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World J Gastrointest Surg 2022 May 27; 14(5): 374-527



OPINION REVIEW

- 374 Comparison between recent sphincter-sparing procedures for complex anal fistulas-ligation of intersphincteric tract *vs* transanal opening of intersphincteric space
Garg P

REVIEW

- 383 Recent advances in diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms
Dai M, Mullins CS, Lu L, Alsfasser G, Linnebacher M

MINIREVIEWS

- 397 Role of surgical treatments in high-grade or advanced gastroenteropancreatic neuroendocrine neoplasms
Que QY, Zhang LC, Bao JQ, Ling SB, Xu X

ORIGINAL ARTICLE**Retrospective Cohort Study**

- 409 Laparoscopic *vs* open liver re-resection for cirrhotic patients with post-hepatectomy hepatocellular carcinoma recurrence: A comparative study
Cheng KC, Ho KM
- 419 Effect of overtime pancreaticoduodenectomy on the short-term prognosis of patients
Zhang JZ, Li S, Zhu WH, Leng XS, Zhang DF
- 429 Para-aortic lymph node involvement should not be a contraindication to resection of pancreatic ductal adenocarcinoma
Pande R, Chughtai S, Ahuja M, Brown R, Bartlett DC, Dasari BV, Marudanayagam R, Mirza D, Roberts K, Isaac J, Sutcliffe RP, Chatzizacharias NA

Retrospective Study

- 442 Prognostic factors for patients with mass-forming intrahepatic cholangiocarcinoma: A case series of 68 patients
Feng J, Liang B, Zhang HY, Liu Z, Jiang K, Zhao XQ
- 452 Short and long-term outcomes between laparoscopic and open total gastrectomy for advanced gastric cancer after neoadjuvant chemotherapy
Cui H, Zhang KC, Cao B, Deng H, Liu GB, Song LQ, Zhao RY, Liu Y, Chen L, Wei B
- 470 Are laparoscopic cholecystectomy and natural orifice transluminal endoscopic surgery gallbladder preserving cholecystolithotomy truly comparable? A propensity matched study
Ullah S, Yang BH, Liu D, Lu XY, Liu ZZ, Zhao LX, Zhang JY, Liu BR

Observational Study

- 482 Application of omental interposition to reduce pancreatic fistula and related complications in pancreaticoduodenectomy: A propensity score-matched study
Li Y, Liang Y, Deng Y, Cai ZW, Ma MJ, Wang LX, Liu M, Wang HW, Jiang CY

SCIENTOMETRICS

- 494 Global research production pertaining to gastrointestinal involvement in COVID-19: A bibliometric and visualised study
Zyoud SH, Al-Jabi SW, Shahwan MJ, Jairoun AA

CASE REPORT

- 506 Aorto-oesophageal fistula after corrosive ingestion: A case report
Scriba MF, Kotze U, Naidoo N, Jonas E, Chinnery GE
- 514 Castleman disease of the pancreas mimicking pancreatic malignancy on ⁶⁸Ga-DOTATATE and ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography: A case report
Liu SL, Luo M, Gou HX, Yang XL, He K

LETTER TO THE EDITOR

- 521 Applying refined pancreaticogastrostomy techniques in pancreatic trauma
Krige J, Bernon M, Jonas E
- 525 Providing higher value care for hepatocellular carcinoma rather than diagnosis: What can current radiologists do?
Yao S, Wei Y, Song B

ABOUT COVER

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WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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Retrospective Study

Short and long-term outcomes between laparoscopic and open total gastrectomy for advanced gastric cancer after neoadjuvant chemotherapy

Hao Cui, Ke-Cheng Zhang, Bo Cao, Huan Deng, Gui-Bin Liu, Li-Qiang Song, Rui-Yang Zhao, Yi Liu, Lin Chen, Bo Wei

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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 the 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 AGC after NACT.

METHODS

We retrospectively collected the clinicopathological data of 136 patients who accepted gastrectomy after NACT from June 2012 to June 2019, including 61 patients who underwent LTG and 75 who underwent OTG. Clinicopathological characteristics between the LTG and OTG groups showed no significant difference. SPSS 26.0, R software, and GraphPad PRISM 8.0 were used to perform

statistical analyses.

RESULTS

Of the 136 patients included, eight acquired pathological complete response, and the objective response rate was 47.8% (65/136). The LTG group had longer operation time ($P = 0.015$), less blood loss ($P = 0.003$), shorter days to first flatus ($P < 0.001$), and shorter postoperative hospitalization 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 the OTG group and 14 (23.0%) in the LTG group had 30-d postoperative complications, but there was no significant difference between the two groups ($P = 0.503$). The 3-year overall survival (OS) rate was 60.6% and 64.6% in the LTG and OTG groups, respectively [hazard ratio (HR) = 0.859, 95% confidence interval (CI): 0.522-1.412, $P = 0.546$], while the 3-year disease-free survival (DFS) rate was 54.5% and 51.8% in the LTG and OTG group, respectively (HR = 0.947, 95%CI: 0.582-1.539, $P = 0.823$). Multivariate cox analysis showed that body mass index and pTNM stage were independent risk factors for OS while vascular invasion and pTNM stage were independent risk factors for DFS ($P < 0.05$).

