

# Prognostic Impact of Number of Resected and Involved Lymph Nodes at Complete Resection on Survival in Non-small Cell Lung Cancer

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**Background:** Lymph node (LN) status is a major determinant of stage and survival in patients with lung cancer. In the 7th edition of the *TNM Classification of Malignant Tumors*, the number of involved LNs is included in the definition of pN factors in breast, stomach, esophageal, and colorectal cancer, and the pN status significantly correlates with prognosis.

**Methods:** We retrospectively investigated the prognostic impact of the number of resected LNs (RLNs) and involved LNs in the context of other established clinical prognostic factors, in a series of 928 consecutive patients with non-small cell lung cancer (NSCLC) who underwent complete resection at our institution between 2000 and 2007.

**Results:** The mean number of RLNs was 15. There was a significant difference in the total number of RLNs categorized between less than 10 and  $\geq 10$  ( $p = 0.0129$ ). Although the incidence of LN involvement was statistically associated with poor prognosis, the largest statistically significant increase in overall survival was observed between 0 to 3 and  $\geq 4$  involved LNs (hazard ratio = 7.680; 95% confidence interval = 5.051–11.655,  $p < 0.0001$ ). On multivariate analysis, we used the ratio between the number of involved LNs and RLNs. The number of RLNs was found to be a strong independent prognostic factor for NSCLC (hazard ratio = 6.803; 95% confidence interval = 4.137–11.186,  $p < 0.0001$ ).

**Conclusion:** Complete resection including 10 or more LNs influenced survival at complete NSCLC resection. Four involved LNs seemed to be a benchmark for NSCLC prognosis. The number of involved LNs is a strong independent prognostic factor in NSCLC, and the results of this study may provide new information for determining the N category in the next tumor, node, metastasis classification.

**Key Words:** Number of resected lymph nodes, Number of involved lymph nodes, Lymph node dissection, Multivariate analysis.

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Lung cancer has one of the highest worldwide incidence rates and is the leading cause of cancer-related mortality worldwide.<sup>1</sup> In Japan, lung cancer accounts for 60,000 deaths annually, and surgical resections are performed in approximately 27,000 cases, with an overall survival (OS) rate of 60%, according to the annual reports of the Japanese Association for Thoracic Surgery<sup>2</sup> and the Japanese Lung Cancer Registry.<sup>3</sup>

Various pathological and molecular markers have been assessed regarding their status and role in identifying patients at high risk for recurrence. However, the primary tumor, lymph node (LN), and the metastasis (TNM) staging system remain the most important determinant of outcome. Because the prognosis of lung cancer is directly proportional to the presence of LN metastasis, accurate LN assessment is crucial in determining treatment. The role of hilar and mediastinal lymphadenectomy in the staging and treatment of non-small cell lung cancer (NSCLC) remains controversial. Accurate staging of NSCLC requires assessment of the hilar and mediastinal LNs based on pathologic evaluation. In almost all surgical cooperative group trials and clinical settings in Japan, systematic LN dissection in ipsilateral hilar and mediastinal stations is standard. However, there is continual debate regarding the degree to which hilar and mediastinal LNs should be located and removed.

The number of resected LNs (RLNs) has been proven to have prognostic value in colorectal, breast, and bladder cancer.<sup>4–6</sup> Moreover, the number of involved LNs at the time of surgery currently influences staging. However, these items have not yet been incorporated into the latest 7th edition of the TNM classification of lung cancer.<sup>7</sup>

Therefore, we retrospectively investigated the prognostic impact of the number of RLNs and involved LNs in the context of other established clinical prognostic factors, in a series of 928 consecutive patients with NSCLC who underwent complete

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resection at Tokyo Medical University. Specifically, we attempted to clarify the number of LNs that should be resected, and the number of involved LNs needed to make an accurate prognosis.

