

Resection of Pulmonary Metastasis of Non-small Cell Lung Cancer

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Introduction: Management of pulmonary metastasis of non-small cell lung cancer (NSCLC) remains controversial. We reviewed our surgical treatment for pulmonary metastasis of NSCLC.

Methods: Seventy-six patients with pulmonary metastasis of NSCLC underwent pulmonary resections in two institutes during the past 10 years. Eighteen patients with simultaneous same lobe metastasis as the primary lesion underwent mostly lobectomies. Sixteen patients with simultaneous different lobe metastasis underwent combined margin-free resections. Forty-nine pulmonary metastasectomies were performed in 42 patients with recurrent lung cancer. Overall survival and disease-free survival in each group were examined, and factors affecting survivals were investigated.

Results: In the patients with the same lobe metastasis 5-year survival was 79.6%, and median and 5-year disease-free survivals were 39.1 months and 41.3%. In the patients with simultaneous different lobe metastasis median survival and 5-year survival were 37.7 months and 30.7%, and median and 5-year disease-free survivals were 13.3 months and 12.5%, respectively. Multiple pulmonary metastasis and mediastinal node metastasis were identified as significant factors affecting survivals. In the patients with recurrent pulmonary metastasis median survival and 5-year survival were 40.0 months and 34.8%, and median and 5-year disease-free survivals were 23.7 months and 14.4%, respectively. Node metastasis, higher age, and shorter interval from the prior resection were identified as significant factors affecting survivals.

Conclusions: These findings suggest that the simultaneous same lobe metastasis is under the same indication for the primary lesion, and that the simultaneous different lobe metastasis and recurrent pulmonary metastasis should be removed in selected patients.

Key Words: Non-small cell lung cancer, Surgery, Pulmonary metastasis, Recurrence, Metastasectomy.

(*J Thorac Oncol.* 2009;4: 203–207)

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/09/0402-0203

Standard treatment for pulmonary metastasis of non-small cell lung cancer (NSCLC) is not well defined. Simultaneous intralobar metastasis can be removed with an anatomic resection when the primary lesion is indicated for surgical treatment, resulting in a favorable outcome in the literature.^{1,2} Simultaneous different lobe metastasis of the lung cancer is not indicated for resection in the current clinical guideline.³ Furthermore, surgical treatment for recurrent pulmonary metastasis has been controversial.⁴ To reveal the outcome of surgical treatment for pulmonary metastasis of NSCLC, we reviewed our 10 years experience of pulmonary metastasectomy of NSCLC.

PATIENTS AND METHODS

From 1997 to March 2007, 76 patients with pulmonary metastasis of NSCLC underwent 83 pulmonary resections for curative intent in two institutes, Kyoto University Hospital and Gifu National Hospital, Japan. The indication for presumable pulmonary metastasectomy was a solitary or limited number of pulmonary lesions, completely resectable, without other organ metastasis, and tolerable for the surgery. During the same period 1638 thoracotomies for primary lung cancer were performed in the two institutes, indicating that the resections of pulmonary metastasis were 5.1% of the surgeries for lung cancer. Fifty-eight patients were men and 25 were women with the mean age of 65.9 years (ranging 40–83 years). Thirty-four patients had simultaneous pulmonary metastases at the time of primary resection for lung cancer: 18 were in the same lobe as the primary lesion and 16 were in the different lobe. Forty-nine patients had recurrent pulmonary metastases after the previous pulmonary resection for lung cancer. We also performed 28 pulmonary resections for synchronous multiple lung cancers and 35 pulmonary resections for metachronous primary lung cancers during the period. Diagnosis of pulmonary metastasis was based on the pathologic findings; standard hematoxylin-eosin staining was examined in all specimens and additional immunohistochemical staining of p53 was mostly examined in the later period of the study. Based on the similarity of morphology and immunohistochemical staining, diagnosis of the pulmonary metastasis was done by our pathologists. When the definitive diagnosis was not obtained with the pathologic findings, the criteria for diagnosis of multiple primary lung carcinoma by Martini and Melamed⁵ was applied to differentiate metastasis

from multiple primary lung cancer. When multiple pulmonary nodules were identified pathologically similar, the largest nodule was defined as the primary lesion and the other(s) were defined as metastatic lesion(s). According to the lung cancer staging system,⁶ the simultaneous same lobe metastasis, different lobe metastasis, and metachronous pulmonary metastasis were classified to T4-stage IIIB, M1-stage IV, and recurrent lung cancer, respectively; therefore, we examined these patients for survival analysis separately.

