

# Prognostic Value of Pleural Effusion in Patients with Non-Small Cell Lung Cancer

Seiji Sugiura, Yuichi Ando, Hironobu Minami,  
Masahiko Ando, Shuzo Sakai, and  
Kaoru Shimokata<sup>1</sup>

First Department of Internal Medicine, Nagoya University School of Medicine, Nagoya [S. S., Y. A.]; Department of Clinical Preventive Services, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466, [K. S.]; Department of Internal Medicine, Japanese Red Cross Nagoya First Hospital, 3-35 Michishita-cho, Nakamura-ku, Nagoya 464, [S. S.]; and Division of Oncology/Hematology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277, [H. M.], Japan

## ABSTRACT

This study was performed to determine whether pleural effusion in patients with advanced non-small cell lung cancer (NSCLC) has a negative impact on survival. We evaluated 12 prognostic factors in 197 patients with stage IIIB or IV NSCLC. Each factor was dichotomized, and survival curves calculated by the Kaplan-Meier technique were compared using the log-rank test. The Cox proportional hazards regression model was used to confirm the significance of each prognostic factor selected by univariate analysis. We compared the survival times for stage IIIB with pleural effusion with those of stage IIIB without effusion and stage IV. To determine the impact of the cytological results of the effusion on survival, we compared the survival times for cytologically positive and negative effusions. Univariate analysis identified eight significant prognostic factors: pleural effusion, node status, stage, performance status, weight loss, hemoglobin, albumin, and lactate dehydrogenase. Pleural effusion was selected as a prognostic factor in the multivariate analysis, together with stage, performance status, albumin, and node status.

Median survival times for stage IIIB without effusion, stage IIIB with effusion, and stage IV were 15.3, 7.5, and 5.5 months, respectively ( $P < 0.0001$ ). Survival time for stage IIIB with effusion was significantly different from that of stage IIIB without effusion ( $P = 0.0129$ ) but not from that of stage IV ( $P = 0.0797$ ). Among patients with effusion, no significant difference in survival time was observed between cytologically positive and negative effusions. We conclude that pleural effusion in advanced NSCLC is a prognostic factor. Survival time for stage IIIB with pleural effusion is

more similar to that of stage IV rather than that of stage IIIB without effusion.

## INTRODUCTION

In 1986, Mountain described a new international staging system for lung cancer (1), which is useful for assigning therapy and predicting prognosis in patients with NSCLC.<sup>2</sup> Significant survival differences among different stage groups were observed (1). Studies of prognostic factors in advanced NSCLC identified various factors, including clinical stage, that has a definitive impact on survival (2-4). Heterogeneity within each stage with regard to prognosis and the choice of treatment has been demonstrated. Stage IIIA consists of T<sub>3</sub> disease and N<sub>2</sub> disease; patients with T<sub>3</sub> disease have been reported to live longer than those with N<sub>2</sub> disease (5, 6). The eligibility criteria for recent clinical trials involving patients with stage IIIA distinguish between patients with N<sub>2</sub> and other patients (7, 8). Stage IIIB can be divided into T<sub>4</sub> and N<sub>3</sub> diseases. T<sub>4</sub> includes essentially two groups: direct invasion to adjacent organs such as the heart, great vessels, trachea, or esophagus; and malignant pleural effusion.

Recently, chemotherapy plus radiotherapy has been recommended for the treatment of locally advanced NSCLC. However, patients with pleural effusion are not candidates for this strategy. Some Phase II studies of chemotherapy for NSCLC allow the inclusion of patients with stage IIIB and stage IV (9, 10). However, we think that stage IIIB patients without pleural effusion have longer survival times than those with pleural effusion. This presents a confounding factor when we interpret the survival data from the trials.

In this study, therefore, we tested the prognostic significance of pleural effusion in patients with advanced NSCLC and compared the survival times for stage IIIB with pleural effusion with those of stage IIIB without effusion and stage IV. Furthermore, we investigated whether positive cytology in the pleural fluid influences the survival time for patients with pleural effusion.

## PATIENTS AND METHODS

The records of all NSCLC patients who were admitted to the Japanese Red Cross Nagoya First Hospital between January 1989 and December 1993 were reviewed retrospectively. To be eligible for this review, all patients had to have either a histological or cytological diagnosis of NSCLC in stage IIIB or IV according to the international staging system (1). To confirm the stage, we reviewed chest X-ray films, thoracic CT scans, abdominal CT scans, contrasted brain CT scans, and bone scin-

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<sup>1</sup> To whom requests for reprints should be addressed. Phone: +81-52-744-2153; Fax: +81-52-744-2157.

