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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Does Noncompliance in Lymph Node Dissection Affect Oncological Efficacy in Gastric Cancer Patients Undergoing Radical Gastrectomy?

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ABSTRACT

Background. Few reports have examined the prognosis of or possible remedial treatments for patients with noncompliant D2 lymphadenectomy. We investigated the effect of noncompliance in lymph node (LN) dissection on long-term survival in gastric cancer (GC) patients after radical gastrectomy and explored intervention measures.

Methods. Clinicopathological data were retrospectively analyzed in 2401 patients who underwent radical gastrectomy for GC. Noncompliance was defined as patients with more than one empty LN station, as described in the protocol of the Japanese GC Association.

Results. The overall noncompliance rate was 49.1%. The 3-year overall survival (OS) rate was significantly better in compliant than noncompliant patients (74.0% vs. 60.1%, $P < 0.001$). Univariate and multivariate analyses revealed that noncompliance was an independent risk factor for OS. Logistic regression analysis demonstrated that extent of gastrectomy, primary tumor site, history of intraperitoneal surgery, body mass index, and open gastrectomy were independent preoperative predictive factors for noncompliance. Cox analysis demonstrated that age, pT, pN, and extent of gastrectomy independently affected OS in patients with noncompliant lymphadenectomy. However, OS was significantly better in the compliant than noncompliant group regardless of the recommendation for chemotherapy. Stratified analysis demonstrated that OS was significantly better in chemotherapy patients than in patients without chemotherapy and stage II patients (pT1N2/N3M0 and pT3N0M0) in whom chemotherapy was not recommended.

Conclusions. Noncompliance is an independent risk factor after radical gastrectomy for GC. Adjuvant chemotherapy improved the prognosis of patients with pT1N2/N3M0 and pT3N0M0 disease who underwent noncompliant D2 lymphadenectomy.

Qi-Yue Chen and Qing Zhong have contributed equally to this work and should be considered co-first authors.

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BACKGROUND

Gastric cancer (GC) is one of the top five causes of cancer-related death and one of the top three causes of tumor-related death worldwide.[1,2] Tumor–node–metastasis

(TNM) staging impacts clinical decision-making, prognosis, and prediction and is therefore the most important factor for patients undergoing radical gastrectomy, and D2 lymph node (LN) dissection provides accurate LN staging in GC patients.[3–5] D2 LN dissection has gained widespread recognition and is increasingly accepted as the standard treatment for advanced GC.[6–8] However, D2 LN dissection is challenging to perform because of the complex blood vessels of the stomach, the anatomical levels involved, and the various pathways by which metastasis can occur. Therefore, adequate D2 dissection remains a research emphasis and focus for surgeons. Objective evaluation is needed to assess the quality of D2 LN dissection. Quality indexes, such as the number of retrieved LNs, the metastasis rate, and the therapeutic value index, are used, but doubts remain due to conflicting results produced by different centers. The noncompliance rate of D2 LN dissection has received increasing attention in recent years.[9,10] Noncompliance is defined as patients with more than one empty LN station, as described in the protocol of the Japanese GC Association,[11] in cases in which the surgeon did not resect a specified station. The noncompliance rate is an effective index that can be used to evaluate the quality of D2 LN dissection, but few reports have examined its effect on prognosis, the prediction of high-risk factors, or possible remedial treatments in patients with noncompliant D2 lymphadenectomy. Multicenter, prospective, and randomized clinical trials should be performed to provide relevant information, and retrospective research could provide reference values. Therefore, the purpose of this study is to conduct a large-sample retrospective study of the feasibility of using noncompliance as an index for long-term survival and to explore the effect of postoperative chemotherapy on prognosis in these patients.

PATIENTS AND METHODS

Patients

This study retrospectively analyzed a prospective database containing 2401 patients with GC who had undergone D2 radical gastrectomy with the same group of surgeons from June 2007 to December 2013 at Fujian Medical University Union Hospital in China. The patients included 1343 with total gastrectomy (TG) and 1058 with distal gastrectomy (DG). The following inclusion criteria were used: (1) preoperative endoscopic biopsy-proven GC, (2) D2 LN dissection, and (3) no distant metastases or adjacent organ invasion (pancreas, spleen, liver, colon, etc.) prior to surgery. Patients were excluded due to 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 residual GC. 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. Imaging studies included chest radiography, computed tomography (CT) scanning, ultrasonography (US) of the abdomen, bone scanning, and positron emission tomography–computed tomography (PET–CT) as needed to evaluate the clinical stage.[12] We used CT scans and the 7th edition of the International Union Against Cancer (UICC) classification system to assess the clinical and pathological stages. Noncompliance was defined as patients with more than one empty LN station, as described in the protocol for D2 LN dissection from the Japanese GC Association.[11] The therapeutic value of LN dissection was estimated by multiplying the incidence of LN metastasis by the 5-year overall survival (OS) of patients with metastasis at each station. The LN dissection rate was determined by dividing the total number of patients who required dissection at an LN station by the number of patients in whom the corresponding LN was completely harvested. The 2014 edition of the Japanese GC treatment guidelines does not recommend adjuvant chemotherapy for patients with postoperative pathological diagnosis of stage I disease and some patients with stage II (pT1N2M0, pT1N3M0, and pT3N0M0) disease.[13] Patients with other types of stage II or III GC generally received adjuvant chemotherapy based on a relatively uniform regimen of fluorouracil and platinum.

