Efficacy and Limitations of Stereotactic Radiosurgery in the Treatment of Glioblastoma

Tomoyuki KOGA¹ and Nobuhito SAITO¹

¹Department of Neurosurgery, The University of Tokyo Hospital, Tokyo

Abstract

Treatment of recurrent glioblastoma is still challenging. Stereotactic radiosurgery has been accepted as a treatment option for recurrent glioblastoma after standard chemotherapy and irradiation. However, the efficacy of stereotactic radiosurgery at recurrence has been limited, mainly due to the highly infiltrative nature of the tumor which makes the lesion difficult to define as the target. To enhance the efficacy of stereotactic radiosurgery, several methods of targeting based on neuroimaging technology such as positron emission tomography and magnetic resonance imaging have been adopted to irradiate as many of the viable tumor cells as possible and showed some enhanced efficacy. In a trial of intensified treatment by extending the irradiation field, improvement of local control did not result in longer survival. Radiation-induced adverse event is another problem after stereotactic radiosurgery for recurrent glioblastoma because almost all patients underwent irradiation as a part of the initial treatment. To overcome the side effects associated with re-irradiation, use of bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor, has shown some efficacy. Advances in irradiation technology, neuroimaging, and adjuvant treatment are needed to enhance the efficacy of stereotactic radiosurgery for recurrent glioblastoma and reduce the morbidity associated with irradiation.

Key words: gamma knife, stereotactic radiosurgery, glioblastoma

Introduction

Glioblastoma is the most common adult primary brain tumor, and corresponds to grade IV of the World Health Organization classification of tumors of the central nervous system. Standard treatment for patients with glioblastoma includes maximal resection, followed by radiation and chemotherapy. The prognosis for patients with this disease is still poor, although the emergence of a new alkylating agent, temozolomide, has prolonged the progression-free survival and overall survival. Glioblastoma is highly malignant and aggressive with invasive nature, so recurrence is seen in more than 90% of the patients. The median survival duration is 14.6 months following initial presentation even with radiation therapy and temozolomide, and ranges from 5 to 13 months following recurrence. Since the most common pattern of recurrence of glioblastoma is local failure, local control is one of the goals in the treatment of recurrent glioblastoma. Various local treatment strategies for recurrence have been evaluated to prevent or delay disease progression, including repeated operation, conformal radiotherapy, brachytherapy, and local chemotherapy. Stereotactic radiosurgery has been accepted as another option of salvage treatment for recurrent glioblastoma. However, the highly invasive nature of glioblastoma makes this disease uncontrollable by stereotactic radiosurgery, because this targeted irradiation spares viable cells surrounding the target. Therefore, considerable advances are needed to effectively utilize stereotactic radiosurgery for the treatment of this challenging disease. Here we review outcomes of stereotactic radiosurgery and consider its role in the treatment of recurrent glioblastoma.


Efficacy and Limitations

The usefulness of stereotactic radiosurgery is limited for glial tumors, which are the most common intrinsic brain tumors. Although stereotactic radiosurgery can control relatively well-demarcated glioma to some extent, the majority of gliomas infiltrate the brain parenchyma and are difficult to manage by stereotactic radiosurgery. Although recurrent glioblastoma is usually infiltrative and so difficult to target, stereotactic radiosurgery has been accepted as an option of salvage treatment for recurrent glioblastoma otherwise untreatable. Adjuvant stereotactic radiosurgery has also been effective for recurrent glioblastoma, with median survival time of 4.6 to 16 months after stereotactic radiosurgery in patients with recurrent glioblastoma. Local control should be achieved by treatment for recurrent glioblastoma because local relapse is the most frequent pattern of glioblastoma recurrence after fractionated radiotherapy and chemotherapy.

Several studies analyzing patients treated by radiation therapy and temozolomide administration found local relapse in 72–92% of recurrences. However, the local control rate was not satisfactory even after stereotactic radiosurgery for recurrent glioblastoma. Local progression was observed in 65–90% of patients who underwent stereotactic radiosurgery for recurrent glioblastoma. The reason for the lack of efficacy in local control of recurrent glioblastoma may be failure to control lesions outside the irradiated field owing to the steep dose fall-off, the characteristic feature of stereotactic radiosurgery.