All eighteen patients with the simultaneous same lobe metastasis were diagnosed after the pulmonary resection. Histology was adenocarcinoma in 10, squamous cell carcinoma in seven, and large cell carcinoma in one. Clinical staging without additional nodes was stage 1A (T1N0) in five, 1B (T2N0) in eight, 2B (T2N1) in two, and 3A (T1–2N2) in three. Surgical procedures were 16 lobectomies including one sleeve lobectomy and two segmentectomies. All tumors were completely removed. Pathologic node staging was N0 in 12, N1 in two, and N2 in four. Sixteen patients had solitary pulmonary metastasis and two patients had two metastatic nodules in the same lobe. Eight patients received postoperative intravenous platinum-based chemotherapy and six patients received postoperative uracil-tegafur (UFT) administration, whereas seven patients did not receive any adjuvant therapy.

Sixteen patients with the simultaneous different lobe metastasis underwent combined pulmonary resections. Four patients were clinically diagnosed as pulmonary metastasis preoperatively, whereas the other patients were diagnosed after the pulmonary resections. Histology was adenocarcinoma in 12, squamous cell carcinoma in three, and large cell neuroendocrine carcinoma in one. Clinical staging without additional nodules was T1N0 in seven, T2N0 in three, T2N1 in one, T1N2 in two, and T2N2 in three. Surgical procedures were 11 lobectomies with wedge resections/segmentectomies, two segmentectomies with wedge resections, one bilobectomy, and two pneumonectomies. All tumors were completely removed. Ten patients had ipsilateral lung metastasis and six patients had contralateral lung metastasis. Thirteen patients had solitary metastasis, and three patients had two metastatic nodules, one of which was the same lobe metastasis in each patient. Pathologic T-factor was T1 in seven, T2 in six, and T4 (pm 1) in three. Pathologic N-factor was N0 in nine, N2 in five, and N3 in two. Four patients received preoperative intravenous platinum-based chemotherapy. Nine patients received postoperative intravenous chemotherapy and four patients received UFT, whereas six patients did not receive any postoperative chemotherapy.

Forty-nine pulmonary resections for recurrent pulmonary metastasis were performed in 42 patients. Seven patients underwent a repeated pulmonary metastasectomy for recurrence again. Histology of the recurrent lung cancer was adenocarcinoma in 30 and squamous cell carcinoma in 19. Thirty-nine resections were for solitary pulmonary lesion and 10 resections were for multiple (2 ~ 4) pulmonary lesions. Staging of the lung cancer at the time of initial resection was stage I in 25, stage II in seven, stage III in eight, and stage IV in two. The interval from the prior pulmonary resection was

9.1 to 112 months (median 28.0 months). Surgical procedures were essentially margin-free resections; 31 wedge resections, 10 segmentectomies with or without wedge resections, four lobectomies including one sleeve lobectomy, and four completion pneumonectomies. Complete resection was obtained in all patients except one who underwent a pneumonectomy with cancer-positive bronchial stump. Lymph node metastasis along with pulmonary metastasis was identified in four patients. Three patients received preoperative intravenous chemotherapy. Fifteen patients received postoperative intravenous chemotherapy and 14 patients received UFT, whereas 25 patients did not receive any postoperative therapy.

The survival and the date of tumor recurrence after the pulmonary resection were examined in each patient. In the patients with simultaneous pulmonary metastasis, overall survival was defined as the duration from the pulmonary resection to the last follow-up or the death with any reason, and disease-free survival was defined as the duration from pulmonary resection to the date of recurrence or the death with any reason. In the patients with recurrent lung cancer, overall survival was defined as the duration from the first metastasectomy to the last follow-up or the death with any reason, and disease-free survival was defined as the duration from the each pulmonary resection to the date of recurrence or the death with any reason. Continuous data are presented as means, and categorical data are presented as exact numbers. Survival estimates were derived by Kaplan-Meier analysis. Factors including age, sex, histology, T and N factors, number of pulmonary metastasis, operative procedure, and adjuvant chemotherapy were analyzed. Stratified log-rank analysis and Cox proportional-hazard modeling were used to investigate and adjust for major prognostic and stratification factors. A two-sided probability value of less than 0.05 was considered statistically significant. The study was performed in accordance with the Declaration of Helsinki. Kyoto University institutional review board approved this study and waived the requirement for individual patient consent for this retrospective study.

RESULTS

Overall Survival and Disease-Free Survival

Median follow-up of all patients was 29.6 months after the resection of pulmonary metastasis. Forty-one patients (53.9%) were completely followed until their death or more than 5 years after the resection.