CONCLUSION

After NACT, LTG shows comparable 30-d postoperative morbidity as well as 3-year OS and DFS rate to OTG. We recommend that 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), defined as chemotherapy before surgery, is currently a hot research topic of perioperative therapy for advanced gastric cancer. In this study, we focused on the short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) after NACT. We found that the LTG group had longer operation time, less blood loss, shorter time to first flatus, and shorter postoperative hospitalization days. LTG showed comparable 30-d postoperative morbidity as well as 3-year overall survival and disease-free survival rate to OTG. Based on our results, we recommend that experienced surgeons select LTG for proper patients after NACT.

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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 in the treatment of GC. Neoadjuvant chemotherapy (NACT), as a crucial part of integrated therapy, is currently a hot research topic. 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; and (5) Potential survival benefit relative to other interventional treatments. After MAGIC study[6] first proved the surgical safety and long-term survival benefit of perioperative chemotherapy, more prospective randomized clinical trials like FLOT4[7], RESOLVE[8], and RESONANCE[9] sprung up and acquired the initial conclusion that NACT showed superiority in terms of pathological complete response (pCR) rate and long-term survival. This contributed to its further clinical utilization.

Laparoscopy is a representative of minimally 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].

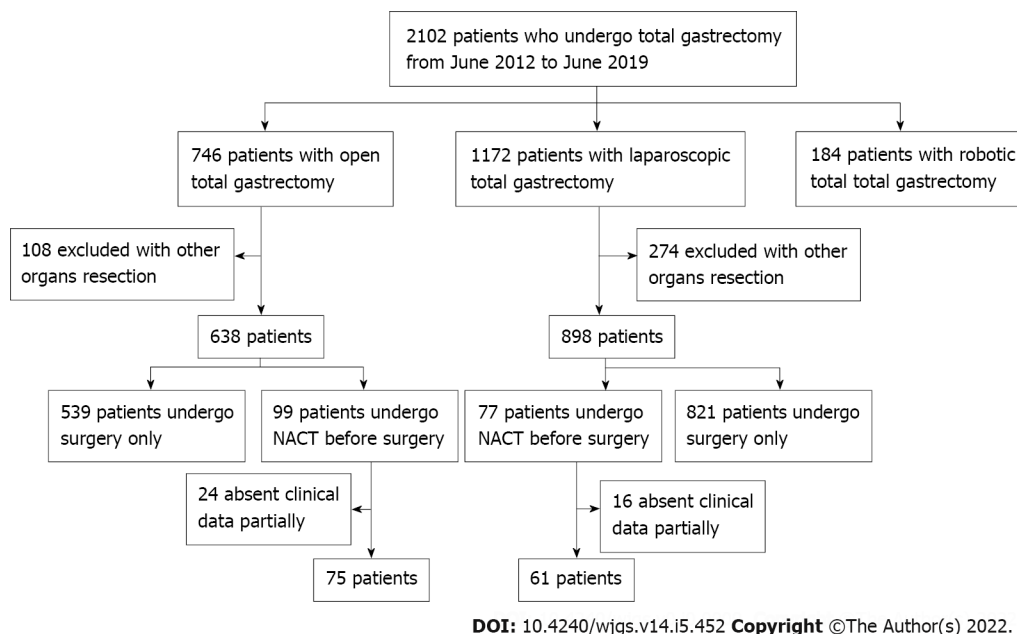


Figure 1 Flow diagram of patient enrollment. NACT: Neoadjuvant chemotherapy.

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 GC by CLASS-02 study[13], the option of LTG is still conservative in the treatment of advanced GC (AGC). At present, a multitude of retrospective articles conducted in experienced medical centers demonstrated comparable short- and long-term outcomes between LTG and OTG[14,15], but prospective studies have not acquired final results.

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 guidelines, van der Wielen *et al*[16] conducted STOMACH trial as the first multi-institutional RCT study which demonstrated the comparable complication rate 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 is still unclear whether LTG has superior short and long-term outcomes compared with OTG or not for AGC patients who accepted NACT in China. As minimally invasive surgery is gaining popularization and great importance is attached to NACT in China, more studies should be conducted for the proper application of LTG after NACT.

MATERIALS AND METHODS

Patients

This is a retrospective study conducted at the General Surgery Department of the Chinese PLA General Hospital. Clinical and pathological data of patients with AGC who accepted NACT before LTG or OTG plus D2 lymphadenectomy from June 2012 to June 2019 were collected. The eligible criteria were: (1) Clinical tumor stage II-III (including Bulky N or large type 3-4) proved by endoscopic ultrasonography, abdominal computed tomography (CT), and positron emission tomography-CT (PET-CT); (2) Histologically proved gastric adenocarcinoma by preoperative gastroscopy and biopsy; (3) Ages ranging from 18 to 75 years; (4) ASA score ≤ III; (5) Integrated clinical and pathological data; and (6) No conversion to OTG in the LTG group. All patients accepted LTG or OTG followed by NACT (chemotherapeutic regimen: SOX, XELOX, SF, or DCF) according to the consultation of a multi-disciplinary team.

Surgical approach

Surgical procedures were conducted according to Japanese Gastric Cancer Treatment Guidelines[17]. D2 lymphadenectomy was performed, including resection of No. 1, 2, 3a, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 11d, and 12a. Dissection of No. 10 lymph nodes was performed when a 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 was carried out under the guidance of surgeons with rich experience.