## PATIENTS AND METHODS

### Patient Selection

From January 2000 to November 2007, a total of 1311 patients underwent resection for primary lung cancer at our institution. Cases of induction therapy, incomplete resection, and limited resection were excluded from this study. Patients whose tumors were classified histologically as small cell lung cancer or low-grade malignant tumors were also excluded. We retrospectively analyzed the remaining 928 consecutive patients with NSCLC who underwent complete resection with curative intent (minimum procedure of lobectomy) with systematic LN dissection of the hilum and mediastinum according to current surgical methods.<sup>8</sup> Patient charts, including pathologic diagnosis and operative reports, were reviewed. Staging was determined according to the international TNM staging system.<sup>9</sup> The histological tumor type was determined according to the World Health Organization classification, 3rd edition. All dissected LNs were examined pathologically and classified according to anatomical location by the numbering system described in the Naruke map.<sup>10</sup> The number of RLNs and involved LNs was confirmed based on the pathological report provided by M.N., J.M., and T.N. These pathologists were blinded to the clinical outcome.

### Patient Characteristics

The characteristics of the 928 consecutive patients who underwent surgery for NSCLC were as follows: age, median (range): 65.0 years (22–87 years); sex: 547 (59.0%) men and 381 (41.0%) women; clinical stages: 768 (82.8%) stage I, 84 (9.1%) stage II, and 76 (8.1%) stage III; pathological stage: 677 (72.9%) stage I, 121 (13.0%) stage II, 129 (13.9%) stage III, and 1 (0.2%) stage IV; histopathological diagnosis: 684 (73.7%) adenocarcinomas, 182 (19.6%) squamous cell carcinomas, 52 (5.6%) large cell carcinomas, and 10 (1.1%) others; surgical procedure: 870 (93.8%) lobectomies, 42 (4.5%) bilobectomies, and 16 (1.7%) pneumonectomies. The mean number of RLNs was 15 (right side, 15.5; left side, 14.3); the mean number of involved LNs was 4.2 (0–22) (Table 1). The median follow-up time was 3.5 years.

### Statistical Analysis

We investigated the association between the total number of RLNs or involved LNs and OS. OS was calculated from the date of surgery to the time of death. Observations were censored at final follow-up if the patient was alive. All patients in this series were categorized into four groups according to the number of RLNs less than 5 versus 5 or more, less than 10 versus 10 or more, less than 15 versus 15 or more, and less than 20 versus 20 or more. On analysis of survival differences based on the number of involved LNs, patients were categorized into groups of those with 0 versus 1 or more, less than 3 versus 3 or more, less than 4 versus 4 or more, and less than 5 versus 5 or more of involved LNs.

**TABLE 1.** Patient Characteristics

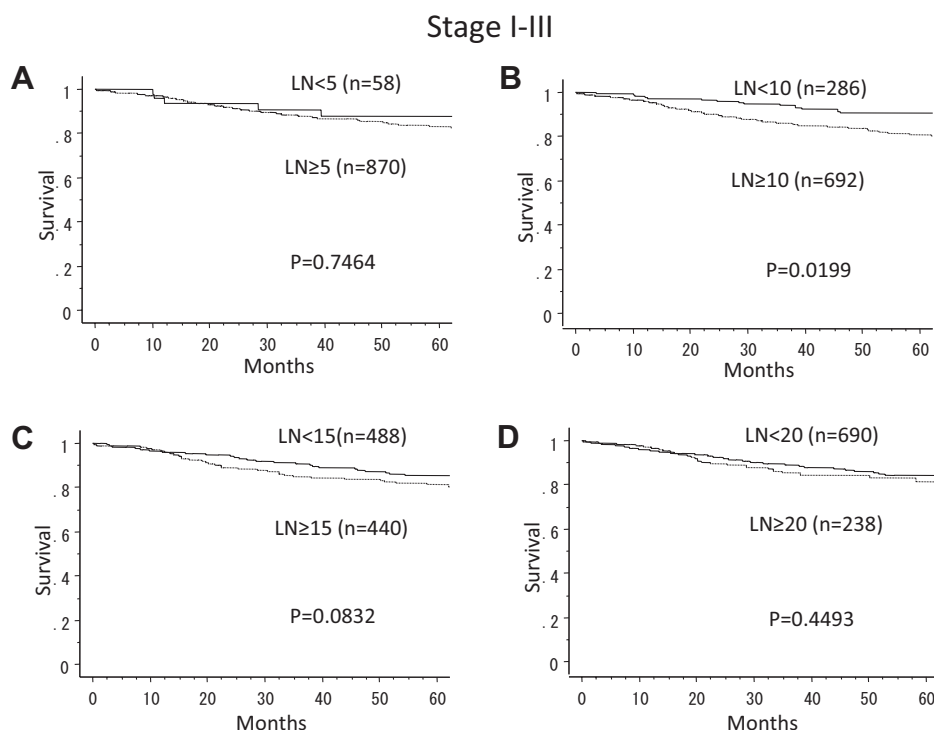
Variable	Category	n (%)
Age (yr)	Mean	65.0
	Range	22–87
Sex	Men	548 (59.0)
	Women	380 (41.0)
Histopathology	Adenocarcinoma	684 (73.7)
	Squamous cell	182 (19.6)
	Large cell	52 (5.6)
	Other	10 (1.1)
Clinical stage	I	768 (82.8)
	II	84 (9.1)
	III	76 (8.1)
Pathological stage	I	677 (72.9)
	II	121 (13.0)
	III	130 (14.1)
Tumor location	Right side	602 (64.9)
	Upper/middle/lower	334/64/204
	Left side	326 (35.1)
	Upper/lower	190/136
Surgical procedure	Lobectomy	870 (93.8)
	Bilobectomy	42 (4.5)
	Pneumonectomy	16 (1.7)
Total number of resected LNs	Mean (range)	15.0 (1–49)
	0–4	59 (6.4)
	5–9	177 (19.1)
	10–14	251 (27.0)
	15–19	201 (21.6)
	≥20	241 (25.9)
Total number of involved LNs in positive cases	Mean (range)	4.2 (1–22)
	0	724 (78.0)
	1–3	122 (13.1)
	≥4	82 (8.9)

