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Original Research Article

A Retrospective Comparative Outcome Assessment between Laparoscopic and Open Total Gastrectomy for Advanced Gastric Cancer after Neoadjuvant Chemotherapy

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Abstract

Aim: To compare the short and long-term outcomes between LTG and OTG for AGC after neoadjuvant chemotherapy (NACT).

Material & Methods: This is a retrospective study of prospectively collected data conducted at the Department of Surgical Gastroenterology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India. Clinical and pathological data of patients with AGC who accepted NACT before LTG or OTG plus D2 lymphadenectomy, over a period of 3 years (from Nov, 2016 to Oct, 2020) were collected.

Results: We collected the clinical data of patients who underwent total gastrectomy over a period of 3 years at the Department of Surgical Gastroenterology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India. After screening, 50 patients were included into this case-control study with 25 patients in NACT-LTG group and 25 patients in NACT-OTG group. The LTG group had significantly longer chemotherapy–surgical procedure interval compared with the OTG group (5.38 ± 1.89 week vs. 4.69 ± 1.81 week; P = 0.05). There was no significant difference in adjuvant therapy between the two groups (P = 0.662). 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).

Conclusion: After NACT, LTG shows comparable 30-d postoperative morbidity as well as 2-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

Background

Gastric cancer is one of the most common malignant tumors in the world. In 2018, there were 1,034,000 new cases and 783,000 deaths of gastric cancer worldwide, accounting for the 5th and 3rd place, respectively, in the incidence and mortality of all cancers [1]. The proportion of early gastric cancer is relatively low,

about 20%. Most of gastric cancers are already in the advanced stage when detected, and the overall 5-year survival rate is less than 50% [2]. Studies have shown that Neo adjuvant chemotherapy (NACT) can reduce tumor size, increase R0 resection rate, and improve the prognosis of patients [3–5]. At present, surgery-based comprehensive treatment is the main mode of gastric cancer treatment [6], but open surgery causes great trauma, large amount of blood loss, and high incidence of complications, and some patients have poor tolerance to surgery and slow postoperative recovery [7–9]. In recent years, with the development of laparoscopic technology, laparoscopic gastric cancer surgery has become a research focus [10]. For advanced distal gastric cancer, NACT combined with laparoscopic radical gastrectomy does not increase complications, incidence and safety risks [9, 11].

Although surgery is the only curative approach for patients with GC, most patients with GC are in an advanced stage at diagnosis, which dramatically lowers the R0 resection rate, leading to poorer prognosis [12-13]. Neoadjuvant chemotherapy (NACT) is now regarded as an effective tumor down staging approach, improving the R0 resection rate, and thereby, improving long-term survival [14-17]. Based on the evidence above, perioperative treatment protocols have been introduced into the national guidelines in many Western countries. Further, clinical stage (cTNM) and post-preoperative therapy stage (ypTNM) have been newly defined in the recent 8th edition of the AJCC Cancer Staging Manual [18-19].

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* 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 [20]. 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. As minimally invasive surgery is gaining popularization and great importance is attached to NACT, more studies should be conducted for the proper application of LTG after NACT.

Material & Methods

This is a retrospective analysis of prospectively collected data conducted at the Department of Surgical Gastroenterology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India. Clinical and pathological data of patients with AGC who accepted NACT before LTG or OTG plus D2 lymphadenectomy, over a period of 3 years (from Nov, 2016 to Oct, 2020) were collected.

The eligible criteria were: (1) Clinical tumor stage II-III (including Bulky N or large type 3-4) proved by abdominal computed tomography (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. All patients accepted LTG or OTG followed by NACT (chemotherapeutic regimen: XELOX or DCF) according to the radiation and medical oncology team.

Surgical procedures were conducted according to Japanese Gastric Cancer Treatment Guidelines [21]. 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.

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

Follow-up started 3 months 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 cut-off value.

We used SPSS statistical package, version 26 (IBM software), R software, and Graph Pad PRISM 8.0 software to perform statistical analyses. Continuous variables are described as mean ± 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 $P < 0.10$.

