Efficacy of Surgical Treatment for Brain Metastasis in Patients with Non-Small Cell Lung Cancer

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Purpose: Patients with non-small cell lung cancer (NSCLC) and simultaneously having brain metastases at the initial diagnosis, presenting symptoms related brain metastasis, survived shorter duration and showed poor quality of life. We analyzed our experiences on surgical treatment of brain metastasis in patients with NSCLC. **Materials and Methods:** We performed a single-center, retrospective review of 36 patients with NSCLC and synchronous brain metastases between April 2006 and December 2011. Patients were categorized according to the presence of neurological symptoms and having a brain surgery. As a result, 14 patients did not show neurological symptoms and 22 patients presented neurological symptoms. Symptomatic 22 patients were divided into two groups according to undergoing brain surgery (neurosurgery group; n=11, non-neurosurgery group; n=11). We analyzed overall surgery (OS), intracranial progression-free survival (PFS), and quality of life. **Results:** Survival analysis showed there was no difference between patients with neurosurgery (OS, 12.1 months) and non-neurosurgery (OS, 10.2 months; p=0.550). Likewise for intracranial PFS, there was no significant difference between patients with neurosurgery (PFS, 6.3 months) and non-neurosurgery (PFS, 5.3 months; p=0.666). Reliable neurological one month follow up by the Medical Research Council neurological function evaluation scale were performed in symptomatic 22 patients. The scale improved in eight (73%) patients in the neurosurgery group, but only in three (27%) patients in the non-neurosurgery group (p=0.0495). **Conclusion:** Patients with NSCLC and synchronous brain metastases, presenting neurological symptoms showed no survival benefit from neurosurgical resection, although quality of life was improved due to early control of neurological symptoms.

Key Words: Non-small cell lung cancer, brain metastasis, neurosurgery, quality of life, treatment outcome

INTRODUCTION

Brain metastases (BMs) are found in approximately 20–40% of all patients with non-small cell lung cancer (NSCLC), especially in adenocarcinoma.[1] The overall

survival (OS) of these patients is generally poor, ranging from 3 to 6 months.[2] Neurologically symptomatic patients have significantly shorter survival times than asymptomatic patients, as the median survival times have been estimated to be 4 and 7.5 months, respectively.[3]

The optimal treatment for patients with neurologically symptomatic, synchronous (simultaneously having brain metastasis at the initial diagnosis), and multiple or solitary brain metastasis from NSCLC still remains controversial. Surgical resection of these metastatic lesions is considered in only 25% of patients.[4] Recently, surgery for stage IV NSCLC (involving an isolated brain or adrenal gland metastasis) has been recommended as a treatment option if mediastinal lymph nodes are not involved.[5] Brain metastatectomy is generally considered for patients who demonstrate good performance status and have a solitary, accessible, symptomatic brain metastasis with significant mass effect, and in addition, for those who need a histologic diagnosis and for those in whom previous radiation therapy has failed.[4] Recently, due to advances in surgical techniques, more lesions are now accessible, and surgical complications and post-surgical morbidity have been reduced compared to the situation in the past.

In this study, we retrospectively evaluated OS, intracranial progression-free survival (PFS), prognostic factors, and optimal treatment for brain metastasis in patients with neurologically symptomatic, synchronous brain metastasis from NSCLC and compared patients in the neurosurgery group, the non-neurosurgery group, and the asymptomatic group.

MATERIALS AND METHODS

Patient characteristics

Medical records at Gangnam Severance Hospital from April 2006 through December 2011 were reviewed to identify patients who presented with synchronous brain metastasis from NSCLC. In all patients, brain metastases were confirmed at the initial diagnosis of the primary lung cancer. The subjects of this study were 36 patients with or without neurological symptoms. Symptomatic patients were divided into two groups according to the surgery performed for the brain metastases. The medical records of each subject were examined for gender, age, smoking history, initial symptoms, pathology, Karnofsky Performance Status (KPS), and Recursive Partitioning Analysis (RPA) class.[6] RPA is the most commonly used model for prospec-

tive survival prediction in patients with BM from various primary malignancies. This model has three classes based on age at diagnosis, presence or absence of extracranial metastases, KPS, and primary tumor status. A higher RPA class represents a worse prognosis. This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine (IRB No: 3-2012-0179), and the necessity for written informed consent was waived since this was a retrospective study and patients were anonymous.

