

Preoperative Prognostic Factors for pN2 Non-small Cell Lung Cancer

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Purpose: The prognosis of non-small cell lung cancer (NSCLC) with pathologic mediastinal lymph node involvement (pN2) is poor in general. The majority of previously reported prognostic factors of pN2 disease are not available preoperatively. When we perform preoperative induction chemotherapy, we should undertake therapeutic planning according to preoperative factors.

Methods: We focused on preoperative clinicopathologic factors, and investigated the prognosis in 78 patients with pN2 NSCLC who received complete resection.

Results: Age, gender, histologic subtype, tumor location, smoking status and cT status were not related to patients' survival. On the other hand patients with cN0 disease and normal serum carcinoembryonic antigen (CEA) level had a significant favorable survival ($p=0.038$ and $p=0.019$, respectively). In addition, comorbidity had a significant survival impact ($p=0.031$). Despite there being no independent prognostic factors by multivariate analysis, the patients without all of cN1-2 disease, elevated serum CEA level and comorbidity had a significant favorable prognosis ($p=0.008$).

Conclusion: Among the preoperative factors examined, pN2 patients with all cN0 disease, normal serum CEA level and no comorbidities might have a favorable prognosis. Combined use of these might be a useful prognostic determinant, and even in the presence of pN2 disease, patients without these unfavorable 3 factors might have a favorable prognosis when treated with surgery alone. (*Ann Thorac Cardiovasc Surg* 2006; 12: 15–20)

Key words: lung cancer, pathologic mediastinal lymph node involvement, preoperative, prognosis

Introduction

The most important predictor of outcome in patients with non-small cell lung cancer (NSCLC) is the presence or absence of mediastinal lymph node involvement (N2) with tumor.^{1,2} Patients with pathologic N2 (pN2) had an unfavorable prognosis. However pN2 disease consist of heterogeneous subgroups, and some groups of patients have a favorable prognosis. Several investigators reported the

prognostic factors in patients with pN2 NSCLC.³⁻¹¹ Although some discrepancies among these studies were found, they reported that patients with complete resection,^{3,5-7} clinical N0 (cN0) disease (an absence of significantly swelling nodes),^{9,10} T1 disease,^{7,9-11} squamous cell histology,^{8,9} skip metastasis without hilar node metastasis,^{10,11} limited location of the involved lymph nodes^{7,11} and metastasis of a single N2 station^{4,5,7-11} had a relatively favorable prognosis in pN2 NSCLC. Our previous studies are demonstrated that bcl-2 expression was a prognostic determinant for pN2 NSCLC, but p53 expression and tumor angiogenesis were not.^{12,13} However the majority of these factors are not known before surgery. Many studies analyzed their data together with pre and post-operative factors.

Recently pN2 disease proven by mediastinoscopy or

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Table 1. Patient characteristics

		Total
Age	60<	32
	60>	46
Gender	Male	52
	Female	26
Histology	Squamous cell carcinoma	14
	others	64
cT	cT1	26
	cT2	31
	cT3	18
	cT4	3
cN	cN0	31
	cN1	11
	cN2	36
Side	Right	40
	Left	38
Tumor location	Upper lobe	43
	Middle lobe	3
	Lower lobe	32
Smoking	Current or former	51
	Never	27
Serum CEA level	Elevated	42
	Normal	36
Comorbidity	Diabetes mellitus	10
	Chronic obstructive lung disease	3
	Heart disease	8
	Liver cirrhosis	1
	Histories of previously treated malignant diseases	8
	None	48

CEA, carcinoembryonic antigen.

transbronchial aspiration cytology prior to surgery led to induction treatment with preoperative chemotherapy in order to treat micrometastatic tumors, thus enhancing resectability. Some studies concluded the superiority of induction therapy.¹⁴⁻¹⁷⁾ However pN2 disease might consist of heterogeneous subgroups, and some groups might be among a favorable prognostic subgroup even when they were treated with surgery alone. At the time of preoperative planning of patients with pN2 disease assessed histologically prior to surgery, we can obtain preoperative factors only. We must decide different therapeutic approaches for each pN2 patient assessed histologically prior to surgery according to preoperatively available factors.

In the present study, we focused on preoperatively available factors and reviewed prognostic factors in completely resected pN2 non-small cell lung cancer patients.

