The Impact of Total Retrieved Lymph Nodes on Staging and Survival of Patients With pT3 Gastric Cancer

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BACKGROUND. The incidence of lymph node metastasis is high in patients who have pT3 gastric cancer. However, the impact of total retrieved lymph nodes (tLNs) on staging and survival of these patients is not clear.

METHODS. For this study, the authors examined 1895 patients with pT3 gastric cancer who underwent surgery at Yonsei University Medical College from January 1987 to June 2000.

RESULTS. Four hundred sixty of 1895 patients (24.3%) were diagnosed with pT3N0 gastric cancer. Patients who had <31 tLNs (25th percentile) had less advanced lymph node (N) stage than the other patients ($P < .001$). Lymph node metastasis had a positive association with the number of tLNs in a logistic regression analysis ($P < .001$; hazards ratio, 1.014; 95% confidence interval, 1.006–1.021). With a median follow-up of 61.1 months, the overall 10-year survival rate (10-YSR) was 42.8%. Patients with pT3N0 disease who had <31 tLNs had a 10-YSR of only 55.4%. Although this 10-YSR did not differ significantly from the rate for patients with N0 disease who had ≥31 tLNs (65.8%; $P = .108$), it approached the rate for the N1 group (53.3%; $P = .207$). In multivariable analyses, the number of tLNs emerged as an independent prognostic predictor in patients with pT3N2 and pT3N3 disease, but not in patients with pT3N0 or pT3N1 disease.

CONCLUSIONS. Increasing numbers of tLNs may improve the accuracy of staging in patients who have pT3 gastric cancer. Because preoperative lymph node staging is difficult, a thorough lymph node dissection is mandatory in all serosa-positive patients. ***Cancer* 2007;110:745–51.** © *2007 American Cancer Society.*

KEYWORDS: gastric cancer, T3, stage migration, survival.

The incidence of lymph node metastasis is >70% in patients who have pT3 gastric cancer, and advanced lymph node (N) stage (N3) also is frequent.[1–3] Based on the International Union against Cancer (UICC) tumor, lymph node, metastasis (TNM) classification system, lymph node metastasis increases the tumor severity from stage II to stage III or even to stage IV.[4] Survival is much poorer for patients who have positive lymph node status.[5,6] Thus, N staging in patients with pT3 gastric cancer, especially for pT3N0 lesions, should be conducted very carefully.

Since its adoption in 1997, the UICC TNM system (5th edition) for lymph node involvement of gastric carcinoma has become widely accepted and is considered superior to the prior classification system.[7–9] According to this system, >15 retrieved and analyzed lymph nodes (tLNs) for each patient is required for optimal staging.[4,10] However, because of the extremely high incidence of lymph node metastasis, it is unclear whether 15 tLNs are adequate to accurately stage

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pT3 gastric cancer, especially for pT3N0 lesions. To the best of our knowledge, there is no such study.

Increasing the number of tLNs, which may provide an indication of the extent of lymph node dissection, reportedly had a survival benefit for certain subsets of gastric cancer patients who underwent curative resection.[6,11] Thus, we hypothesized that more tLNs also could lead to a better prognosis for patients with pT3 disease. The objective of the current study was to investigate the impact of increasing numbers of tLNs on the staging and survival of patients with pT3 gastric cancer.

MATERIALS AND METHODS

Surgery and Stage Classification

A prospective database was reviewed for this study. Between January 1987 and June 2000, 5532 patients with gastric cancer underwent surgery at the Department of Surgery, Yonsei University College of Medicine. Of these, 2091 patients had a pathologic diagnosis of pT3 gastric cancer, because the primary tumor penetrated the serosa without invading adjacent structures.[4] One hundred thirty-one patients who had pT3 gastric cancer with peritoneal and/or distant metastasis were excluded along with 65 patients who underwent palliative surgery. Finally, 1895 patients were enrolled in this study, including 32 patients who had <15 tLNs. In addition, for the purposes of comparison, we evaluated 1452 patients with pT1 disease and 885 patients with pT2 disease who were enrolled using the same criteria.

