Original Article

Survival of Non-small Cell Lung Cancer Patients with Postoperative Recurrence at Distant Organs

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Background: Recurrence after complete resection of non-small cell lung cancer (NSCLC) is often observed. However, its influence on the prognosis of patients with recurrence is still unclear.

Patients and methods: Of 468 consecutive patients with NSCLC undergoing complete resection over 10 years, 118 experienced recurrence at distant organs. In such patients, the influence of the following variables on post-recurrent survival was analyzed ; sex, age at recurrence, disease-free interval, cell type, pathological (p-) stage at operation, adjuvant therapy (thoracic radiation and/or chemotherapy), site of recurrence, and treatment against recurrence. To identify independent factors, multivariate analysis was performed for variables which were considered to be influential in univariate analysis.

Results: Mean post-recurrent survival time was 418 days, and survival rate at 2-years was 15.7 %. Multivariate analysis revealed that female, early p-stage, younger age at recurrence, metastasectomy and intra-pulmonary metastasis were the significant favorable factors in patients with distant metastases. Adjuvant therapy and bone metastasis were marginally significant unfavorable factors. Chemotherapy for recurrence tended to prolong survival. Length of disease-free survival and post-recurrent survival exhibited a positive relationship with p-stage. Seven out of 16 patients who underwent metastasectomy survived more than 1000 days after recurrence.

Conclusions: Patients even with recurrence in distant organs can expect a long survival if they are in the early p-stage of primary cancer or a resectable recurrent disease. (Ann Thorac Cardiovasc Surg 2001; 7: 204–9)

Key words: non-small cell lung cancer, post-recurrent survival, metastasectomy, pathological stage, and adjuvant therapy

Introduction

Recurrence of non-small cell lung cancer (NSCLC) is observed in the majority of patients who have undergone complete resection, with distant metastasis occupying more than two thirds of that population. However, prognostic factors as well as guidelines for treatment for recurrent NSCLC have not been well elucidated. Recently, our group reported that post-recurrent survival was significantly better in female patients and those without any adjuvant therapy prior to recurrence than in the counterparts.[1)]

In this study, post-recurrent survival was further analysed for patients with distant metastasis. To focus the effect of the selection of treatment for recurrent disease, a cohort of patients was selected from the decade 1985 to 1994, when cis-platinum (CDDP) had become a standard choice of chemotherapy in both adjuvant set-

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tings and as a treatment for recurrence.

Patients and Methods

Patients

During the period between 1985 and 1994, a consecutive series of 468 patients with non-small cell lung cancer underwent a complete resection with mediastinal lymph node dissection at the Department of Chest Surgery, National Kyushu Cancer Center, and a total of 154 of these patients experienced a recurrence by April, 1999, 118 of whom had a recurrence in distant organs. The histological diagnosis of the tumors was based on the criteria of the World Health Organization,[2] and the TNM stage was determined according to the criteria revised in 1996.[3] Standard operations such as a lobectomy or pneumonectomy with a complete dissection of the hilar and mediastinal lymph nodes were performed on all patients. In an adjuvant setting, combination chemotherapy including CDDP was performed on 35 patients, on 11 of whom thoracic radiation was also performed, with 10 patients receiving thoracic radiation only. A follow-up examination was, in general, done every 2 months for the first 2 years and thereafter every 3 to 4 months. The follow-up included a physical examination, complete blood count, blood chemistry, and chest radiography. Although a few patients routinely received screening examinations by CT or radionuclide bone scanning once or twice per year after their operation, the majority of patients underwent CT or a radionuclide bone scan only when symptoms related to recurrence appeared. The recurrent disease was then confirmed by biopsy if clinically feasible. In patients for which that was not feasible, radiographic evidence (roentogenography, CT, or radionuclide scan) was accepted. Differentiation between secondary primary lung cancer and intra-pulmonary metastasis was, in general, performed according to the guideline proposed by Martini and Melamed.[4] However, imagings obtained by CT or detailed pathological findings were also referred.

Treatments for recurrence

For the recurrent diseases, systemic chemotherapy was performed on 42 patients, with radiotherapy and metastasectomy performed in combination on 16 and 5 patients, respectively. Since the patients were treated over a 10-year span, the regimen of chemotherapy was not uniform. However, all patients underwent CDDP-based combination chemotherapy. Radiotherapy was performed on 59 patients, of whom 8 also underwent surgery. Metastasectomy was performed on 16 patients, 5 of whom had no other treatments. Metastatic organs that were resected included lung in 5 patients, brain in 5, cervical lymph node in 5, and one each in kidney, adrenal gland and subcutaneous tissue.

