The Comparison of the Short and Long-Term Outcomes Between Laparoscopic Total Gastrectomy and Open Total Gastrectomy for Locally Advanced Gastric Cancer After Neoadjuvant Chemotherapy

Hao Cui  
Nankai University School of Medicine  https://orcid.org/0000-0003-1185-5322

Ke-Cheng Zhang  
Chinese PLA General Hospital

Bo Cao  
Chinese PLA General Hospital

Huan Deng  
Chinese PLA General Hospital

Run-kai Chen  
Chinese PLA General Hospital

Tian-yu Xie  
Nankai University School of Medicine

Wen-quan Liang  
Chinese PLA General Hospital

Yi Liu  
Chinese PLA General Hospital

Ning Wang  
Chinese PLA General Hospital

Lin Chen  
Chinese PLA General Hospital

Bo Wei (✉️ 18431143691@163.com)  
Chinese PLA General Hospital

Research Article

**Keywords:** Neoadjuvant chemotherapy, Gastric cancer, Laparoscope, Total gastrectomy, Morbidity, Survival
Abstract

Background

Neoadjuvant chemotherapy (NACT) combined with surgery is regarded as an effective treatment for advanced gastric cancer. Laparoscopic surgery represents mainstream of minimally invasive surgery. Currently, surgeons focus more on surgical safety and oncological outcomes of laparoscopic gastrectomy after NACT. Thus, we sought to evaluate short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) after NACT.

Method

This is a mono-institutional retrospective study conducted by Chinese PLA general hospital. After screening according to inclusion and exclusion criteria, we collected clinicopathological data of 140 patients who accepted gastrectomy after NACT from June 2012 to June 2019, including 62 patients in LTG group and 78 patients in OTG group. SPSS 26.0 and GraphPad Prism 8.0 were used to perform statistical analysis.

Result

Clinicopathological characteristics between LTG and OTG group showed no significant difference. In 140 patients, 10 patients acquired pCR while 58 patients presented ORR. Mentioning to perioperative outcomes, we found that LTG group had longer operation time (P=0.013), less blood loss (P=0.003), shorter first flatus days (P<0.001) and postoperative days (P<0.001). Even though LTG spent more surgical cost than OTG (P<0.001), total hospitalized cost of LTG was less than OTG (P<0.001). 21 (26.9%) patients in OTG group and 14 (22.6%) patients in LTG group had 30-day postoperative complication, with no significant difference (P=0.295). Long-term follow up demonstrated that 3-year OS rate was 59.3% and 65.7% in LTG and OTG group (HR: 0.690, 95%CI: 0.413~1.152, P=0.151) while 3-year DFS rate was 51.1% and 53.4% in LTG and OTG group respectively (HR: 0.796, 95%CI: 0.488~1.300, P=0.357).

Conclusion

After NACT, LTG showed comparable 30-day postoperative morbidity as well as 3-year OS and DFS rate in comparison with OTG. We recommended experienced surgeons select LTG other than OTG for proper AGC patients after NACT.

Background

Gastric cancer (GC) is the fifth prevalent malignant tumor and its tumor-related death ranks fourth according to the updated database of GLOBOCAN in 2020[1]. In China, it is the second lethal factors which can post threat to patients’ life with malignant tumor [2]. Perioperative integrated therapy is taken into account for curing gastric cancer gradually. Neoadjuvant chemotherapy (NACT) is regarded as a crucial part of integrated therapy which is currently a research hotspot. Unlike postoperative chemotherapy, NACT
put chemotherapy prior to surgery which bring advantages as follows: (1) More possibility of reducing tumor stage and surgical risk; (2) Better tolerance to chemotherapy before surgery; (3) Guarantee higher complete rate of total chemotherapy; (4) Potential survival benefit compared with other interventional treatment. After MAGIC study\cite{3} firstly proved the surgical safety and better long-term survival benefit of perioperative chemotherapy, more prospective randomized clinical trials like FLOT4\cite{4}, RESOLVE, RESONANCE etc. spring up rapidly and acquire initial conclusion that show superiority of NACT on higher pCR rate and better long-term survival, which may result in more clinical utilization further.

Laparoscopy is the representative of minimal invasive surgery techniques in the 21st century. Since Kitano et al.\cite{5} reported first laparoscopic gastrectomy in 1994, laparoscopy has become a standard surgical approach especially for distal gastrectomy proved by several high-quality trials\cite{6,7}.

The application of laparoscopic total gastrectomy (LTG) carries out relatively late due to its complex surgical procedure and anastomotic technical difficulty. Although LTG has been proved safely compared with open total gastrectomy (OTG) for clinical stage I gastric cancer by CLASS-02 study\cite{8}, the option of LTG is still conservative when mentioned to advanced gastric cancer (AGC). At present, multitude of retrospective articles demonstrated comparable short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) conducted in experienced medical center\cite{9,10}, prospective studies haven’t acquired final conclusion.

