Role of Gamma Knife surgery for intracranial atypical (WHO Grade II) meningiomas

Clinical article

Shunya Hanakita, M.D.,¹ Tomoyuki Koga, M.D., Ph.D.,¹ Hirosi Iwaki, M.D., Ph.D.,² Naoya Murakami, M.D., Ph.D.,² Soichi Oya, M.D., Ph.D.,¹ Masahiro Shin, M.D., Ph.D.,¹ and Nobuhiro Saito, M.D., Ph.D.¹

Departments of ¹Neurosurgery and ²Radiology, University of Tokyo Hospital, Tokyo, Japan

Object. Atypical meningioma often recurs even after resection. As a salvage modality, radiotherapy or stereotactic radiosurgery (SRS) is attempted for this aggressive tumor. This retrospective study was performed to evaluate the efficacy of SRS that involved Gamma Knife surgery (GKS) for atypical meningioma.

Methods. The authors reviewed records from 22 patients with histologically proven atypical meningioma who underwent GKS for 28 lesions at the authors' institute. The median patient age was 70 years (range 24–91 years), and the median tumor volume for each procedure was 6.0 cm³ (range 1.6–38.7 cm³). The margin dose ranged from 14 to 20 Gy (median 18 Gy). Follow-up periods ranged from 3 months to 98 months (median 23.5 months).

Results. In total, 39 GKS procedures were performed for 28 lesions. The local control rates at 1, 2, and 5 years were 74%, 39%, and 16%, respectively. Volume less than 6 cm³ (p = 0.01), a margin dose higher than 18 Gy (p = 0.02), and a Karnofsky Performance Scale (KPS) score of 90 or more (p = 0.02) were factors associated with a longer duration of tumor control in the univariate analysis.

Conclusions. Atypical meningioma could be more successfully controlled when a higher margin dose was used to treat patients with a good performance (KPS score of ≥90) status and smaller tumor volumes. It would be desired if patients are treated with a relatively higher margin dose, ideally as high as the dose applied for malignant tumor. A boost SRS after fractionated radiotherapy may be effective to achieve better local control.

Key Words: atypical meningioma · Gamma Knife surgery · stereotactic radiosurgery · oncology

During the last 2 decades, stereotactic radiosurgery (SRS) has been widely accepted as an effective treatment option for benign intracranial meningiomas.¹³ Especially in patients with tumors associated with a relatively high risk of recurrence when resected, SRS plays an important role as an adjuvant treatment modality after tumor resection or as the first choice of treatment, which can achieve a tumor control rate of more than 90% for 10 years with minimum neurological complications.⁸,¹³,¹⁷,²⁰

Despite its reputation in the treatment of intracranial benign meningiomas, SRS’s efficacy is still controversial for meningiomas classified as higher grade, such as atypical meningiomas or anaplastic meningiomas. There are only a few published studies reporting their outcomes of SRS in which the results of these 2 histological types were analyzed together, with tumor control rates at 5 years ranging from 25% to 83%.³,⁵,⁶,¹⁰ Thus, at present, the role of SRS in the treatment strategy of atypical meningiomas alone remains unclear.

In the present study, we retrospectively evaluated our experience and analyzed the outcomes of Gamma Knife surgery (GKS) for atypical meningiomas to clarify the role of GKS in the treatment of this intractable disease.

Methods

Patient Population

Between March 1991 and January 2012, 22 consecutive patients with atypical meningioma underwent GKS at the University of Tokyo Hospital. All cases were histologically diagnosed as atypical meningioma according to WHO classification.¹⁰,¹⁴ There were 2 patients who received tumor resection before 2000 and their lesions were diagnosed as atypical meningioma; specimens of the tumors in these 2 cases were reassessed according to WHO 2007 criteria.¹⁴ Medical records were reviewed, and patients with neurofibromatosis Type 2, other WHO Grade II meningiomas, and WHO Grade III meningiomas were excluded from this study. The internal review board of the University of Tokyo Hospital approved the study protocol, and written informed consent was obtained in all cases prior to participation in this study.

Radiosurgical Treatment

Details of the radiosurgical techniques in our hospital were previously reported in other articles.²,⁹ Briefly, after a Leksell frame was fixed on the heads of the patients,
GKS for atypical meningioma

Stereotactic imaging was performed to obtain precise information on the shape, volume, and 3D coordinates of the tumors. Computed tomography was used before July 1996. Magnetic resonance imaging using 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequences was used for stereotactic imaging. Treatment planning was carried out by a neurosurgeon and radiation oncologists using commercially available software (KULA until 1998; Leksell Gamma Plan [Elekta Instruments, Inc.] thereafter). The median maximum dose was 40 Gy (range 24–45 Gy), and the median margin dose was 18 Gy (range 14–20 Gy). The median tumor volume was 6.0 cm³ (range 1.1–38.7 cm³).