Statistical analysis

The number of days from the detection of the first recurrent site until death constituted the length of post-recurrent survival. Survival curves were prepared by the Kaplan-Meier method,[5] and comparisons among the survival curves were made using the log rank test.[6] The Cox proportional hazards model[7] was used to identify the following factors; gender, age at recurrence, cell type, pathological stage (p-stage) of the primary tumor, adjuvant therapy, disease-free interval, site of recurrence, and choice of treatment for recurrence that might have a jointly significant influence on post-recurrent survival. The difference in disease-free interval or post-recurrent survival among subgroups was examined by a t-test. The data were considered as significant when the p value did not exceed 0.05.

Results

Overall patients with recurrence at distant organs

Of the consecutive 468 patients who underwent complete resection of primary NSCLC, 118 suffered from recurrence at distant organs during a more than 5-year observation. The mean age at recurrence was 63.6 years, and the mean disease-free interval was 448 days, ranging from 22 to 3013 days. The first recurrent site was detected in the lung in 42 patients, bone in 30, brain in 29, lymph node in 16, liver in 12, adrenal gland in 5, kidney in 3, and subcutaneous tissue in one. In 29 patients, more than 2 organs were involved. The mean post-recurrent survival was 418 days, ranging from 3 to 4235 days, and the post-recurrent 2-year survival rate was 15.7%.

Univariate analysis

By univariate analysis of 13 sorts of factors, subgroups consisting of females, early p-stage at the first operation, adenocarcinoma, longer disease-free interval, surgery for recurrent disease, pulmonary metastasis, and no bone metastasis showed significantly longer post-recurrent survival than each counterpart (Table 1). Patients who underwent adjuvant therapy showed shorter post-recurrent survival than those without adjuvant therapy although there was no statistical significance (p=0.1236).

Table 1. Univariate analysis of factors associated with post-recurrent survival in patients with recurrence at distant organs

Variable		2-year survival (%)	Mean survival time (days)	p value
Gender	Male (N=31)	12.5	250	0.0410
	Female (N=87)	25.7	386	
Age at recurrence	Less than 65 (N=62)	20.3	318	0.1327
	65 or more (N=56)	10.7	248	
Cell type[a]	Adeno (N=74)	21.1	300	0.0280
	Others (N=44)	4.3	254	
p-stage at the 1st resection	I (N=39)	23.8	365	0.0112
	II/III (N=79)	10.4	233	
Adjuvant therapy	Yes (N=45)	12.1	257	0.1236
	N0 (N=87)	16.1	315	
Disease-free interval	less than 1 year (N=68)	20.6	385	0.0193
	more than 1 year (N=50)	11.9	208	
Number of metastasis	One (N=89)	17.2	299	0.302
	Two or more (N=29)	4.8	260	
Pulmonary metastasis	Yes (N=45)	24.7	410	0.0105
	No (N=73)	10.1	228	
Bone metastasis	Yes (N=35)	2.9	170	0.0189
	No (N=83)	21.8	315	
Brain metastasis	Yes (N=30)	27.5	339	0.2556
	No (N=88)	14.1	260	
Operation for recurrence	Yes (N=16)	49.2	467	0.0072
	No (N=102)	14.1	278	
Chemotherapy for recurrence	Yes (N=42)	19.0	350	0.0928
	No (N=76)	18.7	229	
Radiotherapy for recurrence	Yes (N=59)	15.3	252	0.4483
	No (N=59)	16.6	344	

[a] Adeno: adenocarcinomas; Other: 32 squamous cell carcinomas, 9 adenocarcinomas and 3 large cell carcinomas were included

Although age at recurrence and chemotherapy against recurrence were likely to affect post-recurrent survival, no significance was observed in this analysis with p values of 0.1327 and 0.0928, respectively (Table 1).

Multivariate analysis

The 10 factors showing p values less than 0.2 in the univariate analysis were subjected to multivariate analysis. Female sex, early p-stage determined after the first operation, incidence of pulmonary metastasis, and metastasectomy were revealed as significantly favorable factors for post-recurrent survival with hazard ratios of 0.542, 0.516, 0.531, 0.416, respectively (Table 2). Age at recurrence also affected post-recurrent survival significantly (p=0.0052), although the hazard ratio of elderly patients was relatively low (1.036). The selection of adjuvant therapy worsened post-recurrent survival with a marginal p value of 0.0545 (hazard ratio of 1.611). Chemotherapy for distant metastasis showed a marginal benefit for post-recurrent survival with a hazard ratio of 0.638 (p=0.0603). Although disease-free interval was likely to be a strong prognostic factor in univariate analysis (p=0.0193), there was no significance in multivariate analysis (p=0.9803), suggesting the existence of a positive relationship with other influential variables (Table 2).