Materials and Methods

The present study was conducted from 1994 through 2002, and included all patients with lung cancer who had not received complete resection consisting of either a lobectomy or a pneumonectomy together with regional lymph nodes dissection. The pN2 was present when any mediastinal node was histologically involved. Patients who did not receive complete resection, died of other diseases within 5 years after surgery or were lost to follow-up within 5 years were excluded. Seventy-eight consecutive lung cancer patients with pN2 disease who fulfilled the inclusion criteria were included in this study. There were 52 men and 26 women, ages ranged from 19 to 79 years, with an average of 61.3 years. The baseline characteristics and stage are summarized in Table 1. Overall follow-up ranged from 24-127 months. Clinical Tumor-Node-

Metastasis (cTNM) staging was recorded for all patients. The cTNM stage had been diagnosed using chest roentgenography, chest computed tomography (CT), upper abdominal CT scan, brain magnetic resonance imaging, and general bone scintigraphy. The 10-mm thick contiguous sections were used to evaluate cN2 status. Although some patients underwent mediastinoscopy and/or positron emission tomography with fluorodeoxyglucose (PET-FDG) imaging, these findings were not included for cTNM staging in the present study. Performance status (PS) was determined according to the ECOG scale. In our series, the majority of patients were diagnosed as PS 0. Therefore, in the present study, PS was not investigated. Serum carcinoembryonic antigen (CEA) level was measured by means of the two-site immunoenzymometric assay. The normal upper limit for this assay was 5 ng/mL. The time interval between serum CEA examination and staging or surgical resection was less than a month in all the patients.

The follow-up information, including cause of death, was acquired through clinic follow-up notes and direct or family contact. Survival curves were obtained according to the Kaplan-Meier method. Comparison of survival curves was carried out using the log rank test. Factors related to prognosis were analyzed by multivariate analyses according to the Cox proportional hazards model. Statistical calculations were conducted with StatView (Abacus Comp. Inc. Berkeley, CA) and values of p less than 0.05 were accepted as significant.

Results

As shown in Figs. 1A and 1B, our comparisons of survival curves showed that cN status (cN0 vs. cN1-2) and serum CEA level (normal vs. elevated) were related to patients' prognosis ($p=0.038$ and $p=0.019$, respectively by log rank test), while other factors were not. Some patients had comorbidities: 10 diabetes mellitus, 3 chronic obstructive lung diseases, 8 heart diseases, 1 liver cirrhosis and 8 histories of previously treated malignant diseases. Since the number of patients with each disease was small, the comorbidity severity was not examined. Patients were subdivided into 2 groups: one, with at least one of these comorbidities, and the other, with none of these comorbidities. As shown in Fig. 1C, patients with comorbidity had poor prognosis ($p=0.031$).

The results of univariate analysis are summarized in Table 2. The cN status (cN0 vs. cN1-2), serum CEA level (normal vs. elevated) and comorbidity (positive vs. nega-

