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〈脳腫瘍〉

The early effect of Gamma knife surgery for brain metastases

Seiji FUKUOKA, Yoshinobu SEO, Masami TAKANASHI, Jyoji NAKAGAWARA, Shuhei TAKAHASHI, Takehiko SASAKI, Jun-ichi NAKAMURA, Katsumi SUEMATSU*

*Department of Neurosurgery, Nakamura Memorial Hospital, Sapporo, Japan and *Hokkaido Brain Research Foundation , Sappro , Japan.*

Summary : One hundred and sixty lesions in 68 patients with brain metastases were treated with gamma knife. Thirty four patients had multiple metastases. The mean follow-up was 8.3 months (1 to 25 months). More than 50% reduction rate of tumors were observed 88% of all lesions in one month, 90% in final follow-up. Mean Karnofsky performance status score raised in values from 75% to 89% in one month after gamma knife surgery. Progressive neurological symptoms improved in 89 % of patients with symptoms within one week. Recurrences occurred in 4 %, and transient neurological deteriorations were observed in 7 % of all patients. No permanent deficits was recognized. The median survival was 10 months of all patients, while 9 months in single lesion and 13 months in multiple lesions respectively. There was no significant difference between these two groups (p=0.96). These data may indicate that gamma knife surgery has rapid effect for brain metastases and is effective for even multiple brain metastases.

Key words :
- gamma knife
- brain metastases
- radiosurgery
- SPECT

Introduction

Brain metastases are the most common malignant tumor of the brain. Untreated patients have a median survival of about 1 month (17). With the objective of improving local control of brain metastases, surgical removal of tumor may be useful in selected cases[4) 10) 19) 21) 22) 23)]. A recent study with surgical resection followed by whole brain radiotherapy in single metastases showed longer survival and less frequent recurrence rate[19)]. However, surgery can be performed only in patients with reasonably long life expectancy for its inherent risk. Furthermore, brain lesions are multiple in more than 50 % of all brain metastases[2) 6) 11)], or often located in less surgically accessible areas. Today, radiosurgery have provided an alternative to conventional therapy for brain metastases even multiple lesions to attain better local control with lower risk as an outpatient basis[1) 13) 14) 16)]. The recovery time from neurological deterioration after radiosurgery has not been well reported, however, if rapid neurological improvement could be offered by radiosurgery, patients may have longer independent life despite of limited life expectancy. This report describes the rapid effect of gamma knife surgery for brain metastases, which may contribute to a better quality of life of patients.

Materials

One hundred and sixty lesions in 68 patients (50 men and 18 women) were treated with gamma knife. Patients ranged in age from 19 to 80 years (mean:61 years). 34 cases (50%) had multiple brain metastases. Prior to gamma knife surgery, in each patient, whole brain was examined by 3 mm sliced, no gapped gadlinium-enhanced MRI to detect small lesions[7) 24)]. The volume of lesions ranged from 0.01 to 35 ml and 79% of all tumors

中村記念病院 脳神経外科 *財団法人 北海道脳神経疾患研究所

were less than 10 ml, 89% were within 20 ml. Among 68 patient, the primary malignancy was from lung in 37 (55 %), gastrointestinal tract in 14 (21 %), breast in 5 (7 %), kidney in 4 (6 %); liver, thyroid, uterus, larynx, and mediastinum in 1. Three patients classified from unknown origin. In unknown origin cases, one had previously surgical removal of tumor, which was histologically adenocarcinoma from unknown origin and the new lesion was treated by gamma knife. The other two cases were diagnosed as multiple brain metastases from neuroimaging. Fifty three (78%) out of 68 cases developed progressing neurological signs and symptoms. The most common sign was hemiparesis in 28 (52 %), and following;ataxia in 13 (25 %), aphasia in 3 (6 %), cranial nerves palsy in 2 (4 %), and headache due to increased intracranial pressure in 7 (13%).

Survival curves were drawn by Kaplam-Meier product-limited method (12). The log-rank test was applied to evaluated the difference between subgroups.

