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ORIGINAL ARTICLE

The clinicopathological characteristics and prognosis of patients with node-positive gastric cancer after curative surgery

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Abstract

Background: Lymph node (LN) metastasis is one of the independent prognostic factors of gastric cancer (GC). The difference in survival rates and initial recurrence patterns in patients with node-positive GC with retrieved LN numbers greater than or less than 16 is worthy of further study.

Methods: A total of 1314 patients with node-positive GC were enrolled. The clinicopathological characteristics, retrieved LN numbers, adjuvant chemotherapy, initial recurrence patterns, and survival differences between serosa-negative and serosa-positive GC were investigated.

Results: For serosa-negative GC, patients with retrieved LN numbers ≥16 were associated with fewer tumor recurrences, locoregional recurrences, distant metastases, and better 5-year overall survival (OS) rates and disease-free survival (DFS) rates. For serosa-positive GC, patients with retrieved LN numbers ≥16 were associated with similar locoregional and distant metastasis and similar 5-year OS and DFS rates compared with those with retrieved LN numbers <16. Retrieved LN numbers fewer than 16 can cause stage migration compared with retrieved LN numbers ≥16. Multivariate analysis showed that both the retrieved LN numbers (≥ or <16) and adjuvant chemotherapy were independent prognostic factors affecting OS in serosa-negative GC, while adjuvant chemotherapy but not the retrieved LN numbers was an independent prognostic factor of OS in serosa-positive GC.

Conclusion: For serosa-negative GC, retrieved LN numbers fewer than 16 can cause stage migration, a higher tumor recurrence rate and worse OS and DFS rates compared with patients with retrieved LN numbers ≥16. Due to a high tumor recurrence rate in serosa-positive GC, adjuvant chemotherapy rather than retrieved LN numbers played an important role in improving patient prognosis.

Keywords: Adjuvant chemotherapy; Gastric cancer; Node-positive; Retrieved LN numbers; Serosa-negative; Serosa-positive

1. INTRODUCTION

Extended lymph node (LN) dissections have been reported to have a survival benefit for patients with gastric cancer (GC) compared with limited dissections.[1] For patients with node-negative GC, occult LN metastasis not diagnosed by histological examination was associated with poorer prognosis,[2] and the number of retrieved LN was an independent prognostic factor.[3] Moreover, insufficient LN dissection might cause incorrect tumor staging and tumor recurrence, and extended LN dissection might lead to stage migration.

According to the GC treatment guidelines by the Japanese Gastric Cancer Association,[4] limited LN dissections (D1+) are performed on early GC, whereas extended LN dissections (D2) are recommended and routinely performed on advanced GC, especially in Asian countries. However, for node-positive GC, whether retrieved LN numbers have survival benefits in both serosa-negative and serosa-positive GC patients is obscure.

The aim of the present study was to compare the survival difference and initial recurrence patterns between GC patients with retrieved LN numbers ≥16 and those with retrieved LN numbers <16. For subgroup analyses, multivariate analyses were performed for investigating whether survival benefit could be achieved with retrieved LN number ≥16 in both serosa-negative and serosa-positive GC.

2. METHODS

2.1. Patients enrollment

Between January 1992 and December 2014, 1314 patients with node-positive GC receiving curative surgery were enrolled. None of the enrolled patients in the present study received neoadjuvant chemotherapy. The ethics committees of our hospital reviewed and approved this study (No. 2019-10-006BC).

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The gross features of the pathological specimens were evaluated according to the tumor location, tumor size, and Borrmann's classification. The microscopic features of lymphovascular invasion patterns were analyzed. The pathological staging of GC was defined according to the eighth American Joint Committee on Cancer/Union for International Cancer Control Tumor, Node, Metastasis (TNM) classification.[5] Serosa-negative GC was defined as a gastric tumor with pathological T1–T3, while serosa-positive GC was defined as a gastric tumor with pathological T4. All the pathological reports were confirmed by the same pathologist, Li A.F.Y., who specialized in the pathological diagnosis of GC. The data were prospectively collected and were updated regularly throughout the follow-up period.

