The Safety and Efficacy of Laparoscopic Gastrectomy for Patients with Locally Advanced Gastric Cancer Following Neoadjuvant Chemotherapy

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Abstract

Background: Limited researches focused on the application of laparoscopic gastrectomy (LG) in locally advanced gastric cancer (LAGC) patients following neoadjuvant chemotherapy (NACT). In this study, we aimed at illustrating the surgical and survival outcome of LG in LAGC patients following NACT.

Methods: We performed a retrospective study of patients with LAGC who received either LG following NACT or upfront LG at Fujian Provincial Hospital between March 2013 and October 2018. Perioperative parameters, short-term and long-term outcomes were compared. The Kaplan-Meier estimator was used to describe the survival curves, and the differences were examined by the log-rank test.

Results: In total, 76 consecutive patients were enrolled into the NACT-LG (41 patients) and LG (35 patients) group, respectively. There was no significant difference between the two groups for baseline characteristics, including age, sex, BMI, Eastern Clinical Oncology Group performance status, tumor size, location, Borrmann type, Lauren type, differentiation, cT stage, and surgical type (all $P>0.05$). The surgical trauma in terms of incision length and blood loss, and postoperative recovery in terms of first aerofluxus time, first time on liquid diets, drainage duration, and hospital stays were similar between the two groups (all $P>0.05$). The operation time was significantly longer for NACT-LG than for LG (286.5 vs. 248.9 min, $P=0.008$). There was no significant difference in surgical morbidity (19.5% vs. 22.9%, $P=0.721$) between the two groups. No patient died of postoperative complications in the NACT-LG group, and one patient (1/35, 2.9%) died of postoperative complications in the LG group ($P=0.461$). After NACT, the R0 resection rate was significantly higher (95.1% vs. 77.1%, $P=0.049$), and metastatic lymph nodes were less for NACT-LG than for LG (1 vs. 8, $P=0.001$). Compared with the LG group, the NACT-LG group had a significantly better DFS (59.4% vs. 14.4%, $P=0.034$) and better OS (69.0% vs. 37.4%, $P=0.009$) at 3 years.

Conclusions: NACT does not decrease safety of LG for patients with LAGC and offer higher R0 resection rate and better disease-free and overall survival. For patients with LAGC, LG following NACT should be the priority treatment.

Background

Gastric cancer is a life-threatening disease, and surgical resection remains the only curative treatment [1, 2]. However, the long-term outcome is still far from satisfactory for patients who receive surgery alone, especially in patients with locally advanced gastric cancer (LAGC). Approximately 70% patients with LAGC died within 5 years after surgery [3, 4]. Therefore, perioperative therapy is imperatively required to improve the survival.

Neoadjuvant chemotherapy (NACT) is generally accepted to benefit prognosis by downstaging tumor, increasing complete resection rate and eradicating micro-metastases [5, 6]. The MAGIC study has illustrated a survival benefit of perioperative chemotherapy and consequently opened the era of neoadjuvant therapy in patients with LAGC [7]. Although NACT has demonstrated several strengths as mentioned above, surgeons concerned about its negative effects on the surgical safety. Destruction of

anatomical dissection plane induced by tissue edema and fibrotic changes may complicate laparoscopic surgeries. In addition, chemotherapy related adverse effects deteriorate the nutritional and immune status of patients, which may impair the prognosis of patients [8–10].

With the development of laparoscopic technique and accumulation of evidence from clinical trials in recent years, laparoscopic surgery has been recommended to patients with LAGC [11]. Nevertheless, limited studies focused on the application of laparoscopic gastrectomy (LG) in patients receiving NACT. There is an urgent need for researches comparing patients receiving laparoscopic surgery after NACT or upfront laparoscopic surgery. However, conducting prospective trials targeting on the issue is impractical for the reason that NACT has been widely accepted in patients with locally advanced gastric cancer (LAGC) due to its positive effects on patients' survival [12–14].

Therefore, this retrospective study was conducted to evaluate the safety and efficacy of LG for patients with LAGC following NACT, focusing on whether NACT decreased the safety of LG for patients with LAGC.

