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ORIGINAL ARTICLE

Laparoscopic total gastrectomy for upper-middle advanced gastric cancer: analysis based on lymph node noncompliance

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Abstract

Background Increasing number of clinical studies have shown that laparoscopic distal gastrectomy (LDG) with D2 lymph node (LN) dissection is an effective method for the treatment of advanced gastric cancer (AGC). However, reports on the technical feasibility and oncology efficacy of laparoscopic total gastrectomy (LTG) in the treatment of AGC are rare.

Methods A retrospective analysis of the clinicopathologic data of 1313 patients with clinical stage of cT2-4aN0-3M0 undergoing laparoscopic radical gastrectomy with D2 LN dissection from June 2007 to December 2013 was performed. Noncompliance was defined as patients with more than one LN station absence as described in the protocol for D2 lymphadenectomy in the Japanese Gastric Cancer Association (JGCA). According to the literature, it was subdivided into LN compliance group (all LN stations were detected), minor LN noncompliance group (1–2 LN stations were not detected), major LN noncompliance group (more than 2 LN stations were not detected). Based on the LN noncompliance, the surgical indications of LTG were analyzed with LDG as control.

Results Among the 1313 patients, 197 (39.20%) patients and 321(39.71%) patients in the LDG group and the LTG group had minor LN noncompliance, 59(11.70%) patients and 163(20.10%) patients had major LN noncompliance. The difference in the extent of LN noncompliance between the two groups was statistically significant ($p < 0.001$). COX proportional hazards regression analysis elucidated that the LN noncompliance was an independent prognostic factor for overall survival (OS). BMI ≥ 25 kg/m^2 and the history of previous abdominal surgery (PAS) were independent risk factors for major LN noncompliance in LTG group ($p < 0.05$), with which patients were defined as a LN noncompliance high-risk group. With the exception of LN noncompliance high-risk group, the difference in the extent of LN noncompliance between LTG group and LDG group was still statistically significant ($p = 0.008$). Tumor diameter > 60 mm is a preoperative risk factor for station #5 LN noncompliance, and no preoperative risk factors for station #6 LN noncompliance were found, with which patients were defined as LN noncompliance middle-risk group.

Conclusion LN noncompliance is an independent prognostic factor for poor prognosis in patients after LTG. Based on this finding, patients with BMI ≥ 25 kg/m^2, history of PAS and tumor diameter > 60 mm in the advanced stage of upper-middle gastric cancer represent high/middle-risk groups with LN noncompliance in LTG surgery, which should be carefully selected.

Keywords Gastric cancer · Laparoscopic total gastrectomy · D2 lymph node dissection · Lymph node noncompliance · Prognosis

Introduction

Worldwide, gastric cancer (GC) is an important health problem, ranking fourth among the most common malignancies and second among the leading causes of cancer death [1]. Gastrectomy with adequate peri-peripheral LN dissection is the only possible way to cure GC, and it can improve the survival rate of patients [2–5]. Since Kitano

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first reported laparoscopic early gastric cancer (EGC) surgery, the development of laparoscopic instruments and the accumulation of surgeons' experience has led to the expansion of the use of laparoscopic surgery for EGC to its use for AGC [6–10]. Unlike EGC, adequate D2 LN dissection must be achieved in the surgical treatment of AGC, and an increasing number of clinical studies have shown that LDG with D2 LN dissection is an effective method for the treatment of AGC [5, 10–12]. CLASS-01 by the Chinese Laparoscopic Gastrointestinal Surgical Society (CLASS) confirmed that the short-term and long-term outcomes of LDG in the treatment of AGC were not inferior to that of open distal gastrectomy [13, 14]. 3-year disease-free survival of patients assigned to the laparoscopic distal gastrectomy group was not inferior to that of patients assigned to the open distal gastrectomy group [14]. The COACT1001 trial from Korea confirmed the definite oncology efficacy of LDG for the treatment of AGC based on the LN noncompliance rate [15]. These studies suggest that the indication for LDG could be extended to locally AGC. Epidemiological studies have shown that the occurrence of upper-middle gastric cancer that currently requires total gastrectomy has increased in recent years [16]. At present, the comparative study of LTG and open total gastrectomy (OTG) in upper-middle AGC has clinical significance. However, high-level evidence-based medicine reports on the technical feasibility and oncology efficacy of LTG in the treatment of AGC are rare. Meanwhile, the tumor site, tumor characteristics, surgical difficulty and LN dissection scope of patients in the LTG group are different from those in the LDG group, so it is difficult to directly compare the oncology efficacy of these two surgical methods through survival analysis. At the same time, due to the technological difficulty and possible complications of LTG, it is less popular than LDG in clinical practice. Therefore, a long time frame is required to carry out a multicenter prospective study with a sufficient number of cases to compare the long-term outcome of LTG with ODG in AGC. In view of the DGCT study, the LN noncompliance rate was a surrogate indicator for the long-term survival of patients with GC [17, 18]. CRITICS, COACT1001 and other clinical trials also use the LN noncompliance rate as a quality control indicator for D2 radical surgery in GC, and the evaluation of the LN noncompliance rate does not rely on the scope of gastrectomy, such as total gastrectomy or distal gastrectomy [15, 19, 20]. Therefore, this study takes the LN noncompliance rate as a quality control indicator to compare the oncology efficacies of LDG and LTG. Therefore, this study aims to explore the indications of LTG for the treatment of upper and middle AGC through a large-volume retrospective study of the LN noncompliance rate, which can provide a reference for future prospective randomized controlled trials.

