PROGNOSTIC FACTORS OBTAINED BY A PATHOLOGIC EXAMINATION IN COMPLETELY RESECTED NON-SMALL-CELL LUNG CANCER

An analysis in each pathologic stage

We attempted to clarify what factors predominantly influence the survival of patients with non-small-cell lung cancer in each pathologic stage on the basis of information generally obtained by a pathologic examination of completely resected non-small-cell lung cancer. The subjects included 243 patients with stage I, 63 with stage II, and 108 with stage IIIA disease. Pathologic features used in the analysis were as follows: the greatest tumor size (≤3.0 cm versus >3.0 cm), the histologic cell type (squamous versus nonsquamous cell carcinoma), the grade of differentiation, and tumor invasion of pleura and vessels. In stage IIIA, the extent of the metastasis to the lymph nodes was also included in the analysis. The significant prognostic factors ($p < 0.05$) in stage I demonstrated by a univariate analysis of the survival curves included the tumor size, the grade of differentiation (well differentiated versus moderately and poorly differentiated tumor), pleural involvement, and invasion of the artery and vein. In addition, the histologic cell type and the pleural involvement in stage II and invasion of the vein and the extent of metastasis to the lymph nodes (N0 and N1 versus N2) in stage IIIA were also found to be significant prognostic factors. A multivariate prognostic factor analysis showed that the grade of differentiation, pleural involvement, and venous invasion in stage I; the histologic cell type and pleural involvement in stage II; and venous invasion and mediastinal lymph node metastasis in stage IIIA were all predominant prognostic factors. These observations therefore suggest that a pathologic examination can identify the patients with a poor prognosis, which is different among the stages. (J THORAC CARDIOVASC SURG 1995;110:601-5)

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The survival of patients with non-small-cell lung cancer who undergo a complete resection is known to be closely correlated to the pathologic stage of the disease.[1] Many studies of resected specimens have been recently performed to determine the prognostic factors other than the pathologic stage for these patients. For example, an abnormal expression of p53 protein, a mutation of the *ras* gene, or aneuploidy by a deoxyribonucleic acid flow cytometry analysis have all been reported to be related to a poor prognosis.[2-5] On the whole, however, no prognostic factor that has a greater impact on the survival than the pathologic stage has yet been identified.

An ordinary pathologic examination also provides important information on survival.[6-13] So far, the grade of differentiation of the tumor and the presence of either pleural involvement or vessel invasion have been reported to be prognostic factors. To our knowledge, however, it still remains unclear as to which pathologic feature has a predominant impact on the survival in each pathologic stage. Therefore, in the present study we attempted to clarify this issue.

Patients and methods

In the period between April 1972 and December 1988, 485 patients who had undergone a complete surgical

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Supported in part by a grant-in-aid (5S-1) for cancer research from the Ministry of Health and Welfare, Japan.

Received for publication August 19, 1994.

Accepted for publication Dec. 20, 1994.

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0022-5223/95 $5.00 + 0 **12/1/63013**

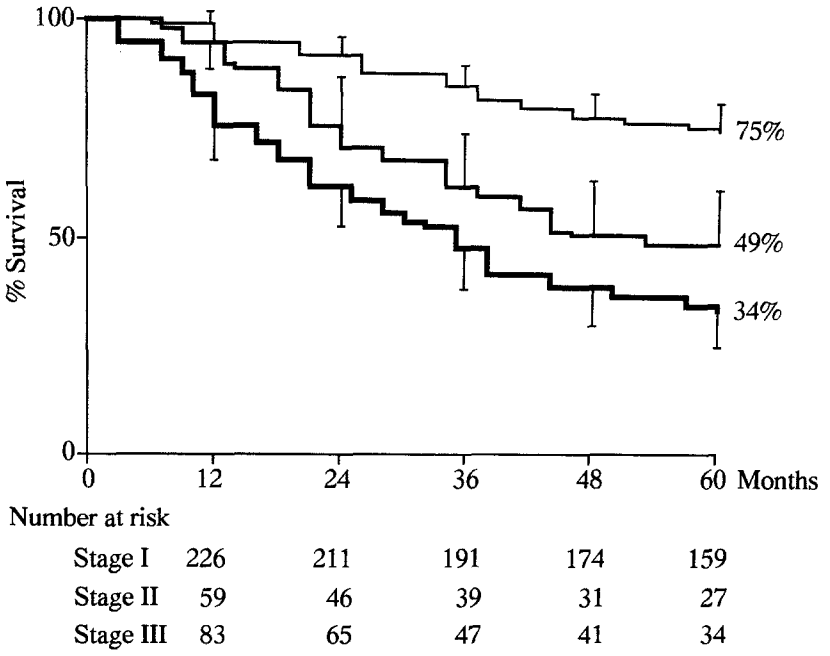

Fig. 1. Survival curves in stage I through IIIA disease. Survival curve between stage I (*thin line, n* = 243) and stage II (*medium line, n* = 63) or stage III (*thick line, n* = 108) shows statistically significant difference by means of log-rank test ($p = 0.000$). Difference between stages II and III is marginal ($p = 0.077$). *Bars* indicate 95% confidence intervals.