Methods

Patients

We reviewed our prospectively maintained gastric cancer database at Fujian Provincial Hospital. Clinical data of LAGC patients underwent either LG following NACT or upfront LG between March 2013 and October 2018 were analyzed. The inclusion criteria were listed as follows: (1) stomach adenocarcinoma, histologically confirmed by endoscopic biopsy; (2) clinical stage $\geq$ (cT3/4a, N+, M0) according to the 8th edition of the AJCC/UICC staging system [15], diagnosed using computed tomography (CT), endoscopic ultrasonography (EUS), or laparoscopic exploration. The exclusion criteria were listed as follows: (1) cancer of the esophagogastric junction; (2) residual gastric cancer; (3) malignant tumor history; and (4) emergency surgery due to complications (obstruction, bleeding, or perforation). All patients signed written informed consent, and this study was approved by the ethics committee of the Fujian Provincial Hospital.

Treatment

Patients in the NACT-LG group received three to six cycles of NACT (XELOX regimen) at three-weekly intervals. Surgery was performed four to five weeks after the last cycle. Patients in the LG group received upfront surgery after preoperative evaluation. Laparoscopic total or distal gastrectomy with D2 lymphadenectomy was performed for patients according to the location of tumor. Reconstruction of the gastrointestinal tract was all completed using Roux-en-Y anastomosis. All the operations were performed by one experienced surgeon team. Within five weeks after surgery, patients were treated with three to six cycles of postoperative chemotherapy (XELOX regimen) at three-weekly intervals.

Clinical and pathologic assessment

Clinicopathological variables, such as age, sex, body mass index (BMI), Eastern Clinical Oncology Group performance status (ECOG PS) [16], tumor size, tumor location, Borrmann type, Lauren type, cT stage, as

well as perioperative data, such as surgical type, incision length, operation time, blood loss, first aerofluxus time, drainage duration, postoperative hospital stay, and surgical radicalness were analyzed. Clavien-Dindo classification system was applied to evaluate postoperative complication [17, 18]. Postoperative mortality were defined as death of any cause within 30 days after surgery. Pathological findings including number of harvested and metastatic lymph nodes, pathological stage, and tumor regression grade (TRG) were also compared between groups. The TRG was evaluated according to the NCCN guideline [12].

Follow-up

All the patients received postoperative follow-up every 3 months within 2 years after surgery and every 6 months for the next 3 years. Recurrence was defined as local recurrence identified by contrast CT scan or endoscopy biopsy, or distant recurrence identified by CT scan, ECT bone scan or PET/CT. Immediate follow-up occurred in patients with worsening or new symptoms. The disease-free survival (DFS) was calculated from surgery to recurrence, death, or last follow-up; the overall survival (OS) was calculated from beginning of treatment to death or last follow-up.

Statistical analysis

Continuous variables with normal distribution were expressed as the mean $\pm$ standard deviation (SD) while non-normal variables were expressed as the median (range). T-test or Mann-Whitney rank-sum test were used to evaluate differences between the two groups according to the distribution of data. The Kaplan-Meier method was performed using a log-rank test to estimate differences in DFS and OS. SPSS version 20 was used for the statistical analysis, and P values less than 0.05 (two-sided) were considered statistically significant.

Results

Patients

There were 76 patients in this study, 41 (53.9%) patients in the NACT-LG group and 35 (46.1%) patients in the LG group, respectively. The characteristics of patients were detailed in Table 1. The two groups were balanced in baseline characteristics in term of age, sex, BMI and ECOG PS (all $P > 0.05$). There were also no differences between groups in tumor size, tumor location, Borrmann type, Lauren type, differentiation and cT stage (all $P > 0.05$).