Materials and methods

General information

A retrospective analysis was performed using the clinical and pathological data of 2401 patients who underwent GC surgery from the same group of surgeons in the Department of Gastroenterology, Union Hospital of Fujian Medical University, from June 2007 to December 2013. The inclusion criteria were as follows: (1) preoperative endoscopic biopsy confirmed gastric cancer; (2) preoperative examination confirmed no distant metastasis; and (3) intraoperative D2 radical surgery. The exclusion criteria were as follows: (1) distant metastasis; (2) exploration or palliative surgery; (3) preoperative radiotherapy and chemotherapy; (4) residual gastric cancer; (5) intraoperative combined organ resection; (6) postoperative pathology confirmed as nongastric adenocarcinoma; and (7) missing follow-up information. Finally, 1313 patients who underwent laparoscopic radical gastrectomy with preoperative clinical stage cT2-4aN0-3M0 were included in the study. All patients were informed in detail and signed informed consent before surgery. The retrospective study was approved by the ethics committee of Union Hospital of Fujian Medical University. Preoperative imaging studies were routinely performed following endoscopic and upper gastrointestinal examinations with contrast to confirm the tumor location and included computed tomography (CT) scanning, endoscopic ultrasound (EUS), and positron emission tomography-computed tomography (PET-CT) as needed to evaluate the clinical stage. Based on the criteria of obesity released by 2004 World Health Organization (WHO), that is, < 25 kg/m^2(normal), 25–29.9 kg/m^2 (pre-obesity), 30–34.9 kg/m^2 (obesity class I), ≥ 35 kg/m^2 (obesity class II), patients were classified into two groups according to their body mass index (BMI). Patients with BMI < 25 kg/m^2 were designated as the low-BMI group, while patients with BMI ≥ 25 kg/m^2 were designated as the high-BMI group in this study.

Postoperative pathology examination

After resecting the specimens, surgeons positioned each LN station according to the location of the blood vessel clips retained in the specimens during the operation and sorted each LN station according to the Japanese Research Society for Gastric Carcinoma (JRSGC) criteria. The specimens were immediately sent to the department of pathology after repacking, and the lymph nodes of each station were examined by two or more experienced pathologists through

palpation and microscopy. In each LN station defined by the JRSGC, if more than one LN station is not detected, it is determined as LN noncompliance, which was subdivided into the LN compliance group (all LN stations were detected), the minor LN noncompliance group (1–2 LN stations were not detected), and the major LN noncompliance group (more than 2 LN stations were not detected) [17, 19–22].

Follow-up

Postoperative follow-up was performed in the outpatient department every 3 months for the first 2 years, every 6 months during years 3–5, and once a year after year 5. Most routine patient follow-up appointments included a physical examination, laboratory tests (including assessment of CA19-9, CA72-4, and CEA levels), chest radiography, abdominopelvic US or CT, and an annual endoscopic examination. The OS was calculated from the day of surgery until death or until the final follow-up date, whichever occurred first.

Statistical analysis

All statistical analyses were performed using SPSS v. 25.0 for Windows (SPSS Inc., Chicago, IL, USA). All continuous variables are presented as the mean ± standard deviation. Chi-square or Fisher's exact tests were used to analyze categorical variables. Cumulative survival rates were compared using the Kaplan–Meier method and log-rank test. Regression analysis was performed using the Cox proportional hazards regression model in multivariate analyses. Logistic regression analysis was used to analyze risk factors. Values of $p < 0.05$ were considered statistically significant.

