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ORIGINAL ARTICLE

Lymph Node Noncompliance Affects the Long-Term Prognosis of Patients with Gastric Cancer after Laparoscopic Total Gastrectomy

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Abstract

Background Our study investigated the effect of lymph node (LN) noncompliance on the long-term prognosis of patients after laparoscopic total gastrectomy (LTG) and explored the risk factors of LN noncompliance.

Methods The clinicopathological data of gastric cancer (GC) patients who underwent LTG with D2 lymphadenectomy from June 2007 to December 2013 were prospectively collected and retrospectively analyzed. The effects of LN noncompliance on the long-term prognosis of patients with GC after LTG were explored.

Results The overall LN noncompliance rate was 51.9%. The survival rate of patients after LTG with LN compliance was significantly superior to that of patients with LN noncompliance ($p = 0.013$). The stratified analysis of TNM stage indicated that there was no difference between the OS of stage I patients with LN compliance and those with LN noncompliance; OS of stage II/III patients with LN compliance was significantly better than that of those with LN noncompliance. Cox regression analyses showed that LN noncompliance was an independent risk factor for OS. Logistic regression analysis showed that high BMI ($\geq 25\ kg/m^2$) was an independent risk factor for preoperative prediction of LN noncompliance in cStage II/III patients. Patients with a high BMI were more likely to have LN noncompliance during surgery, especially during the dissections of #6, #8a, and #12a LN stations.

Conclusions LN noncompliance was an independent risk factor for poor prognosis in patients with advanced gastric cancer (AGC) after LTG. Patients with high BMI were more likely to have LN noncompliance, especially during the dissections of #6, #8a, and #12a LN stations. LN tracing was recommended for these patients to reduce the rate of LN noncompliance.

KEY WORDS gastric carcinoma · laparoscopic total gastrectomy · D2 lymphadenectomy · LN noncompliance · prognosis

BACKGROUND

Gastric cancer (GC) ranks second in cancer mortality worldwide.[1] Lymph node (LN) metastasis is the main pattern of gastric cancer metastasis.[2] Lymphadenectomy is the key to gastric cancer surgery, and adequate lymphadenectomy is helpful for accurate postoperative pathological staging and improving the prognosis of patients with GC.[3, 4] Since Japanese scholars proposed standardized guidelines for GC surgery, the D2 lymphadenectomy in patients with advanced gastric cancer (AGC) has become the consensus approach in Asian countries.[5] The 15-year follow-up results of Dutch Gastric Cancer Trial (DGCT) based on a Western population also indicated that the D2 lymphadenectomy group had a lower local recurrence rate and tumor-related mortality than the D1 group, which laid a solid foundation for the recommendation of D2 lymphadenectomy as the standard operation for GC in the European guidelines.[6, 7] In 1994, Kitano first used laparoscopic surgery for early gastric cancer (EGC).[8] With the rapid development of laparoscopic techniques and instruments, the advantages of minimally invasive surgery make

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this approach increasingly accepted as the standard of care in many hospitals globally.[9–11] However, D2 complete nodal dissection in laparoscopic surgery, especially in LTG, is known to be a technically challenging surgical procedure, and surgical quality varies among surgeons. Therefore, efforts to standardize the efficient completion of D2 extended lymphadenectomy using laparoscopy to achieve radical tumor removal have received increasing attention in recent years. LN noncompliance has been proposed as a way to assess the quality of D2 lymphadenectomy. In previous studies, LN noncompliance was used as the quality measure for D2 radical resection during open gastrectomy.[12–17] A phase II multicenter trial named COACT1001 used LN noncompliance to evaluate the feasibility of laparoscopic distal gastrectomy (LDG),[18] but there were no reports describing LN noncompliance in LTG. To evaluate the status of LN noncompliance in LTG in a way that enhances patient survival, high-volume, multicenter, prospective, randomized controlled trials are eventually needed. Retrospective research could provide reference values. Therefore, the purpose of this study was to explore the effect of LN noncompliance on the long-term prognosis of patients after LTG and to explore the risk factors of LN noncompliance through a high-volume retrospective study to guide both clinical decision-making and outcome research.

