Gamma Knife surgery for benign meningioma

AURELIA KOLLOVÁ, M.D.,1,2 ROMAN LIŠČÁK, M.D., PH.D.,1 JOSEF NOVOTNÝ JR., M.S.C., PH.D.,1 VLIBALD VLADYKA, M.D., PH.D.,1 GABRIELA SIMONOVÁ, M.D., PH.D.,1 and LADISLAVA JANOUŠKOVÁ, M.D., PH.D.2

Departments of 1Stereotactic and Radiation Neurosurgery and 2Radiology, Na Homolce Hospital, Prague, Czech Republic; and 2Department of Neurosurgery, University Hospital of L. Pasteur, Kosice, Slovak Republic

Object. Meningioma is the most frequent benign tumor treated with Gamma Knife surgery (GKS); however, the assessment of its efficacy and safety in slow-growing tumors is an ongoing process, requiring analysis of long-term results.

Methods. Three hundred sixty-eight patients harboring 400 meningiomas treated between 1992 and 1999 at Na Homolce Hospital were evaluated. The median patient age was 57 years (range 18–84 years). The median tumor volume was 4.4 cm³ (range 0.11–44.9 cm³). The median tumor margin dose to the 50% isodose line was 12.55 Gy (range 6.5–24 Gy). Descriptive analysis was performed in 331 patients (90%); 325 patients had a follow-up longer than 24 months (median 60 months), and six patients were included because of posttreatment complications. The volume of treated tumors decreased in 248 cases (69.7%), remained the same in 99 (27.8%), and increased in nine (2.5%). The actuarial tumor control rate was 97.9% at 5 years post-GKS. Perilesional edema after radiosurgery was confirmed on neuroimaging in 51 patients (15.4%). The temporary and permanent morbidity rates after radiosurgery were 10.2 and 5.7%, respectively.

Results. A significantly higher incidence of tumor volume increase was observed in men compared with women and in tumors treated with a margin dose lower than 12 Gy. Significant risk factors for edema included an age greater than 60 years, no previous surgery, perilesional edema before radiosurgery, a tumor volume greater than 10 cm³, a tumor location in the anterior fossa, and a margin dose greater than 16 Gy.

Conclusions. Stereotactic radiosurgery is a safe method of treatment for meningiomas. A minimum margin dose of 12 to 16 Gy seems to represent the therapeutic window for benign meningiomas with a high tumor control rate in a midterm follow-up period. (DOI: 10.3171/JNS-07/08/0325)

Key Words • Gamma Knife • meningioma • stereotactic radiosurgery

Meningiomas are tumors arising from arachnoidal cap cells and represent approximately 20% of all intracranial neoplasms. Ninety to 95% of diagnosed meningiomas are benign (World Health Organization Grade I). Their incidence in the population is reported to be 1 to 6 per 100,000 persons.10,60 Superficially located, these lesions are often considered an ideal target for resection, but their skull base localization represents a complex surgical challenge accompanied by a lot of controversy regarding their treatment. Because of refinements in surgical equipment, improved imaging techniques, and advanced skull base approaches, surgical intervention for meningiomas has greatly evolved. Total excision is the determining factor for recurrence.57 Even though total excision is usually achieved in almost 100% of convexity meningiomas, the rate has been reported to be 20 to 97.8% in meningiomas located in the skull base according to the latest published data.3,8,9,11,13,18,21,40,50,59,61,62,77 Note, however, that there is evidence that even benign meningiomas invade brain tissue, blood vessels, and cranial nerves.26,29,68 Because the lifespan of patients harboring meningiomas is rarely limited by the lesion itself, the quality of life together with the control of tumor growth is paramount.

Radiosurgery as a treatment option for meningiomas fulfilling particular criteria is well established. Data from studies with 5- to 10-year follow-ups have confirmed tumor control in 84.3 to 100% of cases.2,7,14,15,17,23,24,30,32,35,36,38,42,51,52,54,56,60,64,70–73 Optimal doses, conformity issues, and the prevention of adverse effects are still being discussed.22,38,57,65,74

In this study we gathered information drawn from a large cohort of patients with a median follow-up of 60 months.

Clinical Material and Methods

Between 1992 and 2005, 1149 patients with meningiomas were treated using the Leksell Gamma Knife at the Na Homolce Hospital, Prague. This number represents 17.4% of all treated patients at this center. For the purposes of this study, 368 patients harboring 400 meningiomas treated between 1992 and December 31, 1999, were evaluated.
Patients with atypical and malignant meningiomas were excluded, as were patients in whom neurofibromatosis Type 2 was diagnosed. Locations of the meningiomas are presented in Table 1. The majority of the treated group were women (287 patients [78%]); 81 men were treated. The ages of the patients ranged from 18 to 84 years (median 57 years). The Karnofsky Performance Scale score ranged from 30 to 100 (median 80).

