

Is retrieval of at least 15 lymph nodes sufficient recommendation in early gastric cancer?

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Purpose: The evaluation and extent of lymph node (LN) retrieval is clinically relevant for staging because lymphatic invasion is the most common mechanism leading to up-staging of carcinoma. However, the optimal number of LN retrievals for early gastric cancer (EGC) is unclear. With the aim of clarification, we analyzed our database to investigate the optimal number of retrieved LNs in EGC.

Methods: Three hundred twenty-six gastric cancer patients who underwent curative gastrectomy with D2 LN dissection at Ewha Womans University Hospital (Dongdaemun and Mokdong) were analyzed according to sex, age, tumor location, size of tumor, macroscopic type, histological classification, depth of invasion, LNs metastasis, TNM stage and type of surgery.

Results: In LN negative cases, patients with 15–25 retrieved LNs had a 5- and 10-year survival rate of 88% and 54%, respectively, whereas retrieval of ≥ 26 LNs was associated with 5- and 10-year survival rate of 90% and 75%, respectively ($P = 0.105$). In LN positive cases, the 5- and 10-year survival rate was 50% and 30% for the 15–25 group, and 77% and 67% for the ≥ 26 group, respectively ($P = 0.044$).

Conclusion: LN metastasis is an independent factor of survival and the number of retrieved LNs significantly relate to the long-term survival benefit in node metastatic EGC. Also, our data suggest that the retrieval of at least 15 LNs may not be sufficient to warrant recommendation for more curative surgery, and that qualified LN dissection should be considered if LN metastasis is in doubt, even in EGC.

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Key Words: Lymph node, Stomach neoplasms, Harvest

INTRODUCTION

In gastric cancer, curative surgery requires tumor resection with enough negative resection margin along with its corresponding lymph nodes (LNs). The evaluation and extent of LN retrieval is clinically relevant for staging because number of LN invasion is the most common mechanism leading to up-staging of carcinoma and one of the most important prognostic factors [1,2]. However, the optimal number of LNs that should be retrieved in the staging of gastric cancer is debatable. In advanced gastric cancer, retrieval of more than 25 LNs has been associated with an overall survival advantage in advanced gastric cancer patients [3,4]. Smith et al. [5] reported

that the stage subgroup-specific survival depended strongly on the total number of LNs examined and culminated in the highest survival for counts of 40 or more LNs, a strong incentive in favor of extended lymphadenectomy. While there is no universally accepted minimum number of LNs necessary for accurate staging of gastric cancer, retrieval of at least 15 LNs is recommended to avoid stage migration in National Comprehensive Cancer Network (NCCN) guidelines version 2.2013 [3,5-8].

The number of LNs that should be retrieved after gastrectomy has varied according to the institution and country [8]. In many Asian centers, surgeons do the sampling and submission of individual LNs for histological analysis, whereas surgeons in

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the West submit *en bloc* resected specimens and rely upon pathologists to retrieve LNs. Therefore, LN enumeration can depend upon both the surgeon and pathologist [9]. However, studies from Asia and the United States have concentrated on the LNs in cases of advanced cancer [10,11] with no adequate data concerning the optimal number of retrieved LNs in early gastric cancer (EGC) [12,13].

With the aim of clarification, we analyzed our database to investigate the optimal number of retrieved LNs in EGC.

METHODS

We retrospectively reviewed the database of patients who underwent gastrectomy due to gastric carcinoma at Ewha Womans University Hospital, Seoul, Korea, from January 1995 to December 2009. Among 576 EGC patients, we enrolled 326 EGC patients who underwent curative gastrectomy with D2 LN dissection. All patients with fewer than 15 retrieved LNs and endoscopic/laparoscopic treatment were excluded. Sex, age, tumor location, size of tumor, macroscopic type, histological classification, depth of invasion, LN metastasis, TNM stage, and type of surgery were analyzed. Histologic classification was divided into differentiated and undifferentiated subgroups. The depth of tumor invasion and TNM stage were classified according to the 7th edition of the American Joint Committee on Cancer/International Union Against Cancer [14]. LN metastasis was grouped as negative and positive involvement of tumor. Patients were stratified into two groups by number of retrieved LNs using the cut-point of 25 LNs: $15 < \text{LN} < 25$ vs. $\text{LN} > 26$. Subgroup analysis of patient demographic, clinical, and pathologic factors was also performed according to the number of retrieved LNs. Most surgeries in our data were done by a single surgeon, and the LNs from the specimens were sampled by general surgeons.

