ORIGINAL ARTICLE

Survival of Resected Non-small Cell Lung Cancer Patients According to Pathological Stage

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ABSTRACT —— ***Objectives.*** To survey resected non-small cell lung cancer patients who died of cancer and estimate the progression rate of death at each stage in order to determine what stages are particularly associated with micrometastasis. ***Methods.*** Of the 815 patients who underwent surgery for primary lung cancer between January 1986 and December 1995, 699 patients without preoperative chemo/radiotherapy were registered. Among these patients, those who died of cancer after at least five years of follow-up were reviewed regarding complete/incomplete resection and pathological stage. ***Results.*** A total of 198 patients who underwent complete resection by lobectomy or pneumonectomy died of cancer. The median survival times of these patients were 34.8, 31.5, 33.7, 21.5, 23.5, 20.4 months for stages IA, IB, IIA, IIB, IIIA, IIIB, respectively. There were no significant differences between stages IA and IB (P＝0.1088), IB and IIA (P＝0.3393), IIB and IIIB (P＝0.4907), IIIA and IIIB (P＝0.5880). Patients in Group A (stages IA, IB, IIA) died significantly later than those in Group B (stages IIB, IIIA, IIIB) [P＜0.0001]. Of 119 incompletely resected patients, 103 died of cancer (Group C). The median survival time of Group C patients was 16.7 months. The difference between Group B and C was not significant (P＝0.2100). ***Conclusion.*** Two patterns were recognized among the patients. Although patients in Group A and B had different 5-year survivals, patients receiving complete resection and who died of cancer, had a similar curve that of patients who had undergone incomplete resection. (*JJLC*. 2002;42:181-186)

KEY WORDS —— Non-small cell carcinoma, Lung cancer, Isolated tumor cell, Micrometastasis

INTRODUCTION

Lung cancer is the leading cause of death from cancer among men and women in both Japan and the United States.[1] In spite of several new screening, diagnostic and therapeutic techniques, 5-year survival for patients with stage I disease is 70%, and only 50 % for those with stage II, and the overall 5-year survival rate remains approximately 14%.[1] Unfortunately, most patients with lung cancer still present with advanced stage disease.

For non-small cell lung cancer patients with limited disease, pulmonary resection remains the most effective treatment. However, even if the detected tumor is small, micrometastases may already be present. Some studies have suggested that metastases may occur at the time of angiogenesis when lesions are approximately 1 to 2 mm in diameter, and perhaps even earlier as tumors invade adjacent normal blood vessels.[2-4] With only surgical resection, tumors accompanied by micrometastases are inevitably incurable, and relapse occurs earlier if the primary lesion is incompletely resected macroscopically or microscopically. To select appropriate therapeutic strategies and plan clinical trials, such as induction chemotherapy, it is important to assess whether or not a tumor is associated with micrometastases.

In this study, we reviewed the survival curves of patients who underwent surgery and died of cancer at every stage, and deduced the stage at which micrometastases occurred.

