

Number of Examined Lymph Nodes as a Risk Factor for Recurrence in pT1N+ or pT2-3N0 Gastric Cancer

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Abstract. *Background/Aim:* Japanese Gastric Cancer Treatment Guidelines do not recommend adjuvant chemotherapy after radical gastrectomy for pathological stage (p) T1N+ or pT2-3N0 gastric cancer. However, some patients experience disease recurrence. This study aimed to identify the risk factors for recurrence in pT1N+ or pT2-3N0 gastric cancer. *Patients and Methods:* The study included 157 patients with diagnosed pT1N+ or pT2-3N0 gastric cancer who underwent radical gastrectomy at our institution between January 2001 and December 2020. Clinicopathological data and surgical data were obtained. Independent prognostic factors were analyzed using a Cox proportional hazards regression model. *Results:* Thirteen patients (8.3%) experienced disease recurrence. Multivariate analysis revealed that the number of examined lymph nodes was an independent prognostic factor for recurrence-free survival (hazard ratio=10.90; 95% confidence interval=1.39-85.86; $p=0.023$). The group with ≤ 35 examined lymph nodes had significantly worse recurrence-free survival compared with the group with ≥ 36 examined lymph nodes (80.7% versus 98.7%; $p=0.0005$). *Conclusion:* The number of examined lymph nodes (≤ 35) was an independent risk factor for recurrence after radical gastrectomy with pT1N+ or pT2-3N0 gastric cancer.

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Key Words: Examined lymph nodes, pT1N+ or pT2-3N0, gastric cancer, risk factor, recurrence.

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Gastric cancer is a common digestive malignant disease and one of the leading causes of cancer mortality (1, 2). In Japan, mortality from gastric cancer has decreased significantly over the past 20 years because of advances in various treatment methods such as surgery and chemotherapy (3).

Pathological stage (p)T1N0 gastric cancers are classified as Stage IA according to the Japanese Classification of Gastric Carcinoma (4) and show a very good prognosis with a 5-year overall-survival rate of 99.0% (5). In pT1N+ or pT2-3N0 gastric cancer, pT1N1 and pT2N0 are classified as Stage IB, pT1N2 and pT3N0 as Stage IIA, and pT1N3 as Stage IIB or Stage IIIB. Katai *et al.* reported a 5-year overall-survival (OS) rate of 93.2% for Stage IB, 79.9% for Stage II, and 41.2% for Stage IIIB (5). Thus, gastrointestinal surgeons often encounter recurrence after radical gastrectomy in pT1N+ or pT2-3N0 gastric cancer.

The Japanese Gastric Cancer Treatment Guidelines (6) recommend postoperative adjuvant chemotherapy after curative surgery for patients with pathological stage II or III gastric cancer (7, 8). However, this guideline does not recommend postoperative adjuvant chemotherapy for pT1N+ or pT2-3N0 gastric cancer, despite the risk of recurrence. We hypothesized that the prognosis of pT1N+ or pT2-3N0 gastric cancer might be improved, for example by using adjuvant chemotherapy in subgroups at high risk for recurrence, if risk factors of recurrence could be determined. This retrospective study was designed to analyze the risk factors of recurrence in pT1N+ or pT2-3N0 gastric cancer.

Patients and Methods

Patient selection. The Institutional Review Board of our institution approved the study (Approval number #21111504). This study was eligible for the exemption of informed consent.

This retrospective study collected data from 914 patients who underwent gastrectomy for gastric cancer between January 2001 and December 2020 at the Nagasaki University Graduate School of Biomedical Science. All cases were pathologically diagnosed, and 177 patients were diagnosed with pT1N+ or pT2-3N0 gastric cancer based on the 15th Japanese Classification of Gastric Carcinoma (4).

Patients who underwent neoadjuvant chemotherapy (n=5) or adjuvant chemotherapy (n=3), patients with remnant gastric cancer (n=11), and a patient who underwent palliative resection (n=1) were excluded. Overall, a total of 157 patients were eligible for this analysis (Figure 1).