The number of treated meningiomas ranged from one to six in each patient. In nine patients two lesions were treated; in five, three; in one, four; and in one, six.

One hundred nine patients (29.6%) in the study group underwent surgery consisting of one to three procedures 1 to 384 months before Gamma Knife treatment. Fifty-seven patients underwent Gamma Knife treatment within 1 year of excision. Postoperative neurodeficits remained in 17.5% of patients after open surgery. In those who had not undergone surgery, the diagnosis was based on radiological findings typical of meningiomas. In 12 patients (3.3%), radiotherapy was used 5 to 156 months before radiosurgery. Note that radiosurgery was used as a primary treatment modality in 259 patients (70.4%).

After applying a local anesthetic, radiosurgery was performed using the Leksell Gamma Knife (model B; Elekta Instruments AB). The treatment was planned using CT scans in 67 patients (18.2%); MR images were used in 301 patients (81.8%). The T1-weighted, contrast-enhanced spin echo sequences in both the axial and coronal planes, at a slice thickness of 3 mm, were obtained on a 1-tesla Magnetom Impact Expert (Siemens) to visualize the meningiomas. Plans were created using the GammaPlan (Elekta Instruments AB) in the first 21 cases (5.3%); 379 patients (29.6%) in the study group underwent surgery consisting of one to three procedures 1 to 384 months before Gamma Knife treatment. Fifty-seven patients underwent Gamma Knife treatment within 1 year of excision. Postoperative neurodeficits remained in 17.5% of patients after open surgery. In those who had not undergone surgery, the diagnosis was based on radiological findings typical of meningiomas. In 12 patients (3.3%), radiotherapy was used 5 to 156 months before radiosurgery. Note that radiosurgery was used as a primary treatment modality in 259 patients (70.4%).

Treatment was planned using the KULA planning system (Elekta Instruments AB) in the first 21 cases (5.3%); 379 plans were created using the GammaPlan (Elekta Instruments AB). The tumor volume ranged from 0.11 to 44.9 cm³ (median 4.4 cm³, mean 6.3 ± 6.1 cm³). The margin dose to the median 50% isodose line (range 40–90% isodose line) ranged from 6.5 to 24 Gy (median 12.55 Gy). The maximum radiosurgical dose ranged from 13 to 45 Gy (median 24 Gy). The number of isocenters ranged from one to 16 (median six isocenters).

In 10 patients (2.7%) with large meningiomas, staged radiosurgery was performed: the first half of the meningioma volume was treated initially and the second half was usually treated 6 months later.

Compression and displacement of the chiasm were not regarded as hindrances to the radiosurgical treatment of meningioma. In such cases a small rim of the tumor adjacent to the optic pathway was covered with a lower isodose to keep the dose to the optic nerve within safe limits (< 8 Gy). Contact with visual pathways was recorded in 63 meningiomas (15.8%), and contact with the brainstem was noted in 74 meningiomas (18.5%). The dose to the optic tract was kept below 8 Gy, and the dose to the brainstem was lower than 14 Gy. A dose greater than 8 Gy to the optic pathways and total coverage of the tumor volume were used to treat only the patients with blindness, which usually occurred as a result of previous surgery. In those who had undergone previous radiotherapy, the dose to the optic pathways did not exceed 3 Gy.

Edema before treatment was observed in 14 patients (3.8%); hyperostosis occurred in 7.5% cases, and cysts in 5.3%. A smooth margin was observed in the majority of treated tumors (71.5%), a lobulated margin in 26%, and a multilocular margin in 2.5%. A heterogeneous appearance of the tumor on images after the administration of the contrast medium (on either CT or MR imaging) was found in 32.5% of treated meningiomas.

Results

Among the group of 368 patients, 12 (3.3%) were lost to follow-up. Thirty-one patients underwent a follow-up shorter than 24 months; however, we included six of these patients in our descriptive statistical analysis because they had a postradiation complication. Although 25 of the 31 patients with the shorter follow-up were not included in our descriptive statistics (11 of them died of unrelated reasons, and the rest refused further follow-up because of an advanced age), their data could be used without limitation in the actuarial analysis. Follow-up data were analyzed in 331 patients (90%) with 356 meningiomas (89%) for descriptive statistics and in 368 patients for actuarial analysis using Kaplan–Meier statistics and a Cox regression. The follow-up protocol included the first follow-up scanning study and the follow-up clinic visits 6 months, 1 year, and every year thereafter for up to 5 years after treatment and then every 3 years thereafter. In patients with intra- and parasellar meningiomas, visual fields were tested before treatment and during follow-up.