Follow-Up and Evaluation

Statistical Analysis

After GKS, follow-up clinical examinations were performed at our hospital or by referring physicians. The patients underwent CT or MRI every 3–6 months. Images were separately evaluated by neurosurgeons and radiologists. The follow-up images were compared with the MRI or CT image acquired during the treatment-planning phase. The type of recurrence pattern was categorized according to the definition in previous reports as follows: local recurrence (tumor progression extended > 2 cm out of the prescription dose line); marginal recurrence (tumor newly grew out of the prescribed line but < 2 cm from its margin); and distant recurrence (noncontiguous region from the site where the tumor initially existed). Typical patterns of local recurrence, marginal recurrence, and distant recurrence are illustrated in Fig. 1. Regardless of marginal or distant recurrence, local control (LC) was achieved when the tumor was controlled and showed no more than 2 mm of progression.

The LC rates and the overall survival (OS) rates were calculated using the Kaplan-Meier method. The LC rate was calculated from the date of first GKS to the date when disease progression was confirmed on the radiographic images. The period of LC rates were censored at the time of the last radiographic follow-up. The period of OS was calculated from the date of first GKS to the date of death. If the patient was alive, the OS rate was censored at the date of the last follow-up. Factors potentially affecting LC rates were evaluated by log-rank test for univariate analysis. The continuous variables were dichotomized at their median values. Multivariate analysis was performed using the Cox regression analysis method. All statistical analyses were performed using JMP 9 software (SAS Institute Inc.).

Results

Patients and Characteristics of Lesions

The characteristics and clinical features of patients are summarized in Table 1. There were 11 men and 11 women whose median age was 70 years (range 24–91 years). Two patients died of tumor progression within 12 months (at 3 months and 8 months), and the median observation period was 23.5 months (range 3–98 months). All the patients initially underwent resection, and GKS was offered either after tumor recurrence or as an adjuvant therapy for the residual tumor. The median interval from the last treatment to GKS was 12 months (range 3–70 months). In 8 patients, 2 GKS procedures were performed for a recurrent tumor. In 3 cases, more than 3 procedures were performed (2 patients underwent 3 procedures and 1 patient underwent 5 procedures). In total, 39 GKS procedures were performed. Fractionated radiation therapy of 50 Gy was added in the clinical course before GKS in 3 patients. The median Karnofsky Performance Scale (KPS) score was 90 (range 40–100). Twelve patients had a KPS score of 90 or greater at the time of radiosurgical treatment.

Survival Rates

In the present series, 13 (59%) of 22 patients were
TABLE 1: Summary of 22 patients with atypical meningioma treated by GKS

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>22</td>
</tr>
<tr>
<td>male/female ratio</td>
<td>11:11</td>
</tr>
<tr>
<td>median age in years (range)</td>
<td>70 (24–91)</td>
</tr>
<tr>
<td>median observation period in mos (range)</td>
<td>23.5 (3–98)</td>
</tr>
<tr>
<td>median KPS score (range)</td>
<td>90 (40–100)</td>
</tr>
<tr>
<td>no. of patients ≥ 90</td>
<td>12</td>
</tr>
<tr>
<td>no. of patients &lt; 90</td>
<td>10</td>
</tr>
<tr>
<td>median interval from last treatment to GKS in mos (range)</td>
<td>12 (3–70)</td>
</tr>
<tr>
<td>no. of lesions</td>
<td>28</td>
</tr>
<tr>
<td>no. of GKS procedures</td>
<td>39</td>
</tr>
<tr>
<td>no. of patients who received 2/3/5 GKSs</td>
<td>8/2/1</td>
</tr>
<tr>
<td>median margin dose in Gy (range)</td>
<td>18 (14–20)</td>
</tr>
<tr>
<td>median maximum dose in Gy (range)</td>
<td>40 (24–45)</td>
</tr>
<tr>
<td>median target vol in cm³ (range)</td>
<td>6.0 (1.1–38.7)</td>
</tr>
<tr>
<td>location of tumors (no. of lesions)</td>
<td></td>
</tr>
<tr>
<td>skull base region</td>
<td>12</td>
</tr>
<tr>
<td>non–skull base region</td>
<td>16</td>
</tr>
</tbody>
</table>

alive at the last follow-up (range 12–65 months). Eight patients died of tumor progression, and 1 patient died of an unrelated cause (colon cancer). Among these, 2 deaths shortly after infield recurrence were confirmed. The OS rates at 1, 2, and 5 years after GKS were 91%, 68%, and 68%, respectively.