<sup>2</sup> The abbreviations used are: NSCLC, non-small cell lung cancer; CT, computed tomography; PS, performance status.

tigraphy. No patients underwent mediastinoscopy to diagnose metastasis to intrathoracic lymph nodes. Aspiration needle biopsy was performed to obtain cytological evidence of supraclavicular lymph node metastasis. Of 221 patients who were diagnosed with stage IIIB or IV NSCLC by clinicians, 24 patients were excluded, including 14 with incomplete staging procedures and 10 with a second cancer within 5 years. The remaining 197 patients with stage IIIB or IV NSCLC were selected for this review. We analyzed 12 possible pretreatment prognostic factors: age, gender, histology, T status, N status, stage, the existence of pleural effusion, Eastern Cooperative Oncology Group PS, weight loss during the previous 6 months, and the levels of hemoglobin, serum albumin, and lactate dehydrogenase. Each factor was dichotomized based on previous reports (2, 3, 6), clinical implications, or statistical significance and was analyzed for survival time.

Survival time was calculated from the day of pathological diagnosis to the day of death or the date of analysis. One hundred seventy patients died, and 27 patients (14 alive and 13 lost to follow-up) were censored. Survival curves were calculated using the Kaplan-Meier technique (11) and were compared using the log-rank test (12). Multivariate analysis was performed using the Cox proportional hazards regression model (13).  $P < 0.05$  was considered significant. After we confirmed that pleural effusion was a significant prognostic factor according to the Cox model, we compared the survival of stage IIIB patients with pleural effusion to that of stage IIIB patients without pleural effusion and that of stage IV patients. Furthermore, to examine whether the cytological results of pleural effusion affect survival, we analyzed the difference between survival times of patients with cytologically positive and negative effusions.

## RESULTS

The overall survival times of patients with stage IIIB or IV NSCLC at 1, 2, and 3 years were 29, 11, and 5%, respectively, with a median survival of 6.5 months. The results of the univariate analyses for survival are summarized in Table 1. A statistically significant difference in survival time was observed between patients with and without pleural effusion. Median survival times for patients with and without pleural effusion were 7.5 and 5.5 months, respectively.  $N_3$  status, stage IV, PS  $\geq 2$ , 10% or more weight loss during the previous 6 months, hemoglobin  $< 11.0$  mg/dl, albumin  $< 4.0$  g/dl, and lactate dehydrogenase  $\geq 380$  IU/liter were other pretreatment indicators of poor prognosis. No significant differences in survival were observed based on age, gender, histology, and T status.

Multivariate regression analysis was performed to select the independent prognostic factors among the eight significant variables identified in univariate analyses. Pleural effusion was selected as a significant prognostic factor in the Cox proportional hazards regression model ( $P = 0.0481$ ), together with stage, PS, N status, and albumin (Table 2).

To confirm the effect of pleural effusion on survival time, we compared the survival curves of three patient groups: stage IIIB patients without pleural effusion, stage IIIB patients with pleural effusion, and stage IV patients (Fig. 1). Median survival times for stage IIIB without pleural effusion, stage IIIB with

Table 1 Univariate analyses of prognostic factors for patients with advanced NSCLC

Variable	No. of patients	Median survival (mo)	P by log-rank test
Age			
<75 yr	153	7.0	0.666
$\geq 75$ yr	44	6.4	
Gender			
Female	64	6.8	0.657
Male	133	6.8	
Histology			
Squamous	56	8.0	0.173
Non-squamous	141	6.5	
T status			
1-3	98	6.7	0.436
4	99	7.0	
N status			
0-2	115	7.7	0.003
3	82	5.6	
Stage			
IIIB	66	10.7	<0.001
IV	131	5.5	
Pleural effusion			
No	135	7.5	0.011
Yes	62	5.5	
PS			
0-1	152	7.8	<0.001
2-4	45	3.0	
Weight loss			
<10%	104	8.2	0.009
$\geq 10\%$	93	5.2	
Hemoglobin			
$\geq 11.0$ mg/dl	155	7.4	0.013
$< 11.0$ mg/dl	42	4.0	
Serum albumin			
$\geq 4.0$ g/dl	84	10.1	<0.001
$< 4.0$ g/dl	113	4.8	
LDH			
$< 380$ IU/l	154	7.4	0.002
$\geq 380$ IU/l	43	4.0	

pleural effusion, and stage IV were 15.3, 7.5, and 5.5 months, respectively ( $P < 0.0001$ ). When we compared the groups, survival times of stage IIIB patients with and without pleural effusion differed significantly ( $P = 0.0129$ ), but stage IIIB patients with pleural effusion and stage IV patients did not show significant differences ( $P = 0.0797$ ).