Surgical Procedures

The following lymphadenectomy sequences were performed: (1) for DG, no. 6 → no. 7, 9, 11p → no. 3, 1 → no. 8a, 12a, 5 → no. 4sb; and for (2) TG: no. 6 → no. 7, 9, 11p → no. 8a, 12a, 5 → no. 1 → no. 4sb → no. 10, 11d → no. 2. For additional details, please see the references.[14–17]

Postoperative Pathological Examination

Surgeons removed specimens via macroscopic examination, and the specimens were divided into groups according to the Japanese classification of GC. Surgeons examined all specimens, which were sent immediately to the pathology department. Two or more experienced pathology experts examined each LN using palpation

without size restriction. All pathological examinations were performed in a standard manner.

Follow-Up

The last follow-up was conducted in January 2017. The overall follow-up rate was 90.3%, and the median follow-up duration was 42 months (range 1–112 months). Postoperative follow-up was performed in the outpatient department every 3 months for the first 2 years, every 6 months from years 3–5, and once a year after 5 years. Most routine patient follow-up appointments included a physical examination, laboratory tests [including assessment of carbohydrate antigen (CA)19-9, CA72-4, and carcinoembryonic antigen (CEA) levels], chest radiography, abdominopelvic US or CT, and an annual endoscopic examination. OS was calculated from day of surgery until death or until final follow-up date, whichever occurred first.[18–20]

Statistical Analysis

All statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). All continuous variables are presented as mean ± standard deviation. Chi-square or Fisher's exact tests were used to analyze categorical variables. OS was calculated from time of surgery until death or final follow-up date, whichever occurred first, and disease-free survival was defined as time from surgery to time of recurrence or death from any cause. 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.[21] Values of $P < 0.05$ were considered statistically significant.

RESULTS

Patient Characteristics

Table 1 presents the clinicopathological characteristics of all patients. A total of 1179 (49.1%) out of 2401 patients were noncompliant in LN dissection. TG was performed in 1343 (55.9%) of the total included patient population, and the noncompliance rate was 61.7%; DG was performed in 1058 (44.1%) of the patients, with a noncompliance rate of 33.2%. The average number of retrieved LNs was 31.5 ± 13.

TABLE 1 Sociodemographic and clinicopathological variables of all patients (n = 2401)

	No. of patients	%
All patients (n = 2401)		
Sex		
Female	603	25.1
Male	1798	74.9
Age (years)		
< 65	1476	61.4
≥ 65	925	38.5
ASA score		
I	1626	67.7
II	723	30.1
III–IV	52	2.2
Charlson score		
0	1626	67.7
1–2	735	30.6
3–5	40	1.7
BMI (kg/m^2)		
< 18.5	273	11.4
18.5–24.9	1782	74.2
≥ 25.0	346	14.4
Previous abdominal surgery		
No	2041	85.0
Yes	360	15.0
Previous intraperitoneal surgery		
No	2246	93.5
Yes	155	6.5
Smoking		
No	1727	71.9
Yes	674	28.1
cT		
cT1	529	22.0
cT2	267	11.1
cT3	487	20.3
cT4	1118	46.6
cN		
cN0	1137	47.4
cN+	1264	52.6
Size (cm)		
Mean ± standard deviation	4.9 ± 2.7	
< 2	234	9.7
2–5	1266	52.7
> 5	901	37.5
Examined LNs, no.		
Mean ± standard deviation	31.5 ± 13.0	
≤ 15	161	6.7
> 15	2240	93.3
Depth of invasion		
T1	529	22.0
T2	270	11.2

TABLE 1 continued

	No. of patients	%
T3	593	24.7
T4	1009	42.0
Nodal status		
N0	824	34.3
N1	332	13.8
N2	394	16.4
N3a	504	21.0
N3b	347	14.5
Primary site		
Lower	1061	44.2
Upper	426	17.7
Middle	615	25.6
Overlapping lesion of stomach	299	12.5
Grade		
Differentiated	1000	41.6
Undifferentiated	1401	58.4
Macroscopic type		
EGC	558	23.2
AGC, Borrmann 1–3	1539	64.1
AGC, Borrmann 4	304	12.7
Lymphovascular invasion		
Negative	1770	73.7
Positive	631	26.3
Perineural invasion		
Negative	2099	87.4
Positive	302	12.6
LN compliance		
Noncompliant	1179	49.1
Compliant	1222	50.9
Surgery type		
Open	656	27.3
Laparoscopic	1745	72.7
Gastrectomy		
Total	1343	55.9
Distal	1058	44.1
Complications		
None	2009	83.7
I–II[a]	299	12.5
III–IV[a]	93	3.9
Chemotherapy		
No	1659	69.1
Yes	742	30.9
Follow-up (months)		
Median	42	
Range	1–112	

[a]Clavien–Dindo classification

LN Dissection

Figure 1 and Supplementary Table 1 show the LN dissection rate and the number of LNs dissected in TG and DG patients at each station, and Supplementary Table 2 shows that an average of 32.6 ± 14.2 and 30.2 ± 11.1 LNs were harvested in TG and DG patients, respectively. In TG patients, the LN metastasis rate at each station ranged from 7.1 to 62.5%, and the metastasis rate was highest (839/1343, 62.5%) at LN no. 3, followed by no. 7 (546/1343, 40.7%). The therapeutic value range was 2.3–28.1, and this index was highest at LN no. 3 (28.1%) and lowest at LN no. 10 (2.3%) (Supplementary Table 1). In TG patients, the dissection rate of LNs was highest at LN no. 3 and lowest at LN no. 10 (27.6%). Univariate Cox proportional hazards model analysis revealed that dissection at LNs no. 1, 2, 6, 7, 8a, 9, 10, 11, and 12a improved OS ($P < 0.05$). Multiple factor analysis demonstrated that dissections at LN no. 2 and no. 8a were independent protective factors for OS (Supplementary Table 3).