resection of non-small-cell lung cancer were found to have pathologic stage I, II, or IIIA disease on the basis of the classification of the new international staging system.[1] All patients underwent mediastinal node dissection. Out of these 485 patients, all the pathologic features described in this section were noted in 414 patients. The subjects consisted of 243 patients with stage I, 63 with stage II, and 108 with stage IIIA disease.

The histopathologic features were analyzed for tumor typing and the grade of differentiation, classified according to the World Health Organization,[14] and examined for pleural and vascular invasion of the tumor. Sections of the tumor were stained with hematoxylin and eosin, alcian blue, and periodic acid–Schiff stains. Staining of the elastic and connective tissue was done when necessary. Vascular invasion was determined by identification of the tumor cells in the lumen of the endothelium-lined channel. The classification of pleural involvement according to the Japan Lung Cancer Society is as follows[15]: p0, tumor having no pleural involvement or reaching the visceral pleura but not extending beyond its elastic layer; p1, tumor extending beyond the elastic layer of the visceral pleural but not exposed on the pleural surface; p2, tumor exposed on the pleural surface but not involving the parietal pleura; p3, tumor extending to the parietal pleura. In the present study, because the number of patients with p1 or p2 tumors was relatively small and it was sometimes difficult to distinguish p1 from p2 tumors, p1 and p2 tumors were combined and analyzed as merely an invasion of the visceral pleura.

The minimum follow-up period was 5 years. The survival curves of the patients were drawn by means of the Kaplan-Meier method, and the statistical evaluation of the curves was done by means of the log-rank test. The parameters for the determination of a predominant impact on survival were evaluated by Cox's multivariate regression models.[16] The data were considered significant when the p value did not exceed 0.05.

Results

Survival in each stage. Fig. 1 shows the survival curves of stages I through IIIA. The 5-year survival was 75% in stage I, 49% in stage II, and 34% in stage IIIA. The survival between stages I and II or IIIA demonstrated a statistically significant difference.

Stage I. The survival and statistical evaluation of related factors by means of the log-rank test in patients with stage I disease are shown in Table I. Of the seven factors, tumor size, grade of differentiation, pleural involvement, and invasion of the artery and vein were considered to be significant prognostic factors by a univariate analysis of the survival curves (Table I). In addition, invasion of lymphatic vessels tended to have an impact on the survival ($p = 0.09$).

Multivariate analyses were done to determine which of these six factors had a predominant impact

Table I. *Survival classified according to the histopathologic factors in stage I (n = 243)*

Prognostic factor	No.	Survival (%) 2 yr	3 yr	5 yr	χ^2	p Value
Tumor size						
≦3.0 cm	119	92.3	89.7	84.4	6.2882	0.0132*
≧3.1 cm	124	86.8	75.7	66.0		
Histologic classification						
Squamous	87	91.8	83.5	77.1	0.0682	0.7952
Nonsquamous	156	88.2	82.1	74.0		
Differentiation						
Well differentiated	59	98.3	96.6	87.4	9.4157	0.0029*
Moderate and poor	184	86.6	78.1	71.1		
Pleural involvement						
p0	159	91.8	85.2	89.9	8.9329	0.0036*
p1,2	84	85.0	77.4	65.7		
Invasion of artery						
−	210	91.2	85.2	78.0	4.2816	0.0407*
+	33	78.8	66.7	57.4		
Invasion of vein						
−	216	91.9	85.6	78.6	13.0908	0.0005*
+	27	70.4	59.3	48.1		
Invasion of lymphatic vessel						
−	116	96.5	89.4	80.3	2.9252	0.0903
+	127	83.0	76.4	70.3		

*$p < 0.05$, considered statistically significant.