LN, lymph nodes.

Survival curves were plotted using the Kaplan-Meier method. Differences in survival among the groups were examined using the log-rank test. A two-category comparison was performed using the Pearson  $\chi^2$  test and the Student *t* test for quantitative data. Multivariate analysis was performed using the Cox proportional hazards model to examine any possible association between the ratio of the total number of RLNs and involved LNs and survival, with adjustment for the effects of other potential prognostic factors, including age, sex, histology, tumor factor, and type of surgery performed. All tests were two sided, and *p* values of less than 0.05 were considered to represent statistically significant differences. StatView version 5.0 software (SAS Institute Inc., Cary, NC) was used for statistical analysis.

### Ethical Considerations

The approval of the Institutional Review Board of Tokyo Medical University was obtained, but as this was a retrospective study the need to obtain written informed consent from either the patients or their representatives was waived, in accordance with the AMA Manual of Style (10th edition).



**FIGURE 1.** Survival curves according to the number of resected LNs at the time of complete resection in patients with stages I to III non-small cell lung cancer. *A*, LN, five nodes as cutoff; a significant difference in survival was observed. *C*, LN, 15 nodes as cutoff. *D*, LN, 20 nodes as cutoff.

**TABLE 2.** Correlations between Overall Survival and Total Number of Resected Lymph Nodes

Valuables	<i>p</i>	HR	95% CI
5 vs. $\geq 5$	0.7464	1.135	0.528–2.440
6 vs. $\geq 6$	0.5464	1.233	0.624–2.437
7 vs. $\geq 7$	0.1611	1.591	0.831–3.047
8 vs. $\geq 8$	0.744	1.725	0.948–3.140
9 vs. $\geq 9$	0.0217	1.783	1.088–2.923
10 vs. $\geq 10$	0.0199	1.795	1.098–2.912
11 vs. $\geq 11$	0.0295	1.651	1.051–2.595
12 vs. $\geq 12$	0.0473	1.521	1.005–2.302
13 vs. $\geq 13$	0.0907	1.394	0.949–2.050
14 vs. $\geq 14$	0.1137	1.354	0.930–1.973
15 vs. $\geq 15$	0.0832	1.388	0.956–2.014

HR, hazard ratio; CI, confidence interval.

## RESULTS

### Survival and Number of RLNs

We investigated the prognostic impact of the number of RLNs (mean number of RLNs = 15). Patients were categorized into four representative groups according to the total number of RLNs: less than 5 versus 5 or more, less than 10 versus 10 or more, less than 15 versus 15 or more, and less than 20 versus 20 or more (Figure 1). Table 2 presents each *p* value, hazard ratio (HR), and 95% CI comparing each subgroup categorized according to total number of RLNs. The largest significant difference was found in the total number of RLNs categorized between less than 10 and 10 or more (*p* = 0.0199, HR = 1.795, 95% CI = 1.098–2.912).

