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

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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[3] firstly proved the surgical safety and better long-term survival benefit of perioperative chemotherapy, more prospective randomized clinical trials like FLOT4[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.[5] reported first laparoscopic gastrectomy in 1994, laparoscopy has become a standard surgical approach especially for distal gastrectomy proved by several high-quality trials[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[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[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[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;4ASA score ≤III5Integrated clinical and pathological data6no 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 [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 months 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[13].We defined Clavien-Dindo classification≥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 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**, 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□100-300□ml *vs.* 200□200-300□ml, 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≥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 χ^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 χ^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[15] . At present, Surgeons focus mainly on the impact of NACT on gastrectomy[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%[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[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[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[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[21].

Adhesion of tissue, lack of anatomical layer, peri gastric edema and fibrosis etc. might occur after NACT which leaded 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[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 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[22] and Hoya Y's[23] study. Gosselin-Tardif A[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[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[9] and Komatsu S's[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[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.

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Not applicable.

Consent for publication

Not applicable.

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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

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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/m^2,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	17	23	
No	45	55	
Differentiation			0.404
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			0.332
Cycle 1-2	14	12	
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	53	61	0.271
Yes			
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	

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	
IIIa	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/m^2,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

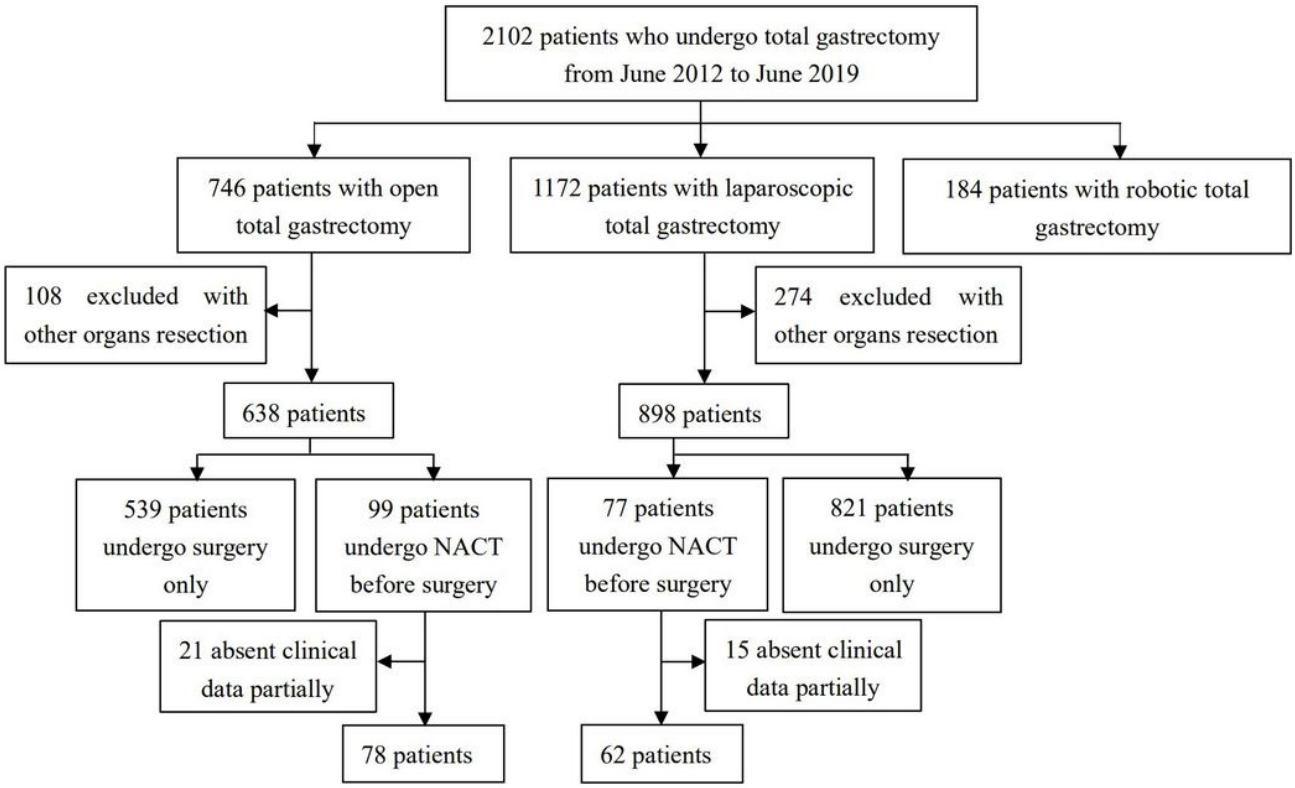

Figure 1

Flow diagram of patient enrollment

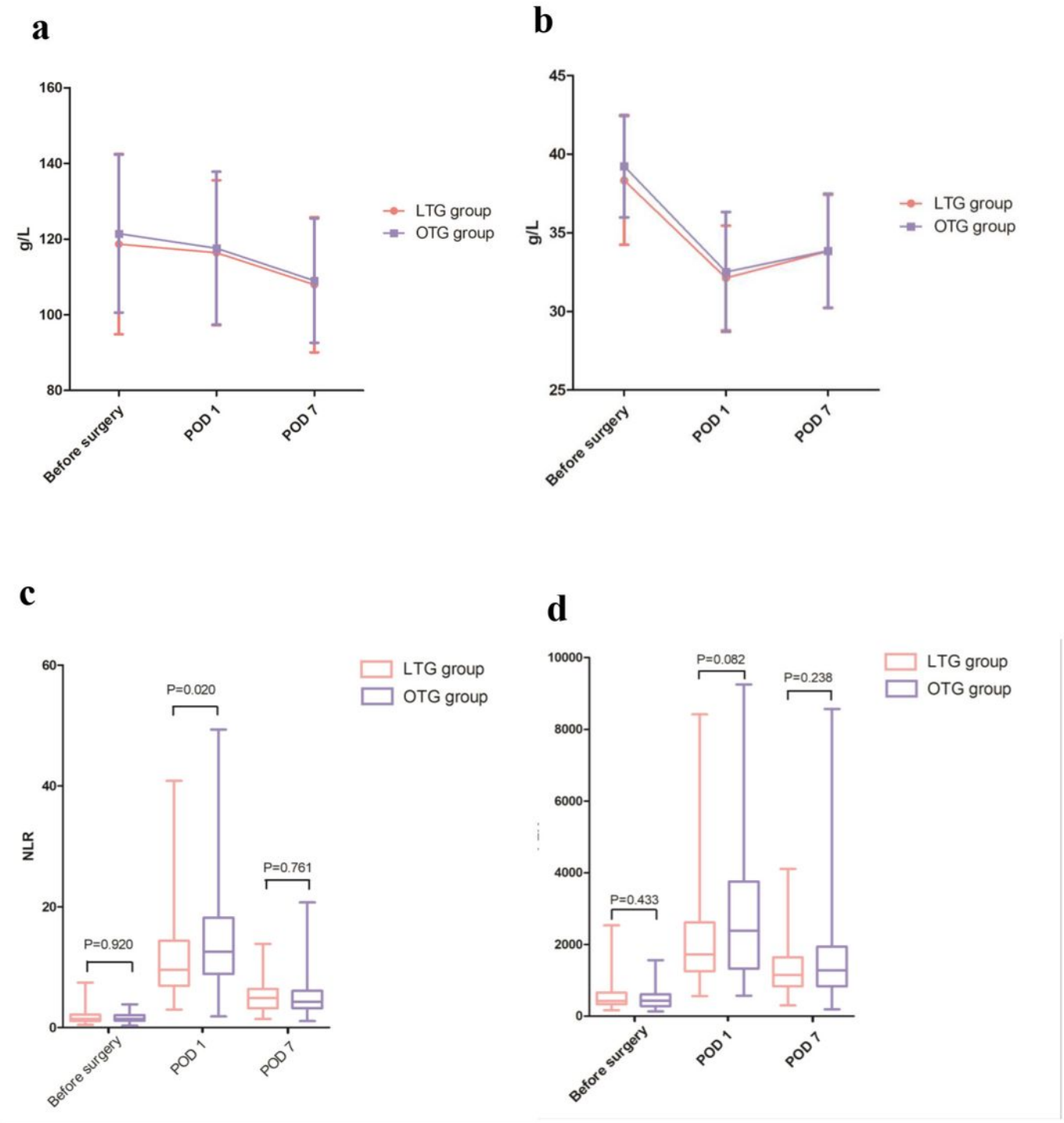

Figure 2

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.