Statistical analyses

Chi-square analysis and Student t-test were used to compare the subgroup parameters. All deaths including non-cancer-related mortality were regarded as events. The numerical data were expressed as the mean and standard deviation. Survival analyses were performed using the Kaplan-Meier method and comparisons across different strata were made with the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression model for the analysis of prognosis. The statistical analyses were performed using the IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). The results were evaluated with a confidence interval of 95%, and P-values below 0.05 were considered to be statistically significant.

RESULTS

A total of 326 patients with gastric carcinoma were enrolled. Their mean follow-up period was 113.4 ± 56 months (range, 2–168 months). The characteristics of patients according to number of retrieved LNs are shown in Table 1. The mean age at diagnosis was 58.4 ± 12.9 years in males and 57.7 ± 13.3 years in females. Overall, 197 (60.4%) were male and 129 (39.5%) were female. No statistical differences between patients with 15–25 and ≥ 26 retrieved LNs were evident according to gender, age, location, size, and histology. The elevated tumor (type I) and depressed tumor (type III) showed higher LN yields ($P < 0.001$). The greater the degree of local invasion of the tumor, the more retrieved LNs were identified ($P = 0.037$). Likewise, the LN involvement of tumors was associated with higher LN retrieval ($P < 0.001$). The overall mean number of retrieved LNs per patient was 36.37 ± 18.2 (35.02 ± 17.2 in node negative patients, 43.05 ± 21.8 in node positive patients). Tumor location

Table 1. Characteristics of early gastric cancer patients according to lymph node retrieval (n = 326)

Characteristic	No. of retrieved lymph node		P-value
	15–25 (n = 178)	≥ 26 (n = 148)	
Gender			0.910
Male	107 (60.1)	90 (60.8)	
Female	71 (39.8)	58 (39.2)	
Age (yr)	58.4 ± 12.9	57.7 ± 13.3	0.094
Location			0.479
Upper	15 (8.4)	17 (11.5)	
Middle	22 (12.4)	22 (14.9)	
Lower	141 (79.2)	109 (73.6)	
Size (cm)	2.49 ± 2.9	2.8 ± 2.7	0.591
Macroscopic type			<0.001
I	7 (3.9)	12 (8.1)	
II	160 (89.9)	108 (73.0)	
III	11 (6.2)	28 (18.9)	
Histology			0.655
Differentiated	103 (57.9)	82 (55.4)	
Undifferentiated	75 (42.1)	66 (44.6)	
Depth of invasion			0.037
Tis	3 (1.7)	1 (0.7)	
T1a	94 (52.8)	59 (39.9)	
T1b	81 (45.5)	88 (59.5)	
Lymph node metastasis			<0.001
No	166 (93.3)	118 (79.7)	
Yes	12 (6.7)	30 (20.3)	
Type of surgery			<0.001
Total gastrectomy	12 (6.7)	29 (19.6)	
Subtotal gastrectomy	166 (93.3)	119 (80.4)	

Values are presented as number (%) or mean \pm standard deviation.

($P = 0.479$) and size ($P = 0.591$) were not related with LN retrieval, but total gastrectomy was more common in patients with >25 retrieved LNs ($P < 0.001$).

The overall 5- and 10-year survival rates were 86% and 59%, respectively. The respective rates in patients with 15–25 retrieved LNs were 85% and 52%. In patients with ≥ 26 retrieved LNs the respective rate was 87% and 73% ($P = 0.069$) (Table 2, Fig. 1). In LN negative cases, the respective survival rates in the 15–25 group were 88% and 54%, and the respective rates in the ≥ 26 group were 90% and 75% ($P = 0.105$) (Table 2, Fig. 2). In LN positive cases, the respective rates in the 15–25 group were 50% and 30%, and the respective rates in the ≥ 26 group were 77% and 67% ($P = 0.044$) (Table 2, Fig. 3).