Radiologic parameters of brain metastasis

Reviewed radiologic parameters of the brain metastases included number, size, location, and functional grade.[7] In addition, radiologic findings such as edema, hemorrhage, and necrosis were included. BM size was defined as the maximal orthogonal diameter based on T1-weighted gadolinium-enhanced magnetic resonance imaging (MRI).

Treatment options for brain metastasis

Therapeutic approaches to brain metastases included surgery, whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and chemotherapy. Many patients were treated with combinations of these modalities. Treatment decisions took into account several parameters such as age, neurologic symptoms, functional status, and intracranial lesions. The decision as to whether intracranial lesions were surgically resected were based on neurologic symptoms and signs of intracranial hypertension unresponsive to adequate medical therapy (e.g., intravenous corticosteroid and/or mannitol), insufferable headaches, progressive motor weakness, gait disturbance, or dysarthria. Surgical indications were based on lesion-related relevant symptoms and radiologic brain imaging showing accessible location and a mass effect due to edema unresponsive to medical therapy.

Patients with an asymptomatic brain lesion or patients with symptoms showing poor performance status were recommended to undergo WBRT alone without surgery. In these patients, WBRT was delivered with 37.50 gray in 15 fractions by two lateral beams of photons of 6 megavolts or 30.00 gray in 10 fractions in patients with poor general health status and estimated survival less than 3 months. Once patients received surgery or radiotherapy, systemic platinum-based chemotherapy was started. Initially, two cycles of systemic chemotherapy were administered. Following response assessment after the first two cycles of chemo-

therapy and in the absence of progression either at the primary lung tumor or BM, chemotherapy was indicated. Four patients harboring sensitive epidermal growth factor receptor (EGFR) mutations continuously received EGFR-tyrosine kinase inhibitors (EGFR-TKIs) following surgery or radiotherapy. Palliative treatment only (steroids and anti-convulsants) was administered to patients with poor performance status or high comorbidity, or to patients who did not agree to undertake invasive treatment.

Follow-up schedules

Follow-up for primary lung cancer was performed with computed tomography, generally every 2 months. Follow-up for brain metastases was conducted by MRI, usually every two months. Treatment response in patients with BM was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria after every two cycles in chemotherapy or radiotherapy.

The tumor response in the BM was evaluated by enhanced brain MRI and neurological findings. Neurological status was assessed using the Medical Research Council (MRC) neurological function scale at 1 month after intracranial treatment.[8] If there were measurable lesions, the tumors were evaluated based on the RECIST version 1.1 criteria. If there were no measurable lesions, the tumor response was classified as partial response, stable disease, or progressive disease based on the enhanced brain MRI findings and neurological findings. Intracranial progression after neurosurgical resection or radiotherapy was defined as either progressive enlargement of the enhancing lesion or no change in tumor size but persistent, symptomatic edema.

Statistical analysis

Data were analyzed with SAS 9.2 version (SAS Institute Inc., Cary, NC, USA). OS was defined as the time elapsed from the starting date of treatment of the brain metastasis or pulmonary lesions to the date of death or the date of last follow-up. Intracranial PFS was defined as the time from the date of the start of treatment to the date of documented disease progression or death from any cause. Risk factors affecting the survival rate were found using Fisher's exact test and log-rank test, thus multiple survival analyses with adjusted and associated risk factors were performed using Cox's proportional hazard regression model. Median time to intracranial progression and OS were analyzed by the Kaplan-Meier estimator. Significance was set at a p-value of <0.05. All tests were two-sided.