Currently, surgical safety and oncological outcomes after NACT have gradually attracted surgeons to pay attention. Based on standardization of NACT for AGC in western countries which was advised by European Guideline, van der Wielen N et al. conducted STOMACH trial as the first multi-institutional RCT study which demonstrated the comparable complications and non-inferiority of 1-year OS and DFS between LTG and OTG after NACT in western countries\cite{11}. However, it’s not clear whether LTG had superior short and long-term outcomes compared with OTG or not for advancer gastric cancer patients who accepted NACT in China. Under the background of popularization of minimally invasive surgery and attaching importance of NACT in China, indispensable study should be conducted to direct application of LTG after NACT appropriately.

**Patients And Methods**

This is a single-institutional retrospective study conducted by General Surgery Department in Chinese PLA general hospital. Clinical and pathological data of patients with AGC who accepted NACT before laparoscopic or open total gastrectomy plus D2 lymphadenectomy from June 2012 to June 2019 were collected. Eligible criteria includes as follows:(1) Clinical tumor stage ranges from II~III (including Bulky N or large type 3~4) proved by EUS, abdominal CT and PET-CT ; (2)Histologically proved gastric cancer by preoperative gastroscopy; (3) Ages ranged from 18 to 75\(\leq\)ASA score ≤III\(\leq\)IV; (4)Integrated clinical and pathological data\(\leq\)NO conversion to OTG in LTG group. All patients accepted LTG or OTG followed by NACT (chemotherapeutic regimen: SOX, XELOX, SF, FOLFOX) according to the consultation of the Multi-disciplinary team.
Surgical procedure was conformed with Japanese Gastric Cancer Treatment Guidelines\textsuperscript{[12]}. D2 lymphadenectomy was performed including No. 1, 2, 3a, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 11d, and 12a. The dissection of No.10 lymph node was performed when tumor was located in the upper stomach invading the greater curvature Roux-en-Y reconstruction was achieved after tumor dissection. One month after surgery, residual adjuvant chemotherapy carried out under the guidance of surgeons with their experiences.

We collected clinicopathologic indicators including blood loss, operation time, first flatus time, postoperative days, surgical and hospitalized cost, retrieved lymph nodes, tumor length et al. retrospectively. 30-days morbidity and mortality were recorded form case report form and its severe degree was assessed in accordance with Clavien-Dindo classification\textsuperscript{[13]}. We defined Clavien-Dindo classification$\geq$IIIa as severe complication.

Follow-up started 3 months after operation by outpatient or telephone until patients’ death. Frequency of adjuvant chemotherapy, survival status, recurrence or not were mentioned during inquiries. If patients dropped out, time of last accessible follow-up or last discharge was defined as cutoff value.

This protocol was approved by the Clinical Research Ethics Committee at Chinese PLA general hospital.

**Statistical analysis**

We used SPSS statistical package, version 26 (IBM software) and GraphPad Prism 8.0 software to perform statistical analysis. Continuous variables described as means±standard deviation for normal distributions while we used medians and interquartile ranges to represent skew distributions. Comparison tests were performed with Student’s t test and Mann–Whitney U tests as appropriate. With regarded to categorical variables, frequencies with percent were adopted to describe it and Chi square test was performed to demonstrate difference of categorical variables between two groups. Moreover, the difference of perioperative laboratorial index between two groups vividly presented by histogram and box diagram.

To show long-term oncological outcomes, overall survival (OS) rate and disease-free survival (DFS) rate were calculated using Kaplan-Meier method and log-rank test was used to determine significance. The HR and 95%CI were calculated using the Cox proportional hazard model to compare OTG group first as the reference. All tests were two-sided and statistical significance was set at $p\leq0.05$

**Results**

**Clinicopathologic characteristics**

We collected clinical data of 2102 patients who underwent total gastrectomy from June 2012 to June 2019 acquired from Big Data Center of general surgery in Chinese PLA general hospital. After screening described in Figure 1, 140 patients included into this case-control study with 62 patients in NACT-LTG
group and 78 patients in NACT-OTG group. Clinicopathologic characteristics of patients in the two groups are summarized in Table 1 and Table 2. Groups were comparable according to sex, age, BMI, CCI score, proportion of previous abdominal surgery, tumor diameter, clinical and pathologic TNM stage, tumor location, nerve or vascular invasion, and histological type so that we needn’t to reduce baseline bias by Propensity Score-Matched Analysis.

**Neoadjuvant chemotherapy**

All 140 patients accepted neoadjuvant chemotherapy before surgery. Among them, 112 patients acquired SOX regimen (44 in LTG group and 68 in OTG group), 19 patients acquired XELOX regimen (8 in LTG group and 9 in OTG group) and 7 patients accepted other regimen like DCF, SF, or S-1), no significant difference of disparate regimen was found in two groups(P=0.140). Cycle of NACT was determined mainly by patients’ chemotherapeutic reaction and tumor response with no significant difference between two groups(P=0.332). We recorded adverse event during chemotherapy by patients’ self-report and laboratorial index and classified severe degree via CTCAE Version 4.0. We found that patients in LTG and OTG group had comparable adverse events with no significant difference (P=0.519). Also the LTG group had a significant longer chemotherapy–surgical procedure interval compared with the OTG group (5.56±1.66 weeks vs 5.04±1.31 weeks; P=0.041). There was no significant difference in receiving adjuvant therapy between two groups(P=0.271).