The follow-up period ranged from 24 to 126 months (mean 60 months, mean 68.4 ± 12.7 months) in 325 patients. Six patients with follow-up periods of 3, 9, 10, 10, 18, and 22 months each were included in the descriptive analysis because of posttreatment complications. The volume of treated tumors decreased in 248 cases (69.7%), remained unchanged in 99 (27.8%), and increased in nine (2.5%). The actuarial tumor control rate at 5 years postradiosurgery was 97.9% (Fig. 1).

Ten patients underwent further treatment after an initial radiosurgical procedure: five patients (1.5%), excision; four patients, a second session of stereotactic radiotherapy; and one patient, fractionated radiotherapy. Among these 10 patients, the tumor showed growth in six, and surgery was
performed in two because of postradiation edema and in another two for unknown reasons given that tumor growth had not been detected. Perilesional edema after radiosurgery was radiologically confirmed in 51 patients (15.4%) and was symptomatic in 32 (9.7%); it was temporary in 23 (6.9%) and persistent in nine (2.7%). The onset of edema was observed a median of 9 months after treatment (range 1–36 months). Radiologically, edema resolved 7 to 55 months after radiosurgery; clinically, symptoms disappeared 0.5 to 48 months (median 12 months) after the treatment.

Eighteen patients (4.9%) were on steroids at the time of treatment. In another 16 patients (4.3%) steroids were administered after the Gamma Knife treatment for a median of 4 months (mean 5.8 ± 5.3 months).

Neurological deficits without evidence of edema were temporary in 11 patients (3.3%) and permanent in 10 patients (3%). Overall, the temporary morbidity rate was 10.2% and the permanent morbidity rate was 5.7% (Table 2).

There were seven patients in whom the tumor initially increased in size and subsequently shrank as a result of intratumoral edema (Fig. 2). Edema onset was detected 5 to 16 months after treatment and resolved in 6 to 36 months after radiosurgery, with subsequent shrinkage of the tumor volume of 10 to 80%, a mean 54% of the pretreatment volume. Six of these seven patients experienced intratumoral edema along with collateral postradiation edema.

Overall, improvement of neurological symptoms caused by meningiomas was observed in 61.9% of cases (Table 3).

Two patients died as a result of edema, which developed around the treated meningioma. The first patient (77 years old) was unfit for open surgery and underwent staged radiosurgery for a large parasagittal meningioma (the largest treated volume in the study was 44.5 cm³). Because of progressive perilesional swelling, which developed 9 months after radiosurgery and despite steroid administration, this patient died 18 months after treatment. A second patient (52 years old) with parasagittal meningioma causing mass effect refused open surgery for religious reasons. Staged radiosurgery was planned; however, worsening of preexisting edema around the treated meningioma occurred, and the patient died 4 months after treatment of the first half of the tumor volume.

Other causes of death were unrelated to the treated meningioma: cancer in six, ischemic heart disease in five, stroke in five, and unknown in 10 patients.

To find the influence of various factors during the radiosurgical treatment of meningiomas, 10 different variables were evaluated. These factors were divided into two groups: pretreatment and treatment. Pretreatment variables included a patient’s sex and age, previous surgeries, edema before treatment, lobulated margin of meningioma, heterogeneous appearance of the tumor, tumor volume, tumor location (anterior cranial fossa, middle cranial fossa, posterior cranial fossa, convexity, falx, tentorium, and cerebellum). Treatment variables included maximum tumor dose and tumor margin dose.

Altogether, seven different events were studied as potentially dependent on these evaluated factors. The events observed after stereotactic radiosurgery were as follows: tumor volume decrease, tumor volume increase, edema occurrence, neurodeficit improvement, temporary impairment due to neurodeficit, permanent impairment due to neurodeficit, and epilepsy improvement in patients with the disorder before treatment.

To point out factors influencing the time dependence of the aforementioned events, univariate and multivariate statistical analyses were performed. Univariate analysis was performed using the Kaplan–Meier statistic with the log–rank test. Multivariate analysis was performed using the Cox proportional-hazards model with the backward stepwise (conditional likelihood ratio) method. Analyses were performed with the SPSS statistical software (version 10.0; SPSS, Inc.). Variables with significant probability values (p ≤ 0.050) in at least one of two actuarial analyses were considered possible risk factors for the event (Table 4).

### Tumor Volume Decrease After GKS

There was a significantly higher incidence of a tumor volume decrease in patients in whom the maximum radiosurgical dose was greater than 22 Gy (p = 0.005, log–rank test; p = 0.045, Cox proportional hazards), and the tumor margin dose was greater than or equal to 12 Gy (p = 0.012, log–rank test; Figs. 3 and 4).
There was a significantly greater incidence of a tumor volume increase in men compared with women (p = 0.005, log-rank test; p = 0.013, Cox proportional hazards) and in patients in whom the tumor margin dose was lower than 12 Gy (p = 0.047, log-rank test).

