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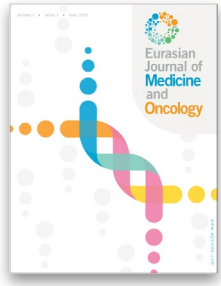


Research Article

# Multi-Session Radiosurgery for Numerous Small Brain Metastases

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## Abstract

**Objectives:** Treatment of multiple brain metastases more than 10 is challenging. Whole brain radiotherapy (WBRT) is generally believed to be the first treatment choice. In order to escape from mental deterioration after WBRT, we have performed Gamma Knife stereotactic radiosurgery (GKS) for numerous small brain metastases.

**Methods:** Twelve cases of numerous (more than 30) brain metastases were treated by GKS. Mean total session number was 5.42 times, ranging 2 to 17. Each tumor was treated with the margin dose between 14 to 20 Gy. The tumor number treated in whole sessions was ranged from 31 to 144 (mean, 70.8).

**Results:** Almost all the irradiated tumors either disappeared or shrank at the patient's death or at the last follow-up, though new metastatic tumors were subsequently developed in some cases which required an additional treatment with GKS. At the last follow-up (3 to 51 months after GKS), nine cases were alive and well and three were dead. As adverse effects, two cases demonstrated seizures by radiation brain injury and another showed a gait disturbance. No apparent mental deterioration was observed during follow-up.

**Conclusion:** Radiosurgery for numerous small brain metastases may be preferable rather than WBRT.

**Keywords:** Brain, Gamma Knife, metastasis, multiple, stereotactic radiotherapy, stereotactic radiosurgery

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Among brain metastasis, numerous small lesions may develop occasionally, which requires some kinds of treatment procedures. When most of them are very tiny and not large in tumor size, whole brain radiotherapy (WBRT) has been currently considered as a first treatment choice. However, WBRT may often cause mental decline later and believed to be not always adequate, and not always effective. Since the effects of radiosurgery for brain metastases in limited number have been established,[1,2] this treatment method has a certain possibility to be utilized for the numerous small ones. A long treatment time is seemingly required for the radiosurgery against numerous tumors and here we have to discuss whether the successful results are obtainable or not with multi-session radiosurgery.

## Methods

This retrospective study was approved by the Ethical Committee Board of Ookuma Hospital (No. 14-1) and Shin-Yurigaoka General Hospital (No. 20211227-3). The need for patient consent was waived.

## Cases

Retrospectively, 12 cases of numerous (more than 30) brain metastases were treated by Gamma Knife (Elekta, Stockholm) stereotactic radiosurgery (GKS) during a period from July, 2016 to June, 2021 at Gamma Knife Center, Ookuma Hospital. Case characteristics of 12 cases are shown in Table 1. There are seven males and five females, with a mean

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**Table 1.** Characteristics of 12 cases of numerous brain metastasis treated with number-fractionated radiosurgery

| Factors | Contents |
|---|---|
| Sex | Male 7, Female 5 |
| Age | 36 - 73 (mean 63.4) yrs. |
| Primary cancer | Lung cancer 12 |
| Current treatments | Chemotherapy (8),<br>Immune checkpoint inhibitor (5)<br>Irradiation (2) |
| Activity of primary cancer radiosurgery | EGFR mutation (3), ALK mutation (3) |
| Neurological status at | No neurological deficit (10)<br>Minor neurological signs (2)<br>Major neurological deficit (0) |
| Reason to choose radiosurgery | Refusal of WBRT (12/12) |
| Mental condition (MMSE) | No trouble (12) |

Characteristics of the cases with numerous brain metastasis are demonstrated. All of them are non-small cell lung cancer. The main reason to select this treatment methods is refusal of whole brain radiation therapy (WBRT) because of probable mental decline. LCNEC: large cell neuroendocrine carcinoma; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; MMSE: mini-mental state examination.

age of 63.4 years, and histologically all of them were lung cancer including 11 cases of adenocarcinoma and a case of large cell neuroendocrine carcinoma (LCNEC). The main reasons for choosing this treatment methods depend on the refusal of WBRT by the patients because of a fear of cognitive impairments. Among the cases, mutation of EGFR (epidermal growth factor receptor) was found in three and ALK (anaplastic lymphoma kinase) in other three patients.

