

## Outcomes after Reirradiation for Brain Metastases

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We retrospectively analyzed the outcomes in patients who underwent reirradiation for brain metastasis. Twenty-three patients with brain metastases who were initially treated with palliative brain radiotherapy and were retreated with a second course of brain RT between June 2008 and December 2012. WBRT, 3DCRT and SRS were used for brain metastasis. The median dose of the first course of WBRT was 30 Gy (range, 23.4~30 Gy). The dose of the first course 3DCRT for lesion was 30 Gy in 3 Gy per fraction. The median dose of the first course of SRS was 16 Gy in 1 fraction (range, 12~24 Gy). The median dose of the second course of WBRT was 27.5 (range, 12~30 Gy). The median dose of the second course of 3DCRT for lesion was 30 Gy (range, 25~30 Gy). The dose of the second course of SRS was 16 Gy in 1 fraction. The second course of WBRT was administered on radiographic disease progression with symptom in all patients. With median follow-up of 25 months, overall symptom resolution rates were 47.8%. Rate of palliative efficacy was 82.6% including stable disease. The median survival time after initiation of reirradiation was 3.2 months. Median value of KPS prior to reirradiation was 30. Median value of KPS after reirradiation was 60. Reirradiation of brain metastasis maybe feasible and effective in select patients with a good performance status  $KPS \geq 60$  (: ECOG 0~2) prior to reirradiation.

**Key Words:** Brain metastasis, Reirradiation, Performance status, KPS

### Introduction

Metastatic brain tumor occurs ten times more than the primary brain tumors. This happens to 24~45% of all cancer patients.<sup>1)</sup> As life expectancy of cancer patients has increased along with development of chemotherapy, surgery and radiotherapy for treatment of Lung cancer and Breast cancer, the incidence of brain metastases have been increased.<sup>2,3)</sup> In the case of lung cancer or breast cancer which cancer spreads to the brain often, when there are brain metastases with symptoms, the status of patients became terminal. Those patients should be considered for appropriate treatment of radiation therapy or surgery.<sup>4)</sup>

As life expectancy of cancer patients has increased with development of chemotherapy, surgery and radiotherapy the chance of treatment for metastatic brain tumor has increased as well. Those patients with neurologic symptom such as headache, visual disturbance, ataxia could be identified with brain CT or brain MRI. Lung cancer or breast cancer has high propensity to spread to the brain. A proper radiotherapy of brain metastases can be a benefit to survival in some patient with palliation of symptoms.<sup>5)</sup>

The patient with brain metastases undergo palliative radiotherapy. Of these patients disease progression with neurologic symptom can be included in a second course of irradiation. Reirradiation of brain lesion could be controversy because of treatment related side effects and palliative efficacy<sup>6-10)</sup>.

We analyzed the outcome of reirradiation for cranial metastases patients at our institution to assess appropriate selection of patient with favorable factor.

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## Materials and Methods

### 1. Patients

This retrospective study included twenty-three patients with brain metastases underwent reirradiation between June 2008 and December 2012. Inclusion criteria were patients with pathologically proven breast cancer and lung cancer who were initially treated measurable metastatic brain lesion with neurologic symptom. The most common primary disease site was lung (11 patients with non-small-cell lung cancer, 4 with small-cell lung cancer), followed by breast (8 patients). None of the patients received surgical resection for brain lesion. Survival time was defined as time from the start of reirradiation to the date of death using the Kaplan-Meier method. Statistical analysis was carried out using the log-rank test to test whether there was a difference between the survival times of different group of patients and treatment factors. Extracranial disease status was determined by official radiologic images. Patients' characteristics are listed in Table 1.

