INTRODUCTION

Brain metastases develop in up to 50% of all patients with cancer [1]. Multiple brain metastases are a common occurrence in patients with cancer, with an incidence between 12 and 50% in this population [2-4]. Autopsy reports indicate that between 60% and 85% of patients with brain metastases have multiple lesions [5-7]. Recently, the detection sensitivity of brain metastases has increased secondary to improvement in imaging technology [8]. When only computed tomography (CT) was widely utilized, almost all detected brain metastases were symptomatic; however with the introduction of magnetic resonance imaging (MRI), detection of asymptomatic brain metastases has increased [9]. Brain metastases are symptomatic in approximately two-thirds of metastatic brain tumor patients [5,10]. Because of its poor prognosis, their mean survival is approximately 6 months, even after receiving whole brain radiation therapy (WBRT). Patients diagnosed with multiple (>3) metastatic lesions used to be treated with WBRT with or without stereotactic radiosurgery [11]. The current accepted practice to manage these patients is not to offer surgery except in the presence of a life-threatening lesion, the presence of two lesions that can be removed in a single craniotomy, and the need of pathologic diagnosis [12].

Recently, advances in microsurgical technology, such as navigation systems, intra-operative imaging, and cortical map-
ping, have elevated surgical intervention higher along the list of therapeutic options for these patients [13-15]. The primary benefit of surgical resection of symptomatic metastatic lesions is prompt eradication of mass effect and neurologic symptoms. Eventually, surgery may confer modest survival benefits in non-small cell lung cancer (NSCLC) patients with multiple brain metastases by providing them the opportunity to receive post-operative systemic chemotherapy. Therefore, cerebral metastatectomy should be considered in patients with controlled systemic disease, and concurrent, multiple symptomatic brain metastases that result in significantly deteriorated performance status, when reasonable systemic treatment options are available. Patients with one or more symptomatic brain metastases due to mass effect may be considered for metastatectomy. It must be considered that many of surgical candidates have also asymptomatic tumors and these patients may also be eligible for surgery.

This study aimed to investigate the outcome of surgical resection for the symptomatic cerebral lesions followed by chemotherapy or radiotherapy for asymptomatic lesions in NSCLC patients with multiple brain metastases.

**MATERIALS AND METHODS**

**Clinical characteristics of the patients**

Fifty one NSCLC patients with multiple brain metastases underwent surgical metastatectomy between 2001 and 2007. The mean age was 55.3 years (range 29-73). There were 36 men and 15 women. Thirty seven patients (72.5%) showed better Karnofsky performance scale score than 70. Of these 51 patients, seven patients were categorized to recursive partitioning analysis (RPA) class I, thirty two patients to RPA II, and twelve patients to RPA class III. Twenty five patients (49%) had stable systemic disease at the time of brain surgery. Twenty

