Gameta Knife Radiosurgery in Recurrent Glioblastoma

Josa M. Frischer\textsuperscript{a} Christine Marosi\textsuperscript{b} Adelheid Woehrer\textsuperscript{e}
Johannes A. Hainfellner\textsuperscript{e} Karin Ute Dieckmann\textsuperscript{d} Helmut Eiter\textsuperscript{f} Wei-Te Wang\textsuperscript{a}
Ammar Mallouhi\textsuperscript{c} Adolf Ertl\textsuperscript{a} Engelbert Knosp\textsuperscript{a} Martin Filipits\textsuperscript{b} Klaus Kitz\textsuperscript{a}
Brigitte Gatterbauer\textsuperscript{a}

Departments of \textsuperscript{a}Neurosurgery, \textsuperscript{b}Medicine I/Institute of Cancer Research, \textsuperscript{c}Radiology and \textsuperscript{d}Radiotherapy, and 
\textsuperscript{e}Institute of Neurology, Medical University Vienna, Vienna, and \textsuperscript{f}Department of Radiooncology, Academic Teaching Hospital, Feldkirch, Austria


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Abstract

Background: We evaluated Gamma Knife radiosurgery (GKRS) as a treatment option for patients with recurrent glioblastoma. Patients and Methods: 42 patients with histopathologically diagnosed recurrent grade IV tumor were treated with GKRS. All patients had undergone standard multimodal first-line treatment. The average time from diagnosis to GKRS was 17.0 months. The median target volume was 5.1 cm\textsuperscript{3}. The median margin dose was 10 Gy and the median central dose 20 Gy. In a subset of patients, O\textsubscript{6}-methylguanine methyltransferase (MGMT) promoter methylation analysis by pyrosequencing was performed. Results: Most patients did not develop complications after GKRS. Time to radiological progression after initial GKRS was 4.4 months (95% CI: 3.1–5.7 months). Radiological progression mainly occurred beyond the GKRS-irradiated area. The median survival time after initial GKRS was 9.6 months (95% CI: 7.7–11.5 months). The median overall survival time from diagnosis was 25.6 months (95% CI: 21.8–29.3 months). Patients with MGMT promoter methylation survived significantly longer (33.4 months; 95% CI: 21.2–45.5 months) compared to patients without MGMT promoter methylation (16.0 months; 95% CI: 8.0–23.9 months). Conclusion: GKRS seems to be a relatively safe salvage treatment option for recurrent glioblastoma for highly selected patients but must be seen as part of a multimodal treatment algorithm.

Introduction

Glioblastoma (GBM) remains the most common malignant primary brain tumor in adults. Despite significant improvement in the treatment of patients with GBM, survival remains limited [1–3]. The current standard-of-care first-line treatment for GBM includes gross total micro-

Portions of this work were presented in abstract form at the WFNS in Seoul, Korea, 2013, in poster form at the EANS, Tel Aviv, Israel, 2013, and as oral presentation at the 7th LGKS meeting in New York, 2014.
surgical resection, followed by radiotherapy with concomitant and adjuvant temozolomide [2–5]. Even with improvement in microsurgical techniques, radical resection is hardly feasible because of the infiltrative nature of malignant gliomas [1, 6]. Thus, GBM inevitably recurs. Treatment options for recurrent GBM remain controversial and depend on tumor size, location, and the patients’ performance state [7]. Reoperation and retreatment with radiotherapy have been associated with increased complication and morbidity rates [8–10]. Treatment for recurrent GBM mainly comprises chemotherapy, which presents its own toxic side effects [7, 11, 12].

In a recent review the longest median overall survival was found with Gamma Knife radiosurgical treatment (GKRS) as a salvage therapy following gross total resection, concomitant or adjuvant temozolomide, and radiotherapy. GKRS patients were also treated with additional second-line chemotherapy [13, 14]. Skeie et al. [1] further suggested that GKRS might be an alternative treatment option to open surgery for recurrent GBM. Insufficient data exist to establish new guidelines for the treatment of recurrent GBM.