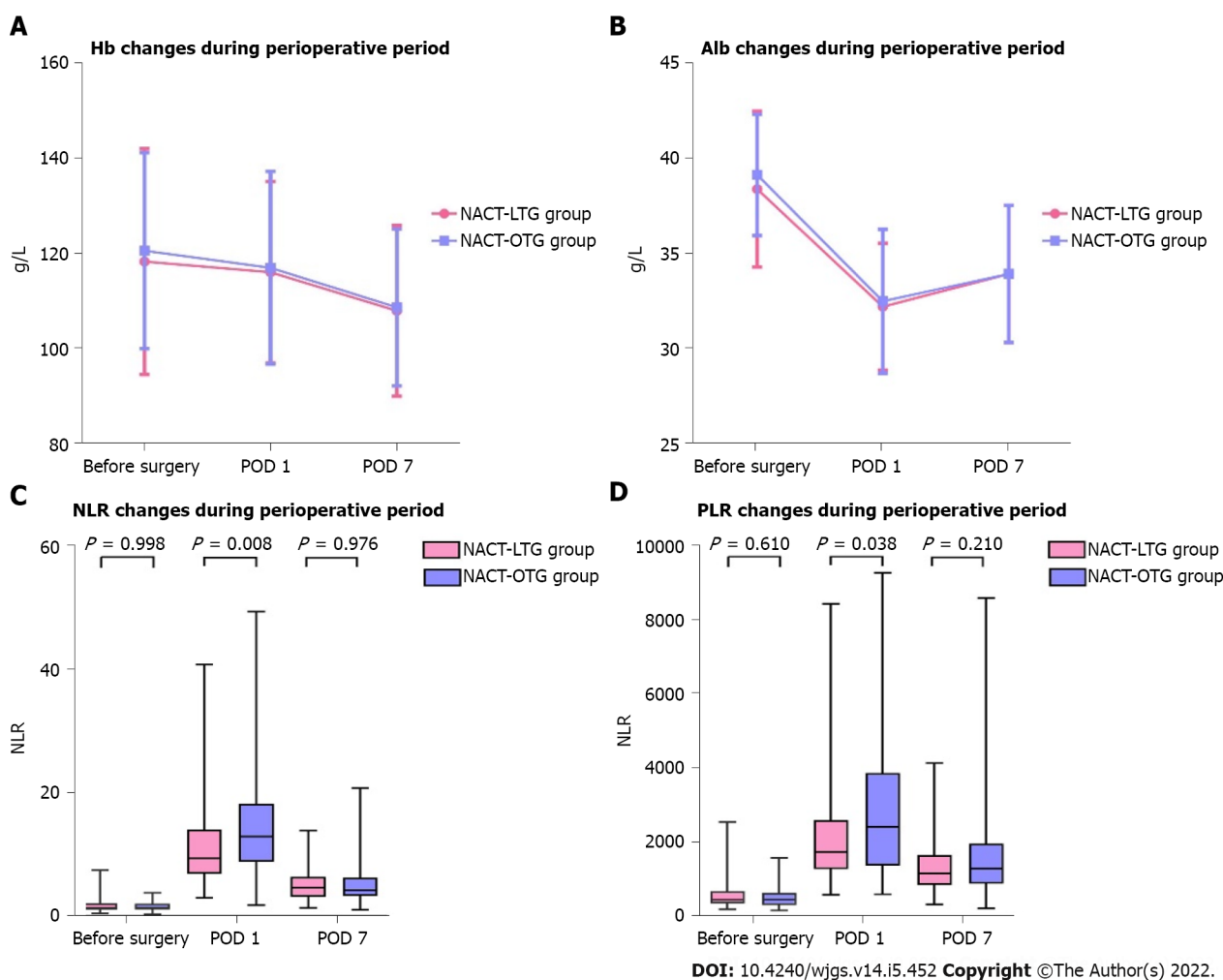


Figure 2 Comparisons of laboratorial indexes during the perioperative period. A: Hemoglobin changes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) groups; B: Albumin changes between LTG and OTG groups; C: Neutrophil-to-lymphocyte ratio changes between LTG and OTG groups; D: Platelet-to-lymphocyte ratio changes between LTG and OTG groups. NACT: Neoadjuvant chemotherapy; LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio.

Perioperative indexes

We retrospectively collected clinicopathologic indicators including blood loss, operation time, time to first flatus (days), postoperative hospitalization days, surgical and hospitalized cost, retrieved lymph nodes, tumor length, *etc.* The 30-d morbidity and mortality were recorded from case report form and its severe degree was assessed in accordance with the Clavien-Dindo classification[18]. We defined Clavien-Dindo classification \geq IIIa as severe complication.

Follow-up started 3 mo after operation by outpatient visit or telephone until patients' death. Frequency of adjuvant chemotherapy, survival status, and recurrence or not were mentioned during inquiries. If patients dropped out, the 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 analyses. Continuous variables are described as mean \pm SD for normal distributions, while medians and interquartile ranges are used to represent skew distributions. Comparison tests were performed by the Student's *t* test and Mann-Whitney U test as appropriate. Categorical variables are described as frequencies with percent, 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 is vividly presented by line chart and box diagram.

To show long-term oncological outcomes, overall survival and disease-free survival were analyzed 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 $P < 0.05$.