Gamma knife technique

All patients underwent application of the Leksell stereotactic coordinate frame under local anesthesia. After that procedure, all lesions were imaged by gadlinium-enhanced MRI. The dose planning was calculated in 3 dimensions using the Kula®. In small lesions, 50-90% isodose curve could be adjusted to the tumor margin in single shot. In large tumors, usually 40% to 50% isodose line with multiple shots was used for periphery to fit the irregular margin of tumors. Treatment dosage was from 14 to 30 Gy at the margin of tumor, but, mainly 25 to 30Gy were selected as the peripheral dose.

Follow-up examinations

Following treatment, patients were monitored with serial neurological and radiological examinations in each month. Contrast enhanced-MRI or CT was used to measure the volume of tumors, which were calculated approximately as follows ; the volume = π XYZ/ 6 (X ; mediolateral, Y ; anteroposterior, Z ; rostrocaudal distances of tumor). The reduction rate ; [(the volume of tumor before surgery - volume of tumor after surgery) /volume of tumor before surgery] were calculated. Neurological status were evaluated as well as Karnofsky Performance Status score. In some cases, we assessed the sequential SPECT using ^{201}TlCl and ^{99m}Tc-DTPA-HSA (human serum albumin) to evaluate the effectiveness of gamma knife surgery and to distinguish tumor recurrence from radiation damage.

Results

The mean follow-up time for 68 patients was 8.3 months with range of 1 to 25 months. The reduction rate of tumors in one month after gamma knife surgery

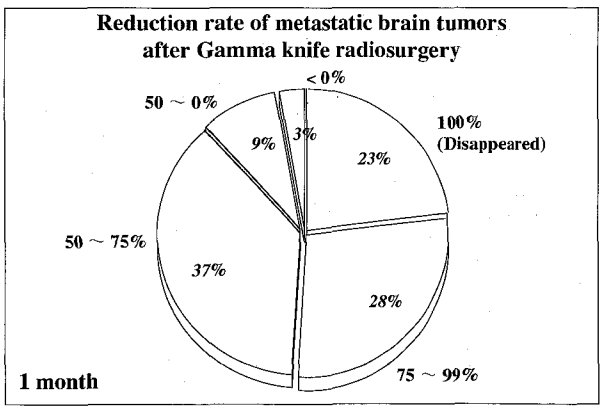


Fig. 1 (left) The reduction rate of tumors in one month after gamma knife surgery. 23% of tumors disappeared, and 88 % of tumors were decreased in size more than 50%.

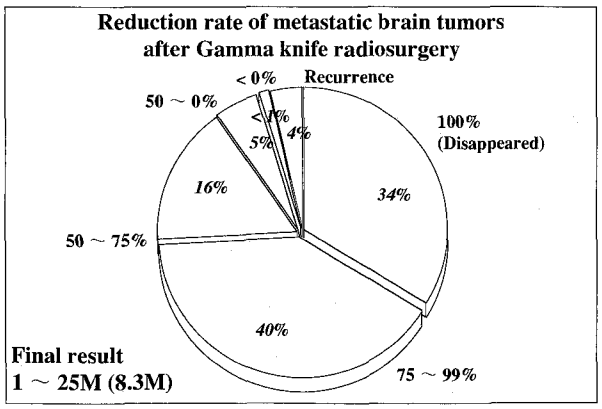


Fig. 1 (right) The reduction rate of tumors in final follow-up (mean 8.3 months). 34% of tumors disappeared, and 90 % of tumors were decreased in size morethan 50%. Recurrences were recognized in 4 % of all lesions.

were followed (**Fig. 1 left**) ; thirty one (23 %) were disappeared, and 121 (88 %) were decreased in size more than 50 %. The swelling or expansion of tumors were recognized in 4 (3 %).

The final reduction rate in this follow-up time were followed (**Fig. 1 right**) ; fifty four (34 %) were disappeared, and 144 (90 %) were decreased in size more than 50 %. Recurrences were recognized in 7 (4 %) of all lesions.

