

## ORIGINAL ARTICLE

# Risk factors for recurrence after complete resection of pathological stage N2 non-small cell lung cancer

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## Keywords

Mediastinal lymph node; non-small cell lung cancer; recurrence; risk factors; stage N2.

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## Abstract

**Background:** Tumor recurrence is the most common cause of treatment failure, especially after complete resection of pathological stage N2 non-small cell lung cancer (NSCLC). In this study, we investigated the clinicopathological characteristics in order to identify independent risk factors for postoperative recurrence.

**Methods:** Between January 2001 and December 2013, 96 patients who underwent surgical resection for pathological N2 NSCLC were retrospectively reviewed. Recurrence-free survival (RFS) was calculated by the Kaplan-Meier method to explore risk factors, while the Cox proportional hazard model was used to assess independent predictors.

**Results:** The median and five-year RFS rates were 15 months and 27.4%, respectively. Univariate analysis showed a significantly poorer prognosis for non-regional N2 metastasis, more than three metastatic N2 lymph nodes, multiple N2 station, and multiple N2 zone involvement. Multivariate analysis demonstrated that non-regional N2 metastasis (hazard ratio [HR] 1.857, 95% confidence interval [CI] 1.061–3.249,  $P=0.030$ ) and more than three metastatic N2 lymph nodes (HR 2.555, 95% CI 1.164–5.606,  $P=0.019$ ) were independent risk factors for RFS. Additionally, the incidence of non-regional N2 metastasis was higher in patients with a primary tumor in the left lower (57.1%) or right lower lobe (48.1%), followed by left upper (31.8%), right middle (14.3%) and right upper lobe (7.7%).

**Conclusion:** The combination of the distribution and number of metastatic N2 lymph nodes provides a more accurate prediction for N2 NSCLC regarding recurrence. Non-regional N2 metastasis could occur with a primary tumor in any lobe, but occurs more frequently in the lower lobe.

## Introduction

Completely resected non-small cell lung cancer (NSCLC) with pathologically confirmed N2 disease affects a heterogeneous population, with reported five-year survival rate ranges from 25% to 50%.<sup>1–5</sup> Tumor recurrence is the most common cause of treatment failure after surgical resection and the main obstacle for long-term survival. The identification of factors related to recurrence after surgery may help to predict the outcome of N2 disease and, subsequently, to select optimal postoperative therapeutic strategy. One of the reasons for the variance in prognosis may come from differences in the pattern of lymph node metastasis. In the classification of N2 disease by the pattern of mediastinal lymph node (MLN) metastasis, various subgroups may be

recognized. Previous studies have reported that prognosis was affected by these subgroups. Therefore, a new classification of N2 disease has been proposed. In our study, the incidence of recurrence was investigated in patients diagnosed with pathological N2 NSCLC, and factors affecting recurrence-free survival (RFS) based on the patterns of MLN metastases were examined.

## Patients and methods

### Patients

We retrospectively reviewed the records of 96 patients who underwent complete resection for pathological N2 NSCLC between January 2001 and December 2013. Inclusion criteria

for the current study were as follows: standard major lung resection was performed including lobectomy, bilobectomy or pneumonectomy; complete resection without either microscopic or macroscopic residual tumor; at least three hilar and interlobar nodes and at least three N2 stations (including the subcarinal station) lymph nodes were completely dissected; and histologically proven NSCLC stage T1-4N2M0 according to the 7th edition of the tumor node metastasis (TNM) classification.<sup>6</sup> Patients who received adjuvant therapy were included in the study. Patients who had neoadjuvant therapy (chemotherapy and/or radiation therapy), and those who presented with simultaneous or sequential second primary cancers were excluded. Patients who died of complications within 30 days after surgery were excluded. This study was reviewed and approved by the institutional review board in our hospital.

Preoperative evaluation generally included clinical assessment, blood tests, computed tomography (CT) of the chest, CT or ultrasonography of the abdomen, CT or magnetic resonance imaging (MRI) of the brain, whole-body bone scintigraphy in all cases, and positron emission tomography (PET)/PET-CT in recent cases. In this study, patients with MLN enlargement (>1 cm) in the short axis on CT scan were considered to have cN2 lesions; mediastinoscopies or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) were only performed to exclude N3 disease in cases of suspected contra-lateral mediastinal lymphadenopathy. For patients with pre-operatively diagnosed N2 disease, a multidisciplinary team including experienced thoracic surgeons devised the therapeutic plan; we considered patients with unresectable (particularly bulky, multiple station) N2 disease to have a contraindication for initial surgical resection and recommended induction chemotherapy. We recommended that patients undergo adjuvant chemotherapy based on platinum doublets, based on consideration of the performance status of patients after surgery.

