To date, it has been reported that stereotactic radiosurgery is a safe and effective treatment for patients with pathologically benign meningiomas not only as an adjuvant therapy but also as an initial treatment. Complete resection is the preferred treatment for benign meningiomas, as they are generally encapsulated. However, complete tumor resection is not always possible, particularly in skull base lesions, because some lesions are not only located close to adjacent critical neurovascular structures but also infiltrate them. In this situation, complete resection remains a challenge even for experienced neurosurgeons, despite the recent advances in microsurgery. However, this is not the case with convexity or falcine meningiomas. The majority of convexity or falx meningiomas can be completely removed. In cases of parasagittal lesions, complete tumor resection is not easy because the tumors often invade the superior sagittal sinus, the sacrifice of which causes severe brain edema and venous infarction. In general, it is considered that radiosurgery is more likely to cause symptomatic edema when applied to convexity, parasagittal, or falcine meningioma than to skull base meningioma. Despite this fact, stereotactic radiosurgery has been increasingly used as a primary treatment, particularly in cases in which patients are at a high risk of operative morbidity or death, or refuse open surgery. In this study, we evaluated the results of GKS for meningiomas, focusing on convexity, parasagittal, and falx locations. In addition, the risk of radiation-induced edema was assessed.

Methods

Patient Characteristics

One hundred twelve patients with convexity, parasagittal, or falcine meningiomas underwent GKS at Komaki City Hospital between 1991 and 2008. Cases involving atypical and anaplastic meningiomas were excluded. As 10 patients had multiple lesions, a total of 125 tumors were treated. Patient characteristics are summarized in Table 1. Eighty-one patients (72%) were female and 31 (28%) were male. The median age at the time of GKS was 57 years (range 23–80 years). Forty-six patients (41%) un-
Radiosurgery for convexity, parasagittal, or falcorine meningiomas

TABLE 1: Summary of characteristics in 112 with meningiomas

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (yrs)</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>57</td>
</tr>
<tr>
<td>range</td>
<td>23–80</td>
</tr>
<tr>
<td>male/female (%)</td>
<td>31:81 (28:72)</td>
</tr>
<tr>
<td>no. of prior ops (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>46 (41)</td>
</tr>
<tr>
<td>1</td>
<td>47 (42)</td>
</tr>
<tr>
<td>2</td>
<td>15 (13)</td>
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<tr>
<td>3</td>
<td>3 (3)</td>
</tr>
<tr>
<td>4</td>
<td>1 (1)</td>
</tr>
<tr>
<td>follow-up</td>
<td></td>
</tr>
<tr>
<td>median (mos)</td>
<td>72</td>
</tr>
<tr>
<td>range (mos)</td>
<td>4–184</td>
</tr>
<tr>
<td>≥5 yrs (%)</td>
<td>71 (66)</td>
</tr>
<tr>
<td>≥10 yrs (%)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>lost</td>
<td>4</td>
</tr>
</tbody>
</table>

derwent GKS as the initial treatment, diagnosed based on clinical signs and radiological findings of wide-based well-enhanced masses with a dural tail sign. The patients were selected for GKS as the initial treatment in many cases based on older age or comorbidities that made resection less desirable. Sixty-six patients (59%) underwent resection before GKS, confirming histologically benign meningiomas. There were 54 parasagittal lesions (43%), 41 falx lesions (33%), 23 convexity lesions (18%), and 7 cerebellar convexity lesions (6%). The median tumor diameter was 24.7 mm (range 7.7–49.2 mm), and the median tumor volume was 7.9 cm³ (range 0.2–62.7 cm³). The median maximum and margin doses were 30.0 Gy (range 20.0–50.0 Gy) and 16 Gy (range 10.0–20.4 Gy), respectively. The median number of isocenters was 5 (range 1–23).

Dose Selection

In an early era of GKS at our institution, 15 Gy or greater to the tumor margin was administered in patients with small meningiomas (<10 cm³) regardless of tumor location, whereas patients with relative large meningiomas (≥10 cm³) were treated at a reduced margin dose of less than 15 Gy. Accordingly, many patients included in this study may have received a higher dose than the current optimal dose of 12–14 Gy. In recent cases, we generally deliver 14 Gy or less to the tumor margin depending on meningioma volume in patients who undergo GKS as an initial treatment, whereas 15 Gy or greater to the tumor margin is sometimes used in cases of recurrent meningiomas when it is predicted that a risk of radiation-induced edema is low, because these tumors are considered to be relatively aggressive.