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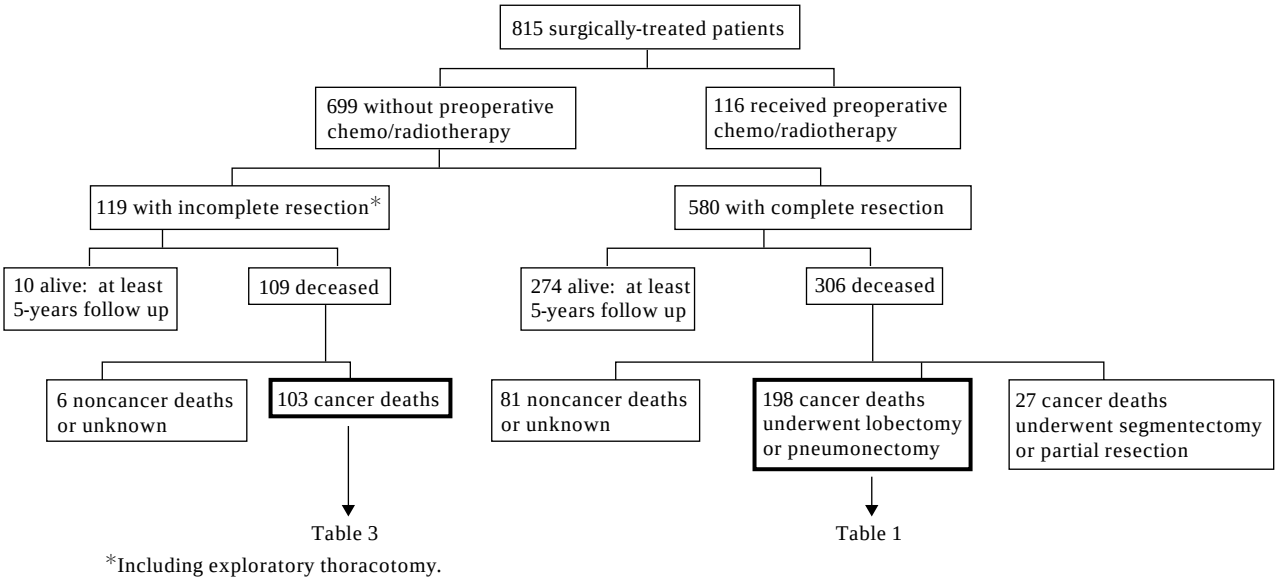


Figure 1. Disease progression during surveillance.

METHODS

From January 1986 through December 1995, 815 patients were operated on for primary non-small cell lung cancer in our institute. Of these 699 patients without preoperative chemo/radiotherapy were enrolled in this study. Among the 699, those who died of cancer as of December 31, 2000, after at least 5 years of follow-up for all living patients, were analyzed regarding complete/incomplete resection and pathological stage. Information about the cause of death was collected by phone interviews and death certificates. Noncancer deaths and deaths of unknown causes were excluded. Two operative deaths, accounting for 0.25% of all resected patients, were excluded.

Pathological stage was based on the New International Staging System for Lung Cancer.[5] In this investigation, we did not consider pleural lavage cytology before resection in determining the pathological stage and completion of resection.[6]

All values are presented as means ± SD, and were analyzed using the Stat View program (SAS Institute, Heidelberg, Germany). Differences in survival were estimated by Cox's proportional hazards regression model. A p value of less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Disease Progression During Surveillance

Among the 699 patients, there were 580 with no residual tumor macroscopically or microscopically on postoperative pathological examination, *i.e.*, "complete resection" had been achieved. Among these 580, 306 patients had died as of December 31, 2000. The other 274 patients remain alive, after at least 5 years of follow-up. Among the 306, 198 patients had undergone lobectomy or pneumonectomy and died of cancer which 27 patients had undergone segmentectomy or partial resection and died of cancer. The other 81 patients died of noncancer causes or other unknown diseases. Of the 119 patients judged to have undergone incomplete resection, 103 patients died of cancer. Six patients died of noncancerous or unknown diseases. The other 10 patients remain alive, after at least 5 years of follow-up (Figure. 1).

Analysis of Patients Who Underwent Complete Resection of Tumor by Lobectomy or Pneumonectomy With Regard to Pathological Stage

There were 153 men and 45 women with a mean age of 62.5 years (range, 30-88). Of the 198, 123 patients had adenocarcinomas, 62 had squamous cell carcino-

Abbreviations. MST indicates median survival times; SD, standard deviation; HR, hazard ratio; 95% CI, 95% confidence interval; and N.S., not significant.