In DG patients, the LN metastasis rate ranged from 5.8 to 37.8% at each station, and the metastasis rate was highest at LN no. 3 (401/1058, 37.8%), followed by no. 6 (341/1058, 32.1%). The therapeutic value range was 2.3–23.8, and the index was highest at LN no. 3 and lowest at no. 10 (Supplementary Table 2). In DG patients, the LN dissection rate was highest at LN no. 3 and lowest at LN no. 11. Univariate Cox analysis revealed that dissection of LNs no. 1, 6, 8a, 9, and 12a was beneficial to OS ($P < 0.05$). Multivariate analysis demonstrated that dissections of LN no. 12a and no. 8a were independent protective factors for OS (Supplementary Table 4).

Effect of Noncompliance on LN Dissection and Its Preoperative Predictors

Supplementary Table 5 shows the effects of noncompliance on LN dissection. In TG patients, there were fewer retrieved LNs (27.8 ± 12.6 vs. 40.3 ± 13.3, $P < 0.001$) and fewer metastatic LNs (7.5 ± 9.5 vs. 10.0 ± 11.6, $P < 0.001$) in noncompliant than compliant patients. There were statistically significant differences in the numbers of retrieved LNs and metastatic LNs between DG patients with compliant and noncompliant lymphadenectomy. Logistic regression analysis of preoperative factors that predicted LN dissection noncompliance revealed that sex, age, BMI, extent of gastric resection, primary tumor site, cT, cN, previous operation history, preoperative complications, American Society of Anesthesiologists (ASA) score, and surgery type were all significant factors ($P < 0.05$). Further multivariate analysis demonstrated that BMI, primary tumor site, range of gastrectomy, history of abdominal surgery, and surgery type were independent

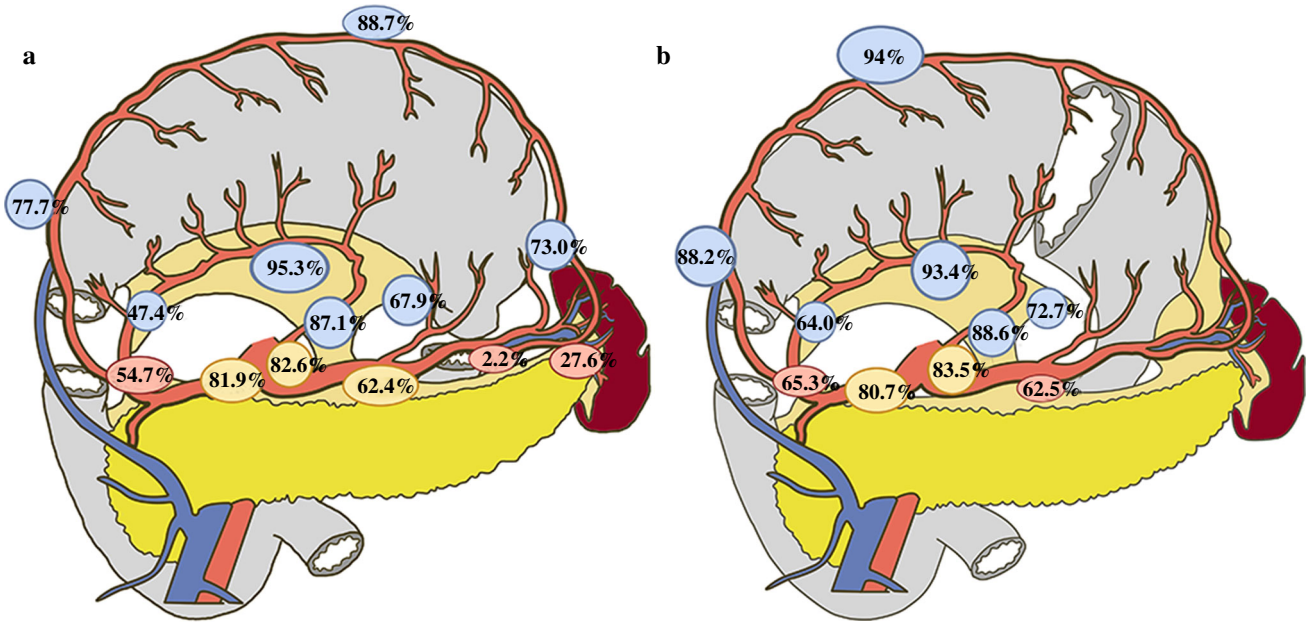

FIG. 1 Lymph node dissection rate at each station in total and distal gastrectomy with D2 lymph node dissection. **a** Total gastrectomy: no. 1: 67.9%, no. 2: 73.0%, no. 3: 95.3%, no. 4: 88.7%, no. 5: 47.4%, no. 6: 77.7%, no. 7: 87.1%, no. 8a: 81.9%, no. 9: 82.6%, no. 10: 27.6%, no. 11p: 62.4%, no. 11d: 2.2%, no. 12a: 54.7%. **b** Distal gastrectomy: no. 1: 72.7%, no. 3: 93.4%, no. 4: 94.0%, no. 5: 64.0%, no. 6: 88.2%, no. 7: 88.6%, no. 8a: 80.7%, no. 9: 83.5%, no. 11p: 62.5%, no. 12a: 65.3%

factors ($P < 0.05$) that predicted noncompliance in LN dissection (Supplementary Table 6).

