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Clinical Outcomes of Surgical Resection for Brain Metastases from Non-small Cell Lung Cancer

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Abstract. *Background/Aim: Recent advances in systemic chemotherapy, including molecularly targeted therapy, have dramatically improved survival for patients with advanced non-small cell lung cancer. We retrospectively analyzed the clinical outcomes of surgical resection for brain metastases of non-small cell lung cancer cases performed at the Department of Neurosurgery of Kindai University Hospital, Osaka, Japan. Patients and Methods: Craniotomy and tumor resection were performed for 56 patients with brain metastases of non-small cell lung cancer. Adenocarcinoma was the most common histological type, appearing in 40 cases, of which 18 were positive for driver gene mutations. Results: Median survival for all 56 patients was 14.5 months, and single brain metastasis and adenocarcinoma were identified as favorable prognostic factors. Analysis limited to the 40 cases of adenocarcinoma identified single brain metastasis as a favorable prognostic factor. Although no significant difference was found for systemic chemotherapy, patients who received molecularly targeted therapy showed a better prognosis than those who received cytotoxic chemotherapy. Analyses of both the entire group and of adenocarcinoma patients alone found that whole-brain radiotherapy showed no significant association with survival. Conclusion: Single brain metastasis and adenocarcinoma were identified as favorable prognostic factors, but did not confirm any benefit from whole-brain radiotherapy. These results suggest that multimodal treatment strategies utilizing various methods of treatment, including systemic chemotherapy, may help prolong patient survival in the future.*

Recent advances in cancer treatment have improved therapeutic outcomes of patients with advanced cancers. For non-small cell lung cancer (NSCLC) in particular, the advent of molecularly targeted therapy has dramatically improved their survival. Progression-free survival of the patients with activated mutation of epidermal growth factor receptor (EGFR) is 10 months when they are treated with gefitinib (an EGFR tyrosine kinase inhibitor), whereas the survival of those treated with platinum doublet therapy is 6 months (1). In contrast, conventional chemotherapies have offered little benefit; the response rate of the conventional platinum doublet chemotherapy (carboplatin and paclitaxel) is as low as 20% (2). An issue of previous studies to report the impacts of molecularly targeted therapies of brain metastases is that most of them have addressed asymptomatic or small brain lesions, which lacks characteristics of symptomatic or large brain lesions that need to be removed. To clarify the impacts of molecularly targeted therapies on relatively large brain lesions, we retrospectively analyzed the clinical data of the patients with brain metastases originated from NSCLC who had undergone surgical resection for the brain lesions and discussed future treatment strategies for this disease.

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Key Words: Brain metastases, non-small cell lung cancer, surgical resection, molecularly targeted therapy.

Patients and Methods

Among 136 patients who underwent surgical resection for brain metastases at the Department of Neurosurgery of Kindai University Hospital between 2007 and 2017, 56 patients suffered from brain metastases originated from NSCLC and were included in this study. Indications for surgical resection of brain metastases were the feasibility of general anesthesia and a lesion with maximum diameter ≥25 mm. Postoperative adjuvant therapy was considered individually in consultation with a medical oncologist and a therapeutic radiologist. We conducted comparative analyses of the patients' survival along with numbers of brain metastases, histopathology, and the use of whole-brain radiotherapy and/or systemic chemotherapy. The patients' survival was evaluated by Kaplan-Meier estimates. Prognostic factors were identified by log-rank test for univariate analysis. Values of $p<0.05$ were considered statistically significant.

Results

Table I shows the characteristics of the 56 patients included in the study. Forty out of the 56 patients (71%) possessed adenocarcinoma, 18 of whom were positive for driver gene mutations. Fifty-two of the 56 patients (93%) showed ≤4