Radiosurgical Techniques

In our institute, patients are admitted to the hospital the day prior to treatment and discharged the day after treatment. A Leksell stereotactic frame (Model G; Elekta Instruments) is used for GKS. The frame is applied after mild sedation and local anesthesia. After frame application, all patients undergo MR imaging. Axial and coronal contrast-enhanced T1-weighted images are usually used for dose planning. All treatments were planned using a KULA system (Elekta Instruments) until 1996, and thereafter with GammaPlan software (Elekta Instruments). After dose planning, GKS was performed using a Leksell Model B or C Gamma Knife (Elekta Instruments).

Follow-Up

Radiological studies were requested at 3-month intervals for the first year after GKS, at 6-month intervals for the next 2 years, and then annually thereafter. Simultaneously, clinical data including neurological signs and symptoms were obtained. Tumor enlargement or regression was defined as a change of ±2 mm in any direction, as measured on follow-up studies with calipers. Clinical follow-up data were obtained from either the patients or their referring doctor if they lived too far away for convenient follow-up visits to our institution. When necessary, patients were contacted by telephone to update their outcomes for the purposes of this study.

Statistical Analysis

Tumor control was assessed by PFS and LTC rates using the product limit of Kaplan and Meier. When calculating PFS, treatment failure was defined as tumor progression either inside or outside the GKS treatment volume (in-field or out-of-field treatment failure). Out-of-field treatment failure does not mean the appearance of any new meningiomas in the other location but, rather, a kind of local recurrence outside the isodose line of the margin dose. Local tumor control refers to lesion control inside the GKS treatment volume. To analyze factors correlating with PFS, LTC, or the development of radiation-induced edema, the following were assessed: age, sex, maximum dose, margin dose, tumor volume, tumor location (falx or parasagittal versus convexity), and number of prior surgery. Factors affecting PFS, LTC, and the development of radiation-induced edema were assessed using the log-rank test and the Cox proportional hazards model. A final multivariate analysis was calculated using a stepwise backward elimination. A p value less than 0.05 was considered statistically significant.

Results

Of 112 patients, 4 patients with 6 lesions were lost to follow-up. The median follow-up period was 72 months (range 4–184 months). During the follow-up period, 5 patients had died. Of them, 1 patient died of meningioma progression, 3 of systemic disease, and 1 of another intracranial brain tumor.

Tumor Control

Of 119 lesions that could be evaluated with imaging, 49 lesions (41%) had regressed, 52 (44%) remained stable, and 18 (15%) had in-field tumor progression demonstrated...
Radiation-Induced Edema

Factors Associated With PFS or LTC

The number of prior surgeries significantly affected PFS (p = 0.0020, HR 1.761) and LTC (p = 0.0356, HR 1.629). The actuarial 5- and 10-year PFS rates were 93% and 84%, respectively, in patients in whom GKS was the initial treatment compared with 68% and 35%, respectively, in patients who had undergone prior surgery. Similarly, the actuarial 5- and 10-year LTC rates were 94% and 84%, respectively, in patients in whom GKS was the initial treatment compared with 82% and 62%, respectively, in patients who had undergone prior surgery. Age was also statistically significant for LTC. In-field treatment failure was significantly more present older patients (p = 0.0349). The actuarial 5- and 10-year LTC rates 74% and 65% in older patients (≥ 65 years old), respectively, compared with 91% and 75% in younger patients (< 65 years old). On the basis of tumor location, the actuarial 5- and 10-year PFS rates were 76% and 55%, respectively, in patients with convexity meningiomas compared with 79% and 54%, respectively, in patients with falx or parasagittal meningiomas. Similarly, the actuarial 5- and 10-year LTC rates were 88% and 74%, respectively, in patients with convexity meningiomas compared with 86% and 71%, respectively, in patients with falx or parasagittal meningiomas. Tumor location was not statistically significant for PFS or LTC. The other factors did not affect PFS and LTC significantly. In multivariate analysis calculated by Cox proportional hazards model using stepwise backward elimination, the number of prior surgeries for PFS (p = 0.0020) and LTC (p = 0.0356) and age for LTC (p = 0.0325) remained significant.