Overall survival curve and disease-free survival curve of patients with the same lobe metastases are shown in Figure 1. The 5-year survival rate was 79.6%. Median disease-free survival was 39.1 months and the 5-year disease-free survival rate was 41.3%. Overall survival curve and disease-free survival curve of patients with the different lobe metastasis are shown in Figure 2. Median survival was 37.7 months and the 5-year survival rate was 30.7%. Median disease-free survival was 13.3 months and the 5-year disease-free survival rate was 12.5%. Overall survival curve and disease-free survival curve of 42 patients with recurrent pulmonary metastasis are shown in Figure 3. Median survival was 40.0 months and the 5-year survival rate was 34.8%. Median

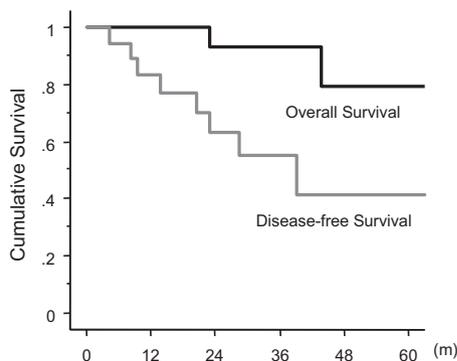


FIGURE 1. Kaplan-Meier survival curves of patients with simultaneous same lobe metastasis. Solid and dashed lines represent the overall survival and the disease-free survival (overall 5-year survival: 79.6%, median and 5-year disease-free survivals: 39.1 months and 41.3%, respectively).

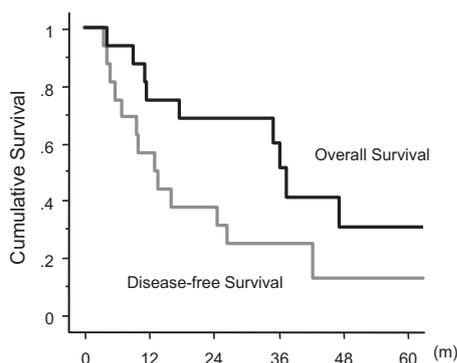


FIGURE 2. Kaplan-Meier survival curves of patients with simultaneous different lobe metastasis. Solid and dashed lines represent the overall survival and disease-free survival (median and 5-year overall survivals: 37.7 months and 30.7%, median and 5-year disease free survivals: 13.3 months and 12.5%, respectively).

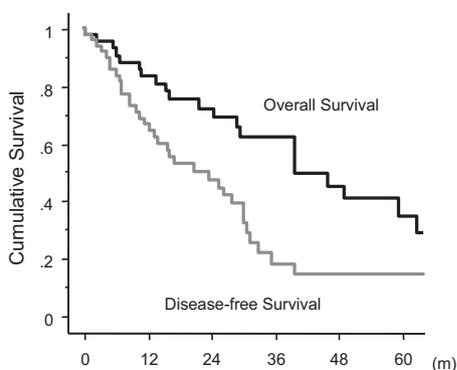


FIGURE 3. Kaplan-Meier survival curves of patients with recurrent pulmonary metastasis. Solid and dashed lines represent the overall survival and disease-free survival (median and 5-year overall survivals: 40.0 months and 34.8%, median and 5-year disease free survivals: 23.7 months and 14.4%, respectively).

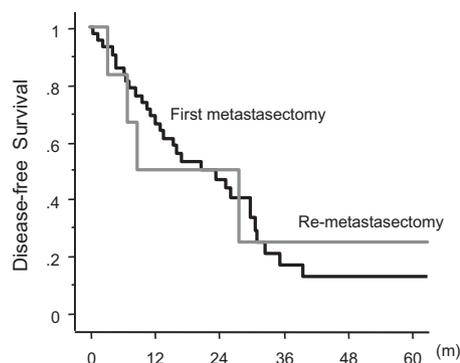


FIGURE 4. Kaplan-Meier disease-free survival curves of patients with recurrent pulmonary metastasis. Solid and dashed lines represent the first metastasectomy and re-metastasectomy. No significant difference was seen between the disease-free survivals.

disease-free survival was 23.7 months and the 5-year disease-free survival rate was 14.4%. Between the first metastasectomy ($n = 42$) and re-metastasectomy ($n = 7$), no significant difference was seen in the disease-free survivals (Figure 4).