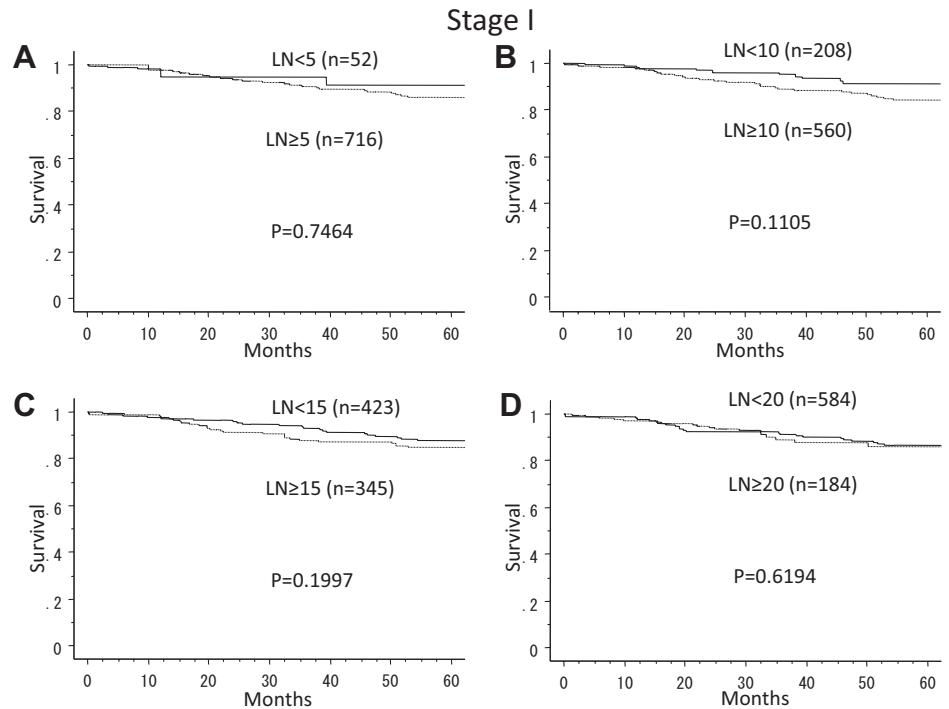
However, even 15 or more RLNs had no significant prognostic impact on the survival of patients with NSCLC in the present series. There was no sign of incremental improvement in or impairment of survival after the resection and evaluation of 15 or more LNs for curative resection of NSCLC. There were no statistically significant differences in survival according to the total number of RLNs in cases of stage I NSCLC (Figure 2).

As shown in Table 3, the mean numbers of RLNs on both the right and left sides were significantly higher in pN1 or pN2–3 cases than in pN0 cases (right side: *p* = 0.0007, *p* = 0.0002, left side: *p* = 0.0068, *p* = 0.0162, respectively). The mean number of RLNs in cases with right-sided tumors was significantly higher than that in cases with left-sided tumors.

### Survival and Number of Involved LNs

We analyzed the number of involved LNs that could provide the most appropriate indicator of OS in NSCLC. Although the incidence of LN involvement was associated with poor prognosis, the largest statistically significant increase in OS was observed between zero to three and four or more involved LNs (HR, 7.680; 95% CI, 5.051–11.655, *p* < 0.0001) (Figure 3). Although patients with no involved LNs had a better outcome than those with 1 to 3 involved LNs, there was no significant difference in survival between the two groups (*p* = 0.1831). Patients with four or more involved LNs had a significantly worse outcome than those with one to three involved LNs (*p* < 0.0001). These results suggest that four or more involved LNs would be the best benchmark of OS in NSCLC (Figure 4).

**FIGURE 2.** Survival curves according to the number of resected LNs at the time of complete resection in patients with stage I, non-small cell lung cancer. A, LN, five nodes as cutoff. B, LN, 10 nodes as cutoff. C, LN, 15 nodes as cutoff. D, LN, 20 nodes as cutoff. No significant difference in survival was observed in any group.



