Volume reduction in meningiomas after gamma knife surgery

GUENTHER C. FEIGL, M.D., OTTO BUNDSCHUH, M.D., ALIREZA GHRABAGHI, M.D., MADJID SAMII, M.D., AND GERHARD A. HORSTMANN, M.D.

International Neuroscience Institute, Hannover; University of Tübingen, Tübingen; and Gamma Knife Center, Krefeld, Germany

Object. The purpose of this study was to evaluate the volume-reducing effects of gamma knife surgery (GKS) of meningiomas with and without previous surgical treatment.

Methods. A group of 127 patients with a mean age of 57.1 years (range 9–81 years) with 142 meningiomas (128 World Health Organization Grade I and 14 Grade II) were included in this study. The management strategy reduces tumor volume with surgery when necessary (81 patients). Stereotactic GKS with a Gamma Knife model C was performed in all tumors of suitable size. Magnetic resonance imaging follow-up examinations with volumetric tumor analysis was performed 6 months after treatment and annually thereafter.

The mean tumor volume was 5.9 cm³ (range 5 to 40 cm³). The mean follow-up time after GKS was 29.3 months (range 11–61 months). The mean prescription dose was 13.8 Gy (range 10–18 Gy). A reduction in volume occurred in 117 (82.4%) of all tumors, and in 20 tumors (14.1%) growth ceased. The overall tumor control rate of 96.4%. The mean volume reduction achieved with GKS was more than 46.1%. Only five tumors (3.5%) showed a volume increase.

Conclusions. Gamma knife surgery was effective in reducing meningioma volume at short-term follow up. Further studies are needed to examine the development of these findings over a longer period.

KEY WORDS • meningioma • radiosurgery • gamma knife • tumor control • volume reduction

Abbreviations used in this paper: GKS = gamma knife surgery; MR = magnetic resonance; WHO = World Health Organization.
ated, setting their main focus on tumor control rate and tumor recurrence rates.**21,31,46,47** The effectiveness of GKS and its short-term and long-term side effects have been shown in several studies,6,7,16,27,42,46,47,49 but GKS was looked at primarily as an adjunct treatment, inhibiting progression of residual meningiomas after resection. Based on the known effects of GKS we set the focus of this study on tumor volume changes. This study was based on a prospective treatment and follow-up protocol. We evaluated not only the tumor control rate of GKS in patients with meningioma but we also quantitatively analyzed the effect of tumor volume reduction of meningiomas achieved with GKS.

**Clinical Material and Methods**

**Patient Population**

A data analysis in 127 patients (Table 1) was performed. Patients were entered in a prospective treatment and follow-up protocol between January 1999 and September 2003. The study group consisted of 32 men (25.2%) and 95 women (74.8%). Of all patients evaluated 81 (63.8%) underwent surgery before undergoing GKS. Presenting neurological deficits (Table 2) were defined as symptoms that patients had on the day of admission. The neurological outcome was analyzed based on neurological findings presented at the last follow-up examination of each patient.

**Tumor Definition**

Gamma knife surgery treatment planning was based on MR images with T1-weighted three-dimensional MP-rage sequences before and after administration of contrast medium as well as T2-weighted sequences and computerized tomography scans. A total of 142 tumors were diagnosed in 127 patients. Surgically treated tumors were allocated to a WHO category based on the histological material gathered at operation. In patients in whom no previous surgery was performed aimed at maximizing the dose within the target, achieving a high-dose target conformity while ensuring a steep fall of radiation dose outside the target.11 Neuro-radiological follow-up examinations included contrast-enhanced T1-weighted MP-rage MR images, which were used for the volumetric analysis, and T2-weighted MR imaging was performed to determine the presence or absence of brain edema. The first follow-up examinations were performed 6 months after GKS and annually thereafter for 5 years and then every 2 years. Patients with WHO Grade II meningiomas had their first follow-up examination 3 months after GKS and then every 6 months. Thorough neurological examinations were performed during each follow-up visit. The neurological findings were scored according to the ISO 9001 certified quality management system of the Krefeld Gamma Knife Center in four steps: 0 = no symptoms; 1 = occasional symptoms; 2 = permanent symptoms that need no special therapy and do not affect the patient's performance in daily life; and 3 = permanent symptoms with an effect on a patient's performance. Assessment of general neurological impairment was performed before GKS and at every follow-up visit by using the Karnofsky Performance Scale.