Recurrence Patterns and the Factors for Tumor Control

Eighteen (81.8%) of 22 patients had tumor recurrence during the follow-up periods: 12 had local recurrence, 4 had marginal recurrence, and 2 had distant recurrence. In the recurrent cases, 16 patients underwent additional treatment (repeat GKS in 10, GKS with resection in 2, resection in 2, hypofractionated radiotherapy with CyberKnife in 1, and GKS with conventional FRT [fractionated radiation therapy] in 1). At the repeat GKS, we principally applied the margin dose of 18 Gy except in 2 cases. In 1 case, we had to reduce the margin dose to 15 Gy because the lesion was adjacent to the optic nerve; in the other patient, who was previously treated with the margin dose of 18 Gy for the lesion at the cavernous sinus, we decreased the margin dose to 12 Gy to avoid causing adverse events. Of the 4 cases of marginal recurrence, 2 tumors recurred at the dura mater where the tumor had been primarily located at the initial resection, and the other 2 tumors arose from adjacent dura mater apparently separated from the dural tail of the original tumor.

Considering the distant and marginal lesions as de novo tumors, 28 lesions were treated by GKS in total. Local control rates of the 28 lesions at 1, 2, and 5 years after GKS were 74%, 39%, and 16%, respectively. The favorable factors associated with LC for all lesions in the univariate analysis were the tumor volume less than 6 cm³ (p = 0.01), a margin dose higher than 18 Gy (p = 0.02), and a KPS score of 90 or more (p = 0.02) (Fig. 2). Those factors were further evaluated in the multivariate analysis, and all were also shown to be significant (target volume < 6 cm³: p = 0.05; KPS score ≥ 90: p = 0.01; and margin dose > 18 Gy: p = 0.003) (Table 2).

Adverse Events

Adverse events related to GKS were observed in only 1 patient. She had initially undergone GKS with the margin dose of 18 Gy, but a 4-month follow-up MRI showed further regrowth of the irradiated tumor. In the second procedure, a margin dose of 18 Gy was applied. The patient then presented with facial dysesthesia 11 months after the second GKS, and this symptom persisted at the last follow-up. Since the tumor was located at the temporal base, this adverse event was assumed to be radiation-induced neuropathy of the trigeminal nerve. After 3 years of follow-up, the lesion could not be controlled; there were no apparent findings suggesting radiation-induced change of the trigeminal nerve on MRI.

Discussion

In the treatment strategy of atypical meningioma, resection plays the most important role in confirming the histological diagnosis and reducing the tumor volume. While it is evident that longer tumor control can be achieved by means of gross-total resection (GTR) than by subtotal resection (STR), GTR does not always equate with complete tumor removal in cases of atypical meningioma. The progression-free survival rates after GTR are reported to range from 41% to 87% at 5 years, indicating that even GTR does not guarantee cure of the disease. Postoperative adjuvant radiation therapy is recommended but still lacks sufficient evidence of its efficacy. Two Phase II clinical trials concerning the atypical meningioma are currently ongoing (Radiation Therapy Oncology Group trial 0539 and European Organization for Research and Treatment of Cancer 22042–26042) to evaluate the efficacy of radiotherapy after GTR or STR.