brain metastases. The most common method of radiotherapy was whole-brain radiotherapy (n=29; 52%), and systemic chemotherapy was conducted for 44 patients. Twenty-six patients received systemic platinum-based cytotoxic chemotherapy; 18 patients who were positive for driver mutations received molecularly targeted therapy. Median overall survival was 14.5 months, and the 1-, 2- and 5-year survival rates were 57%, 35%, and 9%, respectively (Figure 1). Survival analysis of all the 56 patients revealed single brain metastasis and adenocarcinoma as favorable prognostic factors (Table II). Although no significant difference was observed regarding systemic chemotherapy, patients who received molecularly targeted therapy showed better prognoses than those who received cytotoxic chemotherapy (Table II). No significant difference was observed between use and non-use of whole-brain radiotherapy (Table II). We then performed the same analyses for the 40 adenocarcinoma patients and identified single brain metastasis as a favorable prognostic factor (Table III). While no significant difference was observed regarding systemic chemotherapy, patients who received molecularly targeted therapy showed better prognoses than those who received cytotoxic chemotherapy (Table III). No significant difference was observed between use and non-use of whole-brain radiotherapy (Table III). Additional analysis of the 18 patients who received molecularly targeted therapy revealed that 12 patients had developed brain metastases before the initiation of molecularly targeted therapy and that 6 patients after the initiation of the therapy. Survival analysis of these two groups revealed that, although the difference was not significant, patients who had developed brain metastases before the initiation of molecularly targeted therapy tended to display a more favorable prognosis (Table III).

Table I. *Clinical characteristics of patients with brain metastases.*

Baseline patient characteristics (n=56)	No of patients (%)
Age in years at diagnosis of brain metastases	
Median (range)	66.5 (45-84)
Gender	
Male	34 (60.7%)
Female	22 (39.3%)
Histopathological classification	
Adenocarcinoma	40 (71.4%)
Positive for EGFR/ALK mutations	18 (32.1%)
Squamous cell carcinoma	9 (16.1%)
Large cell carcinoma	3 (5.4%)
Unknown	4 (7.1%)
No. of brain metastases	
Single	34 (60.7%)
Multiple	22 (39.3%)
2-4	18
>5	4
Post-operative treatment	
Whole-brain radiotherapy	29 (51.8%)
SRS/SRT	9 (16.1%)
Systemic chemotherapy	44 (78.6%)
Cytotoxic chemotherapy	26
Molecularly targeted therapy	18

EGFR: Epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; SRS: stereotactic radiosurgery; SRT: stereotactic radiotherapy.

Discussion

NSCLC is the most common primary disease of brain metastases, accounting for approximately half of all cases according to Japanese brain tumor statistics (3). Therapeutic strategy of NSCLC has advanced dramatically since 2000, with the advent of molecularly targeted therapy (1). These molecularly targeted therapies are as effective against brain metastases as they are against extracerebral lesions; they have been reported useful even for meningeal carcinomatosis, for which few treatment options are available (4-6). Therefore, molecularly targeted therapy is now considered as a useful option for the treatment of brain metastases, particularly in combination with conventional radiotherapy and surgery (2, 4-7). We have now entered an era of multimodal treatment strategies. Molecularly targeted therapies utilize tyrosine kinase inhibitors, some of which target EGFR mutations and the anaplastic lymphoma kinase (ALK) fusion gene. Mutations in the EGFR gene are present in approximately 50% of Japanese patients, and the ALK fusion gene in approximately 5% (1). The response rate of EGFR tyrosine kinase inhibitors to brain metastases has been 58-85% (5, 8, 9, 10). Even in patients without driver mutations, cytotoxic chemotherapy in combination with bevacizumab has shown good results with the improvement in the patients' outcomes compared to previous results (11, 12). In this study of the patients with brain metastases originated from NSCLC, the pathological finding of adenocarcinoma was found as a favorable prognostic factor. It appears to reflect the impact of molecularly targeted therapy on the metastatic lesions. However, we also found that prolongation of survival was greatly affected by the onset of brain metastases. That is, if brain metastases had developed before the initiation of molecularly targeted therapy, median survival was as good as 20 months. In contrast, if brain metastases developed after the initiation of molecularly targeted therapy, survival was only 10.5 months. Possible reasons for this observation would reflect the possible resistance of the cancer cells to molecularly targeted therapy or the clinical situation that systemic chemotherapy could not be continued due to poor performance status by brain metastases. Consistent with our findings, the onset of brain metastases has been reported as an important prognostic factor (13). Furthermore, we found that whole-brain radiotherapy did not contribute to the

