

## Gamma Knife Radiosurgery for Recurrent Glioblastoma Resistance to the Temozolomide

Ken-ichi SATO, M.D., Tamio ITO, M.D., Masami TAKANASHI, M.D., Yoshimaru OZAKI, M.D., Mitsuteru OIKAWA, M.D., Yoshinori SUGIO, M.D. and Hirohiko NAKAMURA, M.D.

Department of Neurosurgery, Brain Tumor Center, Gamma Knife Center, Nakamura Memorial Hospital and Hokkaido Brain Research Foundation, Sapporo, Japan

### Abstract:

**Purpose:** The current standard of care for newly diagnosed glioblastoma is surgical resection to the extent feasible, followed by radiotherapy plus concomitant and adjuvant temozolomide. Ultimately despite this current standard treatment, almost all patients with glioblastoma will have relapse.

Gamma knife stereotactic radiosurgery (GK-SRS) is a safe and less invasive treatment used as adjuvant therapy for patients with glioblastoma. Several studies have yielded conflicting results in the effectiveness of radiosurgery in glioblastoma. This article describes the results of our institutional experience with GK-SRS adjuvant therapy in the treatment of patients with recurrent glioblastoma resistance to the temozolomide.

**Method:** Twenty-six patients with newly diagnosed glioblastoma were treated with operation and concomitant temozolomide radio-chemotherapy from 2006 to 2010. Eleven patients with recurrent glioblastoma were treated with GK. Seven patients were male and 4 were female. The median age at primary diagnosis of the tumor was 64.8 years (range, 51-81 yrs). All patients were received debulking surgery. Histology evaluations of all patients revealed glioblastoma. In all patients radiotherapy was performed as first-line therapy, applied as fractionated external beam radiotherapy with concomitant temozolomide chemotherapy. The median interval between initial diagnosis and primary GK was 9.0 months (range, 4-17 mos). The median target tumor size was 8.4 cm<sup>3</sup> (range, 0.65-38.8 cm<sup>3</sup>). The median dose applied was 17.5 Gy (range, 15-20 Gy) prescribed to the 53.5% (range, 45-95%) isodose line that encompassed the target volume. The median follow-up time was 19.6 months (range, 11-48 months).

**Result:** Median survival time of patients treated with GK was 21.0 months and without GK was 14.0 months. Treatment was well tolerated by all patients. Acute toxicities CTCAE Grade II occurred in one patient. **Conclusion:** Gamma knife radiosurgery is a relative safe and less invasive treatment and may play an important role in the treatment of recurrent glioblastoma resistance to the temozolomide.

**Keyword:** glioblastoma, Gamma knife radiosurgery, temozolomide

## Purpose

The current standard of care for newly diagnosed glioblastoma multiforme (GBM) is surgical resection to the extent feasible, followed by radiotherapy plus concomitant and adjuvant temozolomide<sup>1</sup>. Ultimately despite this current standard treatment, almost all patients with GBM will have relapse.

Gamma knife stereotactic radiosurgery (GK-SRS) is a safe and less invasive treatment used as adjuvant therapy for patients with GBM. Several studies have yielded conflicting results in the effectiveness of radiosurgery in GBM. This article describes the results of our institutional experience with GK-SRS adjuvant therapy in the treatment of patients with recurrent GBM resistance to the temozolomide.

## Patients and Methods

### Study Population

Twenty-six patients with newly diagnosed GBM were treated with operation and concomitant temozolomide radio-chemotherapy from 2006 to 2010. Eleven patients with recurrent GBM were treated with GK-SRS. Seven patients were male and 4 were female. The median age at primary diagnosis of the tumor was 64.8 years (range, 51-81 years). All patients were received debulking surgery. Histology

evaluations of all patients revealed GBM. In all patients radiotherapy was performed as first-line therapy, applied as fractionated external beam radiotherapy (EBRT) with concomitant temozolomide chemotherapy (Table 1).

