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Retrospective Study

Comparison of the short and long-term outcomes between laparoscopic and open total gastrectomy for locally advanced gastric cancer after neoadjuvant chemotherapy

Comparison of short and long outcomes between LTG and OTG after NACT

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Abstract

BACKGROUND

Neoadjuvant chemotherapy (NACT) combined with surgery is regarded as an effective treatment for advanced gastric cancer (AGC). 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.

AIM

To compare the short and long-term outcomes between LTG and OTG for locally advanced gastric cancer after NACT.

METHODS

We retrospectively collected clinicopathological data of 136 patients who accepted gastrectomy after NACT from June 2012 to June 2019, including 61 patients in LTG group and 75 patients in OTG group. Clinicopathological characteristics between LTG and OTG group showed no significant difference. SPSS 26.0 and GraphPad Prism 8.0 were used to perform statistical analysis.

RESULTS

In 136 patients, 8 patients acquired pathological complete response(pCR) while the objective response rate(ORR) was 47.8%（65/136）. LTG group had longer operation time(P = 0.015), less blood loss（P=0.003）, shorter first flatus days(P＜0.001) and postoperative days（P＜0.001）. LTG spent more surgical cost than OTG (P＜0.001) while total hospitalized cost of LTG was less than OTG(P＜0.001). 21 (28.0%) patients in OTG group and 14 (23.0%) patients in LTG group had 30-day postoperative complication, with no significant difference (P = 0.503). 3-year overall survival (OS) rate was 60.6% and 64.6% in LTG and OTG group (HR: 0.859, 95%CI : 0.522~1.412, P =

0.546) while 3-year disease-free survival (DFS) rate was 54.5% and 51.8% in LTG and OTG group respectively (HR: 0.947, 95%CI : 0.582~1.539, *P* = 0.823). Multivariate cox analysis showed that BMI and pTNM stage were independent risk factors of OS while vascular invasion and pTNM stage were independent risk factors of DFS (P＜0.05).

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.

Key Words: Neoadjuvant chemotherapy; Gastric cancer; Laparoscope; Total gastrectomy; Morbidity; Survival

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Core Tip: Neoadjuvant chemotherapy (NACT) was defined as chemotherapy before surgery which was currently hotspot of perioperative therapy for advanced gastric cancer.We focus on the short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) after NACT.In this study, we found that LTG group had longer operation time, less blood loss、shorter first flatus and postoperative days. LTG showed comparable 30-day postoperative morbidity as well as 3-year OS and DFS rate with no significant difference in comparison with OTG. Based on our results, we recommended experienced surgeons select LTG for proper patients after NACT.

INTRODUCTION

Gastric cancer (GC) is the fifth most 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 most lethal tumor [2]. Perioperative integrated therapy is gradually taken into account by the treatment of gastric cancer. Neoadjuvant chemotherapy (NACT), as a crucial part of integrated therapy, is currently a research hotspot. Unlike postoperative chemotherapy, NACT puts chemotherapy prior to surgery, which brings advantages as follows: (1) More possibility of reducing tumor stages and increasing R0 resection rate [3]; (2) Better tolerance to chemotherapy before surgery; (3) Identical surgical safety compared with surgery-first therapy [4,5]; (4) high complete rate of total chemotherapy; (5) Potential survival benefit relative to other interventional treatments. After MAGIC study [6] first proved the surgical safety and good long-term survival benefit of perioperative chemotherapy, more prospective randomized clinical trials like FLOT4[7], RESOLVE [8], RESONANCE [9] sprung up and acquired the initial conclusion that showed superiority of NACT in pathological complete response (pCR) rate and long-term survival. This contributed to its further clinical utilization.

Laparoscopy is the representative of minimal invasive surgery techniques in the 21st century. Since Kitano *et al* [10] reported the first laparoscopic gastrectomy in 1994, laparoscopy has emerged as a standard surgical approach especially for distal gastrectomy proved by several high-quality trials [11,12].

The laparoscopic total gastrectomy (LTG) was carried out relatively late due to its complex surgical procedure and anastomotic technical difficulty. Although LTG has been proved safer than open total gastrectomy (OTG) for clinical stage I gastric cancer by CLASS-02 study [13], the option of LTG is still conservative in the treatment of advanced gastric cancer (AGC). At present, a multitude of retrospective articles on studies conducted in experienced medical centers demonstrated comparable short- and long-term outcomes between LTG and OTG [14,15], but prospective studies haven't acquired conclusion.

Currently, surgical safety and oncological outcomes after NACT have gradually attracted surgeons' 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 overall survival (OS) and disease-free survival (DFS) between LTG and OTG after NACT in western countries [16]. However, it has been not clear whether LTG has superior short and long-term outcomes compared with OTG or not for advanced gastric cancer patients who accepted NACT in China. As minimally invasive surgery is gaining popularization and great importance is attached to NACT in China, indispensable study should be conducted for the proper application of LTG after NACT.

