ORIGINAL ARTICLE

Prognostic factors in patients with postoperative brain recurrence from completely resected non-small cell lung cancer

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Abstract

Background: Treatment strategies for brain metastasis from lung cancer have been making progress. The aim of this retrospective analysis was to investigate the post-recurrent prognostic factors in patients with brain metastasis after complete resection of non-small cell lung cancer (NSCLC).

Methods: We retrospectively reviewed the medical records of 40 patients found to have postoperative brain metastasis from NSCLC in our institution from 2002 to 2008. All patients had undergone radical pulmonary resection for the lung cancer. The impact of numerous variables on survival were assessed, including gender, age, carcinoembryonic antigen (CEA), tumor size, N status, histological type, number of brain metastases, tumor size of brain metastasis, presence of symptoms from the brain tumor(s), and use of perioperative chemotherapy.

Results: The median follow-up was 20.6 months (range, 3.4–66 months). The five-year survival rate from the diagnosis of brain recurrence was 22.5%. In univariate analysis, the favorable prognostic factors after brain recurrence included a normal range of CEA, no extracranial metastasis, no symptoms from the brain metastasis, brain metastasis (less than 2 cm), and radical treatment (craniotomy or stereotactic radiosurgery [SRS]). The multivariate Cox model identified that a small brain metastasis and radical treatment were independent favorable prognostic factors.

Conclusions: This study found that the implementation of radical therapy for metastatic brain tumor(s) when the tumor is still small contributed to an increase in patients' life expectancy.

Introduction

The central nervous system (CNS) is a frequent site of metastasis of non-small cell lung cancer (NSCLC). Brain metastases occur in 30 to 50% of patients with NSCLC, and confer a worse prognosis and quality of life.[1–3] About 50% of stage 3A and 3B NSCLC patients will develop brain metastasis during treatment for lung cancer.[4] Some investigators have reported long-term survival after the resection of a solitary recurrence as brain metastasis.[5–7] The treatment modalities used for metastatic brain tumors, such as stereotactic radiosurgery (SRS), have been improved in recent years.[8] Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), such as erlotinib or gefitinib, have been reported to be an effective treatment for NSCLC patients with brain metastasis and activating mutations in the EGFR gene.[9] Therefore, the role and indications for radical therapy for metastatic brain lesions have remained under discussion.

In this study, to elucidate the prognostic factors for long-term survival of brain metastasis from lung cancer, we reviewed the clinical records of cases treated at our institution.

Patients and methods

This was a retrospective single-center study. It included patients with postoperative brain metastasis as the initial relapse site from surgically resected lung cancer. We reviewed medical records and follow-up data from the Osaka Medical Center for Cancer and Cardiovascular Diseases. Between January 2002 and December 2008, 1091 patients underwent R0-resection and received complete follow-up. Of these

patients, 40 cases (3.6%) with postoperative brain metastasis as initial relapse site were included in this study. The pathological stages of all patients were determined according to the 7th edition of the International Staging System.[10] Standard operations, such as lobectomy or pneumonectomy with complete dissection of the hilar and mediastinal lymph nodes, were performed on all patients.

Follow-up data were obtained by outpatient visits and correspondence with the patients' primary physicians. Our follow-up procedures included physical examinations, chest roentgenography and blood tests, including tests for tumor markers, such as carcinoembryonic antigen (CEA). Chest computed tomography (CT) or 18-fluorodeoxyglucose (FDG) positron emission tomographic (PET) scans were generally performed every six months. In addition, brain CT or magnetic resonance imaging (MRI) was performed annually to detect any brain recurrence. Other metastatic workup also included a bone scan at time of diagnosis to evaluate the patients for bone metastasis.

Postoperative brain recurrence was diagnosed mainly by radiological examination. The histological diagnosis of brain metastasis from NSCLC was confirmed only when we performed craniotomy. In our institution, cranial nerve surgeons determined the operability criteria for brain metastasis. Our inclusion criteria for craniotomy were basically that the tumor location was surgically accessible and we could assure negative surgical margins. After 2004, our indications for SRS were that the tumor size was less than 3 cm, and the number of brain metastases was one to three. In this study, SRS and craniotomy are defined as radical treatments for brain metastasis. Whole brain radiation therapy (WBRT) was performed, not only to prevent recurrence after radical treatments, such as craniotomy or SRS, but also for palliative treatment when the patient could not receive radical treatment for the brain metastasis.