**Data Management and Statistical Analysis**

MeDigS-Archive V1.1 (www.medigs.com) was used to

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>General patient data in 127 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Value</td>
</tr>
<tr>
<td>no. of patients</td>
<td>127 (w/ 142 tumors)</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>32:95</td>
</tr>
<tr>
<td>mean age (range)</td>
<td>57.1 yrs (9–81 yrs)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Gamma knife surgery treatment data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Value</td>
</tr>
<tr>
<td>tumor types</td>
<td>128 WHO Grade I (90.1%)</td>
</tr>
<tr>
<td>mean tumor vol (range)</td>
<td>5.9 cm(^3) (0.07–48.3 cm(^3))</td>
</tr>
<tr>
<td>surgery pre-GKS (%)</td>
<td>81 patients (63.8%)</td>
</tr>
<tr>
<td>mean prescription dose in Gy (range)</td>
<td>13.8 (10–18)</td>
</tr>
<tr>
<td>isocenters (range)</td>
<td>20 (2–50)</td>
</tr>
<tr>
<td>mean follow up in mos (range)</td>
<td>29.3 (11–61)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Functional outcome in 127 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>Time of Finding</td>
</tr>
<tr>
<td>Seizures</td>
<td>Headache</td>
</tr>
<tr>
<td>pre-GKS</td>
<td>post-GKS</td>
</tr>
<tr>
<td>II</td>
<td>III–VI</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>47</td>
<td>40</td>
</tr>
<tr>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>19</td>
<td>18</td>
</tr>
</tbody>
</table>

after GKS. For the purpose of statistical analysis tumors were grouped in three sizes, smaller than 5 cm\(^3\), 5 to 10 cm\(^3\) and larger than 10 cm\(^3\). The definition of successful tumor control was defined as lack of tumor growth or tumor volume reduction. In this study a tumor volume reduction of more than 10% compared with the volume before GKS was defined as a volume reduction and an increase of more than 10% was defined as tumor growth.

**Treatment and Follow Up**

All patients were treated with a Leksell Gamma Knife model C with the automatic positioning system (Elekta Instrument AB). Multiisocenter dose planning was performed aimed at maximizing the dose within the target, achieving a high-dose target conformity while ensuring a steep fall of radiation dose outside the target. Neuro-radiological follow-up examinations included contrast-enhanced T1-weighted MP-rage MR images, which were used for the volumetric analysis, and T2-weighted MR imaging was performed to determine the presence or absence of brain edema. The first follow-up examinations were performed 6 months after GKS and annually thereafter for 5 years and then every 2 years. Patients with WHO Grade II meningiomas had their first follow-up examination 3 months after GKS and then every 6 months. Thorough neurological examinations were performed during each follow-up visit. The neurological findings were scored according to the ISO 9001 certified quality management system of the Krefeld Gamma Knife Center in four steps: 0 = no symptoms; 1 = occasional symptoms; 2 = permanent symptoms that need no special therapy and do not affect the performance in daily life; and 3 = permanent symptoms with an effect on a patient’s performance. Assessment of general neurological impairment was performed before GKS and at every follow-up visit by using the Karnofsky Performance Scale.

**Data Management and Statistical Analysis**

MeDigS-Archive V1.1 (www.medigs.com) was used to

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Tumor volumes after GKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Value (%)</td>
</tr>
<tr>
<td>overall tumor control rate</td>
<td>96.4</td>
</tr>
<tr>
<td>no. w/ reduced tumor vol</td>
<td>117 (82.3)</td>
</tr>
<tr>
<td>no. w/ unchanged tumor vol</td>
<td>20 (14.1)</td>
</tr>
<tr>
<td>no. w/ increased tumor vol</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>mean tumor vol reduction magnitude</td>
<td>46.1 (range 10.7–91.8)</td>
</tr>
</tbody>
</table>
manage all patient and digital image data. GammaPlan version V5.3 was used for dose planning and tumor volume analysis before GKS. CONVIS DICOM (www.convis.com) viewer and GammaPlan were used during each follow-up examination for volume analysis, and SPSS version 11.0 (www.SPSS.com) was used to perform all statistical tests.