Table 1. Characteristics of the 198 patients who underwent complete resection and later died of cancer

Characteristic	All patients (n=198)	Stage IA (n=29)	Stage IB (n=33)	Stage IIA (n=12)	Stage IIB (n=30)	Stage IIIA (n=69)	Stage IIIB (n=25)
Sex							
Male	153	20	26	10	26	54	17
Female	45	9	7	2	4	15	8
Mean age(years)	62.5 ＋/－9.8＊	62.6 ＋/－10.5＊	66.2 ＋/－9.1＊	59.5 ＋/－8.8＊	61.9 ＋/－10.3＊	62.2 ＋/－9.4＊	60.6 ＋/－10.4＊
Histology							
Adenocarcinoma	123	25	17	6	13	44	18
Squamous cell	62	3	12	4	13	23	7
Large cell	6	0	1	1	3	1	0
Others	7	1	3	1	1	1	0
Operative Procedure†							
Lobectomy	184	29	32	12	29	62	20
Pneumonectomy	14	0	1	0	1	7	5
Median survival time(months)	25.7	34.8	31.5	33.7	21.5	23.5	20.4

＊Values means ＋/－ standard deviation.

† Segmentectomies and partial resections were excluded.

Table 2. Cox proportional hazards analysis of staging and postoperative survival after complete resection(deceased patients only)(every stage vs. stage IIIB)

Stage	Hazard ratio	CI(95%)	p value
Stage IA	0.295	0.160-0.544	＜0.0001
Stage IB	0.580	0.334-0.929	0.0325
Stage IIA	0.407	0.186-0.875	0.0216
Stage IIB	0.823	0.473-1.432	0.4907
Stage IIIA	0.881	0.556-1.395	0.5880

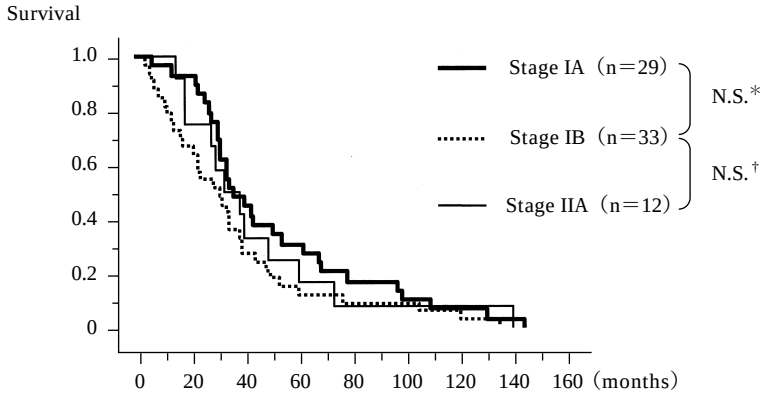
CI indicates confidence interval.

mas, 6 had large cell carcinomas and there were 8 other types. There were 184 lobectomies and 14 pneumonectomies. There were 29 stage IA, 33 stage IB, 12 stage IIA, 30 stage IIB, 69 stage IIIA and 25 stage IIIB patients. The median survival times were 34.8, 31.5, 33.7, 21.5, 23.5 and 20.4 months for stages IA, IB, IIA, IIB, IIIA and IIIB, respectively (Table 1). There was a significant difference between stages IIIB and IIA [P＝0.0216, hazard ratio (HR)＝0.407, 95% confidence interval(CI); 0.186-0.875], IIIB and IB [P＝0.0325, HR＝0.580, 95% CI; 0.334-0.929], and IIIB and IA [p＜0.0001, HR＝0.295, 95% CI; 0.160-0.544](Table 2). There was no significant difference in the survival between stages IA and IIA [P＝0.1088, HR＝0.661, 95% CI; 0.398-1.097] or between IB and IIA [P＝0.3393, HR＝1.397, 95% CI; 0.704-2.558](Figure. 2). On the other hand, there was no significant difference between stages IIB and IIIB [P＝0.4907, HR＝0.823, 95% CI; 0.473-1.432] or IIIA and IIIB [P＝0.5880, HR＝0.881, 95% CI; 0.556-1.395](Figure. 3).

Group A patients (stage IA, IB and IIA) had significantly longer survival than Group B (stage IIB, IIIA and IIIB) [P＜0.0001, HR＝0.472, 95% CI; 0.347-0.644](Figure. 4).