Results

Patient characteristics

Table 1 lists the clinicopathological values of 1313 patients with GC (503 LDG vs. 810 LTG). There were 981 men and 332 women, aged from 12 to 87 years (61.67 ± 11.1 years). According to the UICC/AJCC 8th gastric cancer staging, there were 194 patients (14.78%) in the cT2 stage, 392 patients (29.86%) in the cT3 stage, and 727 patients (55.36%) in the cT4 stage. BMI, ASA scores, PAS, histologic type, and postoperative complications were not significantly different between the LTG group and the LDG group, but in the LTG group, there were more patients who were elderly and male patients with larger tumor diameters and later tumor stages ($p < 0.05$). The average operation time of the LTG group was 192.51 ± 54.55 min, and the blood loss was approximately 79.54 ± 117.46 ml. The total number of lymph nodes retrieved in the LTG group and the LDG group was 34.62 ± 13.62 and 32.29 ± 11.48, respectively, and the difference was statistically significant ($p < 0.001$).

Extent of LN noncompliance

In all patients, the LN compliance rates of the LDG group and the LTG group were 49.10% and 40.20%, respectively, and the minor LN noncompliance rates were 39.20% and 39.70%, respectively. The major LN noncompliance rates were 11.70% and 20.10%, respectively. The difference was statistically significant ($p < 0.001$) (Table 2). Figure 1 shows that the major LN noncompliance rates in the LDG group ranged from 9.60 to 13.40% from 2007 to 2013, while the major LN noncompliance rates in the LTG group decreased year by year from the year of operation, from 29.80% in 2007 to 12.10% in 2013. The difference in the LN noncompliance rates between the LTG group and the LDG group was mainly caused by the LN noncompliance of the #4, #5, #6, and #12a LN stations (Supplementary Table 2).

Survival analysis

The Kaplan–Meier survival curve showed (Fig. 2) that there were statistically significant differences in OS among patients with LN compliance, minor LN noncompliance and major LN noncompliance in the whole group ($p < 0.001$). In particular, the OS of patients with major LN noncompliance was the worst, and this trend still existed in the LDG group and LTG group. Multivariate COX regression analysis of the LDG group showed that age, pN and LN noncompliance were independent prognostic factors for OS ($p < 0.05$). Multivariate COX regression analysis of the LTG group showed that age, tumor diameter, pT, pN, and LN noncompliance were independent prognostic factors for OS ($p < 0.05$) (Table 3).

Preoperative high-risk factors for major LN noncompliance in the LTG group

Table 4 lists the preoperative risk factors of major LN noncompliance in the LTG group by univariate and multivariate logistic analysis. Multivariate analysis showed that BMI ≥ 25 kg/m^2 and PAS were independent risk factors for major LN noncompliance in the LTG group ($p < 0.05$). Therefore, we defined patients with BMI ≥ 25 kg/m^2 or PAS as the LN noncompliance high-risk group and defined the remaining patients as the LN noncompliance nonhigh-risk group. In the LTG group, there was a statistically significant difference in the extent of LN noncompliance between the high-risk group and the nonhigh-risk group ($p = 0.003$). However, in the LDG group, there was no significant

Table 1 Clinicopathological characteristics

Variables	LDG ($n=503$)	LTG ($n=810$)	p
Age (year)	60.03 ± 11.58	62.68 ± 11.36	< 0.001
Sex [n(%)]			0.031
Female	144(28.6%)	188(23.2%)	
Male	359(71.4%)	622(76.8%)	
Smoking [n (%)]			0.525
No	359(71.4%)	592(73.1%)	
Yes	144(28.6%)	218(26.9%)	
BMI (kg/m^2)	22.17 ± 3.2	21.91 ± 2.98	0.139
Previous abdominal surgery [n (%)]			0.52
No	434(86.3%)	688(84.9%)	
Yes	69(13.7%)	122(15.1%)	
ASA score [n (%)]			0.253
I	277(55.1%)	483(59.6%)	
II	203(40.4%)	291(35.9%)	
III–IV	23(4.6%)	36(4.4%)	
Size (mm)	44.94 ± 19.76	60.98 ± 27.44	< 0.001
Tumor location [n (%)]			< 0.001
Lower	475(94.4%)	40(4.90%)	
Middle	12(2.4%)	265(32.7%)	
Upper	5(1%)	328(40.5%)	
Overlapping lesion	11(2.2%)	177(21.9%)	
Histologic type [n (%)]			0.376
Differentiated	190(37.8%)	286(35.3%)	
Undifferentiated	313(62.2%)	524(64.7%)	
cT stage [n (%)]			< 0.001
cT2	117(23.3%)	77(9.5%)	
cT3	158(31.4%)	234(28.9%)	
cT4	228(45.3%)	499(61.6%)	
cN stage [n (%)]			0.063
cN0	213(42.3%)	301(37.2%)	
cN +	290(57.7%)	509(62.8%)	
pT stage [n (%)]			< 0.001
T1	30(6%)	12(1.5%)	
T2	111(22.1%)	78(9.6%)	
T3	161(32%)	281(34.7%)	
T4a	185(36.8%)	390(48.1%)	
T4b	16(3.2%)	49(6%)	
pN stage [n (%)]			< 0.001
N0	140(27.8%)	160(19.8%)	
N1	74(14.7%)	116(14.3%)	
N2	115(22.9%)	146(18%)	
N3a	111(22.1%)	225(27.8%)	
N3b	63(12.5%)	163(20.1%)	
Lymphovascular invasion [n (%)]			0.082
No	348(69.2%)	522(64.4%)	
Yes	155(30.8%)	288(35.6%)	
Postoperative complication [n (%)]			0.381
None	427(84.9%)	688(84.9%)	
Grade I–II	62(12.3%)	89(11%)	
Grade III–IV	14(2.8%)	33(4.1%)	
Adjuvant chemotherapy [n (%)]			0.855

