GENERAL THORACIC SURGERY

THE PROGNOSIS OF SURGICALLY RESECTED N2 NON-SMALL CELL LUNG CANCER: THE IMPORTANCE OF CLINICAL N STATUS

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Background: Clinical trials dealing with multimodal strategy for N2 non-small cell lung cancer are now being watched with keen interest, and the feasibility of this strategy is to be confirmed. N2 lung cancer, however, is composed of several subgroups with different prognoses. The prognostic factors still remain controversial. **Methods:** Between January 1986 and July 1997, 222 patients with lung cancer underwent surgical intervention at our institute; these patients were eventually given a diagnosis of metastasis to ipsilateral mediastinal lymph nodes. All patients underwent mediastinal lymph node dissection or sampling. Sixteen clinicopathologic factors were investigated by univariable and multivariable analyses to identify significant prognostic factors among resected N2 disease. Clinical N status was evaluated by computed tomographic scan. **Results:** The overall 5-year survival was 27%. Multivariable analyses among overall patients revealed 4 significant prognostic factors ($P < .05$): clinical N2 status, incomplete resection, larger tumor size, and multiple diseased N2 nodes. Based on the result, 32 patients with both clinical N2 status and pathologic multiple N2 nodes showed a 5-year survival of 5%, whereas 76 patients with neither of the factors showed a 5-year survival of 57% ($P < .001$). **Conclusion:** The prognosis of surgically resected N2 disease varies tremendously according to the 4 significant prognostic factors. These factors should be clearly described in reporting clinical trials on N2 lung cancer. Clinical N status evaluated by computed tomographic scan should be 1 criterion to perform a clinical trial for N2 disease among a homogeneous population with respect to prognosis. (J Thorac Cardiovasc Surg 1999;118:145-53)

The prognosis of surgically resected non-small cell lung cancer with metastasis to ipsilateral mediastinal lymph node (N2 disease) is poor, although highly selected patients with N2 disease achieve a 5-year survival.¹⁻³ Because the failure pattern of N2 disease is

mostly distant metastasis, most patients with N2 disease require a multimodal strategy, and recent efforts to improve the outcome of the disease have focused on this strategy.⁴⁻¹³ Some of the trials have shown promising results. In particular, induction chemotherapy followed by surgical resection was reported to be superior to surgery alone in at least 2 phase III clinical trials.^{8,13} Concurrent chemoradiation either alone or given as neoadjuvant therapy before surgical resection has also been reported to be promising and cures about 30% of N2 disease.^{10,14}

On the other hand, the reported prognosis of N2 disease varies tremendously. In non-small cell lung cancer, N2 disease is known to be a heterogeneous subcategory, and some authors^{1,3,15-18} have suggested several significant prognostic factors among surgically resected N2 disease. However, controversy still remains as to

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Supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare.

Received for publication Dec 1, 1998; revisions requested Feb 11, 1999; revisions received March 1, 1999; accepted for publication March 15, 1999.

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0022-5223/99 \$8.00 + 0 12/1/98582

Table I. Characteristics of patients with surgically resected N2 non-small cell lung cancer

Variables	Clinical N0-1	Clinical N2	P value*
Total (n)	135	87	—
Age (y)			
<60	55	34	.81
≥60	80	53	
Gender			
Male	76	64	.009†
Female	59	23	
CEA			
<5.0 ng/mL	51	18	.11
≥5.0 ng/mL	59	36	
Clinical T status			
cT1-2	121	52	<.001†
cT3-4	14	34	
Location of the main tumor‡			
RUL/RML	48	26	.69
RLL	32	18	
LUL	38	30	
LLL	17	12	
Histologic condition			
Adenocarcinoma	97	46	.004†
Squamous cell	27	34	
Adenosquamous	9	5	
Large cell	2	2	
Tumor size			
≤2.0 cm	14	8	.77
>2.0 cm	121	79	
Pathologic T status			
T1	38	16	.002†
T2	58	23	
T3	16	22	
T4	23	25	