Clinical response was another evitable factor defined in accordance with RECIST criteria[14]. In this study, 10 (7.1%) patients received completed response(CR) while 58(41.4%) patients had partial response(PR). However, other patients didn’t have obvious downstage after NACT and were defined as stable disease (SD, 62 patients) and progressive disease (PD, 9 patients).

**Surgical indicator and postoperative recovery**

59 (95.2%) patients in LTG group and 77(98.7%) patients in OTG group acquired R0 resection(P=0.457). Compared with OTG group, LTG group had longer operation time (255.69±39.77 min vs. 238.71±39.78min, P=0.013) and less blood loss [150±100-300ml vs. 200±200-300ml, P=0.003]. The number of retrieved lymph nodes were similar in both groups (33.52±13.19 in LTG group vs. 34.88±16.46 in OTG group, P=0.595).

Regarding postoperative recovery, we found that LTG group showed advantages of ERAS in comparison with OTG group on first flatus days(4.34±1.29 d vs. 5.41±1.41 d, P=0.001) and postoperative days 9.39±4.01 d vs. 11.88±3.32 d, P=0.001) as respected. Interestingly, even OTG group spent less surgical cost, when we mentioned to hospitalized total cost, LTG group seemed more economical with less expenditure (P=0.001).

Perioperative expenditure was another concern to evaluate cost-effectiveness of different surgical approach. In this study, even though LTG group spent more surgical cost than OTG ( P=0.001), LTG
seemed more economical compared with OTG in terms of total hospitalized cost ($P<0.001$). Explicit indicator mentioned above was presented in Table 4.

In subgroup analysis, we compared the difference between LTG and OTG group on the basis of different pathologic tumor stage. After balancing the baseline characteristics, the similar results were presented like above in ypTNM 0~II patients (Table 5). Whereas, for patients with ypTNM III-IV, no significant difference was observed on surgical time ($P=0.313$) and blood loss ($P=0.143$) in two groups (Table 6).

**Laboratorial index before surgery, POD1 and POD 7**

We selected partial laboratorial indexes like hemoglobin (Hb) and albumin (Alb) in perioperative period to figure out the changes of perioperative nutritional status between LTG and OTG. In spite of different timelines including before surgery, postoperative day 1 (POD 1), and postoperative day 7 (POD 7), there were no significant difference in Hb and Alb between LTG and OTG group.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were also calculated through laboratory test. In this study, except for higher NLR of OTG compared with LTG group in POD 1 ($P=0.020$), no significant difference was observed between two groups in other period. Visualized comparison was depicted in Figure 2.

**30-day postoperative morbidity**

In total 140 patients who underwent surgery after NACT, 21 (26.9%) patients in OTG group and 14 (22.6%) patients in LTG group had over Grade II postoperative complications quantified by Clavien-Dindo classification, with no significant difference ($P=0.295$). 2 (3.2%) patients who underwent LTG occurred severe complications (C-D grade $\geq$ IIIa), wherein one patient died because of septic shock in POD 3. The rate of severe complications after OTG (2/78, 2.6%) did not differ significantly from those in LTG group ($P=0.816$). Table 4 gave detailed items of complications.

Subgroup analysis showed that regardless of ypTNM 0~II or ypTNM III-IV patients, there were no significant difference on overall and severe complication rate between two groups ($P>0.05$) Table 5, Table 6. 

**Long-term oncological outcomes**

130 of total (92.9%) patients completed follow-up. The median follow-up period was 56 (range 1~96) months. 3-year OS and DFS rates were compared between LTG and OTG group after NACT. 3-year OS rate was 59.3% and 65.7% in LTG and OTG group respectively [HR: 0.690, 95%CI 0.413~1.152], which demonstrated no significant difference between two groups (log-Rank $\chi^2=2.059 P=0.151$). 3-year DFS rate was 51.1% and 53.4% in LTG and OTG group respectively [HR: 0.796 0.488~1.300], which presented no significant difference (log-Rank $\chi^2=0.848 P=0.357$). Kaplan-Meier curves mentioned above were drawn in Figure 3.
Additionally, we set up three subgroups according to different ypTNM stage to explore the oncological impact of two surgical approach deeply. For ypTNM 0~I patients, there were no significant difference in 3-year OS rate (P=0.883) and DFS rate (P=0.695) between LTG and OTG, so were the subgroup of ypTNM II patients and ypTNM III~IV patients (P>0.05). These results illustrated the similar long-term outcomes between LTG and OTG after NACT no matter what ypTNM stage was. Kaplan-Meier curves for different subgroups were drawn in Supplementary Figure 1.

Discussion

The application to NACT for AGC rapidly increased because of its potential oncological benefit\cite{15}. At present, Surgeons focus mainly on the impact of NACT on gastrectomy\cite{11,16}. In this study, we reported mono-institutional retrospective outcomes aiming to evaluate surgical safety and oncological efficacy between LTG and OTG after NACT in China, which could present Chinese perspective and provide reference to reasonable utilization of minimally invasive surgery for AGC patients who accepted NACT.

