How soon will the patient with metastasis return for radiosurgery?

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Object. Stereotactic radiosurgery for brain metastasis has become one of the standard treatment options in recent years. Some patients must undergo repeated stereotactic radiosurgery for new lesions. The authors retrospectively reviewed their data to estimate how soon the patients undergo repeated radiosurgery for new lesions.

Methods. Between October 1999 and March 2006, 1081 patients with brain metastases underwent Gamma Knife surgery (GKS) at Tokyo Women’s Medical University. One hundred and forty-nine patients in whom GKS had been performed two or more times were evaluated. There were 68 men and 81 women with a median age of 61 years (range 29–90 years). The authors analyzed data on patient age, number of treated lesions, and period between GKSs. Follow-up imaging was performed in almost all patients every 2 to 3 months after GKS.

The number of lesions treated in a single session varied from one to 35. The median interval between GKSs was 26 weeks (range 3–175 weeks) for patients with breast cancer and 23 weeks (range 4–179 weeks) for patients with non–small cell lung carcinoma.

Conclusions. It would appear that follow-up imaging studies should be obtained every 2 to 3 months after GKS to monitor patients for tumor recurrence.

KEY WORDS • brain metastasis • Gamma Knife surgery • follow-up interval • breast cancer • non–small cell lung carcinoma • repeated radiosurgery

Brain metastases occur in 20 to 40% of adults with cancer and are most common in patients with cancer of the lung and breast.1,2,4,6 Whole-brain radiotherapy is the treatment of choice for most patients with brain metastases; however, radiosurgery for the treatment of brain metastases has increased in popularity. Radiosurgery is especially useful in patients with a single lesion who are unable to tolerate surgery and in those who harbor surgically inaccessible lesions. In patients with a single brain metastasis, surgery and stereotactic radiosurgery provide comparable survival rates, although retrospective review data suggest that stereotactic radiosurgery may be associated with lower rates of local recurrence.1,4,6 Improvements in systemic care may also lead to longer patient survival. Because the recurrence rates of brain metastases are associated with survival period, some patients may undergo repeated radiosurgery more often.1,4 Repeated radiosurgery is performed in patients for new intracranial metastases, with the intent to avoid or delay whole-brain radiotherapy for as long as possible.

We retrospectively analyzed data in patients who had undergone repeated GKS. We focused on how often and how soon after initial GKS these patients underwent repeated GKS.

Clinical Material and Methods

Patient Characteristics

One thousand and eighty-one patients with brain metastases underwent GKS between October 1999 and March 2006 at Tokyo Women’s Medical University. We reviewed data from this entire series and evaluated patients with metastases from breast cancer or NSCLC.

Thirty-one (21.5%) of 144 patients with breast cancer and 118 (17.2%) of 686 patients with NSCLC underwent GKS two or more times during the period. All patients with breast cancer were women. Of the patients with NSCLC, 49 were women and 66 were men. The mean patient age was 56 years (range 29–74 years) for those with breast cancer and 61 years (range 29–90 years) for those with NSCLC. The median total tumor volume was 1.9 cm³ (range 0.13–13.6 cm³) and 2.5 cm³ (range 0.1–17.4 cm³), respectively. Patient characteristics by groups are displayed in Table 1.

Radiosurgical Technique

All patients underwent treatment with a Leksell Gamma Knife unit (model B or C; Elekta Instruments AB, Stockholm, Sweden). All GKS procedures were performed...
subsequent to obtaining stereotactic MR images. Sagittal high-resolution Gd-enhanced T1-weighted MR images were obtained first to localize the area of interest. To define the target volume, multiplanar volume acquisition contrast-enhanced MR imaging was performed to cover the entire lesion and the surrounding critical structures. These images were exported to a high-speed computer workstation for radiosurgery planning. Axial data were reconstructed into coronal and sagittal images by using GammaPlan software (Elekta Instruments AB). After finalizing the plan, a maximal dose to the tumor margin was determined. Gamma Knife surgery was performed by positioning the targets serially at the x, y, and z coordinates of each isocenter. The stereotactic frame was removed immediately afterward, and the patients were discharged within 24 hours.

Follow-Up Data

After GKS, patient follow-up data were obtained during evaluations at Tokyo Women’s Medical University. Follow-up contrast-enhanced MR imaging was scheduled every 1 to 3 months. We counted the number of days between the initial and subsequent treatment as the primary GKS interval time. From the time of the second GKS, we defined the term as a repeated GKS interval time.

Statistical Analysis

Univariate analysis of the correlation between interval time and treatment factors, patient age, number of tumors, total tumor volume, SIR, and RPA was performed using the Spearman rank correlation. The Mann–Whitney U-test was used to analyze the relationship between interval time and single or multiple (> two lesions) metastases.