Table 1 Baseline characteristics of 136 gastric cancer patients after neoadjuvant chemotherapy (mean \pm SD)

Clinical characteristic	LTG group (n = 61)	OTG group (n = 75)	P value
Gender			0.821
Male	47	59	
Female	14	16	
Age (yr)	57.56 \pm 10.35	56.84 \pm 11.95	0.712
BMI (kg/m ²)	22.81 \pm 2.67	23.67 \pm 3.31	0.099
CCI score, n (%)			0.982
0-2	43	53	
> 2	18	22	
History of abdominal surgery			0.179
No	54	60	
Yes	7	15	
Clinical tumor stage			
cT			0.695
T2	1	6	
T3	22	23	
T4	38	46	
cN			0.191
N0	7	4	
N+	54	71	
cTNM			0.468
II	5	9	
III	56	66	
Historical factor			0.088
2012-2015	22	38	
2016-2019	39	37	

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; CCI: Comprehensive complication index; BMI: Body mass index; NACT: Neoadjuvant chemotherapy.

RESULTS

Clinicopathologic characteristics

We collected the clinical data of 2102 patients who underwent total gastrectomy from June 2012 to June 2019 at the Chinese PLA General Hospital. After screening as described in [Figure 1](#), 136 patients were 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 [Tables 1](#) and [2](#). Groups were comparable according to sex, age, body mass index (BMI), comprehensive complication index score, proportion of previous abdominal surgery, tumor diameter, clinical and pathologic TNM stage, tumor location, nerve or vascular invasion, and histological type with no significant difference.

NACT

All the 136 patients accepted NACT before surgery. Among them, 113 patients adopted SOX regimen (48 in LTG group and 65 in OTG group), 17 used XELOX regimen (8 in LTG group and 9 in OTG group), and 6 accepted other regimens like DCF and SF; no significant difference was found in the utilization of chemotherapy regimen between the two groups ($P = 0.143$). Cycles of NACT was determined mainly by patients' chemotherapeutic reaction and tumor response, with no significant difference between the two groups ($P = 0.467$). We recorded adverse events during chemotherapy by patients' self-report and

Table 2 Pathological characteristics of 136 gastric cancer patients after neoadjuvant chemotherapy

Pathological characteristic	LTG group (n = 61)	OTG group (n = 75)	P value
Tumor diameter, cm (median, IQR)	4.0 (2.5-6.5)	4.0 (2.0-6.0)	0.366
Site of tumor			0.244
Upper 1/3	30	27	
Middle 1/3	21	29	
Diffused	10	19	
ypT			0.751
T0	1	7	
T1	5	5	
T2	10	14	
T3	34	30	
T4	11	19	
ypN			0.190
N0	19	35	
N1	14	11	
N2	12	11	
N3	16	18	
ypTNM			0.300
0	1	7	
I	8	17	
II	22	16	
III	29	34	
IV	1	1	
Nerve invasion			0.545
Yes	20	21	
No	41	54	
Vascular invasion			0.982
Yes	18	22	
No	43	53	
Differentiation			0.616
Well/moderate	27	30	
Poor/undifferentiated	34	45	

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy.

laboratorial index, and classified severe degree *via* CTCAE version 4.0. We found that patients in the two groups had comparable adverse events with no significant difference ($P = 0.535$). The LTG group had significantly 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 adjuvant therapy between the two groups ($P = 0.545$) (Table 3).

Clinical response was another factor defined in accordance with RECIST criteria[19]. In this study, 8 (5.9%) patients achieved a completed response while 57 (41.9%) had a partial response. However, other patients did not have obvious downstage after NACT and were defined as stable disease (62 patients) and progressive disease (9 patients).

Table 3 Neoadjuvant chemotherapy characteristics

Variable	LTG group (n = 61)	OTG group (n = 75)	P value
Number of cycles of NACT			0.467
1-2	13	12	
3-4	45	59	
> 4	3	4	
NACT regimen			0.143
SOX	48	65	
XELOX	8	9	
Other	5	1	
Clinical response			0.659
CR	1	7	
PR	28	29	
SD	28	34	
PD	4	5	
Adverse effects after NACT			0.535
Grade 0	13	17	
Grade I	16	21	
Grade II	17	23	
Grade III	11	12	
Grade IV	4	2	
Chemotherapy-surgical procedure interval (wk)	5.07 ± 1.67	4.55 ± 1.33	0.047
Adjuvant therapy			0.545
Yes	52	61	
No	9	14	

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy; CR: Complete response; PR: Partial response; PD: Progressive disease.

Surgical indicators and postoperative recovery

Of 58 (95.1%) patients in the LTG group and 74 (98.7%) patients in the OTG group acquired R0 resection ($P = 0.471$). Compared with the OTG group, the 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 was similar between the two 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 the LTG group showed advantages of enhanced recovery after surgery in comparison with the OTG group with regard to days to first flatus (4.36 ± 1.28 d *vs* 5.41 ± 1.16 d, $P < 0.001$) and postoperative hospitalization days (9.48 ± 3.98 d *vs* 11.89 ± 3.36 d, $P < 0.001$).

Perioperative expenditure was another concern to evaluate cost-effectiveness of different surgical approaches. In this study, even though LTG spent more surgical cost than OTG ($P < 0.001$), LTG seemed more economical compared with OTG in terms of total hospitalized cost ($P < 0.001$). Specific indicators mentioned above are presented in [Table 4](#).

In subgroup analysis, we compared the difference between the LTG and OTG groups on the basis of different pathological tumor stages. After balancing the baseline characteristics, similar results were obtained like above in ypTNM 0-II patients ([Table 5](#)). Whereas, for patients with ypTNM III-IV, no significant difference was observed on surgical time ($P = 0.332$) or blood loss ($P = 0.159$) between the two groups ([Table 6](#)).