PATIENTS AND METHODS

Patients

This study retrospectively analyzed a prospective database containing 2401 patients with GC who had undergone D2 radical gastrectomy by the same group of surgeons from June 2007 to December 2013 at Fujian Medical University Union Hospital in China. The following inclusion criteria were used: (1) preoperative endoscopic biopsy-proven GC, (2) D2 lymphadenectomy, and (3) no distant metastases or adjacent organ invasion (pancreas, spleen, liver, colon, etc.) prior to surgery. Patients were excluded due to a preoperative diagnosis of T4b or distant metastasis, exploratory or palliative surgery, preoperative chemotherapy, combined organ resection, histological identification of a tumor type other than adenocarcinoma, incomplete histopathological data, or remnant GC. The current study excluded 1058 patients with distal gastrectomy and 395 patients with open total gastrectomy and included 948 patients with laparoscopic total gastrectomy. All patients signed informed consent forms prior to surgery. This retrospective study was approved by the ethics committee of Fujian Medical University Union Hospital.

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. We used CT scans, EUS, and the 7th edition of the International Union Against Cancer (UICC) classification system to assess the clinical and pathologic stages. 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).[2, 19] 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), $\geq$ 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.

Surgical Procedures

The following sequence of lymphadenectomies during LTG was performed: No. 6 → Nos. 7, 9, 11p → Nos. 8a, 12a, 5 → No. 1 → No. 4sb → Nos. 10, 11d → No. 2. For details, please see the indicated references.[20–22]

Postoperative Pathological Examination

Each station of lymph nodes was immediately dissected according to the location of blood vessel clips retained in the specimens in the operation room after the specimens were removed by surgeons. Lymph nodes were divided and sorted into stations according to the protocol for D2 lymphadenectomy in the JGCA. All lymph node specimens were assembled and immediately sent to the department of pathology for examination by at least two experienced pathologists through palpation and microscopy. If more than one station of lymph nodes were not detected, this specimen was considered lymph node noncompliance. All pathological examinations were performed in a standard manner.

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 to 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. 20.0 for Windows (SPSS Inc., Chicago, IL, USA). All continuous variables are presented as their 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. Stepwise backward variable removal was applied to the multivariate model to identify the most accurate and parsimonious set of predictors.[23] Values of $p < 0.05$ were considered statistically significant.

RESULTS

Patient Characteristics and LN Noncompliance

Of the 948 patients with gastric cancer who underwent LTG, 492 (51.9%) had LN noncompliance. LN noncompliance decreased over time, starting at 73.3% in 2007 and reducing to 31.6% in 2013 (Supplementary Fig. 1). Figure 1 shows the status of LN dissection in all stations during the procedure of LTG. Meanwhile, the rate of LN noncompliance in #10, #5, and #12a is high at 68.25%, 50.21%, and 33.44%, respectively, and the rate of LN noncompliance in #3, #4, and #7 is low at 4.22%, 9.39%, and 9.49%. Table 1 shows the clinicopathological data of patients, including 80.3% of patients with cStage II/III and 82.6% of patients with pStage II/III. Age, BMI, ASA score, tumor size, tumor location, macroscopic type, TNM stage, and the total number of retrieved LNs were significantly correlated with LN noncompliance (all p values were < 0.05).

OS Analysis of all Patients

The last follow-up of all patients was in January 2017. The overall follow-up rate was 90.3%, and the 5-year OS of all patients was 49%. The Kaplan–Meier curve of all patients revealed that OS was significantly higher in LN compliant patients than in LN noncompliant patients ($P = 0.013$), of which 5-year OS was 53 and 45%, respectively (Fig. 2). The Kaplan–Meier survival curve suggested that among the patients with more than 15 LNs retrieved, the prognosis of patients with LN noncompliance were still worse than those with LN compliance and the difference was statistically significant ($p = 0.045$) (Supplementary Fig. 2).

Stratification analysis of cTNM stage showed that for cStage I patients, the OS of LN compliant patients was similar to that of LN noncompliant patients ($p = 0.484$). Regarding cStage II patients, the OS of LN compliant patients was slightly, but not significantly, higher than that of LN noncompliant patients ($p = 0.138$). However, compared with LN noncompliant patients, LN compliant patients showed a significant OS benefit in the cStage III group ($p < 0.001$). The OS of LN compliant patients with cT3 and cT4 was significantly better than that of LN noncompliant patients (p values were 0.008 and 0.001, respectively). The OS of LN compliant patients with cN+ was superior to that of LN noncompliant patients ($p = 0.003$), while the OS of LN compliant patients with cT1–2 and cN0 was not significantly different from that of LN noncompliant patients (all p values were > 0.05) (Fig. 3).

According to pTNM stage stratification analysis, the OS of pStage I LN compliant patients was similar to that of LN noncompliant patients ($p = 0.890$), while the survival of stage II and stage III LN compliant patients was significantly superior to that of LN noncompliant patients (all p values were < 0.05). The OS of pT4a or pN2-3b patients with LN compliance was significantly better than that of patients with the same staging and LN noncompliance (all p values were < 0.01), while the survival of patients with pT1–3 and pN0–1 was not affected by the status of LN dissection (all p values were < 0.05) (Supplementary Fig. 3). The results of the forest plot also indicated that the OS of stage II/III patients with LN compliance was significantly better than that of stage II/III patients with LN noncompliance (Supplementary Fig. 4).