Table 1 (continued)

Variables	LDG ($n=503$)	LTG ($n=810$)	p
No	346(68.8%)	553(68.3%)	
Yes	157(31.2%)	257(31.7%)	
LN retrieved	32.29 ± 11.48	34.62 ± 13.62	0.001
Operation time (min)	173.64 ± 55.26	192.51 ± 54.55	< 0.001
Blood loss (ml)	72.56 ± 100.36	79.54 ± 117.46	0.286

Table 2 Extent of LN noncompliance

	All ($n=1313$)		LDG ($n=503$)		LTG ($n=810$)		p
Compliance	573	44%	247	49.10%	326	40.20%	< 0.001
Noncompliance							
Minor noncompliance[a]	518	39%	197	39.20%	321	39.70%	
1	323		120		203		
2	195		77		118		
Major noncompliance[a]	222	17%	59	11.70%	163	20.10%	
3	103		32		71		
4	40		5		35		
5	14		4		10		
6	7		1		6		
7	20		15		5		
8	35		2		33		
9	3		0		3		

Data are presented as n (%)

[a]Number of intended lymph node stations not removed

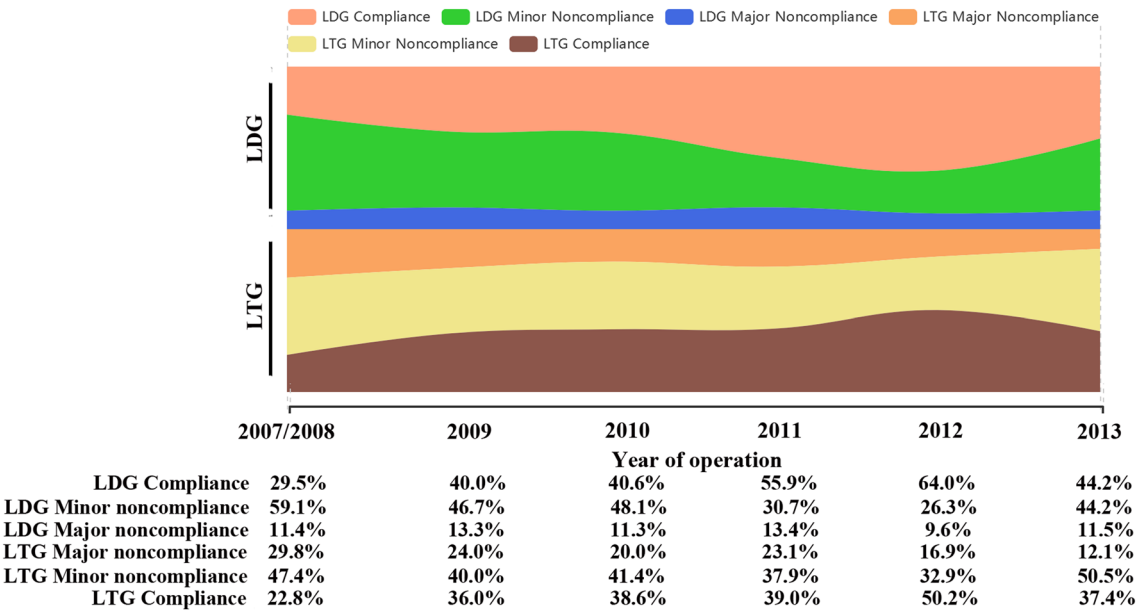


Fig. 1 Extent of LN noncompliance of LDG group and LTG group over time

difference in the extent of LN noncompliance between the high-risk group and the nonhigh-risk group ($p=0.456$) (Supplementary Table 1). In addition, we retrospectively analyzed the clinicopathological data of patients who underwent open and laparoscopic radical total gastrectomy in our center from 2007 to 2013 (Supplementary Table 3).