In the univariate analysis, gender, age, histology, depth of invasion, LN metastasis, and stage correlated significantly with overall survival, while location, size, and macroscopic type did not. Multivariate regression analysis (Table 3) revealed that independent variables showing predictive ability were gender ($P = 0.008$), age ($P < 0.001$), LN metastases ($P < 0.001$), and stage ($P = 0.001$).

Table 2. Overall 5-year and 10-year survival rate according to the LNs retrieval

LNs	5-Year survival rate (%)	10-Year survival rate (%)	P-value
Total			0.069
15–25	85	52	
≥ 26	87	73	
LNs (-)			0.105
15–25	88	54	
≥ 26	90	75	
LNs (+)			0.044
15–25	50	30	
≥ 26	77	67	

LN, lymph node.

Table 3. Prognostic factors of early gastric cancer patients

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Male vs. female	0.409 (0.254–0.659)	<0.001	0.510 (0.311–0.836)	0.008
Age	1.052 (1.031–1.073)	<0.001	1.052 (1.029–1.075)	<0.001
Location	1.070 (0.753–1.519)	0.706		
Size	0.992 (0.922–1.068)	0.837		
Macroscopic type	1.114 (0.927–1.339)	0.249		
Histology	0.852 (0.740–0.981)	0.026		
Depth of invasion	1.243 (1.067–1.447)	0.005		
Lymph node metastasis	1.269 (1.081–1.473)	0.003	1.152 (1.071–1.238)	<0.001
Stage	1.428 (1.012–2.013)	0.042	1.738 (1.268–2.384)	0.001

HR, hazard ratio; CI, confidence interval.

DISCUSSION

LN involvement of gastric cancer is one of the strongest

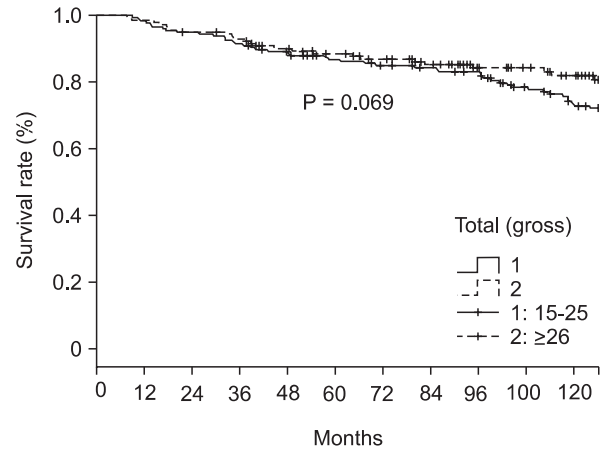


Fig. 1. Survival rate according to the number of lymph nodes retrieval in whole cases.

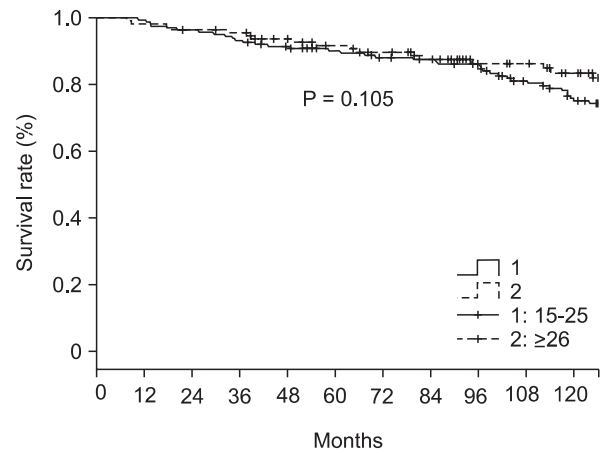


Fig. 2. Survival rate according to the number of lymph nodes retrieval in node negative cases.

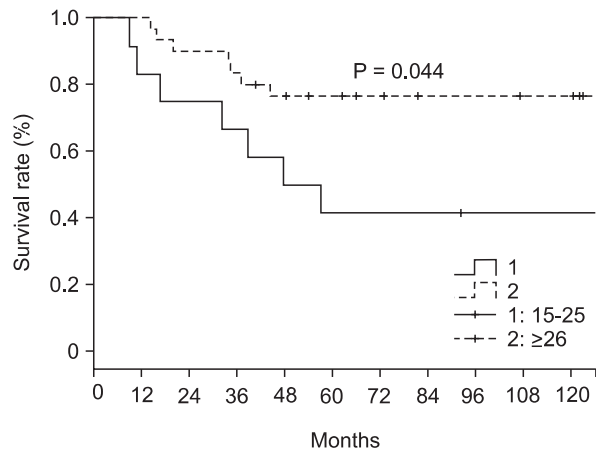


Fig. 3. Survival rate according to the number of lymph nodes retrieval in node positive cases.