NACT before surgery had several advantages such as tumor regression, better tolerance, improving R0 resection etc. compared with surgery first for advanced gastric cancer. Previous studies which consisted of over 100 cases of NACT showed that pCR rate ranged from 5%~17.2%\cite{17}. In the present research, 10(7.1%) patients acquired pathologic complete response while 68(48.5%) patients gained objective response that was consistent with results above. Better chemotherapeutic response was the crucial premise of radical gastrectomy. 59(95.2%) patients in LTG group and 77(98.7%) patients in OTG group achieved R0 resection with no significant difference (P=0.457) in our study. These results indicated that LTG could ensure considerable R0 resection in comparison to OTG after NACT.

Perioperative laboratorial index could evaluate extent of surgical damage and nutritional status, even might predict prognosis\cite{18}. In our series, we found that Alb and Hb didn't perform significant difference between LTG and OTG at three timepoints including before surgery, POD 1, and POD7. The incidence of hypoproteinemia seemed lower in LTG group (3.2%) compared with OTG group (10.3%) but the difference was not remarkable (P=0.203) which indicated that LTG after NACT didn't significantly improve postoperative nutritional status with advantages of minimally invasive surgery. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were regarded as potential markers to predict further prognosis\cite{19}. Our results found no significant difference in PLR between LTG and OTG group before surgery, POD 1, and POD 7, so were NLR between two groups before surgery and POD 7, which implied that LTG and OTG after NACT had analogical long-term outcomes up to a point. However, higher NLR was presented in OTG at POD 1 compared with LTG. We attributed this interesting phenomenon to stronger stress response at early period after OTG\cite{20} which might elevate inflammation and suppress inherit immunity, leading to higher NLR. Hence, most studies selected NLR and PLR before surgery as better factors rather than other timepoints\cite{21}.

Adhesion of tissue, lack of anatomical layer, peri gastric edema and fibrosis etc. might occur after NACT which led to surgical difficulty increasing. Laparoscope has several advantages like delicate
manipulation, regional amplification, faster recovery and damage control that might weaken the surgical risk of NACT. Li et al. found that laparoscopic distal gastrectomy had significant lower postoperative morbidity compared with open distal gastrectomy (20% vs. 46%, \( P=0.007 \)) for patients with AGC who received NACT\cite{16}. In this study, our perioperative clinical indicators showed that even operation time increased (\( P=0.013 \)), LTG offered benefits of less blood loss (\( P=0.003 \)), shorter first flatus day and postoperative day (\( P \leq 0.001 \)) compared with OTG, which illuminated specific superiority of minimally invasive surgery. LTG also could achieved adequate lymph nodes dissection with comparable retrieved lymph nodes between LTG and OTG (33.52±13.19 vs. 34.88±16.46, \( P=0.595 \)). Meanwhile, we found an interesting phenomenon that LTG cost more on operation and cost less on total hospitalization compared with OTG, which was similar to Tegels JJ\cite{22} and Hoya Y’s\cite{23} study. Gosselin-Tardif A\cite{24} also presented Canadian perspective that the application to laparoscopic gastrectomy was cost-effective compared with open gastrectomy. We reckoned that even expensive disposable surgical instruments mostly rely on import might elevate surgical cost in LTG, faster postoperative recovery could offset deviations by reducing other costs, which predicted LTG as a probable cost-effective alternative surgical approach after NACT.

In terms of perioperative complication, KLASS-03 trial conducted by South Korea demonstrated that LTG performed by experienced surgeons had acceptable postoperative morbidity with 20.6% for clinical stage I gastric cancer\cite{25}. STOMACH trial showed no significant difference in postoperative complications between OTG and LTG, with a total of 42.9% in OTG and 34.0% in LTG after NACT in western countries (\( p=0.408 \)). Back to our study, we found that LTG group didn’t significantly increase or decrease 30-day postoperative complications compared with OTG group after NACT (overall morbidity of LTG vs. OTG: 22.6% vs. 26.9%, \( P=0.295 \), severe morbidity of LTG vs. OTG: 3.2% vs. 2.6%, \( P=0.816 \)), which was similar to studies above. These results still existed in different ypTNM stage patients. Thus, we considered that the application of LTG after NACT could be safe and feasible whatever tumor stage was and we recommended to initiate relative prospective studies to give high-grade evidence in East Asia.

Long-term outcomes were inevitable to evaluate oncological benefit caused by different surgical approach. Gambhir S’s\cite{9} and Komatsu S’s\cite{26} studies both pointed out comparable long-term survival between LTG and OTG, nevertheless it remained uncertain between LTG and OTG group after NACT. Our results of follow-up focused on 3-year OS and DFS rate showed no significant difference between two groups (LTG compared to OTG: 3-yr OS: 59.3% vs. 65.7%, \( P=0.151 \); 3-yr DFS: 51.1% vs. 53.4%, \( P=0.357 \)). Subgroup analysis according to different ypTNM stage also showed no significant difference on 3-year OS and DFS rate. These findings suggested that patients with LTG after NACT had similar oncological benefits compared with whom in OTG group irrespective of staging and LTG after NACT could be regarded as an alternative surgical approach with its acceptable short and long-term outcomes.