## GKS and Follow-up

Multi-session radiosurgery for numerous small brain metastases was planned and managed to treat them consecutively one by one. With a long irradiation time, 5-10 tumors were treated in each session. The treatment was repeated daily, either with fixed rigid head frame or Extend System (Elekta, Stockholm) of Gamma Knife by mouth-piece head fixation. After taking computed tomography (CT) scan, co-registration of CT images with Gd (gadolinium)-enhanced magnetic resonance imaging (MRI) is carried out. After careful dose planning, tiny tumors were irradiated with GKS among continuing several treatment sessions. For treating multiple brain metastases by GKS, it takes approximately 10 minutes to accomplish irradiation for each small metastatic focus. Currently, Extend System with mouth-piece fixation are used and repeated the treatment every day until the whole metastatic foci are totally covered. After the treatment, follow-up MRI studies are carried out every 3 months, and subsequent GKS are performed at the time once new metastatic foci are found. Hasegawa's Test, and Mini-Mental State Examination (MMSE)[3] for checking possible dementia or mental decline are carried out at the same time. Meanwhile, treatments for primary cancer and other metastatic foci were performed concurrently by each specialist.

The treatment summary of the cases is shown in Table 2, including total session number ranging 2 to 17 with a mean of 5.42 times, in which some were treated consecutively for 2-3 days, or with staged treatment with certain intervals, or daily irradiation with mouth-piece fixation. Thus, the total treatment time required between 204 to 1287 minutes

**Table 2.** Treatment results of number fractionation

| Case No | Sex Age | Primary Tumor | Session No | Total Treat Time. | No.of Total shots | Margin Dose (Gy) | Total Spillage (Gy) | Total Energy (J) | Lesion No (PTV) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F 68 | Ad | 3 | 475.9 | 57 | 16-22 | 2.7 | 9.8 | 57 (14.9) |
| 2 | M 36 | Ad | 4 | 776.9 | 133 | 16-20 | 5.7 | 19.05 | 118 (12.3) |
| 3 | M 64 | LCNEC | 2 | 453.8 | 59 | 15-17 | 2.7 | 10.7 | 56 (6.3) |
| 4 | F 59 | Ad | 3 | 426.4 | 70 | 18-20 | 3.3 | 10.73 | 60 (7.2) |
| 5 | M 71 | Ad | 2 | 204.2 | 31 | 18 | 1.3 | 4.9 | 31 (2.8) |
| 6 | F 71 | Ad | 9 | 504.4 | 54 | 14-17 | 2.9 | 9.21 | 54 (3.6) |
| 7 | M 73 | Ad | 2 | 459.6 | 58 | 16-18 | 2.6 | 10.5 | 48 (12.7) |
| 8 | M 66 | Ad | 2 | 457.9 | 68 | 15-17 | 2.7 | 10.5 | 49 (11.0) |
| 9 | M 73 | Ad | 3 | 679.8 | 130 | 15-16 | 8.4 | 20.9 | 125 (19.4) |
| 10 | F 67 | Ad | 17 | 1287.0 | 144 | 15-16 | 7.3 | 24.64 | 144 (6.4) |
| 11 | M 46 | Ad | 3 | 311.9 | 37 | 16-20 | 1.9 | 6.56 | 37 (1.64) |
| 12 | F 70 | Ad | 5 | 924.2 | 75 | 16-22 | 3.5 | 11.76 | 70 (16.7) |
| mean | 63.4 yrs. | Ad 11, LCNEC 1 | 5.42 | 580.1 min. | 76.3 | range 14-22 | 3.4 | 11.7 | 70.8 (9.6 ml) |

Twelve cases of numerous brain metastasis were treated with number fractionation method. Several sessions are required to accomplish radio surgery to all the tumors. In average, 580 minutes are required for treating 70.8 tumors, resulting in 3.4 Gy of spillage and 11.7 J (joule) of mean total energy; M: male; F: female; Ad: lung adenocarcinoma; LCNEC: large cell neuroendocrine carcinoma; Spillage: irradiation to the entire skull (Gy); PTV: planning target volume (ml).

with a mean of 580 minutes. Each tumor was treated with the marginal dose between 14 to 22 Gy and the spillage over the entire brain was 3.4 Gy (mean) ranging 1.3 to 8.4 Gy. Likewise, the total energy delivered to the brain was 11.7 J (joule) in mean. The total tumor number treated in whole sessions ranged from 31 to 144 (mean, 70.8). One of the illustrated cases is shown with 3D imaging (Fig. 1), in which 54 lesions are treated with nine GKS sessions. At the radiosurgery, status of primary cancer was stable and the patients had no serious neurological deficits.