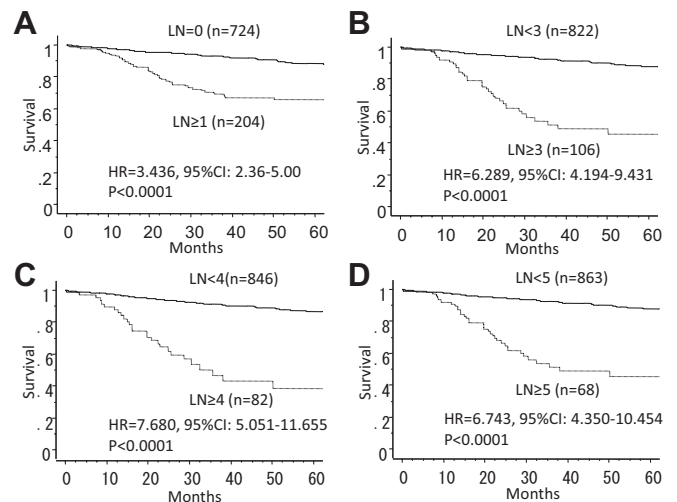
**TABLE 3.** Mean Number of Resected Lymph Nodes on Right or Left Side

	Mean Number	<i>p</i>
Right side lymph nodes, <i>n</i> = 602		
Total	15.5	
pN0	14.7	
pN1	18.2	0 vs. 1: <i>p</i> = 0.0007 <sup>a</sup>
pN2–3	19.0	0 vs. 2–3: <i>p</i> = 0.0002 <sup>a</sup> ; 1 vs. 2–3: <i>p</i> = 0.7199
Left side lymph nodes, <i>n</i> = 326		
Total	14.3	
pN0	13.5	
pN1	16.6	0 vs. 1: <i>p</i> = 0.0068 <sup>a</sup>
pN2–3	16.3	0 vs. 2–3: <i>p</i> = 0.0162; 1 vs. 2–3: <i>p</i> = 0.8985
Right vs. left		<i>p</i> = 0.0323 <sup>a</sup>

<sup>a</sup> Statistical significance.

### Correlations between Number of RLNs, Involved LNs and pN Status

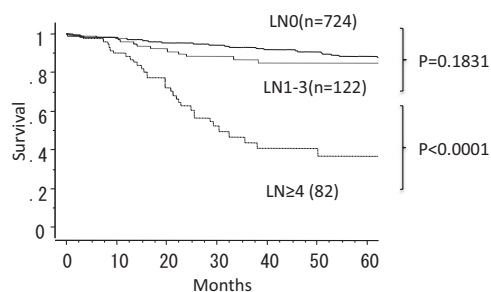
Before analyzing the possibility of RLNs and involved LNs as possible independent prognostic factors by multivariate analysis, we examined whether RLNs, involved LNs and pN status were confounding factors. The mean and range of the total number of RLNs in our series were 15.0 and 1 to 49, respectively. The mean number of RLNs was significantly increased in pN1 or pN2–3 cases compared with pN0 cases (*p* < 0.0001 and *p* < 0.0001, respectively), whereas the mean and range of the total number of involved LNs in our



**FIGURE 3.** Survival curves according to the number of involved LNs at the time of complete resection in patients with stages I to III, non-small cell lung cancer. A, LN, one node as cutoff. B, LN, three nodes as cutoff. C, LN, four nodes as cutoff. D, LN, five nodes as cutoff. Although the incidence of lymph node involvement was statistically associated with poor prognosis, the largest statistically significant increase in OS was seen between zero to three and 4 or more involved LNs.

pN-positive series were 4.2 and 1 to 22, respectively. The mean numbers of involved LNs in pN1 and pN2–3 cases were 2.15 and 6.56, respectively. The number of involved LNs was significantly higher in pN2–3 cases than in pN1 cases (*p* < 0.0001). These results demonstrate that each of these prognostic factors (i.e., the number of RLNs and involved LNs,





**FIGURE 4.** Survival curves according to the number of involved LNs at the time of complete resection in patients with stages I to III, non-small cell lung cancer. Although patients with no involved LNs had a better prognosis than those with one to three involved LNs, there was no significant difference in survival between the two groups. Patients with four or more involved LNs had a significantly worse outcome than those with one to three involved LNs.