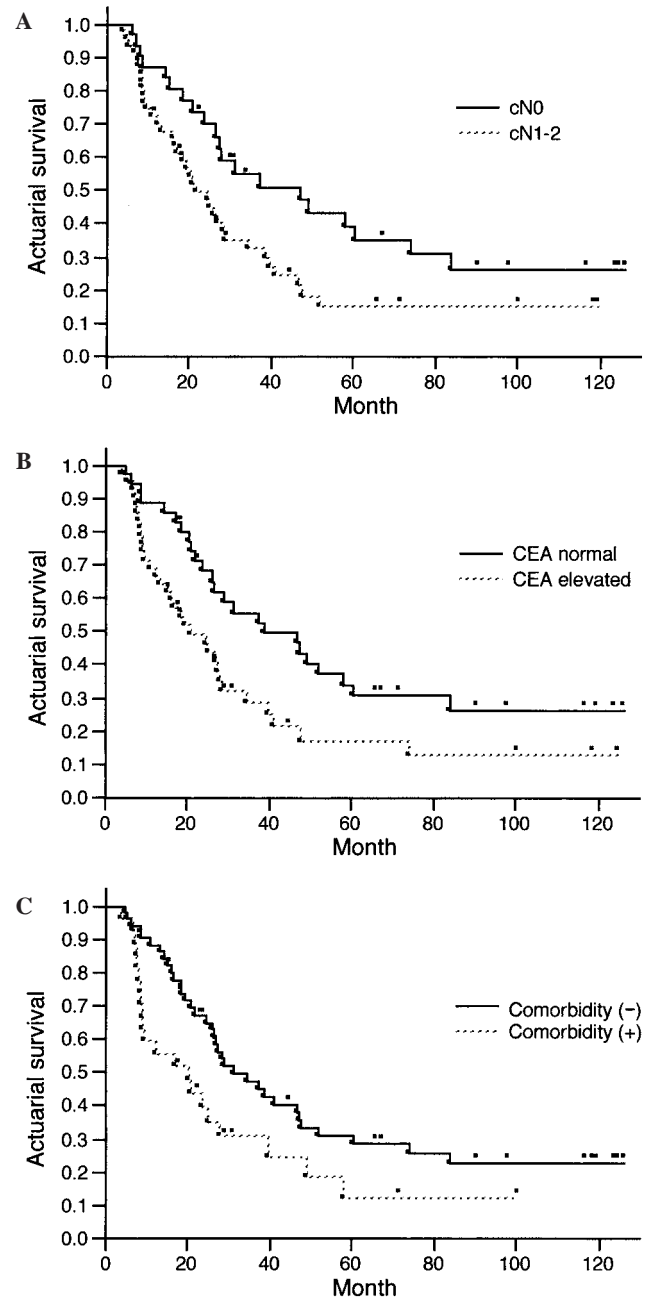


Fig. 1. Survival of patients according to cN status (A), serum CEA level (B) and comorbidity (C) ($p=0.038$, $p=0.019$ and $p=0.031$, respectively by log rank test).

tive) were related to patients' prognosis ($p=0.040$, $p=0.022$ and $p=0.033$, respectively). On the other hand, age ($60 <$ vs. $60 >$), gender (male vs. female), histologic subtype (squamous cell carcinoma vs. others), cT status (cT1 vs. cT2-4), side of tumor (right vs. left), tumor location and preoperative smoking status (current or former vs. never) were not related to patients' prognosis.

Table 2. Univariate analysis

Factors		Hazard ratio	95% CI	<i>p</i> value
Age	60< vs. 60>	1.185	0.415-1.242	0.2360
Gender	Male vs. female	0.74	0.449-1.436	0.4593
Histology	Squamous vs. others	0.391	0.575-2.288	0.6960
cT	cT1 vs. cT2-4	1.072	0.400-1.308	0.2839
cN	cN0 vs. cN1-2	2.051	0.321-0.975	0.0403
Side	Right vs. left	0.735	0.720-2.063	0.4621
Location	Middle	1.000		
	Upper	0.645	0.206-2.221	0.5189
	Lower	0.760	0.185-2.106	0.4470
Serum CEA level	Normal vs. elevated	2.295	0.310-0.912	0.0217
Smoking	Current or former vs. never	1.211	0.804-2.517	0.2260
Comorbidity	Positive vs. negative	2.128	0.319-0.954	0.0334

CI, confidence interval; CEA, carcinoembryonic antigen.

Table 3. Multivariate analysis

Factors		Hazard ratio	95% CI	<i>p</i> value
cN	cN0 vs. cN1-2	1.223	0.380-1.251	0.2213
Serum CEA level	Normal vs. elevated	1.434	0.363-1.170	0.1516
Comorbidity	Positive vs. negative	1.672	0.357-1.085	0.0945

CI, confidence interval; CEA, carcinoembryonic antigen.

The results of multivariate analysis including all variables for which $p < 0.05$ on univariate analysis are summarized in Table 3. Of the variables that were included in the multivariate analysis, there were no independent prognostic determinants ($p = 0.221$, $p = 0.152$, and $p = 0.095$, respectively).

Since cN status, serum CEA level and comorbidity were related to patients' prognosis, comparison of survival curves was also carried out between patients with at least one of these 3 unfavorable factors (group P) and those without these (group N). As shown in Fig. 2, patients with one of these 3 factors had a significantly poor prognosis ($p = 0.008$).

Discussion

The majority of reported prognostic factors of pN2 disease, including single N2 station and skip metastasis,^{4,5,7-11} are not available preoperatively. There are only a few studies regarding preoperative prognostic factors of patients with pN2 disease proven by mediastinoscopy or transbronchial aspiration cytology. Among preoperatively available factors, our results demonstrated that cN status, serum CEA level and comorbidity were related to patients' prognosis on univariate analysis.