Surgical treatment and data collection. All patients underwent radical gastrectomy with lymphadenectomy according to the Japanese Gastric Cancer Association guidelines (6). The treatment plan was determined in consideration of the clinical tumor (T), nodes (N), and metastases (M) classification and patient background through a meeting with surgeons including multiple specialists in gastrointestinal surgery.

We obtained the following data for all patients: age, sex, tumor location, type of gastrectomy, level of lymphadenectomy, postoperative complication, histology, pathological T and N factor, tumor diameter, number of examined lymph nodes (eLNs), lymphatic invasion, and venous invasion. Tumor location was classified as upper third, middle third or lower third, after dividing the stomach into three equal parts according to the 15th Japanese Classification of Gastric Carcinoma. Cases with tumor spread to three regions of the stomach were defined as whole stomach. Types of gastrectomy included total gastrectomy (TG), proximal gastrectomy (PG), and distal gastrectomy (DG). Lymphadenectomy with less than D2 dissection was defined as non-D2. In histological analyses, tumors that were classified as undifferentiated included poorly differentiated tubular adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma. Cases satisfying at least one of lymphatic invasion or venous invasion were defined as having lymphovascular invasion. Postoperative complications were defined as complications of Clavien-Dindo (CD) grade (9) 1 or higher that occurred within 30 days of the primary surgery.

Follow-up. All patients were followed every 3 or 6 months at our hospital and affiliated hospitals until 5 years after surgery or death. The routine examination during follow-up included a physical examination, blood test, computed tomography scans and endoscopy in accordance with the surveillance described in the Japanese Gastric Cancer Association guidelines. Recurrence-free survival (RFS) was calculated using the time to recurrence defined as the date of surgery to the date when the recurrence was first detected.

Statistical analysis. Continuous data are expressed as median (range). The optimal predictive cutoff value for recurrence was determined for each parameter by the analysis of receiver operating characteristic (ROC) curves. Survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazard models were used to perform univariate and multivariate analyses. Hazard ratios (HR) and 95% confidence intervals (CI) were generated. Factors with a *p*-value of <0.05 in the univariate analysis were adopted for the multivariate analysis. A two-tailed *p*-value of <0.05 was considered significant. Statistical analysis was performed using JMP13 for Windows.

Results

Clinicopathological characteristics and long-term outcome. A total of 157 patients were eligible for the study. The patient clinicopathological characteristics are shown in Table I. A total of 104 males and 53 females were included in this study,

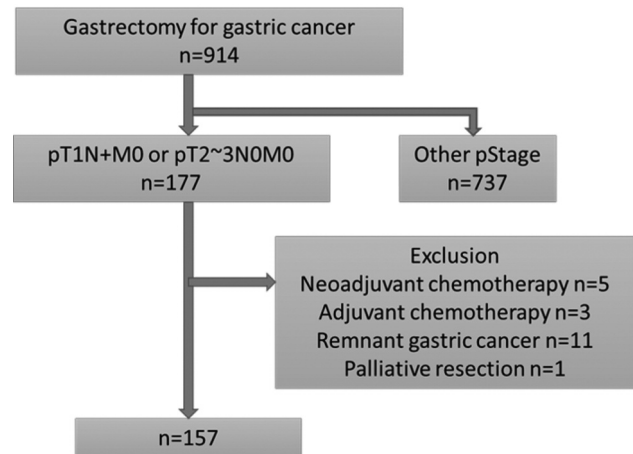


Figure 1. Flow diagram of the study.

and median age was 67 years. The types of gastrectomy were TG in 49 cases, PG in eight cases, and DG in 100 cases. There were 71 patients who underwent D2 lymphadenectomy and 86 patients who underwent non-D2 lymphadenectomy. On histopathological examination, the median tumor size was 38 mm, and 77 cases had undifferentiated type. pT and pN factors were pT1N1 in 38 cases, pT1N2 in eight cases, pT1N3 in two cases, pT2N0 in 65 cases, and pT3N0 in 44 cases. Lymphovascular invasion was observed in 128 cases. The median number of eLNs was 36. Postoperative complications of CD grade I or higher were observed in 29 patients, and there were no surgery-related deaths.