Results

Patients and Clinical Outcome

The distribution of the studied patient group was 3:1 female/male. The mean age was 57.1 years (range 9–81 years) (Table 1). Neurological symptoms on admission (Table 2) were generalized epileptic seizures in eight patients (6.3%), headaches in 22 patients (17.3%), focal neurological deficits of the optic pathways in 23 patients (18.1%), ophthalmoplegia in 47 (37%), symptoms of the fifth cranial nerve in 44 patients (34.6%), palsies of the seventh cranial nerve in 12 patients (9.4%), and deficits of the eighth cranial nerve in 19 patients (15%).

After GKS generalized epileptic seizures were less frequent and improved in two patients and one patient had a generalized epileptic seizure for the first time after GKS. Headaches improved in six patients with no new occurrences after GKS. There were no changes in patients with deficits related to the visual pathways. Palsies of the third and fourth cranial nerves improved in seven patients but one patient developed a new deficit after GKS. Symptoms of the fifth cranial nerve improved in 11 patients and occurred for the first time in two patients after GKS. Palsies of the seventh cranial nerve improved in two patients with no new cases reported. Deficits of the eighth nerve improved in two patients after GKS and there was no new reported eighth nerve deficit after GKS. Patient evaluation showed a mean Karnofsky Performance Scale score of 87 before and 89 after GKS. Acute side effects of GKS were rarely observed and mild in all cases. Headaches lasting as many as 3 days after GKS were reported in four cases and nausea and vomiting were reported in three cases. All seven patients suffering from these acute side effects were symptom free within 4 days after GKS.

Tumors, Treatment, and Follow Up

Grading of all 142 tumors according to the WHO classification showed 128 (90.1%) Grade I and 14 (9.9%) Grade II meningiomas. Neuroradiological analysis of tumor localization showed 14 (9.9%) petroclival, 40 (28.2%) cavernous sinus, one (0.7%) sagittal sinus, 16 (11.3%) related to the sphenoid wing, eight (5.6%) in the posterior fossa, two (1.4%) in the middle cranial fossa, five (3.5%) in the anterior cranial fossa, nine (6.3%) tentorium meningiomas, 17 (12%) falx meningiomas, eight (5.6%) meningiomas of the cerebellopontine angle, 10 (7%) convexity meningiomas, three (2.1%) tumors of the orbit, four (2.8%) tumors in the sellar region, two (1.4%) clival meningiomas, and three (2.1%) other meningiomas.

The mean tumor volume before GKS was 5.9 cm³ (range 0.07–48.3 cm³). The mean prescription dosage was 13.8 Gy (range 10–18 Gy) (Table 3). The mean margin isodose was at the 52% level. The mean number of isocenters was 20 (range two–50). All patients treated were discharged immediately after completion of GKS. The mean follow-up time was 29.3 months (range 11–61 months). The mean tumor-free survival period was 30 months. The tumor control rate was 96.4% (Table 4). A tumor volume reduction of more than 10% compared with the initial tumor volume was achieved in 117 tumors (82.4%). The mean tumor volume reduction (Fig. 1) was 2.1 cm³ or 46.1%; the range was 0.1 cm³ to 7.4 cm³ or 10.7% to 91.8%. There was no statistically significant difference in the percentage of tumor shrinkage in the three groups of tumor sizes (Fig. 1). The mean time to first signs of tumor volume reduction was 10.8 months (range 3–43 months) as illustrated in Fig. 2. Tumor growth control with no changes in tumor volumes was achieved in 20 tumors (14.1%). Tumor progression after GKS was observed in five tumors (3.5%).

Discussion

Role of GKS in the Treatment of Meningiomas

Optimal management of meningiomas is always chal-
Lenging and in many cases requires a multimodality treatment strategy. Microsurgery is still the most important treatment option for space-occupying lesions due to its instant tumor volume reduction and decompressive effect on the brain tissue, especially in malignant forms of meningiomas. This fact is also shown in our study in which 81 (63.8%) of all patients underwent microsurgery to reduce the tumor volume before undergoing GKS. Tumor location is of course a very important factor in the process of choosing the best treatment options. It has been shown that in certain cases, however, microsurgery has to be performed if involvement of perforating arteries could cause ischemic vascular complications after GKS. The focus of our study was on benign WHO Grade I and II meningiomas. Since the routine use of radiation for meningiomas was first documented in the 1990s numerous studies have been published establishing the ability of radiation treatments to control tumor growth. Over the last decade radiotherapy and especially stereotactic radiosurgery have been accepted as standard adjuvant treatments of meningiomas. Stereotactic radiosurgery with the Leksell Gamma Knife has become more important because GKS has potential advantages over conventional radiotherapy. Some authors go even one step further and suggest that in cases of small- to medium-sized meningiomas and other tumors GKS could be recommended as a primary treatment option; however, the primary role of stereotactic radiosurgery remains as an adjunct to the surgical treatment. Authors of several studies in which the results of stereotactic radiosurgery have been analyzed have shown that meningiomas are “responding” and that a tumor control rate of 100% can be achieved. A review of literature, however, has shown that the important topic of tumor volume reduction achieved with GKS has rarely been evaluated.