For the analysis of overall survival (OS), each patient's survival time was measured from the date of diagnosis of postoperative brain metastasis until the date of death or the most-recent date of follow-up for surviving patients. We evaluated the following factors: the clinicopathological findings at the time of treatment for the primary lung cancer (type of operation, p-stage, histology, use of adjuvant chemotherapy); and the clinical characteristics at the time of treatment for brain metastasis (gender, age, CEA at the time of brain recurrence, interval to brain metastasis after pulmonary resection, number of brain metastases, tumor size, use of radical therapy, presence of symptoms from the brain tumor, use of an EGFR-TKI, chemotherapy after the treatment for brain metastasis). In this study, we defined the size of the brain metastasis as the size of the biggest brain tumor in the patient if that patient had multiple metastatic brain tumors. On the other hand, if that patient had a single brain metastasis, the size of that tumor was considered to be the size of that metastatic tumor.

Table 1 The clinical and pathological characteristics of the 40 patients with postoperative brain metastasis from non-small cell lung cancer

Gender (male/female)	25/15
Age (years)	65.0 ± 8.9 (49–79)
Primary lesion	
Operation (Lobe/Bil-lobe or Pneumo)	33/7
Pathological stage (1a/1b/2a/2b/3a)	7/6/10/9/8
Histologic classification (Ad/Others)	24/16
Adjuvant chemotherapy (Yes/No)	20/20
Brain lesion	
Interval to brain metastasis after surgery (months)	10.2 ± 8.4 (2.1–32.3)
Number of brain meta (Single/Multiple)	26/14
Tumor size of brain metastasis (mm)	21.5 ± 15.5 (5–70)
Radiotherapy† (Yes/No)	14/26
Radical treatment‡ (Yes/No)	29/11
Symptom before Tx (Yes/No)	26/14
CEA level at the time of recurrence (ng/ml)	1.4–78.6
Extracranial metastasis (Yes/No)	17/23
Chemotherapy after treatment for brain (Yes/No)	12/28
EGFR-TKI (Yes/No)	7/33

†SRS and/or WBRT. ‡2 SRS and/or Craniotomy. Ad, adenocarcinoma; CEA, carcinoembryonic antigen; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors.

Univariate survival analyses were performed using the Kaplan-Meier method, and the differences among the groups were analyzed by the log-rank test. For multivariate analysis, a Cox's proportional hazards regression model was used to evaluate the variables that were significant predictors of survival after the diagnosis of brain recurrence. Univariate and multivariate analyses (SPSS V11.5, Chicago, Illinois) were used to identify the prognostic factors in our population. The Chi-square test was used to compare discrete data. A value of $P < 0.05$ was considered to be statistically significant.

Results

A summary of the 40 patients is shown in Table 1. The study population consisted of 25 men and 15 women. The median age at the time of diagnosis of the brain recurrence was 65 years. At the initial operation, 33 patients underwent lobectomy and seven patients received bilobectomy or pneumonectomy for the primary tumor. Of these patients, seven were classified to have pathological stage 1A, six were in stage 1B, 10 were 2A, nine were 2B, and eight patients were in stage 3A. The histopathological subtype was adenocarcinoma in 24 cases and others in 16 cases. Twenty of these patients received adjuvant chemotherapy after pulmonary resection.

The interval to brain metastasis after surgery ranged from four to 32 months (median: 10 months). Twenty-six patients had solitary brain metastasis and 14 patients had multiple metastatic lesions. The CEA status at the time of recurrence

Table 2 Results of univariate analysis of the prognostic factors for overall survival from the date of postoperative brain recurrence

	Cases	P-value	Median Survival (months)
Number of brain metastasis			
Single/Multiple	26/14	0.91	20.4/17.1
EGFR-TKI			
Yes/No	6/34	0.90	26.1/18.7
Interval to brain metastasis from surgery			
>1 year/<1 year	18/22	0.39	21.1/17.4
Adjuvant chemotherapy			
Yes/No	20/20	0.08	26.2/14.2
CEA level at the time of rec			
<5 ng/mL/>5 ng/mL	20/20	0.03	36.3/13.3
Extracranial metastasis			
Yes/No	17/23	0.03	16.6/26.2
Tumor size of brain metastasis			
<2 cm/>2 cm	20/20	<0.01	43.6/13.3
Radical treatment (Craniotomy or SRS)			
Yes/No	29/11	<0.01	27.0/10.8
Symptom from brain metastasis			
Yes/No	26/14	<0.01	17.2/45.4

CEA, carcinoembryonic antigen; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors; SRS, stereotactic radiosurgery.

ranged from 1.4 to 78.6 ng/mL. Twenty-six patients suffered from neurological symptoms caused by the metastatic brain tumor(s). Of these patients, 23 had only brain metastasis and 17 had brain metastasis with extracranial recurrence. Twenty-nine patients received radical therapy, such as SRS or craniotomy, and 11 patients received WBRT.

