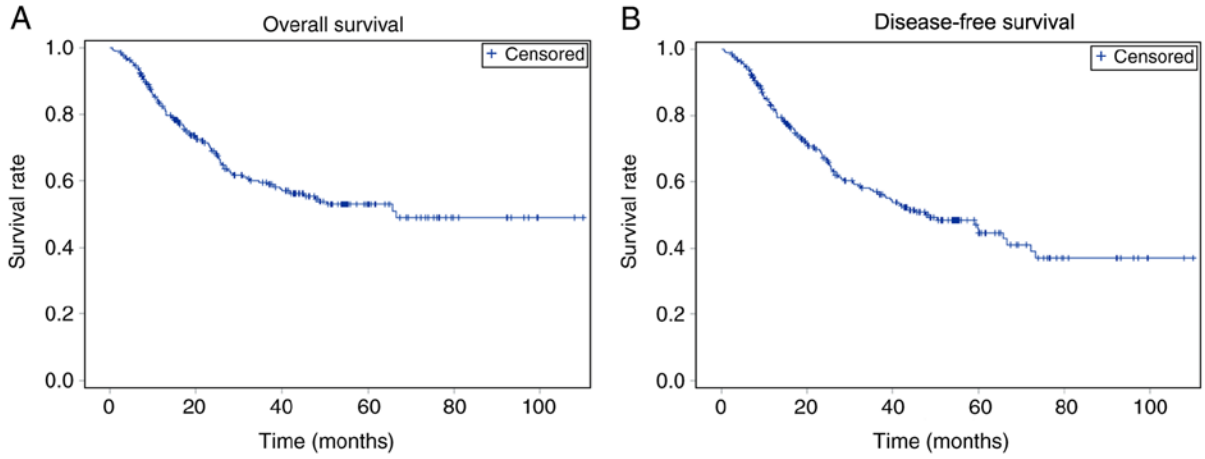

Figure 1. Overall survival and disease-free survival rates of patients who underwent surgery following neoadjuvant therapy.

Tumor-Node-Metastasis (TNM) gastric cancer classification (11). There were 188 male (69.6%) and 82 female (30.4%) patients (male-to-female ratio, 2.29:1; median age, 54.8 years; range, 28-84 years). The database included data on patient demographics, clinical history, past medical history, family history, comorbidities, diagnostic tests, tumor characteristics, therapeutic interventions, pathological data, postoperative parameters and survival outcomes. All data were backed up by source documents and the accuracy of the data was periodically reviewed. The study procedures were approved by the Institutional Review Board at the China National Cancer Center and the patients provided informed consent at the time of sample collection.

Procedures. Patients received a fluoropyrimidine-based chemoradiotherapy regimen preoperatively. Surgery was performed 2-8 weeks after completion of the neoadjuvant therapy. Histopathological examination was evaluated according to the Mandard Tumor Regression Grading evaluation system (12).

Follow-up. Patients were followed-up every 3 months for the first 2 years, every 6 months for the next 3 years, and every 6 months or yearly thereafter. For the postoperative follow-up, a physical examination, complete blood-cell count, liver function tests, serum carcinoembryonic antigen tests and chest radiography were performed every 3 months or 6 months; abdominal and pelvic computed tomography (CT) were performed every 6 months. Gastroscopic examinations were done 1 year postoperatively and once every 2 years thereafter. When a patient missed two consecutive scheduled visits or voluntarily withdrew consent to participate during the follow-up period, the patient was defined as lost to follow-up and their data were censored. The last follow-up was completed in May 2017 and included 251 patients.

Statistical analysis. Data of continuous variables are presented as the mean ± standard deviation, whereas categorical variable data were presented as percentages. Patient demographic and clinical characteristics between the two groups were compared with Student's t-test for continuous variables with normal distribution and χ^2 test for categorical variables. The Kaplan-Meier method was used to estimate disease-free survival (DFS) and overall survival (OS) rates, and the log-rank test was used to compare survival distribution. Multivariate Cox regression analysis was used to adjust for confounding factors that were significant in univariate analysis and for non-balanced between-group variables. Mean survival time (months) and 95% confidence interval (CI) were calculated using the Kaplan-Meier method. A two-sided $P<0.05$ was considered to indicate a statistically significant difference. All analyses were performed using SPSS statistical software version 24.0 (SPSS, Inc.).

