CLINICAL ARTICLE

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The Role of Gamma Knife Radiosurgery for Diffuse Astrocytomas

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Objective : The management of diffuse astrocytomas is one of the most controversial areas in clinical neurooncology. There are numerous reviews and editorials outlining the difficulties in the management of these lesions. In this study, we assess the role of Gamma Knife radiosurgery(GKS) for diffuse astrocytomas.

Methods : Twenty-three patients with a diffuse astrocytoma were treated with GKS as a primary or adjuvant method from February 1995 to October 2003. The mean marginal dose was 13.6 (8.5~17.5)Gy and the mean maximal dose was 27.3 (17.0~35.0)Gy. Local control and the pattern of radiologic response were evaluated. The probable factors affecting local control, such as tumor volume, margin dose, previous history of craniotomy or stereotactic biopsy, and the presence or absence of previous radiotherapy were statistically analyzed. The average duration of follow-up was 39.7 (11.3~101.5) months after GKS.

Results : Of the 23 lesions treated, 16 lesions (69.6%) were controlled during the follow-up period. The mean progression-free interval was 57.4 months and the 5-year progression-free rate was 68%. Only tumor volume was found to be a statistically significant factor for local control. Smaller tumors were better controlled by GKS; it was significantly effective in tumors with less than a 10cm^3 volume.

Conclusion : GKS could be a valuable therapeutic modality both as a primary treatment and as a postoperative adjuvant therapy in some selected cases.

KEY WORDS : Diffuse astrocytoma · Gamma Knife radiosurgery · Radiologic response.

Introduction

The management of diffuse astrocytomas is one of the most controversial areas in clinical neurooncology. The therapeutic options for diffuse astrocytomas include surgery, radiotherapy, and even observation. Surgical strategies and timing of treatment are also debatable matters[15,26]. There are several studies regarding the use of radiosurgery for malignant gliomas, however, there have only been a few reported series on low grade gliomas[8]. The majority of these studies analyzed both WHO grade I and II tumors[9,13]; however, the behavior and prognosis of grade I and II gliomas are quite different.

We studied the possible role of Gamma Knife radiosurgery (GKS) in the treatment of low grade gliomas, especially grade II gliomas. This study included diffuse astrocytomas, which were histologically confirmed by surgical resection or biopsy. GKS was used as a primary treatment method for eloquently located lesions and childhood lesions. For recurrent or residual lesions, GKS was used as a palliative method after surgical resection, with or without external radiotherapy.

Materials and Methods

Patient selection

Twenty-three patients with a diffuse astrocytoma were treated with GKS from February 1995 to October 2003. There were eight men and fifteen women, with a mean age of 28.3 (7.5~57.9) years at the time of GKS. All tumors were histologically confirmed as diffuse astrocytomas. Craniotomies and resections were performed in eight cases, stereotactic biopsies in fourteen cases, and open biopsy in one case. We excluded the cases which were only radiologically diagnosed as a diffuse astrocytoma.

Pre-radiosurgical external radiation therapy was performed in five cases; all of these lesions had been resected prior to

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external radiation. GKS was used as an adjunctive treatment method for these lesions once they recurred. The other eighteen patients who were not treated with external radiation had radiologically discrete, small-volumed, and eloquently located tumors. For these patients, GKS was used as a primary treatment method. GKS was also performed as a primary treatment for the seven patients less than 18 years of age.

Radiosurgical treatments

The mean marginal dose was 13.6 (8.5~17.5)Gy and the mean maximal dose was 27.3 (17.0~35.0)Gy. The mean tumor volume was 14.9 (0.7~55100)mm^3. Radiosurgical targets included distinct lesions, seen as low signal areas in T1-weighted magnetic resonance imaging(MRI) and high signal areas in T2-weighted MRI.

Follow-up and statistical analysis

The average follow-up duration was 39.7 (11.3~101.5) months after GKS. MRI was used for follow-up approximately every three to six months, or when new symptoms or signs developed. The local control, pattern of radiologic response and clinical response were evaluated. Local failure was defined as tumor volume that expanded to 120% or more of pre-GKS volume; in these cases, the tumor subsequently required surgical resection. The probable factors affecting local control, such as tumor volume, margin dose, previous history of craniotomy or stereotactic biopsy, and the presence or absence of previous radiotherapy were statistically analyzed using Cox regression analysis (SPSS 11.0, $p<0.05$). The survival and progression-free interval were estimated using the Kaplan-Meier method (SPSS 11.0).