prognostic parameters after gastrectomy for survival and recurrence. Precise evaluation of the extent of LN metastasis offers the ability to more accurately predict oncologic outcomes for the individual patient. However, the appropriate degree of curative LN dissection differs between Western and Eastern countries. In a Japanese classification, the extent of LN dissection was represented by D0–D3 using the LN station system. The system is complicated and is hard to use due to variations in each category [15]. Instead, the number of the examined LNs has been used as a simpler indicator of the extent of LN dissection. However, the absence of a fixed cutoff number of retrieved LNs for standard treatment in gastric carcinoma is a complication. The optimal extent of regional LNs during the gastrectomy for gastric adenocarcinoma continues to be debated. Baiocchi et al. [3] and Chen et al. [4] proposed that the trend towards superior survival outcome could be followed after the retrieval of more than 25 LNs. Smith et al. [5] presented that the stage subgroup-specific survival depends strongly on the total number of LNs examined and culminates in the highest survival at counts of 40 LNs. Bouvier et al. [16] suggested that staging is not reliable when fewer than 10 LNs are examined. Although a universally accepted minimum number of LNs necessary for accurate staging of gastric cancer has not been recognized, retrieval of at least 15 LNs is recommended to avoid stage migration in NCCN guidelines version 2, 2013 [7].

Presently, the mean number of retrieved LNs per patient was 36.37 ± 18.2 overall, 35.02 ± 17.2 in LN negative patients, and 43.05 ± 21.8 in LN positive patients. These values were higher than other similar studies [3,10,16]. A higher number of retrieved LNs is expected to reduce the bias of stage migration and permit analysis without bias of reliability [5,17-19]. Presently, the higher number of retrieved LNs were identified in depressed lesions (type III, $P < 0.001$) and more invasive

tumors ($P = 0.037$). A tumor invading into the submucosa with depressed lesion might be considered as an advanced carcinoma because of difficult differentiation of depth. In these cases, surgeons endeavor to perform extended LN dissection for curative surgery. Therefore, our data might show a higher number of retrieved LNs in cases of depressed lesions and deeper lesions. But, a direct comparison of our data to previous studies is not possible because of the dissimilarity of the studies.

The presence of LN metastasis was associated with a higher number of retrieved LNs ($P < 0.001$). This may similarly reflect the aforementioned depth of invasion. In other words, if the LN metastasis was in doubt in the operation field, more aggressive LN dissection would be performed. Extended LN dissection would enable surgeons to improve the overall survival in node metastasis cases and to prevent stage migration [1,17,18]. We recorded a greater prevalence of total gastrectomy in the ≥ 26 group compared with the 15–25 group, although there was no significant difference of location and size between groups. There is no precise reason to explain the result, but only that it might be attributed to the depth of invasion and LN metastasis.

Survival analysis according to the number of retrieved LNs did not differ significantly, ($P = 0.258$) with the exception of LN-positive cases, where overall survival was significantly different between the 15–25 group (lower survival) and ≥ 26 group (higher survival) ($P = 0.044$) (Fig. 3). From this result, we could assume higher LN retrieval might more completely remove micrometastatic LNs, which were not identified as metastatic LNs in the pathologic report.

Univariate analysis revealed statistical significance in gender, age, histology, depth of invasion, LN metastasis, and stage on survival. In multivariate analysis, LN metastasis ($P < 0.001$) and stage ($P = 0.001$) were independent predictive factors affecting survival, as in previous studies [13,20,21].

This study has several limitations. It was retrospective and small in size. Also, lacking in data concerning chemotherapy, which might result in better survival in node-positive patients.

In conclusion, LN metastasis is an independent factor of survival and the number of retrieved LNs significantly relate to the long-term survival benefit in node metastatic EGC. The data suggest that the retrieval of at least 15 LNs may not be sufficient to recommend more curative surgery, and that qualified LN dissection should be considered if LN metastasis is in doubt, even in EGC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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