### Definition of regional and non-regional N2 metastasis

The lymph node map proposed by the International Association for the Study of Lung Cancer (IASLC) was used for lymph node and N2 zone classification.<sup>7</sup> Furthermore, regional N2 metastasis was defined as the involvement of an upper or aortopulmonary (AP) zone for a main tumor located in the left upper lobe, upper zone in the right upper lobe, upper or subcarinal zone in the right middle lobe, and subcarinal or lower zone in both lower lobes; non-regional N2 metastasis was defined as the involvement of the subcarinal or lower zone in both upper lobes, lower zone in the right middle lobe, upper or AP zone in the left lower lobe, or upper zone in the right lower lobe (Table 1).

**Table 1** Categorization of N2 based on the site of primary tumor and N2 zone involved

Location of primary tumor	Regional N2	Non-regional N2
LUL	Upper zone, AP zone	Subcarinal zone, lower zone
LLL	Subcarinal zone, lower zone	Upper zone, AP zone
RUL	Upper zone	Subcarinal zone, lower zone
RML	Upper zone, subcarinal zone	Lower zone
RLL	Subcarinal zone, lower zone	Upper zone

AP, aortopulmonary; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

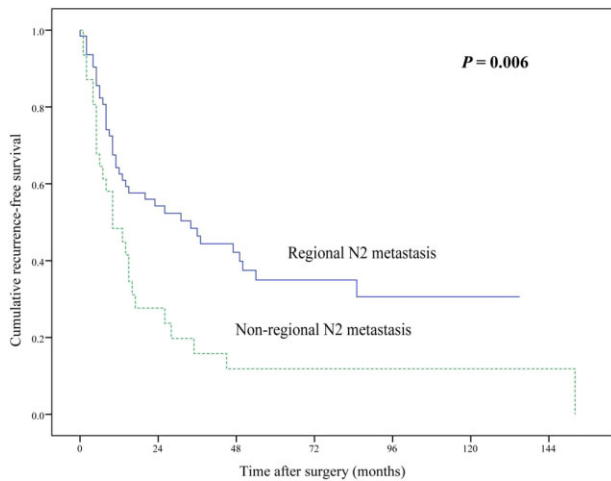
### Follow-up and data collection

Patients were followed up every one to two months and systematically checked every three months after surgery for the first two years and then every six to 12 months thereafter. The postoperative systemic check included clinical assessments, serum levels of tumor marker, chest CT, CT or ultrasonography of the abdomen, CT or MRI of the brain, and whole-body bone scintigraphy. The choices of telephone interviews, mail or direct outpatient clinic visits were offered to each subject. A trained staff member collected information on survival and recurrence during each follow-up session. All of the patients were followed. The follow-up period lasted from the date of surgery to the date of the first recurrence or the last date of follow-up without recurrence. The mean follow-up period was 30 months (range: 6–152 months). Recurrences were diagnosed by physical examination and diagnostic imaging. Histological or cytological confirmation of the recurrence was made when clinically feasible. Second primary lung cancer was differentiated from recurrence according to the criteria proposed by Martini *et al.*<sup>8</sup>

To determine prognostic factors, data were recorded and evaluated in statistical analysis on the basis of age, gender, smoking status, tumor location, pathological T factor, histology, adjuvant therapy, and N2-related factors including: distribution of N2 metastases (regional or non-regional), highest MLN status, subcarinal zone status, presence of skip N2 metastasis (N2 nodal metastasis without N1 nodal metastasis), clinical N status (cN0–N1 or cN2), number of N2 stations involved (single or multiple), and number of N2 zones involved (single or multiple).

### Statistical methods

All statistical analyses were performed using SPSS version 20 software (IBM Co., Armonk, NY, USA). The RFS was calculated according to the Kaplan-Meier and life-table methods. The significance of comparisons was examined using the log-rank test. Multivariate analyses were performed by means of a



**Figure 1** Comparison of recurrence-free survival between patients with regional N2 metastasis and non-regional N2 metastasis ( $P = 0.006$ ).