Univariate and Multivariate Cox Regression Analysis

Univariate Cox regression analysis of all patients showed that age, tumor size, tumor location, macroscopic type, histological type, staging (cT, cN, pT, and pN classification), lymphovascular invasion, and LN noncompliance affected OS (all p values were < 0.05). Further, multivariate Cox regression analysis showed that age, macroscopic type, pT classification, pN classification, and LN noncompliance were independent prognostic factors of OS (all p values were < 0.05) (Table 2).

Preoperative Predictors of LN Noncompliance in cStage II/III Patients

A total of 761 patients with cStage II/III accounted for 80.3% of all patients. Regarding cStage II/III patients, univariate logistic regression analysis showed that high BMI and ASA score > 1 were risk factors for LN noncompliance (all p values were < 0.05). Multivariate logistic regression analysis indicated that high BMI was the only significant parameter affecting LN noncompliance ($p = 0.01$) (Table 3).

Subgroup Analysis of BMI and LN Stations in cStage II/III Patients

BMI subgroup analysis indicated that increasing BMI increased the rate of LN noncompliance. When BMI > 30 kg/

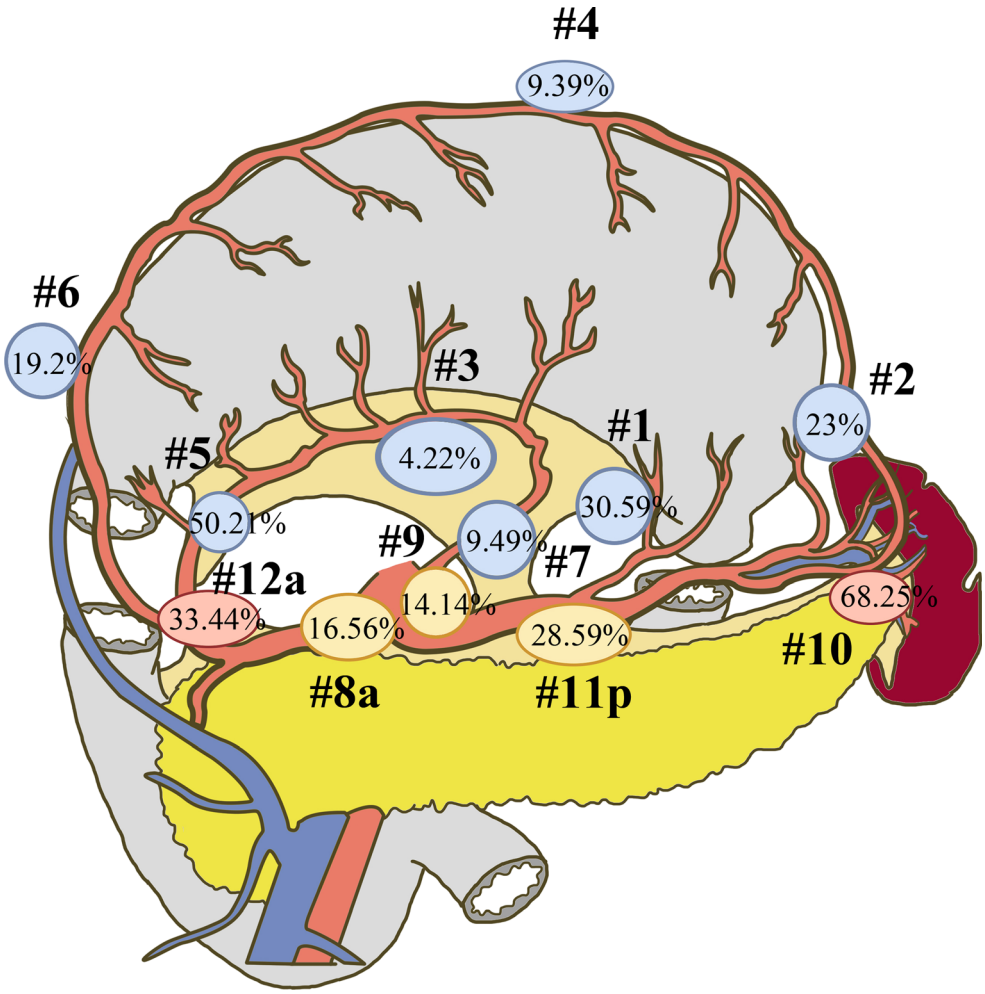

Fig. 1 The rate of LN noncompliance in all stations during LTG.