Our study has several limitations. Principally, this is not a prospective study so that lacks of authentic evidence-based support and exist select bias. Under the trend of climbing application to NACT as a promising treatment for AGC in East Asia\cite{27}, large-scale retrospective or even multi-institutional RCT studies are required to better understand of association between LTG and OTG after NACT. Moreover,
small sample size increases probability of type II mistake and reduces power of test. To decrease the impact of this phenomenon, we alternatively combine adjacent ypTNM stage group into one group to ensure enough sample size in subgroup analysis. Thirdly, although SOX regimen covers main NACT treatment in our study, other regimens like XELOX, DCF, S-1 etc. are also used for a small portion of appropriate patients which may slightly influence short or long-term outcomes. Otherwise, even baseline characteristics included in this study are comparable between LTG and OTG group, some potential imbalance caused by unknown indicators may affect validity of results.

**Conclusion**

To sum up, this study suggested that there were no significant disparities between LTG and OTG on postoperative complication rates, 3-year OS rates, and 3-year DFS rates after NACT for advanced gastric cancer patients. LTG performed by experienced surgeons after NACT had several advantages including less blood loss, faster postoperative recovery and less hospitalized cost which could be regarded as an alternative surgical approach with its safety, feasibility and comparable oncological benefits at any ypTNM stage.

**Abbreviations**

NACT: Neoadjuvant chemotherapy; AGC: Advanced gastric cancer; LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; PLA: People liberation army; BMI: Body mass index; CCI: Comprehensive complication index; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; pCR: Pathological complete response; DFS: Disease-free survival; OS: Overall survival; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; Hb: Hemoglobin; Alb: Albumin; POD: Postoperative day.

**Declarations**

*Data sharing Statement*

The datasets generated and/or analyzed during the current study are not publicly available due to hospital policy but are available from the corresponding author on reasonable request.

*Acknowledgments*

Not applicable.

*Consent for publication*

Not applicable.

*Funding*
This study was supported by National Basic Research Program in China (2019YFB1311505), National Natural Science Foundation of China (81773135,82073192); Outstanding Youth Specialized Foundation of Chinese PLA General Hospital(2017-JQPY-003) and Health cultivating Foundation for Capital Citizens(Z171100000417023). All above-mentioned foundations provided financial support on data collection and statistical analysis.

**Author Contributions**

HC and BW designed the study. LC, BW, and NW provided fund support and performed gastrectomy. HC, KCZ, and BC collected the data. HD, TYX, and RKC analyzed and interpreted the data. HC, WQL, and YL prepared the manuscript. All the authors read and approved the final manuscript.

**Conflict of Interest**

All authors have completed the ICMJE uniform disclosure form. They declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Ethics Statement**

The study involving human participants was reviewed and approved by the Research Ethics Committee of Chinese PLA general hospital. The patients and participants provided their written informed consent to participate in this study.

**Open Access Statement**

This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license).

**References**

[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 Feb 4.

[2] Sun D, Cao M, Li H, et al. Cancer burden and trends in China: A review and comparison with Japan and South Korea. Chin J Cancer Res 2020; 32: 129-139.

[3] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11-20.
[4] Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019; 393:1948-1957.

[5] Kitano S, Iso Y, Moriyama M, et al. Laparoscopy-assisted Billroth I gastrectomy. Surg Laparosc Endosc 1994;4: 146-148.

[6] Yu J, Huang C, Sun Y, et al. Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. JAMA 2019; 321:1983-1992.

[7] Katai H, Mizusawa J, Katayama H, et al. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. Lancet Gastroenterol Hepatol 2020; 5:142-151.

[8] Liu F, Huang C, Xu Z, et al. Morbidity and Mortality of Laparoscopic vs Open Total Gastrectomy for Clinical Stage I Gastric Cancer: The CLASSO2 Multicenter Randomized Clinical Trial. JAMA Oncol 2020; 6:1590-1597.

[9] Gambhir S, Inaba CS, Whealon M, et al. Short- and long-term survival after laparoscopic versus open total gastrectomy for gastric adenocarcinoma: a National database study. Surg Endosc, 2021; 35:1872-1878.

[10] Oh Y, Kim MS, Lee YT, et al. Laparoscopic total gastrectomy as a valid procedure to treat gastric cancer option both in early and advanced stage: A systematic review and meta-analysis. Eur J Surg Oncol 2020; 46:33-43.

[11] van der Wielen N, Straatman J, Daams F, et al. Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. Gastric Cancer. 2021; 24 :258-271.

[12] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer. 2021;24 :1-21.

[13] Katayama H, Kurokawa Y, Nakamura K, et al. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. Surg Today 2016; 46:668-85

[14] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-47

[15] Das M. Neoadjuvant chemotherapy: survival benefit in gastric cancer. Lancet Oncol 2017; 18:e307.
[16] Li Z, Shan F, Ying X, et al. Assessment of Laparoscopic Distal Gastrectomy After Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer: A Randomized Clinical Trial. JAMA Surg 2019; 154:1093-1101.