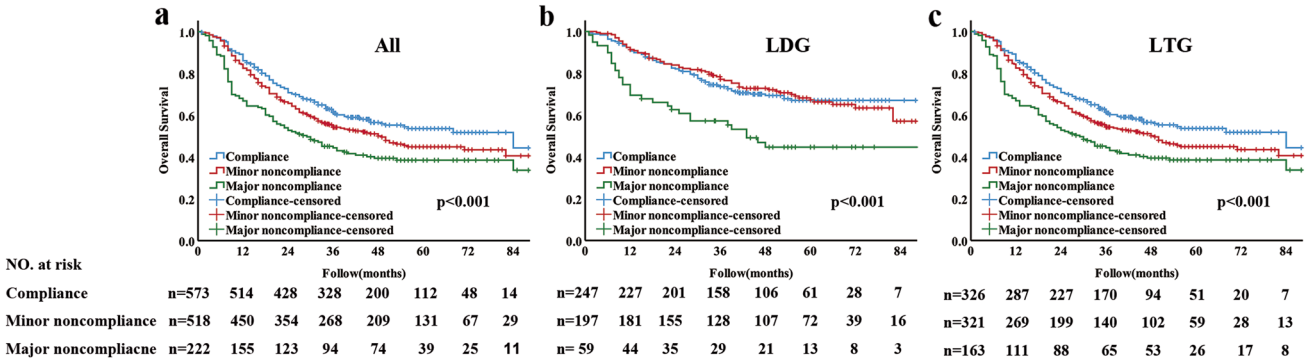


Fig. 2 Comparison of OS between compliance group, minor compliance and major compliance group in **a** all patients, **b** LDG, **c** LTG

Compared with open total gastrectomy, patients who underwent laparoscopic total gastrectomy had significantly higher rates of LN noncompliance, especially major LN noncompliance rate, in the subgroup of PAS(+) or BMI ≥ 25 kg/m^2(Supplementary Table 4).

Middle-risk LN noncompliance patients in the LTG group

In the nonhigh-risk group of LN noncompliance ($n = 964$), the difference in the extent of LN noncompliance between the LTG group and LDG group was still statistically significant ($p = 0.008$) (Supplementary Table 5), which was only caused by LN noncompliance at stations #5 and #6 (Supplementary Table 2). When the LN dissection was completely compliant at stations #5 and #6, there was no difference in the extent of LN noncompliance between the LTG group and LDG group ($p = 0.605$) (Supplementary Table 5). In the nonhigh-risk LN noncompliance patients of the LTG group, logistic regression analysis indicated that a tumor diameter of > 60 mm was the preoperative risk factor for station #5 LN noncompliance, and no preoperative risk factor for station #6 LN noncompliance was found (Supplementary Table 6). Patients with a tumor diameter > 60 mm were defined as the middle-risk LN noncompliance group, and the rest were defined as the low-risk group. The Kaplan–Meier survival curve showed that the overall survival rate of high/middle-risk LN noncompliance patients was significantly lower than that of the low-risk group ($p < 0.001$) (Fig. 3).

Discussion

Except for Japan and South Korea, more than 80% of GC patients in most countries worldwide are diagnosed with AGC. In the past few decades, the incidence of upper-middle GC has increased around the world [16]. Laparoscopic gastrectomy as a minimally invasive surgery is becoming increasingly popular due to advances in surgical techniques. With the accumulation of experience in laparoscopic gastrectomy for EGC, some GC treatment centers have extended the indications for laparoscopic gastrectomy from EGC to AGC. Several clinical studies have shown that surgeons can safely perform laparoscopic gastrectomy for patients with AGC. Compared with traditional open surgery, patients have less postoperative pain, faster recovery, shorter hospital stays and a better quality of life [23, 24]. Unfortunately, most of the multicenter randomized controlled clinical trials of laparoscopic gastrectomy are limited to the results of LDG, and few reports have suggested the technical feasibility and oncologic efficacy of LTG in the treatment of AGC. A large retrospective study of the oncologic efficacy of LTG in the treatment of AGC will be beneficial prior to the release of large multicenter randomized controlled clinical trials.