Results

Tumor locations and diagnostic methods

There were a total of eight surgically resected lesions; five were located at the cortex, and one each was located at the thalamus, insula and mesial temporal lobe. Fifteen patients were diagnosed by stereotactic biopsy. The tumors location were summarized in Table 1.

Tumor control and affecting factors

Of the 23 lesions, 16 (69.6%) were controlled during the follow-up period; 9 had a static course and 7 regressed. Of the 7 lesions that were not controlled, 5 progressed and 2 recurred; all resulted from local failure. After defining them as failures, four patients were treated with craniotomy and tumor resection, one patient was treated with external radiation therapy only and two patients died from tumor progression at 16.9 and 34.5 months after GKS, respectively.

Table 1. Tumor locations

Tumor location	Number of patients
Thalamus, hypothalamus	6
Motor, speech area	6
Subcortex	4
Cortex	5
Brain stem	2

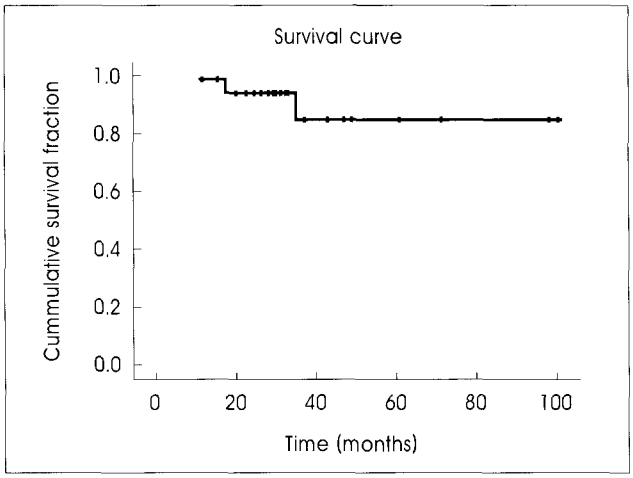

Fig. 1. Kaplan-Meier survival curve. The mean survival time is 91.2 months. Two-year and 5-year survival rates are 95.2% and 85.7%, respectively.

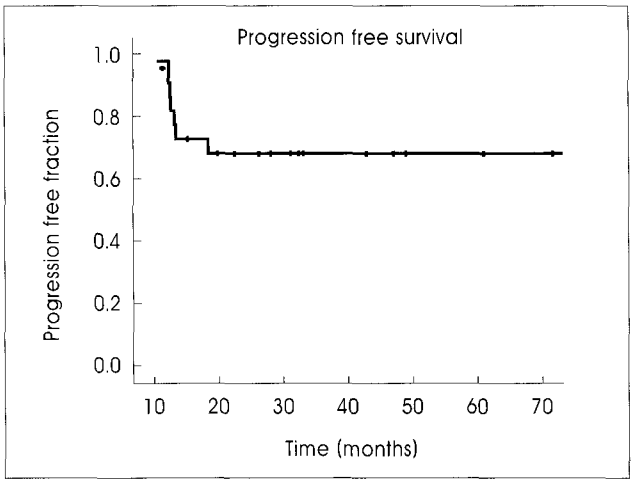

Fig. 2. Kaplan-Meier survival curve for progression-free interval. The mean progression-free interval is 57.4 months, and the 2-year and 5-year progression-free rates are 68.0%.

Of the four patients treated with tumor resection, two patients were histologically diagnosed as malignant transformations. One was a 28-year-old woman who had been treated with tumor resection and diagnosed as diffuse astrocytoma. Three years after resection, non-enhancing solid tumor recurred and GKS was performed. A small enhancing lesion appeared at 19 months after GKS and this lesion was eventually resected at 31 months after GKS. The histologic diagnosis was malignant astrocytoma. The other was a 35-year-old man. He had presented 2 times of generalized seizure and diagnosed low grade

glioma. Six year after the first presentation, the lesion was resected and diagnosed as diffuse astrocytoma. Eleven months after craniotomy GKS was performed. The GKS treated lesion went on growing and it was resected again. Histologic diagnosis was mixed form of radiation necrosis and malignant astrocytoma. Two patients treated with tumor resection after failure were diagnosed as a diffuse astrocytoma mixed with radiation necrosis, or fibrinous change and hyaline thickening of small vessels consistent with radiation effects.