m^2, the rate of LN noncompliance was as high as 86%. The LN noncompliance rate of various LN stations dissected in the high BMI subgroup was more serious than that in the low-BMI subgroup, especially at #6, #8a, and #12a LN stations. In the high-BMI subgroup, the LN noncompliance rates of #6, #8a, and #12a stations were 83%, 83%, and 70%, respectively. In the low-BMI subgroup, the LN noncompliance rates of these three stations were 74%, 75% and 59%, respectively (Fig. 4).

DISCUSSION

As a quantitative index, the LN noncompliance rate has been gradually recognized and applied by multiple RCTs to evaluate the quality of intraoperative lymphadenectomy for GC.[14, 18] The clinical status of the patient, the extent of tumor growth, the operating strategy preferred by the surgeon, and the intensity of the scrutiny by the pathologist in assessing the resection specimens can affect LN noncompliance, which explains why some studies reported that the LN noncompliance rate in radical gastrectomy was different, ranging between 43.2 and 84%.[12–14, 16, 18] However, there is no study that reports the LN noncompliance rate in LTG. We report, for the first time, the LN noncompliance rate in this complex procedure and elucidate its effect on prognosis. In our study, LN noncompliance in LTG was 51.9% and decreased over time due to the accumulation of surgical experience. In the present study, a group of surgeons conducted LN sorting in the operating room, and two or more experienced, senior pathologists conducted palpation examinations of all LNs from the specimens to avoid having the LN assessment process influence LN noncompliance. Therefore, we believe that the main cause of LN noncompliance in this study is the failed intraoperative dissection of LNs at specific stations. The status of LN noncompliance at each station was further analyzed in this study, and the rate of LN noncompliance at #10, #5, and #12a LN stations was relatively high. Oktar Asoglu reported that the LN noncompliance rate at the #5 LN station during D2 lymphadenectomy was the highest, reaching 53%,[24] and the LN noncompliance rate at the #5 LN station was 50.21% in our study. In the LN stations with normal perigastric drainage, there is a considerable difference in the number of LNs per station, and sometimes, small stations (#2, #5, and #10) may not

Table 1 Clinicopathological Characteristics

Characteristic	All patients ($n = 948$)	LN compliance ($n = 456$)	LN noncompliance ($n = 492$)	p
Age (yr), *n* (%)				0.032
< 65	542	277 (60.7)	265 (53.9)	
≥ 65	406	179 (39.3)	227 (46.1)	
Sex, *n* (%)				0.924
Female	205	98 (21.5)	107 (21.7)	
Male	743	358 (78.5)	385 (78.3)	
Smoking, *n* (%)				0.427
No	687	325 (71.3)	362 (73.6)	
Yes	261	131 (28.7)	130 (26.4)	
BMI (kg/m2), *n* (%)				0.005
< 25	822	410 (89.9)	412 (83.7)	
≥ 25	126	46 (10.1)	80 (16.3)	
Previous abdominal surgery, *n* (%)				0.157
No	805	395 (86.6)	410 (83.3)	
Yes	143	61 (13.4)	82 (16.7)	
ASA score, *n* (%)				0.005
I	574	297 (65.1)	277 (56.3)	
II–III	374	159 (34.9)	215 (43.7)	
Size (mm), *n* (%)				0.002
< 30	238	94 (20.6)	144 (29.3)	
≥ 30	710	362 (79.4)	348 (70.7)	
Tumor location, *n* (%)				0.015
Lower	49	21 (4.6)	28 (5.7)	
Middle	399	171 (37.5)	228 (46.3)	
Upper	308	157 (34.4)	151 (30.7)	
Overlapping lesion	192	107 (23.5)	85 (17.3)	
Macroscopic type, *n* (%)				0.022
EGC	137	51 (11.2)	86 (17.5)	
AGC, Borrmann 1–3	650	326 (71.5)	324 (65.9)	
AGC, Borrmann 4	161	79 (17.3)	82 (16.6)	
Histologic type, *n* (%)				0.338
Differentiated	383	177 (38.8)	206 (41.9)	
Undifferentiated	565	279 (61.2)	286 (58.1)	
cT stage, *n* (%)				0.088
cT1	138	55 (12.1)	83 (16.9)	
cT2	77	32 (7.0)	45 (9.1)	
cT3	234	118 (25.9)	116 (23.6)	
cT4	499	251 (55.0)	248 (50.4)	
cN stage, *n* (%)				0.647
cN0	417	197 (43.2)	220 (44.7)	
cN+	531	259 (56.8)	272 (55.3)	
cTNM stage, *n* (%)				0.029
I	187	75 (16.4)	112 (22.8)	
II	125	68 (14.9)	57 (11.6)	
III	636	313 (68.7)	323 (65.6)	
pT stage, *n* (%)				0.008
T1	129	45 (9.9)	84 (17.1)	
T2	82	38 (8.3)	44 (8.9)	
T3	291	146 (32.0)	145 (29.5)	
T4a	446	227 (49.8)	219 (44.5)	
pN stage, *n* (%)				< 0.001
N0	268	113 (24.8)	155 (31.5)	