The Intergroup 0116 trial and other large randomized controlled clinical trials have confirmed that high-quality radical resection is the only way to cure GC, emphasizing the importance of high-quality D2 lymph node dissection [25, 26]. At the same time, DGCT, CRITICS, COACT1001 and other large multicenter randomized controlled clinical trials all used LN noncompliance as a quality control indicator for the oncologic efficacy of D2 radical surgery. Bunt AMG and Sasako M conducted a clinical study comparing the extent of LN dissection, in which, for the first time, LN noncompliance was used as an indicator of surgical quality control [22]. In this study, the LN noncompliance rate of the LTG group was significantly higher than that of the LDG group (specifically, the major LN noncompliance rate of the former was as high as 20.1%), but the major LN noncompliance rate decreased over time. This also confirmed that the oncology efficacy of LTG, a complex surgery, was still worth affirming with the accumulation of surgical experience. Our previous studies have confirmed that LN noncompliance is an independent risk factor for poor prognosis in AGC patients undergoing LTG [27, 28]. This study further confirmed that the OS of patients with minor LN noncompliance and major LN

Table 3 Univariate and multivariate survival analysis of patients by Cox proportional hazards model

Variables	LDG ($n=503$)					LTG ($n=810$)				
	Univariate	Multivariate model				Univariate	Multivariate model			
	p	HR	95% CI		*p*	*p*	HR	95% CI		*p*
Age (years)	0.004				0.016	0.006				< 0.001
<65	Ref	Ref				Ref	Ref			
≥ 65	0.004	1.5	1.078	2.085	0.016	0.006	1.651	1.346	2.025	< 0.001
Sex	0.591					0.288				
Female	Ref					Ref				
Male	0.591					0.288				
Smoking	0.191					0.591				
No	Ref					Ref				
Yes	0.191					0.591				
BMI (kg/m^2)	0.385					0.419				
< 25	Ref					Ref				
≥ 25	0.385					0.419				
Previous abdominal surgery	0.568					0.676				
No	Ref					Ref				
Yes	0.568					0.676				
Charlson score	0.099					0.12				
0	Ref					Ref				
1–2	0.036					0.411				
3–5	0.474					0.049				
ASA score	0.005				0.465	0.68				
I	Ref	Ref				Ref				
II	0.004	1.211	0.765	1.917	0.413	0.38				
III–IV	0.028	1.602	0.749	3.428	0.224	0.907				
Lymphovascular invasion	0.21					0.21				
No	Ref					Ref				
Yes	0.21					0.21				
Complications	0.559					0.559				
None	Ref					Ref				
I–II[a]	0.293					0.293				
III–IV[a]	0.751					0.751				
Adjuvant chemotherapy	0.411					0.411				
No	Ref					Ref				
Yes	0.411					0.411				
Tumor diameter (mm)	< 0.001				0.069	< 0.001				0.001
< 30	Ref	Ref				Ref	Ref			
30–60	< 0.001	1.34	0.896	2.004	0.154	< 0.001	1.594	1.254	2.026	< 0.001
> 60	0.962	0.408	0.14	1.19	0.101	< 0.001	1.418	1.023	1.966	0.036
Primary site	0.301					< 0.001				0.574
Lower	Ref					Ref	Ref			
Upper	0.134					0.663	1.103	0.691	1.763	0.681
Middle	0.262					0.067	0.937	0.586	1.5	0.787
Overlapping lesion	0.743					0.345	1.102	0.679	1.787	0.694
cT status	< 0.001				0.136	< 0.001				0.461
cT2	Ref	Ref				Ref	Ref			
cT3	0.025	1.637	0.697	3.845	0.258	0.025	1.316	0.608	2.849	0.486
cT4	< 0.001	2.123	0.987	4.565	0.054	< 0.001	0.994	0.493	2.002	0.986
cN status	< 0.001				0.567	< 0.001				0.6

Table 3 (continued)