Patients and Methods

Patient Sample and Data Evaluation

Patient characteristics are summarized in table 1. All patients included in this study had histopathologically confirmed grade IV tumor (glioblastoma multiforme: n = 40, gliosarcoma: n = 2) and received standard first-line multimodal treatment after GBM diagnosis. Recurrent tumor before GKRS and tumor progression after GKRS were evaluated in collaboration with the Department of Radiology and the Department of Oncology at the Medical University Vienna and based on the Response Assessment in Neuro-Oncology (RANO) criteria [15–17]. Clinical data were obtained by retrospective chart review. The median follow-up time after GKRS was 9.7 months (range: 0.8–121.2 months). The patients were rated according to the Karnofsky Performance Status Scale (KPS) [18]. Tumor progression after GKRS on follow-up MRIs was rated: no recurrence, recurrence within the irradiated area, recurrence within and beyond the irradiated area, and recurrence outside of the irradiated area. The study was approved by the ethical review committee of the Medical University Vienna (EK 1105/2014).

Radiosurgical Technique

At the time of presentation at the Gamma Knife Unit, the patients were diagnosed with a series of follow-up MRI sequences. Each follow-up MRI included at least T1-weighted ± contrast enhancement, T2-weighted imaging, FLAIR, and more recently also diffusion and perfusion sequences. Patients who received radiosurgery were treated with a Leksell Gamma Knife® (Model B; Elekta AB, Stockholm, Sweden). The Gamma Plan (Elekta AB) was used. MRI planning sequences were performed on a 1.5-tesla magnet. Gadolinium contrast-enhanced T1- and T2-weighted MRI were used in treatment planning. Treatment doses were adapted in accordance with the prior radiotherapy dose, the previously irradiated area, and target volume. The median margin dose was 10 Gy (range: 6–16 Gy). The median maximum dose was 20 Gy (range: 12–32 Gy). GKRS was mainly administered on the 50% isodose line (range: 40–50%). In the majority of patients (95%), GKRS was performed within the previously irradiated field. In 2 patients (5%), GKRS was administered outside of the previously irradiated field and thus with a higher margin dose of 16 and 19 Gy.

Forty-nine foci were irradiated (table 2). The target volume was defined as the recurrent contrast-enhancing area on T1-weighted sequences (fig. 1a, c). Tumor mass as visualized on T2-weighted sequences was considered as well. Due to the infiltrative nature of GBMs we chose to apply a safety margin around the contrast-enhancing area if target localization and volume allowed it. The median margin dose was 10 Gy (range: 6–16 Gy). The median maximum dose was 10 Gy (range: 6–16 Gy). The median maximum dose was 20 Gy (range: 12–32 Gy). GKRS was mainly administered on the 50% isodose line (range: 40–50%). In the majority of patients (95%), GKRS was performed within the previously irradiated field. In 2 patients (5%), GKRS was administered outside of the previously irradiated field and thus with a higher margin dose of 16 and 19 Gy.

Table 1. Sample characterization

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Time of diagnosis</th>
<th>Time of fGKRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55.6</td>
<td>57.2</td>
</tr>
<tr>
<td>Range</td>
<td>14.1–81.1</td>
<td>15.7–81.9</td>
</tr>
<tr>
<td>Female:male ratio</td>
<td>18.24</td>
<td>18.24</td>
</tr>
<tr>
<td>KPS, %</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Range</td>
<td>70–90</td>
<td>50–90</td>
</tr>
<tr>
<td>Neurological symptoms, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>5 (11.9)</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>Sensory disturbances</td>
<td>0</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Cranial nerve deficits</td>
<td>2 (4.8)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (11.9)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1 (2.4)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>4 (9.5)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Seizures</td>
<td>16 (38.1)</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>7 (16.7)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Mnestic disorders</td>
<td>1 (2.4)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Microsurgical treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single surgery</td>
<td>–</td>
<td>34 (81.0)</td>
</tr>
<tr>
<td>Multiple surgeries</td>
<td>–</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>Standard first-line treatment, n (%)</td>
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<td></td>
</tr>
<tr>
<td>EBRT</td>
<td>–</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>–</td>
<td>41 (97.6)</td>
</tr>
<tr>
<td>Including temozolomide</td>
<td>–</td>
<td>31 (75.6)</td>
</tr>
<tr>
<td>Other than temozolomide</td>
<td>–</td>
<td>10 (24.4)</td>
</tr>
</tbody>
</table>

Patient sample characterization at the time of initial diagnosis of the GBM and at the time of first GKRS for recurrent tumor. EBRT = External beam radiotherapy.
Table 2. Lesion localization