Table 1 (continued)

Characteristic	All patients ($n = 948$)	LN compliance ($n = 456$)	LN noncompliance ($n = 492$)	p
N1	128	54 (11.8)	74 (15.0)	
N2	154	79 (17.4)	75 (15.2)	
N3a	230	105 (23.0)	125 (25.5)	
N3b	168	105 (23.0)	63 (12.8)	
pTNM stage, *n* (%)				0.002
I	165	59 (12.9)	106 (21.5)	
II	203	101 (22.2)	102 (20.7)	
III	580	296 (64.9)	284 (57.8)	
Lymphovascular invasion, *n* (%)				0.101
No	642	297 (65.1)	345 (70.1)	
Yes	306	159 (34.9)	147 (29.9)	
Total retrieved LNs	34.18 ± 13.77	40.32 ± 13.14	28.49 ± 11.73	< 0.001
Postoperative complication, *n* (%)				0.802
None	799	388 (85.1)	411 (83.5)	
Grade I–II	108	49 (10.7)	59 (12.0)	
Grade III–IV	41	19 (4.2)	22 (4.5)	
Adjuvant chemotherapy, *n* (%)				0.074
No	679	339 (74.3)	340 (69.1)	
Yes	269	117 (25.7)	152 (30.9)	

contain any LNs at all, which indicates biological variability.[25, 26] Therefore, even if the surgeon dissected all the lymph nodes in all stations according to the standard of D2 radical gastrectomy for gastric cancer, there may be no lymph nodes in the dissected specimens. Taking into account this biological variation, the DGCT study considered that lymph node dissection for gastric cancer allowed one station of lymph nodes to be absent, but dissection was ruled out to be noncompliant if more than one station of lymph nodes were not detected. The definition of lymph node noncompliance in this study conforms to this standard. This biological variation may also be reported as another important cause of LN noncompliance. Although the results of prior studies indicate that inadequate LN dissection may potentially affect the prognosis of GC patients,[27, 28] studies on the relationship between LN noncompliance and the prognosis of patients after GC surgery are scarce. The current study hypothesized that LN noncompliance was closely related to the long-term prognosis of GC patients after surgery. Compared with LN compliant patients, LN noncompliant patients exhibited poorer survival after LTG for GC. TNM stage stratification analysis showed that the OS of stage I LN compliant patients was consistent with that of LN noncompliant patients, while the survival of stage II and stage III LN compliant patients was significantly better than that of LN noncompliant patients, which was similar to the forest plot results for OS. In theory, based on a lower risk of LN metastases in EGC, LN without metastasis may be left in the patient, so LN noncompliance does not really affect the survival of patients. However, advanced gastric cancer (AGC) has grown into a systemic disease, and the risk of LN metastasis is greatly increased in AGC. Therefore, LN noncompliance, especially when it occurs in these patient groups with high metastasis risk, can significantly influence the survival of patients. This is consistent with the results of this study.

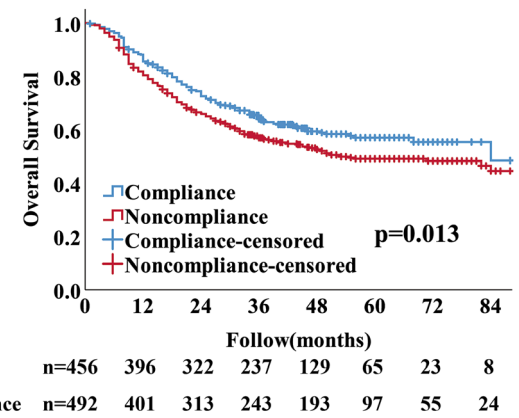

Fig. 2 Comparison of overall long-term survival rate between LN compliance group and LN noncompliance group