The mean survival time was 91.2 months (95% confidence interval 77.4~104.9). Two-year and 3-year survival rates were 95.2% and 85.7%, respectively. No patients died 3 years after GKS (Fig. 1). The mean progression-free interval was 57.4 months. Two-year and 5-year progression-free rates were 68.0% (Fig. 2). In 12 patients (52.1%), new symptoms occurred after GKS. Neurological deterioration was observed in 9 patients; 7 with tumor recurrence, 2 with new cyst, and 1 with peritumoral edema. The neurological signs were transient in 3 patients with new cyst or peritumoral edema. Other newly developed symptoms were transient seizure and headache due to aggravated cyst or peritumoral edema.

With regards to factors affecting local control, we analyzed tumor volume, margin doses, presence or absence of previous radiation therapy, and previous tumor removal or stereotactic biopsy. Among these factors, only tumor volume was statistically significant ($p<0.05$). Smaller tumors could be better controlled by GKS, and especially those with a volume less than $10cm^3$. Of the 13 cases with tumor volumes less than $10cm^3$, 2 (15.4%) failed local control, whereas 5 of the 10 cases (50.0%) with tumor volumes greater than $10cm^3$ failed local control ($p<0.05$).

Radiologic responses after GKS

On retrospective review of the treated lesions, 12 (52.2%) patients showed postradiosurgical enhancements. Enhancement with volume expansion was noted in 7 cases; 5 of these patients eventually failed treatment. Enhancement without volume change was noted in 2 cases and enhancement with volume reduction in 3 cases.

Volume enlargement always accompanied increased peritumoral edema. The degree of peritumoral edema was measured by subtracting the maximal diameter(cm) of the tumor from that of the peritumoral edema on the T2 weighted MR image. Preradiosurgical edema was excluded. In 10 patients (43.5%), the newly developed or aggravated peritumoral edema was identified on follow-up MRI. However, in 6 patients, the peritumoral edema was related to tumor enlargement, and only in 4 patients (17.4%), radiation-related edema were identified. Only 2 patients were transiently symptomatic. The radiation-related edema developed at a mean of 6.4 months (range 3.3 to 11.5 months) after GKS and was sustained for 15.5 months (range 9.0 to 32.4 months).

Table 2. Radiologic responses after gamma knife radiosurgery

Post-GKS response	Number of patients	Failures
Enhancement	12	6
with increased volume	7	5
without volume change	2	1
with decreased volume	3	0
New cyst	2*	-
Cyst progression	2*	-
Progressive reduction	5	1
No change	2	-

*Three patients needed cyst aspirations due to transient cyst expansions, however solid parts regressed progressively

Mass effect resulted from tumor volume enlargement mixed with perilesional edema was direct cause of death in two patients. In other three patients who had the enhanced and enlarged tumors and eventually failed treatment, tumor enlargement was 200 to 400% and new or additional edema was 3 to 5cm. All they were needed tumor resection with steroid administration. Other radiologic findings included cysts in 4 patients; 3 of these patients needed cyst aspirations due to transient cyst expansion, but the solid parts regressed progressively. Progressive tumor reduction was evident in 5 of the 23 cases; of these, 2 disappeared completely and 1 recurred. Finally, 2 of the 23 cases never showed an imaging change (Table 2).

Illustrative Cases

Case 1

A 55 year-old male with a cortical lesion underwent a craniotomy and tumor removal procedure with subsequent external radiation, twice. On follow-up images, the gyrus was thickened and was considered to be a recurrence. GKS was preformed with a dose of 12.5Gy to the 50% margin. At eight months post- GKS, the gyrus had shrunk (Fig. 3).

Case 2

A 9 year-old girl with a mesial temporal tumor had an episode of generalized tonic-clonic seizure. The lesion was confirmed as a diffuse astrocytoma by stereotactic biopsy. GKS with a marginal dose of 14Gy was performed as a primary treatment. At ten months after radiosurgery, the tumor was enhanced, but not combined with volume expansion. At the twenty-two month follow-up, the lesion has remained static, without further change (Fig. 4).

Case 3

This 12 year-old girl had a non-enhancing precuneus mass; its pathology was a diffuse astrocytoma confirmed by stereotactic biopsy. GKS was done with a margin dose of 14Gy.