Results

Between January 2007 and December 2016, 270 patients that underwent neoadjuvant therapy received LG (n=49) or OG (n=221). None of the patients had a metastatic lesion detected before or during the surgery. There were no deaths during the first 3 months after surgery. The OG and LG groups were balanced in terms of their baseline characteristics, combined comorbidities, clinical staging before neoadjuvant therapy, and chemotherapy regimens. The number of neoadjuvant therapy cycles was statistically different between the two groups (P=0.016). According to RECIST criteria (version 1.1) (13) and tumor regression grade, response on neoadjuvant therapy was not significantly different between the two groups (Table I).

Postoperative stay was shorter and the number of metastatic lymph nodes harvested was lower in the LG group compared with that in the OG group (Tables I and II). The number of resected lymph nodes was similar between the two groups (Table I). The incidence of complications, surgery time, blood loss and postoperative mortality were not significantly different between the two groups (Table II).

Fig. 1 shows the rates of DFS and OS of all patients, whereas Table III and Fig. 2 demonstrate the rates of DFS and OS in the LG and OG groups. The 75% DFS time was 15.6 (11.5-20.0) months for the OG group and 25.7 (12.3-41.3) months for the LG group. The 1-, 2-, 3- and 5-year OS rates for the LG group were 89.6, 82.1, 75.6 and 65.8%, respectively, and for the OG group were 81.6, 65.9, 55.9 and 49.7%, respectively.

Table I. Demographic and clinicopathological characteristics in laparoscopy and open gastrectomy group.

Variable	Laparoscopy group (n=49)[a]	Open gastrectomy group (n=221)[a]	P-value
Age, years	54.4 (10.9)	54.9 (11.3)	0.80
Body mass index, kg/m^2			0.89
<18.5	3 (6.1)	11 (5.0)	
18.5-22.9	22 (44.9)	91 (41.2)	
23.0-27.4	20 (40.8)	94 (42.5)	
≥27.5	4 (8.2)	25 (11.3)	
Sex, n (%)			0.97
Male	34 (69.4)	154 (69.7)	
Female	15 (30.6)	67 (30.3)	
Comorbidities, n (%)			0.58
Diabetes	3 (6.1)	16 (7.2)	
Coronary artery disease	0 (0.0)	11 (5.0)	
Hypertension	10 (20.4)	42 (19.0)	
Cerebral infraction	0 (0.0)	5 (2.3)	
Hypothyroidism	0 (0.0)	2 (0.9)	
Chronic obstructive pulmonary disease	0 (0.0)	3 (1.4)	
Hepatitis B	0 (0.0)	4 (1.8)	
Hepatitis C	0 (0.0)	1 (0.5)	
Previous abdominal surgery, n (%)			0.78
Yes	5 (10.2)	19 (8.6)	
No	44 (89.8)	202 (91.4)	
Tumor location, n (%)			0.74
Upper 1/3	13 (26.5)	54 (24.4)	
Middle 1/3	11 (22.5)	44 (19.9)	
Low 1/3	9 (18.4)	61 (27.6)	
Upper-middle	3 (6.1)	16 (7.2)	
Middle-low	13 (26.5)	45 (20.4)	
Body-antrum	0 (0.0)	1 (0.5)	
Family history of cancer, n (%)			0.47
Yes	13 (26.5)	48 (21.7)	
No	36 (73.5)	173 (78.3)	
Clinical TNM stage, n (%)			0.08
II	4 (8.2)	5 (2.3)	
III	45 (91.8)	216 (95.5)	
Neoadjuvant therapy regime, n (%)			0.10
XELOX	3 (6.1)	11 (5.0)	
FOLFOX	1 (2.0)	19 (8.6)	
SOX	13 (26.5)	53 (24.0)	
SP	2 (4.1)	19 (8.6)	
TXT+XELOX	6 (12.2)	17 (7.7)	
TCF	5 (10.2)	28 (12.7)	
DOS	7 (14.3)	20 (9.1)	
TXT+SP	0 (0.0)	14 (6.3)	
Others	5 (10.2)	28 (12.7)	
Cycle of neoadjuvant therapy, n (%)			0.02[b]
1-3	23 (46.9)	87 (39.4)	
4-6	21 (42.9)	117 (52.9)	
>6	0 (0.0)	12 (5.4)	

Table I. Continued.

