Low-grade gliomas treated by fractionated gamma knife surgery

GABRIELA SIMONOVÁ, M.D., PH.D., JOSEF NOVOTNY JR., M.SC., PH.D., AND ROMAN LISCÁK, M.D., PH.D.

Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic

Object. The authors sought to evaluate local tumor control, complications, and progression-free survival in patients harboring low-grade gliomas who were treated with Leksell gamma knife surgery (GKS).

Methods. During a 6-year period 70 patients were treated for verified low-grade gliomas (Grade I or II) by GKS. Statistical analysis was based on 68 patients; two patients were lost to follow up. The median patient age was 17 years. The median target volume was 4200 mm$^3$. The median prescription dose was 25 Gy. The median number of fractions was five. Ninety-five percent of patients were treated in five daily fractions.

Partial or complete tumor regression was achieved in 83% of patients with a median time to response of 18 months. There was moderate acute or late toxicity in not more than 5% of patients. In this series the progression-free survival was 92% at 3 years and 88% at 5 years.

Conclusions. Relatively high local tumor control with minimal complications was achieved.

KEY WORDS  low grade glioma • gamma knife surgery • radiosurgery • local tumor control • long-term survival

Material and Methods

Patient Characteristics

During a 6-year period 70 patients with LGGs underwent GKS. Two patients were lost to follow up. The series consists of 34 (50%) patients with Grade I gliomas and 34 (50%) patients with Grade II. Sixteen patients (24%) were pretreated with external-beam radiotherapy, 18 (26%) patients had undergone neurosurgery, 25 patients (37%) were treated using both methods, and in nine (13%) GKS was the only treatment and was performed after stereotactic biopsy. The minimum interval from previous treatment was set at 6 months to differentiate postoperative changes from the tumor on imaging method. The patients’ median age was 17 years (range 3–42 years) and 91% of patients were younger than 18 years. The median target volume was 4200 mm$^3$ (ranged 400–20000 mm$^3$). The median prescription dose was 25 Gy (range 25–30 Gy). The median number of fractions was five (range one–five). Seven patients underwent single-session GKSs and 61 (90%) in five daily fractions. The fractionation scheme was chosen to reduce radi-
ation toxicity and better reflect the radiobiological behavior of LGGs. The fractionation method, dose calculation, and quality control for this treatment modality have been described elsewhere.\textsuperscript{20,29} The following MR sequences were obtained in all patients: T\textsubscript{1}-, T\textsubscript{2}-weighted, and T\textsubscript{1} postcontrast. The severity of neurological symptoms was scored as an NFC, as shown in Table 1. The median pretreatment NFC was 2 (range 1–3). Nineteen (28\%) patients were asymptomatic (NFC 1), 43 (63\%) had moderate neurological findings, and six (9\%) had severe symptoms. All patients were followed up at regular intervals with physical, neurological, and MR imaging examinations, which were performed every 6 months during the 1st year after treatment and then every 12 months during the next 5 years. The minimum follow up was 48 months for those patients who survived. Toxicity was evaluated using the RTOG and EORTC scoring systems. The SOMA/LENT scales have been designed by EORTC and RTOG to achieve a worldwide and appropriate method of recording and registering radiation-induced morbidity.\textsuperscript{1,16} Acute toxicity was identified from the 1st day to 90 days after GKS and all later changes were recorded as late toxicity. The radiological response was assessed using MR imaging and described at the time of maximal response. Complete regression was defined as no evident pathological lesion on MR imaging and partial regression (reduction of tumor volume by approximately 50\% or more). Stabilization represents cessation of tumor growth. Progression was defined as continuing tumor growth and local recurrence as new growth after an initial partial or complete regression localized to the region of the treated volume.

### Statistical Analysis

Statistical evaluation was performed with commercially available statistical software (SPSS version 10.0). Three separate parameters were examined to assess their effect on LGG patient survival in this series. These factors were tumor histological grade, prescription dose, and target volume. Kaplan–Meier survival curves and the Log rank test were performed to assess the significance of these parameters. Variables with significant probability values (p < 0.05) were considered as possible risk factors in patient survival.

### Results

Complete and partial regression were achieved in 58 (83\%) patients, stabilization in eight (11\%), and progression was observed in four (6\%) patients.