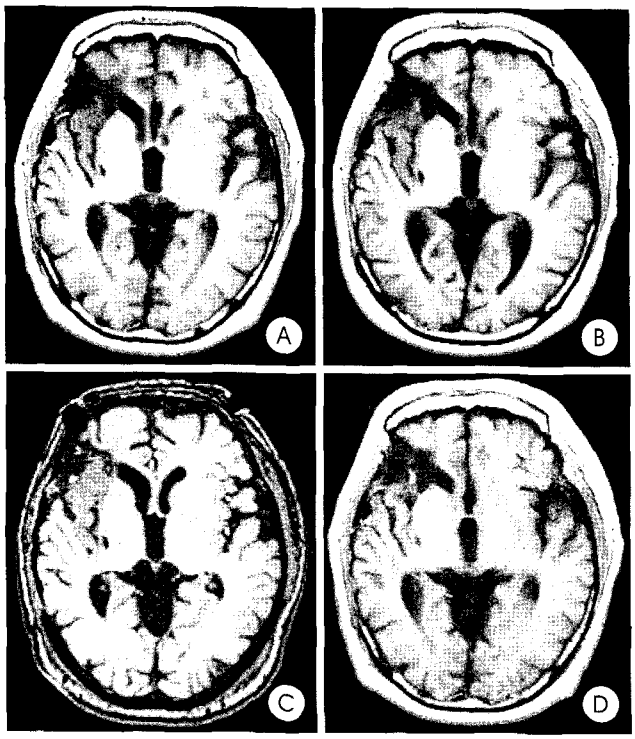

Fig. 3. A : Precontrast brain magnetic resonance(MR) imaging showing a low signal lesion on the right temporal cortex after resection and external radiation. B : Precontrast MR image, 28 months later, showing gyral thickening, which is considered a recurrence. C : T1-weighted MR image on the day of Gamma Knife radiosurgery(GKS). D : Eight months after GKS, follow-up MR image showing significant gyral shrinkage.

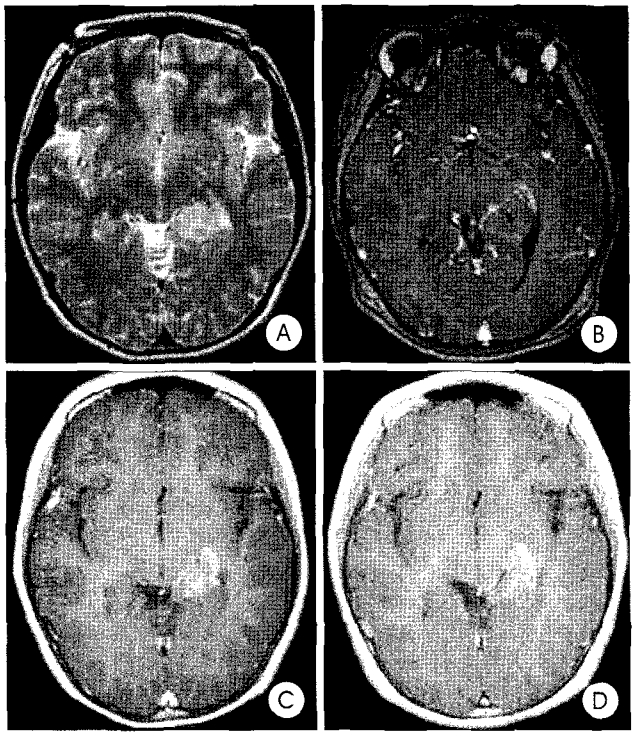

Fig. 4. A : T2-weighted magnetic resonance MR imaging showing a non-enhancing lesion in the left mesial temporal area. B : T1-weighted enhanced MR image at the time of Gamma Knife radiosurgery(GKS) showing a signal defect due to previous stereotactic biopsy. C : Tumor is enhanced 10 months after GKS. D : No significant change on MR image 22 months after GKS.

During follow-up, the lesion showed enhancement and progressive volume expansion. The lesion needed resection thirteen months after GKS (Fig. 5). Pathologic diagnosis was diffuse astrocytoma and radiation necrosis.