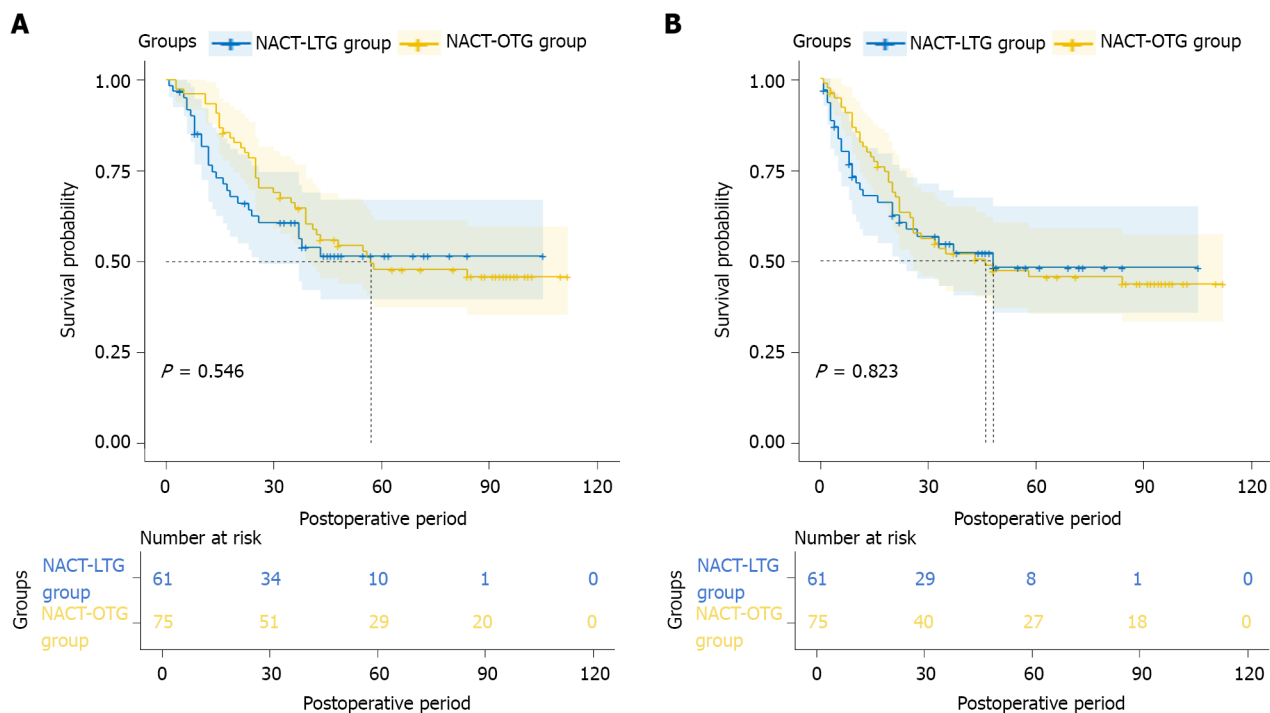
Laboratorial indexes before surgery and at postoperative days 1 and 7

We selected partial laboratorial indexes like hemoglobin (Hb) and albumin (Alb) in the perioperative

Table 4 Perioperative clinical indexes and postoperative outcomes between laparoscopic total gastrectomy and open total gastrectomy groups after neoadjuvant chemotherapy (mean ± SD)

Variable	LTG group (n = 61)	OTG group (n = 75)	P value
Surgical time, min	255.66 ± 40.10	238.59 ± 40.30	0.015
Blood loss, mL (median, IQR)	150 (100-300)	200 (200-300)	0.003
Blood loss (mL), n (%)			0.003
< 200	31	13	
200-400	20	51	
> 400	10	11	
Retrieved lymph nodes, n	33.38 ± 13.26	34.75 ± 16.69	0.603
No. 10 lymph nodes dissection			0.339
No	41	56	
Yes	20	19	
Extent of resection			0.471
R0	58	74	
R1/R2	3	1	
Time to first flatus, d	4.36 ± 1.28	5.41 ± 1.16	0.000
Postoperative stay, d	9.48 ± 3.98	11.89 ± 3.36	0.000
Surgery costs, \$	5419.99 ± 1315.39	4162.36 ± 791.93	0.000
Hospitalization costs, \$ (median, IQR)	13105.92 (11713.18-14640.53)	14873.96 (13501.66-17131.31)	0.000
Total complication rate (%)	14 (23.0)	21 (28.0)	0.503
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 (3.3)	2 (2.7)	1.000

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy.



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Figure 3 Overall survival and disease-free survival in neoadjuvant chemotherapy-laparoscopic total gastrectomy and neoadjuvant chemotherapy-open total gastrectomy groups. A: Overall survival between the two groups; B: Disease-free survival between the two groups. NACT: Neoadjuvant chemotherapy; LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy.

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 POD 7, there were no significant difference in Hb or Alb between the two groups.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were also calculated through laboratory tests. In this study, except for a higher NLR in the OTG group compared with the LTG group at POD 1 ($P = 0.008$) and PLR in the OTG compared with the LTG group at POD 1 ($P = 0.038$), no significant difference was observed between the two groups in other periods. Visualized comparison is depicted in Figure 2.