#### Representative Cases

A verified Grade I tumor before treatment is illustrated in Fig. 1 left. Tumor regression at 39 months after treatment is seen in Fig. 1 right. Progression of a cystic component was observed in two patients with pilocytic gliomas, as seen in Fig. 2. Figure 2 left shows the tumor before GKS and Fig. 2 right shows the situation 24 months after treatment.

The regression of both parts of a Grade I glioma is shown in Fig. 3.

Regression of a cystic component is seen in Figs. 4A and B.

Two patients died of a recurrence, and repeated histological examination revealed a high-grade gliomas. Moderate late toxicity (Grade 2) was observed in three (4\%) patients. Severe toxicity (Grade 3) was observed in two patients who underwent a single-session GKS with a minimum dose of 20 Gy. The median NFC after treatment was 1 and the minimum follow up in survivors was 48 months. An improvement in neurological symptoms was achieved in three of six patients.

### Table 1

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<thead>
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<th>NFC</th>
<th>Definition</th>
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<tr>
<td>1</td>
<td>able to work, neurological findings minor or absent</td>
</tr>
<tr>
<td>2</td>
<td>able to be at home, although nursing care may be required, neurological findings present, but not serious</td>
</tr>
<tr>
<td>3</td>
<td>requires hospitalization &amp; medical care w/ major neurological findings</td>
</tr>
<tr>
<td>4</td>
<td>requires hospitalization &amp; in serious neurological state, including coma</td>
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patients (pretreatment NFC 3), 32 of 43 (pretreatment NFC 2). Seventeen of 19 (pretreatment NFC 1) remained with no symptoms. The median time to a local response was 18 months. The median survival time was 77 months. Fifty-two (74%) patients have undergone follow up for more than 5 years with a 5-year PFS of 88%. The Kaplan–Meier PFS curve is shown in Fig. 5. Although there were observed trends in patient survival (shorter survival was observed in patients with higher tumor histological grade, lower minimum tumor dose, and larger planning treatment volume), none of the proposed factors was statistically significant.

Discussion

The choice of treatment of LGGs is location and age dependent. The treatment choice for patients with accessible tumors is complete resection, particularly for those with Grade I tumors in the posterior fossa. Several decades of accumulated evidence point to the important role of neurosurgery in LGGs and was recently summarized by Keles, et al.14 The role of postoperative radiotherapy, which improves PFS in patients with incompletely resected LGGs has also been documented.11–14 Another finding has been that the more cells that are present after treatment, the more likely they are to undergo transformation to malignant tumors. In patients who underwent neurosurgery only there was a higher incidence of malignant transformation when compared with those who underwent postoperative radiotherapy.9,10,14 The role of postoperative radiotherapy in the treatment of the low grade gliomas remains debated. Nonetheless, a randomized trial of the EORTC Study No. 22845 documented that early postoperative conventional external-beam radiotherapy appears to increase the time to progression or the PFS; however, an increase in overall survival time for patients with LGGs was not documented.11–13 The long-term follow up of the patients in this study continues, and the final analysis will be reported later.11–13 External-beam radiotherapy is generally reserved for older children and adults with symptomatic, progressive, and unresectable LGGs or those (children) in whom chemotherapy has failed.4–9,11–13,21,25

FIG. 2. Magnetic resonance images revealing an LGG (Grade I) before GKS (left) and progression of cystic and regression of solid parts 24 months after treatment (right).

FIG. 3. Magnetic resonance images revealing cystic and solid parts of an LGG (Grade I) before GKS (left) and regression 48 months after treatment (right).
Radiation-induced toxicity is mentioned every time the role of radiotherapy in LGGs is discussed. The late complication rate would seem to depend on the radiation dose and the volume of irradiated normal tissue. Late adverse effects following therapeutic external-beam radiotherapy may develop after a latency of several years, typically 1 to 5 years after treatment.\textsuperscript{1,8,16,19,24,26} The injury of adjacent normal brain tissue has been reported to cause cognitive sequelae of varying degrees, endocrine disturbances, and late effects on the optic pathway with changes in visual function.\textsuperscript{3,16,19,24,26} During follow-up changes in white matter can be diagnosed on T2-weighted MR imaging near the treated volume or typi-