Table II. *A multivariate prognostic factor analysis in stage I disease*

Factors	Hazard ratio	95% CI	p Value
Tumor size			
≦3.0 cm vs ≧3.1 cm	1.4319	0.8822-2.3241	0.1463
Differentiation			
Well vs moderately and poorly differentiated	2.2150	1.1131-2.4834	0.0235*
Pleural involvement			
p0 vs p1,2	1.8463	1.1557-2.9495	0.0103*
Invasion of artery			
Absence vs presence	1.2153	0.6703-2.2036	0.5207
Invasion of vein			
Absence vs presence	2.1592	1.1846-3.9355	0.0120*
Invasion of lymphatic vessel			
Absence vs presence	1.2670	0.7825-2.0515	0.3358

CI, confidence interval.
*$p < 0.05$, considered a predominant prognostic factor.

on survival. As shown in Table II, the grade of differentiation (well versus moderately and poorly), visceral pleural involvement, and invasion of the veins were found to be predominant prognostic factors. The 5-year survival was 87% in 41 patients with well-differentiated p0 tumor and 60% in 66 patients with either a moderately or poorly differentiated p1,2 tumor.

Table III. *Survival classified according to the histopathologic factors in stage II disease (n = 63)*

Prognostic factor	No.	Survival (%) 2 yr	3 yr	5 yr	χ^2	p Value
Tumor size						
≦3.0 cm	16	87.5	81.3	50.0	0.5423	0.4655
≧3.1 cm	47	68.1	55.3	48.9		
Histologic classification						
Squamous	27	77.8	70.4	63.0	5.7377	0.0184*
Nonsquamous	36	69.4	55.6	38.7		
Differentiation						
Well differentiated	9	88.9	77.8	55.6	0.0255	0.3957
Moderate	34	70.6	61.8	44.1		
Poor	20	70.0	55.0	55.0	0.7236	0.8800
Pleural involvement						
p0	43	81.4	67.4	55.8	6.6236	0.0101*
p1,2	20	55.0	50.0	35.0		
Invasion of artery						
−	51	74.5	64.7	48.9	0.1868	0.6694
+	12	66.7	50.0	50.0		
Invasion of vein						
−	46	76.1	65.2	49.9	0.0610	0.8066
+	17	64.7	52.9	47.1		
Invasion of lymphatic vessel						
−	13	76.9	53.8	46.2	0.0010	0.9748
+	50	72.0	64.0	49.9		

*$p < 0.05$, considered statistically significant.

Table IV. *A multivariate prognostic factor analysis in stage II disease*

Factors	Hazard ratio	95% CI	p Value
Histologic classification			
Squamous vs nonsquamous	2.0415	1.0118-4.1194	0.0463*
Pleural involvement			
p0 vs p1,2	2.0107	1.0470-3.8613	0.0359*

CI, Confidence interval.
*$p < 0.05$, considered a predominant prognostic factor.

Stage II. As shown in Table III, the histologic classification and pleural involvement were considered to be significant prognostic factors by a univariate analysis of the survival curves. A multivariate analysis also revealed both the histologic classification and pleural involvement to be predominant prognostic factors (Table IV). The 5-year survival was 71% in 21 patients with p0 squamous cell

Table V. *Survival classified according to the histopathologic factors in stage IIIA disease (n = 108)*

Prognostic factor	No.	Survival (%) 2 yr	3 yr	5 yr	χ^2	p Value
Tumor size						
≦3.0 cm	30	73.3	59.6	38.6	1.0504	0.3064
≧3.1 cm	78	56.6	39.5	31.6		
Histologic classification						
Squamous	48	68.1	55.2	44.1	1.8704	0.1785
Nonsquamous	60	56.0	37.3	25.3		
Differentiation						
Well differentiated	14	71.4	56.3	40.2	0.0184	0.6258
Moderate	59	64.4	47.5	32.2		
Poor	35	51.7	36.5	33.5	0.2422	0.8946
Pleural involvement						
p0	49	63.3	42.6	27.5	0.1261	0.2666
p1,2	27	55.6	44.4	33.3		
p3	32	63.4	50.1	43.4	1.2635	0.7261
Invasion of artery						
−	87	61.6	47.5	34.5	0.0010	0.9748
+	21	60.0	35.0	30.0		
Invasion of vein						
−	83	67.9	51.7	36.6	4.8751	0.0281*
+	25	40.0	24.0	24.0		
Invasion of lymphatic vessel						
−	38	62.2	51.4	43.1	1.5343	0.2190
+	70	60.9	41.8	28.4		
N factor						
N0,1	29	72.4	69.0	62.1	7.5791	0.0062*
N2	79	57.2	36.1	22.7		

*$p < 0.05$, considered statistically significant.

carcinoma and 36% in 14 patients with p1,2 nonsquamous cell carcinoma.