<table>
<thead>
<tr>
<th>Localization</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>5</td>
<td>10.2</td>
</tr>
<tr>
<td>Parietal</td>
<td>7</td>
<td>14.3</td>
</tr>
<tr>
<td>Temporal</td>
<td>11</td>
<td>22.4</td>
</tr>
<tr>
<td>Temporomesial</td>
<td>6</td>
<td>12.2</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>9</td>
<td>18.4</td>
</tr>
<tr>
<td>Central</td>
<td>3</td>
<td>6.1</td>
</tr>
<tr>
<td>Occipital</td>
<td>3</td>
<td>6.1</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>2</td>
<td>4.1</td>
</tr>
<tr>
<td>Cingulate gyrus</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Ventricles</td>
<td>2</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Localization of the irradiated lesions. In 42 patients, 49 areas of recurrent GBM were irradiated. The majority of the lesions were located in the temporal lobe or in the corpus callosum.

19%). In 14% (n = 7/49), the GKRS-irradiated area was surrounded by brain parenchyma.

Five patients (12%) were treated with a second GKRS for tumor recurrences distant from the initial GKRS-irradiated areas. Treatment planning for the second radiosurgical interventions occurred exclusively on the 50% isodose line. The median margin dose was 10 Gy (range: 9–12 Gy), and the median central dose was 20 Gy (range: 18–24 Gy). A median target volume of 8.1 cm³ (range: 0.9–16.0 cm³) was irradiated during the second GKRS also mainly (n = 4/5; 80%) located at the edge of the previous tumor resection cavity or close to the ventricles.

O6-Methylguanine Methyltransferase Pyrosequencing
In a subset of 22 out of 42 patients, sufficient formalin-fixed, paraffin-embedded tumor material was available for subsequent O6-methylguanine methyltransferase (MGMT) pyrosequencing. One 10-μm section of each specimen was used for MGMT promoter methylation analysis. MGMT pyrosequencing was performed as previously described by our group [19]; bisulfite modification was carried out using the Epi Tect Fast FFPE Bisulfite kit (Qiagen, Germany, article No. 59844). Analysis of the MGMT promoter methylation status was performed using the Therascreen MGMT Pyro Kit (Qiagen, Germany, article No. 971061). Cases with a mean methylation percentage of <8% were classified as MGMT promoter unmethylated and cases with a mean methylation percentage of ≥8% were classified as MGMT promoter methylated. [19, 20]. Since pyrosequencing became available in our center in autumn 2013 and patients included in this study were all treated prior to 2013, MGMT promoter methylation results were not known at the time of treatment decision.

Statistical Analysis
Statistical calculations included the Wilcoxon signed-rank test for paired samples and the Mann-Whitney U and χ² tests for independent samples. Time to radiological recurrence after GKRS and survival data were estimated according to the Kaplan-Meier method and compared using the Mantel-Cox log-rank or generalized Wilcoxon-Breslow test. Interdependence of the variables was evaluated with the Spearman nonparametric correlation test. p values of <0.05 were considered statistically significant. SPSS 20.0 software (SPSS Inc., Chicago, Ill., USA) was used.

Results

Treatment Prior to GKRS
For GBM diagnosis microsurgical treatment comprised gross total resection (n = 33; 78%), subtotal resection (n = 7; 17%), or biopsy (n = 2; 5%). Consecutive, 8 patients (19%) underwent multiple surgeries. All patients received radiotherapy after microsurgical resection. The median total dose was 60 Gy (range: 56–66 Gy). All but 1 patient (2%) were treated with chemotherapy. Chemotherapy included temozolomide in 31 patients (74%). Before temozolomide was available as first-line treatment, patients (n = 10; 24%) were treated with alkylating agents, e.g. dacarbazine and fotemustine [21]. Chemotherapy comprised only temozolomide in 16 patients (38%). Six patients (14%) were treated with a single chemotherapeutic substance other than temozolomide. Four patients (10%) were treated with ≥2 other chemotherapeutics besides temozolomide. An additional 15 patients (36%) received ≥2 chemotherapeutics including temozolomide.