RESULTS

Demographic characteristics

A total of 36 patients were histologically confirmed as NSCLC and radiologically diagnosed as having brain metastasis between April 2006 and December 2011. Fourteen patients did not present with neurological symptoms and 22 patients presented with neurological symptoms at admission. Of the neurologically symptomatic 22 patients, 11 patients were treated with neurosurgical treatment and 11 patients were not treated with neurosurgery. Non-neurosurgery group was treated with WBRT or palliative therapy. Table 1 shows the characteristics of 22 patients with neurologically symptomatic, synchronous brain metastasis from NSCLC. Between the neurosurgery and non-neurosurgery groups, there were no significant differences in any characteristics evaluated. Current or past smoking status, performance status, prognostic factors, and neurological scale by MRC neurological function evaluation at initial diagnosis showed no differences between the two treatment groups.

Pathology, number of brain metastasis and treatment modalities

Table 2 shows the pathologic diagnosis and the number of brain metastases and treatment modalities which the symptomatic 22 patients and asymptomatic 14 patients underwent. In the neurosurgery group, six patients (55%) showed multiple synchronous metastases and five patients (45%) showed solitary metastasis. In the non-neurosurgery group, 7 patients (64%) showed multiple metastasis and 4 (36%) patients showed single metastasis. These patients were classified for treatment modality. Of the 11 patients in the neurosurgery group, 10 patients were followed by WBRT or SRS and AS patients received WBRT or SRS only.

In all patients in the neurosurgery group, the one lesion that was the largest, symptomatic, and surgically accessible was resected. The resected lesions ranged in size from 1.9 to 5.6 cm (median 3.4 cm). The characteristics of multiple metastatic lesions, each patient's performance scale, and OS are summarized in Table 3.

Treatment outcomes

We analyzed OS and PFS, after excluding 4 patients (3 patients treated with neurosurgery group; 1 patient treated without neurosurgery) harboring sensitive EGFR mutations and treated with EGFR-TKIs following neurosurgery or ra-

Table 3. Features of Six Patients with Neurologically Symptomatic, Synchronous and Multiple Brain Metastasis Who Received Neurosurgery

	1	2	3	4	5	6
Brain image						
No. of metastasis	5	2	2	3	10	3
No. of resection	1	1	1	1	1	1
Size (cm)	3.1	5.6	1.9	2.5	2.7	4.6
Site	Parietal	Cerebellum	Cortex	Cerebellum	Parietal	Cerebellum
Edema	+	+	+	+	+	+
Hemorrhage	+	-	-	-	-	+
Necrosis	+	-	-	-	-	-
Mass effect	+	+	+	+	+	+
PS						
KPS score	≥70	≥70	≥70	<70	<70	≥70
RPA class	II	II	II	III	III	I
OS (month)	13	4	23	4	13	16
EGFR						
Mutation analysis	-	-	Mutant	Mutant	Wild	Mutatn
Selected regimen	-	-	Erlotinib	Gefitinib	-	Gefitinib

PS, performance status; KPS, Karnofsky Performance Status; RPA, recursive partitioning analysis status; OS, overall survival; EGFR, epidermal growth factor receptor.
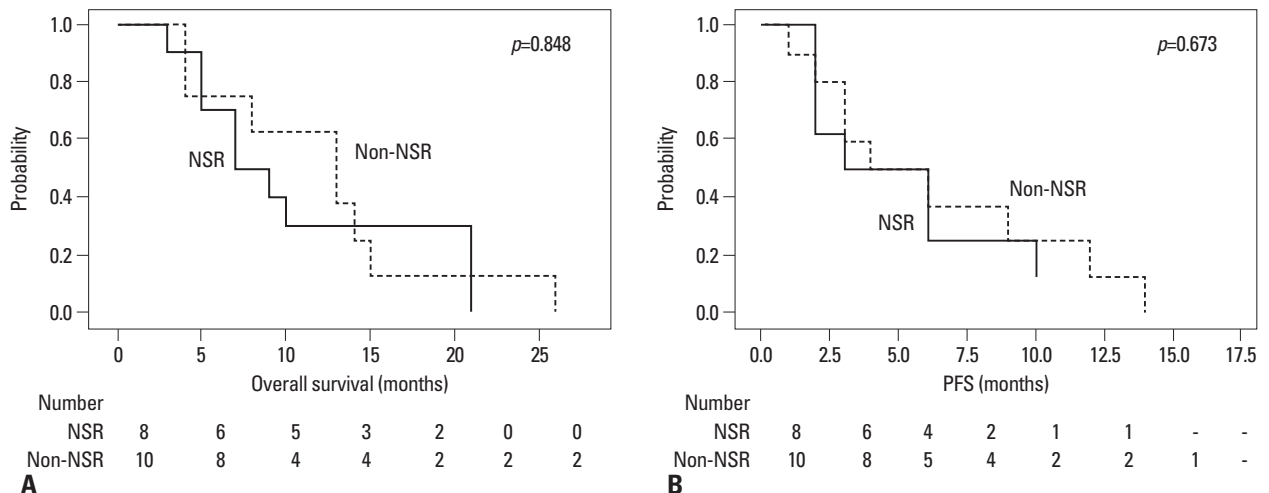