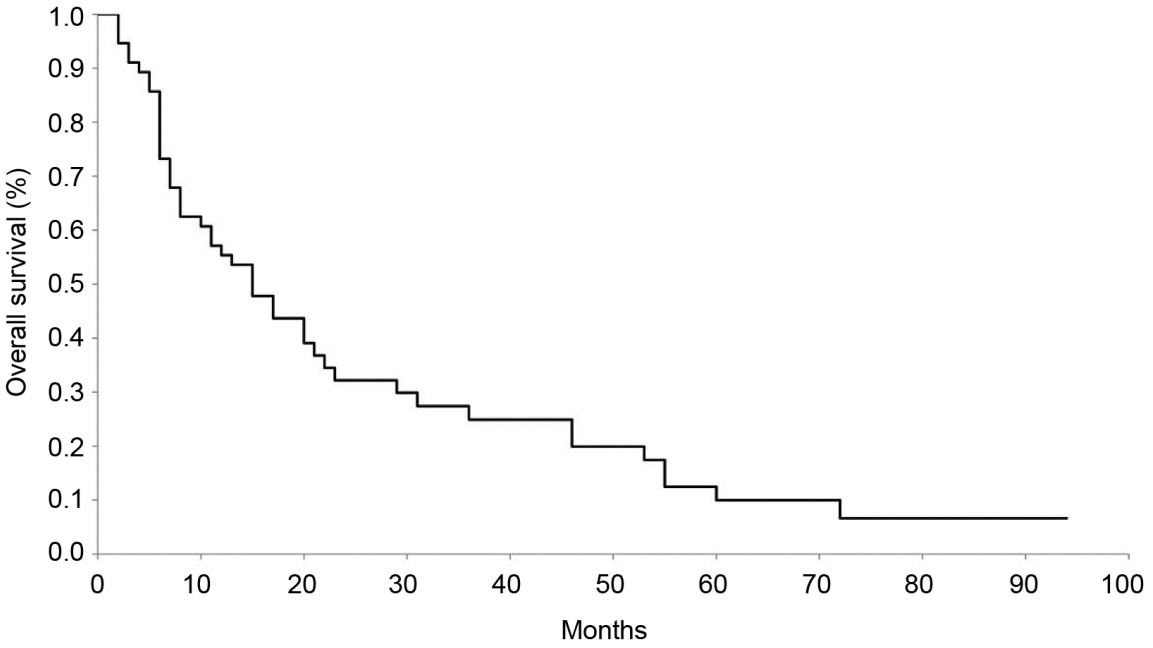

Figure 1. *Overall survival in 56 patients after diagnosis of brain metastases from non-small cell lung cancer. Median overall survival time was 14.5 months.*

Table II. *Univariate analysis for overall survival (non-small cell carcinoma).*

Prognostic factor	No. of patients	Median survival (months)	*p*-Value (univariate)
Histopathological classification			0.001
Adenocarcinoma	40	16.5	
Non-adenocarcinoma	16	7	
No. of brain metastases			0.0075
Single	34	19	
Multiple	22	8	
Whole-brain radiotherapy			0.232
Yes	29	10	
No	27	15	
Systemic chemotherapy			0.082
Cytotoxic chemotherapy	26	10.5	
Molecularly targeted therapy	18	19.5	

Table III. *Univariate analysis for overall survival (adenocarcinoma).*

Prognostic factor	No. of patients	Median survival (months)	*p*-Value (univariate)
No. of brain metastases			0.0018
Single	24	21.5	
Multiple	16	9.5	
Whole-brain radiotherapy			0.232
Yes	20	10	
No	20	15	
Systemic chemotherapy			0.462
Cytotoxic chemotherapy	15	15	
Molecularly targeted therapy	18	19.5	
Molecularly targeted therapy started			0.509
Before brain metastases onset	6	10.5	
After brain metastases onset	12	20	

prolongation of survival. Recent large-scale clinical trials have also found that whole-brain radiotherapy is ineffective in the prologation of survival and that the risk of neurocognitive dysfunction as a late adverse event is now a matter of concern (14, 15). The indications for whole-brain radiotherapy should be considered with even greater circumspection, particularly for patients with driver gene mutations, as they can be expected to survive long-term despite brain metastases.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

Authors' Contributions

Design of the study: TO. Data collection: TN, TO, HY. Data analysis: TO, MF. TN and TO wrote the first draft, and all authors contributed to improving the paper. All Authors approved the final version.

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