Patient Presentation and Posttreatment Complications
Neurological symptoms and KPS scores are summarized in table 1. The vast majority of patients (88%) was in good clinical condition (KPS 80% or above). The majority of patients (n = 31; 74%) did not develop any complications after GKRS. Nine patients (21%) showed radiation-induced edema at 3–6 months of follow-up. One patient developed necrosis (2%) and 1 patient a cyst (2%). Following GKRS complications, patients were treated with dexamethasone (5/11) or routinely monitored (5/11). One patient suffered from severe edema and midline shift; thus, microsurgical intervention was necessary. In this patient the GKRS target had been completely surrounded by brain parenchyma. Three out of 7 patients (43%) with GKRS-treated lesions surrounded by brain parenchyma suffered from posttreatment complications.

Time to Second Surgical Intervention after GBM Diagnosis and Overall Survival
After GBM diagnosis, the median time to GBM recurrence was 17.0 months (range: 3.9–57.9 months). GKRS was the second (radio-)surgical intervention after GBM diagnosis in 34 patients (81%). In 7 patients (17%), GKRS...
Fig. 1. Two case reports from our series. a, b The first patient was diagnosed with a right parieto-occipital GBM. After microsurgical resection, a multimodal treatment with 60-Gy radiotherapy in 30 fractions and concomitant temozolomide was administered. Eighteen months after the microsurgical resection, GKRS was planned on the 40% isodose line with a 10-Gy prescription dose and 25-Gy central dose for recurrent GBM adjacent to the microsurgical resection cavity. a T1-weighted sequence with contrast enhancement. After GKRS, the patient received temozolomide and imatinib. After 3.5 months, the patient presented with a gait disturbance and radiological progression within and beyond the irradiated area. b T1-weighted sequence with contrast enhancement. Four months later, the patient succumbed to the disease. c, d The second patient was diagnosed with a right temporal GBM. After microsurgical resection, a multimodal treatment with 60-Gy radiotherapy in 30 fractions and temozolomide and nimustine was administered. Seven months after microsurgical resection, GKRS was planned on the 50% isodose line with a 10-Gy prescription dose and a 20-Gy central dose for recurrent GBM adjacent to the microsurgical resection cavity. c T1-weighted sequence with contrast enhancement. After GKRS, the patient received chemotherapy with temozolomide. Thirty months after GKRS, the patient was alive with a stable radiological status. d T1-weighted sequence with contrast enhancement at 30 months of follow-up.
was used as a third intervention. The remaining patient (2%) underwent 3 microsurgical resections prior to GKRS. No significant difference (p = 0.277) was found in the overall survival between patients with GKRS and those who underwent another microsurgical resection as the second intervention. At the last follow-up, 41 patients (98%) had succumbed to the disease. One patient was still alive with KPS scores of 80% (36 months after diagnosis). Thus, the median overall survival after GBM diagnosis was 25.6 months (95% confidence interval, CI: 21.8–29.3 months).

Treatment after GKRS
The majority of patients (n = 35; 83%) received chemotherapy after GKRS. In addition to chemotherapy, 5 patients (12%) were treated with a second GKRS intervention for tumor recurrences distant to the initially GKRS-irradiated area. The median time between the first and second radiosurgical interventions was 3.8 months (range: 1.5–5.7 months). Three patients (7%) underwent another microsurgical resection (2 for distant tumor recurrence and 1 GKRS complication). Six patients (14%) received no further treatment after GKRS, and 1 (2%) was treated with a second GKRS alone.

Tumor Recurrence and Survival after GKRS
Tumor recurrence after GKRS was well documented by follow-up MRIs in 32 patients (76%). One patient (2%) showed no signs of radiological progression until the time of follow-up (fig. 1c, d), and 1 patient (2%) died of renal failure, without signs of radiological progression at the last follow-up MRI. Thus, the calculated median time between GKRS-1 and radiologically documented recurrence was 4.4 months (95% CI: 3.2–5.6 months). In 8 patients (19%), no further follow-up MRI showing the radiological progression was performed because of sudden and rapid clinical deterioration that had led to patient death. Assuming that patients who died of rapid clinical deterioration suffered from progression, the rate of progression-free survival after 6 months was 32%.