Discussion

Radiosurgery for diffuse astrocytomas

Glial tumors can have an infiltrative margin and a heterogeneous pathologic spectrum within one tumor; it has therefore been arguable to treat gliomas by stereotactic radiotherapy or radiosurgery[15]. Although there have been several studies on radiosurgery of glial tumors, most are about malignant gliomas. There are few reports about WHO grade II gliomas[2,4,13]. Kida et al.[13] reported results of GKS for 51 patients with low grade gliomas. For a mean follow-up period of 27.6 months, the control rate of grade I tumors was 91.7% and that of grade II was 87.2%. All patients received GKS as a primary treatment because the majority of their tumor location was near the optic nerve or hypothalamus. They used a prescription dose of 15.7 Gy for grade II tumors and noted a high rate of radiation-induced edema. They did not discuss the favorable factors for tumor control. Chun et al.[4] reported results of 17 patients with low grade gliomas treated with GKS for a mean follow-up of 7.6 years. In their report, using a mean margin dose of 18.2Gy, the tumor control rate was 52.9% and the postradiosurgical complication rate was 58.8%. They discussed the effects of tumor volume and tumor control; in volumes less than or greater than 10cm^3, the control rate was 72.7% and 33.3%, respectively. Sarkar et al.[25], studied survival rates after GKS on oligodendrogliomas or mixed oligoastrocytomas. They concluded that the survival rate was improved in younger patients and in patients with smaller tumors.

In the current study, the tumor control rate was 65.2% at 39.7 months. Considering we had a progression-free interval of 57.4 months, Chun et al.'s poor results[4] may come from their longer follow-up duration.

Regarding complications, radiation-related edema or necrosis was considered as local failure in our series. The discrimination between radiation necrosis and tumor recurrence or malignant transformation is not always feasible, even with advanced imaging techniques. Actually, there are many cases with mixed lesions of radiation necrosis and tumor recurrence[7,10,11]. Therefore, it seems reasonable to count lesions that need to be removed as a failure rather than a complication. The high complication rate of Chun et al.'s series[4] was related to high doses. The proper dose between tumor control and adverse effects needs to be further determined with clinical trials.

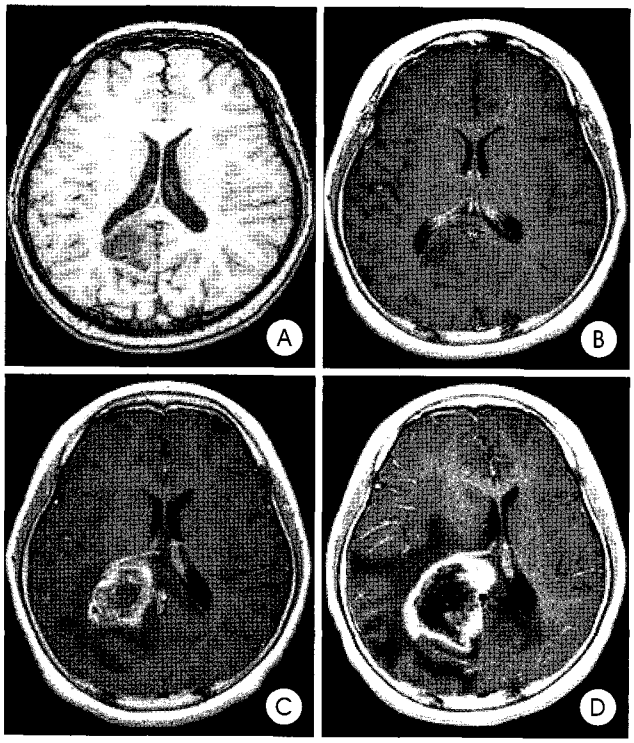

Fig. 5. A : Non-enhancing mass in the right precuneus area and a signal defect due to previous stereotactic biopsy. B : Follow-up T1-weighted enhanced magetic resonance(MR) imaging 7 months after Gamma Knife radiosurgery(GKS) showing no noticeable change. C : MR image 9 months after GKS showing enhancement combined with volume expansion. D : MR image 12 months after GKS showing tumor enlargement and peritumoral edema that needed microsurgical resection.

