Preservation of quality of life by preradiotherapy stereotactic radiosurgery for unresectable glioblastoma multiforme

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Object. The authors conducted a retrospective study to evaluate the efficacy of Gamma Knife surgery (GKS) followed by radiotherapy for the treatment of unresectable glioblastomas multiforme (GBMs) on patient survival and quality of life.

Methods. A total of 19 patients with unresectable GBMs located in eloquent areas of the brain were eligible for this study. Beginning in January 2002, 10 patients underwent GKS followed by fractionated radiotherapy. Nine patients who had undergone radiotherapy alone after biopsy-proven diagnosis served as the control group. The mean patient ages were 53 years and 56 years, respectively. Preoperative Karnofsky Performance Scale (KPS) scores were 80 (range 60–100) and 90 (range 50–100), respectively. The median margin dose for GKS was 12 Gy (9–16 Gy), and the total dose for radiotherapy was 60 Gy in 30 fractions. The mean follow-up duration was 7.2 months, the median patient survival time was 52 weeks (95% confidence interval [CI] 22–110.6 weeks) in the GKS group, and the median overall survival time was 28 weeks (95% CI 22.5–33.5 weeks) in the control group. The difference was not statistically significant (p = 0.0758). The estimated progression-free survival rate at 3 months was 75% in the GKS group and 45% in the control group (p = 0.082). The posttreatment KPS scores were either unchanged or improved in the GKS group, whereas it deteriorated by 20 or more points in six of nine patients of the control group (p = 0.004).

Conclusions. Gamma Knife surgery prior to radiotherapy may be helpful in preserving patients’ daily activities in the adjuvant management of unresectable GBM.

KEY WORDS • Gamma Knife surgery • radiosurgery • radiotherapy • quality of life • glioblastoma multiforme

The treatment of GBM is still one of the most challenging in central nervous system tumors; it is an extremely aggressive tumor characterized by local invasiveness. Over the past decade, radical resection followed by postoperative radiotherapy has been accepted as a standard treatment modality, resulting in a median patient survival of 8 to 12 months.7,17 Resection may not be feasible for the lesions located in the eloquent areas, for example, the thalamus, basal ganglia, and brainstem. In those cases, fractionated radiotherapy alone as the initial treatment is known to yield a disappointing outcome.2,15 It is necessary to establish the best combination of the various treatment modalities and new approaches to improve the prognoses.18

The use of SRS as the primary treatment for malignant gliomas was first reported by Colombo, et al.,3 in 1985; since then it has been applied effectively in the treatment of a variety of malignant brain tumors.2,4,5,11,14,15 Some authors have suggested that SRS might be an effective tool to control GBMs as the initial treatment or an alternative to radiotherapy for residual/recurrent tumors.4,10,13,16 To date, there has been only one randomized trial in which the initial role of SRS for GBMs has been evaluated.20 We postulated that GKS followed by radiotherapy might improve patient QOL or provide a better prognosis for survival in patients with GBMs that could not be surgically removed. Thus, the purpose of the present study was to evaluate the efficacy of GKS followed by radiotherapy for unresectable GBMs and the subsequent effects on patient survival and QOL.

Clinical Material and Methods

Patient Population

Between January 2000 and November 2005, a total of 19 patients harboring an unresectable GBM located in an eloquent area of the brain were enrolled in a study at our center. The inclusion criteria were as follows: 1) enhancing tumor < 3 cm; 2) patient age range from 30 to 80 years; and 3) unresectable tumor located in an eloquent area of the brain. The eloquent areas were defined...
TABLE 1

Characteristics in patients at the time of diagnosis*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GKS Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>female/male ratio</td>
<td>6:4</td>
<td>5:4</td>
</tr>
<tr>
<td>age in yrs (range)</td>
<td>53 (31–77)</td>
<td>56 (32–73)</td>
</tr>
<tr>
<td>initial KPS score (range)</td>
<td>80 (60–100)</td>
<td>90 (50–100)</td>
</tr>
<tr>
<td>tumor location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thalamus</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>basal ganglia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>corpus callosum</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>brainstem</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>postradiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chemo-therapeutic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>carmustine</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>cisplatin</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>temozolomide</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*There was no statistical significant difference (p > 0.05) between the two groups by the Wilcoxon signed-rank test.