All patients in the study underwent the following standard operations: 1) total or distal subtotal gastrectomy, depending on the location and macroscopic appearance of the primary tumor, and 2) at least D2 lymphadenectomy. The definitions for lymphadenectomy are based on the Japanese Research Society for Gastric Cancer (JRSGC) rules, which classify the regional lymph nodes of the stomach into 4 compartments.[12] A D2 lymphadenectomy includes a complete dissection of compartments I and II; whereas a D3 lymphadenectomy includes a complete dissection of compartments I, II, and III. Compartment I consists of perigastric lymph nodes. Compartment II consists of lymph nodes along the left gastric artery, the common hepatic artery, the splenic artery, and around the celiac axis. However, when the cancer is located in the lower third of the stomach, lymph nodes along the splenic artery are classified as located in compartment III. Compartment III also consists of lymph nodes in the hepatoduodenal ligament, at the posterior aspect of the head of the pancreas, and at the root of the mesentery. Compartment IV consists of lymph nodes along the middle colic vessels and paraaortic lymph nodes.

Resected specimens were examined carefully for accurate pathologic staging according to the JRSGC rules.[12] Depth of invasion was determined precisely by examining the deepest portion of gastric wall invasion. The classification of dissected lymph nodes was verified by surgeons who reviewed the excised specimens after surgery. All lymph nodes that were retrieved were stained with hematoxylin and eosin and were examined for metastasis by specialized pathologists using light microscopy.

Statistical Analysis

All statistical analyses were conducted using the statistical program, SPSS (version 13.0; SPSS, Chicago, Ill). Pretreatment characteristics were analyzed using the 2-tailed chi-square test, the Kruskall-Wallis test, and the 2-tailed *t* test. The relation between the number of tLNs and the number of metastatic lymph nodes (mLNs) was assessed both by correlation test and by curvilinear regression. Logistic regression was used to determine the independent risk factors for lymph node metastasis. Survival analyses were assessed using the Kaplan-Meier method and a Cox proportional-hazards regression model. In all statistical analyses, a P value $<.05$ was considered significant.

RESULTS

Patient Characteristics

Table 1 provides a detailed description of patient characteristics. The ratio of men to women was 1.99 to 1 (1262 men and 633 women), and the mean age was 55 years. The median number of tLNs was 41, and the 25th and 75th quartiles were 31 tLNs and 53 tLNs, respectively. Four hundred sixty patients (24.3%) had their disease staged as pT3N0. The incidence of lymph node metastasis was 75.7% in this study. Six hundred eighty-seven patients (36.3%) had pT3N1 disease, 435 patients (23.0%) had pT3N2 disease, and 313 patients (16.4%) had pT3N3 disease; thus, the final stage grouping settled at stage III or IV.

Correlations Between tLNs and mLNs

The distribution of N stage differed significantly between patients who had <31 tLNs and all other patients ($P < .001$) (Table 1). The patients with <31 tLNs had less advanced disease. The number of mLNs was correlated highly with the number of tLNs ($P < .001$). Curvilinear regression revealed a linear correlation (R^2) between tLNs and mLNs ($P < .001$;

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%)			*P*
	All	tLN ≤30	tLN >30	
Total no.	1895	432	1463	
Mean age, y	55	56	55	.062
Gender				
Men	1262	276 (63.9)	986 (67.4)	.543
Women	633	156 (36.1)	477 (32.6)	
Macroscopic (Bormann) type				
I	94	21 (4.9)	73 (4.99)	.375
II	328	88 (20.4)	240 (16.4)	
III	1213	271 (62.7)	942 (64.39)	
IV	241	48 (11.1)	193 (13.19)	
Unknown	19	4 (0.9)	15 (1.03)	
Location				
Upper third	301	67 (15.5)	234 (15.99)	.181
Middle third	753	168 (38.9)	585 (39.99)	
Lower third	782	188 (43.5)	594 (40.60)	
Diffuse	30	2 (0.5)	28 (1.91)	
Unknown	29	7 (1.6)	22 (1.5)	
Mean size, cm	5.8	5.3	5.9	<.001
Histologic type				
Differentiated	621	146 (33.8)	475 (32.47)	.404
Undifferentiated	1270	285 (66)	985 (67.33)	
Unknown	4	1 (0.2)	3 (0.21)	
Mean no. of tLNs	43	24	46	<.001
Pathologic LN status				
pN0	460	121 (28)	339 (23.17)	<.001
pN1	687	195 (45.1)	492 (33.63)	
pN2	435	96 (22.2)	339 (23.17)	
pN3	313	20 (4.6)	293 (20.03)	

tLNs indicates total retrieved lymph nodes; LN, lymph node.