### 2. Treatment

Treatment is listed in Table 2. Three radiotherapy technique for brain metastases were whole brain radiotherapy (WBRT),

three dimensional conformal radiotherapy (3DCRT) of partial brain radiotherapy and stereotactic radiosurgery (SRS). The median dose of the first course of WBRT was 30 Gy in 3 Gy per fraction (range, 23.4~30 Gy). The dose of the first course of partial brain RT for lesion was 30 Gy in 3 Gy per fraction. The median dose of the first course of SRS was 16 Gy in 1 fraction (range, 12~24 Gy). The median dose of the second course of WBRT was 27.5 (range, 12~30 Gy). The median dose of the second course of 3DCRT for lesion was 30 Gy (range, 25~30 Gy). The dose of the second course of SRS was 16 Gy in 1 fraction (Table 2).

### 3. Palliative treatment efficacy

Response criteria were defined as follows: relief of symptoms, stable status, aggravation of symptoms. Using the medical records, Karnofsky performance status (KPS) at time prior to reirradiation and KPS after reirradiation were obtained.

## Results

The most common technique of RT was whole brain radiotherapy (WBRT) as a initial course followed by 3-dimensional conformal radiotherapy (3DCRT) as reirradiation 8 (34.8%) of 23 patients. Among the patients who underwent WBRT, three patient received WBRT as reirradiation. The mean time inter-

Table 1. Clinical characteristics of patients.

| Parameter                    | No. of patient (n=23) |
|------------------------------|-----------------------|
| Gender                       |                       |
| Male                         | 7                     |
| Female                       | 16                    |
| Age (years)                  |                       |
| Median (range)               | 54 (43~67)            |
| Primary tumor                |                       |
| Breast                       | 8                     |
| Lung                         |                       |
| NSCLC                        | 11                    |
| SCLC                         | 4                     |
| KPS before the reirradiation |                       |
| 100~70                       | 4                     |
| 60~40                        | 7                     |
| <30                          | 12                    |
| RPA classification           |                       |
| I                            | 3                     |
| II                           | 1                     |
| III                          | 19                    |

Table 2. Radiation therapy details and number of patients.

| 1 <sup>st</sup> course of RT | Reirradiation | No. of patients |
|------------------------------|---------------|-----------------|
| WBRT                         | 3D CRT        | 8               |
|                              | WBRT          | 3               |
|                              | SRS           | 2               |
| 3D CRT                       | 3D CRT        | 2               |
|                              | WBRT          | 2               |
| SRS                          | WBRT          | 4               |
|                              | 3D CRT        | 2               |

Table 3. Palliative efficacy of treatment.

| Response                | No. of patient |
|-------------------------|----------------|
| Relief of symptoms      | 11 (47.8%)     |
| Stable (maintaining)    | 8 (34.8%)      |
| Aggravation of symptoms | 4 (17.4%)      |

val between the two courses of brain RT was 13.6 months (median, 11.1; range, 1~38).

The palliative efficacy of symptoms are listed in Table 3. Of 23 total patients, 11 (47.8%) patients experienced more than partial resolution of symptoms. 8 patients did not experience any symptom improvement. 4 (17.3%) patients had symptom aggravation.

The performance status was compared before and after reirradiation. At the time prior to brain reirradiation, the mean KPS was 42.2 (median, 30). The mean KPS after irradiation was 52.7 (median, 60). At the 3-month follow-up, 8 patients were deceased with disease progression, and the mean KPS before reirradiation was 32.5 (median, 30) (Fig. 3). Two patients died of progressive primary disease during the course of reirradiation.

The median overall survival after the reirradiation of brain metastases was 3.2 months (Fig. 1). The median overall survival for RPA class I patient (3 of 23) was 16 months, compared with 25 months for RPA class II (1 of 23) and 3 months for RPA class III (19 of 23). There was statistically significant correlation between survival and KPS value (Fig. 2). The median overall survival for patient good performance status (KPS  $\geq 60$ ) was 16 months, compared with 3 months for patient with KPS under 60 ( $p=0.015$ ).

Acute and chronic toxicity were assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE, version 4.0). No patients experienced radiation necrosis after second course of brain RT.