as the thalamus, brainstem, basal ganglia, and corpus callosum. Since the Leksell Gamma Knife unit (model 3C; Elekta Instruments AB, Stockholm, Sweden) was introduced at our institute in January 2002, we have performed GKS as the first-line treatment followed by radiotherapy in patients with unresectable GBMs. To determine and compare the outcome of this treatment modality with the conventional treatment modality, a historical control group was selected from among those patients with unresectable GBMs treated between January 2000 and January 2002, prior to the installation of the Gamma Knife unit. The inclusion criteria for the control group were the same; the records of these patients were selected from our department’s database. In both groups, the mean ages were 53 years (31–77 years) and 56 years (32–73 years), respectively (Table 1).

Treatment Protocols

Following histological confirmation of GBM by stereotactic biopsy, the patients underwent GKS on the same day. They underwent radiotherapy 1 to 2 weeks later. Treatment doses in the GKS were prescribed to the 50% isodose line that encompassed the contrast-enhancing tumor. All patients in the historical control group underwent radiotherapy alone immediately after the stereotactic biopsy for histological confirmation of the tumor type. Following the completion of the radiation treatment protocols, various chemotherapeutic regimens (temozolomide, cisplatin, and carmustine) were administered to the remaining survivors in each group. Clinical records and available neuroimaging data were reviewed in all patients.

Evaluation of Response

For an accurate measurement of tumor size, an outline of the tumor in each MR slice was downloaded to a personal computer with an image scanner, and the area of the tumor was measured with commercially available image software (SCION Corp. Frederick, MD). The tumor volume was calculated by multiplying the total tumor areas in all slices with the slice interval; these measurements were made preoperatively and again 3 months postoperatively. Response evaluation was based on published criteria. Complete response was defined as the disappearance of all measurable disease with improved neurological function in the absence of corticoid therapy. Partial response was a 50% decrease in tumor size with an improved or stable neurological function. Stable disease was less than a 50% decrease or less than a 25% increase in the tumor size with an improved or stable neurological function. Progressive disease was a greater than 25% increase in tumor size or the appearance of new lesions.

Statistical Analysis

The demographic and clinical characteristics of the patients were compared by performing the Wilcoxon signed-rank test. The primary end point was overall survival and progression-free survival. The secondary end points were QOL and severity of radiation toxicity. We assessed QOL by using the KPS, which was administered at baseline and every 3 months thereafter. The Kaplan–Meier method was used to estimate the overall survival time and the survival of the group.

Results

Nineteen patients with unresectable GBMs located in eloquent areas of the brain formed the basis for this study. The mean tumor volume was 11.1 cm$^3$ (4–26 cm$^3$) and 8.1 cm$^3$ (1–31 cm$^3$) in each group. In the GKS group, the median margin isodose was 12 Gy (9–16 Gy), and the total dose for radiotherapy was 60 Gy in 30 fractions (Fig. 1). In the control group, the total dose for radiotherapy was 50 to 60 Gy in 30 fractions. The preoperative KPS score was 80 (60–100) in the GKS group and 90 (50–100) in the control group. Baseline KPS scores differed little between groups.

During the mean follow-up duration of 7.2 months, the median overall survival in the GKS group was 52 weeks (95% CI 22–110.6 weeks), and the median survival was 28 weeks (95% CI 22.5–33.5 weeks) in the control group. This difference was not statistically significant (p = 0.0758) (Fig. 2). The estimated progression-free survival rate (complete response, partial response, and stable disease) at the 3-month follow-up was 75% in the GKS group and 45% in the control group (p = 0.082). Following completion of the treatment protocols, the posttreatment to pretreatment tumor volume ratio was 0.63 in the GKS group and 1.87 in the control group (Table 2). The posttreatment KPS score was unchanged or improved in all patients in the GKS group, whereas it declined by 20 or more points in six of nine patients in the control group (p = 0.004) (Fig. 3). During the treatment period, no severe toxicity was reported in either group, and there were only negligible changes revealed on MR imaging. No patient underwent further tumor resection after GKS and/or radiotherapy.