Table 1
Patient baseline characteristics in the NACT-LG and LG groups

	NACT-LG (n = 41)	LG (n = 35)	P
Age (y)			0.112
< 60	19 (46.3)	10 (28.6)	
≥ 60	22 (53.7)	25 (71.4)	
Sex			0.231
Male	32 (78.0)	23 (65.7)	
Female	9 (22.0)	12 (34.3)	
BMI (kg/m ²)	23.2 ± 1.9	22.6 ± 2.8	0.238
ECOG PS			0.760
0	26 (63.4)	21 (60.0)	
1	15 (36.6)	14 (40.0)	
Tumor size (cm)			0.577
< 5	26 (63.4)	20 (57.1)	
≥ 5	15 (36.6)	15 (42.9)	
Tumor location			0.187
Upper third	15 (36.6)	6 (17.1)	
Middle third	14 (34.1)	14 (40.0)	
Lower third	12 (29.3)	14 (40.0)	
Total	0 (0)	1 (2.9)	
Borrmann type			0.117
I	1 (2.4)	2 (5.7)	
II	7 (17.2)	1 (2.9)	
III	32 (78.0)	29 (82.9)	
IV	1 (2.4)	3 (8.6)	
Lauren type			0.913
NACT, neoadjuvant chemotherapy; LG, laparoscopic gastrectomy; BMI, body mass index; ECOG PS, Eastern Clinical Oncology Group performance status; Fisher's exact test was used as an alternative to Chi-square test when the number in one of the cells is smaller than 5.			

	NACT-LG (n = 41)	LG (n = 35)	P
Diffused	9 (22.0)	9 (25.7)	
Intestinal	18 (43.9)	14 (40.0)	
Mixed	14 (34.1)	12 (34.3)	
cT stage			0.367
T3	18 (43.9)	19 (54.3)	
T4	23 (56.1)	16 (45.7)	
NACT, neoadjuvant chemotherapy; LG, laparoscopic gastrectomy; BMI, body mass index; ECOG PS, Eastern Clinical Oncology Group performance status; Fisher's exact test was used as an alternative to Chi-square test when the number in one of the cells is smaller than 5.			

Surgical procedures

All patients received an LG with D2 lymphadenectomy. The surgical data were compared in Table 2. No significant difference was found in the surgical trauma in terms of incision length and blood loss, and postoperative recovery in terms of first aerofluxus time, and first time on liquid diets between the two groups (all $P > 0.05$). Patients in LG group tended to have shorter drainage duration (8 vs. 7d, $P = 0.061$) and shorter postoperative hospital stay (10 vs. 9d, $P = 0.059$), however no significant difference was observed. Despite having a longer operation time (286.5 vs. 248.9 min, $P = 0.008$), the NACT-LG exhibited a significantly greater R0 resection rate (95.1% vs. 77.1%, $P < 0.05$). R1 resection was performed in two (4.9%) patients in the NACT-LG group with positive proximal margins and eight (22.9%) patients in the LG group, including four (11.4%) patients with positive proximal margins and four (11.4%) patients with positive distal margins.

Table 2
Comparison of surgical procedures between the NACT-LG and LG groups

	NACT-LG (n = 41)	LG (n = 35)	P
Surgical type			0.327
LTG	30 (73.2)	21 (60.0)	
LDG	11 (26.8)	14 (40.0)	
Incision length (cm)	6.0 (3.0–8.0)	5.0 (4.0–7.0)	0.109
Operation time (min)	286.5 (205.0-470.0)	248.9 (140.0-360.0)	0.008
Estimated blood loss (mL)	100.0 (20.0-450.0)	100.0 (30.0-2500.0)	0.395
The first aerofluxus time (days)	3.0 (1.0–6.0)	3.0 (1.0–6.0)	0.303
Time to pull drainage (days)	8.0 (5.0–13.0)	7.0 (5.0–14.0)	0.061
First time on liquid diets (days)	3.0 (2.0–12.0)	3.0 (1.0–12.0)	0.118
Hospital stay after surgery (days)	10.0 (6.0–20.0)	9.0 (6.0–21.0)	0.059
Surgical radicalness			0.049
R0	39 (95.1)	27 (77.1)	
R1	2 (4.9)	8 (22.9)	
NACT, neoadjuvant chemotherapy; LG, laparoscopic gastrectomy; LTG, laparoscopic total gastrectomy; LDG, laparoscopic distal gastrectomy; Fisher's exact test was used as an alternative to Chi-square test when the number in one of the cells is smaller than 5.			

Surgery morbidity and mortality

The postoperative complications were detailed in Table 3. Postoperative complications occurred similarly in two groups, 8 patients (19.5%) in the NACT-LG group and 8 patients (22.9%) in the LG group ($P = 0.721$). The most common postoperative complications were intra-abdominal infection (7/76, 9.2%), followed by abdominal bleeding (6/76, 7.9%) and pulmonary infection (5/76, 6.6%), respectively. Three (8.6%) patients suffered major complications (grade III–IV) requiring invasive interventions in the LG group; one (2.9%) patient with anastomotic leakage recovered after active abdominal drainage; one (2.9%) patient with heart failure recovered after ICU care, and one (2.9%) patient died of respiratory failure. No patient died of postoperative complications in the NACT-LG group ($P = 0.461$).