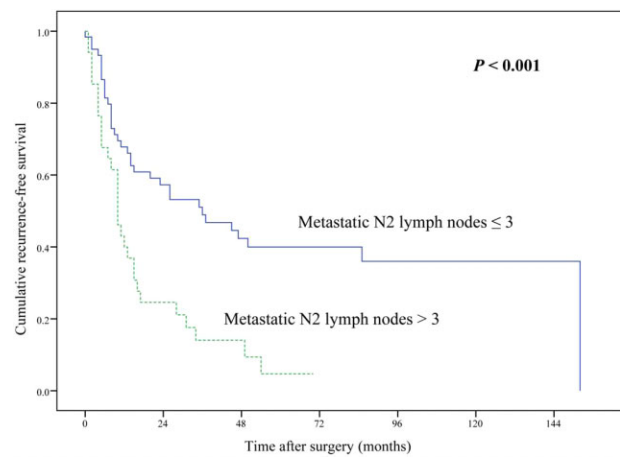
Cox proportional hazards model. The mean shrinkage (95% confidence interval) was calculated. Differences were considered statistically significant when  $P$ -value  $< 0.05$ .

## Results

During the follow-up period, recurrence was observed in 65 patients: 46 patients had local-regional recurrences; distant metastases were identified in 14 cases; and both local-regional recurrence and distant metastases occurred in five cases. The most common site of local-regional recurrence was the mediastinal lymph node in 30 cases, followed by the lung in 15 cases, pleura in eight cases, and bronchial stump in two cases. The brain was the most common site of distant metastases (8 cases), followed by bone (7 cases), and liver (6 cases). The median RFS and five-year RFS rate for all 96 patients with pN2 status was 15 months and 27.4%, respectively. Univariate analysis showed a significantly poorer prognosis regarding non-regional N2 metastasis (Fig. 1), metastatic N2 lymph nodes  $> 3$  (Fig. 2), multiple N2 stations, and multiple N2 zones involved (Table 2).

The joint effects of these four factors were examined using a Cox proportional hazard model. Multivariate analysis confirmed that non-regional N2 metastasis and metastatic N2 lymph nodes  $> 3$  were the independent and significant factors predicting RFS (hazard ratio [HR], 1.857;  $P = 0.030$  and HR, 2.555;  $P = 0.019$ , respectively) (Table 3).

The distribution and number of metastatic N2 lymph nodes were combined to define an accurate risk classification for predicting prognosis. The patients were stratified into three risk groups: regional N2 metastasis and metastatic N2 lymph nodes 1–3 were placed in the low-risk group; regional N2 metastasis and metastatic N2 lymph nodes  $> 3$  or non-regional N2 metastasis and N2 lymph nodes 1–3 were in the



**Figure 2** Comparison of recurrence-free survival between patients with metastatic N2 lymph nodes  $\leq 3$  and  $> 3$  ( $P < 0.001$ ).

medium-risk group; and non-regional N2 metastasis and metastatic N2 lymph nodes  $> 3$  were in the high-risk group. There were 48, 31, and 17 patients in the low, medium, and high-risk groups, respectively. The survival data of these groups decreased along with the increased risk, and the differences between each group were statistically significant (Fig. 3) (Table 4).

The relationship between the site of the primary tumor and involved N2 zone was investigated: the incidence of non-regional N2 metastasis was higher in patients with a primary tumor in the left lower (57.1%) or right lower lobe (48.1%), followed by left upper (31.8%), right middle (14.3%) and right upper lobe (7.7%) (Table 5).

## Discussion

The TNM system remains the most important and principal method for assessing the extent of disease, determining prognosis and affecting treatment strategies. The presence and extent of metastasis to the ipsilateral mediastinal lymph nodes (N2) are important prognostic factors in completely resected NSCLC. However, resectable N2 NSCLC represents a heterogeneous group.<sup>9</sup> Many studies have investigated various clinicopathologic factors to identify more accurate predictors for relapse, such as the number of N2 stations or N2 zones involved, the number or rate of N2 lymph nodes involved,<sup>10</sup> the presence of a skip metastasis, metastasis to the highest MLN, and metastasis to the subcarinal lymph node.<sup>11,12</sup> These factors may help us to select therapeutic strategies for individual patients with the same pathological stage of disease. In our study, the combination of the distribution and number of metastatic N2 lymph nodes provides a more powerful predictor for postoperative recurrence.