Among those patients with well-documented radiological progression, recurrent tumor growth mainly occurred outside of the GKRS-irradiated area (n = 17; 53%), followed by progression within and beyond (adjacent to) the irradiated area (n = 13; 41%). Two patients (6%) showed radiological progression mainly in the irradiated area. The KPS score at the time of documented radiological progression (median: 70%; range: 10–80%) was on average significantly lower (p < 0.001) than at the first GKRS (median: 80%; range: 50–90%). After documented radiological progression, the median survival time was 4.6 months (95% CI: 3.2–5.9 months). No correlations between time to tumor recurrence after GKRS and volume of irradiated area or time to tumor recurrence and applied margin dose were observed. Further, KPS score and target volume did not show a significant impact on survival after GKRS.

The median survival after the first GKRS was 9.6 months (95% CI: 7.7–11.5 months). GKRS was mainly administered on the 50% isodose line with a 10-Gy margin dose (n = 27; 55%). Fewer radiosurgical procedures were performed with a margin dose of <10 Gy (n = 10; 20%) or >10 Gy (n = 12; 25%). The effect of the margin dose on the survival after GKRS was not statistically significant.

MGMT Promoter Methylation Status and Overall Survival

MGMT pyrosequencing was performed in a subset of 22 cases with sufficient material available for further analysis. The median overall survival among those 22 patients was 24.7 months. Tumor MGMT promoter methylation was seen in 12 patients (55%). Interestingly, patients with MGMT promoter methylation had a significantly longer median overall survival (33.4 months; 95% CI: 21.2–45.5 months) compared to patients without MGMT promoter methylation (16.0 months; 95% CI: 8.0–23.9 months; p < 0.001). Then, 67% of patients (n = 8) with a methylated MGMT promoter received temozolomide before or after GKRS. All patients (n = 10) with unmethylated MGMT were treated with temozolomide before GKRS.

Discussion
Treatment for recurrent GBM mainly comprises chemotherapy, which presents its own toxic side effects [7, 11, 12]. Repeated irradiation has been linked to higher complication rates [4, 22–24]. Stereotactic radiosurgery (SRS) has only recently been introduced to the treatment of GBM but remains controversial. The best timing for GKRS has yet to be established. The addition of SRS to initial GBM management has not led to significant improvements in overall survival. In contrast, the use of GKRS as a salvage therapy following recurrence after standard first-line therapy has been linked to an improved median overall survival [13, 14, 25]. Insufficient data exist to establish new guidelines for the treatment of recurrent GBM.
According to the treatment regimen at our center, patients underwent standard first-line treatment prior to GKRS comprising radiotherapy and concomitant chemotherapy. Treatment options for recurrent tumors are limited because of treatment-related toxicity and consequent high morbidity [4, 22–24]. Existing initial data indicate that GKRS might be an alternative to open surgery, even for first recurrences [1]. Several other studies included both patients who underwent GKRS as part of the initial treatment plan and at tumor recurrence [26–29]. We only applied GKRS as a treatment option for recurrent GBM for patients who had received first- and often second-line standard therapy. Several patients underwent multiple microsurgical resections prior to GKRS. Our patient demographics agree with previously published epidemiological data [4].

Limitations of our study include its retrospective nature and the inability to evaluate the impact of different treatment modalities after GKRS on the overall survival and progression-free survival because of the limited number of patients.

As previously described, differentiating recurrent GBM from treatment-related changes is a frequent diagnostic challenge [15]. In our study, after tumor resection, initial histopathological diagnosis of GBM and consecutive multimodal treatment, multiple MRI control series were performed. Only newly occurring contrast-enhancing lesions were treated. More importantly, recurrent tumor before GKRS and tumor progression after GKRS were evaluated in collaboration with the Department of Radiology, Medical University Vienna, based on the RANO criteria. Those require the evaluation of both the enhancing and nonenhancing components of the tumor on T2-weighted and FLAIR images and in most cases also based on MR perfusion and diffusion-weighted imaging findings. According to RANO criteria, any new contrast-enhancing lesion beyond the radiation field, a 25% increase in tumor dimensions, or a significant increase in T2-weighted/FLAIR hyperintensities of the nonenhancing lesion was considered as a tumor progression. Furthermore, and especially for new contrast-enhancing lesions within the radiation field, the elevated lesional relative cerebral blood volume ratios on perfusion MRI and decreased apparent diffusion coefficient values in the contrast-enhancing abnormality were considered as an indicator of tumor progression [15–17].