There was a significantly higher incidence of edema in patients older than 60 years (p = 0.019, log-rank test), in those who had not undergone a surgical procedure before GKS (p = 0.013, log-rank test; p = 0.035, Cox proportional hazards), in those with edema before GKS (p < 0.001, log-
rank test; \( p < 0.001 \), Cox proportional hazards), in those with a tumor volume larger than 10 cm\(^3\) (\( p = 0.002 \), log-rank test; \( p < 0.001 \), Cox proportional hazards), in those with a tumor location in the anterior fossa (\( p = 0.025 \), log-rank test; \( p = 0.001 \), Cox proportional hazards), in those with a maximum radiosurgical dose that was greater than 30 Gy (\( p = 0.013 \), log-rank test; \( p = 0.018 \), Cox proportional hazards), and in those in whom the tumor margin dose was greater than 16 Gy (\( p < 0.001 \), log-rank test; Figs. 5 and 6).

**Neurodeficit Improvement After GKS**

There was a significantly higher incidence of neurodeficit improvement in patients who had undergone a surgical procedure before GKS (\( p = 0.003 \), log-rank test), those with a lobulated tumor margin (\( p = 0.032 \), log-rank test), those with a tumor volume larger than 5 cm\(^3\) (\( p < 0.001 \), log-rank test), those with a tumor location in the middle and posterior fossae (\( p < 0.001 \), log-rank test), those receiving a maximum tumor dose lower than or equal to 30 Gy (\( p = 0.047 \), log-rank test), and those with a tumor margin dose lower than or equal to 16 Gy (\( p = 0.018 \), log-rank; \( p = 0.002 \), Cox proportional hazards).

**Temporary Impairment due to Neurodeficit After GKS**

There was a significantly greater incidence of temporary impairment due to neurodeficit in patients with a tumor volume larger than 10 cm\(^3\) (\( p = 0.014 \), log-rank test; \( p = 0.002 \), Cox proportional hazards).

**Permanent Impairment due to Neurodeficit After GKS**

There was a significantly higher incidence of permanent impairment due to neurodeficit in patients with edema before GKS (\( p = 0.008 \), log-rank test) and with tumor volume larger than 10 cm\(^3\) (\( p = 0.050 \), log-rank test; \( p = 0.002 \), Cox proportional hazards).

**Seizure Improvement or Disappearance After GKS**

There was a significantly higher incidence of seizure frequency improvement or disappearance in patients without perilesional edema before GKS (\( p = 0.017 \), Cox-proportional hazards) and in those with a tumor location in the

\begin{table}[h]
\centering
\caption{Improved symptoms after radiosurgery in 331 patients*}
\begin{tabular}{l l}
\hline
Symptom & No. (%) \\
\hline
imbalance & 38 (11.4) \\
trigeminal symptom & 29 (8.8) \\
oculomotor palsy & 31 (9.4) \\
seizure & 29 (8.8) \\
hemiparesis & 25 (7.5) \\
vertigo & 21 (6.3) \\
facial nerve palsy & 14 (4.2) \\
mental change & 9 (2.7) \\
dysphasia & 6 (1.8) \\
hearing & 6 (1.8) \\
hydrocephalus & 1 (0.3) \\
total symptoms & 209 (63.1) \\
total patients & 205 (61.9) \\
\hline
\end{tabular}
\footnotesize{* More than one symptom occurred in some patients.}
\end{table}

\begin{table}[h]
\centering
\caption{Overview of studied events and factors in present analysis*}
\begin{tabular}{l c c c c c c c c c}
\hline
Variable & Tumor Vol & Decrease & Tumor Vol & Increase & Edema & Occurrence & Seizure & Improvement & Neurodeficit & Temporary & Neurodeficit & Improvement & Permanent & Neurodeficit & Improvement & Seizure & Disappearance \\
\hline
\hline
\end{tabular}
\footnotesize{* Significant probability values are also presented for factors having significant influence on the studied event. Abbreviation: X = not a risk factor.}
\end{table}
anterior fossa, middle fossa, and posterior fossa (p = 0.009, log-rank test; p = 0.009, Cox proportional hazards).

**Discussion**

To assess the results of meningiomas as slow-growing tumors, the follow-up is an important issue. In our study the median time was 60 months, which is one of the longest follow-up periods reported to date. The 5-year actuarial tumor control rate, defined as an unchanged or decreased volume of meningioma, was achieved in 97.9% of cases, which is within the range of published results (Table 5). Note, however, that further evaluation in the future will show whether the same results will remain. The first cohort of patients from our group with a follow-up exceeding 10 years makes our expectations high. In the present study we tried to identify the factors related to successful treatment as well as to risk factors.

The indication for Gamma Knife treatment of meningioma was residual or recurrent tumor after a previous resection. Primary radiosurgery was indicated when the meningioma showed growth on previous images or when waiting for further growth would make the treatment more risky, especially in cases of skull base lesions in contact with important structures, such as the optic nerve, or with brainstem compression.