In this study, the follow-up period after the time of brain recurrence ranged from 3.4–66 months (median: 20.6 months). The five-year OS rate after the time of recurrence was 22.5%.

Table 2 summarizes the results of the univariate regression model analysis. In this analysis, the favorable prognostic factors after brain recurrence included: a normal range of CEA; no extracranial metastasis; no symptoms from the brain metastasis; small metastatic brain tumor; and radical treatment (craniotomy or SRS). The median OS of patients with a high CEA level was 13.3 months, while that of patients with a normal CEA level was 36.3 months. For the patients with extracranial metastasis, the median OS was 16.6 months, compared with 26.2 months for the patients without extracranial metastasis. The median survival of patients who received radical treatment was 27.0 months compared with 10.8 months for patients who did not receive radical treatment. For the patients with symptoms from the brain metastasis, the median OS was 17.2 months. Statistically significant differences were seen between the two groups in all of these parameters ($P < 0.05$).

Table 3 Results of multivariate analysis of the prognostic factors for overall survival from the date of postoperative brain recurrence

Factor	Odds ratio (95% CI)	P-value
CEA level at the time of rec		
<5 ng/mL/>5 ng/mL	0.966 (0.376–2.292)	0.940
Extracranial metastasis		
Yes/No	1.605 (0.786–3.590)	0.181
Symptom from brain metastasis		
Yes/No	2.061 (0.719–5.909)	0.178
Tumor size of brain metastasis		
<2 cm/>2 cm	2.509 (1.023–6.151)	0.041
Radical treatment (Craniotomy or SRS)		
Yes/No	3.619 (1.514–8.652)	<0.01

CEA, carcinoembryonic antigen; CI, confidence interval; SRS, stereotactic radiosurgery.

These five variables showing differences with values of $P < 0.05$ in the univariate analysis were selected for subsequent multivariate analysis (Table 3). The multivariate analysis using Cox's proportional hazards model revealed that a small size of brain metastasis and radical therapy were independent favorable prognostic factors in this patient group ($P = 0.04$, $P = 0.01$). Figure 1 shows the Kaplan-Meier survival plot generated from curves stratified by these factors.

Discussion

The majority of postoperative recurrences of NSCLC are distant metastasis.[11,12] Brain metastases occur frequently as the initial relapse site during the follow-up period after pulmonary resection for NSCLC.[11,13] For lung cancer, some investigators have reported acceptable survival after the resection of distant recurrent lesions, but others have shown
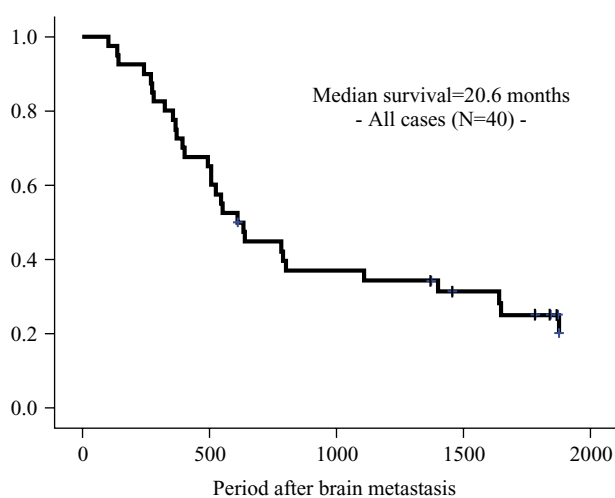
Figure 1 The Kaplan-Meier survival curves for the entire cohort.

data contradicting these conclusions. Abrahams *et al.* demonstrated a satisfactory outcome in patients with brain metastasis, with a median survival time of 18 months and a five-year survival rate of 28.9%.[7] On the contrary, Saitoh *et al.* conducted 24 brain resections, and noted a five-year survival rate of only 8.3%.[5] In this study, the median survival time after recurrence was 20.6 months, and the five-year OS rate after the time of recurrence was 22.5%.

The prognostic factors for survival after the treatment for brain metastasis have not been clarified. In this study, the results of the univariate analyses of the favorable prognostic factors after brain recurrence included normal range of CEA, no extracranial metastasis, no symptoms from the brain metastasis, small metastatic brain tumor, and radical treatment (craniotomy or SRS). The multivariate Cox model identified that a small size of brain metastasis and radical treatment were independent favorable prognostic factors.