$R^2 = 0.091$) (Fig. 1). In univariate analysis, upper-third tumor location, more aggressive macroscopic type, larger primary tumor size, and more tLNs were associated with lymph node metastasis. When a logistic regression was performed, lymph node metastases were associated with sex ($P = .029$), macroscopic type ($P = .001$), tumor size ($P < .001$), and the number of tLNs ($P < .001$; hazards ratio, 1.014; 95% confidence interval [95% CI], 1.006–1.021) (for details, see Table 2). When the same logistic regression model was used to evaluate patients with pT1 and pT2 disease, the number of tLNs did not emerge as a significant variable in either group (data not show).

Outcomes

By December 15, 2005 (the cut-off date for this study), the median follow-up was 61.1 months (95% CI, 53.3–69 months), and the overall 10-year survival rate (10-YSR) was 42.8%. The 10-YSR for patients with N0, N1, N2, and N3 disease was 62.9%, 53.3%, 29.1%, and 9.1%, respectively ($P < .001$) (Fig. 2). The 5-YSR was 50.4% for all patients and was 74.0%, 59.8%, 36.7%, 14.4% for patients with N0, N1, N2, and N3 disease, respectively ($P < .001$). The patients with pT3N0 disease who had <31 tLNs (25th percentile; N = 121 patients) had a 10-YSR of 55.4%. Although this 10-YSR did not differ significantly from the 10-YSR of other N0 patients (65.8%; $P = .108$; N = 339 patients) (Fig. 3a), it approached the 10-YSR

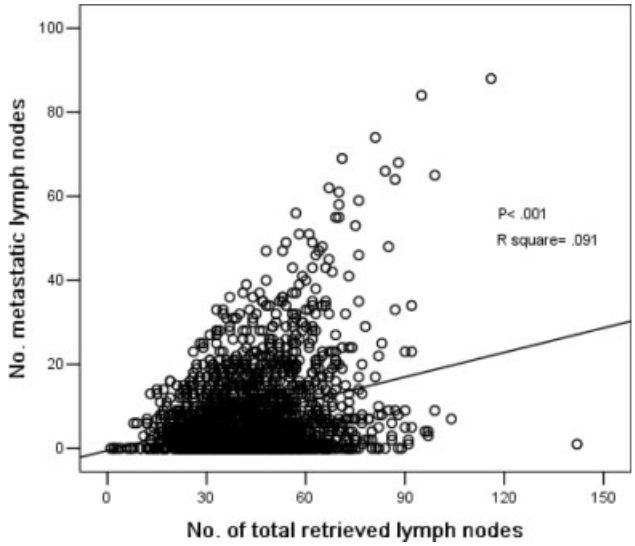


FIGURE 1. This scatterplot shows the distribution of metastatic lymph nodes according to the number of retrieved lymph nodes (tLNs). Curvilinear regression revealed a linear correlation (R^2) between tLNs and metastatic lymph nodes ($P < .001$; $R^2 = 0.091$).

TABLE 2
Univariate and Multivariate Analyses of Lymph Node Metastasis by Logistic Regression

Variable	Univariate analysis	Multivariate analysis		
	P	HR	95% CI	*P*
Age*	.819			
Sex†	.103	1.294	1.026–1.631	.029
Macroscopic (Bormann) type	<.001			.001
II‡		1.453	0.866–2.437	.157
III‡		1.902	1.185–3.053	.008
IV‡		3.032	1.687–5.449	<.001
Location	.048			
Histologic type	.075			
Size*	<.001	1.101	1.050–1.154	<.001
No. of tLNs*	<.001	1.014	1.006–1.021	<.001

HR indicates hazards ratio; 95% CI, 95% confidence interval; tLNs, total retrieved lymph nodes.
* Consecutive variables; others were categorized variables.
† Men compared with women.
‡ Compared with Bormann type I.

