Gamma Knife surgery for metastatic brain tumors from renal cell carcinoma

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Object. The authors evaluated the results of Gamma Knife surgery (GKS) for the treatment of metastatic brain tumors from renal cell carcinoma (RCC).

Methods. The authors conducted a retrospective review of the clinical characteristics and treatment outcomes in 69 patients with metastatic brain tumors from RCC who underwent GKS at the authors’ institution. Fifty-one patients were men, and 18 were women. The mean patient age was 64.2 years (range 45–85 years).

The 69 patients underwent a total of 104 GKS procedures for treatment of 314 tumors. Eighteen patients received repeated GKS. Follow-up magnetic resonance (MR) imaging was used at a mean of 7.1 months after GKS to evaluate the change in 132 tumors after treatment. The mean prescription dose at the tumor margin was 21.8 Gy. The tumor growth control rate was 82.6%. Tumor volume and the delivered peripheral dose were significantly correlated with tumor growth control on univariate and multivariate analyses. Sixty (45.5%) of the 132 tumors assessed with MR imaging were associated with apparent peritumoral edema at the time of GKS. After treatment, peritumoral edema disappeared in 27 tumors, decreased in 13, was unchanged in 16, and progressed in four. Newly developed peritumoral edema after GKS was rare. The delivered peripheral dose was significantly correlated with control of peritumoral edema. The overall median survival time after GKS was 9.5 months. In this study, 34 patients died of systemic disease and 10 died of progressive brain metastases. Multivariate analysis showed that the number of lesions at the first GKS, the Karnofsky Performance Scale score at the first GKS, the recursive partitioning analysis classification, and the interval from diagnosis of RCC to brain metastasis were significantly correlated with survival time.

Conclusions. Gamma Knife surgery is effective for metastatic brain tumors from RCC. The disappearance rate of tumors is relatively low, but growth control is high. The delivered dose to the tumor margin is significantly correlated with the control of peritumoral edema. Gamma Knife surgery should be used as the initial treatment modality, if possible, even in patients with multiple metastases. Repeated GKS is recommended for newly developed brain metastases because of the low sensitivity of RCC to conventional radiation therapy.

KEY WORDS • cerebral metastasis • renal cell carcinoma • radiosurgery • Gamma Knife surgery

Clinical Material and Methods

We used GKS as the initial treatment for tumors less than 3 cm in maximum diameter, even if the tumor location was surgically accessible. On the other hand, we recommended direct surgery for large tumors (more than 3 cm in maximum diameter). In principle, we did not recommend WBRT even for multiple brain metastases because of the low sensitivity of RCC to conventional radiation therapy.

This study included 69 patients (51 men and 18 women, with a mean age of 64.2 years, range 45–85 years) with metastatic brain tumors from RCC who underwent GKS at our hospital. The Leksell Gamma Unit Model B (Elekta Instrument AB, Stockholm, Sweden) and Gamma Plan treatment software (Elekta) were used for GKS.

The retrospective review included analysis of the calculated tumor volume, extent of peritumoral edema before and after GKS, prescription dose to the tumor margin, and change in tumor size on follow-up MR imaging. Change in tumor size was defined as an increase or decrease greater than 25% in maximum diameter. The first author (T.S.) measured tumor sizes on the axial MR images. The effect of

Abbreviations used in this paper: GKS = Gamma Knife surgery; KPS = Karnofsky Performance Scale; MR = magnetic resonance; RCC = renal cell carcinoma; RPA = recursive partitioning analysis; WBRT = whole-brain radiotherapy.
GKS was evaluated on follow-up MR imaging and classified using the following categories: complete remission (complete disappearance of the tumor), partial remission (decrease in tumor size of more than 25% but not disappearance), no change (no apparent change in size), and progression (increase in tumor size of more than 25% or decrease followed by increase in tumor size).

The statistical analyses were performed using the statistical software package StatView 5.0 (SAS Institute, Cary, NC). Logistic regression analysis was used to analyze the significant factors affecting tumor growth control and the presence of peritumoral edema after GKS. The log-rank test and the Cox proportional hazards model were used to analyze factors affecting patient survival. The Fisher exact probability test was used to analyze the extent of peritumoral edema control by a peripheral dose of 20 Gy or more. Probability values of less than 0.05 were defined as statistically significant.