The OS and RFS of 48 patients with pT1N+ and 109 patients with pT2~3N0 are shown in Figure 2. There was no significant difference in OS (pT1N+; 79.0% versus pT2~3N0; 86.7% at 5 years, *p*=0.35) (Figure 2A) or RFS (pT1N+; 88.8% versus pT2~3N0; 91.3% at 5 years, *p*=0.55) (Figure 2B) between the two groups.

Univariate and multivariate analysis for RFS. Prognostic factors for 5-year RFS are shown in Table II. Univariate analysis revealed that age ≥ 71 years and eLNs ≤ 35 were significantly associated with poor RFS (HR=5.69; 95%CI=1.57-20.71; *p*=0.008 and HR=15.04; 95%CI=1.95-115.9; *p*=0.009, respectively). Multivariate analysis revealed that less than 35 eLNs was an independent prognostic factor for RFS (HR=10.90; 95%CI=1.39-85.86; *p*=0.023).

Prognostic implication of the number of eLNs. Based on the results of multivariate analysis, the patients were divided into two groups, the eLNs ≤ 35 group and the eLNs ≥ 36 group, and RFS was compared using a log-rank test. The eLNs ≤ 35 group had significantly worse RFS compared with the eLNs ≥ 36 group (80.7% versus 98.7%; *p*=0.0005) (Figure 3).

Table I. Patient characteristics and clinicopathological features.

	n=157
Age (years)	67 (33-86)
Sex male:female	104:53
Tumor location	
Upper	27
Middle	62
Lower	64
Whole	4
Type of gastrectomy	
Total gastrectomy	49
Proximal gastrectomy	8
Distal gastrectomy	100
Lymphadenectomy	
Non-D2	86
D2	71
Postoperative complication (≥CD1)	29
Histology	
Differentiated type	80
Undifferentiated type	77
Pathological T and N category	
pT1N1	38
pT1N2	8
pT1N3	2
pT2N0	65
pT3N0	44
Diameter (mm)	38 (7-135)
Number of examined lymph nodes	36 (0-90)
Lymphatic invasion	
+	117
-	40
Venous invasion	
+	95
-	62
Lymphovascular invasion	
+	128
-	29
Recurrence	13

Values represent the median (range) or number. CD: Clavien-Dindo classification.

Discussion

Our study showed that the number of eLNs was an independent risk factor for recurrence in pT1N+ and pT2~3N0 gastric cancer. The Union for International Cancer Control and American Joint Commission for Cancer the most commonly used guidelines to determine pathologic T and N staging for resected gastric cancer – recommend the examination of no less than 15 lymph nodes for accurate determination of nodal metastatic status (10, 11). The latest National Comprehensive Cancer Network Guidelines also recommend the examination of no less than 16 regional lymph nodes (12). Furthermore, the 15th Japanese Classification of Gastric Carcinoma clearly states that examination of no less than 16 lymph nodes is recommended