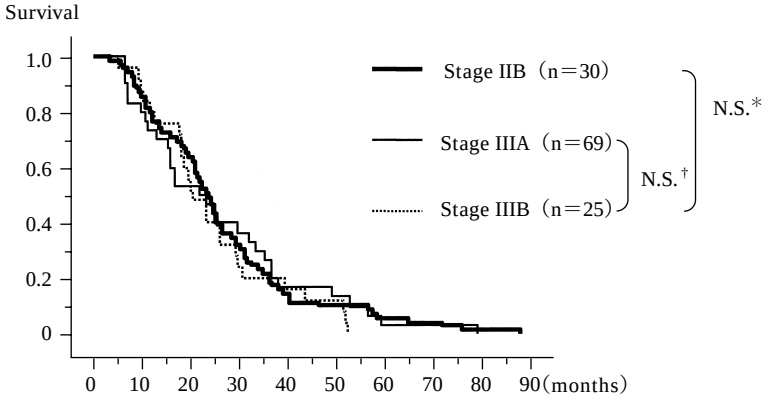
Analysis of the 103 Patients With Incomplete Resection Who Died of Cancer (Group C)

There were 68 men and 35 women with a mean age of 63.1 years. Eighty-one patients had adenocarcinomas, 16 had squamous cell carcinomas, 4 had large cell carcinomas and there were 2 other types. There were 48 lobectomies, 4 segmentectomies, 16 pneumonectomies, 11 wedge resections and 24 exploratory thoracotomies. There were 43 patients with malignant pleural effusion or dissemination, 21 with confirmed microscopic residual tumor on postoperative pathological examination, 19 with pulmonary metastasis excluding the lobes containing the primary lesion and 12 with distant metastasis, excluding the cases of exploratory thoracotomies. The median survival time was 16.7 months (Table 3). There was no significant difference between Group B (stages IIB, IIIA and IIIB with complete resection) and Group C [P＝0.2100, HR＝1.185, 95% CI; 0.909-1.546](Figure 4).



*P=0.1088; Hazard Ratio: 0.661; 95% Confidence Interval: 0.398-1.097.
†P=0.3393; Hazard Ratio: 1.397; 95% Confidence Interval: 0.704-2.558.

Figure 2. Survival curves of stage IA, IB, and IIA patients who underwent complete resection and then died of cancer.



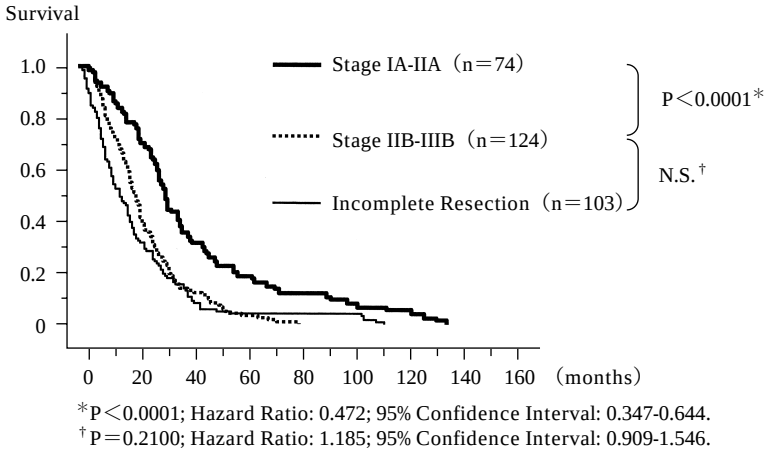
*P=0.4907; Hazard Ratio: 0.823; 95% Confidence Interval: 0.473-1.432.
†P=0.5880; Hazard Ratio: 0.881; 95% Confidence Interval: 0.556-1.395.

Figure 3. Survial curves of stage IIB, IIIA and IIIB patients who underwent complete resection and died of cancer.