**Table 1. Clinical characteristics of 51 patients with multiple brain metastases**

| Characteristic                  | No. of patients (%)       | Symptomatic lesion-only resection (n=38) | Complete resection (n=13) | Overall (n=51) | p value  |
|--------------------------------|---------------------------|----------------------------------------|---------------------------|---------------|----------|
| Gender                         |                           |                                        |                           |               |          |
| Male                           | 26 (68.4)                 | 10 (76.9)                              | 36 (70.6)                 |               | 0.730*   |
| Female                         | 12 (31.6)                 | 3 (23.1)                               | 15 (29.4)                 |               |          |
| Mean age (range, yrs)          | 55.9 (29-73)              | 53.5 (39-71)                           | 55.3 (29-73)              |               | 0.490†   |
| Tumor location                 |                           |                                        |                           |               |          |
| Supratentorial                 | 29 (76.3)                 | 11 (84.6)                              | 40 (78.4)                 |               | 0.706*   |
| Infratentorial                 | 9 (23.7)                  | 2 (15.4)                               | 11 (21.6)                 |               |          |
| Number of tumors               |                           |                                        |                           |               | <0.001*  |
| ≥5                             | 9 (23.7)                  | 0 (0.0)                                | 20 (39.2)                 |               |          |
| 3-4                            | 19 (50.0)                 | 2 (15.4)                               | 21 (41.2)                 |               |          |
| <3                             | 10 (26.3)                 | 11 (84.6)                              | 10 (19.6)                 |               |          |
| Timing of metastasis           |                           |                                        |                           |               |          |
| Synchronous metastasis         | 23 (60.5)                 | 4 (30.8)                               | 27 (52.9)                 |               | 0.064†   |
| Metachronous metastasis        | 15 (39.5)                 | 9 (69.2)                               | 24 (47.1)                 |               |          |
| Karnofsky performance scales   |                           |                                        |                           |               | 0.472*   |
| ≥70                            | 26 (68.4)                 | 11 (84.6)                              | 37 (72.5)                 |               |          |
| <70                            | 12 (31.6)                 | 2 (15.4)                               | 14 (27.5)                 |               |          |
| RPA class                      |                           |                                        |                           |               |          |
| Class I                        | 6 (15.8)                  | 1 (7.7)                                | 7 (13.7)                  |               | 0.576*   |
| Class II                       | 22 (57.9)                 | 10 (76.9)                              | 32 (62.7)                 |               |          |
| Class III                      | 10 (26.3)                 | 2 (15.4)                               | 12 (23.5)                 |               |          |
| Primary tumor control          |                           |                                        |                           |               |          |
| Controlled                     | 19 (50.0)                 | 6 (46.2)                               | 25 (49.0)                 |               | 0.811†   |
| Uncontrolled                   | 19 (50.0)                 | 7 (53.8)                               | 26 (51.0)                 |               |          |
| Chemotherapy                   |                           |                                        |                           |               |          |
| Performed                      | 29 (76.3)                 | 10 (76.9)                              | 39 (76.5)                 |               | 1.000*   |
| Not performed                  | 9 (23.7)                  | 3 (23.1)                               | 12 (23.5)                 |               |          |
| Postoperative RT               |                           |                                        |                           |               | 1.000*   |
| Performed                      | 13 (34.2)                 | 4 (30.8)                               | 17 (33.3)                 |               |          |
| Not performed                  | 25 (65.8)                 | 9 (69.2)                               | 34 (66.7)                 |               |          |

*Pearson’s chi-square test, †t-test. RPA: recursive partitioning analysis, RT: radiotherapy
seven (52.9%) patients had synchronous brain metastases, and twenty four patients had metachronous metastases. The patients’ clinical characteristics are summarized in Table 1. In terms of number of lesions, there were two lesions in 20 patients, three lesions in 12 patients, four lesions in 9 patients, and ten patients harbored more than five lesions. After surgical intervention, 38 patients had remnant asymptomatic lesions after resection of symptomatic lesions, and in 13 patients, all cerebral metastases were resected.

**Table 2. Additional treatments after brain surgery**

| Treatment                        | Symptomatic lesion resection (n=38) | Total resection (n=13) | Overall (n=51) |
|----------------------------------|------------------------------------|-----------------------|----------------|
| Chemo followed by RT             | 8 (21.1)                           | 3 (23.1)              | 11 (21.6)      |
| Chemo only                       | 12 (31.6)                          | 5 (38.5)              | 17 (33.3)      |
| RT followed by Chemo             | 9 (23.7)                           | 2 (15.4)              | 11 (21.6)      |
| RT only                          | 5 (13.2)                           | 3 (23.1)              | 8 (15.7)       |
| No treatment                     | 4 (10.5)                           | 0 (0.0)               | 4 (7.8)        |