To compare the reduction rate between two figures, more than 50 % reduction rate could be obtained in 88 % in one month and 90 % of all lesions in final result. This finding shows metastatic tumors shrank rapidly after gamma knife surgery.

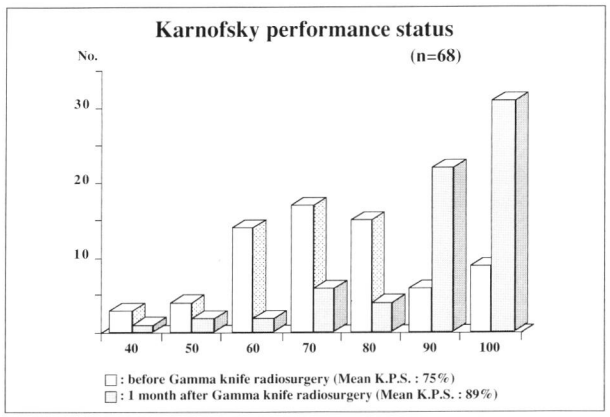


Fig. 2 Karnofsky performance status (KPS) score before and one month after gamma knife surgery. KPS scores improved from 74 % to 88 %.

Karnofsky performance status (KPS) were evaluated before and 1 month after gamma knife surgery (**Fig. 2**). Mean KPS score raised in values from 75 % to 89 % one month after gamma knife surgery. Furthermore, progressing neurological deterioration dramatically improved or disappeared within one week in 47 cases (89 %).

As side effects of gamma knife treatment, we experienced transient swelling of tumors or perifocal edema in some cases. These were as followed ; four cases showed neurological deterioration due to transient expansion of tumors. Three cases improved within one month with decreasing in size of tumors (**Fig. 3**). One case, who developed ataxia before gamma knife surgery, had to be carried out surgical removal the next day after gamma knife surgery, because the lesion located in cerebellar

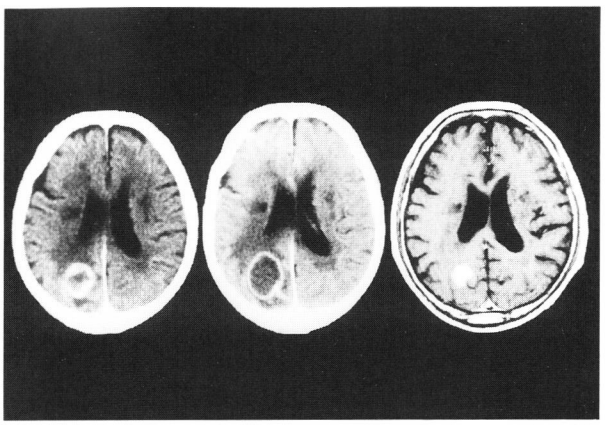


Fig. 3 Serial contrast CT and MRI of 71 years-old-man who developed left parietal sign. A.Left parietal mass from lung squamous cell carcinoma with perifocal edema was recognized. B.In one week after gamma knife surgery, this patient developed minimal right hemiparesis with expansion of tumor. C.This patient recovered form this sign in a few days after administration of steroids. The MRI showed that the tumor was decreased in size in one month.

hemisphere from lung small cell carcinoma swelled with increased edema and caused consciousness disturbance. The tumor volume was 9.4ml. This patient could become to walk by himself 2 months after surgical resection.

Four cases demonstrated increased perifocal edema in one week to 4 months. One case (from lung adenocarcinoma) showed transient neurological deterioration such as aphasia and hemiparesis in one week due to slightly increased edema despite of same size of tumor. This patient recovered from these deficits within one month. Other 3 cases showed only headache controlled by steroids.

One case (from clear cell carcinoma) developed hemiplegia 3 days after gamma knife surgery due to intratumoral bleeding, recovered to the previous condition three month later. In this case, 5 of all 6 lesions demonstrated high density area in CT scans which meant intratumoral bleeding before gamma knife surgery and rebleeding occurred in one of 5 previously bled lesions. It is hard to determine that this rebleeding may be related to the treatment of gamma knife.