Variable	Laparoscopy group (n=49)[a]	Open gastrectomy group (n=221)[a]	P-value
Neoadjuvant therapy toxicity, n (%)			0.47
No toxicity	13 (26.5)	74 (33.5)	
Grade I/II	33 (67.4)	128 (57.9)	
Grade III/IV	3 (6.1)	19 (8.6)	
Time between neoadjuvant therapy and surgery, days	36.4 (15.4)	36.9 (18.0)	0.86
RECIST criteria (version 1.1), n (%)			0.93
Partial response	34 (69.4)	150 (67.9)	
Stable disease	13 (26.5)	64 (29.0)	
Progressive disease	2 (4.1)	7 (3.1)	
Gastrectomy, n (%)			0.63
Distal	29 (59.2)	117 (52.9)	
Proximal	4 (8.2)	27 (12.2)	
Total	16 (32.7)	77 (34.8)	
Borrmann type (22), n (%)			0.37
I	4 (8.2)	8 (3.6)	
II	18 (36.7)	62 (28.1)	
III	23 (46.9)	123 (55.7)	
IV	4 (8.2)	25 (11.3)	
Unknown	0 (0.0)	3 (1.4)	
Lauren type (23), n (%)			0.35
Intestinal	13 (26.5)	43 (19.5)	
Diffuse	17 (34.7)	66 (29.9)	
Mixed	8 (16.3)	34 (15.4)	
Unknown	11 (22.5)	78 (35.3)	
Primary pathology, n (%)			0.65
Poorly differentiated adenocarcinoma	32 (65.3)	146 (66.1)	
Moderately differentiated adenocarcinoma	10 (20.4)	31 (14.0)	
Well differentiated adenocarcinoma	1 (2.0)	3 (1.4)	
Signet ring cell carcinoma	1 (2.0)	13 (5.9)	
Minor adenocarcinoma remains	2 (4.1)	6 (2.7)	
No adenocarcinoma remains (complete response)	2 (4.1)	18 (8.1)	
Other	1 (2.0)	4 (1.8)	
Resected lymph nodes, n (%)	32.9 (13.6)	30.0 (14.0)	0.19
Metastatic lymph nodes, n (%)	2.4 (3.4)	6.0 (9.1)	<0.0001[b]
Mandard Tumor Regression Grading (12), n (%)			0.06
1	2 (4.1)	17 (7.7)	
2	10 (20.4)	32 (14.5)	
3	22 (44.9)	62 (28.1)	
4	2 (4.1)	8 (3.6)	
5	13 (26.5)	102 (46.2)	

[a]Data are presented as the mean (standard deviation) for continuous variables and number (percentage) for categorical variables. [b]P<0.05. XELOX, oxaliplatin and capecitabine; FOLFOX, folinic acid, fluorouracil and oxaliplatin; SOX, S-1 and oxaliplatin; SP, S-1/cisplatin; TXT, docetaxel; TCF, docetaxel, carboplatin and 5-fluorouracil; DOS, docetaxel, oxaliplatin and S-1; RECIST, response evaluation criteria in solid tumors.

The 1-, 2-, 3- and 5-year DFS rates for LG group were 89.6, 79.8, 70.4 and 53.3%, respectively, and for OG group were 81.1, 64.4, 54.1 and 43.7%, respectively. No significant difference was observed in OS and DFS between the two groups. In addition, no significant difference was observed in 1-, 2-, 3- and 5-year DFS and OS.

Table II. Comparison of perioperative parameters between the laparoscopic and open gastrectomy groups.