Radiation-Induced Edema

For the first 3 years after GKS, serial MR imaging was performed in 103 patients who were eligible for evaluation of radiation-induced edema. Of these, 42 patients underwent GKS as the initial treatment. Follow-up imaging in 29 patients (28%) revealed newly developed or deteriorated peritumoral edema at 3–12 months after GKS (Fig. 2). Eleven patients had parasagittal lesions, 10 patients had falx lesions, 4 had cerebellar convexity lesions, and 4 had convexity lesions. Of these 29 patients, 7 were symptomatic, 5 of whom had falx or parasagittal lesions and 2 patients of whom had convexity and cerebellar convexity lesions. The actuarial symptomatic radiation-induced edema rate was 7%. The mean tumor volume was 13.3 cm³, and the mean margin dose was 14.6 Gy. On the basis of a history of surgery, 21 (72%) of 29 patients had GKS as the initial treatment. Of 7 patients with symptomatic edema, 6 patients underwent GKS as the initial treatment and 1 underwent GKS as an adjuvant treatment. Two patients with parasagittal meningioma developed motor weakness requiring resection of the lesion. One patient with a parasagittal meningioma suffered seizures caused by severe edema and required resection. One patient with falx meningioma developed severe edema 3 months after GKS and died of pneumonia at 29 months. One patient with a falx meningioma experienced a transient headache without neurological symptoms. One patient with cerebellar convexity meningioma developed transient ataxic gait. One patient in whom radiation-induced left temporal convexity meningioma suspected developed memory disturbance and required resection.

Of 46 patients who underwent GKS as the initial treatment, 6 (13% [4 falx or parasagittal meningiomas and 2 convexity meningiomas]) had peritumoral edema before GKS. Although 1 patient with a convexity meningioma remained asymptomatic and 1 patient with a falx meningioma had transient headache alone after GKS, patients with 2 parasagittal, 1 falx, and 1 convexity meningioma developed severe panhemispheric edema, resulting in neurological deterioration.

Radiosurgery in 27 patients involved a relatively low margin dose of 14 Gy or less. Nine (33%) of these patients developed radiation-induced edema including 3 individuals with symptomatic edema. Of 11 patients treated in who GKS was the initial treatment and in whom the mean tumor size was 3 cm in diameter, 7 (64%) had radiation-induced edema. Of 3 patients with pretreatment peritumoral edema, all were symptomatic and 2 required craniotomy.

In the univariate analysis, fewer prior treatments (p = 0.0021), low margin dose (p = 0.0103), and female sex (p = 0.0317) were significant factors for radiation-induced edema. In the multivariate analysis, fewer prior treatments (p = 0.0021) and low margin dose (p = 0.0098) remained significant.

Salvage Treatment

Of 17 patients (18 lesions) who had in-field tumor progression, 12 required craniotomy, 2 underwent repeat GKS, and 3 selected observation. One patient who underwent repeat GKS eventually required a craniotomy for perifocal edema after the second procedure. In 1 patient
with 2 treated lesions, both of which were resected for in-field tumor progression, the pathological diagnosis was atypical meningioma in spite of benign meningioma before GKS. Of the 10 patients in whom out-of-field tumor progression developed, 9 underwent radiosurgery (8 GKS and 1 LINAC-based radiosurgery). One patient alone selected craniotomy for a new distant lesion.

Discussion

Tumor Control

The results of meningiomas in various locations following stereotactic radiosurgery have been reported numerous publications, demonstrating LTC rates of 75%–100% at 5–10 years.4,6–9,11,13,16,21,23–25,27,28,30,34 To our knowledge, there have been few large studies focusing on convexity, parasagittal, and falcine meningiomas alone treated with stereotactic radiosurgery, as most neurosurgeons prefer resection to radiosurgery to treat this type of benign tumor. In a multicenter review of data obtained in 203 patients with GKS-treated parasagittal meningiomas, Kondziolka et al.13 reported actuarial 5-year tumor control rates of 93% ± 4% and 60% ± 10% in a primary and adjuvant treatment groups, respectively. Additional therapy and worsened neurological function were absent in patients with small tumors (< 7.5 cm³) and those who had not undergone prior open surgery. The report also insisted that most treatment failures resulted from out-of-field tumor progression. Similarly, in their recent series of convexity meningiomas, the actuarial 3- and 5-year tumor control rates in patients with benign meningiomas and those who had not undergone prior surgery were 95% and 86%, respectively.15 On the basis of our data, the actuarial 5- and 10-year PFS rates were 78% and 55%, respectively, whereas the actuarial 5- and 10-year LTC rates 87% and 71%, respectively. These results seem to be a slightly worse than those associated skull base meningiomas. In our previous report of long-term results in 111 patients with GKS-treated cavernous sinus meningiomas, the actuarial 5- and 10-year LTC rates were 94% and 92%, respectively. Lee et al.16 also documented actuarial tumor control rates of 97.5% at both 5 and 10 years in 79 patients harboring cavernous sinus meningiomas. Kollová et al.12 reported the results of 368 patients who had benign meningiomas in all locations (median follow-up 60 months). The report demonstrated an actuarial 5-year tumor control rate of 98%, and the authors found that treatment failures significantly occurred in men and in tumors treated at a margin dose of less than 12 Gy. Recently, Kondziolka et al.14 reported on a large series of 972 patients with 1045 GKS-treated intracranial meningiomas. They demonstrated that the overall control rates in patients with benign meningiomas and those without previous histological confirmation were 93% and 97%, respectively. Although the differences of tumor control among convexity, parasagittal, or falcine meningiomas and skull base meningiomas may be caused simply by patient selection, we speculate that these meningiomas are more radioresistant than skull base meningiomas because, in our experience, skull base meningiomas are likely to decrease in volume sooner after GKS. Treatment failure tends to occur from the tumor margin or outside the treatment volume, because GKS has a characteristic heterogeneous dose distribution, indicating that the radiation dose is highest at the center of the tumor and gradually decreases toward the tumor margin. In addition, it is sometimes difficult to differentiate the tumor margin from normal dural tissue or superior sagittal sinus, especially in cases of parasagittal lesions. This may lead to relatively lower tumor control rates.