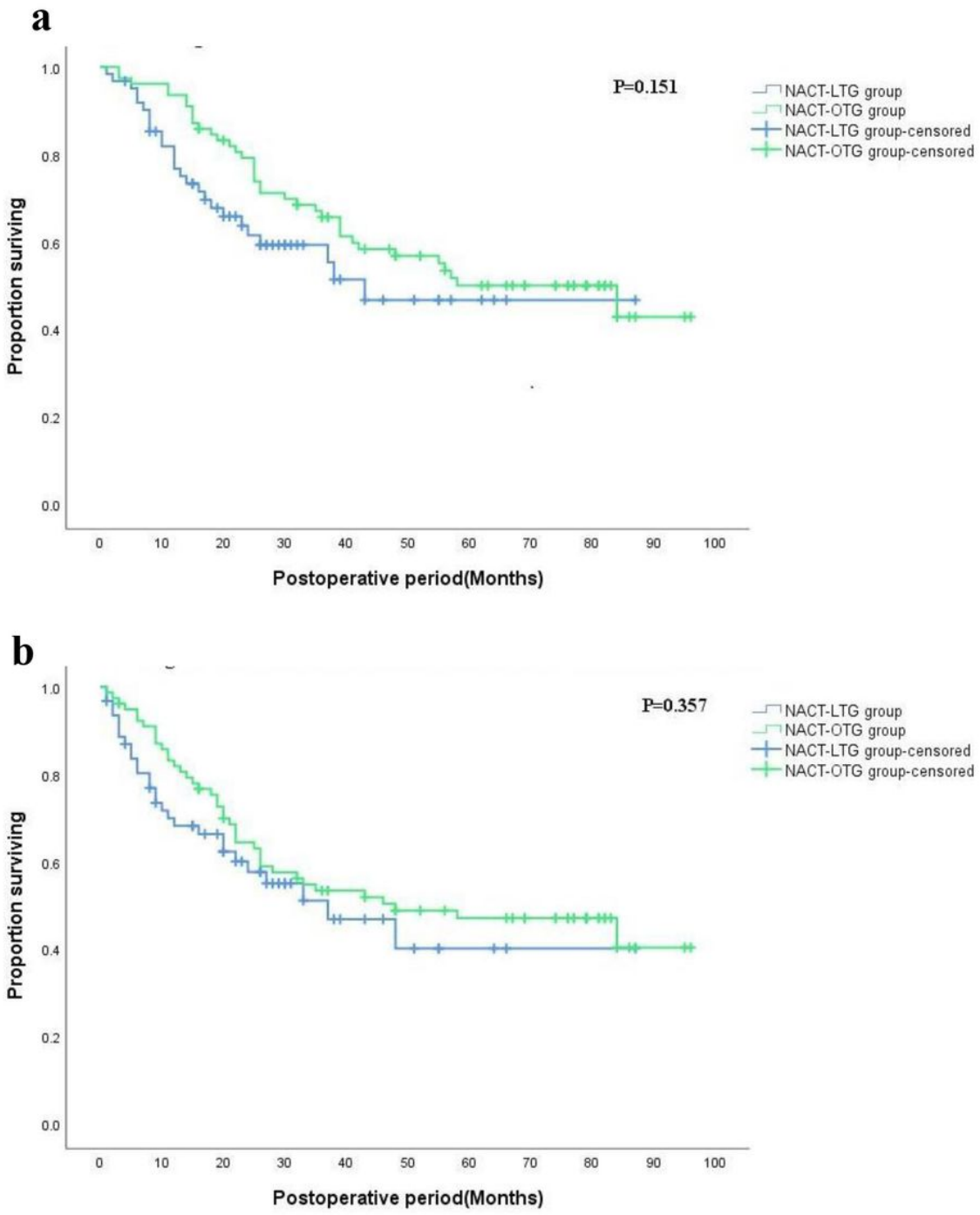

Figure 3

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.

- Ethicapprovaldocument01.pdf
- Ethicapprovaldocument02.pdf
- STROBEchecklist.docx
- Supplementaryfigure1.pdf