30-d postoperative morbidity

Of the 136 patients who underwent surgery after NACT, 21 (28.0%) in the OTG group and 14 (23.0%) in the LTG group developed Grade II or above postoperative complications evaluated by the Clavien-Dindo classification, with no significant difference between the two groups ($P = 0.503$). Two (3.3%) patients who underwent LTG had severe complications, wherein one patient died because of septic shock at POD 3. The rate of severe complications after OTG (2/75, 2.7%) did not differ significantly from that in the LTG group ($P = 1.000$). Table 4 gives the detailed items of complications.

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

Long-term oncological outcomes

Of the 136 patients included, 127 (93.4%) completed follow-up. The last follow-up day was December 30, 2021. The median follow-up period was 69 (range, 1–112) mo. The 3-year OS rate was 60.6% and 64.6% in the LTG and OTG groups, respectively [hazard ratio (HR) = 0.859, 95% confidence interval (CI): 0.522-1.412], which demonstrated no significant difference between the two groups (log-rank $\chi^2 = 0.364$, $P = 0.546$). The 3-year DFS rate was 54.5% and 51.8% in the LTG and OTG groups, respectively (HR = 0.947, 95%CI: 0.582-1.539), which presented no significant difference (log-rank $\chi^2 = 0.05$, $P = 0.823$). Kaplan-Meier curves are shown in Figure 3.

Additionally, we set up two subgroups according to different ypTNM stages to explore the oncological impact of the two surgical approaches. For ypTNM 0-II patients, there was no significant difference in 3-year OS rate ($P = 0.264$) or DFS rate ($P = 0.262$) between LTG and OTG, neither 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 are shown in Supplementary Figure 1.

Table 5 Clinical characteristics and perioperative indexes in ypTNM 0-II patients after neoadjuvant chemotherapy (mean \pm SD)

Variable	LTG group (n = 31)	OTG group (n = 40)	P value
Gender			0.841
Male	25	33	
Female	6	7	
Age (yr)	59.10 \pm 10.51	57.63 \pm 11.16	0.574
BMI (kg/m ²)	22.58 \pm 2.77	23.72 \pm 2.93	0.102
CCI score			0.594
0-2	22	26	
> 2	9	14	
Tumor diameter, cm (median, IQR)	3.00 (2.20-4.50)	2.30 (1.42-4.00)	0.158
Surgical time, min	260.97 \pm 37.20	237.93 \pm 35.51	0.010
Blood loss, mL (median, IQR)	150 (100-200)	200 (200-300)	0.002
Blood loss (mL), n (%)			0.000
0-200	19	5	
200-400	9	31	
> 400	3	4	
Retrieved lymph nodes, n	34.00 \pm 15.11	36.38 \pm 17.64	0.552
Time to first flatus, d	4.32 \pm 1.28	5.45 \pm 1.24	0.000
Postoperative stay, d	8.94 \pm 3.63	11.65 \pm 3.03	0.001
Surgery costs, \$	5641.18 \pm 1351.17	4163.48 \pm 627.86	0.000
Hospitalization costs, \$	13389.70 \pm 2254.38	15024.88 \pm 23358.95	0.004
Total complication rate (%), C-D classification	5 (16.1)	9 (22.5)	0.503
II	4	8	
IIIa	0	1	
V	1	0	
Severe complication rate (%)	1(3.2)	1 (2.5)	1.000

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy; CCI: Comprehensive complication index; BMI: Body mass index; C-D classification: Clavien-Dindo classification

Multivariate Cox analysis of OS and DFS

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

DISCUSSION

The application of NACT to 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 provide a reference to the reasonable utilization of minimally invasive surgery for AGC patients who accepted NACT.

NACT before surgery has several advantages over surgery first for AGC, 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

Table 6 Clinical characteristics and perioperative index in ypTNM III-IV patients after neoadjuvant chemotherapy (mean \pm SD)

Variable	LTG group (n = 30)	OTG group (n = 35)	P value
Gender			0.931
Male	22	26	
Female	8	9	
Age (yr)	55.97 \pm 10.10	55.94 \pm 12.90	0.993
BMI (kg/m ²)	23.03 \pm 2.60	23.63 \pm 3.73	0.468
CCI score			0.514
0-2	21	27	
> 2	9	8	
Tumor diameter, cm	5.5 (3.5-8.0)	5.0 (4.0-8.0)	0.916
Surgical time, min	250.17 \pm 42.99	239.34 \pm 45.69	0.332
Blood loss, mL (median, IQR)	200 (100-350)	300 (200-400)	0.159
Blood loss (mL), n (%)			0.404
0-200	12	8	
200-400	11	20	
> 400	7	7	
Retrieved lymph nodes, n	32.73 \pm 11.24	32.89 \pm 15.58	0.965
Time to first flatus, d	4.40 \pm 1.30	5.37 \pm 1.09	0.002
Postoperative stay, d	10.03 \pm 4.30	12.17 \pm 3.73	0.036
Surgery costs, \$	4793.57 (4032.20-6242.77)	3871.55 (3686.28-4416.86)	0.000
Hospitalization costs, \$	13190.05 (12036.98-14591.47)	15263.28 (13162.85-17143.01)	0.000
Total complication rate (%), C-D classification	9 (30.0)	12 (34.3)	0.647
II	8	11	
IIIa	1	1	
Severe complication rate (%)	1 (3.3)	1 (2.9)	1.000

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy; CCI: Comprehensive complication index; BMI: Body mass index; C-D classification: Clavien-Dindo classification.

achieved a pathologic complete response while 65 (47.8%) gained an objective response that was consistent with the results mentioned above. Better chemotherapeutic response was the crucial premise of radical gastrectomy. In this study, 58 (95.1%) patients in the LTG group and 74 (98.7%) in the OTG group achieved R0 resection, and no significant difference ($P = 0.471$) was found between the two groups. These results indicated that LTG could ensure considerable R0 resection in comparison to OTG after NACT.