DISCUSSION

The objectives of the TNM classification and staging system are to describe the condition of a cancer accurately, allowing optimal treatment and proper determination of prognosis. For those purposes, various survival curves have been developed and analyzed statistically. Common survival curves consist of two different components. One is the" cure rate ", namely the rate of patient survival after an adequate follow-up period, for example 5 years. This 5-year survival rate generally reflects prognosis. The other component is the slope of the curve plotting the time of death of patients who die during the follow-up period. This curve is closely related to the disease-free survival. When the death rate of patients in one group during the early postoperative period was extremely high, even if the group had a high overall survival rate, the deceased patients might have had micrometastases at the time of surgery such that their resections were essentially incomplete. Each stage appears to have a different survival curve because each has a distinct cure rate, based on having the same death rate in the early postoperative period. Thus, these two components, the cure rate and the slope of the curve must be analyzed separately to ascertain the systemic condition of a cancer.

An experimental study showed that a 1-cm tumor could shed approximately 3-6 million cells into the blood every 24 hours.[7] Some investigators have



*P<0.0001; Hazard Ratio: 0.472; 95% Confidence Interval: 0.347-0.644.
†P=0.2100; Hazard Ratio: 1.185; 95% Confidence Interval: 0.909-1.546.

Figure 4. Survival curves of patients who underwent complete or incomplete resection and later died of cancer.

Table 3. Characteristics of the 103 patients with residual tumor who died of cancer

Characteristic	All incomplete resection patients (n=103)	All complete resection patients (n=198)	Stage ⅠA-ⅡA of CR ‡ (n=74)	Stage ⅡB-ⅢB of CR ‡ (n=124)
Sex				
Male	68	153	73	102
Female	35	45	21	29
Mean age(years)	63.1	62.5	63.7	61.9
	＋/－9.7*	＋/－9.8*	＋/－9.8*	＋/－9.7*
Histology				
Adenocarcinoma	81	123	48	75
Squamous cell	16	62	19	43
Large cell	4	6	2	5
Others	2	7	5	2
Operative Procedure				
Lobectomy	48	184	73	111
Segmentectomy	4	0 †	0 †	0 †
Pneumonectomy	16	14	1	13
Wedge resection	11	0 †	0 †	0 †
Exploratory thoracotomy	24	0	0	0
Median survival time(months)	16.7	25.7	34.2	20.8

* Values means ＋/－ standard deviation.
† Segmentectomies and partial resections were excluded.
‡ CR indicates complete resection.

found tumor cells in the peripheral blood and bone marrow of patients with lung cancers of all sizes and stages.[8-10] Every micrometastatic focus originates from the shed, isolated tumor cells. In reality, however, the shed cells are less clonogenic and less tumorigenetic than those of the primary tumor, but are more apoptotic.[7] Thus, only a very small percentage (0.05%) of these circulating cancer cells survive and initiate a metastatic focus.[11]

Patients who have only circulating tumor cells will have a relatively good prognosis if a portion of them lead to micrometastasis. Hermanek advocated that detection of isolated tumor cells could be distinguished from micrometastasis (occult metastasis).[12] In this investigation, patients, who had undergone complete resection and died of cancer, produced two

types of curves. One group (Group A), which included stage IA, stage IB and stage IIA, had a median survival of 34.2 months. The other group (Group B), which included stage IIB, stage IIIA and stage IIIB, had a median survival of 20.8 months. There was a difference of more than one year in median survival, which was statistically significant. We speculate that the Group B patients who died might already have had occult metastatic lesions at the time of surgery, because there was no significant difference between Group B and those in whom incomplete resections had been performed (Group C). On the other hand, almost all Group A patients might have had only circulating isolated tumor cells, systemically. The one-year lag between Group A and Group B might be the time from isolated tumor cell dissemination until micrometastasis.

When preoperative or postoperative adjuvant trials are planned, this grouping must be taken into consideration. The same adjuvant therapeutic trial as that used for stage IIIA may be also adapted for stage IIB.

CONCLUSION

Two patterns were recognized among the patients. Although patients in Group A and B had different 5-year survivals, patients receiving complete resection and who died of cancer, had a similar curve that of patients who had undergone incomplete resection.

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