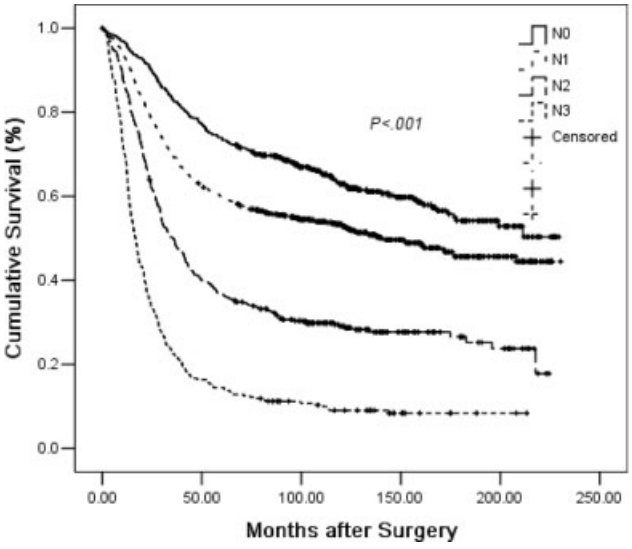
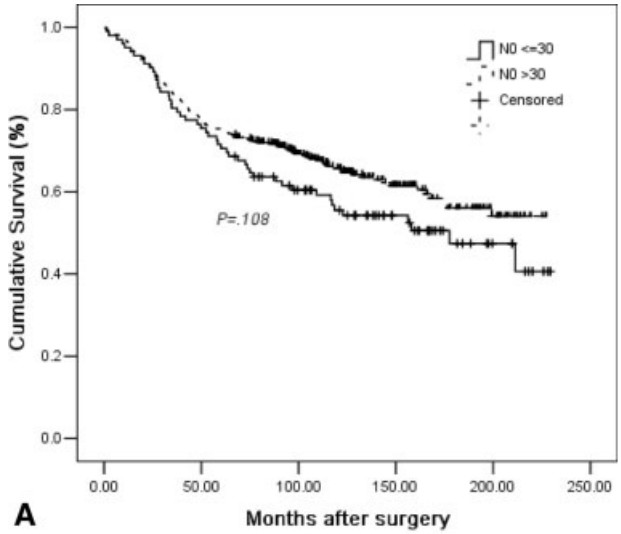
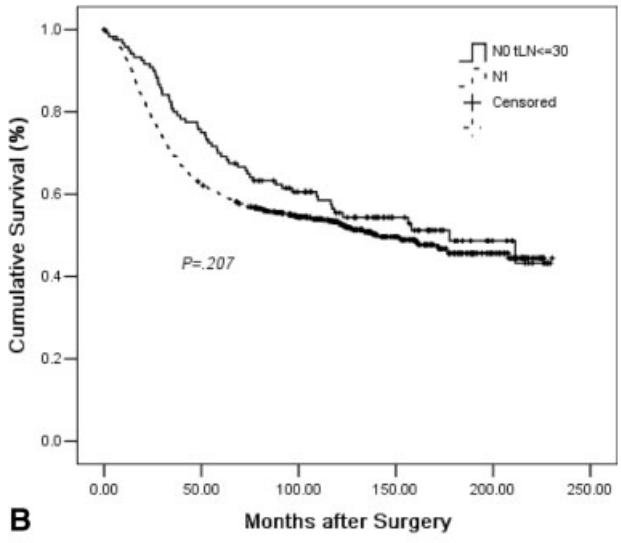


FIGURE 2. Cumulative survival according to each lymph node (N) stage. The 10-year survival rate for the N0, N1, N2, and N3 subgroups was 62.9%, 53.3%, 29.1%, and 9.1%, respectively ($P < .001$). The 5-year survival rate for these groups was 74.0%, 59.8%, 36.7%, and 14.4%, respectively ($P < .001$).

of the N1 group (53.3%; $P = .207$) (Fig. 3b). Figure 3c provides a combination of these 2 analyses for a clear comparison. None of the clinical pathologic features differed significantly between these 3 groups (age, $P = .711$; sex, $P = .068$; macroscopic type, $P = .073$; tumor location, $P = .073$; tumor size, $P = .711$; and histologic type, $P = .502$). This was not observed in other lymph node groups (eg, N1 patients who had <31 tLNs compared with N2 patients; both $P < .001$).