As patients with advanced stage NSCLC will receive multidisciplinary treatment after surgical resection, therapeutic

**Table 2** Patient characteristics and comparison of RFS based on variables

Variable	No. of patients	5-year RFS (%)	P-value
Age			0.540
<65	42	33.3	
≥65	54	21.6	
Gender			0.961
Male	63	32.7	
Female	33	19.4	
Smoking history			0.445
Yes	63	26.2	
No	33	29.9	
Extent of resection			0.258
Lobectomy	82	29.1	
Bilobectomy	11	18.2	
Pneumonectomy	3	33.3	
Tumour location			0.103
LUL	22	38.6	
LLL	14	24.5	
RUL	26	29.4	
RML	7	42.9	
RLL	27	17.9	
Histology			0.099
Adenocarcinoma	65	28.0	
Others	31	30.1	
Adjuvant therapy			0.126
Chemotherapy	46	32.9	
Others	50	21.8	
pT stage			0.061
T1	13	44.9	
T2	56	32.7	
T3	23	16.8	
T4	4	0	
Distribution of metastatic N2			0.006
Regional	65	35.0	
Non-regional	31	11.8	
Highest MLN status			0.161
Negative	47	38.4	
Positive	49	15.8	
Subcarinal zone status			0.073
Negative	51	31.5	
Positive	45	24.2	
Skip N2 metastasis			0.434
Yes	37	29.5	
No	59	26.5	
Clinical N status			0.505
cN0-1	60	29.5	
cN2	36	23.8	
No. of metastatic N2 lymph nodes			0.000
≤3	62	40.0	
>3	34	4.7	
N2 station involved			0.002
Single	51	43.8	
Multiple	45	11.3	
N2 zone involved			0.009
Single	56	40.0	
Multiple	40	12.5	

LLL, left lower lobe; LUL, left upper lobe; MLN, mediastinal lymph node; RFS, recurrence-free survival; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

**Table 3** Comparison of factors affecting RFS in multivariate analysis using a Cox proportional hazard model

Variable	Hazard ratio (95% CI)	P-value
Distribution of metastatic N2 (non-regional/regional)	1.857 (1.061–3.249)	0.030
No. of metastatic N2 lymph nodes (>3/≤3)	2.555 (1.164–5.606)	0.019
N2 station involved (multiple/single)	1.647 (0.661–4.102)	0.284
N2 zone involved (multiple/single)	0.532 (0.199–1.421)	0.208

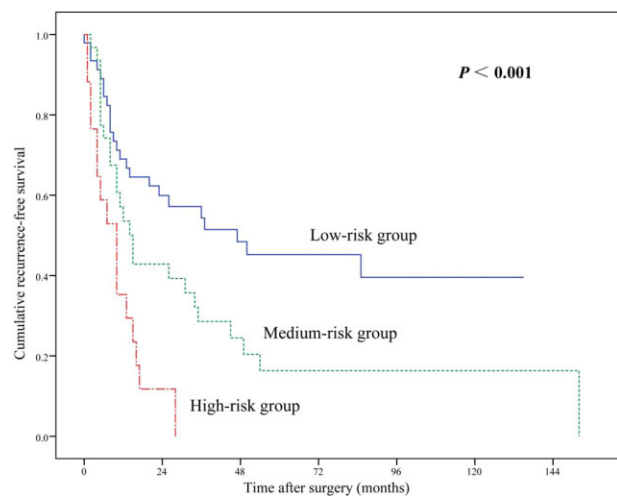
CI, confidence interval; RFS, recurrence-free survival.

**Table 4** Comparison of 5-year RFS rate according to risk classification

Subgroup	No. of patients	5-year RFS rate (%)	Reference	P-value
Low risk	48	45.2	Vs. high risk	0.000
Medium risk	31	16.3	Vs. low risk	0.029
High risk	17	0	Vs. medium risk	0.009

RFS, recurrence-free survival.

strategies including chemotherapy, radiotherapy, and targeted therapy significantly prolong overall survival even after local-regional relapse or distant metastases. Therefore, multiple lines of therapy and non-malignant causes of death potentially diluted overall survival; it may not be the best end point for assessing the efficacy of initial resection based on the patterns of MLN metastases. Additionally, recurrences remain the major causes of treatment failure in completely resected NSCLC. For these reasons, recurrence-free survival was chosen as a valid and reasonable surrogate outcome in our study.