Variable	Laparoscopy group (n=49)[a]	Open gastrectomy group (n=221)[a]	P-value
Complication, n (%)	6 (12.2)	26 (11.8)	0.752
Central line infection	0 (0.0)	1 (0.5)	
Wound infection	0 (0.0)	3 (1.4)	
Renal failure	0 (0.0)	1 (0.5)	
Multiple organ failure	0 (0.0)	1 (0.5)	
Delayed gastric emptying	1 (2.0)	1 (0.5)	
Gastrointestinal hemorrhage	0 (0.0)	5 (2.3)	
Pleural effusion	1 (2.0)	2 (0.9)	
Pneumonia	0 (0.0)	3 (1.4)	
Fat liquefaction	1 (2.0)	2 (0.9)	
Postoperative ileus	0 (0.0)	3 (1.4)	
Intra-abdominal infection	1 (2.0)	3 (1.4)	
Duodenal stump fistula	1 (2.0)	1 (0.5)	
Anastomotic leak	1 (2.0)	4 (1.8)	
Reoperation	1 (2.0)	1 (0.5)	
Postoperative mortality	0 (0.0)	0 (0.0)	
Surgery time, min	221.5 (69.9)	201.1 (56.7)	0.060
Estimated blood loss, ml	260.2 (232.1)	241.1 (186.3)	0.590
Time to pull gastric tube, days	5.5 (2.0)	6.6 (3.3)	0.002[b]
Postoperative stay, days	11.1 (4.4)	13.0 (7.3)	0.020[b]

[a]Data are presented as the mean (standard deviation) for continuous variables and number (percentage) for categorical variables.

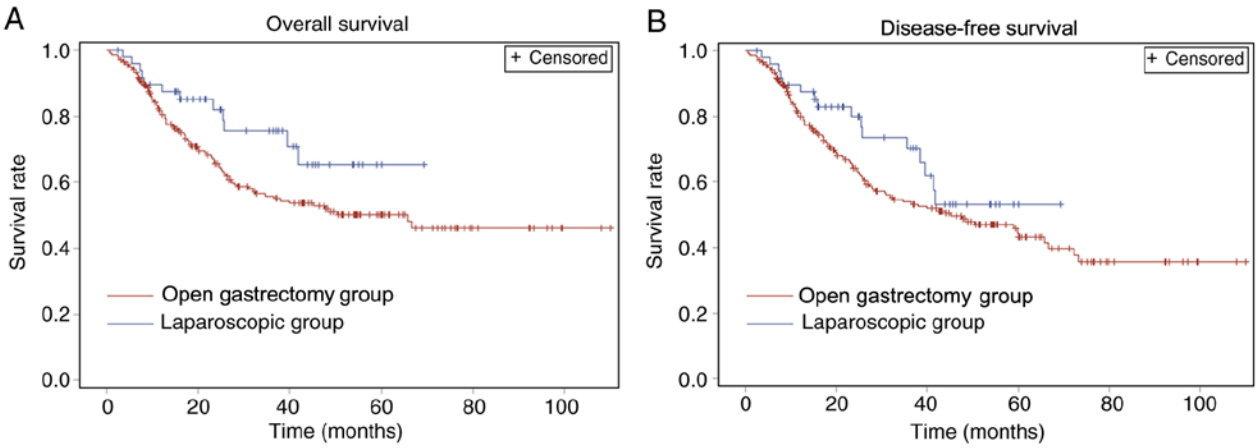

Figure 2. Comparison of the overall survival and disease-free survival rates between the open gastrectomy group and the laparoscopic group.

Discussion

According to the Clinical Practice Guidelines in Oncology Gastric Cancer (version 2.2018), patients with potentially resectable cT2 or higher, any N, and cM0 tumors are recommended to receive perioperative chemotherapy (category 1) or perioperative chemoradiaton (category 2B) (14). Previous randomized control trials and retrospective studies have demonstrated the safety and efficacy of LG for LAGC (15-18). However, the evidence of safety and long-term results of laparoscopic surgery for the treatment of LAGC after neoadjuvant therapy were scarce.

A higher number of patients underwent conventional OG following neoadjuvant therapy in the China National Cancer Center compared with those that underwent LG, which may be due to the following reasons. First, OG was selected for patients who were diagnosed with bulky lymph nodes or lymph nodes fused together by CT or MRI following neoadjuvant therapy. Second, a number of surgeons in the China National Cancer Center only perform OG. Third, several patients with severe coronary artery disease or pulmonary disease were assigned to the OG group for surgical safety.