Fig. 1. Kaplan-Meier estimate curves of OS (A) and intracranial PFS (B) for NSR and non-NSR group patients. OS, overall survival; PFS, progression free survival; NSR, neurosurgical resection.

diotherapy, because such patients are usually responsive to EGFR-TKIs and show favorable prognosis.

There was no difference in survival between 8 patients with neurosurgery (OS, 12.1 months) and 10 patients with non-neurosurgery (OS, 10.2 months; p=0.550). Likewise for intracranial PFS, there was no significant difference between the neurosurgery group (6.3 months) and the non-neurosurgery group (5.3 months; p=0.666) (Fig. 1). Additionally, there was no difference in OS (p=0.363) and intracranial PFS between the symptomatic group (neurosurgery group plus non-neurosurgery group) and the asymptomatic group (n=14, p=0.083) (Table 4). Table 4 also shows the response after BM treatment (p=0.669) and the cause of death (p=0.773)

for each group. There were no significant differences between the groups in terms of these characteristics. Currently, two patients are alive without recurrence after treatment of intracranial metastasis. These patients are from the non-neurosurgery.

Neurological function score

Reliable neurological 1-month follow-up using the MRC neurological function evaluation scale was available for 22 symptomatic patients. The MRC scale improved in 8 (73%) neurosurgery patients and did not change in 3 (27%) neurosurgery patients, whereas it improved in 3 (27%) non-neurosurgery patients, worsened in one (9%) non-neurosurgery

Table 4. Clinical Outcome of 32 Patients with Synchronous Brain Metastasis from NSCLC

| Clinical outcome | Symptomatic | | | | Asymptomatic (n=14) | p value* |
	Total (n=18)	NSR (n=8)	Non-NSR (n=10)	p value		
Median OS (month)	9.5	12.1	10.2	0.550	13.1	0.363
Intracranial PFS (month)	4.5	6.3	5.3	0.666	8.4	0.083
BM response (No.)				0.827		0.669
PR	9	5	4		5	
SD	3	1	2		4	
PD	6	2	4		5	
Cause of death (No.)				0.775		0.773
Intracranial	4	2	2		3	
Extracranial	3	2	1		3	
Both	9	4	5		8	
Total	16	8	8		14	