Analysis of Survival and Recurrence Patterns among All Patients

The OS curve in all patients revealed that OS was significantly higher in patients with compliant lymphadenectomy than in patients with noncompliant lymphadenectomy (3-year OS: 74.0% vs. 60.1%, $P < 0.001$) (Supplementary Figure 1). Univariate and further multivariate analyses performed using a Cox proportional hazards model (stepwise backward variable removal) demonstrated that age, tumor size, pT, pN, noncompliance in LN dissection, and number of retrieved LNs independently affected OS ($P < 0.05$) (Table 2). Stratified analyses revealed that OS was worse in patients with noncompliant lymphadenectomy than in patients with compliant lymphadenectomy, regardless of the use of recommended chemotherapy according to the Japanese GC Association (all $P < 0.01$) (Fig. 2). Supplementary Table 7 shows that the rate of locoregional recurrence was higher in patients with noncompliant lymphadenectomy than in patients with compliant lymphadenectomy, but this difference was not significant ($P = 0.065$). Finally, the 3-year disease-free survival rate was 70.3% in the compliant group and 57.2% in the noncompliant group.

OS Analysis of Noncompliant Patients

Cox proportional hazards model analysis demonstrated that age, tumor size, pT, pN, primary tumor site, extent of gastrectomy, pathological differentiation, gross tumor classification, chemotherapy, vascular invasion, nerve invasion, and postoperative complications were univariate factors that significantly predicted noncompliant lymphadenectomy ($P < 0.05$). Further multivariate analysis revealed that older age, high pT, and high pN were independent risk factors for OS ($P < 0.05$), and that DG was a protective factor ($P < 0.05$) (Table 3). Subgroup analysis of patients for whom adjuvant chemotherapy was not recommended ($n = 374$) revealed that OS was similar between patients in pathological stage I who did and did not receive chemotherapy ($P = 0.310$). OS was significantly better in stage II patients who received chemotherapy than in those who did not ($P = 0.035$) (Fig. 3). Univariate and multivariate Cox regression analyses of pathological stage II patients with noncompliant lymphadenectomy in whom chemotherapy was not recommended ($n = 77$) revealed that chemotherapy was a protective factor for OS and that older age (65 years old or older) was a risk factor ($P < 0.05$) (Table 4).

TABLE 2 Univariate and multivariate Cox regression model for overall survival of all patients (n = 2401)

Variable	Univariate model			Multivariate model		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex			0.036			
Female	Ref					
Male	1.14	1.00–1.30	0.036			
Age (years)			< 0.001			< 0.001
< 65	Ref			Ref		
≥ 65	1.46	1.28–1.67	< 0.001	1.43	1.25–1.63	< 0.001
Size (cm)			< 0.001			0.001
< 2	Ref			Ref		
2–5	3.53	2.25–5.53	< 0.001	1.14	0.70–1.85	0.593
> 5	10.20	6.53–15.95	< 0.001	1.50	0.91–2.47	0.109
ASA score			0.001			
I	Ref					
II	1.22	1.06–1.39	0.005			
III–IV	1.50	1.15–1.95	0.002			
Previous abdominal surgery						
No	Ref					
Yes	1.02	0.85–1.22	0.857			
Previous intraperitoneal surgery						
No	Ref					
Yes	0.80	0.60–1.07	0.135			
Smoking						
No	Ref					
Yes	0.95	0.82–1.10	0.463			
Charlson score			0.085			
0	Ref					
1–2	1.11	0.97–1.28	0.139			
3–5	1.51	0.96–2.35	0.072			
Examined LNs, no.			0.002			< 0.001
≤ 15	Ref			Ref		
> 15	0.69	0.55–0.87	0.002	0.43	0.33–0.55	< 0.001
Depth of invasion			< 0.001			< 0.001
T1	Ref			Ref		
T2	3.59	2.27–5.66	< 0.001	2.71	1.69–4.37	< 0.001
T3	8.29	5.62–12.22	< 0.001	4.09	2.64–6.36	< 0.001
T4	16.87	11.62–24.50	< 0.001	5.67	3.66–8.79	< 0.001
Nodal status			< 0.001			< 0.001
N0	Ref			Ref		
N1	1.97	1.47–2.64	< 0.001	1.13	0.83–1.54	0.426
N2	3.73	2.92–4.77	< 0.001	1.96	1.50–2.56	< 0.001
N3a	7.05	5.64–8.81	< 0.001	3.31	2.56–4.28	< 0.001
N3b	12.30	9.78–15.47	< 0.001	5.71	4.34–7.51	< 0.001
Primary site			< 0.001			
Distal third	Ref					
Proximal third	1.84	1.53–2.20	< 0.001			
Mid third	1.57	1.33–1.86	< 0.001			
Overlapping lesion of stomach	2.43	2.00–2.96	< 0.001			
Grade			< 0.001			

TABLE 2 continued

Variable	Univariate model			Multivariate model		
	HR	95% CI	*P*	HR	95% CI	*P*
Differentiated	Ref					
Undifferentiated	1.96	1.70–2.26	< 0.001			
Gross type			< 0.001			
EGC	Ref					
AGC, Borrmann 1–3	8.01	5.82–11.01	< 0.001			
AGC, Borrmann 4	12.32	8.73–17.38	< 0.001			
Lymphovascular invasion			< 0.001			
Negative	Ref					
Positive	1.47	1.27–1.69	< 0.001			
Perineural invasion			< 0.001			
Negative	Ref					
Positive	1.40	1.16–1.69	< 0.001			
LN compliance			< 0.001			< 0.001
Compliant	Ref			Ref		
Noncompliant	1.65	1.44–1.88	< 0.001	1.55	1.34–1.79	< 0.001
Gastrectomy			< 0.001			0.044
Total	Ref			Ref		
Distal	0.45	0.39–0.52	< 0.001	0.85	0.73–1.00	0.044
Chemotherapy			< 0.001			
No	Ref					
Yes	1.53	1.33–1.75	< 0.001			