The criteria used for GK-SRS treatment included:

- 1) Histopathological diagnosis of GBM at tumor resection
- 2) Tumor lesion smaller than 30 cm<sup>3</sup> in size
- 3) Karnofsky performance score (KPS) greater than 60
- 4) Life expectancy greater than 3 months

### GK-SRS Treatment Protocol

Treatment doses were prescribed to the 50% isodose line that encompassed the 5 mm margin to the contrast-enhancing tumors in patients with recurrent tumors. The median target tumor volume was 8.4 cm<sup>3</sup> (range, 0.65-38.8 cm<sup>3</sup>). The median treatment dose was 17.5 Gy (range, 15-20 Gy) prescribed to the 53.5% (range, 45-80%) isodose line, which corresponds to a maximal GK-SRS dose was 33,8 Gy (range, 30-40 Gy).

## Statistical Methods

Patients were routinely followed every 8 to 12 weeks from completion of EBRT or GK-SRS until their time of death. The median follow-up time was 19.6 months (range, 11-48 months). The median interval between initial diagnosis and primary GK-SRS was 8.4 months (range, 6-17 months). Survival was analyzed using Kaplan-Meier method. In addition to overall survival from the time of diagnosis was analyzed.

## Result

Median survival time of patients treated with GK-SRS was 21.0 months and without GK-SRS was 14.0 months (Fig. 1). Treatment was well tolerated by all patients. Acute toxicities CTCAE Grade II occurred in one patient.

Patient and treatment characteristics	
Total patient	n=11
Gender	
Male	7 (64%)
Female	4 (36%)
Age (yr)	
Median age	64.8
Range	51-81
Resection versus biopsy	
Craniotomy gross or subtotal resection	9 (82%)
Biopsy	2 (18%)
Tumor size	
Median tumor volume (cm <sup>3</sup> )	8.4
EGRT	
< 59 Gy	1 (9%)
> 59 Gy	10 (91%)
Dose (Gy)	
Median maximal GK-SRS dose	33.8
Median peripheral GK-SRS dose	17.5
Side effect	
Acute toxicity	0
Symptomatic radionecrosis	1 (9%)
Secondary tumor	0

EBRT: external beam radiation therapy, GK-SRS: gamma knife stereotactic radiosurgery

Table 1 Patient and treatment characteristics

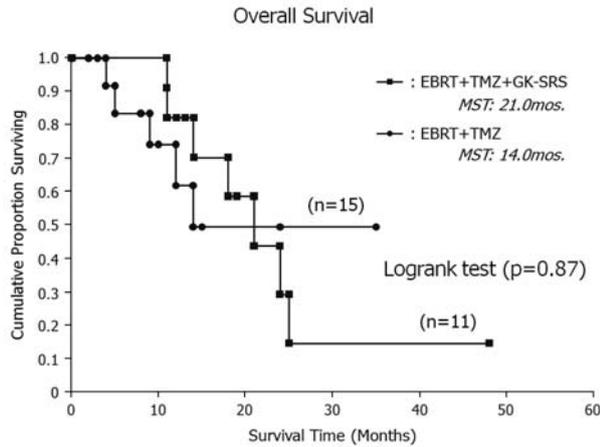


Fig. 1 Overall survival

## Discussion

Appearance of temozolomide seemed whether could put light in treatment of GBM, a lot of patients with GBM did not responded to the temozolomide, even if the standard therapy that uses temozolomide was done<sup>2)</sup>, the median survival was only 14.6 months<sup>1)</sup>. In the extension of the survival time of GBM, the adjuvant therapy becomes important when leading to recurrence after operation and concomitant temozolomide radio-chemotherapy. Molecular target therapy<sup>3)</sup> and cell immunotherapy<sup>4)</sup> are tried as new treatment to GBM in temozolomide resistance, but it's the clinical test stage and there is no adaptation of health insurance by the current state.

GK-SRS is the treatment which applies a gamma ray of high dose to stereotaxically to a small lesion basically, it has been thought that the treatment about the tumor that shows permeated growth is difficult. However, GK-SRS may be enumerated in one of the choices of the adjuvant therapy in the point of limited part controlling a tumor of a certain period as well as the further surgery for a small recurrent tumor after it is removed by the operation all<sup>5)</sup>.