Perioperative laboratorial indexes could evaluate the extent of surgical damage and nutritional status, and even might predict prognosis[23]. In our series, no significant difference was observed in Alb and Hb between LTG and OTG at three time points, including before surgery, POD 1, and POD 7. The incidence of hypoproteinemia seemed lower in the LTG group (3.3%) compared with the OTG group (10.7%), but the difference was not significant ($P = 0.190$), which indicated that LTG after NACT did not obviously improve postoperative nutritional status with advantages of minimally invasive surgery. NLR and PLR were regarded as potential markers to predict further prognosis[24]. Our results found no significant difference in PLR or NLR between the LTG and OTG groups before surgery and at 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 observed at POD 1 in the OTG group than in the LTG group. 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 pre-operation as a factor rather than other time points[26].

Adhesion of tissues, lack of anatomical layer, and peri-gastric edema and fibrosis might occur after NACT, which increased the surgical difficulty. Laparoscopy has several advantages like delicate

Table 7 Univariate and multivariate analyses for overall survival

Factor	Univariate analysis		P value	Multivariate analysis		P value
	HR	95%CI		HR	95%CI	
Sex			0.127			
Male	1.000					
Female	1.541	0.885-2.684				
Age			0.647			
< 65	1.000					
≥ 65	1.129	0.671-1.900				
BMI (kg/m²)			0.091			0.049
< 25	1.000			1.000		
≥ 25	0.601	0.333-1.086		0.547	0.300-0.998	
Surgical approach			0.549			
Laparoscopy	1.000					
Open	1.164	0.708-1.914				
CCI score			0.438			
0-2	1.000					
≥ 2	1.225	0.733-2.049				
pTNM stage			0.000			0.006
0-II	1.000			1.000		
III-IV	2.632	1.569-4.413		2.224	1.258-3.930	
Tumor diameter (cm)			0.039			0.153
≤ 3	1.000			1.000		
> 3	1.838	1.031-3.277		1.577	0.844-2.945	
Operation time (min)			0.483			
≤ 240	1.000					
> 240	1.192	0.730-1.948				
Estimated blood loss (mL)			0.074			0.588
≤ 200	1.000			1.000		
> 200	1.559	0.958-2.536		1.154	0.688-1.935	
Vascular invasion			0.008			0.062
No	1.000			1.000		
Yes	1.987	1.200-3.289		1.712	0.974-3.010	
Nerve invasion			0.079			0.567
No	1.000			1.000		
Yes	1.580	0.949-2.632		0.838	0.456-1.537	
Differentiation			0.261			
Well/moderate	1.000					
Poor/undifferentiated	1.335	0.806-2.212				
Complications			0.662			
No	1.000					
Yes	1.131	0.651-1.968				
Historical factor			0.861			

2012-2015	1.000	
2016-2019	0.957	0.587-1.560

HR: Hazard ratio; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; CCI: Comprehensive complication index; BMI: Body mass index.

manipulation, regional amplification, faster recovery, and damage control that might reduce the surgical risk of NACT. Li *et al*[21] 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 LTG offered benefits of less blood loss ($P = 0.003$), shorter days to first flatus, and shorter postoperative hospitalization dasy ($P < 0.001$) compared with OTG, which illuminated specific superiority of minimally invasive surgery. LTG also could achieve adequate lymph nodes dissection with a comparable number of retrieved lymph nodes between LTG and OTG (33.38 ± 13.26 *vs* 34.75 ± 16.69 , $P = 0.603$). Meanwhile, an interesting phenomenon was found that LTG cost more on operation and less on total hospitalization than OTG, which was similar to the results of the studies by Tegels *et al*[27] and Hoya *et al*[28]. Gosselin-Tardif *et al*[29] also found that the application of laparoscopic gastrectomy was more cost-effective compared with open gastrectomy in Canadians. We reckon that the fact that expensive disposable surgical instruments mostly relied on import might elevate surgical cost in LTG, but fast postoperative recovery could offset deviations by reducing other costs, which suggested LTG as a probable cost-effective alternative surgical approach after NACT.

In terms of perioperative complications, CLASS-02 trial conducted in China demonstrated that LTG performed by experienced surgeons had acceptable postoperative morbidity (19.1%) for clinical stage I GC[13]. STOMACH trial showed no significant difference in the rate of postoperative complications between OTG (42.9%) and LTG (34.0%) in LTG after NACT in Western countries ($P = 0.408$). Wang *et al* [30] demonstrated that LTG had comparable safety to OTG after NACT in the perioperative period and patients in the LTG group could benefit from less intravenous patient-controlled analgesia (IV-PCA) use [30]. Back to our study, we found that LTG did not significantly increase or decrease 30-d postoperative complications compared with OTG after NACT (overall morbidity of LTG *vs* OTG: 23.0% *vs* 28.0%, $P = 0.503$; severe morbidity of LTG *vs* OTG: 3.3% *vs* 2.7%, $P = 1.000$), which was similar to the results of the studies mentioned above. These results still existed in different ypTNM stage patients. Thus, we consider that the application of LTG after NACT could be safe and feasible whatever tumor stage was and we recommend to initiate prospective studies to give high-grade evidence in East Asia.