CI confidence interval, *HR* hazard ratio

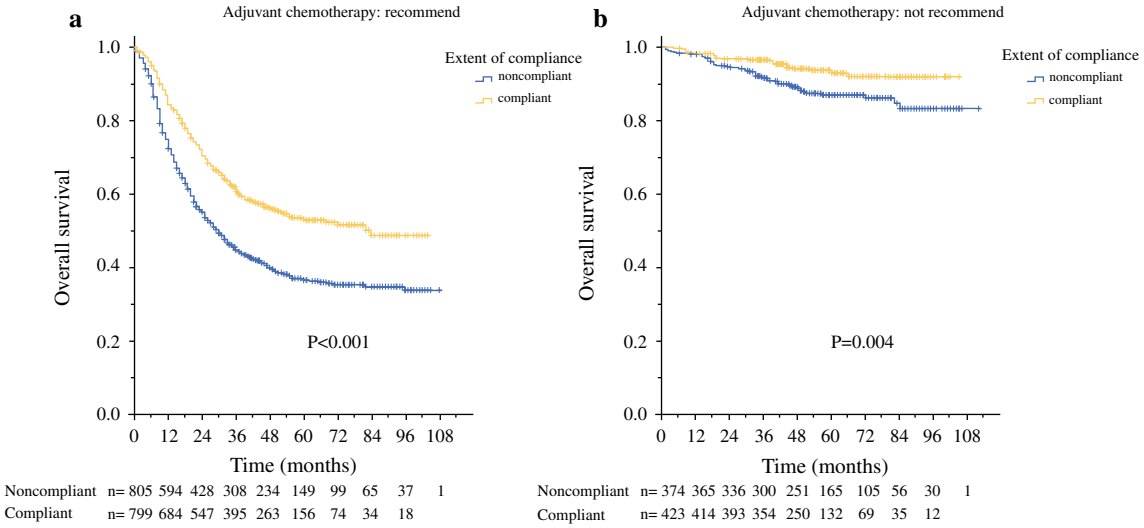

FIG. 2 Overall survival compared between patients with noncompliant and compliant lymphadenectomy. Patients stratified by chemotherapy administration. **a** Patients in whom adjuvant chemotherapy was not recommended. **b** Patients in whom adjuvant chemotherapy was recommended

TABLE 3 Univariate and multivariate Cox regression model for overall survival with noncompliance (n = 1179)

Variable	Univariate model			Multivariate model		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex			0.638			
Female	Ref					
Male	0.95	0.78–1.17	0.638			
Age (years)			< 0.001			< 0.001
< 65	Ref			Ref		
≥ 65	1.39	1.17–1.65	< 0.001	1.45	1.22–1.72	< 0.001
Previous abdominal surgery			0.201			
No	Ref					
Yes	1.15	0.93–1.43	0.201			
Previous intraperitoneal surgery			0.539			
No	Ref					
Yes	1.12	0.78–1.62	0.539			
Smoking			0.866			
No	Ref					
Yes	0.98	0.82–1.19	0.866			
ASA score			0.476			
I	Ref					
II	1.03	0.86–1.23	0.755			
III–IV	1.22	0.89–1.68	0.223			
Charlson score						
0			0.248			
1–2	0.96	0.80–1.15	0.666			
3–5	1.53	0.89–2.61	0.121			
Size (cm)			< 0.001			0.050
< 2	Ref			Ref		
2–5	3.33	1.94–5.71	< 0.001	1.05	0.59–1.87	0.869
> 5	9.43	5.52–16.13	< 0.001	1.35	0.74–2.44	0.327
Examined LNs, no.			0.095			
≤ 15	Ref					
> 15	0.81	0.64–1.04	0.095			
Depth of invasion			< 0.001			< 0.001
T1	Ref			Ref		
T2	4.24	2.26–7.94	< 0.001	3.55	1.86–6.79	< 0.001
T3	9.59	5.52–16.67	< 0.001	5.40	2.92–10.00	< 0.001
T4	17.88	10.46–30.59	< 0.001	7.80	4.23–14.40	< 0.001
Nodal status			< 0.001			< 0.001
N0	Ref			Ref		
N1	1.96	1.38–2.79	< 0.001	1.03	0.71–1.50	0.856
N2	3.65	2.69–4.95	< 0.001	1.62	1.16–2.26	0.005
N3a	6.32	4.80–8.32	< 0.001	2.42	1.77–3.32	< 0.001
N3b	10.71	7.98–14.38	< 0.001	3.68	2.60–5.21	< 0.001
Primary site			< 0.001			< 0.001
Distal third	Ref			Ref		
Proximal third	1.50	1.17–1.92	0.001	0.69	0.49–0.98	0.036
Mid third	1.28	1.02–1.59	0.030	0.67	0.48–0.93	0.016
Overlapping lesion of stomach	2.35	1.80–3.07	<0.001	0.85	0.60–1.21	0.371