Stage IIIA. The category of stage IIIA is determined by the presence of invasion of the parietal pleura (p3), metastasis to the mediastinal lymph nodes (N2), or a tumor in the main bronchus within 2 cm of the carina. Only a few patients had the latter tumor in our experience. Therefore p3 tumor and the extent of metastasis to the lymph nodes (N factor) were added to the analysis as shown in Table V. Because the number of patients with N1 disease was as small as five, both N0 and N1 diseases were classified as one group. Of the eight factors, N factor and invasion of the vein were considered to be significant prognostic factors on the basis of a univariate analysis. A multivariate analysis also revealed venous invasion and N factor to be predominant prognostic factors (Table VI). The 5-year survival was 65% in the 23 patients who had an N0,1 tumor without venous invasion, and it was 16% in the 19 patients with an N2 tumor accompanying venous invasion.

Table VI. *A multivariate prognostic factor analysis in stage IIIA disease*

Factors	Hazard ratio	95% CI	p Value
Invasion of vein			
Absence vs presence	1.7751	1.0521-2.9949	0.0315*
N factor			
N0,1 vs N2	2.1586	1.2368-3.7677	0.0068*

CI, Confidence interval.

*$p < 0.05$, considered a predominant prognostic factor.

Discussion

The most important prognostic factors in resected non-small-cell lung cancer are known to be the pathologic stage of the disease, which is mainly based on tumor size and lymph node metastases.[1] Other morphologic features such as histologic type, degree of differentiation, and vascular or pleural invasion, which are ascertained by an ordinary pathologic examination of the resected samples, have also been reported to be prognostic factors.[6-13] To our knowledge, however, few studies on these pathologic prognostic factors were done after the classification of pathologic stage and there are few reports on the comparison between pathologic prognostic factors and each pathologic stage.

In the present study, visceral pleural involvement was found to be a predominant prognostic factor in stages I and II by a multivariate prognostic factor analysis. Some other reports have made the same conclusion on the basis of a univariate analysis.[11, 12] These observations lend support to the current definition of T staging in which any tumor with visceral pleural invasion is classified as T2 even if the greatest dimension of the tumor is only 3 cm or less.[1]

We found that the degree of differentiation is one of the predominant prognostic factors in stage I but not in stages II and IIIA. The present study shows that patients with well-differentiated tumors in stage I were significantly more likely to survive than were those with moderately or poorly differentiated tumors. The same observation was found in other reports concerning either resected tumors[8, 10, 13] or inoperable advanced tumors.[7] Although we did not mention recurrent cases in detail, it may be of importance to note that the postrecurrent survival in patients with well-differentiated tumors in stage I was significantly longer than that in those with either moderately or poorly differentiated tumors. There-

fore, some part of the biologic aggressiveness of non-small-cell lung cancer may be related to the degree of differentiation. In the present study, the degree of differentiation was not found to be a prognostic factor in stages II and IIIA and this may possibly be because of the small number of patients with well-differentiated tumors in these stages.

Many studies of vascular invasion have concentrated on the veins as a source of blood-borne metastases. In fact, venous invasion is found to be a predominant prognostic factor in stages I and IIIA. Regarding the 88 patients with recurrence in stage I disease, 22 (25%) and 66 (75%) patients had a local and distant recurrent site, respectively. However, the first recurrent site in 15 (85%) of 17 patients with recurrence whose initial tumor had venous invasion was distant (data not shown).

N2 disease is generally accepted as a significant prognostic factor. As shown in the present study, even when various histopathologic factors were examined together, N2 disease was defined as the most important prognostic factor for stage IIIA. The 5-year survival was 23% in N2 disease and 62% in N0,1 disease. Although our 5-year survival in N0,1 disease seems to be better than that in other reports,[17] these observations suggest that T3 N0,1 should be categorized separately from T1 N2 through T3 N2.

In conclusion, we found the grade of differentiation and visceral pleural and venous invasion in stage I, visceral pleural invasion and histologic cell type in stage II, and venous invasion and mediastinal lymph node metastasis in stage IIIA all to be predominant prognostic factors. Therefore the findings obtained from an ordinary pathologic examination may be useful in the determination of an appropriate follow-up schedule or the selection of adjuvant therapy trials.

We express our gratitude to Satoru Inutsuka, MD, of Kyushu University for his help with the statistical analysis, Brian Quinn for his critical review, and Yumiko Oshima and Yuko Ishibashi for their help in the preparation of the manuscript.

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