All patients received chest films, upper gastrointestinal endoscopy, sonography, or computed tomography (CT) scan of the abdomen before surgery. We performed a total or distal subtotal gastrectomy according to the location and size of the tumor.

2.2. Follow-up

Postoperative follow-up examinations were performed every 3 months for the first 5 years, followed by every 6 months until the patient's death. The follow-up studies included physical examinations, blood tests with hemoglobin and tumor marker measurements (including carcinoembryonic antigen and carbohydrate antigen 19-9), chest films, upper gastrointestinal endoscopy, sonography and CT scans of the abdomen.

Before 2008, adjuvant chemotherapy after curative surgery was not routinely performed and was performed when tumor recurrence was diagnosed. Since 2008, adjuvant therapy has been prescribed for stage II or stage III disease in our hospital due to the proven survival benefit.[6] The major adjuvant chemotherapy agent is S-1 (TS-1, Taiho Pharmaceutical), which is an orally active combination of tegafur, gimeracil, and oteracil.[6] The other adjuvant chemotherapy agents are mainly 5-fluouracil (5-FU)-based and platinum-based chemotherapy.

2.3. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 25.0. A χ^2 test with Yates correction or Fisher's exact test was used to compare the categorical data between groups. Overall survival (OS) was calculated from the operation date to the date of death or the final follow-up visit. The disease-free survival (DFS) was measured from the operation date to the final follow-up date for patients who survived without tumor recurrence. The Kaplan–Meier method was used for the univariate analysis of the risk factors of OS and DFS. Cox proportional hazards models were used for the multivariate analysis of the risk factors of OS and DFS. A p value less than 0.05 was defined as statistically significant.

3. RESULTS

3.1. Clinicopathological features

Among the 1314 patients with node-positive GC, 86 (6.5%) had retrieved LN numbers <16 and 1228 had retrieved LN numbers ≥16. Patients with retrieved LN numbers ≥16 were associated with larger tumor sizes and increased occurrences of diffuse-type tumors, extended lymphadenectomy, advanced pathological T and N categories, and more advanced TNM stages than those with retrieved LN numbers <16.

For serosa-negative GC (Table 1), patients with retrieved LN numbers ≥16 were associated with larger tumor sizes and increased occurrences of diffuse-type GC, extended lymphadenectomy, more advanced T and N categories and advanced TNM stages than those with retrieved LN numbers <16. For serosa-positive GC, patients with retrieved LN numbers ≥16 were associated with increased occurrences of extended lymphadenectomy, and an advanced N category than those with retrieved LN numbers <16.

3.2. Stage migration

As shown in Table 2, for serosa-negative GC, there are significantly more advanced N categories and more advanced TNM stages in patients with retrieved LN numbers ≥16 than those with retrieved LN number <16, which was also observed in serosa-positive GC.

3.3. Initial recurrence patterns

Among the 1314 patients, 538 (40.9%) had tumor recurrence. The median follow-up period was 54 months. Patients with retrieved LN numbers ≥16 had fewer tumor recurrences, fewer locoregional

Table 1

Clinical profile in GC patients with retrieved LN numbers ≥ or <16

	Serosa-negative GC			Serosa-positive GC		
Variables	LN < 16 n = 48 n (%)	LN ≥ 16 n = 754 n (%)	*p*	LN < 16 n = 38 n (%)	LN ≥ 16 n = 474 n (%)	*p*
Age			0.425			0.389
<65 y	16 (33.3)	295 (39.1)		10 (26.3)	157 (33.1)	
≥65 y	32 (66.7)	459 (60.9)		28 (73.7)	317 (66.9)	
Gender (male/female)	33/15	530/224	0.821	34/4	372/102	0.108
Tumor size (<5/≥5 cm)	36/12	327/427	<0.001	9/29	76/398	0.223
Gross appearance			0.349			0.211
Superficial type	15 (31.3)	168 (22.3)		5 (13.2)	19 (4.0)	
Borrmann types 1 and 2	12 (25.0)	202 (26.8)		4 (10.5)	83 (17.5)	
Borrmann types 3 and 4	21 (43.8)	384 (50.9)		29 (76.3)	372 (78.5)	
Lauren's classification			0.001			0.288
Intestinal type	35 (72.9)	371 (49.2)		22 (57.9)	232 (48.9)	
Diffuse type	13 (27.1)	383 (50.8)		16 (42.1)	242 (51.1)	
Extent of lymphadenectomy			<0.001			<0.001
<D2	29 (60.4)	116 (15.4)		27 (71.1)	64 (13.5)	
≥D2	19 (39.6)	638 (84.6)		11 (28.9)	410 (86.5)	
Lymphovascular invasion	38 (79.2)	564 (74.8)	0.498	35 (92.1)	445 (93.9)	0.663