Prognostic Factors Affecting Survivals

In the patients with the simultaneous same lobe metastasis, statistical analyses identified no significant factors affecting overall survival or disease-free survival. In the patients with the simultaneous different lobe metastasis, the proportional hazards model showed multiple pulmonary metastases as a significant factor in overall survival, and mediastinal node metastasis as a significant factor in disease-free survival (Table 1). In the patients with recurrent pulmonary metastasis, the age of 70 years or more and node metastasis were identified as significant factors affecting overall survival, and the shorter interval from the prior resection was identified as a factor affecting disease-free survival (Table 2).

DISCUSSION

Pulmonary metastasis of NSCLC is differently staged with regard to the time, simultaneous or metachronous, and the location associated with the primary lesion. In the current tumor, node, metastasis staging system revised in 1997⁶ simultaneous same lobe metastasis as the primary lesion (pm 1) is classified as T4—stage IIIB when distant metastasis is excluded. Simultaneous different lobe metastasis from the primary lesion (pm2) is classified as M1-stage IV disease. Metachronous pulmonary metastasis after the resection of primary lung cancer is a recurrent disease and the treatment for the recurrence depends on the number and the site. Surgical treatment for simultaneous pulmonary metastasis of NSCLC occasionally resulted in a favorable prognosis in the literature^{1,2}; however, the efficacy of the pulmonary resection for recurrent disease remains controversial.

Surgical procedure for pulmonary metastasis is the margin-free resection. The satellite lesion in the same lobe is removed with a lobectomy or a larger anatomic resection indicated for the primary lesion. For simultaneous different

TABLE 1. Multivariate Analysis of Patients with Simultaneous Different Lobe Metastasis

Variable	Overall Survival			Disease-Free Survival		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Male/female	1.202	0.119–12.179	0.877	2.064	0.235–18.014	0.513
Age ≥70/<70	13.821	0.484–394.597	0.125	3.424	0.549–21.375	0.188
Adenocarcinoma/others	0.367	0.006–23.489	0.637	0.243	0.019–3.112	0.277
Contralateral/ipsilateral	0.165	0.005–5.214	0.307	0.173	0.015–1.967	0.157
Pneumonectomy/lobectomy/ lesser resection	1.257	0.090–17.539	0.865	3.774	0.236–60.401	0.348
No. of metastasis	14.023	1.195–164.565	0.036	4.685	0.571–38.458	0.151
Mediastinal node metastasis	3.496	0.943–12.967	0.061	2.885	1.231–6.763	0.015
Adjuvant therapy	2.856	0.156–52.417	0.480	1.068	0.133–8.579	0.951

CI, confidence interval; HR, hazard ratio.

TABLE 2. Multivariate Analysis of Patients with Recurrent Pulmonary Metastasis

Variable	Overall Survival			Disease-Free Survival		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Male/female	0.860	0.130–5.689	0.876	1.425	0.441–4.610	0.554
Age ≥70/<70	6.642	1.599–27.579	0.009	1.880	0.730–4.845	0.191
Ad/Sq	0.924	0.236–3.627	0.910	1.582	0.623–4.019	0.335
No. of metastasis	4.807	0.882–26.198	0.070	1.909	0.727–5.011	0.189
Node metastasis Procedure	16.097	2.355–110.031	0.005	3.568	0.853–14.930	0.082
Pneumonectomy/ lesser resection	3.743	0.453–30.919	0.221	0.488	0.104–2.300	0.364
Adjuvant therapy	0.737	0.406–1.341	0.318	1.136	0.741–1.742	0.558
Interval from prior resection	0.967	0.930–1.005	0.091	0.963	0.930–0.998	0.041
Redo/first metastasectomy	—	—	—	0.384	0.091–1.615	0.191

CI, confidence interval; HR, hazard ratio.

lobe metastasis or recurrent pulmonary metastasis, wedge resection is usually applied. When the tumor is located centrally close to a bronchus or pulmonary vessel or free margin is difficult to obtain with wedge resection, an anatomic resection such as segmentectomy or lobectomy is required. When the tumor is large enough to occupy one lung or invades a main bronchus, a pneumonectomy is applied for few patients.

In this retrospective study, we sought to clarify the role of pulmonary metastasectomy. Although the indications of pulmonary resections, such as the number of nodules, node status, and the site of lesion, were not identical throughout the study, we examined these factors in survivals with the proportional hazards model. We examined not only the survival after the pulmonary resection but also the disease-free survival, which most previous reports of pulmonary metastasectomy did not examine, to investigate the exact role of surgery. Recent advances in chemotherapy for unresectable lung cancer should have improved prognosis even after recurrence.