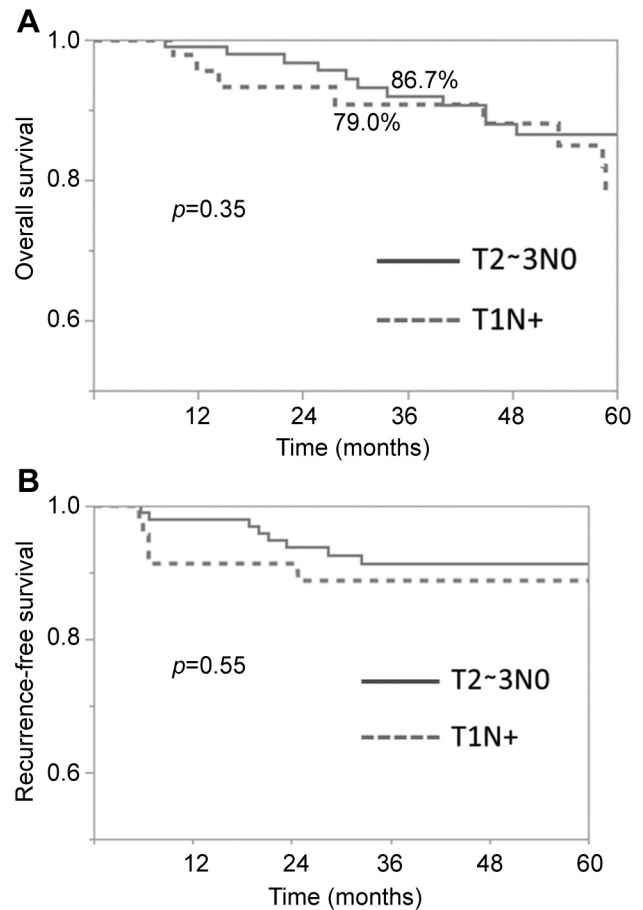


Figure 2. Overall survival (A) and recurrence-free survival (B) after surgery compared between pT1N+ and pT2~3N0.

to determine the N factor (4). Therefore, a sufficient number of eLNs are needed to determine the N factors that affect gastric cancer prognosis.

Previous studies have shown that the number of eLNs affects the prognosis of gastric cancer after radical gastrectomy. Luhu *et al.* showed that a larger number of eLNs is suggested for surgeons to prolong survival of pN0 gastric cancer, especially for pT3 patients (13). Based on this study, exceeding 30 eLNs is strongly recommended for pT3-4N0 patients with gastric cancer. XuGuang *et al.* reported that the number of eLNs could predict the prognosis of node-negative gastric cancer, and that dissection of >15 eLNs is recommended during lymphadenectomy to improve long-term survival (14). Smith *et al.* reported that a greater number of eLNs was associated with better resulting post-gastrectomy survival in T1-3N0-1 gastric cancer. The authors described that there was no isolated cutoff point for the number of eLNs after gastrectomy, but the survival rates tended to improve when LN counts were 40 or higher (15).

Table II. Univariate and multivariate analyses for identifying the predictors of recurrence-free survival.

	Univariate			Multivariate		
	Hazard ratio	95%CI	p-Value	Hazard ratio	95%CI	p-Value
Age (≥ 71 years)	5.69	1.57-20.71	0.008	3.61	0.98-13.32	0.054
Sex (male)	0.78	0.26-2.39	0.67			
Histology (undifferentiated)	1.73	0.57-5.28	0.34			
Lymphadenectomy (non-D2)	1.09	0.37-3.23	0.88			
Number of examined lymph nodes (≤ 35)	15.04	1.95-115.9	0.009	10.90	1.39-85.86	0.023
Lymphovascular invasion (+)	0.67	0.18-2.42	0.54			
Postoperative complication (CD \geq I)	1.26	0.35-4.58	0.73			
Pathological T and N category (T1N+)	1.41	0.46-4.30	0.55			

CD: Clavien-Dindo classification.

Hester *et al.* showed that the number of eLNs ≥ 15 was associated with improved survival in pT1N1 gastric cancer (16). These previous authors described that a small number of eLNs could lead to 'stage migration' because of inappropriately determined N factors (17). In other cancer, for example, in esophageal cancer, the relationship of the eLNs and prognosis have been reported too. Aoyama *et al.* reported that the eLNs < 30 is an independent poor prognostic factor in esophageal cancer having negative lymph nodes metastasis with radical resection (18).