Results

We collected the clinical data of patients who underwent total gastrectomy over a period of 5 years at the Department of Surgical Gastroenterology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India. After screening, 50 patients were included into this case-control study with 25 patients in NACT-LTG group and 25 patients in NACTOTG 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.

All the 50 patients accepted NACT before surgery. No significant difference was found in the utilization of chemotherapy regimen between the two groups ($P = 0.627$). Cycles of NACT was determined mainly by patients' chemotherapeutic reaction and tumor response, with no significant difference between the two groups ($P = 0.683$). We recorded adverse events during chemotherapy by patients' self-report and 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 ($P = 0.771$). The LTG group had significantly longer chemotherapy–surgical procedure interval compared with the OTG group (5.38 ± 1.89 week vs. 4.69 ± 1.81 week; $P = 0.05$). There was no significant difference in adjuvant therapy between the two groups ($P = 0.662$) [Table 3].

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 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 ($P < 0.10$). [Table 5]

Table 1: Baseline characteristics of 50 gastric cancer patients after neoadjuvant chemotherapy (mean ± SD)

Clinical characteristic	LTG group (n = 25)	OTG group (n = 25)	P value
Gender			
Male	20	19	0.482
Female	5	6	
Age (yrs.)	55.8 ± 10.12	56.3 ± 11.20	0.330
CCI score, n (%)			
0-2	19	18	0.729
> 2	6	7	
History of abdominal surgery			
No	22	19	0.391
Yes	3	6	
Clinical tumor stage			
cT			0.283
T2	1	2	
T3	8	10	
T4	16	13	
cN			
N0	3	2	0.382
N+	22	23	
cTNM			
II	3	5	0.611
III	22	20	
LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; CCI: Comprehensive complication index; BMI: Body mass index; NACT: Neoadjuvant chemotherapy.			

Table 2: Pathological characteristics of 50 gastric cancer patients after neoadjuvant chemotherapy

Clinical characteristic	LTG group (n = 25)	OTG group (n = 25)	P value
Tumor diameter, cm (median, IQR)	4.0 (2.1-6.4)	4.2 (2.0-6.7)	0.829
Site of tumor			
Upper 1/3	12	7	0.244
Middle 1/3	9	8	
Diffuse	3	10	
ypT			
T0	1	3	0.621
T1	2	1	
T2	3	3	
T3	15	12	
T4	4	6	
ypN			
N0	9	14	0.883
N1	5	3	

N2	5	3	
N3	6	5	
ypTNM			
0	1	2	
I	2	4	0.472
II	5	5	
III	15	13	
IV	2	1	
Nerve invasion			
Yes	7	9	0.903
No	18	16	
Vascular invasion			
Yes	8	10	0.698
No	17	15	
Differentiation			
Well/moderate	11	13	0.490
Poor/undifferentiated	14	12	
LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy.			

Table 3: Neoadjuvant chemotherapy characteristics

Clinical characteristic	LTG group (n = 25)	OTG group (n = 25)	P value
Number of cycles of NACT			
1-2	5	7	0.683
3-4	19	17	
> 4	1	1	
NACT regimen			
DCF	21	22	0.627
XELOX	3	3	
Other	1	0	
Clinical response			
CR	0	3	0.378
PR	15	9	
SD	9	11	
PD	1	2	
Adverse effects after NACT			
Grade 0	4	3	0.771
Grade I	5	6	
Grade II	12	13	
Grade III	3	2	
Grade IV	1	1	
Chemotherapy–surgical procedure interval (wk)	5.38 ± 1.89	4.69 ± 1.81	0.05
Adjuvant therapy			
Yes	22	20	0.662
No	3	5	
LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy; CR: Complete response; PR: Partial response; PD: Progressive disease.			