Relationship of p-stage to post-recurrent survival

Actuarial recurrence rates in distant organs of each p-stage were 17.0% (39/229) in I, 32.2% (19/59) in II, 35.8% (54/151) in IIIa, and 20.7% (6/29) in IIIb. As summarized in Table 3, post-recurrent survival was appar-

Table 2. Multivariate analysis of factors associated with post-recurrent survival in patients with recurrence at distant organs

Variable	Hazard ratio	95% confidence interval	p value
Gender Female / Male	0.542	0.334-0.881	0.0134
Age at recurrence 65 or more / Less than 65	1.036	1.011-1.062	0.0052
Cell type[a] Adeno / Others	0.738	0.606-1.425	0.9300
p-stage at the 1st resection I / II-III	0.516	0.321-0.831	0.0063
Adjuvant therapy Yes / No	1.611	0.991-2.618	0.0545
Disease-free interval less than 1 year /more than 1 year	0.995	0.647-1.529	0.9803
Pulmonary metastasis Yes / No	0.531	0.322-0.878	0.0136
Bone metastasis Yes / No	1.674	0.998-2.808	0.0510
Operation for recurrence Yes / No	0.416	0.211-0.819	0.0111
Chemotherapy for recurrence Yes / No	0.638	0.400-1.020	0.0603

[a] Adeno: adenocarcinomas; Other: 32 squamous cell carcinomas, 9 adenocarcinomas and 3 large cell carcinomas were included

Table 3. Comparison of disease-free interval and post-recurrent survival in patients with recurrence at distant organs among various p-stages

	I (N=39)	II (N=19)	IIIA (N=54)	IIIB (N=6)	Total (N=118)
Disease-free interval (days)	752 ± 763[a]	500 ± 483	315 ± 320	101 ± 77	448 ± 562
		p = 0.0003			
			p = 0.0457		
Post-recurrent survival (days)	590 ± 698	381 ± 272	257 ± 333	180 ± 208	418 ± 488
		p = 0.0215			

[a] Mean ± standard deviation.

ently shorter in advanced stages ; mean post-recurrent survival time was 590 days in stage I, 381 in II, 257 in IIIa, and 180 in IIIb, and a significant difference was observed between p-stage I and IIIa (p=0.0215). Advanced stages also exhibited a shorter disease-free interval; 752 days in stage I, 500 in II, 315 in IIIa and 101 in IV, and there was a significant difference between p-stage I and IIIa (p=0.0003), and I and IIIb (p=0.0457). From these results, it was postulated that p-stage determined at the first operation had a positive relationship with the prognosis of patients with a relapse in distant organs.

Profile of patients who underwent metastasectomy

Resection of metastases was performed on 6 patients for

Table 4. Profile of patients who underwent resection of recurrent disease

Age / sex[a]	Cell type[b] / p-stage	Recurrent sites[c]	Treatments[d]	Post-recurrent survival (days)
51 / M	Ad/IIIa	Brain	Resection, R	1465 alive
54 / M	Ad/I	Lung	Lobectomy	1440 alive
48 / F	Ad/I	Brain	Resection, R	1256 alive
67 / F	Ad/IIIa	Mediastinal LN	Resection, IOR, C	1183 alive
		Cervical LN	Resection	
76 / M	Ad/II	Lung	Wedge resection, C	1103 dead
63 / M	Ad/I	Lung	Wedge resection	1090 dead
		Brain	R	
63 / M	Ad/I	Adrenal gland	Adrenalectomy, IOR, C	1065 dead
48 / F	Ad/I	Brain	Resection	676 dead
63 / M	Sq/II	Brain	Resection, R	459 dead
62 / M	Sq/IIIb	Kidney	Nephrectomy, R	452 dead
63 / M	Ad/IIIa	Cervical LN	Resection, C	196 dead
67 / M	Ad/IIIa	Cervical LN	Resection, R	181 dead
66 / M	Ad/I	Brain	Resection, R	169 dead
74 / M	Ad/I	Lung	Completion pn	104 dead
62 / M	Ad/IIIa	Inguinal LN	Resection	103 dead
45 / M	La/IIIb	Brain	Resection	45 dead

[a]M: male; F: female, [b]Ad: adenocarcinoma; Sq: squamous cell carcinoma; and La: large cell carcinoma, [c]LN: lymph node, [d]C: chemotherapy; R: radiotherapy; Pn: pneumonectomy; and IOR: intraoperative radiation.

brain, 4 for lymph node, 4 for lung, one each for kidney and adrenal gland, 4 of whom had adnocarcinomas. Ten patients received multi-modality treatments, 2 of whom had intra-operative radiation. Mean survival time and 2-year survival rate of patients who underwent metastasectomy were 467 days and 49.2 %, respectively. Seven patients survived more than 1000 days, 4 of whom are still alive (Table 4).