and pN status) were confounding factors in our series. Therefore, in the subsequent multivariate survival analysis, we used the ratio between the number of involved and RLNs to reflect both factors in the multivariate analysis similarly to a previously reported method.<sup>11</sup>

### Multivariate Survival Analysis

We performed multivariate analysis to confirm the prognostic impact of the total number of RLNs and involved LNs in NSCLC, using the ratio between the number of involved and RLNs, according to a previously observed correlation.<sup>11</sup> As shown in Table 4, RLNs strongly correlated with poor prognosis on multivariate analysis after adjustments for sex, age, histology, tumor factor, and surgical procedure. We therefore concluded that RLN was a strong independent prognostic factor for NSCLC (HR, 6.803; 95% CI, 4.137–11.186,  $p < 0.0001$ ). Other independent prognostic factors identified on multivariate analysis included sex (HR, 0.620; 95% CI 0.401–0.958,  $p = 0.0313$ ), age (HR, 1.598,

95% CI 1.090–2.341,  $p = 0.0162$ ), and T factor (HR, 0.392, 95% CI, 0.256–0.600,  $p < 0.0001$ ).

### DISCUSSION

We set out to determine the number of LNs that should be resected, and the number of involved LNs for the accurate prediction of outcome in resectable cases of lung cancer. Opinions still vary among surgeons as to whether to remove all, some, or none of the mediastinal LNs at the time of pulmonary resection for lung cancer, and practices vary worldwide. In almost all surgical cooperative group trials in North America, LN sampling is standard, whereas systematic LN dissection is standard in Japan.

LN status is a major determinant of stage and survival in patients with lung cancer. However, the role of mediastinal lymphadenectomy in the staging and treatment of NSCLC remains controversial. The present results indicate that patient survival after complete NSCLC resection is associated with the number of LNs harvested during surgery. The largest significant difference was observed in the total number of RLNs categorized between less than 10 and 10 or more ( $p = 0.0199$ , HR = 1.795, 95% CI = 1.098–2.912). Patients with 10 or more RLNs had significantly worse outcomes than those with less than 10 RLNs (Figure 1), contrary to the findings of previous studies of stage I NSCLC cases.<sup>11–13</sup> As shown in Table 3, the mean number of RLNs on both the right and left sides was significantly higher in pN1 or pN2–3 cases than in pN0 cases (right side:  $p = 0.0007$ ,  $p = 0.0002$ ; left side:  $p = 0.0068$ ,  $p = 0.0162$ , respectively), which may be one reason why patients with NSCLC with 10 or more RLNs had a worse outcome than those with less than 10 RLNs. According to the results of the American College of Surgeons Oncology Group (ACOSOG) Z0030 study, a higher N stage was also associated with increased LN removal (N0:  $19.2 \pm 10.1$ ; N1:  $22.8 \pm 10.9$ ; N2:  $24.5 \pm 10.8$ ;  $p = 0.043$ ).<sup>12</sup> This is possibly because surgeons tend to harvest more LNs in patients with LN-positive disease at the time of surgery, in expectation of therapeutic benefit. However, even 15 or more

**TABLE 4.** Univariate and Multivariate Survival Analyses

Variable	Category	n	Univariate Analysis	Multivariate Analysis		
			p	HR	95% CI	p
Sex	Men	548	0.011 <sup>a</sup>	0.620	0.401–0.958	0.0313 <sup>a</sup>
	Women	381				
Age (yr)	<70	690	0.0209 <sup>a</sup>	1.598	1.090–2.341	0.0162 <sup>a</sup>
	≥70	338				
Histopathology	Non-adenocarcinoma	244	0.015 <sup>a</sup>	0.790	0.518–1.203	0.2719
	Adenocarcinoma	684				
T factor	T2–3	433	<0.0001 <sup>a</sup>	0.392	0.256–0.600	<0.0001 <sup>a</sup>
	T1	495				
Surgical procedure	Lobectomy	912	0.0136 <sup>a</sup>	2.521	0.768–8.280	0.1273
	Pneumonectomy	16				
RLNs	<0.4	882	<0.0001 <sup>a</sup>	6.803	4.137–11.186	<0.0001 <sup>a</sup>
	≥0.4	46				

<sup>a</sup> Statistical significance.

RLNs, ratio between the number of involved and resected lymph nodes; CI, confidence interval; HR, hazard ratio.