**Tumor Volume Reduction With GKS**

Reports on meningioma volume reduction after GKS are very rare and if mentioned are usually described only as changes in tumor volume without quantification of the percentage or volumes in cubic centimeter. Based on a large number of studies and our own experience, the positive effect of GKS on tumor control in more than 90% of patients with WHO Grade I and II meningiomas is beyond any doubt. As shown in this study, GKS is capable of more than just controlling tumor growth. It has been possible to document that in 82.3% of all treated tumors GKS achieved a significant reduction in tumor volume. If the percentage of our tumor volume reduction is added to the percentage of tumors with no volume changes an overall tumor control rate of 96.4% was achieved. The functional results of this study (Table 2) are in agreement with results published in the literature. These results clearly show that more consideration should be given to the volume reduction that can be achieved with GKS and that the term “ radiosurgery” is justified. This suggests that GKS could play a more important role in the treatment strategy for meningiomas. It has been said that the best chance to cure patients with meningiomas is to perform a total surgical removal of the tumor and its origin. Total resection, however, entails the acceptance of a significant percentage of morbidity and mortality, which is a very high price to pay. Taking the volume-reducing effect of GKS into consideration a two-step multimodality treatment strategy seems to be the most favorable option to treat patients with meningiomas compressing brain tissue and causing clinical symptoms. The first step should be microsurgery with the highest priority being the preservation of all nervous and vascular structures. In a second step GKS should be performed to reduce the remnant tumor volume. Subtotal tumor resection does not mean that less skill is required but rather that the skill and experience of the surgeon is redirected to assess the proper point at which surgery should be stopped with a maximum resection obtained at a minimum price in terms of damage to vital neurological and vascular structures. This multimodality strategy allows a much better overall treatment result. The tumor volume reduction effect in Grade I and II meningiomas treated in our study was seen as early as 10.8 months after GKS. Collection of all the data for this study required a close and consistent follow-up routine in all patients. This of course seems to be a problem for many centers because most patients with benign meningiomas improve after GKS and do not return for follow-up...
Volume change after GKS for meningioma

examinations on their own. Comparison of our results with other published data shows that the tumor control in our patients is in the same range as published by other authors,\(^\text{1,4,13,30,36,47}\) however, because there are few published studies in which the tumor volume reduction effect of GKS has been quantified, comparison of our data to other data is limited but is in agreement with those results.\(^\text{23,28,37}\) The results of our study show clearly that the potential of GKS goes further than described in the literature. In our opinion more studies are necessary to prove the tumor volume–reducing effect of GKS beyond any doubt. These results might then change the role of GKS from that of an adjuvant therapy option to a primary therapy option for certain patients with meningioma.

Conclusions

Our results show that GKS is a safe and effective way to treat patients with benign meningiomas. Gamma knife surgery is in most cases an adjuvant treatment following microsurgical tumor resection. Gamma knife surgery has a tumor volume–reducing effect that can be observed within a short follow-up period. More studies should be performed to quantify the volume-reducing effect of GKS. Further studies are necessary to evaluate the long-term side effects of GKS and to evaluate the volume-reducing effect of GKS over a longer period.

References


43. Spetzler RF, Daspit CP, Pappas CT: The combined supra- and infratentorial approach for lesions of the petrous and clival regions: experience with 46 cases. J Neurosurg 76:588–590, 1992


51. Zülch KJ: Brain Tumors: Their Biology and Pathology, ed 3. New York: Springer-Verlag

Address reprint requests to: Guenther C. Feigl, M.D., INI-International Neuroscience Institute Hannover, Germany, Alexis-Carrel-Strasse 4, 30625, Hannover, Germany. email: feigl@ini hannover.de.