which prognostic factors have greater impact on the survival of N2 non-small cell lung cancer. This controversy is probably related to criteria such as patient selection, the limited number of patients with analyzed disease, and inappropriate intraoperative staging (that is, mediastinal lymph node dissection). Although clinically evident N2 disease could be one of the most significant prognostic factors,^{3,19} some authors^{17,20} reported different conclusions. Thus N2 non-small cell lung cancer is composed of a heterogeneous population in terms of prognosis. Therefore it is possible that even phase III clinical trials dealing with N2 disease could draw erroneous conclusions because of patient selection bias. Although many clinical trials investigating multimodal strategy for N2 disease have been reported to be promising, a favorable outcome could be based on this selection bias. Unless the enrolled cases were sufficiently numerous, the outcome of the trial could be influenced by the incidental bias of the prognostic factors among patients in each arm of the phase III trial.

Table I. Continued

Variables	Clinical N0-1	Clinical N2	P value*
Pathologic stage‡			
Stage IIIA	111	61	.019†
Stage IIIB	21	23	
Stage IV	1	3	
Pleural involvement			
P0	61	29	.08
P1-3	74	58	
Vascular invasion			
Positive	101	78	.008†
Negative	33	9	
Intrapulmonary metastasis			
Positive	16	16	.18
Negative	117	70	
Metastatic N2 stations			
Single	83	37	.01†
Multiple	51	47	
Metastatic N2 nodes			
1	32	11	.04†
2 or more	103	76	
Procedure of operation§			
Pneumonectomy	9	24	<.001†
Lobectomy	126	63	
Curativity			
Complete	111	56	.003†
Incomplete	24	31	

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

*P value in the χ^2 test.

†Considered to be statistically significant.

‡ χ^2 Test was performed between stage IIIA vs stage IIIB or IV.

§Dichotomized: lobectomy, bilobectomy vs pneumonectomy.

||Complete resection means no diseased surgical resection margin and no highest mediastinal lymph node involvement.

In this retrospective study, we attempted to clarify several clinicopathologic prognostic factors and define homogeneous subgroups among patients with N2 disease to make it easier to correctly interpret clinical trials for this entity. Especially we will attempt to evaluate the importance of clinical N status in interpreting the outcome of N2 disease and other significant prognostic factors, which should be clearly described in clinical trial reports.

Patients and methods

Selected patients. Between January 1986 and July 1997, 1156 patients with lung cancer underwent surgical intervention at our institute, and 242 (21%) were eventually given a diagnosis of metastasis to ipsilateral mediastinal lymph nodes (N2 disease). Among them, 222 patients with lung cancer, who underwent major lung resection and mediastinal lymph node sampling, were selected to be investigated in this study because possible stage migration could be observed in the other 20 patients. One hundred forty were men and 82 were women. Their ages ranged from 23 to 83

Fig 1. Survival curve for patients with surgically resected N2 stage non-small cell lung cancer. The bar indicates 95% CI.

Table II. The 5-year survival of surgically resected N2 non-small cell lung cancer according to the metastatic mediastinal lymph node stations* and the primary tumor location (%)

	Regional nodal stations				
	TOTAL No. 1-9	Superior No. 1-4	Inferior No. 7-9	Aortic No. 5-6	Superior aortic No. 1-6
Tumor location					
Upper lobe	31 (n = 142)	25 (n = 92)	22 (n = 24)	—	36 [†] (n = 130)
Lower lobe	20 (n = 79)	17 [†] (n = 43)	0 [†] (n = 46)	—	20 (n = 45)
RUL/RML	27 (n = 74)	28 (n = 69)	33 (n = 11)	—	—
RLL	14 (n = 50)	18 (n = 30)	0 [†] (n = 29)	—	—
LUL	35 (n = 68)	18 (n = 23)	13 (n = 13)	40 (n = 54)	37 (n = 61)
LLL	32 (n = 29)	15 (n = 13)	23 (n = 17)	15 (n = 10)	22 (n = 15)
TOTAL	27 (n = 222)	23 (n = 135)	12 (n = 70)	33 (n = 64)	29 (n = 175)

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

*Regional nodal stations according to the lymph node map by Naruke and colleagues²⁴.