Discussion

Resection has been recommended as the initial treatment of choice in the majority of the patients with GBMs; however, in selected patients, the surgery must be limited to stereotactic biopsy because of the tumor location or the patient’s medical conditions. This subgroup represents 35 to 40% of all patients with GBMs. D. S. Kong, et al.
One important advantage in the use of GKS is that a relatively high dose of radiation can be applied in a single fraction, prescribed precisely to a defined target volume while sparing adjacent healthy brain tissue. This can be achieved by a steep dose falloff outside the targeted volume. There have been several series in which the feasibility of GKS boost therapy has been discussed as the initial treatment for GBMs. In contrast, the Radiation Therapy Oncology Group recently stated in their published 93-05 clinical trials that up-front SRS was not more effective than conventional radiotherapy in increasing overall survival and progression-free survival. The results of several studies in which the survival benefit produced by GKS in patients with GBM have been mixed. Although the Radiation Therapy Oncology Group report provided Level I evidence, it mainly provided data on residual GBMs after resection. Our study should be differentiated from that study in that it is necessary to clarify the efficacy of GKS followed by radiotherapy in nonsurgical cases. The direct comparison of results from radiotherapy alone and radiotherapy combined with SRS is difficult because the patients selected for such procedures represent a subgroup with a relatively good prognosis. Most of patients selected may have a relatively good KPS score, a well-circumscribed tumor margin less than 3 cm in diameter, and present with no evidence of surrounding infiltrating...
lesions. Moreover, the identification of appropriate historical control groups can be difficult.  

On the other hand, authors of several studies have recently reported the combined modalities treatment for this subgroup. Barrie, et al., suggested the efficacy of the up-front chemotherapy consisting of carmustine and temozolomide followed by radiotherapy carmustine Frenay, et al., reported on the efficacy of combination chemotherapy consisting of fotemustine/cisplatin/VP-16 before radiotherapy. Stupp and colleagues reported good results using concurrent chemoradiotherapy with temozolomide in a group of patients who underwent biopsy only. In our study, chemotherapeutic agents were administered at least 8 to 10 weeks after histological diagnosis; therefore, it may be difficult to interpret whether chemotherapy affected the KPS scores at 3 months.  

Of course, our study has some limitations. They include limited validated measurement tools other than the KPS for the evaluation of QOL, a small sample size, and the fact that it is a retrospective study. Therefore, it is difficult to draw the conclusion that GKS followed by radiotherapy should be recommended as the first-line treatment for surgically unresectable GBMs. However, despite the small sample size, we think remarkable that during treatment, no significant decrease in QOL was noted, and there was an increase in KPS scores in some patients in the GKS group. There are few reliable data for the effect of SRS on QOL in patients with GBMs. Next to outcome measures patient QOL has become an increasingly important end point in cancer studies. The mechanism of good preservation of QOL in the GKS group is not empirically known, but we hypothesize the following. Glioblastoma multiforme is a very highly aggressive and rapidly infiltrating tumor. By performing GKS in the early period after diagnosis, adequate dose escalation can be more rapidly achieved to stabilize the tumor growth rate and to preserve the neurological status of the patient. Conventional fractionated radiotherapy may require more time to accumulate an adequate dose to control the tumor growth. Therefore, GKS will be helpful in preserving neurological function and maintaining QOL.

Conclusions

These data suggest that GKS is a safe and effective treatment in a subgroup of patients with unresectable GBMs located in the eloquent brain areas. Gamma Knife surgery may be helpful in preserving patients’ daily activities and may play a role in improving survival time without having a negative effect on QOL.

References

7. Deutsch M, Green SB, Strike TA, Burger PC, Robertson JT, Selker RG, et al: Results of a randomized trial comparing BCNU plus radiotherapy, streptozotocin plus radiotherapy, BCNU plus hyperfractionated radiotherapy, and BCNU following misonidazole plus radiotherapy in the postoperative

### TABLE 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GKS Group</th>
<th>Control Group</th>
</tr>
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<tbody>
<tr>
<td>initial vol in cm³ (range)*</td>
<td>11.1 (4–26)</td>
<td>8.1 (1–31)</td>
</tr>
<tr>
<td>vol ratio (preop/postop 3 months)*</td>
<td>0.6363</td>
<td>1.8678</td>
</tr>
<tr>
<td>mean</td>
<td>0.3452</td>
<td>1.9368</td>
</tr>
</tbody>
</table>

*There was no statistically significant difference between the two groups according to the Wilcoxon signed-rank test or t-test (p > 0.05). Abbreviation: SD = standard deviation.

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