Refinement of Treatment

Since the emergence of the gamma knife as the first device for stereotactic radiosurgery, the irradiation equipment has been further refined. The fourth generation of the gamma knife, which entered use in 2004, enabled the coregistration of imaging data taken without frame fixation during treatment planning. This advance has allowed integration of many types of imaging data such as positron emission tomography for treatment planning. Positron emission tomography provides access to metabolic characteristics of lesions during treatment planning. At our institute, we tried to utilize 18F-fluoro-deoxy-glucose positron emission tomography to visualize the possibly active component in the treatment of recurrent glioblastoma. Although our experience of integrating positron emission tomography into treatment planning did not allow the evaluation of outcomes, another study of fractionated radiotherapy targeting using 11C-methionine positron emission tomography achieved median survival time of 9 months. Magnetic resonance spectroscopy provides another example of target definition, although not for recurrences. In this phase II trial from the United States, highly viable lesion was determined using the choline/N-acetylaspartate ratio obtained by magnetic resonance spectroscopy and irradiated by stereotactic radiosurgery prior to conventional treatment using temozolomide chemotherapy and conformal radiotherapy. The median survival was 20.8 months, which was longer than 14.6 months in the historical control of the European Organization for Research and Treatment of Cancer. Furthermore, we tried to extend the irradiation field to overcome the steep fall-off of irradiation dose at the margin. Extending the irradiation field by adding 0.5 to 1 cm margin to the gadolinium-enhanced lesion resulted in significant improvement of local control rate from 55% to 92%.

Local control might lead to improvement of performance status as achieved by surgical mass reduction, but improvements in performance status associated with local control achieved by stereotactic...
radiosurgery remain unclear and further analyses are awaited. Although extended field stereotactic radiosurgery achieved high local tumor control rate, no significant survival benefit was achieved, with overall survival of 9 months compared with 10.5 months after conventional stereotactic radiosurgery \( (p = 0.83) \).\(^9\) The overall survival after extended field stereotactic radiosurgery was also consistent with the results of only stereotactic radiosurgery for recurrent glioblastoma from other institutes at 5.3 to 13 months (median 10 months),\(^2,6-12,14,23,30,35,39\) and apparently represent the limitation of survival benefit achieved by stereotactic radiosurgery for local treatment. In fact, six of seven patients who died after extended field stereotactic radiosurgery in our study, died of remote recurrence or dissemination (data not shown). Control of dissemination is essential to overcome this limitation of stereotactic radiosurgery for local treatment. Clearly, systemic therapy is required since extended field stereotactic radiosurgery did not provide any survival benefit. As an example, adding bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor, would be a possible option since bevacizumab plus hypofractionated stereotactic irradiation for recurrent glioblastoma resulted in median overall survival time of 12.5 months,\(^1\) which was longer than that of 7.9 months after only hypofractionated stereotactic irradiation.\(^2\) Furthermore, bevacizumab is considered to ameliorate radiation-induced vascular permeability, and another case-control study of combined gamma knife stereotactic radiosurgery and bevacizumab administration showed not only longer overall survival (18 months vs. 12 months), but also significantly reduced adverse events associated with radiation (9% vs. 46%).\(^3\)

**Conclusions**

The efficacy of stereotactic radiosurgery for recurrent glioblastoma remains limited, but refinements of the treatment protocols might improve local control or longer survival. Adjuvant treatment incorporating agents such as bevacizumab may reduce morbidity and enhance efficacy. Further developments of systemic treatment are necessary to control recurrent glioblastoma.

**References**


*Neurol Med Chir (Tokyo)* 52, August, 2012


---

*Address reprint requests to: Tomoyuki Koga, MD, Department of Neurosurgery, The University of Tokyo Hospital, 7–3–1 Hongo, Bunkyo-ku, Tokyo 113–8655, Japan.

*e-mail: kouga-tky@umin.ac.jp*