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

Clinical characteristic	LTG group (n = 25)	OTG group (n = 25)	P value
Surgical time, min	250.38 ± 40.29	234.82 ± 40.338	0.05
Blood loss, mL (median, IQR)	150 (100-300)	200 (200-300)	0.05
Blood loss (mL), n (%)			
< 200	15	7	0.05
200-400	6	13	
> 400	4	5	
Retrieved lymph nodes, n	31.48 ± 12.37	33.83 ± 15.88	0.572
No. 10 lymph nodes dissection			
No	18	19	0.799
Yes	7	6	
Extent of resection			
R0	24	25	0.269
R1/R2	1	0	
Clavien-Dindo classification			
Grade II	5	8	
Peritoneal infection	1	1	0.732
Lymphatic leakage	0	0	
Anastomotic leakage	2	1	
Pancreatic fistula	0	0	
Ileus	0	1	
Cardiac failure	0	0	
Hypoproteinemia	0	3	
Anemia	1	0	
Cholecystitis	0	0	
Incision infection	0	0	
Pneumonia	0	0	
Grade IIIa	0	1	
Deep venous thrombosis	0	0	0.662
Pleural effusion	0	0	
Anastomotic leakage	0	0	
Grade V	0	0	
Septic shock	0	0	0.05
Severe complication rate (%)	0	1	

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

Table 5: Univariate and multivariate analyses for overall survival

Factor	Univariate analysis		P value	Multivariate analysis		P value
	HR	95%CI		HR	95 %CI	
Sex			0.552			
Male	1.000					
Female	1.473	0.857-2.462				
Age						
< 65	1.000		0.461			
≥ 65	1.112	0.662-1.910				
BMI						
< 25	1.000	1.000	0.649	1.000	1.000	0.05
≥ 25	0.628	0.320-1.129		0.300-0.997	0.474	
Surgical approach			0.549			
Laparoscopy	1.000					
Open	1.137	0.713-1.937				
pTNM stage						
0-II	1.000		0.000	1.000		0.07
III-IV	2.532	1.462-4.271		1.632-3.966		
Tumor diameter (cm)			0.05			0.166
≤ 3	1.000	1.000				
> 3	1.838	1.031-3.277		1.577	0.844-2.945	
Vascular invasion			0.072			0.77
No	1.000	1.000				
Yes	1.978	1.222-3.267		1.682	0.964-3.027	
Nerve invasion						
No	1.000	1.000				
Yes	1.538	0.942-2.648		0.662	0.488-1.501	
Differentiation			0.372			
Well/moderate	1.000					
Poor/undifferentiated	1.662	0.812-2.285				
Complications			0.447			
No	1.000					
Yes	1.578	0.953-2.648				

Discussion

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 cases of NACT showed that pCR rate ranged from 5%-17.2% [24]. Perioperative laboratorial indexes could evaluate the extent of surgical damage and nutritional status, and even might predict prognosis [25]. 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.

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 [26], 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].

Chen *et al.* reported that laparoscopic gastrectomy is more suitable for LNs diameter from 1.0 to 1.9 cm than open method in an experienced surgical team [27]. Our findings again suggest that laparoscopic technique does not account for the reduction of LNs retrieval, which warrant the credibility of histological findings [28-29].

With the progress of endoscopic instruments such as Fluorescence imaging laparoscopy and 3D laparoscopy, as well as the development and application of tracer materials such as carbon nanoparticles and indocyanine green, the efficiency of laparoscopic lymph node dissection is expected to be improved [30]. The first postoperative exhaust time and postoperative hospital stay in the laparoscopic group were shorter than those in the open group. Due to lesser trauma in the laparoscopic surgery, the intraoperative pull stimulation to the bowel can be reduced, which is conducive to the recovery of postoperative intestinal function. Besides, the incision is small, the postoperative pain is light, the early ambulation can be achieved, the recovery is fast, and the hospital stay is shortened [31].

Conclusion

Gastric carcinoma is deadly disease and mostly present in advanced stage. Because of neoadjuvant therapy many of advanced gastric carcinoma become resectable. After NACT, Laparoscopic Total Gastrectomy shows comparable 30-d postoperative morbidity and oncological specimen harvesting as well as 2-years OS and DFS rate to Open Total Gastrectomy. We recommend that well controlled randomized control study is needed to establish the ideal procedure.

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