MATERIALS AND METHODS

Patients

This is a 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; （4） ASA score ≤III ; （5） Integrated clinical and pathological data ; （6） no conversion to OTG in LTG group. All patients accepted LTG or OTG followed by NACT (chemotherapeutic regimen: SOX, XELOX, SF, DCF) according to the consultation of the multi-disciplinary team.

Surgical approach

Surgical procedure was conformed with Japanese Gastric Cancer Treatment Guidelines [17]. 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 months after surgery, residual adjuvant chemotherapy carried out under the guidance of surgeons with their experiences.

Perioperative index

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[18].We defined Clavien-Dindo classification ≥IIIa as severe complication.

Follow-up started 3 mo 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.

Statistical analysis

We used SPSS statistical package, version 26 (IBM software) , R 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. We used univariate cox analyses to explore the related indexes and put indicators with $P<0.10$ into multivariate analysis. Multivariate

analyses, with backward variable selection, were conducted using the Cox proportional hazards regression model. All tests were two-sided and statistical significance was set at $P<0.05$.

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**, 136 patients included into this case-control study with 61 patients in NACT-LTG group and 75 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 136 patients accepted neoadjuvant chemotherapy before surgery. Among them, 113 patients acquired SOX regimen (48 in LTG group and 65 in OTG group),17 patients acquired XELOX regimen (8 in LTG group and 9 in OTG group) and 6 patients accepted other regimen like DCF, SF), no significant difference of disparate regimen was found in two groups(P = 0.143). Cycle of NACT was determined mainly by patients' chemotherapeutic reaction and tumor response with no significant difference between two groups(P = 0.467). 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 = 0.659). Also the LTG group had a significant longer chemotherapy–surgical procedure interval compared with the OTG group (5.07±1.67 wk *vs* 4.55±1.33 wk; P = 0.047). There was no significant difference in receiving adjuvant therapy between two groups(P = 0.545).

Clinical response was another evitable factor defined in accordance with RECIST criteria[19].In this study, 8 (5.9%) patients received completed response(CR) while 57(41.9%) 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

58 (95.1%) patients in LTG group and 74(98.7%) patients in OTG group acquired R0 resection(P = 0.214). Compared with OTG group, LTG group had longer operation time (255.66±40.10 min *vs.* 238.59±40.30 min, P = 0.015) and less blood loss [150（100-300）ml *vs.* 200（200-300）ml, P = 0.003]. The number of retrieved lymph nodes were similar in both groups (33.38±13.26 in LTG group *vs.* 34.75±16.69 in OTG group, P = 0.603).

Regarding postoperative recovery, we found that LTG group showed advantages of enhanced recovery after surgery (ERAS) in comparison with OTG group on first flatus days (4.36±1.28 d vs. 5.41±1.16 d, P＜0.001) and postoperative days（9.48±3.98 d vs. 11.89±3.36 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 = 0.332) and blood loss(P = 0.159) 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 = 0.008) and PLR of OTG compared with LTG group in POD 1 (P = 0.038), no significant difference was observed between two groups in other period. Visualized comparison was depicted in **Figure 2.**

30-day postoperative morbidity

In total 136 patients who underwent surgery after NACT, 21 (28.0%) patients in OTG group and 14 (23.0%) patients in LTG group had over Grade II postoperative complications quantified by Clavien-Dindo classification, with no significant difference (P = 0.503). 2 (3.2%) patients who underwent LTG occurred severe complications (C-D grade≥IIIa), wherein one patient died because of septic shock in POD 3.The rate of severe complications after OTG (2/75, 2.7%) did not differ significantly from those in LTG group (P = 0.834). **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

127 of total (93.4%) patients completed follow-up. The last follow-up day is Dec 30th ,2021. The median follow-up period was 69 (range 1–112) months.3-year OS and DFS rates were compared between LTG and OTG group after NACT. 3-year OS rate was 60.6% and 64.6% in LTG and OTG group respectively [HR: 0.859, 95%CI（0.522~1.412）],which demonstrated no significant difference between two groups(log-Rank χ^2=0.364 , P=0.546). 3-year DFS rate was 54.5% and 51.8% in LTG and OTG group respectively

[HR: 0.947（0.582~1.539）],which presented no significant difference (log-Rank χ^2=0.05 , P=0.823). 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~II patients, there were no significant difference in 3-year OS rate(*P* = 0.264) and DFS rate(*P* = 0.262) between LTG and OTG, so were the subgroup of 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.**

Multivariate cox analysis of OS and DFS

Cox analyses were shown in **Table 7 and Table 8**. In the univariate analysis, BMI, pTNM stage, tumor diameter, estimated blood loss, vascular and nerve invasion significantly correlated with OS (P < 0.10) and pTNM stage, tumor diameter, estimated blood loss, vascular invasion significantly correlated with DFS (P < 0.10). In the multivariate analysis, BMI and pTNM stage were independent risk factors of OS while vascular invasion and pTNM stage were independent risk factors of DFS (P＜0.05). Historical factor was not significantly associated with OS and DFS (P＞0.05).