In summary, except one case for emergent operation, 5 patients showed clinical deterioration and 4 cases recovered within one month and no case showed permanent

deficits due to the treatment of gamma knife.

Recurrences at the original site were recognized in 7 (4 %) out of 160 lesions. Their volume ranged from 2.1 to 22 ml, 14 to 30Gy as marginal dose (one case was irradiated 30Gy, other 6 lesions were irradiated from 14 to 20Gy), 1 to 7 months as period after gamma knife surgery, and 6 cases were adenocarcinoma and one was clear cell carcinoma as primary pathological findings. The optimal dose to the periphery of metastatic tumors has not been well understood, however, the major cause of recurrence seemed to be sublethal dose to the margin of tumors.

The newly appeared distant metastases were recognized in 13 (19 %) of all patients. Ten cases were subsequently treated by gamma knife. In the other three cases, gamma knife surgery was not carried out for their poor general conditions.

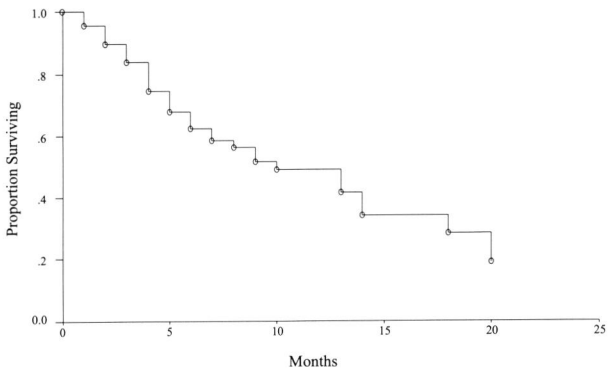


Fig. 4 Median survival of all patients (N=68) was 10 months.

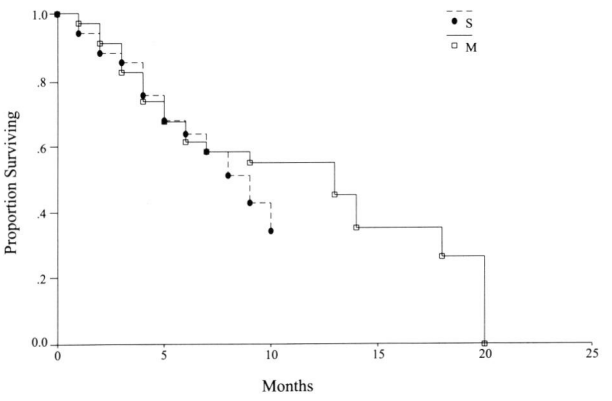


Fig. 5 Median survival of patients with single lesion (N=34, 15 patients died during follow-up), and with multiple lesions (N=34, 21 patients died) were shown respectively. There was no sinnificant difference between these two groups (p=0.96, with log rank test)

During the follow-up period, 36 patients died. The causes of death were from meningeal carcinomatosis in one case, and others died from systemic disease. Survival data for all patients are shown in **Fig. 4**. Median survival was 10 months. Survival data for patients with single and multiple metastases are shown in **Fig. 5**. The median survival were 9 and 13 months respectively. There was no statistically significant difference between these two groups (P=0.96).