In the pT1 group, the patients with N0 disease who had <31 tLNs also had a 10-YSR similar to that of the patients with N1 disease (86.7% vs 83.9%, respectively; $P = .470$); however, in our database, the overall 10-YSR for all patients with pT1N0 disease (88.3%) and pT1N1 disease did not differ significantly





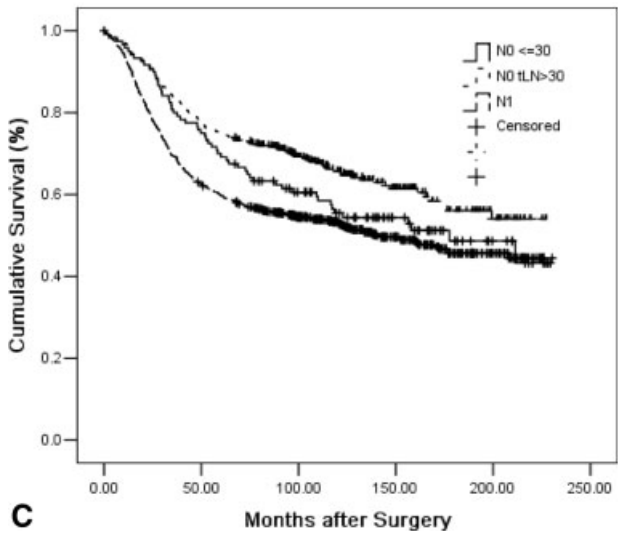


FIGURE 3. (a) Cumulative survival of patients with pT3N0 gastric cancer is illustrated according to the number of total retrieved lymph nodes (tLNs). Patients with pT3N0 disease who had <31 tLNs (25th percentile) had a 10-year survival rate (10-YSR) of 55.5% (n = 102 patients); the other patients with pT3N0 disease had a 10-YSR of 65.8% (n = 339 patients; $P = .108$). (b) Cumulative survival of patients with pT3N0 disease is illustrated for patients who had <31 tLNs compared with patients who had pT3N1 disease. The 10-YSR for patients with pT3N0 disease who had <31 tLNs was 55.5% (n = 102 patients); the 10-YSR for patients with pT3N1 disease was 53.7% (n = 677 patients; $P = .314$). (c) Cumulative survival of the patients from a and b combined.

($P = .172$), which rendered the similarity less meaningful. The patients with pT2N0 disease who had <31 tLNs had a better prognosis than the patients with pT2N1 disease (84.1% vs 66.9%; $P < .001$).

In multivariable analysis, age ($P < .001$), sex ($P = .042$), location of the primary tumor ($P = .006$), and the number of mLNs and tLNs (both $P < .001$) emerged as independent risk factors. In the N0 and N1 groups, the number of tLNs was not an independent prognostic predictor. In the N2 subgroup, an increasing number of tLNs was associated with a better prognosis ($P = .001$; hazards ratio, 0.986; 95% CI, 0.978–0.994). In the N3 subset, the number of tLNs also was a favorable independent prognostic factor ($P = .008$; hazards ratio, 0.988; 95% CI, 0.980–0.997) (for details, see Table 3).

TABLE 3
Multivariate Survival Analyses of Clinical and Pathologic Factors*

Variable	*P*	HR	95% CI
Overall			
Age	<.001	1.01	1.007–1.019
Sex†	.042	1.148	1.005–1.310
Location	.006		
Upper third‡	.069	1.179	0.988–1.407
Middle third‡	.629	1.034	0.902–1.186
Diffuse‡	.001	2.036	1.317–3.148
mLNs	<.001	1.059	1.054–1.064
tLNs	<.001	0.992	0.988–0.996
pT3N0			
Age	.036	1.015	1.001–1.029
Location	.009		
Upper third‡	.908	1.026	0.667–1.578
Middle third‡	.370	0.854	0.605–1.206
Diffuse‡	.002	9.863	2.345–41.477
tLNs§	.326		
pT3N1			
Age	<.001	1.021	1.010–1.031
Location	.004		
Upper third‡	.001	1.676	1.230–2.284
Middle third‡	.015	1.358	1.062–1.737
Diffuse‡	.116	2.237	0.819–6.110
mLNs	.008	1.090	1.022–1.163
tLNs§	.100		
pT3N2			
Location	<.001		
Upper third‡	.273	1.204	0.864–1.678
Middle third‡	.053	0.779	0.605–1.003
Diffuse‡	.002	6.713	2.037–22.124
mLNs	<.001	1.086	1.038–1.137
tLNs	.001	0.986	0.978–0.994
pT3N3			
Age	.008	1.015	1.004–1.026
mLNs	<.001	1.040	1.030–1.050
tLNs	.008	0.988	0.980–0.997