As the prognosis of patients with AGC with LN noncompliance after LTG is significantly poor, it is of great significance to identify preoperative risk factors for these patients. Obviously, compared with the postoperative pathological stage, the study of risk factors for patients with preoperative cStage II/III has more clinical significance. Logistic regression analysis of cStage II/III patients showed that high BMI was the only independent risk factor for LN noncompliance, which was consistent with prior efforts.[24] Previous studies reported

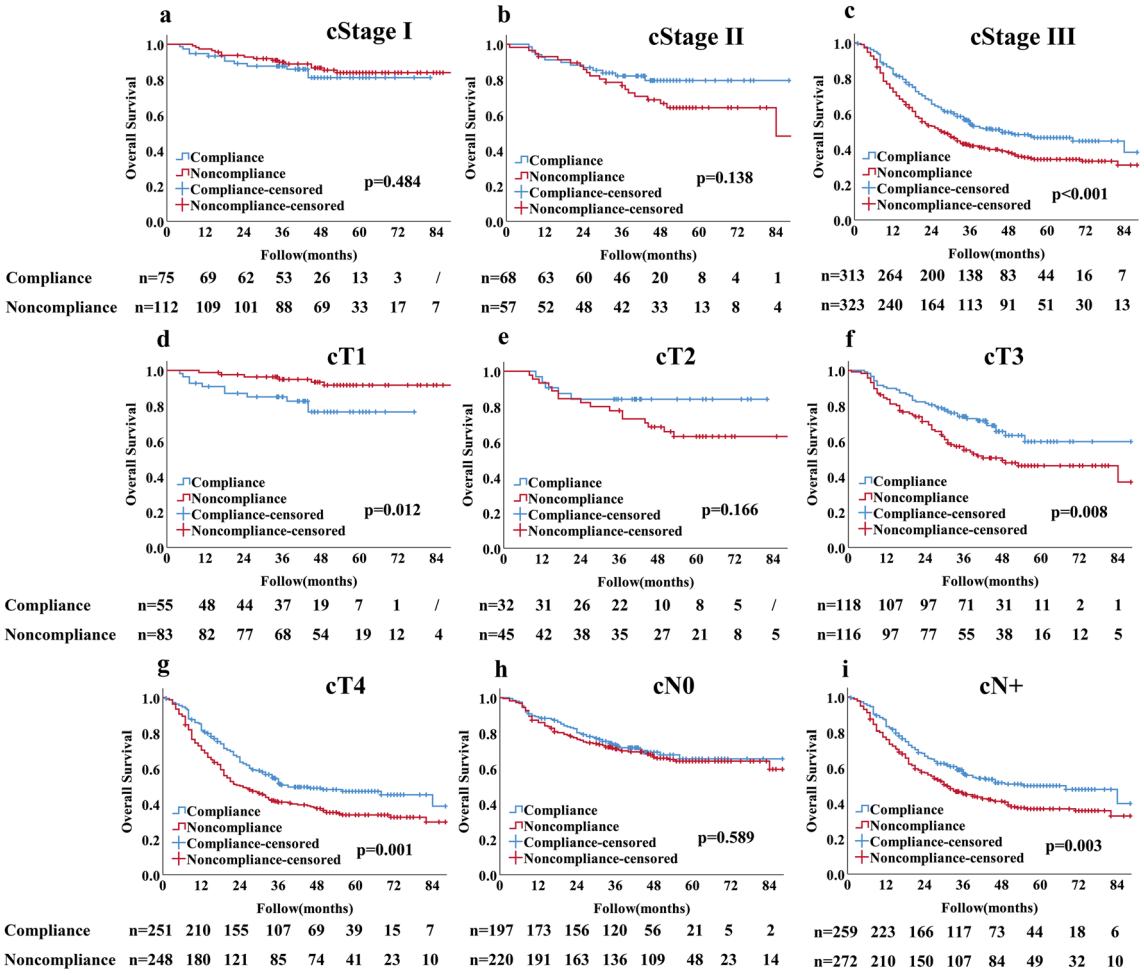

Fig. 3 Comparison of overall long-term survival rate between LN compliance group and LN noncompliance group according to cStage