Discussion

In 1994, Ichinose et al reported that post-recurrent survival of NSCLC patients who underwent complete resection in our department was significantly affected by gender and a history of adjuvant therapy.[1)] In this study, a further examination was made with special references to organs involved in recurrence, therapy for recurrence as well as adjuvant therapy. Therefore, patients with distant metastases were selected from 1985 to 1994 when CDDP had become a key drug in chemotherapy for NSCLC.[8)] In such a cohort, female sex, younger age at recurrence, p-stage at the first operation, selection of metastasectomy and pulmonary metastasis were statistically significant favorable factors for post-recurrent survival.Chemotherapy for recurrence was likely to be beneficial for survival although there was no statistical significance (p=0.0603). A history of adjuvant therapy and bone metastasis were marginally adverse prognostic factors with p values of 0.0545 and 0.0510, respectively. A disease-free interval was not revealed as an independent factor by multivariate analysis, although there was a significant difference among patients with disease-free intervals of less than 1 year and those with more than 1 year in univariate analysis (p=0.0193). The reason for this was that there is a positive relationship among p-stage, disease-free interval, and post-recurrent survival as shown in Table 3.

Post-operative recurrence is considered to be appearance of latently existing cancer cells, so-called micrometastasis. Therefore the positive relationship between advanced p-stage and a high recurrence rate/a short disease-free interval is well understood. Our major question was whether p-stages determined at the first operation were an influential factor for post-recurrent survival. If post-recurrent survival was similar among patients in various p-stages, each p-stage might express a degree of disease in a cross section of a time course for progression. However, one of the strongest prognostic factors for post-recurrent survival was p-stage. Since the time point of recurrence may be considered to be a “reset” point even in patients in various p-stages, such a difference of post-recurrent survival among patients at vari-

ous p-stages may express a difference in the malignant potential of lung cancers. Therefore, a rapidly progressive NSCLC would tend to be recognized as an advanced stage at an initial examination.

The efficacy of local therapy against metastasis may also be attributed to the biological nature of cancer cells as mentioned above. In other words, operable condition of metastasis itself means favorable prognosis of such patients with systemic disease. However, it is difficult to determine the indication of metastasectomy. In our series, 3 patients who underwent resection of pulmonary metastases survived more than 1000 days. In such patients, it is sometimes difficult to discriminate the second primary cancer. They had in fact been pathologically diagnosed as stage I/II adnocarcinoma (Table 4), in which metachronous lung adenocarcinoma is frequently found during post-operative follow-up.[9] However, in a critical review of imagings of pulmonary tumors in the three patients, the lesions were determined as a recurrence because they were multiple and located in the subpleural area in all three cases. Pulmonary metastasis of lung cancer is also postulated as spreading locally through vasculature or lymphatic tissue.[10] Therefore, resection of a pulmonary metastasis should be considered if possible. As to brain metastasis, γ-knife radiosurgery has recently been indicated instead of surgical removal,[11] however, it is yet to be clarified whether or not asymptomatic brain metastasis should be treated or not. The significance of intra-operative radiation therapy against recurrence performed in combination with a surgical resection of adrenal gland metastasis and mediastinal node metastasis needs to be further studied. In the present study, a history of adjuvant therapy was a marginally significant prognostic factor as reported by Ichinose et al.[1] The reason for this result was unclear. It could be hypothesized that the appearance of chemo- and/or radioresistant cancer cells persist and that they are enriched through adjuvant therapy. This hypothesis would be proved if the effect of anti-recurrence chemotherapy was different between patients who had received it and those who had not. However, in our study, there was no difference between them (data not shown), probably because the CDDP-including multi-drug chemotherapy itself was not adequately active against recurrent NSCLC.

In conclusions, we postulated that p-Stage at first operation affects post-recurrent survival, metastasectomy should be considered as an arm of multi-modality if feasible, and that adjuvant therapy possibly worsens post-recurrent survival.

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