## Results

With GKS, almost all the irradiated tumors either disappeared or shrank at the patient's death or at the last follow-up. However, new metastatic tumors were subsequently developed in some cases which required an additional treatment with radiosurgery. No apparent recurrence of treated tumor was confirmed. At the last follow-up (3 to 51 months after GKS), nine cases are alive and well and three were dead. Survival length after the first radiosurgery was 29 months for alive patients. Three patients were dead with a mean of 14.7 months after the 1st radiosurgery. As adverse effects, two cases demonstrated seizures by radiation injury and another showed ataxic gait disturbance with unknown cause (Table 3). No apparent mental deterioration was observed during the follow-up period. A generalized alopecia was seen in a case who had treatment of 144 lesions with 17 sessions. The total spillage was 8.4 Gy, exceeding 6 Gy for scalp, but much less than the standard dose of WBRT (Fig. 2).

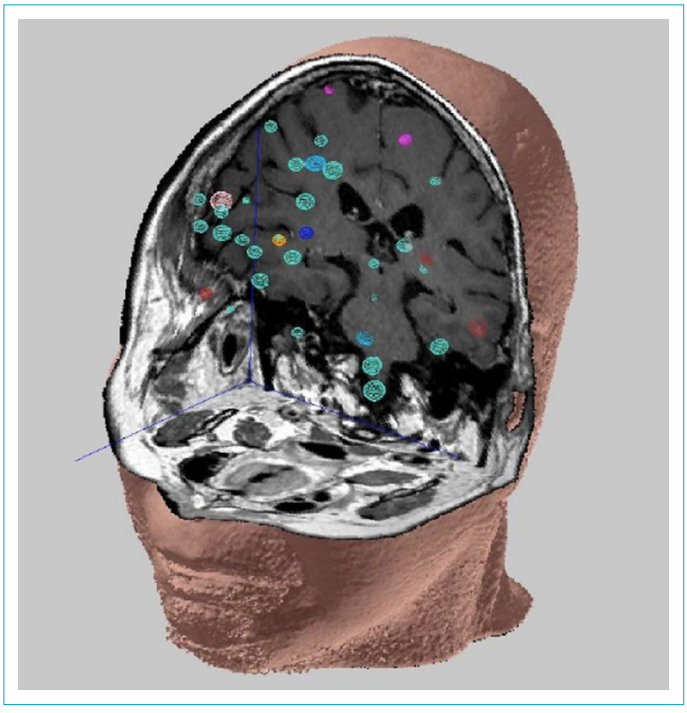

**Figure 1.** Whole metastatic tumors treated with multi-session Gamma Knife stereotactic radiosurgery (GKS).

An example of multi-session GKS of numerous small tumors is shown. Each color dots mean the tumors treated with different sessions and tumor size. For this particular patient, 54 small tumors are treated with 9 sessions, which require 504.4 minutes in total and 2.9Gy of total spillage and 9.2 joule of total energy respectively.

### Illustrative Case

A 37-year-old gentleman, suffering from lung cancer.

Although no neurological deficits were found, his MRI revealed 6 small metastases and treated with 1st radiosurgery, 20 Gy at margins. Two months later 29 new lesions, another 6 months later 50 lesions, and then 12 months later 33 lesions were treated with 16 Gy at the margin respectively (Fig. 3).

Two lesions in bilateral frontal lobe showed a radiation injury during the course causing seizure once. He underwent radiosurgery for 118 lesions in total, with 5.7 Gy of spillage and 19.05 J of total energy. He has fully recovered without any neurological deficits and returned to his daily works. Already 4 years passed after the first and 2 years after the last GKS. MRI and 3D images of the all lesions treated with radiosurgery were shown in the figure (Fig. 3). Both Mini-mental and Hasegawa's Tests scored full marks at the last follow up. Dose rates of Gamm Knife during these periods were between 2.9 to 2.3 Gy/min.