HR indicates hazards ratio; 95% CI, 95% confidence interval; mLNs, metastatic lymph nodes; tLNs, total retrieved lymph nodes; pT, pathologic tumor classification; N, lymph node status.

* Variables that were entered into the regression model were age, sex, macroscopic (Bormann) type, location, size, histologic type, number of mLNs, and number of tLNs. Age, size, number of mLNs, and number of tLNs were consecutive variables; others were categorized variables.

† Men compared with women.

‡ Compared with the lower third.

§ Because tLNs did not emerged as an independent risk factor, the HR was not given.

DISCUSSION

In the current study, we focused on patients with pT3 gastric cancer, in whom lymph node metastasis can increase markedly in the final staging from stage II to stage III or even to stage IV, dramatically affecting their prognosis.[5,6] Inappropriate stage migration can lead to inaccurate survival predictions and sometimes can change the strategy of adjuvant therapy.[13] Because all patients who had pT4 disease were diagnosed with stage IV gastric cancer, we excluded them patients from the current study. Although such patients also have a high risk of developing lymph node metastasis, the effect of lymph node involvement on their survival is relatively weak.[14,15]

In this study, we observed a positive linear correlation between tLNs and mLNs ($P < .001$; $R^2 = 0.091$); patients who had <31 tLNs (25th quartile) had less advanced N-stage disease ($P < .001$). Furthermore, in a logistic regression model, the number of tLNs (defined as a continuous variable) emerged as one of the independent risk factors for lymph node involvement, along with certain clinical pathologic features (sex, Bormann type, and size of the tumor). We observed a positive relation between more tLNs and a greater chance to identify lymph node metastases in patients with pT3 gastric cancer, but not in patients with pT1 or T2 disease.

In our survival analyses, we observed an interesting phenomenon: Although different survival could be distinguished in patients with pT3N0 through pT3N3 disease according to the fifth edition of the UICC classification, the patients with pT3N0 disease who had <31 tLNs had a 10-YSR similar to that for the patients who had pT3N1 disease (55.4% and 53.3%, respectively; $P = .207$) compared with the other N0 patients (65.8%; $P = .108$). However, none of the clinical pathologic features that were analyzed differed significantly between the 3 groups. There are 2 possible explanations for this observation. First, there may have been lymph node metastases that were missed during dissection or pathologic examination in N0 patients who had <31 tLNs, which may have caused *inappropriate understaging*.[16,17] Second, there may be a therapeutic benefit from more extensive lymph node dissection.[17] More tLNs or a lower

lymph node ratio is associated with a better prognosis.[3,6,11,18,19] In the current study, however, the number of tLNs was not an independent predictor of survival for patients with N0 or N1 disease. Therefore, therapeutic benefit is not the likely cause for the similarity in 10-YSR; instead, it is likely that the similarity can be attributed primarily to stage migration.

Stage migration and survival have been studied extensively in the context of cancer diagnosis and treatment.[20–22] More tLNs should increase the opportunity to find mLNs, sometimes leading to unnecessary upstaging, and may improve the survival for each subgroup without changing a single patient's prognosis: the so-called *Will Rogers phenomenon*.[23] However, in our study, the situation was a little different. The patients with N0 disease who had <31 tLNs (who were supposed to have a better prognosis) had a survival rate similar to that of the N1 patients. Thus, we believe that this is a problem of inappropriate understaging rather than upstaging. Some of the patients with N0 disease who had <31 tLNs actually may have been patients with positive lymph node status who had too few lymph nodes dissected and/or examined. The potential mixture of these patients with the patients who had genuine N0 status may have decreased the survival rate for this particular subgroup. Of course, this also could happen in the patients with > 31 tLNs, although the possibility would be much lower. This is consistent with the positive correlation between tLNs and mLNs that we demonstrated in this study. Although we cannot provide direct evidence, such as additional pathologic examinations, this hypothesis is the most probable explanation.