**Cumulative Progression Free Survival**

![Cumulative Progression Free Survival](image)

**Fig. 5.** A Kaplan–Meier PFS curve showing patients with LGG.
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cally along the ventricles. The late side effects following external-beam radiotherapy have been reported many times and despite modifying the total dose and the fractionation regimen the risk of late damage to an immature brain remains an increasing concern when using this method. This complication is a result of the relatively large volume of tissue, which is included in the irradiated volume and the use of higher doses. Late side effects may develop after a latency period of several years, the minimum accepted interval for late toxicity evaluation is 5 years. These late complications after radiotherapy have been recorded many times, especially in children. Studies in children with acute leukemia have shown a decrease in neuropsychological function in those who received additional low-dose prophylactic cranial irradiation in addition to chemotherapy when compared with children who received chemotherapy alone. Curative radiotherapy for gliomas requires higher radiation doses, and the likelihood of toxic reactions in the normal brain is increased. In several studies in which children of all ages were assessed 20 to 40% were observed to have severe cognitive dysfunction. In several other pediatric low-grade astrocytoma series a significant reduction of intelligence quotient was observed in 11 to 23% of patients, the majority of whom had undergone neurosurgery but not postoperative radiotherapy.

These studies highlight the underlying morbidity that occurs from disease and its treatment as well as the need for careful selection of treatment modalities and the precise evaluation of complications.

**Stereotactic Radiosurgery and Radiotherapy**

Stereotactic radiosurgery and stereotactic radiotherapy permit the application of relatively high doses to target volumes with a concurrent reduction of the irradiated volume of normal brain tissues. These techniques can be applied using GKS or a specially adopted linear accelerator. reported the results of GKS in seven patients with tectal LGGs and in two patients with a minimum prescription dose of 30 and 35 Gy in a single session. Permanent late toxicity was observed. The authors recommended a prescription dose of more than 14 Gy. Stereotactic irradiation with sparing of surrounding normal brain tissue plays a crucial role especially in radiotherapy in children and young patients, groups with a long life expectancy. The fractionation scheme in stereotactic radiotherapy represents the other method to reduce radiation-related toxicity and may also be used to boost previous external-beam radiotherapy. We observed Grade 3 toxicity in two patients treated in a single session and no late Grade 3 toxicity in the group of patients treated in five daily fractions.

**Radiation Treatment of LGGs in Children**

The majority of patients with LGGs are children and young patients. In this series there were 33 patients with pilocytic astrocytomas. Pilocytic astrocytomas tend to occur in young patients and are amenable to cure with gross-total resection; there is not a role for routine use of postoperative radiotherapy. Stereotactically guided conformal radiotherapy is also a high precision technique for delivering fractionated stereotactic irradiation and can play an important role in the treatment of postoperative residual pilocytic astrocytomas with their typical characteristics of being relatively well circumscribed with minimum infiltration growth outside postcontrast tumor volume visualized on the images.

Low-grade gliomas typically have a relatively small proportion of cells in a proliferative phase of the cell cycle. For this reason the radiation response is expected 1 to 5 years after treatment and recurrences can be observed several years after the treatment. Stereotactic radiosurgery using the Leksell gamma knife can extend the therapeutic option for patients with LGGs. Longer follow-up study of a larger cohort is necessary to demonstrate the presumed reduction in late treatment-related toxicity maintained local control, and long-term PFS. Fractionated GKS combines the advantages of the conformal three-dimensional dose distribution of radiosurgery with the radiobiological advantage of fractionation. Low-grade gliomas grow slowly and the majority of patients remain asymptomatic over a long period of time. Nonetheless these tumors represent a chronic illness with a real possibility of malignant transformation over time and there is still unsatisfactory long-term and local tumor control.

**Conclusions**

Radiosurgery represents an alternative treatment modality for small residual or recurrent volumes of LGGs with relatively long-term local control. Fractionated GKS achieves a reduction in the volume of normal brain tissue irradiated and the possibility of decreasing late side effects.

**References**


Address reprint requests to: Gabriela Simonova, M.D., Ph.D., Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Roentgenova 2, 150 30 Prague 5, Czech Republic. email:gabriela.simonova@homolka.cz.