[17] Petrelli F, Ghidini M, Barni S, et al. Neoadjuvant chemoradiotherapy or chemotherapy for gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis. Gastric Cancer 2019; 22:245-254.

[18] Wang Y, Wang H, Jiang J, et al. Early decrease in postoperative serum albumin predicts severe complications in patients with colorectal cancer after curative laparoscopic surgery. World J Surg Oncol 2018; 16:192.

[19] Miyamoto R, Inagawa S, Sano N, et al. The neutrophil-to-lymphocyte ratio (NLR) predicts short-term and long-term outcomes in gastric cancer patients. Eur J Surg Oncol 2018; 44:607-612.

[20] Novitsky YW, Litwin DE, Callery MP. The net immunologic advantage of laparoscopic surgery. Surg Endosc 2004; 18:1411-9.

[21] Hirahara T, Arigami T, Yanagita S, et al. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. BMC Cancer 2019; 19:672.

[22] Tegels JJ, Silvius CE, Spauwen FE, et al. Introduction of laparoscopic gastrectomy for gastric cancer in a Western tertiary referral centre: A prospective cost analysis during the learning curve. World J Gastrointest Oncol 2017; 9:228-234.

[23] Hoya Y, Taki T, Tanaka Y, et al. Disadvantage of operation cost in laparoscopy-assisted distal gastrectomy under the national health insurance system in Japan. Dig Surg 2010; 27:343-6.

[24] Gosselin-Tardif A, Abou-Khalil M, Mata J, et al. Laparoscopic versus open subtotal gastrectomy for gastric adenocarcinoma: cost-effectiveness analysis. BJS Open 2020; 4:830-839.

[25] Hyung WJ, Yang HK, Han SU, et al. A feasibility study of laparoscopic total gastrectomy for clinical stage I gastric cancer: a prospective multi-center phase II clinical trial, KLASs 03. Gastric Cancer 2019; 22:214-222.

[26] Komatsu S, Kosuga T, Kubota T, et al. Comparison of short- and long-term outcomes following laparoscopy and open total gastrectomy for gastric cancer: a propensity score-matched analysis. Am J Transl Res 2020; 12:2225-2233.

[27] Terashima M, Yoshikawa T, Boku N, et al. Current status of perioperative chemotherapy for locally advanced gastric cancer and JCOG perspectives. Jpn J Clin Oncol 2020; 50:528-534.

Tables
Table 1: Baseline characteristics of 140 gastric cancer patients after NACT

| Clinical characteristics | NC-LTG group n=62 | NC-OTG group n=78 | P Value |
|--------------------------|--------------------|--------------------|---------|
| Gender                   |                    |                    | 0.911   |
| Male                     | 48                 | 61                 |         |
| Female                   | 14                 | 17                 |         |
| Age (year, mean±SD)      | 57.71±10.33        | 56.24±12.20        | 0.452   |
| BMI (kg/m², mean±SD)     | 22.84±2.67         | 23.67±3.35         | 0.118   |
| CCI score [n (%)]        |                    |                    | 0.782   |
| 0-2                      | 44                 | 57                 |         |
| ≥2                       | 18                 | 21                 |         |
| History of abdominal surgery |              |                    | 0.536   |
| No                       | 54                 | 65                 |         |
| Yes                      | 8                  | 13                 |         |
| Clinical tumor stage     |                    |                    | 0.533   |
| cT                       |                    |                    |         |
| T2                       | 0                  | 9                  |         |
| T3                       | 33                 | 32                 |         |
| T4a                      | 29                 | 37                 |         |
| cN                       |                    |                    | 0.975   |
| N0                       | 11                 | 14                 |         |
| N+                       | 51                 | 64                 |         |
| cTNM                     |                    |                    | 0.367   |
| II                       | 7                  | 13                 |         |
| III                      | 55                 | 65                 |         |

Table 2: Pathological characteristics of 140 gastric cancer patients after NACT
| Pathological characteristics | NC-LTG group\(n=62\) | NC-OTG group\(n=78\) | P Value |
|-------------------------------|-----------------------|-----------------------|--------|
| **Tumor diameters, cm (Median, IQR)** | 3.75(2.5-6.5) | 4.0(2.0-6.0) | 0.286 |
| **Site of tumor** | | | 0.168 |
| Upper 1/3 | 31 | 27 | |
| Middle 1/3 | 21 | 32 | |
| Diffused | 10 | 19 | |
| **ypT** | | | 0.496 |
| T0 | 1 | 9 | |
| T1 | 5 | 5 | |
| T2 | 10 | 15 | |
| T3 | 35 | 30 | |
| T4 | 11 | 19 | |
| **ypN** | | | 0.108 |
| N0 | 19 | 38 | |
| N1 | 14 | 11 | |
| N2 | 13 | 11 | |
| N3 | 16 | 18 | |
| **ypTNM** | | | 0.071 |
| 0 | 1 | 9 | |
| I | 8 | 18 | |
| II | 21 | 16 | |
| III | 31 | 34 | |
| IV | 1 | 1 | |
| **Nerve invasion** | | | 0.373 |
| Yes | 21 | 21 | |
| No | 41 | 57 | |
| **Vascular invasion** | | | 0.788 |
|               | Yes |      | No |    |
|---------------|-----|------|----|----|
|               | 17  | 23   | 45 | 55 |
| **Differentiation** |     |      |    |    |
| Well/Moderate | 29  | 31   |    |    |
| Poor/Undifferentiated | 33  | 47   |    |    |