Several previous studies suggested that staging is reliable when> 10 or 15 lymph nodes are examined.[10,24] However, those studies examined all patients. For the current report, we focused only on patients with pT3 gastric cancer who had an extremely high incidence of lymph node metastasis. We failed to distinguish the patients with N0 disease who had< 31 tLNs from the patients with N1 disease in our survival analyses. Furthermore, our additional evaluation of patients with pT1 and pT2 disease revealed no positive correlation between the number of tLNs and identifying lymph node metastasis. Our survival analyses also produced no particular finding in the pT1 subgroup: Because the survival of all patients with pT1N0 and pT1N1 disease did not differ significantly, it was not meaningful to examine the similarity of survival between patients with pT1N0 disease who had <31 tLNs and patients with pT1N1 disease. Thus, this routine cut-off value of 15 tLNs, which may be enough for the staging of patients with pT1 and pT2 gastric cancer, was not adequate for the correct staging of patients with pT3N0 disease. This may not be easy for Western surgeons to adopt; because, in their population, gastric cancer is not a common disease, and fewer lymph nodes are dissected compared with the number dissected by Eastern surgeons.[3,5,6,24] The Western cut-off value also may be different because of different knowledge and different therapeutic patterns of the disease. When we compared patients with N1 versus N2 disease or patients with N2 versus N3 disease, there was no similar finding, which indicates that analyzing 15 lymph nodes in patients who have confirmed lymph node involvement may be enough to distinguish between N1, N2, and N3. Because the presence of lymph node metastasis is hard to detect preoperatively, all patients who have pT3 gastric cancer should undergo thorough lymph node dissection and careful pathologic examination. Unfortunately, we could not determine an optimal cut-off value for accurate staging based on our data. Further prospective studies in cooperation with a pathology department should be conducted. A strategy of comparing N stage by gradually adding the number of lymph nodes examined from the same specimen could illuminate the benefit from obtaining an increased number of tLNs on N staging and provide an appropriate number of lymph nodes to be analyzed in patients with pT3 gastric cancer.

In all patients with pT3 gastric cancer, and particularly in the subsets of patients with pT3N2 and N3 disease, the number of tLNs was an independent prognostic predictor. All hazards ratios were <1, indicating that an increased number of tLNs is associated with a better prognosis. When we compared the survival of patients between those with <31 tLNs and those with >31 tLNs, the number tLNs only reached statistical significance in univariate analyses for the N2 subset ($P = .0.027$; 5-YSR, 29.9% compared with 38.8%; data not shown). However, we believe that a greater number of tLNs will lead to a better prognosis. Because there are several factors that can affect survival, the results of multivariate analyses are more credible. Unlike other studies in which a survival benefit usually is absent for patients with advanced disease,[6,11] we observed that greater numbers of dissected lymph nodes could lead to a better prognosis in patients with pT3N2 disease and even in patients with pT3N3 disease. This observation may have been because we set the number of tLNs as a consecutive variable rather as a categorized variable, as in previous studies, thus preventing a loss of information. This indicates the important impact of

thorough lymph node dissection on survival, even in patients with pT3N3 gastric cancer, who many believed had incurable disease. However, this remains unclear, and a randomized prospective study should be performed.

We also wondered why tLNs did not emerge as independent prognostic predictor of survival in the N1 group. It is possible that the role of systemic lymph node dissection was limited for patients with localized disease; further studies should be conducted to clarify this issue. Because we could not know the exact N stage before surgery, a radical lymph node dissection was mandatory in all patients.

In conclusion, increasing the number of tLNs could improve the accuracy of N staging in patients with pT3 gastric cancer, and especially in patients with pT3N0 disease. The routine cut-off value of 15 lymph nodes examined should be increased in staging pT3N0 lesions. More tLNs also may be associated with a better prognosis in patients with pT3N2 and pT3N3 disease. Because preoperative lymph node staging is difficult, a thorough lymph node dissection and careful pathologic examination should be performed in all patients who may be serosa-positive.

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