In 70% of treated patients GKS was the first modality, without previous surgery and tissue diagnosis. Treated meningiomas were regarded as benign on the basis of neuroimaging results, its clinical behavior, and favorable response to radiosurgery. The results obtained following the primary treatment of meningioma are better compared with those for previously surgically treated ones, because of the possibility of better conformal planning.

**Tumor Margin and Maximum Dose**

An optimum radiosurgical dose for meningioma is still under debate (Table 5). In the present study, there was a significantly higher decrease in the volume of meningiomas treated with a prescription dose greater than 12 Gy. Doses less than 12 Gy are a reportedly significant factor in the failure to control meningioma growth.\(^{10,24,25,49,52,54,56,71,72}\) In patients in the present study a margin dose lower than 12 Gy was used only in those who had undergone previous fractionated radiotherapy. Furthermore, a margin dose less than 12 Gy was prescribed when the meningioma compressed optic pathways. In such cases the whole tumor volume was covered with a margin dose of 12 Gy, except for a small section of tumor adjacent to optic pathways. This strategy of reducing the radiation dose to the layer of tumor adjacent to the optic pathway to 10 or 12 Gy in our experience has controlled growth of the tumor.\(^{33,34}\)

With regard to location, the most vulnerable structure appears to be the anterior visual pathways, especially for the dose necessary to treat intrasellar and parasellar lesions. No visual field loss was detected in our study. The dose to the optic pathways exceeded 8 Gy only in patients who had been blind since a first surgery; in patients who had previously undergone radiotherapy, the dose was always kept less than 3 Gy. In general, an upper dose limit of 8 Gy to the chiasm has been widely applied.\(^{15,51,52}\) Morita and colleagues\(^{41}\) have stated that the optic apparatus seems to tolerate doses greater than 10 Gy and that the risk of trigeminal neuropathy is related to doses higher than 19 Gy. These authors believe that doses up to 16 Gy delivered to a short segment of the anterior visual pathways are acceptable to avoid undertreatment. Kenai and colleagues\(^{22}\) have reported on five patients who received more than 10 Gy (mean maximum 14.5 Gy) to the anterior visual pathways and underwent follow-ups of 40.8 months. No deterioration occurred among these patients. Nonetheless, we believe it is safest not to exceed 8 to 9 Gy to the optic tract, because delayed damage can occur up to 10 years after treatment.\(^{65}\) Further studies are expected to confirm the safety of higher doses.

In para- and intrasellar meningiomas treated with margin doses of 12 Gy, the mean dose to hypophysis did not exceed 15 Gy—what we consider a safe limit to avoid hypopituitarism caused by radiosurgery\(^{45}\)—and therefore pituitary tests were not routinely performed before or after treatment. No clinical evidence of hypopituitarism was observed during the follow-up.

In patients treated with margin doses higher than 16 Gy, there was a significantly greater occurrence of postradiation edema and thus temporary and permanent posttreatment
sequelae. According to the results of our statistical analysis, a higher margin dose was not related to the tumor control rate, although the risk of complications was increased. As reported by Kondziolka and associates, margin doses greater than 15 Gy did not provide better tumor control. The current practice at our center keeps the margin dose for the benign meningioma in the range of 12 to 16 Gy.

Patient Sex and Age

A relationship between meningioma and the hormonal status of patients has been confirmed. In analyzing tumors that increased in size after GKS treatment, we found that a significantly greater number of them were found in men. Similarly, DiBiase and associates found in 162 cases of benign meningiomas with a median follow-up of 4.5 years that male patients had a worse prognosis. In a group of 40 patients older than 70 years of age with asymptomatic meningiomas, Niiro and colleagues found that the tumor grew in 14 patients and became symptomatic in four men and one woman. Moreover, Nakamura and associates reported that in a group of 47 patients with asymptomatic meningiomas, Nieto and colleagues found that the tumor grew in 14 patients and became symptomatic in four men and one woman. Moreover, Nakamura and associates reported that in a group of 47 patients with asymptomatic meningiomas, the growth rate and doubling time of the tumor were higher in men, although this finding was not statistically significant.

A significantly increased frequency of newly developed edema was observed after treatment in patients older than 60 years. It has been reported that meningiomas in the elderly have a lower progression rate. These facts suggest an issue with the prescribed radiosurgical dose, which should be kept at the lower end of the therapeutic window of 12 to 16 Gy to prevent a decline in the quality of life in the elderly, in whom the life expectancy is shorter.

Previous Surgery

In the present study, previous excision of a meningioma was a factor significantly influencing improvement in the neurodeficit recorded before treatment. Some authors have reported a higher percentage of improved symptoms in patients undergoing GKS as a first treatment modality compared with patients having a history of excision. The percentage of patients who improved after radiosurgery among those who had undergone previous microsurgery can be influenced by the period that elapses from the time to open surgery to GKS. In the present study, more than 40% of patients had GKS within 1 year of excision. This time period is still considered the recovery phase. Nevertheless, the combination of surgery and radiosurgery is becoming more frequently reported on by other authors. A part of the meningioma whose excision would pose a risk of neurological symptoms is referred to radiosurgery.