One (4.3%) patient experienced treatment related Grade 3

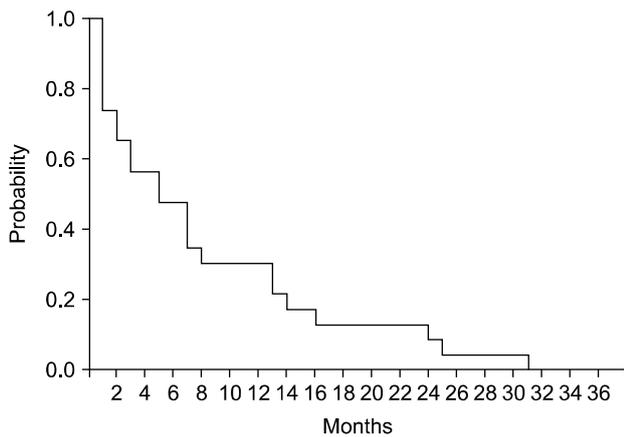


Fig. 1. Overall survival after reirradiation. Median overall survival was 3.2 months.

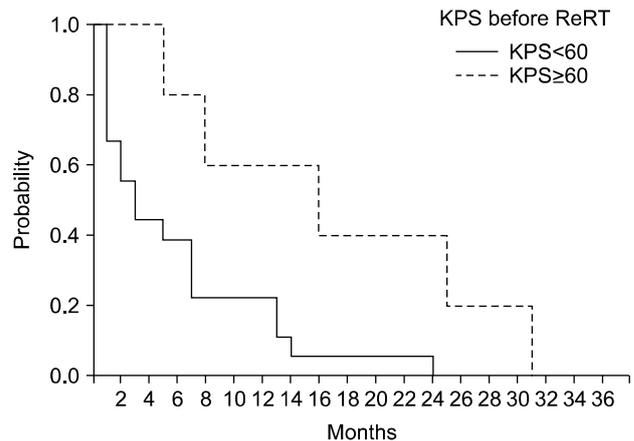


Fig. 2. Overall survival after reirradiation by KPS. Median overall survival for patients with KPS  $\geq 60$  were 16 months, and 3 months for patient with KPS  $< 60$ .

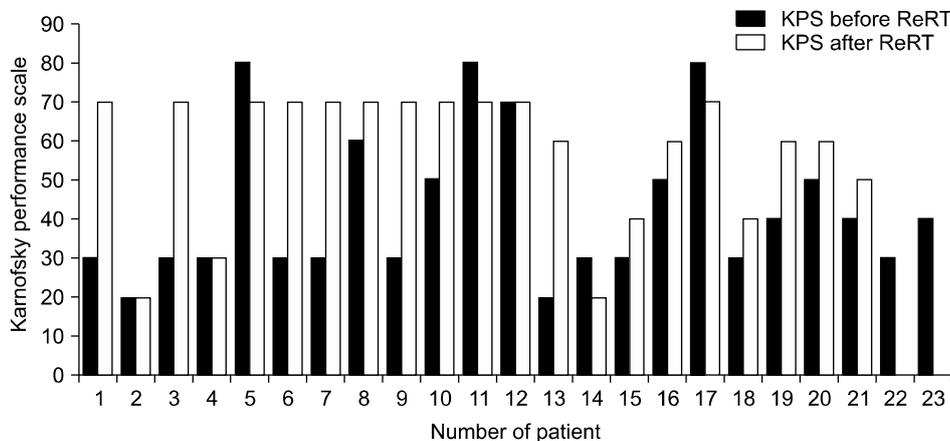


Fig. 3. Comparisons of Karnofsky performance status (KPS) for each ReRT patients.

headache.