The present study revealed that patients with LAGC that underwent LG after neoadjuvant therapy had significantly

Table III. Comparison of survival status between laparoscopic and gastrectomy group.

Variable	Laparoscopy group (n=49)	Open gastrectomy group (n=221)	P-value
DFS, months[a]	25.7 (12.3-41.3)	15.6 (11.5-20.0)	0.27
1-year rate	0.896	0.811	
2-year rate	0.798	0.644	
3-year rate	0.704	0.541	
5-year rate	0.533	0.437	
OS, months[a]	39.5 (12.3-)[b]	16.1 (12.1-22.1)	0.12
1-year rate	0.896	0.816	
2-year rate	0.821	0.659	
3-year rate	0.756	0.559	
5-year rate	0.658	0.497	

[a]75% survival time; since survival rate at the longest time point exceeds 50% for the laparoscopic group, median survival time could not be computed. [b]The upper confidence limit for the 75% OS time among the laparoscopic group could not be calculated due to the right-censoring of the data. OS and DFS times are presented as the mean (95% confidence interval). DFS, disease-free survival; OS, overall survival.

shorter postoperative stay compared to OG (11.1 vs. 13.0; P=0.020). A randomized controlled trial has confirmed that the benefits of the laparoscopic approach measured by early postoperative recovery can safely be offered to select patients with LAGC (19). The results from a prospective study also showed that laparoscopic distal gastrectomy after neoadjuvant therapy has comparable results with open distal gastrectomy in safety and efficacy in the short term (20).

The number of metastatic lymph nodes harvested in the LG group was less than that in the OG group (2.4 vs. 6.0; P<0.0001). Laparoscopic procedures have certain limitations, such as difficult management of tumors with bulky metastasis-positive nodes or large primary tumors, and unusual tissue fibrosis or edema may present following neoadjuvant therapy, which further increases surgical difficulty (21). Therefore, the majority of doctors select conventional OG.

Resected lymph nodes, incidence of complications, surgery time, blood loss and postoperative mortality were not significantly different between the two groups. The results were consistent with previous reports, which confirm the benefit of the laparoscopic approach, measured by early postoperative recovery, and that it can be safely offered to select patients with LAGC after neoadjuvant therapy (14,15).

The OS and DFS of the laparoscopic group were indicated to be longer than the open gastrectomy group; however, there were no statistically significant differences between the two groups. The 75% DFS time was 15.6 (11.5-20.0) months for the open surgery group and 25.7 (12.3-41.3) months for the laparoscopic surgery group (P=0.12). The upper confidence limit for the 75% OS time among the laparoscopic group could not be calculated due to the right-censoring of the data. The right-censoring may cause an underestimate of the mean survival time and its standard error. The major reason may be the small sample size; in addition, the follow-up time was short. The cycle of neoadjuvant therapy was statistically different between the two groups; however, it did not affect the long-term survival result of the study (data not shown).

Strengths and limitations should be considered when interpreting the study results. To the best of our knowledge, this cohort is the largest to date to compare the short-term and long-term survival outcomes between OG and LG for LAGC after neoadjuvant therapy. There were several limitations in this study. First, it is a retrospective study with a limited sample size in a single center. Second, patients were divided into different surgical approach groups, based on their personal choice, because either surgical type can be used according to doctors' clinical judgments. Furthermore, the follow-up time was short, and follow-up of these patients is ongoing.

The results of this study demonstrated that LG for LAGC following neoadjuvant therapy may provide non-inferior short-term and long-term survival outcomes compared with open surgery, suggesting a laparoscopic approach may be justified for patients with LAGC after neoadjuvant therapy. Multicenter randomized controlled trials are required to investigate the positive effects of LG for LAGC following neoadjuvant therapy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YC, DZ, AZ and JJ conceived and designed the study. NW and HH collected the data. YC and YZ analyzed the data. NW wrote the manuscript. YC and DZ reviewed and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All study procedures were approved by the Institutional Review Board at the China National Cancer Center and the patients provided written informed consent at the time of sample collection.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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