DISCUSSION

The application to NACT for AGC rapidly increased because of its potential oncological benefit[20] . At present, Surgeons focus mainly on the impact of NACT on gastrectomy[16,21]. 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 has several advantages over surgery first for advanced gastric cancer, such as tumor regression, better tolerance, and improved R0 resection. Previous studies which consisted of over 100 cases of NACT showed that pCR rate ranged from

5%~17.2% [22]. In the present research, 8(5.9%) patients acquired pathologic complete response while 65(47.8%) patients gained objective response that was consistent with results above. Better chemotherapeutic response was the crucial premise of radical gastrectomy. 58(95.1%) patients in LTG group and 74(98.7%) patients in OTG group achieved R0 resection and no significant difference (P = 0.214) was found between these two groups. These results indicated that LTG could ensure considerable R0 resection in comparison to OTG after NACT.

Perioperative laboratorial index could evaluate the extent of surgical damage and nutritional status, even might predict prognosis [23]. In our series, it is found that no significant difference was observed in Alb and Hb between LTG and OTG at three timepoints, including before surgery, POD 1, and POD7. The incidence of hypoproteinemia seemed lower in LTG group (3.3%) compared with OTG group (10.7%) but the difference was not significant (P = 0.190), which indicated that LTG after NACT didn't obviously 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 [24]. Our results found no significant difference in PLR and NLR between LTG and OTG group 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 and PLR were presented at POD 1 in OTG than those in LTG. We attributed this interesting phenomenon to stronger stress response at early period after OTG [25], which might elevate inflammation and suppress inherit immunity, leading to higher NLR and PLR. Hence, most studies selected before surgery as factors rather than other timepoints [26].

Adhesion of tissues, lack of anatomical layer, peri gastric edema and fibrosis, *etc.* might occur after NACT, which leaded to increased surgical difficulty. Laparoscope has several advantages like delicate manipulation, regional amplification, faster recovery, and damage control that might reduce the surgical risk of NACT. Li *et al* found that laparoscopic distal gastrectomy had remarkably lower postoperative morbidity compared with open distal gastrectomy (20% vs. 46%, P = 0.007) for patients with AGC

who received NACT [21]. In this study, our perioperative clinical indicators showed that with operation time (P = 0.013), LTG offered benefits of less blood loss (P = 0.003), shorter first flatus day and postoperative day (P＜0.001) compared with OTG, which illuminated specific superiority of minimally invasive surgery. LTG also could achieve adequate lymph nodes dissection with comparable retrieved lymph nodes between LTG and OTG (33.38±13.26 vs. 34.75±16.69, P = 0.603). Meanwhile, an interesting phenomenon was that LTG costs more on operation and less on total hospitalization than OTG, which was similar to the results of Tegels JJ [27] and Hoya Y's [28] study. Gosselin-Tardif A [29] also presented Canadian perspective that the application of laparoscopic gastrectomy was more cost-effective compared with open gastrectomy. We reckoned that even expensive disposable surgical instruments mostly relying on import might elevate surgical cost in LTG. While fast 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, CLASS-02 trial conducted by China demonstrated that LTG performed by experienced surgeons had acceptable postoperative morbidity with 19.1% for clinical stage I gastric cancer[13]. 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). Li *et al* demonstrated that LTG had comparable safety and histological findings to OTG after NACT in the perioperative period and patients in LTG group could benefit from less IV-PCA use [30]. 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:23.0% *vs.* 28.0%, P = 0.503, severe morbidity of LTG *vs.* OTG:3.2% *vs.* 2.7%, P = 0.834), 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[14] and Komatsu S's[31] 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: 60.6% *vs*. 64.6%, $P = 0.546$; 3-yr DFS: 54.5% *vs*. 51.8%, $P = 0.823$). 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[32], 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, *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.

ARTICLE HIGHLIGHTS

Research background

Neoadjuvant chemotherapy (NACT) combined with surgery is regarded as an effective treatment for advanced gastric cancer (AGC). Laparoscopic surgery represents mainstream of minimally invasive surgery.

Research motivation

Currently, surgeons focus more on surgical safety and oncological outcomes of laparoscopic gastrectomy after NACT.

Research objectives

We sought to evaluate short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) after NACT.

Research methods

We retrospectively collected clinicopathological data of 136 patients who accepted gastrectomy after NACT from June 2012 to June 2019, including 61 patients in LTG group and 75 patients in OTG group. Clinicopathological characteristics between LTG and OTG group showed no significant difference. We compared the perioperative indexs and long-term outcomes between LTG and OTG group after NACT. SPSS 26.0 and GraphPad Prism 8.0 were used to perform statistical analysis.

Research results

In this study, we found that LTG group had longer operation time, less blood loss、shorter first flatus and postoperative days compared with OTG . LTG showed comparable 30-day postoperative morbidity as well as 3-year OS and DFS rate with no significant difference in comparison with OTG.

Research conclusions

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.

Research perspectives

We recommended experienced surgeons could select LTG for proper patients after NACT.Large-scale retrospective or even multi-institutional RCT studies are required to better understand of association between LTG and OTG after NACT.

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