Table 3
Postoperative complications in the NACT-LG and LG groups

	NACT-LG (n = 41)	LG (n = 35)	P
Grade I	0 (0)	0 (0)	NA
Grade II	8 (19.5)	5 (14.3)	0.546
Transfusion	4 (9.8)	2 (5.7)	0.822
Pulmonary infection	2 (4.9)	3 (8.6)	0.855
Intra-abdominal infection	4 (9.8)	3 (8.6)	> 0.05
Intra-abdominal hemorrhage	1 (2.4)	0 (0)	> 0.05
Grade III	0 (0)	1 (2.9)	0.461
Anastomotic leakage	0 (0)	1 (2.9)	
Grade II	0 (0)	1 (2.9)	0.461
Heart failure	0 (0)	1 (2.9)	
Grade II	0 (0)	1 (2.9)	0.461
Respiratory failure	0 (0)	1 (2.9)	
Surgical morbidity	8 (19.5)	8 (22.9)	0.721
Surgical mortality	0 (0)	1 (2.9)	0.461
NACT, neoadjuvant chemotherapy; LG, laparoscopic gastrectomy; NA, not applicable; Fisher's exact test was used as an alternative to Chi-square test when the number in one of the cells is smaller than 5.			

Pathological outcomes

A comparison of pathologies between the two groups was summarized in Table 4. The number of resected lymph nodes did not differ significantly between the two groups, whereas significantly less metastatic lymph nodes were found in the NACT-LG group than in the LG group (1 vs. 8, $P = 0.001$). Among all patients, there was a greater proportion of less advanced pT stage (T0-2; 29.3% vs. 0%, $P < 0.01$), less advanced pN stage (N0; 36.6% vs. 0%, $P < 0.01$), and less advanced pTNM stage (pTNM 0-II; 51.2% vs. 0%, $P < 0.01$) in the NACT-LG group than in the LG group. In the NACT-LG group, the pathological response was 65.9%, and the samples of each TRG were listed in Fig. 1. Over half of the patients (51.2%) obtained tumor downstaging in the NACT-LG group. Four patients (9.8%) were considered pathological complete responders after preoperative chemotherapy.

Table 4
Comparison of pathologies between the NACT-LG and LG groups

	NACT-LG (n = 41)	LG (n = 35)	P
Number of resected lymph nodes	37 (12–91)	32 (12–69)	0.081
Number of metastatic lymph nodes	1 (0–36)	8 (1–27)	0.001
pT stage			0.008
0–2	12 (29.3)	0 (0)	
3–4	29 (70.7)	35 (100.0)	
pN stage			< 0.01
0	15 (36.6)	0 (0)	
1–3	26 (63.4)	35 (100.0)	
pTNM stage			< 0.01
0–II	21 (51.2)	0 (0)	
III	20 (48.8)	35 (100.0)	
Tumor regression grades			NA
0	4 (9.8)	NA	
1	13 (31.7)	NA	
2	10 (24.4)	NA	
3	14 (34.1)	NA	
Pathological complete response	4 (9.8)	NA	
NACT, neoadjuvant chemotherapy; LG, laparoscopic gastrectomy; NA, not applicable; Fisher's exact test was used as an alternative to Chi-square test when the number in one of the cells is smaller than 5.			

Survival

The overall median follow-up was 23.0 months (6.6–71.5) in this study, 25.6 months (9.5–71.5) in the NACT-LG group, and 18.6 months (6.6–40.6) in the LG group, respectively. The survival curves were shown in Fig. 2. The 3-year disease-free survival rates in the NACT-LG group and LG group were 59.4% and 14.4% ($P = 0.034$), respectively. The 3-year overall survival rates in the NACT-LG group and LG group were 69.0% and 37.4% ($P = 0.009$), respectively.