RLNs had no significant impact on OS in patients with NSCLC in the present series, contrary to the results of a previous large study.<sup>13</sup> There appeared to be neither incremental improvement nor impairment of survival after resecting and evaluating 15 or more LNs with curative intent in NSCLC in the current series. One possible explanation for this is that the presence of approximately 10 dissected LNs increases the staging accuracy.

There was no significant difference in survival according to the total number of RLNs in stage I NSCLC in the current series. Recent retrospective studies from cancer registries,<sup>14</sup> nonrandomized trials,<sup>15</sup> and other institutions,<sup>16–21</sup> have indicated that the number of RLNs is associated with better OS.<sup>16–19</sup> Although LN removal may be therapeutic, the therapeutic benefit is likely to be small for patients with stage IA NSCLC, because all LNs in stage IA should be negative. The other, less likely explanation, is that a more extensive LN dissection such as systematic mediastinal LN dissection may be therapeutic, at least in stage I NSCLC.

The present analysis shows that an increasing number of RLNs during complete NSCLC resection is associated with a statistically significant difference in survival, which peaks at 10 to 14 LNs. Some studies have recommended that the minimum requirements for accurate nodal staging must include the removal of at least six LNs from hilar and mediastinal stations.<sup>7,22,23</sup> However, others have recommended the examination of a minimum of 10 LNs and at least three LN stations.<sup>14,19</sup> Although we are reluctant to recommend a definitive optimal number of LNs, the current data support the conclusion that an evaluation of nodal status should include at least 10 LNs.

Nodal involvement is the most important prognostic factor in determining survival for many malignant tumors. These factors are represented by the N category in the TNM classification and are grouped according to the anatomical location and/or number of LN involvement. In the most recently published 7th edition of the *TNM Classification of Malignant Tumors* (2009),<sup>24</sup> the number of involved LNs is included in the definition of pN factors in breast, stomach, esophageal, and colorectal cancer, and pN status shows a significant correlation with outcome. The nodal system in this edition in lung cancer is still based on the anatomical location of involved LNs. The Naruke map and the American Thoracic Society map have been combined into the International Association for the Study of Lung Cancer map, and the definition of the border between N1 and N2 has been changed, because of its complexity and ambiguity. However, this change is based on the anatomical location, not on the biological issue. In the current study, we predicted patient outcome after complete NSCLC resection according to the number of involved and RLNs, as previous reports have suggested.<sup>25,26</sup> Recently, Asamura and coworkers<sup>27</sup> have provocatively suggested that the number of metastatic LNs provides more accurate pathologic nodal staging than the current method of considering anatomical location of involved nodes. The largest statistically significant increase in OS was observed between zero to three and four or more involved LNs (HR, 7.680; 95% CI, 5.051–11.655;  $p <$

0.0001) (Figure 2). Therefore, the current data indicate that four or more involved LNs serve as a good indicator of outcome after complete NSCLC resection. Because it is possible that the number of RLNs and involved LNs may indicate the quality of surgery in the determination of accurate staging and survival impact after complete NSCLC resection, we used RLNs as a prognostic predictor on multivariate analysis. In addition to T stage, RLNs had a strong independent effect on survival in patients with complete NSCLC resection in the present study. Indeed, the 5-year survival ratio of patients with RLNs  $\geq 4$  is similar to that of patients with pN2 disease in our series (data not shown). Although the nodal classification according to the number of involved LNs is simple and easy to be incorporated in the next TNM classification, there are a few limitations that are not helpful in deciding treatment preoperatively because it is mainly based on pathological assessment. However, this may change in the future with the development of new imaging device.

Our data suggested that the number of involved LNs expands pN category information and may provide additional information for the pN category of the next TNM classification. Further large-scale cohort studies, including global prospective validation analyses and multi-institutional studies are warranted.

## CONCLUSION

We retrospectively evaluated the prognostic impact of the number of RLNs and involved LNs on the survival of patients with complete NSCLC resection. We found that 10 or more LNs harvested with complete LN dissection possibly influenced survival after complete NSCLC resection. Moreover, the presence of four involved LNs seemed to be a good indicator of outcome after complete NSCLC resection. The number of involved LNs was a strong independent prognostic factor in NSCLC, and this may provide new information for the N categorization of the next TNM classification.

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