GC = gastric cancer; LN = lymph node.

Table 2

The stage migration between patients with retrieved LN numbers <16 and those with retrieved LN numbers ≥16 in serosa-negative and serosa-positive GC patients

	Serosa-negative GC n = 802			Serosa-positive GC n = 512		
	Retrieved LN number <16 n = 48	Retrieved LN number ≥16 n = 754	*p*	Retrieved LN number <16 n = 38	Retrieved LN number ≥16 n = 474	*p*
Pathological N category			<0.001			<0.001
N1	34 (70.8)	236 (31.3)		13 (34.2)	75 (15.8)	
N2	12 (25.0)	236 (31.3)		17 (44.7)	126 (26.6)	
N3	2 (4.2)	282 (37.4)		8 (21.1)	273 (57.6)	
Pathological TNM stage			<0.001			<0.001
IB	12 (25.0)	59 (7.8)		…	…	
IIA	14 (29.2)	105 (13.9)		…	…	
IIB	16 (33.3)	172 (22.8)		…	…	
IIIA	5 (10.4)	169 (22.4)		28 (73.7)	163 (34.4)	
IIIB	1 (2.1)	145 (19.2)		9 (23.7)	130 (27.4)	
IIIC	0	104 (13.8)		1 (2.6)	181 (38.2)	

LN = lymph node; GC = gastric cancer; TNM = tumor, node, metastasis.

recurrences, and fewer distant metastases than those with retrieved LN numbers <16. Multivariate analysis confirmed that patients with retrieved LN numbers ≥16 had significantly fewer locoregional recurrences than those with retrieved LN numbers <16.

For serosa-negative GC (Table 3), patients with retrieved LN numbers ≥16 had significantly fewer tumor recurrences, fewer locoregional recurrences, and fewer distant metastases than those with retrieved LN numbers <16. Multivariate analysis showed that patients with retrieved LN numbers ≥16 had significantly fewer locoregional recurrences than those with retrieved LN numbers <16.

For serosa-positive GC (Table 3), both univariate and multivariate analyses showed that patients with retrieved LN numbers ≥16 had similar tumor recurrences, locoregional recurrences and distant metastases compared with those with retrieved LN numbers <16.

3.4. Survival analysis

Among the 1314 patients, the 5-year OS rates (57.2% vs. 53.1%, $p = 0.279$) and DFS rates (49.6% vs. 50.1%, $p = 0.504$) were not significantly different between patients with retrieved LN numbers ≥16 and those with retrieved LN numbers <16.

As shown in Fig. 1a and b, for serosa-negative GC, the 5-year OS rates (50.3% vs. 32.4%, $p = 0.037$) and DFS rates (46.6% vs. 28.4%, $p = 0.049$) were significantly higher in patients with retrieved LN numbers ≥16 than in those with retrieved LN numbers <16. For serosa-positive GC, there was no significant difference in the 5-year OS rates (24.0% vs. 28.3%, $p = 0.456$, Fig. 1c) and DFS rates (19.5% vs. 22.9%, $p = 0.519$, Fig. 1d) between patients with retrieved LN numbers ≥16 and patients with retrieved LN numbers <16.

For stage-II GC, patients with adjuvant chemotherapy had significantly better 5-year OS rates (78.0% vs. 64.5%, $p = 0.038$) and similar 5-year DFS rates (65.0% vs. 62.2%, $p = 0.188$) compared with those without adjuvant chemotherapy. For stage-III GC, patients with adjuvant chemotherapy had significantly better 5-years OS rates (39.1% vs. 24.2 %, $p < 0.001$) and DFS rates (31.3% vs. 21.0%, $p < 0.001$) than those without adjuvant chemotherapy.