In the present series previous surgery was associated with a lower risk of postradiation edema. There are two factors that can explain this fact. First, it is more difficult to distinguish edema from postoperative changes on T2-weighted MR images, unless it causes mass effect. Second, the surgical route decreases the portion of meningioma in contact with brain tissue and thus disrupting the pial blood supply, which is an important factor in the development of peritumoral edema.

Collateral Edema

Peritumoral edema is found in 40 to 60% of intracranial meningiomas. In the present study, edema before treatment was observed in 3.8% of the treated patients. This pre-treatment edema introduced bias into the study because patients with swelling usually present with more pronounced symptoms and are immediately referred for surgery. The fact that patients harboring a meningioma together with peritumoral edema before treatment are at higher risk of worsening preexisting edema, as well as an increased risk of a permanent neurodeficit after treatment speaks in favor of surgery; therefore, an indication for radiosurgery must be justified by other factors. Moreover, patients with seizures have less chance of seizure improvement in the presence of perilesional edema before treatment.

An important role in the development of edema is the impairment of the blood–brain barrier and the secretory activity of the tumor itself, releasing vascular endothelial growth factor, which is a potent inducer of vascular permeability. It’s effect is apparent in meningiomas with a pial blood supply, where the interface between meningioma and brain tissue is not well defined. In addition, mass effect with brain ischemia and impaired venous drainage might play a role.

Besides the pretreatment collateral edema, further risk
factors for the induction of posttreatment edema are a tumor volume larger than 10 cm³, prescription dose higher than 16 Gy, and tumor location in the anterior cranial fossa. There is a need for a common explanation for these facts: tumors located in the anterior cranial fossa have a higher chance of complications than other skull-based meningiomas. In addition, larger tumors can be associated with edema after being exposed to lower doses; in contrast, higher doses can induce extensive edema in small tumors in the same location. A unifying factor for these findings could be the pial interface, which is an open gate for vascular endothelial growth factor to enter surrounding brain tissue, after its increased release from tumorous cells after radiation.

The risks of radiation-induced untoward effects increases with the portion of the tumor volume irradiated.¹¹⁻¹³,⁶⁶,⁷² Tumor volume—in particular, that greater than 10 cm³—was an important factor in the development of swelling and both temporary and permanent complications after radiosurgery in our study. Therefore, patients with meningiomas larger than 10 cm³ must be informed about the increased possibility of side effects. Note that other authors³⁵,⁷¹ have not found a relationship between tumor volume and margin dose, and the occurrence of complications. In contrast, patients in the present study with a larger tumor volume (>5 cm³) had a greater chance for improvement in any neurological symptom if it was present before treatment. This greater likelihood of improvement could be attributable to tumor shrinkage as well as to a decreased concentration of somatostatin receptors on meningioma cells.⁶⁷,⁷³

Ten patients in the present study received staged treatment for meningioma; that is, the bigger portion or the portion in the posterior fossa was treated first, and in another 6 months the smaller portion was treated. Postradiation edema occurred in two of the patients and was symptomatic in one. This approach was used to improve tolerance in treating two smaller parts instead of one large, and therefore the risk associated with the treatment was lower. This therapeutic option was used in patients with large, inoperable skull base tumors.⁵³

According to data in the present study, it is possible to predict the occurrence of posttreatment edema with regard to the location of the meningioma. Patients with meningiomas in the anterior skull base have the highest risk, followed by those harboring convexity and parafalcine meningiomas. Transient symptomatic edema occurred in 16% of treated patients with parasagittal meningiomas, as reported by the Gamma Knife Meningioma Study Group.²⁴ Kim and colleagues³¹ found posttreatment complications related to swelling in 43% of convexity meningiomas. Meningiomas in these locations have a pial blood supply, and a larger volume of brain parenchyma is irradiated, compared with the middle and posterior fossae, where a part of margin faces the cistern with cerebrospinal fluid.⁵,¹⁷,²³,²⁴

**Other Factors**

We hypothesized that the lobulated margin of the tumor and its heterogeneous appearance after contrast administration would be related to a higher risk of complications because of its higher biological activity. There are studies in which these factors were found to be important. According to Nakasu et al.,¹⁴ the shape of a meningioma has a strong relationship to its recurrence, and lobulated and mushrooming meningiomas must be treated more aggressively than smooth and calcified ones. Niirro and associates⁴⁶ found that meningiomas with calcifications are less active. The shape of the meningioma and postcontrast heterogeneity failed to prove statistically significant in the studied events, which suggests no change in treatment strategy with regard to the mentioned morphological features.