TABLE 3 continued

Variable	Univariate model			Multivariate model		
	HR	95% CI	*P*	HR	95% CI	*P*
Grade			< 0.001			
Differentiated	Ref					
Undifferentiated	2.11	1.75–2.54	< 0.001			
Gross type			< 0.001			
EGC	Ref					
AGC, Borrmann 1–3	8.87	5.66–13.90	< 0.001			
AGC, Borrmann 4	12.48	7.70–20.21	< 0.001			
Lymphovascular invasion			< 0.001			
Negative	Ref					
Positive	1.79	1.48–2.16	< 0.001			
Perineural invasion			< 0.001			
Negative	Ref					
Positive	1.59	1.25–2.01	< 0.001			
Gastrectomy			< 0.001			0.009
Total	Ref			Ref		
Distal	0.51	0.41–0.63	< 0.001	0.64	0.46–0.90	0.009
Chemotherapy			< 0.001			
No	Ref					
Yes	1.47	1.24–1.75	< 0.001			
Complication			0.027			0.063
No	Ref			Ref		
Yes	1.27	1.03–1.58	0.027	1.23	0.99–1.52	0.063

DISCUSSION

D2 LN dissection is the most commonly performed routine surgical treatment in Asia, and its contribution to long-term survival has been confirmed.[22,23] However, it remains difficult to achieve a safe and effective dissection. The noncompliance rate of D2 LN dissection is increasingly being used to evaluate the quality of D2 LN dissection, with some randomized controlled trials using noncompliance as the primary indicator of D2 LN dissection quality. Bonenkamp et al.[9] reported that the noncompliance rate was 51% in extended D2 LN dissection in GC. Park et al.[24] reported that the noncompliance rate was 47% in D2 LN dissection in a laparoscopic group based on the COACT1001 results, but there was no significant difference ($P = 0.648$) in the noncompliance rate between the laparoscopic and open surgery groups. In our study, two experienced pathologists examined all specimens to ensure data validity, and experienced surgeons from the same group performed all the surgeries. Standardized procedures were strictly followed. The noncompliance rate was 49.1%, similar to rates found in previous studies. However, we found few reports that explored the effect of the noncompliance rate on long-term prognosis. The present study focused on its effect on long-term patient survival. Bonenkamp et al.[6] concluded that D2 LN dissection should not be used in the West because it did not affect the 5-year OS rate of Dutch Gastric Cancer Trial (DGCT) patients. de Steur et al. (2015) reevaluated the surgical quality of the cases included in the Bonenkamp study and found that, when patients who underwent combined resection of the pancreas and spleen were excluded from the data, D2 LN dissection reduced the incidence of death ($P < 0.05$). de Steur et al. (2015) found that 81.6% of the patients in the Bonenkamp study had inadequate removal of LN stations (i.e., noncompliance) despite the inclusion of intense preparation procedures and controls for quality assurance, which likely outweighed the contribution of D2 LN dissection to patient survival. Further stratification analysis demonstrated that, when cases with noncompliance and D1 contamination were excluded, long-term survival was significantly better in the D2 group than in the D1 group (35.7% vs. 19.9%, $P = 0.041$).[10] Therefore, the study by de Steur et al. (2015) suggests that noncompliance does influence prognosis.

Our study produced a similar finding by showing that noncompliance predicted worse OS. Retrieval of LNs was also far less common in patients with inadequate LN

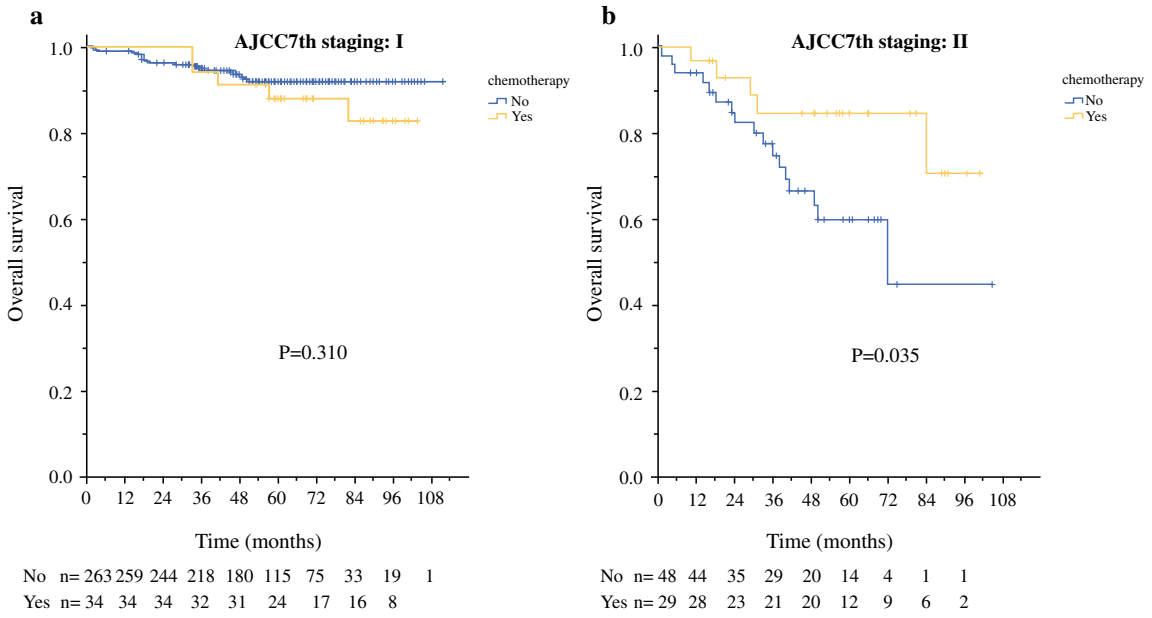

FIG. 3 Subgroup analyses of overall survival among patients with noncompliant lymphadenectomy and compliant lymphadenectomy in whom adjuvant chemotherapy was not recommended. **a** Pathological stage I patients. **b** Pathological stage II patients (pT1N2M0, pT1N3M0, and pT3N0M0)