Variables	LDG ($n=503$)					LTG ($n=810$)				
	Univariate	Multivariate model				Univariate	Multivariate model			
	p	HR	95% CI		*p*	*p*	HR	95% CI		*p*
cN0	Ref	Ref				Ref	Ref			
cN+	<0.001	1.111	0.774	1.595	0.567	<0.001	1.064	0.844	1.342	0.6
pT status	<0.001				0.571	<0.001				0.019
pT1	Ref	Ref				Ref	Ref			
pT2	0.667	0.677	0.25	1.834	0.443	0.708	2054	0	3E+21	0.72
pT3	0.379	0.607	0.219	1.679	0.336	0.686	1782	0	2E+21	0.725
pT4a	0.005	0.824	0.298	2.281	0.709	0.663	3150	0	4E+21	0.705
pT4b	0.017	1.195	0.343	4.163	0.78	0.645	4419	0	5E+21	0.693
pN status	<0.001				<0.001	<0.001				<0.001
pN0	Ref	Ref				Ref	Ref			
pN1	0.15	1.565	0.78	3.139	0.208	0.203	1.122	0.689	1.828	0.644
pN2	0.005	1.914	1.016	3.606	0.045	<0.001	1.804	1.162	2.802	0.009
pN3a	<0.001	3.893	2.114	7.169	<0.001	<0.001	3.189	2.111	4.816	<0.001
pN3b	<0.001	7.291	3.797	13.998	<0.001	<0.001	4.372	2.809	6.804	<0.001
Grade	0.018				0.827	0.018				0.718
Differentiated	Ref	Ref				Ref	Ref			
Undifferentiated	0.018	1.04	0.733	1.474	0.827	0.018	0.958	0.76	1.208	0.718
LN noncompliance	0.001				<0.001	<0.001				<0.001
Compliance	Ref	Ref				Ref	Ref			
Minor noncompliance	0.933	1.166	0.818	1.664	0.396	0.051	1.433	1.135	1.809	0.003
Major noncompliance	<0.001	2.768	1.779	4.307	<0.001	<0.001	2.524	1.921	3.314	<0.001

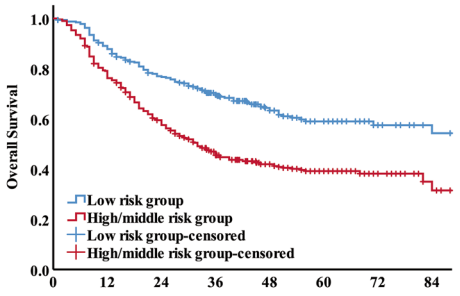
noncompliance was significantly worse than that of patients without LN noncompliance, especially the patients with major LN noncompliance had the worst OS. Therefore, for patients planning to undergo LTG surgery, identifying high-risk groups with major LN noncompliance before surgery is of great importance. Logistic regression analysis showed that the independent risk factors for major LN noncompliance in the LTG group were BMI ≥ 25 kg/m^2 and PAS ($p<0.05$). In recent years, a number of studies have reported that high BMI or increased intra-abdominal fat would lead directly to a reduced number of LNs detected [29–33]. High BMI patients often have massive adipose tissue accumulation in the abdomen, and it is often difficult to distinguish the relationship between pancreatic tissue, fat tissue and LNs during surgery, which makes lymph node dissection more difficult. Moreover, in the process of dissection, there is more exudation of tissue and blood, which affects the exposure of LNs and the resection plane under laparoscopy for the surgeon and assistant. With the popularity of laparoscopic surgery, many patients who have undergone abdominal surgery are also candidates for laparoscopic gastrectomy. A number of retrospective studies have found no difference in the short-term efficacy of laparoscopic-assisted gastrectomy in PAS and non-PAS patients [34–38]. In these studies, however, the included population was limited to a history of upper abdominal surgery. Yamashita first studied the feasibility of LG in all types of abdominal surgery, and the results showed that the rate of conversion to open laparotomy was higher in patients with a previous history of lower gastrointestinal surgery or patients requiring total gastrectomy than in the control group [39]. Since LTG surgery requires a wider scope of lymph node dissection, the adhesion of the previous surgical area undoubtedly increases the difficulty of lymph node dissection and the incidence of LN noncompliance.

In this study, we chose patients for LDG as a reference to assess the surgical results of LTG in the same surgical period because a number of large clinical trials have confirmed the curative effect and technical feasibility of LDG for AGC, and many surgeons have a wealth of experience with LDG, which may provide a theoretical basis for LTG for the treatment of AGC. The LN noncompliance rate, a relatively comparable surgical quality control indicator, was used as the evaluation criterion, and LDG was taken as a reference to analyze the surgical indications of LTG, which is helpful for guiding gastric cancer surgeons in mastering strictly therapeutic indications of LTG for the treatment of advanced upper and middle gastric cancer and ultimately benefiting the survival of patients. Except for the high-risk group with major LN noncompliance, the LN noncompliance rate of the LTG group was still higher than that of the LDG group

Table 4 Univariate and multivariate logistic regression analysis of risk factors for major noncompliance after LTG