In uncontrolled trials, several investigations have previously demonstrated encouraging data with improved survival of patients with GBM after additional adjuvant therapy with GK-SRS. The results of several series investigating the survival benefit of GK-SRS for patients with GBM. In, 1997, Kondzilka, et al.<sup>6)</sup> reported a median overall survival of 26

months in 64 patients with GBM with a mean tumor volume of 6.5 cm<sup>3</sup>.

However, most recently the Radiation Therapy Oncology Group (RTOG) concluded the 93-05 Phase-3 trial with 203 patients randomized to receive GK-SRS followed by radiation therapy plus bischloroethylnitrosourea (BCNU) versus only radiation therapy plus BCNU and reported no difference in survival in the two arms<sup>7)</sup>. They reported a median survival of 13.7 months versus 14.1 months, and concluded by a result of this RCT, it seemed that GK-SRS was denied as standard treatment of GBM which remains clearly after an operation.

But Hsieh<sup>8)</sup> reported that a median survival when GK-SRS was performed at the time of recurrence after early stage treatment in 26 examples of glioblastoma was 16.7 months while a median survival when GK-SRS was performed after early stage treatment in 25 examples of glioblastoma was 10 months. The importance of the timing of GK-SRS as effectiveness and the adjuvant therapy was emphasized.

By the results of our institutional experience with GK-SRS adjuvant therapy in the treatment of patients with recurrent glioblastoma resistance to the temozolomide, the median survival was 21 months. These results exceed a report of Hsieh, but influence of improvement of the effect of temozolomide and the extraction rate by the first time operation is considered.

As the merit of GK-SRS to recurrent GBM, (1) It's low invasive compared with a re-operation. (2) It's possible to treat more than one times. (3) A treatment period is short (by the hospitalization which is 3 days 2 nights, in an irradiation time, from 30, 60 minutes). (4) It's mentioned that health insurance is adaptation in Japan.

In case of recurrent tumor of in the pyramidal tract neighborhood, and a re-operation are performed, a possibility of the motor paralysis after an operation is high. But extension in a living period at home is obtained without KPS decreasing after it treats, preventing invasion with a recurrence tumor to a pyramidal tract by GK-SRS (Gamma defense) (Fig. 2).

As the weak point, the local control of the recurrent tumor by GK-SRS is completely impossible. Recurrence including dissemination from the irradiation outdoors is seen by the majority.

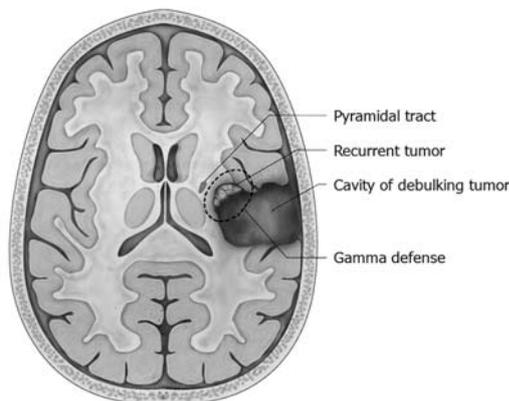


Fig. 2 Gamma defense: Protection of the pyramidal tract

This consideration, retrospective selection bias was consideration, not randomized controlled trial, and had as of the adaptation of GK-SRS when recurring, and moreover it wasn't significant in statistical way by the patient who did GK-SRS and the patient who didn't do GK-SRS. When recurring, the median survival by the good case in the state relatively with adaptation of GK-SRS is the conclusion that it was 21 months. Though the locality control of the tumor was temporarily possible by GK-SRS, there was a case from whom the limited part control became fatal by a difficult example and dissemination finally, and it was thought the limit of the GK-SRS by the current state.