[†]Considered to be statistically significant (log-rank test, $P < .05$).

years, with a median of 63 years. Pretreatment staging consisted of clinical history, physical examination, and peripheral blood analyses, including arterial blood gas analyses, liver function test, renal function test, and serum carcinoembryonic antigen (CEA) in most patients. All patients underwent thoracic and brain computed tomographic (CT) scan preoperatively. The CT experiments were performed on an X-vision/SP (Toshiba, Tokyo, Japan), and 10-mm thick contiguous sections were used to evaluate N2 status. The clinical diagnosis of nodal involvement was determined by diagnostic radiologists and based on the CT findings (that is, mediastinal or hilar lymph nodes 1.0 cm or larger in the shortest axis were diagnosed as metastatic).²¹ Clinical N2

disease was diagnosed in 201 patients, and among them 95 patients (47%) were actually diagnosed to have pathologic N2 disease. Abdominal CT scan or ultrasonography was performed in all patients. Bone scintigraphy was also performed in all patients. Mediastinoscopy was performed in 12 patients, with positive results in 10 patients and negative results in 2 patients. All 12 patients had been enrolled in a previously conducted phase III clinical trial, in which preoperative chemotherapy versus surgical resection alone was investigated. The indications for mediastinoscopy included enlarged mediastinal lymph nodes on CT scan based on the size criteria described earlier. Because the basic strategy for resectable clinical N2 disease, however, had been primary

Table III. Relationship between clinicopathologic factors and 5-year survival in surgically resected pathologic N2 stage non-small cell lung cancer

Prognostic factors	N	5-Year survival (%)	χ^2	P value*
Total	222	27	—	—
Age (y)				
<60	89	27	<0.01	.99
≥60	133	26		
Gender				
Male	140	24	3.36	.067
Female	82	32		
Smoking status				
0≤PY <40	128	31	1.88	.17
40≤PY	85	15		
CEA				
<5.0 ng/mL	76	34	1.46	.23
≥5.0 ng/mL	88	17		
Clinical T status				
cT1-2	173	31	6.43	.011†
cT3-4	48	13		
Clinical N status				
cN0-1	135	43	37.3	<.001†
cN2	87	7		
Histologic condition				
Adenocarcinoma	143	31	0.27	.60
Others	79	21		
Differentiation				
Well	56	31	0.30	.58
Moderate or poor	154	29		
Tumor size				
≤2.0 cm	22	47	4.71	.030†
>2.0 cm	200	25		
Chemotherapy				
Performed	44	27	0.13	.72
Not performed	178	24		

surgical resection in our institute, only patients enrolled in the clinical trial underwent mediastinoscopy.

Histologic typing was determined according to the World Health Organization classification.²² All resected specimens were formalin fixed and sliced at 5- to 10-mm intervals. Primary lung neoplasms and nodules were evaluated microscopically by conventional hematoxylin and eosin stain. Histologic typing of resected lung cancer resulted in 143 adenocarcinomas, 61 squamous cell carcinomas, 4 large cell carcinomas, and 14 adenosquamous carcinomas. Two small cell carcinomas and 3 bronchial carcinoids were excluded from this study. The stage of the disease was based on the TNM classification of the International Union Against Cancer, fifth edition²³; cases with separate tumor nodules in the same lobe were designated as T4, and separate tumor nodules in different lobes as M1. Pathologic examination revealed 55 T1 cases (24%), 81 T2 cases (36%), 38 T3 cases (17%), and 48 T4 cases (22%). A total of 173 patients were classified as having pathologic stage IIIA disease; 45 patients, as stage IIIB disease; and 4 patients, as stage IV disease. Patients who had