OS, overall survival; PR, partial response; SD, stable disease; PD, progression of disease; BM, brain metastasis; NSCLC, non-small cell lung cancer; PFS, progression-free survival; NSR, neurosurgical resection.
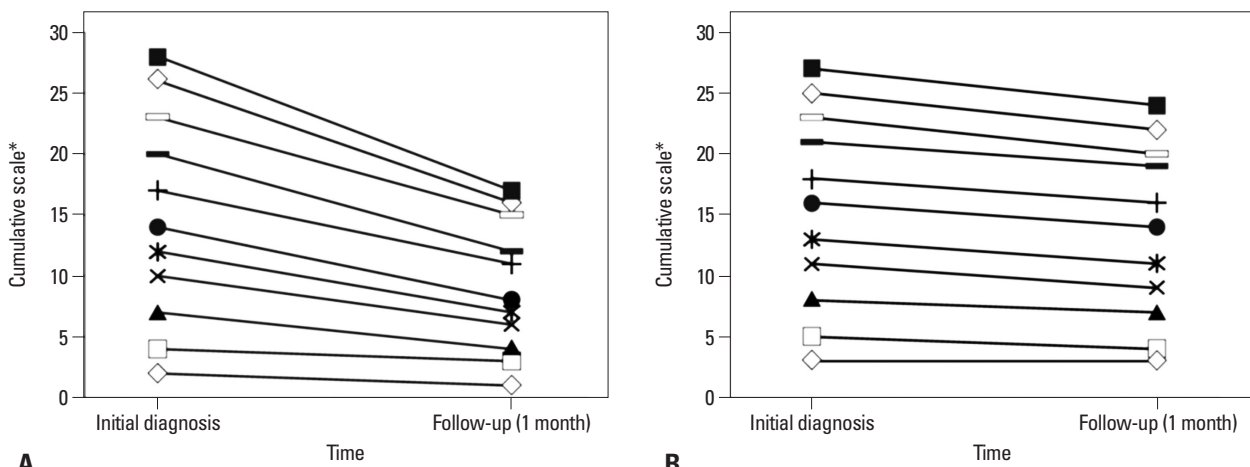*p value between symptomatic vs. asymptomatic patients.

Fig. 2. Cumulative change of MRC neurological function scale at 1-month follow-up after therapy for brain metastasis. (A) NSR group (n=11). (B) Non-NSR group (n=11). p=0.0495. *Medical Research Council (MRC) neurological function scale. NSR, neurosurgical resection.

patient, and did not change in 7 (64%) non-neurosurgery patients.

The cumulative MRC neurological function scale scores of the initial symptom for the two groups were 26 for the neurosurgery group and 27 for the non-neurosurgery group (i.e., there was no difference in scores). However, the cumulative scale scores at 1 month after BM treatment were 16 for the neurosurgery group and 24 for the non-neurosurgery group, indicating a better functional outcome after neurosurgery (p=0.0495) (Fig. 2).

DISCUSSION

Brain metastases are identified in 7.4–10.0% of patients with NSCLC upon initial diagnosis.[9] Moreover, brain metastases occur in 30–50% of patients with NSCLC, and confers a poor prognosis and a negative impact on quality of life (QOL) during the course of their disease.[10-12] Patients with NSCLC and synchronous brain metastasis on initial diagnosis, who presented with neurological deficits, had a short median survival and lower QOL.[3] Studies have been performed on the effect of neurosurgery for brain metastasis in the patients with neurological symptoms on diagnosis; however, their results were limited to patients with a solitary metastasis.[13-16] We performed early surgical treatment of brain metastasis (including multiple metastases) in patients with lowered performance status (i.e., KPS <70 or RPA class II or III) (Table 1). Early surgical treatment controlled the progression of brain metastasis and improved neurologic symptoms, and was followed by better performance status that enabled systemic chemotherapy (Fig. 2).

Recently, surgical intervention has demonstrated increased survival rates and decreased complications of post-operation as positive benefits; therefore, resection of a single brain metastasis has become the standard treatment option in patients with good functional status and controlled extra-cranial disease.[15,16] Advances in surgical techniques have led to lower rates of morbidity and in-hospital mortality, with estimates as low as 1.8% in high-volume centers.[17] However, in the case of multiple brain metastases, surgery is usually limited to patients with a dominant, symptomatic, or life-threatening lesion and to those who require a tissue diagnosis before proceeding with therapy. However, two recent single-center retrospective studies have suggested that patients with good prognostic features and two to three metastases may gain same survival benefit from surgery as patients with one metastasis, if the dominant lesion is resected.[18,19] Despite these benefits of surgical resection, surgical candidates cannot clearly be defined. There is especially insufficient evidence to make a recommendation for patients with poor performance status, advanced systemic disease, or multiple brain metastases.