that parameters affecting surgical difficulty, such as gender, age, and abdominal surgery history, did not significantly affect LN noncompliance.[14, 24] To further explore the effect of BMI on the rate of LN noncompliance at each station, it was found that the LN noncompliance rates of #6, #8a, and #12a LN stations in patients with high BMI were significantly higher than those with low BMI. As we have mentioned earlier in this paper, with patients in the overall group, including patients with gastric cancer in cStages I–III, the noncompliance of LNs in each station was analyzed, and it was found that the noncompliance rates of LNs in stations #10, #5, and #12a were relatively high. However, further analysis of patients with cStages II–III advanced gastric cancer found that the patients with BMI ≥ 25 kg/m^2 had the highest noncompliance rate in station #6, #8a, and #12a. Differences in the study population led to differences in lymph node stations with high noncompliance rates. 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 LN 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 to the surgeon and assistant. In particular, high-BMI patients have very deep LNs in specific areas, such as the celiac trunk and around the head of the pancreas, further increasing the difficulty of accurate localization and dissection. Reducing the noncompliance rate of LN dissection in such patients may become the focus of further research. Previous studies have shown that LN tracing techniques, such as Indocyanine Green (ICG) and nanocarbon tracers, can improve the detection rate of regional LNs in gastric cancer, breast cancer, prostate cancer, and other cancers.[34–39] Therefore, we think that, in these high-risk LN noncompliant patients, using the LN tracer technique intraoperatively may be helpful to dissect LNs and blood vessels and identify LNs within fat tissue, thus finding the right LN dissection plane and improving the rate of LNs retrieved. Surgeons should use a tracer to pay more attention to the #6, #8a, and #12a LN stations to reduce the LN dissection

Table 2 Univariate and Multivariate Cox Regression Model for Overall Survival

Variable	Univariate model	Multivariate model			
	p	HR	95%CI		*p*
Age	0.003				< 0.001
< 65	Ref	Ref			
≥ 65	0.003	1.591	1.302	1.944	< 0.001
Sex	0.152				
Female	Ref				
Male	0.152				
Smoking	0.545				
No	Ref				
Yes	0.545				
BMI (kg/m2)	0.150				
< 25	Ref				
≥ 25	0.150				
Previous abdominal surgery	0.503				
No	Ref				
Yes	0.503				
ASA score	0.366				
I	Ref				
II–III	0.366				
Size	< 0.001				0.957
< 3	Ref	Ref			
≥ 3	< 0.001	1.009	0.718	1.418	0.957
Tumor location	< 0.001				0.19
Lower	Ref	Ref			
Middle	0.089	0.818	0.519	1.289	0.386
Upper	0.755	0.982	0.624	1.548	0.939
Overlapping lesion	0.147	1.088	0.683	1.732	0.723
Macroscopic type	< 0.001				0.036
EGC	Ref	Ref			
AGC, Borrmann 1–3	< 0.001	0.302	0.11	0.834	0.021
AGC, Borrmann 4	< 0.001	0.35	0.124	0.986	0.047
Histologic type	< 0.001				0.774
Differentiated	Ref	Ref			
Undifferentiated	< 0.001	0.967	0.771	1.214	0.774
cT stage	< 0.001				0.393
cT1	Ref	Ref			
cT2	0.013	0.606	0.269	1.366	0.227
cT3	< 0.001	0.862	0.447	1.662	0.657
cT4	< 0.001	0.661	0.363	1.203	0.175
cN stage	< 0.001				0.573
cN0	Ref	Ref			
cN+	< 0.001	1.068	0.849	1.344	0.573
pT stage	< 0.001				< 0.001
T1	Ref	Ref			
T2	< 0.001	23.957	5.634	101.874	< 0.001
T3	< 0.001	22.7	5.479	94.041	< 0.001
T4a	< 0.001	40.989	10.009	167.851	< 0.001
pN stage	< 0.001				< 0.001
N0	Ref	Ref			
N1	0.007	1.085	0.674	1.749	0.737
N2	< 0.001	1.849	1.201	2.845	0.005
N3a	< 0.001	3.217	2.128	4.863	< 0.001
N3b	< 0.001	4.803	3.083	7.483	< 0.001
Lymphovascular invasion	< 0.001				0.988
No	Ref	Ref			
Yes	< 0.001	1.002	0.809	1.239	0.988
Postoperative complication	0.924				
None	Ref				
Grades I–II	0.97				
Grades III–IV	0.692				
Adjuvant chemotherapy	0.128				
No	Ref				
Yes	0.128				
LN noncompliance	0.014				< 0.001
No	Ref	Ref			
Yes	0.014	1.705	1.394	2.086	< 0.001

Table 3 Univariate and Multivariate Analysis of Risk Factors for LN Noncompliance in cStage II/III Patients