For serosa-negative GC (Table 4), the multivariate analysis of factors affecting OS showed that age, tumor size, gross appearance, lymphovascular invasion, pathological TNM stage, adjuvant chemotherapy, and the retrieved LN numbers were independent prognostic factors; for DFS, age, tumor size, gross appearance, lymphovascular invasion, pathological TNM stage, and the retrieved LN numbers were independent prognostic factors. For serosa-positive GC, the multivariate analysis of factors affecting OS demonstrated that age, tumor size, gross appearance, lymphovascular invasion, and adjuvant chemotherapy were independent prognostic factors; for DFS, tumor size, gross appearance, and lymphovascular invasion were independent prognostic factors.

4. DISCUSSION

In this study, node-positive GC patients with retrieved LN numbers ≥16 were associated with better 5-year OS and DFS rates and fewer tumor recurrences than those with retrieved LN numbers

Table 3

The initial recurrence pattern in patients with gastric cancer after curative surgery

	Serosa-negative GC						Serosa-positive GC					
	LN <16 n = 48 n (%)	LN ≥16 n = 754 n (%)	Univariate analysis *p*	Multivariate analysis Odds ratio	CI	*p*	LN <16 n = 38 n (%)	LN ≥16 n = 474 n (%)	Univariate analysis *p*	Multivariate analysis Odds ratio	CI	*p*
Total patients with recurrence	21 (43.8)	228 (30.2)	0.038				25 (65.8)	264 (55.7)	0.227			
Locoregional recurrence	13 (27.1)	78 (10.3)	<0.001	2.85	0.168–0.735	0.005	14 (36.8)	114 (24.1)	0.080	1.83	0.263–1.140	0.107
Distant metastasis	14 (29.2)	134 (17.8)	0.048	1.36	0.360–1.498	0.395	18 (47.4)	201 (42.4)	0.552	1.02	0.483–1.973	0.946
Peritoneal dissemination	3 (6.3)	69 (9.2)					10 (26.3)	134 (28.3)				
Hematogenous metastasis	9 (18.8)	88 (11.7)					7 (18.4)	106 (22.4)				
Distant lymphatic recurrence	6 (12.5)	43 (5.7)					6 (15.8)	69 (14.6)				

Some patients had more than one recurrence pattern.

CI = confidence interval; GC = gastric cancer; LN = lymph node.