Chemo: chemotherapy; RT: radiationtherapy

**Table 3. Factors affecting overall survival in univariate and multivariate analyses (Cox regression model)**

| Variable                  | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | Hazard ratio (95% CI) | p value | Hazard ratio (95% CI) | p value |
| Gender                    |                      |          |                       |         |
| Male                      | 1.09 (0.55-2.19)     | 0.804    | NA                    |         |
| Female                    |                      |          |                       |         |
| Age ≥60                   | 1.28 (0.69-2.38)     | 0.435    | NA                    |         |
| <60                       |                      |          |                       |         |
| Tumor location            |                      |          |                       |         |
| Supratentorial            | 1.83 (0.88-3.77)     | 0.104    | NA                    |         |
| Infratentorial            |                      |          |                       |         |
| Number of tumors          |                      |          |                       |         |
| ≥5                       | 1.80 (0.79-4.09)     | 0.162    |                       |         |
| 3-4                      | 1.07 (0.53-2.17)     | 0.855    |                       |         |
| <3                       |                      |          |                       |         |
| Timing of metastasis      |                      |          |                       |         |
| Synchronous               | 1.10 (0.59-2.03)     | 0.767    | NA                    |         |
| Metachronous              |                      |          |                       |         |
| KPS ≥70                   | 2.04 (1.03-4.04)     | 0.040    | 4.80 (1.02-22.60)     | 0.047   |
| KPS <70                   |                      |          |                       |         |
| RPA class                 |                      |          |                       |         |
| Class I                   | 3.45 (1.04-11.46)    | 0.044    | 1.79 (0.49-6.49)      | 0.379   |
| Class II                  | 4.77 (1.30-17.47)    | 0.018    | 0.39 (0.08-4.49)      | 0.613   |
| Class III                 |                      |          |                       |         |
| Primary tumor control     |                      |          |                       |         |
| Controlled                | 3.85 (1.98-7.50)     | <0.001   | 3.48 (1.66-7.30)      | 0.001   |
| Uncontrolled              |                      |          |                       |         |
| Region of resection       |                      |          |                       |         |
| Total resection           | 1.02 (0.50-2.07)     | 0.968    | 1.52 (0.69-3.32)      | 0.296   |
| Partial resection         |                      |          |                       |         |

CI: confidence interval, NA: not assessed, KPS: Karnofsky performance scale, RPA: recursive partitioning analysis
Surgical treatment and subsequent treatments after surgery

All patients were treated with surgery for brain metastases. We used a technique described in our previous report to promote completeness of resection [15]. We removed only symptomatic lesions in this study. Asymptomatic lesions were subsequently treated with chemotherapy and/or radiotherapy. Post-surgical treatment modalities for asymptomatic brain metastases are summarized in Table 2. Twenty two patients were treated with both chemotherapy and radiotherapy (radiotherapy after chemotherapy in 11, chemotherapy after radiotherapy in 11), seventeen patients were treated with chemotherapy alone, and eight patients were treated with radiotherapy alone.

Follow-up evaluation

Patients were examined clinically monthly, and brain MRIs were obtained every 3 months following surgery.

Statistical analysis

Overall survival was calculated from the date of brain surgery using the Kaplan-Meier method. Univariate comparisons of survival between different groups were performed using the log-rank test. Variables compared include, the number of metastases, types of metastatectomy (resection of all lesions, one or more lesions left unresected), and post-surgical treatments (radiotherapy, chemotherapy). Multivariate analysis was performed to determine if the variables significantly correlated with survival difference under the Cox regression model. The following variables were examined: type of metastatectomy,
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controlled or uncontrolled systemic disease, RPA class and timing of metastases.

RESULTS

Survival analysis
Median survival after brain surgery in patients with multiple brain metastases was 10.8 months in the study population. Median survival of patients with unresected asymptomatic lesions was 10.8 months, and that of patients with no evaluable lesion was 6.5 months. Survival duration did not differ significantly between the two groups ($p=0.97$) (Fig. 1). The overall survival was 44.4% at year 1 and 25.8% at year 2. The survival in the patients with unresected, asymptomatic lesions were 46.5% at year 1 and 24.6% at year 2, and that in patients with no evaluable lesions were 38.5% at year 1 and 28.9% at year 2.