To improve treatment results with GK-SRS for recurrent glioblastoma, setting in an irradiation area and reconsideration of the treatment dose are needed. GBM characteristically infiltrates surrounding normal brain parenchyma with malignant cells that can be identified up to 4 cm from the tumor edge<sup>9</sup>. When building a dosimeter picture to recurrent GBM, the irradiation target was encompassed the 5 mm-1 cm margin to the contrast-enhancing tumors. But recurrence from 2 cm in the range of an irradiation part was insufficient as much local control. Because PET is used when the range of the irradiation target of GBM is decided, the setting of an effective range of the irradiation target is biologically expected (However, PET that uses <sup>11</sup>C-methionine is now outside the adjustment of medical insurance in Japan).

The median treatment dose was 17.5 Gy prescribed to the 50% isodose line) a maximal dose was 33.8 Gy

(range, 30-40 Gy). It is thought that the increase of the treatment dose is possible when it is based that the acute radiation damage of CTCAE Grade II was only one patient taken as an adverse experience. It could be thought that rational irradiation target using PET and increase of the treatment dose was necessary it was based on this treatment results, and to improve local control of a recurrent GBM.

For the irradiation volume to become large for irradiation to a recurrence tumor around the tumor extraction cavity of wide range, such a case to be able to do nothing but decrease the therapeutic dose is thought that the irradiation divided into several-time by a low dose is necessary.

The timing of treatment is important to improve treatment results in GK-SRS for recurrent GBM. An average period from a check to GK-SRS in the first time was 8.4 months by this consideration. A tumor is regarded as the time to tend to recur this time. When treating a recurrence tumor with GK-SRS, it is thought that it is related to the improvement of treatment results to treat smaller lesion by a wide range and a high dose. When doing GK-SRS in a recurrent GBM, it is important to treat GK-SRS from the diagnosis first time about 8 months while it is recognized time when the relapse is caused easily, doesn't overlook a small relapse, and the recurrent lesion is small.

It is necessary to understand the role and the meaning of each treatment method including not only a single treatment method but also the initial treatment and the adjuvant therapy well, and to set up the treatment strategy the collection academically for GBM. Ascertaining the merit of the GK-SRS and the weak point and treating as one of the combined modality therapies are important.

## Conclusion

Gamma knife radiosurgery is a relative safe and less invasive treatment and may play an important role in the treatment of recurrent glioblastoma resistance to the temozolomide.

## Reference

- 1) Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temo-

- zolomide for glioblastoma. *N Engl J Med*, 2005; 352: 987-996.
- 2) Sato K, Ito T, Ozaki Y, et al: Radiotherapy plus concomitant and adjuvant temozolomide for newly diagnosed malignant glioma. *Journal of Hokkaido Brain Research Foundation*, 2007; 18: 15-21.
  - 3) Bokstein F, Shpigel S, Blumenthal DT: Treatment with bevacizumab and irinotecan for recurrent high-grade glial tumors. *Cancer*, 2008; 112: 2267-2273.
  - 4) Izumoto S, Tsuboi A, Oka Y, et al: Phase II clinical trial of Wilms tumor 1 peptide vaccination for patients with recurrent glioblastoma multiforme. *J Neurosurg*, 2008; 108: 963-971.
  - 5) Sato K, Ito T, Takanashi M, et al: Adjuvant gamma knife stereotactic radiosurgery for patients with recurrent malignant glioma. *Journal of Hokkaido Brain Research Foundation*, 2008; 19: 9-14.
  - 6) Kondziolka D, Flickinger JC, et al: Survival benefit of stereotactic radiosurgery for patient with malignant glial neoplasms. *Neurosurgery*, 1997; 41: 776-785.
  - 7) Souhami L, Seiferheld W, Brachman D, et al: Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine for patients with glioblastoma multiforme: Report of RTOG, 93-05 protocol. *Int J Radiat Oncol Biol Phys*, 2004; 60: 853-860.
  - 8) Hsieh PC, Chandler JP, Bhangoo S, et al: Adjuvant gamma knife stereotactic radiosurgery at the time of tumor progression potentially improves survival for patients with glioblastoma multiforme. *Neurosurgery*, 2005; 57: 684-692.
  - 9) Ulm AJ, Friedman WA, Bradshaw P, et al: Radio-surgery in the treatment of malignant gliomas: the University of Florida experience. *Neurosurgery*, 2005; 57: 512-517.