We also examined whether the negative cytology in the pleural fluid had a favorable impact on survival in patients with pleural effusion. All of the 62 subjects (37 men and 25 women; median age, 69 years; range, 30-87 years) with pleural effusion received thoracentesis; none of the patients had transudate. The median survival time of the 48 patients with positive cytology was 6.0 months compared with 3.6 months for the 14 patients with negative cytology. No significant difference was observed between the two survival curves ( $P = 0.5541$ ; Fig. 2).

## DISCUSSION

Although many studies have been performed to identify prognostic factors in NSCLC, pleural effusion has rarely been investigated in this regard (14). In the present study, pleural effusion was a significant prognostic factor for advanced

Table 2 Prognostic factors for patients with NSCLC: results of the Cox regression analysis

Variables	Coefficient	SE( $\beta$ )	Risk ratio	95% CI <sup>a</sup> of risk ratio	P
Stage (IIIB/IV)	0.8220	0.1834	2.275	1.600–3.290	<0.0001
PS (0–1/2–4)	0.7460	0.1787	2.108	1.483–2.989	<0.0001
N status (0–2/3)	0.4156	0.1602	1.515	1.105–2.072	0.0102
Albumin ( $\geq 4.0$ / $<4.0$ g/dl)	0.4077	0.1683	1.503	1.083–2.096	0.0149
Pleural effusion (-/+)	0.3476	0.1730	1.416	1.003–1.978	0.0481

<sup>a</sup> CI, confidence interval.

Fig. 1 Survival curves for stage IIIB disease without pleural effusion, stage IIIB with pleural effusion, and stage IV. Median survival times for the groups were 15.3, 7.5, and 5.5 months, respectively. Survival times for stage IIIB with pleural effusion were significantly different from those of stage IIIB without pleural effusion ( $P = 0.0129$ ) but not from those of stage IV ( $P = 0.0797$ ).

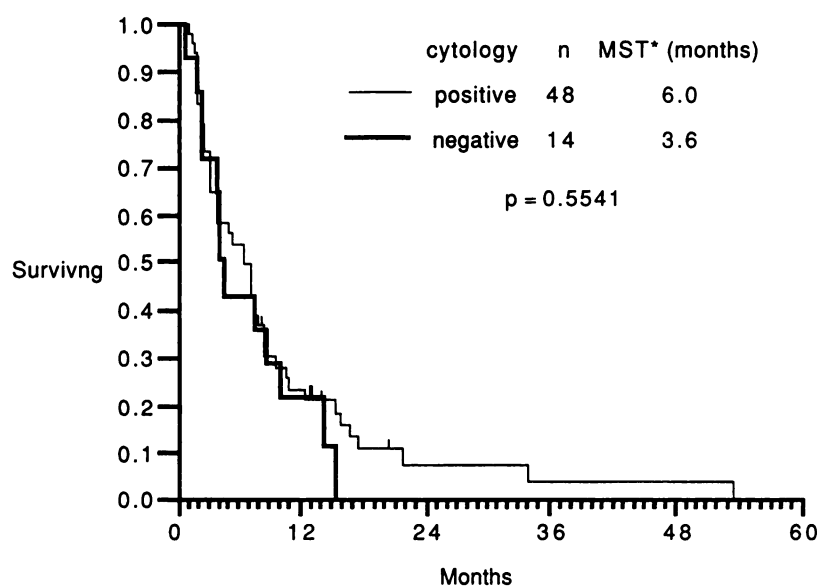
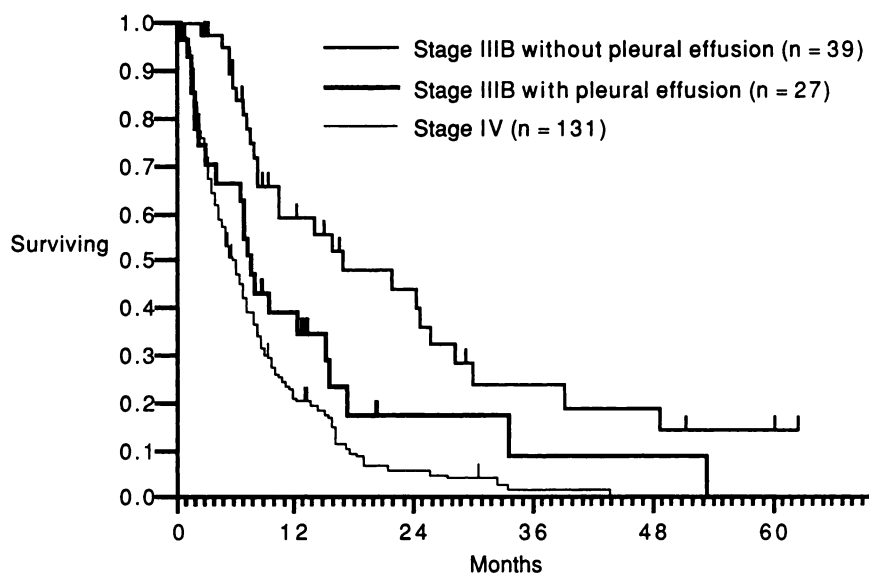