Patients treated with GKRS for recurrent GBM represent a subgroup of patients. A rather small target volume is a prerequisite for effective radiosurgical treatment. In our opinion, it is important to stress that the target area was mainly found at the edge of the previous resection cavity or close to the ventricles. Consequently, the irradiated area was only partly surrounded by normal-appearing brain parenchyma. It seems that patients having GKRS-treated foci surrounded by brain parenchyma were more likely to suffer from posttreatment complications. Further, our target volume was smaller than that in previously published studies [1, 29–32]. Contrast-enhancing areas are dense agglomerations of tumor cells with pathological blood supply. Still, due to the infiltrative nature of GBMs, we chose to apply a safety margin around the contrast-enhancing area if target localization and volume allowed it (fig. 1a). GKRS treatment of these areas should be comparable with surgical tumor mass resection. Since all of our patients received an average of 60-Gy radiotherapy prior to GKRS, our radiosurgical boost irradiation doses were adapted in accordance with the prior dose and the previously irradiated area even when applied on a new, recurrent tumor. Thus, our average prescription dose was lower than some previously published series but overall fell within a comparable prescription dose range [10, 26, 27, 29]. Only in 2 patients was the recurrent tumor outside of the previously irradiated area and was thus treated with higher margin doses. Furthermore, patients were in good clinical condition prior to GKRS. As a result of this patient selection, the risk of severe complications was reduced.

Since the overall survival observed in our group – 25.6 months – was exceptionally long compared to that of other published studies, it might lead to the conclusion that the presented group was extremely selected and not representative of GBM patients [1, 10, 26, 30, 32–34]. Pyrosequencing became available in our center in autumn 2013; thus, MGMT promoter methylation results were not known at the time of treatment decision. We thus performed MGMT pyrosequencing in a subset of cases, revealing MGMT promoter methylation in about 50% of patients. The median overall survival among those patients was representative of the group. Furthermore, the percentage of patients with MGMT promoter methylation was within the range of previously published analyses [20, 35, 36]. The majority of patients received temozolomide as treatment. However, patients with MGMT promoter methylation showed a significantly and exceptionally longer overall survival. In contrast, patients without MGMT promoter methylation presented with an overall survival which was only a few months longer than the expected range [35, 37].

Since GKRS was applied to recurrent tumors and was not part of the initial treatment plan, our median surviv-
al of 9.6 months after GKRS seems encouraging. Previously published studies showed that an effect of SRS on overall survival was evident if the SRS was used for recurrent GBM but not if it was used as part of the initial treatment regimen [27, 29, 38]. This might be partly explained by the fact that if SRS is used in the initial treatment plan, further radiation therapy is limited because of the previously applied high dose to the area. In contrast, if radiotherapy is part of the initial treatment, SRS remains an option for recurrent tumors. After GKRS for recurrent tumors, the majority of patients are further treated with chemotherapy, and a fraction of patients even undergo a second GKRS for another tumor recurrence distant to the previously irradiated area. Few patients are treated with another microsurgical resection after GKRS. Thus, even as a salvage therapy, GKRS is part of an individualized multimodal treatment paradigm for a subgroup of highly selected patients.

When discussing progression-free survival or failure after GKRS, it is important to understand in which treatment algorithm radiosurgery was applied. Our data on recurrent GBM show acceptable local tumor control. Still, progression occurred at high percentages both outside and inside the irradiated area. Only a few comparable studies exist in the literature. Several studies mixed different histopathological tumor grades and treatment time points (e.g. newly diagnosed vs. recurrent tumors) or did not specifically state the time to radiological progression [26, 39–43]. Even when discussing improvements in progression-free survival after GKRS, the effect of the described state-of-the-art multimodal therapy on the outcome must be considered. One recent study also discussed GKRS as an option for recurrent grade IV glioma and reported a similar progression-free survival time after GKRS [1].

Conclusion

GKRS seems to be a relatively safe salvage treatment option for a small subgroup of patients with recurrent GBM. The risk of severe complications after GKRS is acceptable if the treatment is used for well-selected patients. Further, GKRS offers a fair chance of local tumor control but must be seen as part of a multimodal treatment algorithm. We recommend GKRS only for recurrent GBM after standard multimodal therapy. Ideally, patients are in good clinical condition, the target volume is small, there is a single focus, and target localization is at the border of the resection cavity and not completely surrounded by brain parenchyma.

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Disclosure Statement

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References


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