Variables	Univariate model				Multivariate model			
	OR	95% CI		*p*	OR	95% CI		*p*
Age (year)				0.413				
< 65	Ref							
≥ 65	0.865	0.61	1.225	0.413				
Sex				0.704				
Female	Ref							
Male	1.083	0.717	1.636	0.704				
Smoking				0.336				
No	Ref							
Yes	0.822	0.552	1.225	0.336				
BMI (kg/m^2)				0.048				0.049
< 25	Ref				Ref			
≥ 25	1.602	1.005	2.555	0.048	1.589	1.0055	2.538	0.049
Previous abdominal surgery				0.04				0.044
No	Ref				Ref			
Yes	1.592	1.022	2.478	0.04	1.58	1.013	2.463	0.044
ASA score				0.343				
I	Ref							
II	1.299	0.908	1.858	0.153				
III–IV	1.265	0.558	2.868	0.574				
Charlson score				0.076				
0	Ref							
1–2	1.423	0.989	2.049	0.058				
3–5	2.268	0.758	6.781	0.143				
cT status				0.203				
cT2	Ref							
cT3	0.706	0.391	1.277	0.25				
cT4	0.611	0.352	1.059	0.079				
cN status				0.422				
cN0	Ref							
cN	0.866	0.609	1.231	0.422				
Tumor diameter (mm)				0.078				
< 30	Ref							
30–60	0.627	0.417	0.944	0.025				
> 60	0.953	0.567	1.604	0.857				
Grade				0.64				
Differentiated	Ref							
Undifferentiated	1.09	0.759	1.567	0.64				

($p < 0.001$). Further analysis of the LN noncompliance rate of each LN station in LDG and LTG showed that the LN noncompliance rate of stations #5 and #6 in the LTG group was significantly higher than that in the LDG group. If LN dissections for stations #5 and #6 were completely compliant, the difference in the LN noncompliance rate between the LTG group and LDG group disappeared, which further confirmed that the high LN noncompliance rate in the LTG group originated from stations #5 and #6 LN noncompliance. Compared with the LDG group, patients in the LTG group had larger tumor diameters, later tumor stages and other adverse factors, which affected lymph node dissection, especially in the lymph node dissection of the superior and inferior regions of the pylorus. Logistic regression analysis showed that a tumor diameter of > 60 mm was a preoperative risk factor for #5 LN noncompliance. We believe that in the process of laparoscopic radical gastrectomy to dissect #5 LN, a larger tumor in the middle and upper part of the stomach may lead to more limited space in the narrow superior pyloric region, affecting the exposure of lymphatic adipose tissue around the right gastric vascular region and surrounding areas for the surgeon and his or her assistants,



NO. at risk								
Low risk group	n=321	284	239	184	126	69	37	18
High/middle risk group	n=489	383	275	191	123	67	28	10

Fig. 3 Comparison of OS between LN noncompliance low-risk group and high/middle group

which may lead to the omission of lymph node dissection in this surgical field. Therefore, patients with a tumor diameter > 60 mm in the advanced stage of upper-middle gastric cancer represent the middle-risk group with LN noncompliance in LTG surgery, which should be carefully selected. However, similar to other retrospective studies, our research also has the following limitations. First, this is a single-center retrospective study, some potential biases cannot be avoided, and multicenter prospective studies are still needed. Second, with the technological innovation of laparoscopic instruments and the accumulation of laparoscopic operation experience, our center has performed laparoscopic surgery on more and more gastric cancer patients, far more than those who underwent open surgery [28, 40–42]. Therefore, it is difficult to conduct a retrospective comparison study on the LN noncompliance rate between open and laparoscopic total gastrectomy for large number of cases in the same period. We compared the LN noncompliance data of patients who underwent open and laparoscopic radical total gastrectomy in our center from 2007 to 2013. Due to the limited number of patients with open GC surgery, deeper stratification analysis is not possible, we expect to further explore the indications of LTG by directly comparing the rate of LN noncompliance between the OTG group and the LTG group in the future through the high-volume multicenter perspective clinical trials in the same period.

In conclusion, LN noncompliance is an independent prognostic factor for poor prognosis in patients after LTG. Based on this finding, patients with a BMI ≥ 25 kg/m^2, history of previous abdominal surgery and tumor diameter > 60 mm in the advanced stage of upper-middle gastric cancer represent high/middle-risk groups with LN noncompliance in LTG surgery, which should be carefully selected.

Author contributions QYC, GTL, CMH conceived the study, analyzed the data, and drafted the manuscript, CHZ and QZ helped critically revise the manuscript for important intellectual content. PL, JWX, JBW, JXL, JL and LLC helped collect data and design the study.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent or substitute for it was obtained from all patients for being included in the study.

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