removal than in patients with adequate LN removal. Further analyses indicated that noncompliance was an independent risk factor for OS. Peeters et al.[25] examined the relationship between prognosis and the Maruyama index and found a positive correlation between noncompliance and OS among patients undergoing GC surgery. Because LNs are the primary route of metastasis in GC patients, D2 LN dissection should adequately remove the LNs at all possible sites to effectively stop metastasis and potentially achieve better prognosis. Our research results support this assumption, and we therefore suggest that the quality of D2 LN dissection is closely related to patient prognosis. Previous studies and our own research have demonstrated that noncompliance is not rare among GC patients. Therefore, to increase the survival rate among these patients, it is clinically significant to develop an effective remedial treatment for noncompliance. Our analysis shows that the OS rate was higher in the compliant group than in the noncompliant group, regardless of chemotherapy administration, although a stratification analysis demonstrated that chemotherapy increased the survival rate in stage II patients with noncompliant lymphadenectomy. One possible explanation for this finding is that stage I patients have lower risk of LN metastasis, whereas stage II patients have higher risk of metastasis.[26–31] Noncompliance in LN dissection may lead to inadequate removal of metastatic LN. Chemotherapy may be a remedial treatment for noncompliance, because chemotherapy performed after surgery could eliminate any residual undetectable tumor tissue and cells. We evaluated preoperative indicators that predicted that the risk of noncompliance was higher among patients undergoing TG and among patients with history of gastric surgery. Different surgical approaches and adhesions may prevent adequate removal of LNs. However, additional prospective data are needed to test this prediction.

There are significant gender differences in the incidence of GC. Its incidence is higher in male patients than in female patients, especially in East Asia. Based on the global cancer statistics for 2018,[32] in East Asia, the incidence of GC is nearly three times higher in males than in females (male vs. female: 32.1 per 100,000 vs. 13.2 per 100,000), whereas in North America, it is twice as high in males as in females. The latest Chinese cancer statistics[33] also show that there are more than twice as many new cases of GC in males as in females (male vs. female: 477,700 vs. 201,400). These data are consistent with the distribution of GC in both sexes observed in our study. The differences in the rates of GC observed between males and females may be related to differences in the opportunities for males and females to be exposed to carcinogens; For example, in China, smoking, drinking alcohol, and drinking tea are significantly more common in men than in women. However, the specific reasons for these differences remain to be further studied.

Our study has several limitations. First, this was a single-center retrospective study; therefore, unavoidable bias may be present, and multicenter clinical trials are needed to

TABLE 4 Univariate and multivariate Cox regression model for overall survival of pathological stage II patients with noncompliant lymphadenectomy in whom chemotherapy was not recommended (n = 77)

Variable	Univariate model			Multivariate model		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)			0.008			0.007
< 65	Ref			Ref		
≥ 65	3.55	1.39–9.09	0.008	3.78	1.45–9.88	0.007
Sex			0.141			
Female	Ref					
Male	2.98	0.70–12.76	0.141			
ASA score			0.689			
1	Ref					
2–3	0.83	0.34–2.05	0.689			
Previous abdominal surgery			0.112			
No	Ref					
Yes	0.31	0.07–1.32	0.112			
Smoking			0.860			
No	Ref					
Yes	1.08	0.45–2.58	0.860			
Comorbidity			0.863			
No	Ref					
Yes	0.92	0.36–2.36	0.863			
Depth of invasion			0.664			
T1	Ref					
T3	1.38	0.32–5.91	0.664			
Nodal status			0.664			
N0	Ref					
N+	0.73	0.17–3.10	0.664			
Size (cm)			0.299			
< 5	Ref					
≥ 5	1.57	0.67–3.69	0.299			
Examined LNs, no.			0.509			
≤ 15	Ref					
> 15	0.66	0.19–2.26	0.509			
Primary site			0.315			
Distal third	Ref					
Proximal third	0.66	0.07–6.07	0.712			
Mid third	1.90	0.64–5.70	0.250			
Overlapping lesion of stomach	0.47	0.05–4.20	0.496			
Grade			0.292			
Differentiated	Ref					
Undifferentiated	0.63	0.27–1.48	0.292			
Lymphovascular invasion			0.017			0.179
Negative	Ref			Ref		
Positive	2.93	1.21–7.09	0.017	1.88	0.75–4.73	0.179
Perineural invasion			0.061			
Negative	Ref					
Positive	2.64	0.95–7.29	0.061			
Gastrectomy			0.589			
Total	Ref					

TABLE 4 continued

Variable	Univariate model			Multivariate model		
	HR	95% CI	*P*	HR	95% CI	*P*
Distal	0.76	0.28–2.06	0.589			
Chemotherapy			0.043			0.044
No	Ref			Ref		
Yes	0.34	0.12–0.97	0.043	0.32	0.10–0.97	0.044
Complication			0.363			
No	Ref					
Yes	1.77	0.52–6.06	0.363			

confirm the results of our study. Second, social and economic factors may have influenced the results. Moreover, because there are differences in the treatments applied between the East and the West, no conventional postoperative radiotherapy was available for patients in our center, and it was therefore impossible to analyze the survival benefits of adjuvant radiotherapy in GC patients with noncompliant lymphadenectomy. We look forward to the publication of more rigorous prospective studies that assess whether adjuvant radiotherapy benefits patients with noncompliant lymphadenectomy. However, our study is the first to confirm that noncompliance is an independent risk factor that predicts long-term prognosis in patients undergoing radical gastrectomy for GC. In addition, we found that performing chemotherapy after surgery may remedy noncompliance in GC patients with pT1N2/N3M0 or pT3N0MO disease.