**Figure 3** Recurrence-free survival according to risk classification.

**Table 5** Relationship between the site of primary tumour and involved N2 zone

Location of primary tumor	No. of patients	Non-regional N2 metastasis (%)	Upper zone	AP zone	Subcarinal zone	Lower zone
LUL	22	7 (31.8%)	5	21	7	0
LLL	14	8 (57.1%)	5	4	7	1
RUL	26	2 (7.7%)	26	0	2	0
RML	7	1 (14.3%)	3	0	6	1
RLL	27	13 (48.1%)	13	0	23	3

AP, aortopulmonary; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

The relation between primary tumor location and N2 involved represents an important risk factor for recurrence-free survival. The concept of lobe-specific nodes was reported to describe the phenomenon that lymphatic drainage generally follows a fixed route. The most frequently metastatic N2 were considered to be the regional nodes nearest to the primary tumor along the mediastinal lymphatic drainage route.<sup>13,14</sup> However, metastatic non-regional N2 (i.e. subcarinal metastases from an upper-lobe tumor, or superior mediastinal metastases from a lower-lobe tumor) located far from the primary tumor had been observed, and our study demonstrated that this phenomenon had a poor outcome even when these lymph nodes were systematically dissected. Some previous studies support our results. Asamura *et al.*<sup>14</sup> reported that superior mediastinal metastasis should be recognized as an indicator of a poor prognosis in tumors of both lower lobes. Okada *et al.*<sup>15</sup> reported that patients with subcarinal nodes involved from upper-lobe tumors had a significantly worse prognosis than those patients with metastases only to the upper mediastinal or aortic nodes, and patients with nodal involvement of the upper mediastinum from lower-lobe tumors had a significantly worse survival than those patients with metastases limited to the lower mediastinum. These findings indicated that non-regional N2 metastasis correlated with more aggressive disease and poor prognosis.

The number of metastatic lymph nodes is prognostically significant in many forms of cancer including NSCLC.<sup>16–19</sup> Furthermore, in the current TNM staging system, the number of metastatic lymph nodes is included in the definition of pN factors in stomach, esophageal, colorectal, and breast cancers, but has not yet been incorporated in lung cancer.<sup>20</sup> There is increasing evidence that the number of metastatic lymph nodes may be stronger prognostic indicators than current nodal classification. Fukui *et al.*<sup>16</sup> classified nodal categories according to the number of metastatic lymph nodes as 1–3, 4–6, and >6, and Lee *et al.*<sup>9</sup> reviewed 1478 patients who were divided into four subgroups according to the number of metastatic lymph nodes; both determined that the new category was a significant prognostic indicator. In our study, the number of metastatic N2 lymph nodes provides an independent risk factor for postoperative recurrence.

Considering that a combination of the two independent risk factors may provide us with a more accurate method of prediction, we divided the study population into three categories according to the distribution and number of metastatic N2 lymph nodes. Survival data showed significant differences between each subgroup. The new risk stratification system provides a more powerful risk factor for postoperative recurrence. The prognosis of patients with non-regional N2 metastasis and metastatic N2 lymph nodes >3 was extremely poor.

We investigated the ratio of non-regional N2 metastasis for each tumor-bearing lobe and observed that the incidence of non-regional N2 metastasis was higher in both lower lobes than in the upper and middle lobes. Watanabe *et al.*<sup>21</sup> noted that about half of the right middle/lower lobe NSCLC had nodal metastases to the upper mediastinum; nodal metastases to the lower mediastinum from upper lobe NSCLC were found in one-third of cases. Saeteng *et al.*<sup>22</sup> also reported that 40% of lower lobes had nodal metastasis to the upper mediastinal lymph nodes, while 20% of upper lobes had nodal metastasis to the lower mediastinal lymph nodes. On the basis of these findings and our present data, systemic nodal dissection is strongly recommended for stage N2 NSCLC, especially for lower lobe lesions, not only to obtain an accurate staging of the disease, but also to eradicate intrathoracic disease. The method of selective lymph node dissection or lobe-specific nodal removal is insufficient for cancers of advanced stages.

## Conclusion

The distribution (regional vs. non-regional) and number (>3 vs. ≤3) of metastatic N2 lymph nodes were found to influence the RFS of patients with completely resected stage N2 NSCLC. Risk classification based on the two factors can be a useful tool to identify patients at high risk for recurrence. Therefore, it can contribute to the adequate selection of an optimal postoperative therapeutic strategy. However, we acknowledge that as a single-institution and retrospective analysis, our sample size was limited; therefore, validity of the new N2 stratification method needs to be further explored.

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## Disclosure

No authors report any conflict of interest.

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