Table III. Continued

Prognostic factors	N	5-Year survival (%)	χ^2	P value*
Pathologic T status				
pT1-3	174	31	7.87	.005†
pT4	48	14		
Pathologic stage				
Stage IIIA	173	31	9.07	.003†
Stage IIIB or IV	49	14		
Pleural involvement				
P0	90	30†	4.29	.038†
P1-3	132	25		
Vascular invasion				
Positive	179	25	2.95	.086
Negative	42	36		
Intrapulmonary metastasis				
Positive	32	5	11.15	<.001†
Negative	190	31		
Metastatic N2 stations				
Single	120	35	4.18	.041†
Multiple	98	19		
Metastatic N2 nodes				
1	43	47	6.82	.009†
2 or more	179	22		
Procedure of operation‡				
Pneumonectomy	33	13	8.11	.004†
Lobectomy	189	31		
Curativity§				
Complete	167	36	16.37	<.001†
Incomplete	55	0		
Radiation therapy				
Performed	20	0	3.95	.047†
Not performed	202	30		

cN0-1, Patients with clinical N0-1 status; cN2, patients with clinical N2 status. PY, pack-year smoking.

*P value in the log rank test.

†Considered to be statistically significant.‡Dichotomized: lobectomy, bilobectomy vs pneumonectomy.

§Complete resection means no diseased surgical resection margin and no highest mediastinal lymph node involvement.

undergone at least mediastinal lymph node sampling were included. Complete mediastinal lymph node dissection was performed in 206 patients (93%), and dissected lymph nodes were described according to the lymph node map for lung cancer proposed by Naruke and associates.²⁴ All resected lymph nodes were formalin fixed and examined microscopically by standard hematoxylin and eosin stain. The number of dissected lymph nodes ranged from 4 to 86, with an average of 29 dissected lymph nodes. The number of staff surgeons is 4, and they generally perform mediastinal lymph node dissection in the same manner as described by Naruke and associates.²⁴

Investigated clinicopathologic features. The medical record of each patient was examined for age, gender, pack-years of smoking, preoperative serum CEA level (≥5.0 vs <5.0 ng/mL), the location of the primary tumor, clinical T status (cT1-2 vs cT3-4), clinical N status (cN0-1 vs cN2), histo-

Fig 2. Survival for patients with surgically resected N2 state non-small cell lung cancer were compared on the basis of clinical N status. A statistically significant difference was observed between outcomes of clinical N0-1 and N2 disease (log-rank test, $P < .001$). *cN0-1*, Patients with clinical N0-1 status; *cN2*, patients with clinical N2 status.

logic evidence (adenocarcinoma vs others), maximum tumor dimension (centimeters), pathologic T status, pathologic stage, differentiation of tumor (well vs moderate or poor), pleural involvement (P0 vs P1-3), vascular invasion (positive vs negative), intrapulmonary metastasis (present vs absent), number of metastatic mediastinal lymph node stations (single vs multiple), number of metastatic mediastinal lymph nodes (1 vs 2 or more), procedure of operation (pneumonectomy vs lobectomy or limited surgery), curativity of surgical resection (complete vs incomplete), adjuvant radiation (performed vs not performed), and adjuvant chemotherapy (performed vs not performed). Pleural involvement was classified as P0, P1, P2, and P3: P0 included tumor with no pleural involvement or reaching the visceral pleura but not extending beyond its elastic pleural layer; P1 included tumor reaching the visceral pleural elastic layer but not exposed on the pleural surface; P2 included tumor exposed on the pleural surface; and P3 included tumor invading the parietal pleura or chest wall.²⁵ Vascular invasion indicated tumor cells identifiable in the blood vessel lumen. Pulmonary metastasis was defined as an independent mass isolated from the primary malignancy with identical histopathologic features as the primary tumor. Curativity was defined in the following manner: Complete resection indicates no diseased surgical resection margin and no diseased highest mediastinal lymph node, and incomplete resection means the presence of cancer cells at surgical margin histologically or the presence of involved highest mediastinal lymph node.