Results

Time Interval Between the First and Second GKS

Overall treatment rate of repeated GKS is shown in Fig. 1. The peak time for repeated GKS is 6 to 8 months in the breast cancer group and 4 to 6 months in the NSCLC group. Approximately 10% of patients with breast cancer and 5% of patients with NSCLC were retreated after 2 months. Half of repeated GKSs were performed after 6 months and two thirds were performed after 8 months. Approximately 20% of all the patients underwent repeated GKS more than 12 months after their initial treatment.

The time interval for primary GKS compared with repeated GKS in both breast cancer and NSCLC groups is shown in Fig. 2. There was no significant difference in the treatment interval for repeated GKS in NSCLC group; however, 50% of the breast cancer group underwent repeated GKS after 6 months and 80% were retreated after 12 months.

Factors Correlated With Time Interval of Another GKS

We analyzed factors that might correlate with the time interval between GKSs. In the breast cancer group, there was no significant correlation between time interval and the following factors: patient age, number of lesions, total tumor volume, SIR, and RPA (Table 2). There was a corre-
A different brain location. Mindermann\textsuperscript{12} reported that the brain metastases underwent repeated GKS for a tumor in long-term survival in whom GKS had been performed for approximately 48% of their patients with metastatic disease. Kondziolka, et al.,\textsuperscript{10} also reported that approximately 30 to 40%.\textsuperscript{2} brain metastases after stereotactic radiosurgery is approximately 30 weeks in both single and multiple lesion groups. In the NSCLC group, the time interval for patients harboring a single lesion was significantly longer than for those with multiple lesions (p = 0.0036).

### Analysis of Time Interval for Another GKS in Single Compared with Multiple Metastases

Analysis of the time interval when comparing patients with a single metastasis and multiple (≥ two) lesions is shown in Table 3. In the breast cancer group, the mean time interval was approximately 30 weeks in both single and multiple lesion groups. In the NSCLC group, the time interval for patients harboring a single lesion was significantly longer than for those with multiple lesions (p = 0.0036).

### Discussion

Improvement in systemic disease management of cancer has achieved long survival times for patients with cancer. Mindermann\textsuperscript{12} suggested that the recurrence rates of brain metastases are associated with the survival period of patients. Survival rates depend on control of the primary tumor, and patients who live long enough to experience recurrent brain metastases will perforce undergo repeated GKS.

### Recurrence Rate After GKS

It has been reported that the overall recurrence rate of brain metastases after stereotactic radiosurgery is approximately 30 to 40%.\textsuperscript{2,11,13} Detterbeck and Molina\textsuperscript{6} reported that approximately 25% of their patients with Stage IV NSCLC suffered brain metastases as well as other incidences of metastatic disease. Kondziolka, et al.,\textsuperscript{10} also reported that approximately 48% of their patients with long-term survival in whom GKS had been performed for brain metastases underwent repeated GKS for a tumor in a different brain location. Minderman\textsuperscript{12} reported that the tumor recurrence rate of brain metastases after GKS was 67% for malignant melanomas, 18% for breast cancer, and 19% for lung cancer. In our study, the recurrence rate was 21.5% in patients with breast cancer and 17.2% in those with NSCLC. Patients with malignant melanoma are rare in Japan because of regional characteristics. Therefore, the recurrence rate of brain metastases in our study might be lower than that in reports from other countries.

Kihlstrom, et al.,\textsuperscript{9} reported that the percentage of new distant metastases was 13% in patients treated for a single metastasis, 34% in those treated for two or three metastases, and 100% in patients treated for four to five metastases following GKS. Patients in the NSCLC group in our study who underwent repeated GKS for a single metastasis had a significantly longer interval to the repeated GKS than those with multiple lesions. These results suggest that a single brain metastasis from NSCLC has a longer interval to recurrence.

It is interesting that the treatment interval between the second GKS and the subsequent one was shorter than the initial interval time in the breast cancer group (Fig 2A). There was no patient with breast cancer who underwent GKS a third time 1 year after previous GKS; this was not true for the NSCLC group. It may be that in patients with brain metastases from breast cancer, tumor recurrence progresses more rapidly.

### Time Interval to Follow-Up Imaging

It is common for follow-up imaging studies to be scheduled at least every 3 months after GKS, and some institutes schedule them earlier and more frequently.\textsuperscript{2,4,8,13,17,18} Guidelines of National Comprehensive Cancer Network also stipulate that patients should undergo MR imaging every 3 months for 1 year and when clinically indicated thereafter.\textsuperscript{1} We believe patients should undergo follow-up MR imaging in the first 2 to 3 months after GKS to allow monitoring for early tumor recurrence. Based on our rate of repeat treatment, approximately 10% of repeated GKSs have been performed in the first 2 months following the more recent GKS.

### Conclusions

Based on our data, we believe patients should undergo follow-up MR imaging within 2 to 3 months after GKS to monitor early tumor recurrence or new metastasis. We also recommend follow-up imaging at least every 2 to 3 months in the 1st year after GKS. This study reveals that the patients who have recurrent brain metastases often return for retreatment within a few months.

### References


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