Table.3 Neoadjuvant chemotherapy characteristics and responsibility
| Variable                                      | NC-LTG group (n=62) | NC-OTG group (n=78) | P Value |
|----------------------------------------------|----------------------|----------------------|---------|
| **Cycle of NACT**                            |                      |                      |         |
| Cycle 1-2                                    | 14                   | 12                   | 0.332   |
| Cycle 3-4                                    | 45                   | 62                   |         |
| Cycle 4                                      | 3                    | 4                    |         |
| **NACT regimen**                             |                      |                      | 0.549   |
| SOX                                          | 44                   | 68                   |         |
| XELOX                                        | 8                    | 9                    |         |
| Other                                        | 6                    | 5                    |         |
| **Clinical response**                        |                      |                      | 0.437   |
| CR                                           | 1                    | 9                    |         |
| PR                                           | 28                   | 30                   |         |
| SD                                           | 28                   | 34                   |         |
| PD                                           | 4                    | 5                    |         |
| **Adverse effects after NACT**                |                      |                      | 0.519   |
| Grade 0                                      | 14                   | 19                   |         |
| Grade I                                      | 16                   | 21                   |         |
| Grade II                                     | 17                   | 24                   |         |
| Grade III                                    | 11                   | 12                   |         |
| Grade IV                                     | 4                    | 2                    |         |
| **Chemotherapy–surgical procedure interval (wk)** | 5.56±1.66            | 5.04±1.31            | 0.041   |
| **Adjuvant therapy**                         |                      |                      |         |
| Yes                                          | 53                   | 61                   | 0.271   |
| No                                           | 9                    | 17                   |         |

Table 4 Perioperative clinical index and postoperative outcomes
| Variable                                      | NC-LTG group n=62 | NC-OTG group n=78 | P Value |
|----------------------------------------------|-------------------|-------------------|---------|
| Surgical time, min (mean±SD)                 | 255.69±39.77      | 238.71±39.78      | 0.013   |
| Blood loss, ml (median, IQR)                 | 150 (100-300)     | 200 (200-300)     | 0.003   |
| Proportion of blood loss [n (%)]             |                   |                   | 0.162   |
| 0-200ml                                      | 43                | 42                |         |
| 200-400ml                                    | 9                 | 26                |         |
| ≥400ml                                       | 10                | 10                |         |
| Retrieved lymph nodes, n (mean±SD)           | 33.52±13.19       | 34.88±16.46       | 0.595   |
| No.10 Lymph nodes dissection                 |                   |                   | 0.288   |
| Yes                                          | 41                | 58                |         |
| No                                           | 21                | 20                |         |
| Extent of resection                          |                   |                   | 0.457   |
| R0                                           | 59                | 77                |         |
| R1/R2                                        | 3                 | 1                 |         |
| Fist flatus day, d (mean±SD)                 | 4.34±1.29         | 5.41±1.14         | 0.000   |
| Postoperative day, d (mean±SD)               | 9.39±4.01         | 11.88±3.32        | 0.000   |
| Surgery costs, Dollar (mean±SD)              | 5409.99±1306.94   | 4123.20±804.34    | 0.000   |
| Hospitalization costs, Dollar (mean±SD)      | 13513.30±2559.98  | 15107.48±2639.04  | 0.000   |
| Total complication rate (%)                  | 14 (22.6%)        | 21 (26.9%)        | 0.295   |
| Clavien-Dindo Classification                 |                   |                   |         |
| Grade II                                     | 12                | 19                |         |
| Peritoneal infection                         | 2                 | 2                 |         |
| Lymphatic leakage                            | 2                 | 0                 |         |
| Anastomotic leakage                          | 1                 | 0                 |         |
| Pancreatic fistula                            | 1                 | 1                 |         |
| Ileus                                         | 1                 | 2                 |         |
| Cardiac failure                              | 1                 | 0                 |         |
| Hypoproteinemia                              | 2                 | 8                 |         |
| Anemia                                        | 2                 | 2                 |         |
| Condition                      | Count | Total |
|-------------------------------|-------|-------|
| Cholecystitis                 | 0     | 1     |
| Incision infection            | 0     | 2     |
| Pneumonia                     | 0     | 1     |
| **Grade IIIa**                | 1     | 2     |
| Deep venous thrombosis        | 1     | 0     |
| Pleural effusion              | 0     | 1     |
| Anastomotic leakage           | 0     | 1     |
| **Grade V**                   | 1     | 0     |
| Septic shock                  | 1     | 0     |
| **Severe complication rate (%)** | 2(3.2) | 2(2.6) | 0.816 |