Discussion

LAGC is characterized by low radical resection rate, high relapse rate and high mortality. Laparoscopic surgery combined with perioperative therapy has been widely accepted as the mainstream treatment. However, only few studies focused on the safety and efficacy of laparoscopic surgery in patients after NACT. As far as we known, there are only few studies comparing the surgical and survival outcome between upfront LG and LG after NACT. The present study revealed that NACT did not decrease safety of LG for patients with LAGC and might offer survival benefits compared with upfront LG.

We found that LG following NACT did not increase the severity of surgical trauma, or delay postoperative recovery. Although operation time was extended for NACT-LG than for LG, the postoperative complications were comparable, which was in consistent with a previous study reported by An *et al* [8]. It was reported that the negative effects of chemotherapy on operation might be overcome by laparoscope. Laparoscopic surgery offers amplifying visual, better exposure of anatomical hierarchy, and then contributes to delicate anatomy of blood vessels and lymphatic vessels [19]. On the other hand, adverse effects caused by chemotherapy can be attenuated by optimized perioperative care. For instance, malnutrition caused by gastrointestinal side effects can be treated by adequate perioperative nutrition.

Micro-metastases outside the surgical region and microscopic positive margin were the main causes of treatment failure in LAGC [20–22]. NACT may benefit these patients by eradicating metastases and potentially downstaging tumor, thereby increasing the R0 resection rate. Among 41 patients receiving NACT in this study, the pathological response was 65.9%, in concordance with previous studies [23, 24]. Over half of patients achieved tumor downstaging, which seemed attributable to the effects of NACT. Moreover, our study demonstrated the benefits of LG following NACT compared with immediate surgery, with an increase of 18 percent in the R0 resection rate (95.1% *vs.* 77.1%, $P = 0.049$) and a reduction in the number of metastatic lymph nodes (1 *vs.* 8, $P = 0.001$).

The MAGIC trial and the EORTC study disagreed about the survival benefits of perioperative chemotherapy in resectable gastric cancer patients [7, 25]. Since proportions of D2 dissection were different among two studies (MAGIC: 42.5%; EORTC: 95.7%), whether patients with D2 gastrectomy benefited from NACT remained unclear. The present study, with all patients received a D2 lymph node dissection, showed that 3-year DFS and OS were superior for NACT-LG than LG (DFS: 59.4% *vs.* 14.4%, OS: 69.4% *vs.* 37.4%). We speculated that sufficient preoperative chemotherapy courses and better compliance to chemotherapy may enhance the positive effects of NACT on survival. However, multi-center, large-sample clinical trials were required to verify this hypothesis in the future.

Despite positive findings mentioned above, there were several limitations in this study. First, as a retrospective study with non-randomized patient groups, selection bias were inevitable in this study. Second, the generalizability of findings drawn from a single-center study may be limited. Third, the follow-up period was too short to analyze the longer survival situation.

Conclusions

In summary, for patients with LAGC who underwent LG, this study provided supportive evidence favoring the application of NACT. NACT does not decrease safety of LG for patients with LAGC and offer higher R0 resection rate and better disease-free and overall survival. For patients with LAGC, LG following NACT should be the priority treatment.

Abbreviations

BMI, body mass index; DFS, disease-free survival; ECOG PS, Eastern Clinical Oncology Group performance status; LAGC, locally advanced gastric cancer; LDG, laparoscopic distal gastrectomy; LG, laparoscopic gastrectomy; LTG, laparoscopic total gastrectomy; NA, Not applicable; NACT, neoadjuvant chemotherapy; OS, overall survival; TRG, tumor regression grade.

Declarations

Acknowledgments

Not applicable

Authors' contributions

LHL, FL and WHL designed the study. LHL, FL, STL, YL, CSY, SXC acquired the clinical data. LHL and FL performed the statistical analysis. The draft manuscript was prepared by LHL and FL. WHL provided critical revision of drafts. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

This study was approved by the ethics committee of the Fujian Provincial Hospital. All patients signed written informed consent.

Consent for publication

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

The samples of each TRG of patients in the NACT- LG group. a TRG 0 after H-E staining ($\times 20$). b TRG 1 after H-E staining ($\times 10$). c TRG 2 after H-E staining ($\times 4$). d TRG 3 after H-E staining ($\times 20$). TRG, tumor regression grade; NACT, neoadjuvant chemotherapy; LG, laparoscopic gastrectomy.

Figure 2

Kaplan-Meier estimates of a disease-free survival and b overall survival.