Long-term outcomes were inevitable to evaluate oncological benefit caused by different surgical approaches. The studies by Gambhir *et al*[14] and Komatsu *et al*[31] both pointed out a comparable long-term survival between LTG and OTG, nevertheless it remained uncertain between the LTG and OTG group after NACT. Our results of follow-up focused on 3-year OS and DFS rates showed no significant difference between the two groups (LTG compared to OTG: 3-year OS: 60.6% *vs* 64.6%, $P = 0.546$; 3-year DFS: 54.5% *vs* 51.8%, $P = 0.823$). Subgroup analysis according to different ypTNM stages also showed no significant difference in 3-year OS or DFS rate. These findings suggested that patients with LTG after NACT had similar oncological benefits compared with those in the OTG group irrespective of stage, and LTG after NACT could be regarded as an alternative surgical approach with acceptable short and long-term outcomes.

Our study has several limitations. Principally, this is not a prospective study which lacked of authentic evidence-based support and existed selection bias. Under the trend of climbing application of 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 the association between LTG and OTG after NACT. Moreover, small sample size increased the probability of type II error and reduced the power of test. To decrease such impact, we combined patients with adjacent ypTNM stages into one group to ensure enough sample size in subgroup analysis. Third, although SOX regimen was the main NACT treatment in our study, other regimens like XELOX and DCF were also used for a small portion of appropriate patients, which may slightly influence short or long-term outcomes. In addition, even the baseline characteristics of patients included in this study were comparable between the LTG and OTG groups, some potential imbalance caused by unknown indicators may affect the validity of results.

CONCLUSION

To sum up, this study suggested that there are no significant disparities between LTG and OTG in postoperative complication rates, 3-year OS rates, and 3-year DFS rates after NACT for AGC patients. LTG performed by experienced surgeons after NACT has 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.

Table 8 Univariate and multivariate analyses for disease-free survival

Factor	Univariate analysis		P value	Multivariate analysis		P value
	HR	95%CI		HR	95%CI	
Sex			0.259			
Male	1.000					
Female	0.851	0.642-1.127				
Age			0.267			
< 65	1.000					
≥ 65	1.326	0.806-2.181				
BMI (kg/m²)			0.706			
< 25	1.000					
≥ 25	0.706	0.403-1.237				
Surgical approach			0.825			
Laparoscopy	1.000					
Open	0.947	0.582-1.539				
CCI score			0.707			
0-2	1.000					
≥ 2	1.104	0.660-1.847				
pTNM stage			0.000			0.022
0-II	1.000			1.000		
III-IV	2.418	1.471-3.973		1.854	1.095-3.140	
Tumor diameter (cm)			0.022			0.200
≤ 3	1.000			1.000		
> 3	1.954	1.100-3.470		1.484	0.812-2.710	
Operation time (min)			0.710			
≤ 240	1.000					
> 240	1.095	0.679-1.765				
Estimated blood loss (mL)			0.024			0.204
≤ 200	1.000			1.000		
> 200	1.730	1.075-2.785		1.379	0.840-2.263	
Vascular invasion			0.001			0.020
No	1.000			1.000		
Yes	2.245	1.378-3.659		1.824	1.101-3.022	
Nerve invasion			0.203			
No	1.000					
Yes	1.387	0.838-2.295				
Differentiation			0.283			
Well/moderate	1.000					
Poor/undifferentiated	1.311	0.800-2.148				
Complications			0.751			
No	1.000					
Yes	1.093	0.631-1.894				
Historical factor			0.691			

2012-2015	1.000	
2016-2019	1.102	0.683-1.779

HR: Hazard ratio; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; CCI: Comprehensive complication index; BMI: Body mass index.

ARTICLE HIGHLIGHTS

Research background

Neoadjuvant chemotherapy (NACT) combined with surgery is regarded as an effective treatment for advanced gastric cancer (AGC). Laparoscopic surgery represents the 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 the clinicopathological data of 136 patients who accepted gastrectomy after NACT from June 2012 to June 2019, including 61 patients in the LTG group and 75 patients in the OTG group. Clinicopathological characteristics between the LTG and OTG groups showed no significant difference. We compared the perioperative indexes and long-term outcomes between the LTG and OTG groups after NACT. SPSS 26.0, R software, and GraphPad PRISM 8.0 were used to perform statistical analyses.

Research results

In this study, we found that LTG had longer operation time, less blood loss, shorter days to first flatus, and shorter postoperative hospitalization days compared with OTG. LTG showed comparable 30-d postoperative morbidity as well as 3-year OS and DFS rate to OTG.

Research conclusions

This study suggested that there are no significant disparities between LTG and OTG in postoperative complication rates, 3-year OS rates, and 3-year DFS rates after NACT for AGC patients. LTG performed by experienced surgeons after NACT has 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 recommend that experienced surgeons could select LTG for proper patients after NACT. Large-scale retrospective or even multi-institutional RCT studies are required to better understand the association between LTG and OTG after NACT.

FOOTNOTES

Author contributions: Cui H, Zhang KC, Cao B, Chen L, and Wei B designed the study; Cao B, Deng H, and Zhao RY collected the data; Liu Y analyzed and interpreted the data; Cui H and Zhang KC prepared the manuscript; all the authors read and approved the final manuscript.

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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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