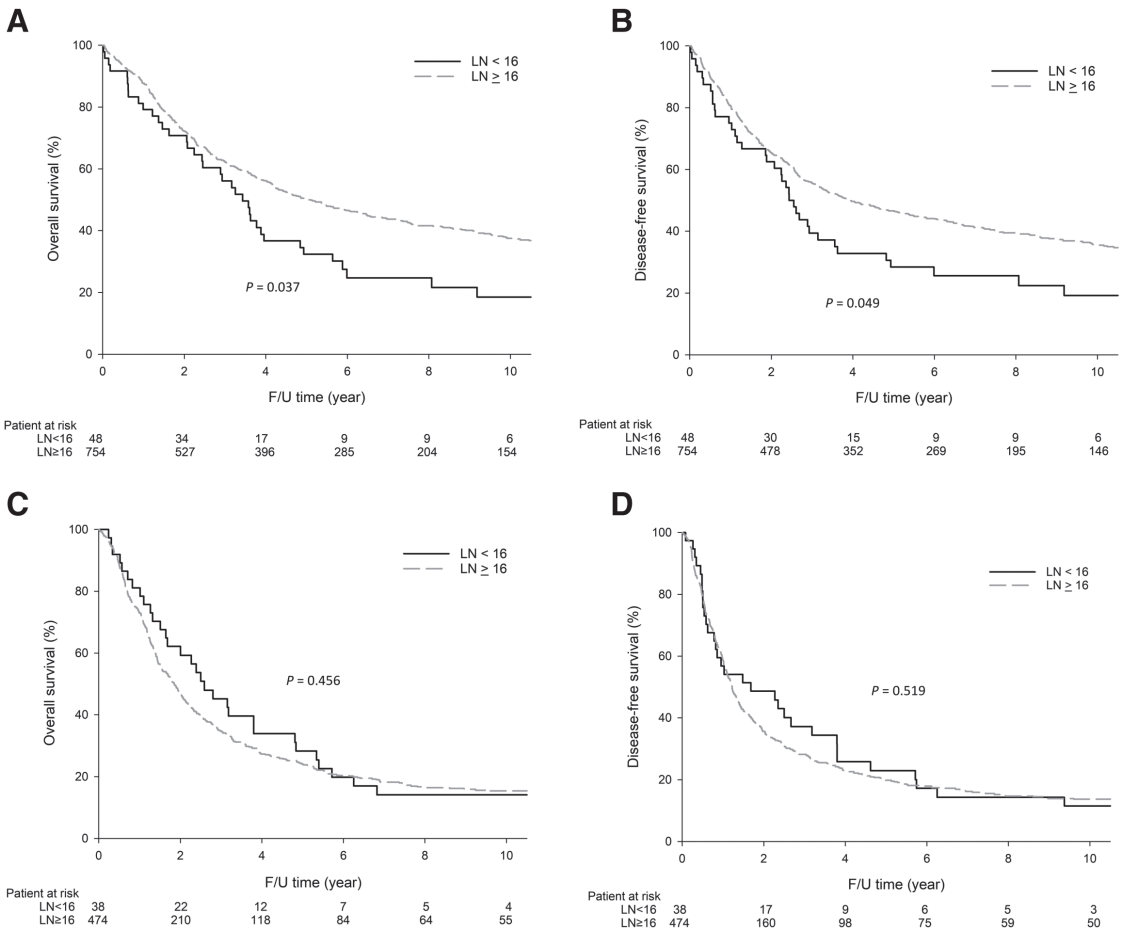

Fig. 1. For serosa-negative GC, patients with retrieved LN numbers ≥16 had significantly better 5-year OS rates (50.3% vs. 32.4%, $p = 0.037$) and DFS rates (46.6% vs. 28.4%, $p = 0.049$) than those with retrieved LN numbers <16. For serosa-positive GC, there was no significant difference in the 5-year OS rates (24.0% vs. 28.3%, $p = 0.456$) and DFS rates (19.5% vs. 22.9%, $p = 0.519$) between patients with retrieved LN numbers ≥16 and patients with retrieved LN numbers <16. (a) The OS curves of serosa-negative GC, (b) the DFS curves of serosa-negative GC, (c) the OS curves of serosa-positive GC, and (d) the DFS curves of serosa-positive GC. DFS = disease-free survival; GC = gastric cancer; LN = lymph node; OS = overall survival.

<16 only in serosa-negative GC, which might be due to stage migration. The retrieved LN number was an independent prognostic factor affecting OS and DFS only for serosa-negative GC.

In the present study, node-positive patients with retrieved LN numbers ≥16 were associated with fewer tumor recurrences than those with retrieved LN numbers <16; however, the 5-year OS and DFS rates were not significantly different. For only serosa-negative GC, patients with retrieved LN numbers ≥16 had better OS and DFS rates than those with retrieved LN numbers <16. Furthermore, stage migration was observed in patients with retrieved LN numbers ≥16 compared with those with retrieved LN numbers <16 in both serosa-negative and serosa-positive GC. In a study by Biondi et al, patients with retrieved LN numbers <16 were associated with worse survival than those with retrieved LN numbers ≥16. They concluded that retrieved LN numbers <16 may cause inaccurate staging and/or inadequate treatment.[7] A large multicenter study in Japan demonstrated that the pathological T and N categories and the number of retrieved LN were independent prognostic factors affecting OS for serosa-negative and locally advanced GC.[8] It seems that the number of retrieved LN can contribute to enhancing the accuracy of TNM classification, and the prognostic difference between the two groups (<16 retrieved LNs and ≥16 retrieved LNs) was only the result of stage migration.