In terms of prognostic factors, tumor control in pa-
tients who had previously undergone surgery was significantly worse in our study. The actuarial 5- and 10-year PFS rates were 93% and 84% in patients who had GKS as the initial treatment, respectively, whereas the rates were 68% and 35%, respectively, in patients with a history of surgery. This may be based on a bias that patients who had GKS for tumor recurrence following resection harbor a more aggressive tumor than in those in whom GKS is the initial treatment. Prior surgery makes creation of a treatment plan more complicated, as it is difficult to distinguish residual tumor from postoperative changes on enhanced MR images. Moreover, the residual tumor is often divided into multiple pieces after surgery. These issues lead to out-of-field treatment failure. Even though out-of-field treatment failure has occurred, however, repeat GKS is effective to safely control the tumor. To avoid these types of treatment failure, a carefully prepared conformal plan, including the correct tumor margin within the treatment volume, is essential. Currently, we usually use multiple isocenters to make a more homogeneous and conformal plan with an automatic positioning system, which helps us treat complicated lesions more efficiently. With regard to radiological features associated with tumor recurrence, lobulated and meningiomas are more aggressive, and smooth and calcified meningiomas are generally less active.20,22

**Radiation-Induced Peritumoral Edema**

Gamma Knife surgery is a safe treatment for meningiomas, as the incidence of morbidity has been reported to be less than 10%, and the majority of deficits were transient.8,12–17,30 However, convexity, parasagittal, or falcine meningiomas are more likely to develop postradiosurgical peritumoral brain edema than skull base meningiomas.3,10,11,26 When postradiosurgical symptomatic edema occurs, a course of steroids should be administered. When patients’ symptoms do not improve despite administration of steroids, we must proceed to open surgery without hesitation. In our study, 21 of (50%) 42 patients in whom GKS was the initial treatment developed peritumoral edema beginning from 3 months after GKS, whereas 8 (13%) of 61 patients who had prior surgery experienced postradiosurgical edema. This indicated that patients who underwent GKS as the initial treatment have a significantly higher risk of postradiosurgical edema (p = 0.0021), although the relatively higher doses used in this study may have been responsible for the incidence of postradiosurgical edema. However, we seldom encounter this type of adverse radiation effect in cases of skull base meningiomas, even though GKS is a primary treatment. According to a review by Rogers and Mehta,26 postradiosurgical edema developed in 25%–78% of patients with nonbasal meningiomas, compared with 0%–22% of patients with skull base meningiomas. Kondziolka et al.13 reported that the rate of transient, symptomatic edema after GKS was 16% in 203 patients with parasagittal meningioma, and this complication was more common in cases involving larger tumors within 2 years. Kollová et al.12 documented that 15% of patients with GKS-treated meningioma had posttreatment peritumoral edema, and significant risk factors for postradiosurgical edema were age over 60 years, no prior surgery, prelesional edema before radiosurgery, tumor volume greater than 10 cm³, tumor location in the anterior fossa, and a margin dose of greater than 16 Gy. Kim et al.11 observed postradiosurgical symptomatic edema in 43% of superficially located meningiomas. They documented that patients with parasagittal lesions had a tendency to develop severe postradiosurgical edema. In their series of 179 convexity, parasagittal, and falx meningiomas that were deeply embedded in the cortex, Chang et al.3 found that the patients developed postradiosurgical edema more frequently and, for this, tumor location was the only risk factor. Approximately 60% of patients with postradiosurgical edema were asymptomatic, and in those who were symptomatic their symptoms were all transient. Postradiosurgical edema was found in 4 (5%) of 79 skull base meningiomas in contrast to 26 (50%) of 52 hemispheric meningiomas. Kalapurakal et al.10 suggested that the parasagittal location, presence of pretreatment edema, and sagittal sinus occlusion were significant predictors for the development of brain edema after stereotactic radiosurgery