Following radical resection, when the radiographic image shows residual tumor or when the tumor recurs, SRS can be an alternative therapeutic option. In previous reports, the 5-year LC rates after GKS for atypical meningioma were highly variable, ranging from 44% to 83% (Table 3). In contrast, the LC rates in the present study were 74% at 1 year, 39% at 2 years, and 16% at 5 years. Although we treated the tumors with relatively small volume using higher margin doses, the LC rates were worse than those in the past reports. The favorable outcomes in the past literature might be partly attributable to the variability of the treated tumors because of vagueness in histological definition of atypical meningioma before the year of 2000. In addition, in recently published cases, a larger portion of the patients underwent prior radiotherapy, which may also be one of the factors leading to the better LC rates in previous reports than in our study. In the present series, there were only 3 patients who received prior radiotherapy. Thus, GKS in combination with prior radiotherapy did not show statistical significance for the LC rate in univariate analysis (p = 0.16). The statistical analysis indicated that treatment with the higher margin dose was significantly associated with a better LC rate and...
that the risk of radiation-induced neuropathy was minimal even when we used a margin dose higher than 18 Gy. These facts suggested that SRS with the escalated margin doses may be justified, with the acceptable risk of the associated neurological deficit, for relatively small tumors. Given that failure of LC after SRS eventually leads to a devastating result in the cases of atypical meningiomas, we should treat these lesions with a protocol similar to the one that is applied in the treatment of malignant brain tumors—that is, using the higher margin dose (ideally > 20 Gy) or using SRS as a localized boost of radiation after FRT.11

At present, the efficacy of SRS for atypical meningiomas is limited and a therapeutic strategy in combination

TABLE 2: Factors associated with tumor control after GKS

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>target vol &lt; 6 cm³</td>
<td>0.01*</td>
<td>0.05*</td>
</tr>
<tr>
<td>KPS score ≥ 90</td>
<td>0.02*</td>
<td>0.01*</td>
</tr>
<tr>
<td>margin dose &gt; 18 Gy</td>
<td>0.02*</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

* Significant at the level of p < 0.05.

with FRT should be considered. Because of the rarity of the disease, a clinical study with a large number of the cases is difficult at a single institution. Multicenter clinical trials will be necessary to definitively determine the efficacy of SRS and finally elucidate the ideal treatment strategy for this devastating disease.

Conclusions

We consider SRS to be a promising therapeutic option at present in the limited cases of atypical meningioma. Patients with small tumor volume and whose performance status is good can be good candidates for SRS. Their tumors should be treated with relatively higher margin doses (ideally > 18 Gy). It is also thought that boost SRS after FRT may be effective to achieve better LC rates.

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: Hanakita, Shin. Acquisition of data: Hanakita, Murakami. Analysis and interpretation of data: Hanakita, Koga, Murakami. Drafting the article: Hanakita,
TABLE 3: Results of GKS for atypical meningioma in previous reports

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients/ Tumors</th>
<th>No. of Prior EBRTs</th>
<th>Margin Dose (Gy)†</th>
<th>LC Rate</th>
<th>Pattern of Tumor Progression After Initial Tx</th>
<th>Target Vol (cm³)†</th>
<th>Clinical FU Period (mos)†</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris et al., 2003</td>
<td>18/NA</td>
<td>NA</td>
<td>14.9‡§</td>
<td>83% at 5 yrs</td>
<td>NA</td>
<td>1 local, 2 marginal, 4 distant</td>
<td>14.6‡</td>
<td>2.3 yrs§</td>
</tr>
<tr>
<td>Huffman et al., 2005</td>
<td>15/21</td>
<td>1 (7%)</td>
<td>16</td>
<td>NA</td>
<td>NA</td>
<td>5</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Pollock et al., 2012‡</td>
<td>37/55</td>
<td>12 (32%)</td>
<td>15§</td>
<td>85% at 1 yr, 45% at 5 yrs</td>
<td>NA</td>
<td>14.6§</td>
<td>38§</td>
<td>26% in total§</td>
</tr>
<tr>
<td>Attia et al., 2012</td>
<td>24/24</td>
<td>11 (46%)</td>
<td>14</td>
<td>75% at 1 yr, 44% at 5 yrs</td>
<td>8 local, 4 marginal, 2 distant</td>
<td>NA</td>
<td>42.5</td>
<td>2 symptomatic edemas</td>
</tr>
<tr>
<td>present series</td>
<td>22/28</td>
<td>3 (14%)</td>
<td>18</td>
<td>74% at 1 yr, 16% at 5 yrs</td>
<td>12 local, 4 marginal, 2 distant</td>
<td>6.0</td>
<td>23.5</td>
<td>1 facial dysesthesia</td>
</tr>
</tbody>
</table>

* EBRT = external-beam radiation therapy; FU = follow-up; NA = data not available; Tx = treatment.
† Mean values.
‡ Consolidated data of WHO Grade II and III meningiomas.
§ Values are the median unless otherwise indicated.

Shin. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hanakita. Study supervision: Koga, Igaki, Shin, Saito.

References


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Address correspondence to: Shunya Hanakita, M.D., Department of Neurosurgery, University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. email: hanakita-s@umin.ac.jp.