Several authors have examined promising prognostic factors in patients with NSCLC who had postoperative brain metastasis. Sakamoto *et al.* reported that local therapy, such as SRS or craniotomy, is one of the significant prognostic factors for NSCLC patients with brain recurrence.[14] In that study, the five-year survival rate after the brain recurrence in patients treated with local therapy was 31.9%, compared to 3.8% for patients without local therapy. In our study, the five-year survival rate of patients treated with local therapy was 31.0%, compared to 0% for patients without local therapy (*P* < 0.01). Based on these results, the patients who receive radical therapy as cerebral local control could be expected to have a longer survival.

To the best of our knowledge, there have been very few reports concerning the relationship between the size of brain metastasis and the prognosis after treatment of brain metastasis. In our study, the median survival of patients whose brain tumor was less than 2 cm was 43.6 months, compared with 13.3 months for patients whose brain tumor was larger than 2 cm. A statistically significant difference was seen between the two groups (*P* < 0.05). The reason for this difference may be that metastatic brain tumors larger than 2 cm are very difficult to control, even when using radical treatment. We found that most of the patients whose brain tumors were larger than 2 cm had intracranial recurrence after treatment for brain metastasis.

By univariate analysis, we also identified that a lack of symptoms from the brain metastasis was a favorable prognostic factor for survival. Aoyama *et al.* showed via multivariate analysis that a good Karnofsky Performance Status (KPS) was a favorable prognostic factor for NSCLC patients with postoperative brain recurrence.[15] In that study, patients with a KPS score of 90 or lower had a 1.69-fold increased risk of death compared with patients with a KPS score of 100. In our report, the five-year survival rate after brain recurrence of patients without symptoms from the brain tumor(s) was

42.8%, compared to 11.5% for patients with symptoms (*P* < 0.01). This difference may be caused by the preservation of the KPS and may be related to the favorable outcome in the patients without symptoms from the brain tumor.

Sakamoto *et al.* reported that the presence of extracranial metastasis at the time of brain recurrence is one of the unfavorable prognostic factors.[14] In our study, a lack of extracranial metastasis at the time of diagnosis for brain metastasis was also a favorable prognostic factor for survival, identified by univariate analysis. However, tumor size of brain metastasis and radical treatment had a greater impact on the patient's survival in our cohort. The patients who had these favorable factors were able to maintain their systemic functions, and as a result, these patients could receive adequate treatment against the extracranial metastasis, including systemic chemotherapy. Therefore, we think that radical treatment for brain tumor(s) might have priority if the patient has brain recurrence with extracranial metastasis.

To date, there have been few prospective studies comparing the survival time after brain metastasis between SRS and craniotomy. Therefore, the evidence based on the current literature is restricted to several retrospective studies, and the results are conflicting. For example, Bindal *et al.* reported that the OS time in patients undergoing resection + WBRT (16.4 months) was statistically longer than that in patients undergoing SRS + WBRT (7.5 months).[16] In contrast, another study revealed a trend toward a longer OS in those receiving SRS + WBRT, but that result did not reach statistical significance.[17] In our cohort, there was no statistically significant difference in the OS time after brain recurrence between the patients who underwent craniotomy and those who underwent SRS (median survival time: 20.4 vs. 26.7 months).

Several authors have recently reported the efficacy of EGFR-TKIs for brain metastasis in NSCLC patients harboring an activating EGFR mutation.[18,19] Park *et al.* revealed that EGFR-TKIs provided high disease control rates, but did not have a significant impact on patient survival. In our cohort, we did not observe any significant difference in the survival time between the patients with and without EGFR mutations (data not shown). However, we did not perform a mutation analysis for all patients because we started the analysis in 2005. Furthermore, the number of patients harboring EGFR mutations was small compared with that of patients without mutations. These factors might have had an impact on the results of the present study. Further accumulation of cases analyzed for mutations will be necessary to perform an adequately powered study of the impact of EGFR mutations and EGFR-TKIs.

Conclusion

In this study, small tumor size of brain metastasis and radical treatment were important favorable predictors for survival in

patients with postoperative brain recurrence. Intracranial recurrence tends to have a greater impact on the patient's systemic activity compared with other sites of recurrence. Therefore, to provide adequate intracranial disease control and to maintain the patient's activities of daily living, it is necessary to detect brain metastases while they are still small during the follow-up period, and patients should undergo radical therapy prior to the development of symptoms from the brain metastasis. To achieve these purposes, the patients' symptoms should be carefully observed, and periodic postoperative follow-up examinations should be performed to detect brain metastases before they become larger than 2 cm.

Disclosure

No authors report any conflict of interest.

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