In our study, 13 of 157 (8.3%) patients of pT1N+ or pT2-3N0 gastric cancer had recurrence after radical gastrectomy. The median number of eLNs was 28 in the recurrence group, compared with a median of 38 in the non-recurrence group. Based on previous studies and our results, 'stage migration' may be more likely with a smaller number of eLNs, with a more advanced stage than that of the final diagnosis being possible.

In a recent Chinese multi-center analysis, Zhang *et al.* reported that a number of eLNs in excess of 31 was required for an accurate prognostic evaluation in patients with gastric cancer, especially those with node-negative stage III gastric cancer (19). In addition, it has been suggested that a large amount of perigastric lymphoid tissue may be associated with better defense against metastasis and robust tumor immunity, and patients with fewer retrieved LNs may thus have lower defense against metastasis and diminished tumor immunity (20-22). It is possible that the association between a low number of eLNs and recurrence risk may also be related to a weakness of the immune response to cancer.

In Japan, radical gastrectomy and adjuvant chemotherapy are the standard treatment for pathological stage II and III gastric cancer based on the results of Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) (23). However, because pT1 and pT3N0 cases were excluded in ACTS-GC, the Japanese gastric cancer treatment guidelines also exclude pT1 and pT3N0 patients from the indications for adjuvant

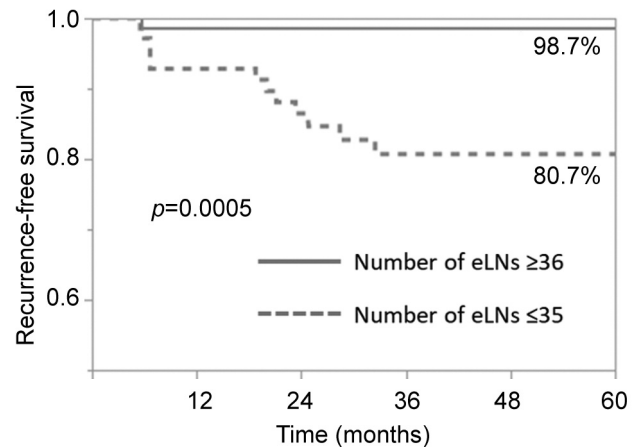


Figure 3. Recurrence-free survival after surgery compared between the examined lymph nodes (eLNs) ≤ 35 and eLNs ≥ 36 groups.

chemotherapy (6). Focusing on the indications for this postoperative adjuvant chemotherapy, two studies analyzed the risk factors for recurrence in pT1N+ and pT2-3N0 gastric cancer. Fujita *et al.* reported that lymphovascular invasion is an indicator of poor prognosis in patients with pT1N+ or pT2-3N0 gastric cancer (24). Tokunaga *et al.* reported that age ≥ 65 years, male sex and clinical T2-4 category are associated with worse OS in patients with pT1N+ or pT2-3N0 gastric cancer (25). There was no data collection or analysis of the number of eLNs in either study. In light of our analysis, the number of eLNs in patients with pT1N+ or pT2-3N0 gastric cancer may be a necessary focus for gastrointestinal surgeons.

Our study has the limitation of the small sample size because it was conducted in a single center. We believe that a multi-center study is required to further explore our findings.

In conclusion, we demonstrated that less than 35 eLNs was an independent risk factor for recurrence after radical gastrectomy with pT1N+ or pT2-3N0 gastric cancer.

Conflicts of Interest

None of the Authors have any funding or financial support to declare. The Authors have no conflicts of interest to declare, and no funding was received specifically for this study.

Authors' Contributions

Masato Nishimuta and Junichi Arai contributed to the planning and composition of this clinical study. Keiko Hamasaki and Yasumasa Hashimoto contributed to the treatment of the patient. Takashi Nonaka, Tetsuro Tominaga, Mitsuhiisa Ishi, Shozaburo Oyama, Masaaki Moriyama, Toru Yasutake, Terumitsu Sawai and Takeshi Nagayasu critically analyzed the data and manuscript. All Authors approved the final article.

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