Statistical analyses. The median follow-up period for 99 patients alive was 44 months. The length of survival was defined as the interval in months between the day of surgical resection of lung carcinoma and the date of death from any

Table IV. Multivariate analyses of prognostic factors in surgically resected pathologic N2 non-small cell lung cancer*

Variables	OR	95% CI	P value
Clinical N status			
cN0-1 vs cN2	2.60	1.79-3.77	<.001
Tumor size (cm) [†]	1.22	1.12-1.32	<.001
Metastatic N2 nodes [‡]	1.08	1.12-1.32	<.001
Curativity [‡]			
Complete vs incomplete	1.58	1.06-2.33	.023

cN0-1, Patients with clinical N0-1 status; *cN2*, patients with clinical N2 status.

*Final models with all significant independent variables are shown.

[†]Entered as a continuous variable into the multiple variable analysis.

[‡]Complete resection means no diseased surgical resection margin and no highest mediastinal lymph node involvement.

cause or last follow-up. The survivals were calculated by the Kaplan-Meier method,²⁶ and univariate analyses were performed by means of the log rank test. Multivariable analyses were performed by means of Cox's proportional hazards model on StatView J 4.11 (Abacus Concepts, Inc, Berkeley, Calif) with a Power Macintosh 8100/100AV (Apple Computer, Inc, Cupertino, Calif).²⁷ Forward and backward stepwise procedures were used to determine the combination of factors that were essential in predicting prognosis. If variables could be used as continuous variables, continuous variables were used instead of dichotomous variables in multivariate analyses. The 0.10 level of significance was the significance level used for entering or removing a covariable from the model. The χ^2 test or Fisher's exact test was used to

Table V. The 5-year survival in subgroups of surgically resected N2 non-small cell lung cancer with multiple poor prognostic factors

Poor prognostic factors	N	5-Year survival (%)	P value*
Clinical N2 status, tumor size larger than 2.0 cm, and incomplete resection			
All factors	30	0	<.001†
1 or 2 factors	181	30	
Neither factor	11	100	
Clinical N2 status, multiple N2 nodes, and incomplete resection			
All factors	27	0	<.001†
1 or 2 factors	167	25	
Neither factor	28	76.1	
Clinical N2 status and tumor size larger than 2.0 cm			
Both factors	79	4	<.001†
Either factor	129	40	
Neither factor	14	76	
Clinical N2 status and multiple N2 nodes			
Both factors	32	5	<.001†
Either factor	114	37	
Neither factor	76	57	
Tumor size larger than 2.0 cm and incomplete resection			
Both factors	51	0	<.001†
Either factor	153	33	
Neither factor	18	55	
Multiple N2 nodes and incomplete resection			
Both factors	47	0	<.001†
Either factor	140	25	
Neither factor	35	65	
Clinical N2 status and incomplete resection			
Both factors	38	44	<.001†
Either factor	79	10	
Neither factor	105	49	

*P value in the log rank test.

†Considered to be statistically significant.

compare several prognostic factors among subgroups in N2 lung cancer.

Results

Among 222 surgically resected N2 non-small cell lung cancers, 135 (61%) were clinical N0-1 status based on the CT scan; 87 (39%) were clinical N2 status. Clinicopathologic features were compared between clinical N0-1 and N2 disease (Table I). Male gender, clinical T3-4 status, squamous cell histologic condition, pathologic T status, vascular invasion, the number of stations of diseased N2 nodes, the number of N2 nodes, pneumonectomy, and curativity were significantly associated with clinical N status ($P < .05$).