Radiotherapy and radiosurgery for diffuse astrocytomas

Radiotherapy has played a role in the treatments of low grade gliomas, even if its benefit remains controversial. Mansur et al.[17] evaluated the progression-free survival in 21 patients with grade II gliomas treated with surgery and adjuvant radiotherapy. The median time to progression was 31.4 months and the 5-year progression-free survival rate was 51%. Although the direct comparison between fractionated radiotherapy and radiosurgery is not appropriate, the results are comparable to ours. In addition to radiotherapy controversies, a variety of treatments using radiation have been tried for gliomas, such as frameless stereotactic radiotherapy[3,24], interstitial radiosurgery[16,28], interstitial brachytherapy[18], and intensity-modulated conformal therapy[12,19]. The proper methodology should be decided, but the current opinion is that stereotactic radiosurgery is advantageous for small and discrete lesions, because treatment planning in the conformation of high isodose lines with the target volume is favorable. It provides a steeper dose gradient outside the target volume and, therefore, a lower toxicity in normal tissue[19]. Moreover, serious side effects such as mental retardation, endocrine dysfunctions, or cognitive dysfunctions have been reported after radiotherapy in childhood[5,6,15]. Radiosurgery may play a role in selective cases of gliomas, with minimizing the neurological sequelae, especially in growing children.

Postradiosurgical radiologic responses

With regards to post-GKS radiologic response, 12 of 23 patients showed solid enhancement in their follow-up imaging study; 6 of these, who also had increased tumor volume, failed to be successfully treated. Postradiosurgery enhancement or transient volume expansion is a known phenomenon in intracranial tumors[3,20]. Enhancement is known to be related to irradiated endothelium; the concurrent production of large numbers of abnormal endothelial cells disrupts microcirculation and results in a breakdown of the blood-brain barrier[1,23]. According to the given doses, the enhancement may represent tissue injury and gliosis or tissue loss[22]. In our cases, surgically extirpated enhancing lesions turned out to be malignant transformations in 2 patients and mixed diffuse astrocytoma with radiation-induced tissue reactions in 2 patients. Although the meaning of volume enlargement and enhancement remains unknown, these responses need close follow-up as well as proper management.

Of the 4 cases with cysts, 1 had a static course; the other three cysts enlarged. The cysts were treated with stereotactic aspirations and Ommaya reservoir insertions. The mechanism of post-GKS cyst formation or enlargement, remains unclear and multiple factors, such as radiation-induced ischemic necrosis, increased vascular permeability or intratumoral hemorrhage may be involved[14,27]. However, if the combined solid parts are responsive to radiosurgery, the cysts can be controlled with aspiration, as in our cases.

Conclusion

GKS seems to be an appropriate alternative or primary therapeutic modality in the treatment of WHO grade II gliomas especially in small, well-demarcated, or deeply located tumors, or in childhood tumors. Post-radiosurgery enhancement with volume enlargement may mean a local failure. Cystic tumor has a tendency to increase in size after GKS and close follow-up is needed. However, if cystic enlargement does not accompany enlargement of the solid portion, possibility of long-term control still exists.

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Commentary

This paper is a very interesting article that can establish a new therapeutic modality to treat progressing low grade astrocytoma using Gamma knife radiosurgery(GKS) and we got much encouraged. The effectiveness of conventional radiation therapy in the management of low grade astrocytoma is still controversial and under discussion. Furthermore, there are serious complications of radiation therapy including acute cerebral edema and long-term and delayed neurotoxicity such as neurocognitive defects, cystic formation and radiation necrosis.

Recently, Plathow et al[3] reported that stereotactic radiotherapy is effective and low toxicity in the treatment of low grade gliomas compared with after conventional radiotherapy. In addition, Marcus et al[2] suggested that stereotactic radiotherapy provides excellent local control for children with small, localized low grade glial tumors. Therefore, GKS also may be a valuable treatment modality in selected cases of low grade glioma. According to this paper, tumor control rate and 5-year progression free rate is about 70% after GKS in low grade astrocytomas, and especially effective in tumor with small tumor volume.

To get optimal therapeutic response after GKS in low grade astrocytoma, we should determine not only indication criteria such as size, location, peritumoral edema, cystic change, neurological deficit and age but also optimal timing of GKS. Also, in GKS, physician should establish optimal radiation dose and extent of radiosurgery through further studies[1]. In order to reduce complication of radiosurgery and elevate the efficiency by use of GKS, effective radiation dose and more strict extent of irradiation with widely acceptable imaging modality such as T2 weighted MR imaging. Additionally, there is the hope that comparison of results with other therapeutic modalities and prognosticators such as extent of enhanced mass, radiation dose, gender and age should be established and long term follow-up is needed.

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