Our result of pulmonary resection for the same lobe metastasis as the primary lesion showed as high as 79.6% of 5-year survival rate although the disease-free survival was lower. This attests the previous reports of favorable prognosis after the pulmonary resection for simultaneous intralobar metastasis of lung cancer. Bryant et al.⁷ reported a 5-year

survival of 57% in 26 patients with lung cancer of T4 (satellite) N0, 87% of whom underwent complete resection and 73% of whom received adjuvant therapy. Osaki et al.⁸ reported a 5-year survival of 26.7% in 36 patients with T4-satellite, 55.6% of whom had nodal metastasis, 91.7% of whom underwent complete resection, and 41.7% of whom received adjuvant therapy. Nakagawa et al.⁹ demonstrated that the 5-year survival in 31 patients with T4-satellite and some node metastasis was 39% after pulmonary resection. The discrepancy of the survival rates in the reports including current study may be explained by the differences in the rates of complete resection, the nodal staging, and the adjuvant therapy. Recently, the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project reported pT4N0-additional nodule(s) in the same lobe (*n* = 363) had a 5-year survival rate of 28% and proposed to classify this stage as T3.¹⁰ Patients with intralobar pulmonary metastasis would have the same indication as that for the primary lesion.

Resection for the simultaneous different lobe metastasis is controversial in the literature.^{11–13} Nakagawa et al.⁹ reported a 5-year survival of 19.3% in 17 patients with ipsilateral different lobe metastasis after pulmonary resection. Okada et al.¹⁴ reported a 5-year survival of 23.4% in 41 patients with ipsilateral different lobe metastasis, and that N0

and N1 diseases were significantly better than N2 and N3 diseases. Okumura et al.¹⁵ showed a 5-year survival of 11% in 18 patients with different lobe metastasis and no significant differences among T or N factors. These studies were conducted retrospectively and in relatively small number of patients, which may explain the differences in the results. The IASLC Lung Cancer Staging Project reported 5-year survival of the patients with ipsilateral pulmonary nodules in nonprimary lobe ($n = 180$) was 22% and proposed to classify as T4.¹⁰ On the contrary, the IASLC Lung Cancer Project reported additional nodules in the contralateral lung showed a 5-year survival rate of 3%.¹⁶ In the latter analysis, surgery was precluded, and it was not possible to differentiate between single and multiple lesions. Current study has the strength of showing disease-free survival as well. Our result of the pulmonary resection for simultaneous different lobe metastasis showed the 5-year survival of 30.7% and median survival of 37.7 months, however, median disease-free survival was 13.3 months. The difference between the median survival and the median disease-free survival of 24.4 months, about two thirds of the overall survival, might have been provided by postrecurrent chemotherapy. In fact most of our patients with postoperative recurrence received chemotherapy as long as they were tolerable for it. Multiple pulmonary metastases and mediastinal node involvement were identified as poor prognostic factors in survivals. The efficacy of surgical therapy for patients with different lobe metastasis is limited when the pulmonary metastasis is solitary or preoperatively unproven.

Objective evidence supporting the role of surgery for recurrent lung cancer is limited. Walsh et al.¹⁷ demonstrated that complete resection or high-dose radiotherapy with curative intent significantly prolonged postrecurrent survival in NSCLC. Sugimura et al.⁴ reported that surgical treatment for 23 patients with recurrent lung cancer confined in only lung resulted in median survival of 32.8 months. Uncertainty exists in differentiating a second primary lung cancer from recurrent lung cancer. Surgical resection is frequently preferred for a solitary metachronous lung cancer, with a 5-year survival of 26 to 33.4%.^{18–20} Our study showed median survival and median disease-free survival of 40.0 months and 23.7 months, respectively, and the 5-year survival rate of 34.8%, which are comparable with these results. In the analysis of prognostic factors higher age and concomitant node metastasis significantly affected the overall survival and the shorter interval from the prior pulmonary resection affected the disease-free survival. Median duration from the previous pulmonary resection was 28 months; in addition, the patients with the duration of less than 2 years showed significantly shorter disease-free survival than those of more than 2 years ($p = 0.039$). These results indicate that rapid recurrence can be predicted with the clinical course before the resection. Pulmonary metastasectomy for recurrent lung cancer can be beneficial for younger patients with limited number of pulmonary nodules, when the interval from the previous pulmo-

nary resection is 2 years or longer. Repeated pulmonary metastasectomy can be considered under the same indication.

In conclusion, simultaneous same lobe metastasis of NSCLC can be removed with an anatomic resection, resulting in favorable prognosis; however, the efficacy of the resection for simultaneous different lobe metastasis is limited. Pulmonary metastasectomy can be a therapeutic option in selective patients with recurrent lung cancer.

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