Serosa-positive GC is one of the independent risk factors for peritoneal recurrence and is associated with a median post-recurrence survival time of 3 months.[9] Our results showed that the tumor recurrence rate was 65.8% in the retrieved LN numbers <16 groups and 55.7% in the retrieved LN numbers ≥16 group. Peritoneal recurrence is the most common recurrence pattern in serosa-positive GC, with 26.3% in the retrieved LN numbers <16 group and 28.3% in the retrieved LN numbers ≥16 group, and the median post-recurrence survival time was less than three months in both the retrieved LN numbers <16 and retrieved LN numbers ≥16 groups. One of our important findings in the present study was that serosa-positive GC was associated with a high tumor recurrence rate and poor prognosis; thus, the number of retrieved LN might not provide significant survival benefit and adjuvant chemotherapy played a more important role in improving patient survival.

In the present study, multivariate analysis demonstrated that the extent of lymphadenectomy was not an independent prognostic factor affecting OS and DFS in node-positive GC. In a study by Hirabayashi et al, the retrieved LN numbers instead of the extent of lymphadenectomy was one of the independent prognostic factors in node-positive GC,[8] that was similar to our results. In the present study, most patients (n = 1078, 82.0%) received at least D2 lymphadenectomy, which may affect the statistical significance of the survival benefit of extended lymphadenectomy since this group was compared with a small number of patients receiving limited lymphadenectomy. Our results demonstrated that adjuvant chemotherapy can improve OS in

Table 4

Multivariate analysis of factors affecting OS and DFS of serosa-negative patients with GC

	OS			DFS		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (y/o)			<0.001			<0.001
<65	1.00			1.00		
≥65	1.72	1.407–2.111		1.65	1.356–2.016	
Gender			0.101			0.072
Male	1.00			1.00		
Female	0.84	0.674–1.036		0.82	0.668–1.017	
Tumor size (cm)			0.009			0.011
<5	1.00			1.00		
≥5	1.30	1.067–1.579		1.27	1.045–1.533	
Gross appearance			0.034			0.046
Superficial type	1.00			1.00		
Borrmann types 1 and 2	0.99	0.727–1.339		0.96	0.711–1.288	
Borrmann types 3 and 4	1.27	0.967–1.670		1.23	0.939–1.599	
Lymphovascular invasion			0.001			0.005
Absent	1.00			1.00		
Present	1.50	1.169–1.912		1.41	1.109–1.780	
Pathological TNM stage			<0.001			<0.001
I	1.00			1.00		
II	1.36	0.874–2.104		1.53	0.989–2.366	
III	3.53	2.238–5.564		3.77	2.398–5.930	
Extent of lymphadenectomy			0.280			0.232
D1	1.00			1.00		
≥D2	0.88	0.690–1.113		0.87	0.683–1.097	
Adjuvant chemotherapy			0.006			0.054
No	1.00			1.00		
Yes	0.72	0.564–0.910		0.80	0.635–1.003	
Retrieved LN numbers			<0.001			<0.001
<16	1.00			1.00		
≥16	0.42	0.291–0.617		0.44	0.302–0.635	

DFS = disease-free survival; LN = lymph node; OS = overall survival; TNM = tumor, node, metastasis.

stage-II and stage-III GC with node-positive. Furthermore, adjuvant chemotherapy was one of the independent prognostic factors affecting OS in serosa-negative GC. For serosa-positive GC, adjuvant chemotherapy rather than the retrieved LN numbers were one of the independent prognostic factors affecting OS. In the present study, node-positive GC patients who were serosa-positive were associated with a poor prognosis; consequently, adjuvant chemotherapy plays a more important role than the retrieved LN numbers in improving patient survival.

There are some limitations in the present study. First, it was a retrospective study and selection bias exists. Second, this was a single institutional study in an Asian population, and the results might not be applicable in other countries with different races.

In conclusion, our results demonstrated that for node-positive GC, the number of retrieved LN was an independent prognostic factor affecting OS and DFS in only serosa-negative GC, which might be the result of stage migration. Serosa-positive GC patients were associated with a higher tumor recurrence rate and a worse survival rate than serosa-negative GC patients; greater retrieved LN numbers could not provide survival benefits for this group of patients, and the role of adjuvant chemotherapy was important in improving patient prognosis.

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