Multivariate analysis
Multivariate analysis using the Cox regression model indicated that variables significantly affecting survival were primary tumor control ($p<0.001$) and RPA classes ($p=0.044$, 0.018) (Table 3). Patients with uncontrolled systemic disease survived 4.7 months and those with controlled systemic disease survived 21.7 months ($p=0.001$) (Fig. 2). Median survival has not been reached in RPA class I, and were 9.6 and 3.3 months in RPA class II and III, respectively ($p=0.001$) (Fig. 3).

Number of tumors
There was no statistically significant difference in survival according to the number of tumors ($p=0.86$, 0.16) (Fig. 4). However, there appeared to be a trend for shorter survival when the number of metastatic brain tumors was more than 5.

Post-surgical treatment
Survival data according to additional treatment modalities in patients with multiple brain metastases were shown in Fig. 5. There was no significant difference in survival with different post-surgical treatment modalities ($p=0.69$). However, patients who did not receive any additional treatment, and who only received radiotherapy to the brain without chemotherapy appeared to have shorter survival.

Comparison of multiple metastases with single metastasis
We compared survival in patients with multiple brain metastases from data we published previously in patients with single brain metastasis after complete resection of the lesion [15]. Comparison of survival data for patients with single and multiple brain metastases are shown in Fig. 6. Median survival was 14 months in patients with single brain metastasis, 10.8 months in patients with multiple brain metastases. Survival for single and multiple brain metastases groups were 57.1% and 44.4%, respectively, at year 1, and 24.6% and 25.8%, respectively, at year 2. Survival duration did not differ significantly between the two groups ($p=0.22$).

DISCUSSION

Treatment outcomes of multiple brain metastases after surgery
Management of patients with multiple brain metastases is considered to be difficult due to the historically poor prognosis of these patients when compared to patients with solitary brain metastasis. Treatment generally consisted of WBRT once the diagnosis of multiple brain metastases was made.

The authors of several reports have shown that tumor resection in a subset of patients with multiple brain metastases is associated with improved outcomes [16-20]. Bindal et al. [16] reported a median survival of 10 months in 82 patients who underwent resection combined with WBRT. In that retrospective study, the authors reported a 14-month average survival after complete removal of multiple metastases in 26 cases, similar to the 14-month survival observed in a control group with matched single tumors [16]. However, in 30 patients with incomplete resection, survival was not longer than that conferred by radiation treatment alone (average approximately 6 months). Hazuka et al. [21], demonstrated a 5-month average survival in 18 patients who underwent resection of multiple metastases. In that study, one patient achieved complete resection of all metastases and survived for 48 months.

Our study suggests that survival of patients with multiple symptomatic brain metastases who underwent metastactectomy while leaving asymptomatic lesions unresected is equiva-
lent to that in patients who underwent complete cerebral metastatectomy.

Patients with multiple metastases who underwent surgery lived substantially longer than the 3-6 month survival time reported by numerous investigators in patients who received radiation treatment alone.

The median survival was 11 months in patients with multiple brain metastases, and this result was comparable to that of 14 months we previously reported in patients with single brain metastasis after resection [15]. This is comparable to the results reported in other series, suggesting that in patients with brain metastases, surgical resection of only symptomatic brain metastases does not result in poorer survival when compared to patients with only single brain metastasis or multiple brain metastases, in which all lesions were resected. Bindal et al. [16] and Hazuka et al. [21], reported poor survival when one or more metastases remained unresected. This finding is different from ours in that there were no significant survival differences between the different types of resection: total resection of single metastasis, complete resection of all metastases, and resection of symptomatic lesions only with one or more remaining asymptomatic metastases. This may suggest that post-operative chemotherapy may confer a survival advantage because most patients with brain metastases die of primary disease progression. We believe that surgical resection remains important for the removal of large symptomatic metastases and if successful, would possibly allow patients to undergo other treatments for the remaining asymptomatic metastatic tumors, due to improved performance status.