Fig. 6 showed pathological findings of the patient who died from heart attack one month after gamma knife surgery. The three metastatic lesions from utrine adenocarcinoma were treated with 30Gy as marginal dose. Microscopic examinations revealed the glial layer covered necrotic tissue which included some islands consisted of

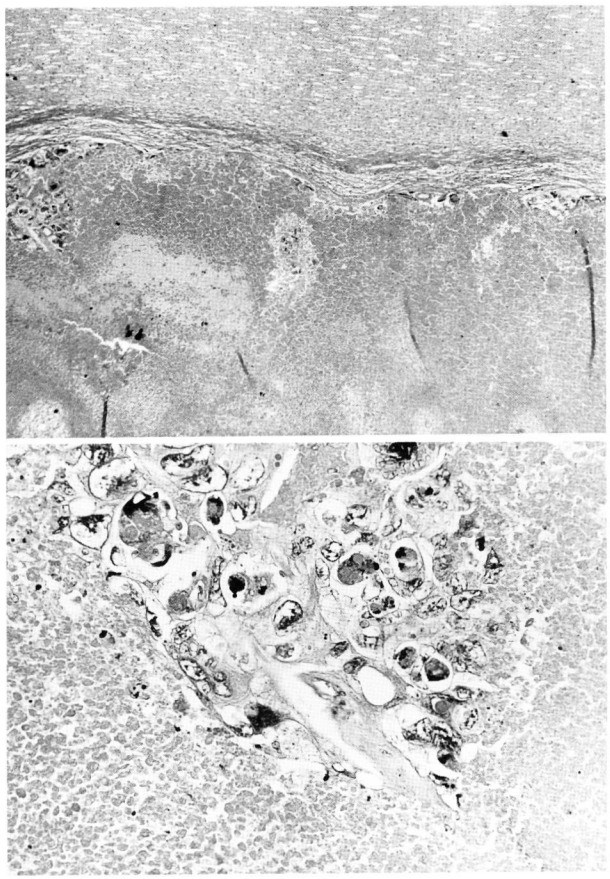


Fig. 6 Pathological findings of a 64-years-old woman who developed right hemiparesis and died for heart attack one month after gamma knife surgery. The glial layer covers necrotic tissue which includes some islands consisted of bizzare giant cells, which seems to have least proliferating potentiality.

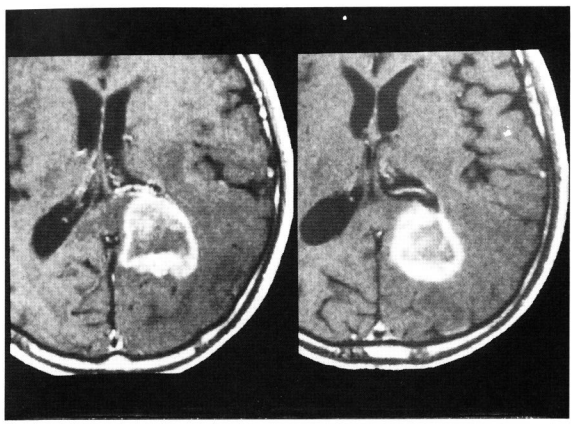
bizarre giant cells. These cells seemed to be least proliferating potentiality and were destined to die. No tumor cells were found outside of the glial layer.

Discussion

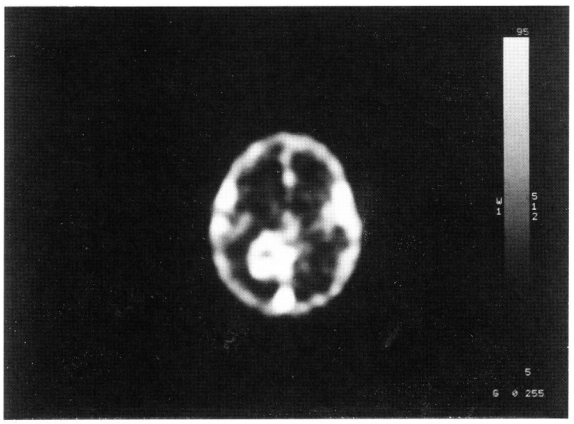
Most metastatic tumors are relatively well-demarcated, and suitable for radiosurgery despite of malignancy[1) 13) 14) 15) 16)]. High control rate have been provided at 73 to 98% by radiosurgery as an outpatient procedure[18)]. The optimal dose to the periphery of metastatic tumors has not been well understood, however, we realized that metastatic lesions would recur unless at least 25 to 30Gy were irradiated as marginal dose from retrospective study of recurrent cases in first six months experiences of this series. After this period, at least 25 to 30Gy were selected as marginal dose, and then, only 1 lesion recurred.