## Discussion

Secondary radiation therapy for brain metastases is a challenging management because of concerns regarding reirradiation include toxicities, limited symptom palliation efficacy that affects quality of life.<sup>11)</sup> The treatment of patients who experience subsequent brain metastases progression can include a second course of brain irradiation, although there is controversy surrounding its safety and efficacy. There are different reirradiation options with regard to the initial course of brain irradiation technique. There are several publications evaluating the effect of reirradiation. Most studies have concluded that reirradiation is effective intervention, with tolerable side effects.<sup>12-18)</sup> Son et al.<sup>12)</sup> examined the outcomes in patients at Massachusetts General Hospital who underwent repeat whole brain radiation therapy (WBRT) as a reirradiation treatment option. The median dose for the first course of WBRT was 35 Gy (range, 28~40 Gy), with a fraction size of 2 to 3 Gy (median, 2.5 Gy). The median dose at reirradiation was 21.6 Gy (range, 14~30 Gy), with a fraction size of 1.5 to 2 Gy (median, 1.8 Gy). The median overall survival after the second course of WBRT was 5.2 months. The median overall survival of patients with stable extracranial disease at the time of reirradiation was 19.8 months compared with 2.5 months for those with progressive extracranial disease ( $p=0.05$ ). Sadikov et al.<sup>19)</sup> presented the time interval between two radiation course ( $\leq 6$  months vs. 6~11.9 months vs.  $\geq 12$  months) did not show any significant differences in survival. The protocol of our institution is to limit the process of brain reirradiation for patients who have at least a 6 month time interval from the completion of the first treatment except a few cases with worsening symptomatic brain metastasis after initial course of RT. This practice is a result of concern for increased risk of neurological toxicities caused by the short time intervals between two consecutive radiation treatments. In our study, one (4.3%) patient had treatment related grade 3 adverse events. The patient underwent two courses of 3D conformal radiotherapy for partial brain metastasis. Dose for the first course of RT was 30 Gy with a fraction size of 3 Gy, followed by reirradiation course of 25 Gy with a fraction size of 2.5 Gy.

The patient developed grade 3 headache. The cumulative biological equivalent doses (BED) of the patient were 105.8 ( $\alpha/\beta=3$  Gy) and 70.2 Gy ( $\alpha/\beta=10$  Gy). The time interval of two courses was 4 months.

In case of whole brain radiation therapy (WBRT) for purpose of palliation, there is controversy about its safety. Emami et al.<sup>20)</sup> reported normal organ tissue tolerance doses in various organs and tissues. These data were applied to a partial dose-volume model, and the TD 5/5 (total radiation dose that can induce 5% of complication within 5 years) of whole brain, 2/3 of brain, and 1/3 of brain were reported as 4,500 cGy, 5,000 cGy, and 6,000 cGy, respectively. More recently, the Quantitative Analysis of Normal Tissue Effects in the Clinic review<sup>21)</sup> refined the normal tissue dose volume tolerance guidelines for the brain of modern era radiotherapy. In our study, three patients who underwent repeated whole brain radiotherapy did not tend to have worse survival outcomes or treatment related side effects than other group of treatment options. The patients had more significant disease burden prior to reirradiation. This result of toxicity could be attributed to the fact that patients with limited follow up time because that the patients might be deceased before late toxicity develops. However, Son et al.<sup>12)</sup> reported 17 patients who received a repeat course of WBRT with no Grade 3 toxicities. Mayer et al.<sup>11)</sup> presented that radiation-induced normal brain tissue necrosis is found to occur at  $NTD_{cumulative} > 100$  Gy. There were no association between the time interval between the initial and reirradiation course and the incidence of radionecrosis.

Prior studies have analyzed correlations between brain reirradiation and historically favorable prognostic factors, including performance status ( $KPS > 70$ ), absence of extracranial disease, and age. Sadikov et al.<sup>19)</sup> found that Eastern Cooperative Oncology Group (ECOG) performance status and Radiation Therapy Oncology Group neurologic function class were also significant prognostic factors. The ECOG performance status before re-irradiation was a strong prognostic factor for survival of patients with brain metastases. Patients with ECOG performance status 0~1 showed better survival outcome (median 6.4 months) than patients with ECOG performance status 2~3 (2.0 months) ( $p < 0.0001$ ). Wong et al.<sup>5)</sup> analyzed eighty-six patients in which performance status ECOG 2 in 47% of patients and ECOG 3 in 44% of patients. Of all patients the per-