## Discussion

Recently, lots of new efforts[4-7] have been made for the treatment of multiple brain metastases. For larger tumors, surgical resection seems to be desirable, but not for multiple ones. Couples of treatment methods including radiation, surgery and chemotherapy, or conservative palliative treatment have been proposed in the literature.[8]

Current treatments for numerous small brain metastases have been considered to be WBRT. Since, cognitive decline may develop often after WBRT and is the serious problem for the patients. Therefore, WBRT is considered to be not ideal nor the best treatment. Currently, successful tumor controls of brain metastases with radiosurgery have been reported by several investigators, especially for the cases bearing less than 5 metastatic foci. Recently more than 5 metastases were also treated with GKS, indicating less inferior results with less than 4 metastases.[9] There is a big discussion how many metastatic brain tumors can be treated by radiosurgery and whether the number of the tumors matter.[10,11] By using co-registration technique with GammaPlan (Elekta, Stockholm), Gamma Knife planning workstation, it is possible to discriminate the treated ones from

**Table 3.** Follow-up results after number fractionation

| Case No | Neurological Status at Last FU | Tumor Control | Last FU (mos. after 1st GK) | Adverse Effects |
|---|---|---|---|---|
| 1 | NP | CR, New T | 51 mos. Alive & well | None |
| 2 | NP | CR, RN(2) | 46 mos. Alive & well | Seizure |
| 3 | NP | NC, New T | 38 mos. Dead | Seizure |
| 4 | NP | CR | 43 mos. Alive & well | None |
| 5 | NP | CR/PR | 38 mos. Alive & well | None |
| 6 | NP | MR | 37 mos. Alive & well | None |
| 7 | Gait disturbance | CR/PR | 9 mos. Alive & well | None |
| 8 | Gait disturbance | CR/PR | 3 mos. Dead | Ataxia |
| 9 | Conscious disturbance | MR | 3 mos. Dead | None |
| 10 | NP | NC | 6 mos. Alive & well | None |
| 11 | NP | CR/NC | 11 mos. Alive & well | None |
| 12 | NP | CR/NC | 20 mos. Alive & well | None |
| Mean | NP: 8, Gait dist.: 2, Seizure: 1 | CR/PR: 8, MR: 2, NC: 2 | Alive 9, Dead 3 | None 9, Seizure 2, Ataxia 1 |

After the fractionation, the patients were neurologically stable and each tumor controls were excellent. After the fractionation, three patients were dead because of seizure in one and by worsening of primary cancer in two. The mean survival period of the alive patients is 29 months after the first session of Gamma Knife treatment. Two cases developed seizure by radiation injury. NP: nothing particular; CR: complete remission (disappearance of tumor); PR: partial remission (more than 50% decrease in tumor diameter); MC: minor response (25-50% decrease in tumor diameter); NC: no change, New T: progression with new tumor; RN: radiation necrosis, FU: follow-up, mos.: months.

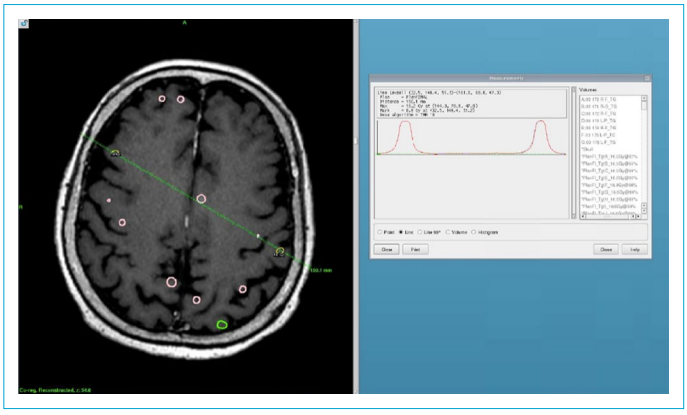

**Figure 2.** Dose distribution of the case showing alopecia.

Dose distribution on the green line was demonstrated. There are two tumors just on the line and the peak dose is 16 Gy. On the contrary, bilateral scalp doses were less than 0.5 Gy, however, alopecia appeared because of piled up 17 sessions and of the total spillage slightly over 6 (6.4) Gy.