**Treatment outcomes of patients with metastatic brain tumors from non-small cell lung cancer**

In most clinical studies concerning brain metastases, multiple different cancers were involved in each study which made the ratio of each pathological entity different between series. We believe that it is important to analyze survival in a single pathological entity. There have been several retrospective studies analyzing survival of NSCLC patients with brain metastases, who underwent brain and pulmonary lesions resection. In that series, the overall survival was 56% at 1 year, 28% at 2 years, and 11% at 5 years. However, only 4 patients from the study population had multiple brain metastases. Iwasaki et al. [23] analyzed 70 NSCLC patients with brain metastases. The authors reported that in patients who underwent lung and brain metastases resection, the survival was 66.4% and 21.9% at 1 year and 3 years, respectively. In the lung lesion-only resection group, the 1 and 3 years survival were 33.2% and 6.6%, respectively. Abrahams et al. [24] reported a median survival of 12.9 months in their series of 70 NSCLC patients with brain metastases. In their series, 1-, 2-, 3-years survivals were 52.2, 30.7, 18.1%, respectively. Our results were similar to these previous reports. Survival of the single and multiple brain metastases groups were 57.1% and 44.4%, respectively, at 1 year and 24.6% and 25.8%, respectively, at 2 years. Five-year survival for the single brain metastases group was 18.8%.

**Treatment for the asymptomatic brain metastases**

In our previous study, we demonstrated that patients with asymptomatic brain metastases may be treated with systemic chemotherapy alone as an initial treatment without jeopardizing their clinical outcomes [25]. WBRT may be reserved for the future as long as the brain metastases are controlled with systemic chemotherapy. This appears to be a reasonable approach when recent advances in systemic chemotherapy and molecular-targeted therapy are taken into consideration. Most NSCLC patients with brain metastases died of progressive systemic disease rather than the progression of metastatic brain lesions, even in patients who did not receive WBRT [25]. This may suggest that WBRT may not always be necessary in patients with asymptomatic brain metastases. Recently, in one retrospective study, Kim et al. [26] suggested a potential role of systemic chemotherapy instead of WBRT as an initial treatment of NSCLC patients with synchronous, asymptomatic brain metastases. After surgical resection of symptomatic lesions in patients with multiple brain metastases, the clinical status of patients is similar to those with asymptomatic brain metastases. Therefore, post cerebral metastatectomy, systemic chemotherapy may have a role in the treatment of the remaining cerebral and systemic disease. In our series, when systemic chemotherapy was administered following resection of symptomatic brain lesions, although median survival appeared to be longer than in patients who did not receive chemotherapy (12 months vs. 4 months), the difference was not statistically significant (p=0.50).

**Recommendations for the treatment of multiple brain metastases**

We advocate the role of systemic chemotherapy in the initial treatment of NSCLC patients with advanced systemic disease and concurrent asymptomatic or minimally symptomatic brain metastases. Patients with one or more symptomatic brain metastases due to mass effect may be considered for surgery. If one or two lesions are life threatening or highly symptomatic, surgical removal may improve the quality of life and survival of the patient. Chemotherapy and/or radiotherapy including radiosurgery may be used to treat the remaining lesions. Based on the results of our current and previous studies, primary ch-
emotherapy for asymptomatic brain metastases may be more efficacious than WBRT and radiosurgery in case of advanced and progressive systemic disease. WBRT and radiosurgery may be helpful when the systemic disease is controlled and/or when brain lesions progress even after receiving effective systemic chemotherapy.

Survival in NSCLC patients with multiple brain metastases who underwent resection for symptomatic lesions alone is similar to that in patients who underwent complete cerebral metastatectomy. The remaining asymptomatic lesions may be treated with chemotherapy or radiotherapy. The optimal treatment modality, however, needs to be defined in prospective trials encompassing larger patient cohort.

Conflicts of Interest

The authors have no financial conflicts of interest.

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