Variable	Univariate model	Multivariate model			
	p	OR	95%CI		*p*
Age	0.032				0.214
< 65		Ref			
≥ 65	0.032	1.192	0.904	1.573	0.214
Sex	0.924				
Female					
Male	0.924				
Smoking	0.427				
No					
Yes	0.427				
BMI (kg/m2)	0.006				0.01
< 25		Ref			
≥ 25	0.006	1.679	1.129	2.496	0.01
Previous abdominal surgery	0.158				
No					
Yes	0.158				
ASA score	0.006				0.975
I		Ref			
II–III	0.006	0.992	0.611	1.612	0.975
cT	0.089				
cT1					
cT2	0.807				
cT3	0.049				
cT4	0.03				
cN	0.639				
cN0					
cN+	0.639				
Histologic type	0.338				
Differentiated					
Undifferentiated	0.338				
Size	0.164				
≤ 3					
> 3	0.164				
Macroscopic type	0.023				0.075
EGC		Ref			
AGC, Borrmann 1–3	0.006	0.639	0.434	0.941	0.023
AGC, Borrmann 4	0.04	0.707	0.438	1.14	0.155
Tumor location	0.016				0.063
Lower		Ref			
Middle	0.293	0.77	0.414	1.432	0.409
Upper	1	1.024	0.556	1.887	0.938
Overlapping lesion	0.109	0.655	0.343	1.251	0.2

noncompliance rate. However, further exploration in prospective research is still needed.

Similar to other retrospective studies, our study also has several limitations. First, our study was a single-center retrospective study; therefore, it may be somewhat unavoidably biased. Multicenter clinical trials are needed to confirm the results of our study. Second, social and economic factors may have influenced the results. In such a country with vast territory like China, economic level, medical service, and patients' beliefs and medical consciousness vary sharply from

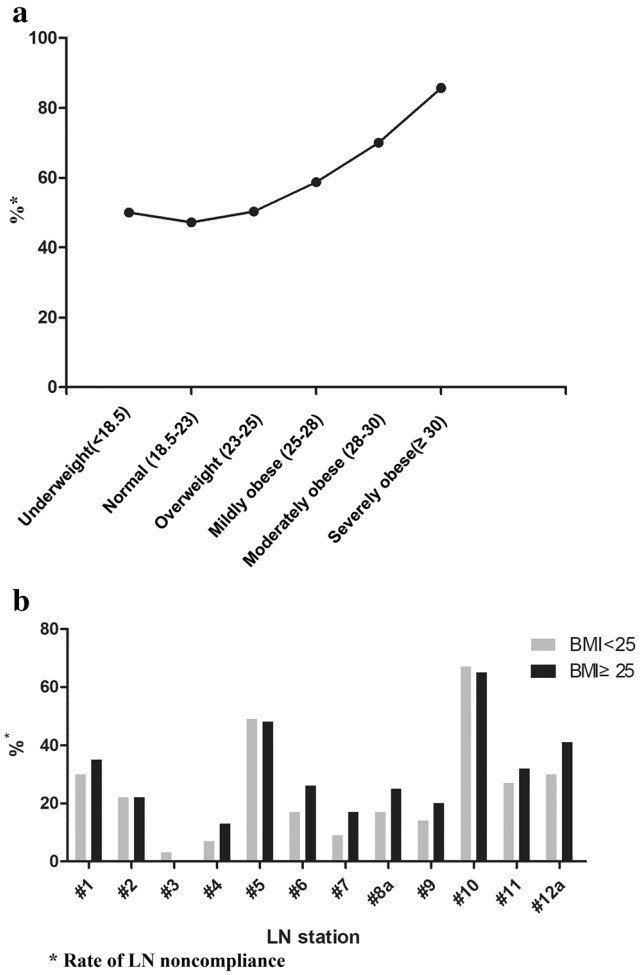

Fig. 4 Subgroup analysis of BMI and LN stations in cStage II/III patients

one region to another region. Some of the patients in vulnerable situations, being elderly or underprivileged, tend to refuse to accept postoperative adjuvant chemotherapy, which will affect the implementation of the comprehensive treatment strategies for gastric cancer. These social and economic factors may act as limiting factors and may influence short-term or long-term outcomes. Third, our study lacks historical institutional data from the "open era." We look forward to a further multicenter prospective control study on the LN noncompliance rate in laparotomy and laparoscopic surgery, which will be further elaborated in the subsequent series of articles on the LN noncompliance rate. However, our research is the first study to confirm that LN noncompliance is an independent risk factor for predicting the long-term prognosis of patients undergoing LTG for GC.

Author Contributions GTL, CMH, and CHZ conceived and designed the study. QYC, PL, JWX, JBW, and JXL performed the study. GTL and QYC analyzed the data. ZNH, LLC, ML, RHT, and JLL contributed the reagents/materials/analysis tools. GTL wrote the manuscript. All authors read and approved the final manuscript.

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Compliance with Ethical Standards

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

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