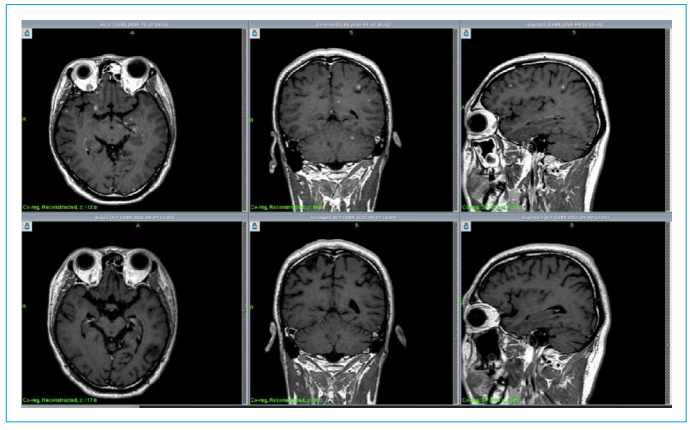

**Figure 3.** Illustrative case.

Numerous brain metastases were treated by radiosurgery as shown with the upper row. In total, 118 metastatic foci were treated with 4 sessions with the marginal doses between 16 to 20 Gy by 4 sessions. Although two lesions temporarily showed a radiation injury for certain period of time, but a complete remission is finally available as shown with the lower row, and he has just returned to his job. He always reveals a full mark for MMSE studies.

Upper row: At the first gamma knife treatment. Lower row: At the last follow-up.

the newly appeared lesions precisely. In our study, small numerous foci also tend to promptly respond to radiosurgery and disappear with the marginal doses between 15 to 20 Gy, which is lower than the standard marginal dose for medium-sized ones.[12] With the recent advances of chemotherapy, especially molecular targeted drugs are often effective for primary cancer, but also for brain lesions as well, since these drugs more easily penetrate blood-brain-barrier and blood-tumor-barrier.[13] Moreover, successful control of primary cancer may or might improve the overall survival and reduce the occurrence of further brain metastasis.

Among numerous brain metastases, most of them are very tiny in each tumor size and often not accompanying larger ones. They are very similar to the so-called brain metastases reported in the past.[14,15] As a result, these metastases rarely show severe neurological deficits at least in early stage

of brain metastasis. Numerous brain metastases which we have treated were very small in tumor size and almost always no neurological deficits. They readily achieved complete or partial tumor response, and a longer progression free survival are available. When the cases showed the recurrence, tumors were always small in size as original ones, and the mutation of EGFR or ALK may be involved for such unique metastasis. For primary lung cancers with positive mutation of EGFR, tyrosine kinase inhibitors (TKIs) work for the control of tumor growth.[16] Different from chemotherapeutic agents which cannot penetrate blood-brain-barrier (BBB), some TKIs can pass through the BBB and blood-tumor-barrier (BTB) and more positively works for the control of brain metastases.[17] Since the mental decline seems to be the big burden for the long survivors, indications for WBRT should be reconsidered.[17-19]

This time, multi-session treatment procedure applied only for the patients who dislike and refuse WBRT. Further prospective studies should be done and establish how to treat these numerous brain metastases.

In conclusion, even though a long treatment time is required for treating metastatic foci, the effects of radiosurgery for small brain metastases are constant and remarkable. Subsequent treatment is required only for newly appeared metastatic foci. These small numerous metastases have certain clinical specifics. First, tumors are so many, but in second not causing neurological symptoms at least in the early stage, and the last each tumor readily respond to radiosurgery. Recent progress of chemotherapy and immunotherapy are remarkable. Even the patients with numerous brain metastases may have a chance to be a long survivor, and therefore the mental deterioration with WBRT has to be escaped. In conclusion, paradigm shift to escape WBRT for numerous brain metastases should be searched for.

### Disclosures

**Ethics Committee Approval:** This retrospective study was approved by the Ethical Committee Board of Ookuma Hospital (No. 14-1) and Shin-Yurigaoka General Hospital (No. 20211227-3).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – Y.M., Y.K.; Design – Y.M.; Supervision – Y.K.; Materials – Y.Ma.; Data collection &/or processing – Y.K.; Analysis and/or interpretation – Y.M.; Literature search – Y.K.; Writing – Y.K.; Critical review – Y.M.

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