Fig. 2 Survival curves according to cytological examination of pleural effusion. MST, median survival time.

NSCLC in both univariate and multivariate analyses, in addition to factors reported by previous investigators: stage, PS, N status, and albumin. Furthermore, it was notable in this study that survival times of stage IIIB patients with pleural effusion were

more similar to those of stage IV patients than those of stage IIIB patients without pleural effusion. This implies that stage IIIB patients with pleural effusion should be regarded as a separate prognostic group than stage IIIB patients without pleu-

ral effusion. Recently, combined chemotherapy and radiotherapy has been accepted as standard treatment for locally advanced NSCLC (15). However, patients with pleural effusion cannot be treated with this combined therapy. Therefore, distinguishing stage IIIB with pleural effusion from stage IIIB without pleural effusion is also necessary for treatment selection. Previous investigators have reported that patients with pleural effusion have short survival times ranging from 3.0 to 7.8 months (16–18). Median survival times of our patients with pleural effusion fell into this range (5.5 months). We also reviewed the records of all patients with NSCLC, including those treated outside clinical trials, and believe that our results can be generalized.

In this study, there was no significant difference in survival times between patients with cytologically positive and negative pleural effusions. Other investigators also reported that a cytological diagnosis of benign or nonmalignant effusion was not an indicator of improved prognosis in cancer patients (16). Survival times of patients with cytologically negative pleural effusion were reported to be even shorter than those of patients with cytologically positive effusion (19–21). Our results support the general opinion that the survival time of patients with pleural effusion is short, whether the cytology is positive or not (22–25). Therefore, we do not believe that patients with cytologically positive and negative pleural effusion should be treated differently.

Although this study is retrospective and needs to be confirmed prospectively, 197 of 221 consecutive patients with lung cancer in our hospital had full staging procedures including chest and abdominal CT, enhanced brain CT, and bone scintigraphy, and only 13 patients were lost to follow up.

We conclude that pleural effusion in advanced NSCLC is an independent indicator of poor prognosis. The survival times of stage IIIB patients with pleural effusion are more similar to those of stage IV patients rather than those of other stage IIIB patients. We propose that stage IIIB with pleural effusion be distinguished from stage IIIB without pleural effusion.