and radiotherapy. They noted that all patients who developed severe posttreatment life-threatening panhemispheric edema had parasagittal meningiomas. The development of brain edema is considered to be associated with impairment of the blood-brain barrier, vascular endothelial growth factor affecting vascular permeability, mass effect with brain ischemia, and impaired venous drainage.12 In particular, the development of peritumoral edema in meningiomas is considered to be strongly related to the pial blood supply.2,23 Meningiomas with greater pial blood supply tend to have peritumoral edema because vascular endothelial growth factor is strongly expressed.33 Convexity, parasagittal, and falcine meningiomas have a broader pial interface and greater pial blood supply than skull base meningiomas surrounded by cistern. Accordingly, a larger volume of adjacent brain parenchyma is irradiated and, thereby damaged, consequently leading to severe brain edema. Furthermore, tissue damaged by high-dose irradiation may prompt vascular endothelial growth factor related to vascular permeability and activate macrophages or monocytes to enter the peritumoral normal brain tissue, leading to the genesis of edema in convexity, parasagittal, or falcine meningiomas with greater pial blood supply. In patients who had prior surgery, postradiosurgical edema is less common because the brain parenchyma is dissected from the tumor surface, disrupting the pial blood supply, at the time of open surgery.12 Superior sagittal sinus or bridging vein occlusion may also contribute to the development of postradiosurgical edema.

Although we found that a lower margin dose was significantly associated with the development of post-GKS brain edema, this must have been caused by a bias that lower margin dose was selected in patients harboring large tumors with a higher risk of post-GKS brain edema. In this study, the majority of radiation-induced edema was asymptomatic. Seven patients with symptomatic radiation-induced edema had relatively large tumors (mean tumor 13 cm³). Additionally, 5 of 7 patients had pre-GKS peritumoral edema. Thus, cases involving large tumors with pretreatment edema are not appropriate for
Radiosurgery for convexity, parasagittal, or falce meningiomas

radiosurgery. Dose reduction may lead to a low risk of radiation-induced edema, although it remains unclear whether low-dose radiosurgery is effective for tumor control over 10 years.

Management Strategy

Patients with tumor recurrence and residual tumor after open surgery are good candidates for GKS. In particular, a tumor invading the superior sagittal sinus should be treated with GKS after removal of the extrasinus tumor. Also, small- to medium-sized primary tumors can be safely treated with a high rate of long-term tumor control. Even though tumor size is relatively large (mean diameter ≥ 3 cm), low-dose radiosurgery may halt tumor growth. However, in patients harboring large symptomatic tumors or those with peritumoral edema demonstrated on pre-radiosurgical MR images, we strongly recommend open surgery as the initial treatment, except in older patients or in those with medical comorbidities, in whom low-dose radiosurgery can be a treatment option. Particularly in large parasagittal or falce meningiomas with peritumoral edema, resection is recommended to avoid severe pan-hemispheric radiation-induced edema. Patients harboring asymptomatic tumors without peritumoral edema may be observed with follow-up serial imaging or may select open surgery or radiosurgery depending on age, tumor size, and location, if patients provide informed consent, especially when further tumor growth would make the treatment more risky.

Conclusions

Gamma Knife surgery is effective for convexity, parasagittal, and falce meningiomas as well as skull base meningiomas. Although radiation-induced peritumoral edema was more common in patients who had convexity, parasagittal, or falce meningiomas treated using GKS as the initial treatment, the majority of patients are asymptomatic. To avoid postradiosurgical symptomatic edema, GKS should be restricted to patients with small- to medium-sized tumors without preradiosurgical edema.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Hasegawa. Acquisition of data: all authors. Analysis and interpretation of data: Hasegawa. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Hasegawa.

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