Metastatic mediastinal lymph node status was investigated in detail. The prognosis of N2 disease according to the site of diseased N2 nodes is shown in Table II. The overall 5-year survival was 27% ($n = 222$; Fig 1).

The prognosis of patients with diseased inferior N2 nodes ($n = 70$) was significantly worse than the others (5-year survival, 12%; $P < .05$). As for tumors located in the upper lobes, superior aortic N2 ($n = 130$) disease had a significantly better prognosis (5-year survival, 36%; $P < .05$). As to tumors located in the lower lobes, no patients with inferior diseased N2 nodes survived 5 years. In contrast, when the primary tumor was located in the left upper lobe, patients with N2 nodes in the aortic region had a 5-year survival of 40%, although this was not statistically significant.

The prognosis of surgically resected N2 non-small cell lung cancer was investigated according to several clinicopathologic prognostic factors (Table III). Significant differences in outcome were observed in relation to several clinicopathologic features. The 5-year survival of 87 patients with clinical N2 status was only 7%, although the survival of 135 patients with clinical N0-1 status was 43% ($P < .001$; Fig 2). Multivariable analyses with Cox's proportional hazard model disclosed 4 independent prognostic factors (Table IV): clinical N2 status, larger tumor size, multiple diseased N2 nodes, and curativity. On the basis of the results, we could identify a subgroup with poorer prognosis among resected N2 disease (Table V). Patients with both clinical N2 status and pathologic multiple N2 nodes ($n = 32$) showed a 5-year survival of 5%; 76 patients with neither of the factors showed a 5-year survival of 57% ($P < .001$; Fig 3).

Discussion

Suggestions that N2 disease actually consists of many heterogeneous subgroups were confirmed by the present study. Our results have shown that clinical N status is one of the most significant prognostic factors, on the basis of multivariable analysis. Tumor size, the number of diseased N2 nodes, and curativity were also selected as significant. We investigated the prognostic factors among stage IIIA N2 lung cancer. The 5-year survival of 173 patients classified as stage IIIA N2 disease was 30%. Multivariable analyses disclosed the same 4 significant prognostic factors as those in overall patients. Among stage IIIA N2 disease, 97 patients with clinical N0-1 who underwent complete resection had a 5-year survival of 55%, although the other 76 patients had less than 10% survival ($P < .001$). Thus even among stage IIIa N2 disease cases, which have been dealt with in the same category, the prognosis of resected N2 disease varies tremendously, and clinical N2 still had a significant impact on the prognosis.

Therefore, in interpreting a clinical trial on N2 disease, it is important to know these prognostic factors; other-

Fig 3. Survival for patients with surgically resected N2 stage non-small cell lung cancer were compared based on clinical N status and the number of diseased N2 nodes. A statistically significant difference was observed (log-rank test, $P < .001$). *cN0-1*, Patients with clinical N0-1 status; *cN2*, patients with clinical N2 status.

wise, even a phase III trial could allow misinterpretation unless the number of enrolled patients was sufficiently large. Sugarbaker and associates²⁸ suggested that N2 status at resection predicts long-term outcome after induction therapy for stage IIIA non-small cell lung cancer. They stated that surgical restaging of mediastinal nodes may be useful in patient treatment selection. Furthermore, if patients show no diseased mediastinal nodes after induction therapy, they could be a surgical candidate because of their better prognosis. However, they did not show clinical N status evaluation on the basis of the CT scan for these patients, and it is possible that these patients who showed no diseased mediastinal nodes after induction therapy would have either clinical N0-1 status on the basis of the CT evaluation or single mediastinal nodal involvement, and completely resectable. On the basis of the results, these patients were among a favorable prognostic subgroup even when they were treated with surgery alone: the good prognosis could not be due to the induction strategy but due to the patient selection conditions. Thus clinical trials dealing with N2 disease should be designated considering these factors, and at least clinical N status based on CT scan should always be described. Ideally, these should be separate clinical trials on the clinical N2

population and the clinical N0-1 population, although some previously reported clinical trials dealt with these populations in the same trial.^{5,6,8-11}