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REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2015;61(2):69–90
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortettieulent J, Jemal A. GLOBOCAN 2012: estimated cancer incidence mortality and prevalence worldwide in 2012. 2015.
3. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical co-operative group. *Br J Cancer.* 1999;79(10):1522–1530
4. Schwarz RE, Smith DD. Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage. *Ann Surg Oncol.* 2007;14(2):317–328
5. Seevaratnam R, Bocicariu A, Cardoso R, et al. How many lymph nodes should be assessed in patients with gastric cancer? A systematic review. *Gastric Cancer.* 2012;15(1):70–88.
6. Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet.* 1995;345(8952):745.
7. Siewert JR, Böttcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. *Ann Surg.* 1998;228(4):449–461.
8. Songun I, Putter H, Kranenbarg EM, Sasako M, Cj VDV. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol.* 2010;11(5):439–449.
9. Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. *N Engl J Med.* 1999;340(12):908.
10. De Steur WO, Hartgrink HH, Dikken JL, Putter H, Van de Velde CJ. Quality control of lymph node dissection in the Dutch Gastric Cancer Trial. *Br J Surg.* 2015;102(11):1388–1393.
11. Association. JGC. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer.* 2011;14(2):101–112.
12. Chen QY, Zheng CH, Li P, et al. Which method is more suitable for advanced gastric cancer with enlarged lymph nodes, laparoscopic radical gastrectomy or open gastrectomy? *Gastric Cancer.* 2018;28(suppl_3):1–11.
13. Association JGC. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer.* 2011;14(2):113–123.
14. Huang CM, Chen QY, Lin JX, et al. Laparoscopic suprapancreatic lymph node dissection for advanced gastric cancer using a left-sided approach. *Ann Surg Oncol.* 2015;22(7):2351.
15. Huang CM, Chen QY, Lin JX, et al. Laparoscopic spleen-preserving no. 10 lymph node dissection for advanced proximal gastric cancer using a left approach. *Ann Surg Oncol.* 2014;21(6):2051.
16. Chen QY, Huang CM, Lin JX, et al. Laparoscopic infrapyloric area lymph node dissection with no. 14v enlargement for advanced lower gastric cancer in middle colic vein approach. *Ann Surg Oncol.* 2016;23(3):951.

17. Huang CM, Chen QY, Lin JX, Zheng CH, Li P, Xie JW. Huang's three-step maneuver for laparoscopic spleen-preserving No. 10 lymph node dissection for advanced proximal gastric cancer. *Chin J Cancer Res.* 2014;26(2):208–210.
18. Lin JX, Huang CM, Zheng CH, et al. Evaluation of laparoscopic total gastrectomy for advanced gastric cancer: results of a comparison with laparoscopic distal gastrectomy. *Surg Endosc.* 2016;30(5):1988.
19. Lu J, Wang W, Zheng CH, et al. Influence of total lymph node count on staging and survival after gastrectomy for gastric cancer: an analysis from a two-institution database in China. *Ann Surg Oncol.* 2017;24(2):1–8.
20. Tu RH, Lin JX, Zheng CH, et al. Development of a nomogram for predicting the risk of anastomotic leakage after a gastrectomy for gastric cancer. *Eur J Surg Oncol.* 2016;43(2): 485–492.
21. Grambsch PM, Therneau TM (1994) Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 81(3):515–526
22. eong O, Park YK. Clinicopathological features and surgical treatment of gastric cancer in South Korea: the results of 2009 nationwide survey on surgically treated gastric cancer patients. *J Gastric Cancer.* 2011;11(2):69–77.
23. Miyahara R, Niwa Y, Matsuura T, et al. Prevalence and prognosis of gastric cancer detected by screening in a large Japanese population: data from a single institute over 30 years. *J Gastroenterol Hepatol.* 2007;22(9):1435–1442.
24. Park YK, Yoon HM, Kim YW, et al. Laparoscopy-assisted versus open D2 distal gastrectomy for advanced gastric cancer: results from a randomized phase II multicenter clinical trial (COACT 1001). *Ann Surg.* 2017;42(9):S98–S99.
25. Peeters KC, Hundahl SA, Kranenbarg EK, Hartgrink H, Cj VDV. Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1-D2 trial. *World J Surg.* 2005;29(12):1576–1584.
26. Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than Number? An analysis of 1038 patients. *Ann Surg.* 2000;232(3):362–371.
27. Liu X, Long Z, Cai H, Huang H, Shi Y, Wang Y. Analysis of lymph node metastasis correlation with prognosis in patients with T2 gastric cancer. *PLoS ONE.* 2014;9(8):e105112.
28. Nitti D, Marchet A, Mocellin S, Rossi GM, Ambrosi A, Mencarelli R. Prognostic value of subclassification of T2 tumours in patients with gastric cancer. *Br J Surg.* 2009;96(4):398–404.
29. Oh SY, Lee KG, Suh YS, et al. Lymph node metastasis in mucosal gastric cancer: reappraisal of expanded indication of endoscopic submucosal dissection. *Ann Surg.* 2016;265:1.
30. Pokala SK, Zhang C, Chen Z, et al. Lymph node metastasis in early gastric adenocarcinoma in the United States of America. *Endoscopy.* 2018;50(5):479–486.
31. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer.* 2000;3(4):219–225.
32. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin. 2018;*8:*394–424.*
33. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* 2016;66(2):115–132.