**Adverse Effects**

In the majority of cases, the morbidity associated with

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**TABLE 5**

**Literature review of data on radiosurgery for meningioma**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Lesion Location</th>
<th>Years of Study</th>
<th>Margin Dose (Gy)</th>
<th>Lesion Vol (cm³)</th>
<th>Follow Up (mos)</th>
<th>Rate of Tumor Control (%)</th>
<th>Rate of Morbidity Rate (%)</th>
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<tbody>
<tr>
<td>Gamma Knife</td>
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<td>41</td>
<td>tentorial</td>
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<td>skull base</td>
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<td>all</td>
<td>1987–1992</td>
<td>16</td>
<td>4.7</td>
<td>NA</td>
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<td>5</td>
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<td>1990–1998</td>
<td>16</td>
<td>8.2</td>
<td>40</td>
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<td>Lee et al., 2002</td>
<td>176</td>
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<td>1987–2000</td>
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<td>52.6</td>
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**LINAC**

<table>
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<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Lesion Location</th>
<th>Years of Study</th>
<th>Margin Dose (Gy)</th>
<th>Lesion Vol (cm³)</th>
<th>Follow Up (mos)</th>
<th>Rate of Tumor Control (%)</th>
<th>Rate of Morbidity Rate (%)</th>
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*LINAC = linear accelerator; NA = not available.*
stereotactic radiosurgery is temporary. Permanent complications have been reported in 2.5 to 9%, although some authors have reported a higher incidence of 43% for convexity meningiomas.\textsuperscript{7,23,24,41,56,69,71} This posttreatment deficit is rarely disabling, and the majority of patients carry on their pretreatment activities. The results of surgical treatment, especially for skull base meningiomas, mean major changes in lifestyle for more than 50% of patients because of a new neurological deficit. One cannot underestimate its effects on the patient as well as his or her caregiver.\textsuperscript{3,28} As our study data confirm, complications can be predicted by the characteristics of meningioma, its location, size, and peritumoral edema.

A rare complication has been reported by Pollock\textsuperscript{44} and Stafford and associates.\textsuperscript{71} They reported on two patients with damage to the carotid artery. In one patient internal carotid artery stenosis occurred 5 years after treatment; and internal carotid artery occlusion, 35 months after treatment. Retrospectively calculated doses exceeded 25 Gy to the affected arteries. These same authors have also reported peritumoral cyst formation that required surgical decompression. Other cysts were described by Shuto et al.\textsuperscript{66} In a series of 160 patients with benign meningiomas and a follow-up longer than 2 years, a cyst formed adjacent to the tumor in five patients. At the time of treatment, three cysts were present, two of which enlarged and three of which developed after the Gamma Knife treatment. Even though such cysts are rare, one has to think about their possible occurrence once symptoms appear. None of these complications was found in the present study.

Seven patients in the present study had intratumoral swelling, which developed 5 to 16 months after treatment. In all of them the tumors shrank and symptoms settled. This information is very important, because the referring neurosurgeon could mistake the intratumoral edema for further tumor growth, especially in the presence of clinical symptoms, and might proceed with microsurgery at the least favorable time because of acute postradiation changes. Under these circumstances, a course of steroids should be administered.

The time elapsed since treatment could act as a guideline to distinguish intratumoral edema from tumor growth. In our experience the growth of meningioma is always detected at least 2 years after radiosurgery, whereas intratumoral edema with a temporary volume increase occurs within 2 years of radiosurgical treatment.

**Natural History**

The availability of CT and MR imaging increases the finding of incidental meningiomas. Such lesions are often concerning, even though they are asymptomatic, and a majority of cases in the elderly will remain asymptomatic. Therefore, the optimum treatment should be considered.\textsuperscript{27} Results published on the growth of asymptomatic meningiomas differ. Niiro and colleagues\textsuperscript{46} followed up 40 patients older than 70 years of age with asymptomatic meningioma and found that for a mean period of 41.8 months, 65% of the lesions showed no growth. Ten percent of the patients, who were initially asymptomatic and whose tumor growth was confirmed, became symptomatic. In general, asymptomatic meningiomas were not surrounded by edema. In a study of 60 patients with asymptomatic meningiomas, Olivero and coworkers\textsuperscript{49} found that 58% of them showed no growth during the mean follow-up of 29 months. Similarly, Nakamura and associates\textsuperscript{43} followed up 47 meningiomas for a mean 43 months, and six of them were finally treated using surgery. Yoneoka and colleagues\textsuperscript{72} found growth in 24.3% of a group of 37 asymptomatic meningiomas. To reveal the natural history of petroclival meningiomas in particular, Van Havenbergh and coworkers\textsuperscript{35} followed up 21 conservatively treated patients for a median of 85 months. During the follow-up period, radiological growth was observed in 76% of patients; among this group 63% showed functional deterioration. Interestingly, small tumors (< 2 cm in diameter) showed growth in 100% of cases. Thus, the 24 to 76% rate of meningioma growth suggests that active treatment is necessary in most cases.