Our investigation of mediastinal nodal involvement showed the prognostic value of the site of the involved mediastinal lymph nodes. Inferior mediastinal nodes (ie, 7-9 nodes, based on the Naruke map²⁴) had a negative impact on prognosis, especially when the primary tumor was located in a lower lobe. The reason for this phenomenon remains unclear. Superior aortic nodes (ie, 1-6) had a better outcome than N2 disease in other locations, when the primary tumor was located in an upper lobe. The prognosis of aortic nodes with positive N2 status was excellent when the primary tumor was located in the left upper lobe. In contrast, the prognosis was poor when the primary tumor was located in a lower lobe even if N2 disease was due to diseased aortic nodes. The prognostic significance of the site of diseased N2 nodes according to the tumor location still remains controversial, and a further prospective study is mandatory.

The prognostic significance of CT scans in resected N2 lung cancer has been reported by Cybulsky and colleagues.¹⁶ Other authors^{3,16,18,19,29} also have reported that clinical N2 status was a significant prognostic fac-

tor in surgically resected N2 disease. However, the clinical N2 status in these reports was mostly based on plain x-ray films, except for the report by Cybulsky's group. Our result confirmed the prognostic significance of CT-demonstrated nodal status in patients with N2 lung cancer in whom N2 status was confirmed by more complete intraoperative nodal staging (eg, mediastinal lymph node dissection). In contrast, some authors^{17,20} reported no significance of clinical N status, but the number of investigated N2 patients were small in these reports. Thus we considered that clinical N status is the most significant prognostic factor in surgically resected N2 non-small cell lung cancer.

As mentioned earlier, complete resection was one of the most significant prognostic factors among resected N2 disease. So we also investigated the prognostic factors among completely resected N2 lung cancer. In 167 such cases the 5-year survival was 36%. Multivariable analysis revealed the following 4 significant prognostic factors: clinical N2 status ($P < .001$; odds ratio [OR], 2.77; 95% confidence interval [CI], 1.78-4.31), the presence of intrapulmonary metastasis ($P = .027$; OR, 1.99; 95% CI, 1.08-3.66), and the number of metastatic N2 nodes (analyzed as a continuous variable: $P < .001$; OR, 1.07; 95% CI, 1.03-1.12). It should be noted that intrapulmonary metastasis was one of the most significant prognostic factors among completely resected N2 disease. Most intrapulmonary metastases in our study were diagnosed pathologically and were diagnosed postoperatively. This means that postoperative histologic examination of the whole resected lung specimen should always be performed intensively to determine the presence of intrapulmonary metastases.

Although the International Union Against Cancer TNM staging system has been revised, controversies still remain.³⁰ With regard to N2 disease, despite its heterogeneous population, significant prognostic factors such as clinical N status, curativity, maximum tumor dimension, or status of involved mediastinal lymph nodes have rarely been taken into consideration. As a result, the outcome of surgically resected N2 non-small cell lung cancer population has varied tremendously. This heterogeneity could cause erroneous conclusions in clinical trials dealing with N2 disease.

We have shown the wide variety of outcome in surgically resected N2 disease. To perform a clinical trial with multimodal treatment for N2 disease among a homogeneous population with respect to prognosis, clinical N status evaluated by CT scan should be one criterion. Furthermore, completeness of surgical resection, the status of diseased N2 nodes, and also maximum tumor dimension should be mentioned in reports,

even in phase III trials. Stratification of surgically resected N2 disease in this manner would help in accurately interpreting important results of clinical trials dealing with N2 disease.

We thank Dr Satoshi Sasaki (Epidemiology and Biostatistics Division, National Cancer Center Research Institute East) for his technical support in statistical analyses and Professor J. Patrick Barron (International Medical Communications Center, Tokyo Medical College) for reviewing the English manuscript.

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