The demonstration of a favorable prognosis in patients having cN0 disease is consistent with previous studies.^{9,10} On the basis of these results, pN2 disease might comprise two subgroups: cN0-pN2 disease and cN1-2-pN2 disease. When compared to cN2 disease, cN0 disease might have less potential for tumor proliferation,¹⁰ thereby indicating that pN2 patients with tumor may have less potential for tumor proliferation and might have a favorable prognosis. Although we used 10-mm thick contiguous sections for evaluating cN2 status, the criteria for cN2 disease on CT vary among the institutes. However it was reported that the difference in the criteria of cN2 disease did not cause any great change in the diagnosis of pN2 disease.¹⁸

CEA is a serum tumor marker commonly used in lung cancer patients. Several reports, including our previous study, had indicated that elevated preoperative serum CEA levels are associated with more advanced disease and with very poor survival after surgical resection.¹⁹⁻²³ However these studies did not limit to pN2 disease. Therefore it was unknown whether serum CEA level is a prognostic determinant for pN2 patients. Takamochi et al.²⁴ reported that the elevated serum CEA level is a clinical predictor of pN2 disease. Thus it is considered that serum CEA level of pN2 patients might be higher than that of pN0-1.

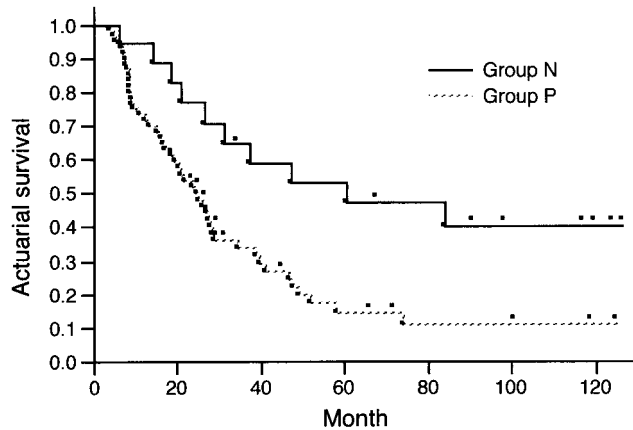


Fig. 2. Comparison of survival between patients with at least one of 3 factors shown in Fig. 1 (group P) and those without these factors (group N) ($p=0.008$).

In fact, the mean serum CEA level of our series is high (10.13 ± 13.26 ng/mL). In spite of high mean levels, the present result showed that serum CEA level is a prognostic determinant for patients with pN2 disease.

The previous reports on the survival impact of comorbidity have been controversies.^{25,26} This discrepancy is probably related to criteria such as patient selection and the limited number of patients with analyzed disease. Our results demonstrate a prognostic significance of comorbidity by univariate analysis. It is generally accepted that efforts to improve survival after treatment of lung cancer need to be directed both toward reducing the incidence of recurrent disease and toward optimizing the management of coexisting medical illness. Since many lung cancer patients have comorbidities, comorbidity should not be ignored in patient treatment selection. Because of the small number of patients, we could not investigate the significance of comorbidity. Battafarano et al.²⁵ showed a significant relationship between comorbidity severity and survival.

Despite prognostic significance on univariate analysis, cN status, serum CEA level and comorbidity were not independent prognostic factors by multivariate analysis. On the basis of this result, strong independent prognostic indicators, such as single N2 station and skip metastasis, are not available preoperatively. Therefore it may be difficult to predict the prognosis of pN2 patients by a preoperatively available single factor. However there was a significant difference in patients' survival between patients with at least one of these 3 unfavorable factors and those without these factors. This result indicated that combined use of these 3 factors might be useful. Based on

our result, even in the presence of pN2 disease, patients without these 3 unfavorable factors might have a favorable prognosis when they were treated with surgery alone. In contrast, patients with at least one of these factors were among an unfavorable subgroup, and there is a possibility that induction chemotherapies might be useful for these patients. To date, it has been still unknown what type of pN2 patients has effective responses to induction chemotherapies. Thus it is also unknown whether induction chemotherapy for pN2 patients with these 3 unfavorable factors is useful or not. This subgroup of pN2 patients could represent a reasonable study population for an induction therapy trial. Further prospective studies in this area are required.

In conclusion, among the preoperatively factors examined, pN2 patients with all cN0 disease, normal serum CEA level and no comorbidities had a favorable prognosis. Even in the presence of pN2 disease, patients without these 3 unfavorable factors might have a favorable prognosis when treated with surgery alone.

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