Table 5 Clinical characteristics and perioperative index in ypTNM 0~II patients
| Variable                                      | NC-LTG group\(n=31\) | NC-OTG group\(n=43\) | P Value |
|-----------------------------------------------|-----------------------|-----------------------|---------|
| Gender                                        |                       |                       | 0.935   |
| Male                                          | 25                    | 35                    |         |
| Female                                        | 6                     | 8                     |         |
| Age (year, mean±SD)                          | 59.10±10.52           | 56.49±11.75           | 0.328   |
| BMI\((kg/m^2, mean±SD)\)                     | 22.58±2.77            | 23.72±3.00            | 0.100   |
| CCI score                                     |                       |                       | 0.746   |
| 0-2                                           | 22                    | 29                    |         |
| ≥2                                            | 9                     | 14                    |         |
| Tumor diameters ,cm\((mean±SD)\)              | 3.0±2.2-4.5           | 2.1±1.3-4.0           | 0.116   |
| Surgical time, min\((mean±SD)\)              | 260.97±37.02          | 238.19±34.79          | 0.009   |
| Blood loss, ml \((median, IQR)\)              | 150±100-200           | 200±200-300           | 0.003   |
| Proportion of blood loss \([n (\%)]\)         |                       |                       | 0.410   |
| 0-200ml                                       | 24                    | 29                    |         |
| 200-400ml                                     | 4                     | 10                    |         |
| ≥400ml                                        | 3                     | 4                     |         |
| Retrieved lymph nodes, n \((mean±SD)\)       | 34.00±15.11           | 36.51±17.15           | 0.516   |
| Fist flatus day, d \((mean±SD)\)             | 4.33±1.30             | 5.44±1.20             | 0.000   |
| Postoperative day, d \((mean±SD)\)           | 8.94±3.63             | 11.65±2.98            | 0.001   |
| Surgery costs , Dollar \((mean±SD)\)         | 5842.87±1399.48       | 4238.69±690.94        | 0.000   |
| Hospitalization costs, Dollar\((mean±SD)\)   | 13868.44±2334.98      | 15471.01±2425.43      | 0.006   |
| Total complication rate \(\%(\%\)\)          | 5\(\%\)16.1\(\%\)    | 9\(\%\)20.9\(\%\)    | 0.603   |
| II                                            | 4                     | 8                     |         |
| Illa                                          | 0                     | 1                     |         |
| V                                             | 1                     | 0                     |         |
| Severe complication rate \(\%(\%\)\)          | 1\(\%\)3.2\(\%\)     | 1 \(\%\)2.3\(\%\)    | 0.666   |

Table.6 Clinical characteristics and perioperative index in ypTNM III~IV patients
| Variable                                         | NC-LTG group n=31 | NC-OTG group n=35 | P Value |
|-------------------------------------------------|--------------------|--------------------|---------|
| Gender                                          |                    |                    | 0.935   |
| Male                                            | 25                 | 26                 |         |
| Female                                          | 6                  | 9                  |         |
| Age (year, mean±SD)                             | 56.32±10.12        | 55.94±12.90        | 0.896   |
| BMI (kg/m², mean±SD)                            | 23.11±2.58         | 23.62±3.73         | 0.519   |
| CCI score                                       |                    |                    | 0.567   |
| 0-2                                             | 22                 | 27                 |         |
| ≥2                                              | 9                  | 8                  |         |
| Tumor diameters, cm (mean±SD)                   | 5.78±2.56          | 6.09±3.023         | 0.658   |
| Surgical time, min (mean±SD)                    | 250.42±42.28       | 239.34±45.69       | 0.313   |
| Blood loss, ml (median, IQR)                    | 200–100-300        | 300–200-400        | 0.143   |
| Proportion of blood loss [n (%)]                |                    |                    | 0.181   |
| 0-200ml                                         | 19                 | 13                 |         |
| 200-400ml                                       | 5                  | 15                 |         |
| ≥400ml                                          | 7                  | 7                  |         |
| Retrieved lymph nodes, n (mean±SD)              | 33.03±11.18        | 32.89±15.58        | 0.966   |
| Fist flatus day, d (mean±SD)                    | 4.35±1.31          | 5.37±1.09          | 0.001   |
| Postoperative day, d (mean±SD)                  | 9.84±4.36          | 12.17±3.73         | 0.022   |
| Surgery costs, Dollar (mean±SD)                 | 5363.98±1284.09    | 4309.86±989.55     | 0.000   |
| Hospitalization costs, Dollar (mean±SD)         | 14124.49±2968.06   | 15864.64±3092.87   | 0.023   |
| Total complication rate (%)                     | 9% 29.0%           | 12% 34.3%          | 0.647   |
| II                                              | 8                  | 11                 |         |
| IIIa                                            | 1                  | 1                  |         |
| Severe complication rate (%)                    | 1% 3.2%            | 1% 2.9%            | 0.723   |

**Figures**
Figure 1

Flow diagram of patient enrollment
Figure 2

Changes of laboratorial indexes in the perioperative period (a). Hb changes between LTG and OTG group; (b). Alb changes between LTG and OTG group; (c). NLR changes between LTG and OTG group; (d). PLR changes between LTG and OTG group.
Figure 3

Overall survival and disease-free survival of NACT-LTG and NACT-OTG group (a). Overall survival between two groups; (b). Disease-free survival between two groups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