The early effect by gamma knife surgery could be observed. The improvement in Karnofsky performance status from 75% to 89% in one month was thought to be correlated to the rapid reduction of tumor size in one month. Furthermore, rapid neurological improvements were recognized in 89% of patients with symptoms within one week. **Fig. 7** showed ^{99m}Tc-HSA (human serum albumin) -SPECT findings. Marked decreased uptake of this tracer in delayed image in one week suggested decrease of permeability from tumor vessels[18)], which resulted in improvement of perifocal edema. Rapid clinical improvement seems to strongly related to decreased perifocal edema.

A Recent investigation suggested that surgery followed whole brain radiation therapy statistically prolonged survival and reduced local failure[19)]. However, local failure in original or distant lesions still occurred in 20%[9) 19)] of patients, and this therapy consumes a considerable part of remaining life of patients. In this series, control rate at original site was 96%, and distant lesions were recognized in 19% of all patients, most of them were subsequently treated by gamma knife. These data may indicate that whole brain radiation therapy is not always suppress the development of distant metastases. Furthermore, Asai, et al., [3)] reported radiation-induced brain



A



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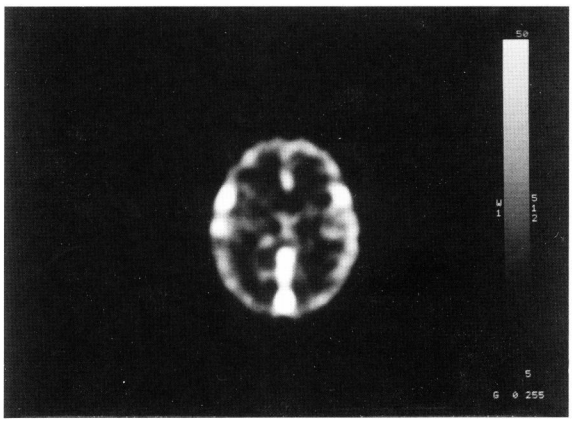

C

Fig. 7 A Contrast MRI of a 68-years-old man before and one week after gamma knife surgery. Left parietal large tumor (the tumor volume was 28ml) decreased in size about 50% in one week after gamma knife surgery. The patient recovered from right hemiparesis and left parietal signs. B, C ^{99m}Tc-HSA-SPECT findings before and one week after gamma knife surgery. Marked decreased uptake of albumin tracer in delayed image (5 hours) was noted.

atrophy (leukoencephalopathy) can be induced in the normal brain by as low as a dose as 30Gy with fractionated radiation therapy. Especially, they also reported that more than 50 percents of patients who were older than 50 years would develop dementia with radiation induced brain atrophy a few months after extended radiotherapy including whole brain radiation therapy. Since the majority of patients with brain metastases is older than 50 years (in this series, 87% of all patients were older than 50 years), whole brain radiation therapy may worsen the quality of life of patients. It is now obvious that the primary goal of the treatment of brain metastases is local control of lesions and to prolong the useful life of patients whose life expectancy are limited, therefore, routine whole brain radiation therapy for brain metastases should be limited to minimize the risk of radiation-induced brain atrophy which may obstruct this goal.

There was no statistically significant difference in median survival time between cases with single and multiple lesions (**Fig. 4**). These data show that multiple metastases could be an indication for gamma knife surgery if all of them are successfully treated by gamma knife[13].

Transient neurological deteriorations were observed in 7 % of all patients and most of them recovered within one month, and no permanent deficit was recognized. These complication rate may be lower compared to surgical resection followed whole brain radiation therapy[19]. Further follow-up in long-term survivors will be necessary to evaluate late complications.

Conclusions

Gamma knife surgery could contribute to the longer independent life of patients even with multiple metastases, with rapid neurological effect and low rate of recurrences and complications.

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