## REFERENCES

- Mountain, C. F. A new international staging system for lung cancer. *Chest*, *89*: 225S–233S, 1986.
- Kaasa, S., Mastekaasa, A., and Lund, E. Prognostic factors for patients with inoperable non-small cell lung cancer, limited disease. The importance of patients' subjective experience of disease and psychosocial well-being. *Radiother. Oncol.*, *15*: 235–242, 1989.
- Pater, J. L., Loeb, M. Nonanatomic prognostic factors in carcinoma of the lung: a multivariate analysis. *Cancer (Phila.)*, *50*: 326–331, 1982.
- Hespanhol, V., Queiroga, H., Magalhães, A., Santos, A. R., Coelho, M., and Marques, A. Survival predictors in advanced non-small cell lung cancer. *Lung Cancer*, *13*: 253–267, 1995.
- Green, M. R., and Lilienbaum, R. C. Stage IIIA category of non-small-cell lung cancer: a new proposal. *J. Natl. Cancer Inst.*, *86*: 586–588, 1994.
- Bonomi, P., Gale, M., Rowland, K., Taylor, S. G., IV, Purl, S., Reddy, S., Lee, M. S., Phillips, A., Kittle, C. F., Warren, W., and Faber, L. P. Pre-treatment prognostic factors in stage III non-small cell lung cancer patients receiving combined modality treatment. *Int. J. Radiat. Oncol. Biol. Phys.*, *20*: 247–252, 1991.
- Albain, K. S., Rusch, V. W., Crowley, J. J., Rice, T. W., Turrisi, A. T., III, Weick, J. K., Lonchyna, V. A., Presant, C. A., McKenna, R. J., Gandara, D. R., Fosmire, H., Taylor, S. A., Stelzer, K. J., Beasley, K. R., and Livingston, R. B. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J. Clin. Oncol.*, *13*: 1880–1892, 1995.
- Kirn, D. H., Lynch, T. J., Mentzer, S. J., Lee, T. H., Strauss, G. M., Elias, A. D., Skarin, A. T., and Sugarbaker, D. J. Multimodality therapy of patients with stage IIIA, N2 non-small-cell lung cancer. Impact of preoperative chemotherapy on resectability and downstaging. *J. Thorac. Cardiovasc. Surg.*, *106*: 696–702, 1993.
- Erkisi, M., Doran, F., Burgut, R., and Kocabas, A. A randomised trial of two cisplatin-containing chemotherapy regimens in patients with stage III-B and IV non-small cell lung cancer. *Lung Cancer*, *12*: 237–246, 1995.
- Vallejo, C. T., Rabinovich, M. G., Perez, J. E., Rodriguez, R., Machiavelli, M. R., Leone, B. A., Romero, A. D., Lacava, J. A., Cuevas, M. A., Langhi, M. J., Acuña, L. A. R., Acuña, J. R., Amato, S., and Barbieri, M. R. High-dose cisplatin with dipyrindamole in advanced non-small cell lung cancer: a Grupo Oncológico Cooperativo del Sur study. *Am. J. Clin. Oncol.*, *18*: 185–188, 1995.
- Kaplan, E. L., and Meier, P. Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.*, *53*: 457–481, 1958.
- Mantel, N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother. Rep.*, *50*: 163–170, 1966.
- Cox, D. R. Regression models and life-tables. *J. Royal Stat. Soc.*, *34*: 187–202, 1972.
- Coen, V., van Lancker, M., de Neve, W., and Storme, G. Prognostic factors in locoregional non-small cell lung cancer treated with radiotherapy. *Am. J. Clin. Oncol.*, *18*: 111–117, 1995.
- Bonomi, P. Treatment of locally advanced non-small cell lung cancer. *Lung Cancer*, *9* (Suppl. 2): S49–S60, 1993.
- van de Molengraft, F. J. M., and Vooijs, G. P. Survival of patients with malignancy-associated effusions. *Acta Cytol.*, *33*: 911–916, 1989.
- Monte, S. A., Ehya, H., and Lang, W. R. Positive effusion cytology as the initial presentation of malignancy. *Acta Cytol.*, *31*: 448–452, 1987.
- Sears, D., and Hajdu, S. I. The cytologic diagnosis of malignant neoplasms in pleural and peritoneal effusions. *Acta Cytol.*, *31*: 85–97, 1987.
- Tandon, R. K. The significance of pleural effusions associated with bronchial carcinoma. *Br. J. Dis. Chest*, *60*: 49–53, 1966.
- Brinkman, G. L. The significance of pleural effusion complicating otherwise operable bronchogenic carcinoma. *Dis. Chest*, *36*: 152–154, 1959.
- Chernow, B., and Sahn, S. A. Carcinomatous involvement of the pleura: an analysis of 96 patients. *Am. J. Med.*, *63*: 695–702, 1977.
- Mountain, C. F. Prognostic implications of the international staging system for lung cancer. *Semin. Oncol.*, *15*: 236–245, 1988.
- Stanley, K. E. Prognostic factors for survival in patients with inoperable lung cancer. *J. Natl. Cancer Inst.*, *65*: 25–32, 1980.
- Mountain, C. F., McMurtrey, M. J., and Frazier, O. H. Regional extension of lung cancer. *Int. J. Radiat. Oncol. Biol. Phys.*, *6*: 1013–1020, 1980.
- Mountain, C. F. The new international staging system for lung cancer. *Surg. Clin. North Am.*, *67*: 925–935, 1987.

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