formance status of 30 patients (35%) improved after re-irradiation and remained unchanged in 42 patients (49%). Various potential prognostic factors were evaluated for associations with survival. There were two statistically correlational prognostic factors for survival were identified: absence of extracranial metastasis and solitary brain lesion. There were no association between the performance status and survival. We analyzed Karnofsky performance status (KPS) at time prior to reirradiation and KPS after reirradiation on the base of medical record retrospectively. In our study, the mean KPS of patients with brain metastases was 42.2 (median, 30) at the time prior to brain reirradiation. The mean KPS after reirradiation was 52.7 (median, 60). Table 3 lists the evaluation of response assessed after reirradiation. Brain reirradiation was beneficial in symptom palliation. More than partial relief rates of symptom including complete relief was 11 (47.8) of 23 patients. The patients with stable status of symptom were 8 (34.7%) of 23. Of all patients 4 (17.4%) experienced aggravation of symptoms. These patients were RPA class III and had primary disease progressive status. Time interval between two courses of irradiation was not factor of palliative efficacy. We analyzed association of segmented KPS with survival of patients (Fig. 3). There was statistically significant correlation between survival and KPS value of 60 (Fig. 2). The median overall survival for patient good performance status ( $KPS \geq 60$ ; ECOG 0~2) was 16 months, compared with 3 months for patient with KPS under 60 ( $p=0.015$ ). In comparison with previous studies, patient population of our study was not quite favorable performance status, with a median initial KPS of 30 and majority of lung cancer patient number than breast cancer. We found that there was a trend for better survival for patients with primary breast cancer and with stable extracranial disease.

### Conclusion

Within the limitations of a retrospective review, we found clinical benefit to reirradiation in 82.6% of patients including maintained symptom, and a median survival of 3.2 months in patients who have progressed or relapsed after an initial course of radiation therapy for brain metastases.

This study demonstrated that it may be most useful in patients with a good performance status  $KPS \geq 60$  (: ECOG 0~

2) prior to reirradiation and with stable extracranial disease. In our study, even patients with poor prognostic factors experienced the palliation efficacy of reirradiation.

In conclusion, brain reirradiation could be appropriate in symptom palliation efficacy with tolerable toxicity.

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## 방사선 재치료를 시행한 뇌전이환자의 결과 분석

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유제상 · 최지훈 · 마선영 · 정태식

방사선 재치료를 받은 뇌전이 환자를 대상으로 치료결과와 결과에 영향을 미치는 인자를 알아보려고 하였다. 2008년 6월부터 2012년 12월까지 완화목적의 뇌 방사선치료를 받은 후 방사선 재치료를 받은 23명의 환자의 결과를 분석하였다. 첫 번째 전뇌 방사선치료 선량의 중앙값은 30 Gy (23.4~30 Gy) 이었다. 삼차원입체치료의 선량은 하루에 3 Gy로 총 30 Gy를 분할조사하였다. 정위적 방사선수술의 선량은 16 Gy를 1회 조사하였다. 방사선 재치료에서 전뇌 방사선치료, 삼차원 입체조형 치료의 중앙값은 각각 27.5 Gy와 30 Gy 이었다. 정위적 방사선수술의 재치료 선량은 16 Gy를 1회 조사하였다. 완화목적의 뇌 방사선치료 이후 뇌전지로 인한 증상 악화를 동반하고 영상학적으로 병변 진행이 확인되는 환자에서 방사선 재치료를 시행하였다. 경과 관찰기간의 중앙값은 25개월 이었다. 증상 관해율은 47.8%였고, 증상 완화의 효과 비율은 증상 유지 환자를 포함하여 82.6% 이었다. 재치료 후 생존기간의 중앙값은 3.2개월이었다. 방사선 재치료 이후의 중앙값은 60으로 재치료 이전의 KPS 중앙값 30에 비해 향상되었다. 뇌전이 환자에서 방사선 재치료의 증상 완화 효과는 치료이전 KPS값이 60이상( ECOG 0~2)의 전신수행상태가 좋은 환자에서 적합한 것으로 결과를 나타내었다.

중심단어: 뇌전이, 방사선 재치료, KPS