In our present study, surgery was performed for accessible brain metastasis causing a mass effects, peri-tumoral cerebral edema, and insufferable neurological deficits even if patients had poor performance status or multiple brain metastases. There were no complications in 11 patients from the neurosurgery group. Neurological symptomatic complaints of neurosurgery group patients were relieved significantly compared to those of the non-neurosurgery group 1 month after surgery, as indicated by the MRC neurological function evaluation scale (Fig. 2). Furthermore, it is important to confirm tissue pathology before proceeding with therapy because it is recommended as an option for the first line treatment of NSCLC patients who have a brain metastasis and harbor an EGFR mutation with EGFR-TKIs.[20,21] Moreover, discordance in the EGFR mutation status between the primary and metastatic brain lesions has been recently reported in several studies and the discordance rate was reported to reach 27–28%.[22,23] In our study, early EGFR-TKI treatment was conducted in three of nine patients receiving systemic chemotherapy, after identification of the EGFR mutation on the metastatic brain tissue (Table 2).

Diverse clinical studies have been carried out to provide a guideline for the optimal treatment of patients with a symptomatic, synchronous brain metastasis from NSCLC. The median survival of patients treated with only supportive care (such as corticosteroids) has been estimated to be 1–2 mon-

ths.[24] For patients with favorable prognostic features [good performance status, younger age (<65 years), well-controlled status of the primary lung cancer, and absence of extra-cranial metastasis[6,25-27]], treatment with SRS and WBRT could prolong OS to 11.6 months.[28] Using RPA as a prognostic factor, meta-analyses by the Radiation Therapy Oncology Group trials on brain metastasis treated with SRS showed that the median survival of the best prognosis group (RPA class I: age <65 years, KPS ≥70, and a controlled systemic disease) was 7.1 months. The expected survival of the worst prognosis group (RPA class III: KPS <70) was only 2.3 months.[6] Until now, treatment for brain metastases includes surgery, SRS, WBRT, or a combination of these modalities, and has achieved median survival ranging from 6.5 to 11.0 months.[28-32]

In our present study, neurosurgery group showed no significant differences in survival rate (OS, 12.1 months) compared with non-neurosurgery group (OS, 10.2 months) (Table 4), and showed a favoring trend with 1.9 months, even though patients with a poor prognostic factor (RPA class II or III) were included, compared with the previous data.[28,32] A previous study showed a prolonged survival only in patients in the AS group compared to symptomatic synchronous patients.[3] Our study showed a similar survival rate between patients in the AS group (OS, 13.1 months) and patients in the neurosurgery group (OS, 12.1 months), and failed to show any statistical significance between the neurosurgery group (OS, 12.1 months) and the non-neurosurgery group (OS, 10.2 months) (Table 4).

In patients with a symptomatic, synchronous brain metastasis from NSCLC, the brain lesion mostly has life-threatening mass effects and causes focal neurological deficits that may considerably decrease the functional grade. Thus, early surgery can immediately provide symptom relief and improve QOL in the patients.

There are several limitations in the present study. First, it was a retrospective study, the study population was small, and the research was carried out in a single institution, consequently, it is difficult to generalize this result to other settings. Second, we compared OS between three treatment groups without considering the control of primary lung cancer. We could not exclude systemic chemotherapeutic effect for primary lung cancer, and brain metastasis is usually considered most crucial factor in mortality. A large-scale prospective randomized study is needed for generalization of this result.

In conclusion, patients with synchronous brain metastasis,

presenting with neurological symptoms, showed no survival benefit from combined treatment with neurosurgical resection, although their QOL was improved due to early resolution of the neurological symptoms. Future studies, incorporating the role of resection for more than one brain metastasis with or without additional adjuvant therapy, will help clarify whether the benefits of resection discussed above apply to multiple lesions. However, prospective clinical trials should be done to confirm the benefits of this treatment.

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