**Open Surgery and Radiotherapy**

Surgery remains the treatment of choice in patients with large meningiomas causing significant compression of surrounding structures, surrounded by edema, and in an accessible location; of course, these patients must be fit for a long surgical procedure. Given the rapid progress in imaging techniques and neurosurgery itself, it is difficult to compare the results of surgery, decade by decade.

Because intracranial meningiomas are a heterogeneous group with specific features in various locations, a majority of authors present in detail the outcome associated with meningiomas in particular areas, which is beyond the scope of this paper. For the majority of convexity meningiomas it is possible to achieve a Simpson Grade 1 excision with reasonably low morbidity and death. The reports on skull base meningiomas represent a wide range of totally resected meningiomas, 20 to 97.8% with 16 to 27% morbidity, 0 to 9.7% mortality, and 5 to 16% recurrence rate. Incompletely resected meningiomas often proceed to radiotherapy, radiosurgery, or repeated excision for recurrent tumor.\textsuperscript{1,3,4,6–11,13,21,39,48,50,59,61,77} Despite technical improvements, microsurgery for meningiomas remains a challenge, especially for skull-based lesions and tumors in the elderly.

For large meningiomas in patients not fit for open surgery and for World Health Organization Grade II and III meningiomas, radiotherapy is the modality of choice. Tumor control after partial excision followed by radiotherapy is reported to be approximately 80 to 92%. However, the side effects of the radiotherapy, such as cognitive decline and the risk of malignancy, cannot be underestimated, because survival is usually not limited by the meningioma itself and fractionated radiation can induce the growth of meningiomas de novo.\textsuperscript{16,37,40,47,55,63} Nutting and colleagues\textsuperscript{47} reported on a group of 82 patients with benign meningiomas of the skull base, whose progression-free survival was 92% 5 years after treatment and 83% 10 years after treatment. Visual impairment occurred in six patients, although none of the cranial nerves were found to be affected. Data from the study by Maire et al.\textsuperscript{37} showed slightly less favorable results: in 91 patients with a median follow-up of 3.5, and 10 years, the progression-free interval was 86, 71, and 40%, respectively, with six patients suffering late delayed injuries, such as hemiplegia, visual loss, and cognitive decline. Note, however, that there is a significant bias in favor of tumors that are more aggressive or for patients with lower Karnofsky Performance Scale scores.
We have mentioned the risk of malignancy with radiation treatment. To date, 6502 patients overall have been treated at our institution for more than 13 years. Thus far, there is no evidence of malignancy related to the treatment. For radiosurgery, accessibility of the meningioma as well as the vascular supply are not limiting factors. The only limiting factor is the tumor volume and in some cases the relationship to critical structures, for example, inclusion of the optic nerve in the orbit. Current experience shows that radiosurgery could be used in patients who were not considered suitable for the therapy in the past, such as those with cavernous sinus meningiomas close to the optic tract, because of advances in the imaging modality and 3D planning. Since the very first meningioma was treated using stereotactic radiosurgery back in 1976, these lesions have become the most frequently treated in some centers.33,35

An optimum treatment modality or a combination of modalities must be selected for every particular patient to achieve the best result. Gamma Knife surgery should be considered as the treatment of choice for small and medium meningiomas in the skull base. Microsurgery is warranted in cases of optic nerve sheath meningiomas to decompress the nerve or to debulk a large meningioma. Radiosurgery should also be considered for small to medium meningiomas of the falx and parasagittal region, without surrounding edema. A wait-and-see policy is often beneficial for asymptomatic elderly patients with calcified meningiomas, especially in the convexity, with the availability of regular MR imaging. Radiosurgery should be applied more cautiously in patients with meningiomas associated with collateral edema, in the anterior skull base, and larger than 10 cm3. Of course, minor complications related to radiosurgery must be weighed against the risks of other available treatment options. In such cases, the decision-making process often leads to radiosurgery.

Conclusions
Stereotactic radiosurgery is a safe method for treating meningiomas. The 5-year actuarial tumor control rate is 97.9%. We suggest a prescription dose of 12 to 16 Gy to the tumor margin. Higher margin doses are associated with higher treatment risks but not an improved tumor control in cases of optic nerve sheath meningiomas to decompress the nerve or to debulk a large meningioma. Radiosurgery could be used in patients who were not considered suitable for the therapy in the past, such as those with cavernous sinus meningiomas close to the optic tract, because of advances in the imaging modality and 3D planning. Since the very first meningioma was treated using stereotactic radiosurgery back in 1976, these lesions have become the most frequently treated in some centers.33,35

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Gamma knife surgery for benign meningiomas