Results

Sixty-nine patients underwent a total of 104 GKS procedures (mean 1.5 procedures). Only one procedure was performed in 51 patients, two procedures in nine, and three procedures in six. Four, five, and eight procedures were performed in one patient each. The interval from diagnosis of RCC to GKS ranged from 1 month to 20 years (mean 5.2 years). Seven patients received treatment for brain metastases before diagnosis of RCC. Before receiving GKS, two patients had received WBRT and 16 patients had undergone craniotomy. No patient received prophylactic GKS directed at metastatic brain tumors. The steroid therapy was managed by the authors or the referring physician, and oncologists were not involved. Data on the factors affecting disappearance or decrease of peritumoral edema after GKS are shown in Table 1. The results of univariate and multivariate analyses showed that only the delivered peripheral dose was significantly correlated with control of peritumoral edema. In addition, a delivered peripheral dose of more than 20 Gy was significantly correlated with better control of peritumoral edema (p = 0.048, Fisher exact probability test).

The overall median survival time was 9.5 months (range 0.1–44.0 months) (Fig. 1). Forty-four patients had died by the date of data collection. Thirty-four patients died of systemic disease, and ten died of progressive brain metastases. The patients with a diagnosis of RCC established after the occurrence of brain metastases tended to have shorter survival times, but the difference was not significant (p = 0.10, log-rank test). The number of treated tumors at the first GKS (p = 0.002, log-rank test) (Fig. 2), KPS score at the first GKS (p = 0.00, log-rank test) (Fig. 3), RPA classification (p = 0.03, log-rank test), and presence of other systemic metastases (p = 0.03, log-rank test) were significantly correlated with the survival time. Survival analysis using the Cox proportional hazards model showed that the number of lesions at the first GKS, KPS score at the first GKS (< 70), poor RPA classification, and interval from diagnosis of RCC to brain metastasis were significantly correlated with a shorter survival time (Table 3). Eighteen patients received repeated GKS (range of two to eight procedures) for further metastases after the first GKS. By the time of follow up, 12 of these patients had died after a median survival time of 13.3 months, and six patients were still alive. Nine of the 12 patients who received repeated GKS died of systemic disease regardless of recurrent brain metastases.

Discussion

Radiosurgery can be used to achieve good tumor growth.
Gamma Knife surgery for brain tumors from RCC

TABLE 2
Factors affecting peritumoral edema control after GKS in patients with brain metastases from RCC

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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</thead>
<tbody>
<tr>
<td>male sex</td>
<td>0.22</td>
<td>0.29</td>
</tr>
<tr>
<td>smaller tumor vol</td>
<td>0.60</td>
<td>0.90</td>
</tr>
<tr>
<td>high delivered peripheral dose*</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>steroid therapy</td>
<td>0.19</td>
<td>0.22</td>
</tr>
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</table>

* Significantly correlated with peritumoral edema control in both univariate and multivariate analyses.

control for radioresistant tumors such as RCC and melanoma. Tumor growth control rates of more than 90% have been reported (Table 4), but these rates include cases in which no change in tumor size was detected. Disappearance of treated tumor on follow-up imaging has been reported in 17–28% of cases. The complete response rate of RCC has been lower (11%). Tumor regression has been observed in 41–69.6% of cases. The tumor control rate obtained with radiosurgery is very high for tumors that show no change on follow-up imaging and are thus considered stable and defined as “controlled.” Our finding of tumor growth control in 82.6% of treated tumors also suggests good tumor growth control. The irradiated tumors were small (mean volume 1.5 cm³), but many of these tumors were associated with severe edema despite their small size and thus tended to become symptomatic. Therefore, findings of no change in tumor size on follow-up imaging do not mean that the treatment had been a clinical failure.

Brain metastases from RCC are often associated with severe edema surrounding the tumor. Peritumoral edema often causes severe neurological symptoms, such as motor weakness, aphasia, and general convulsions, which can affect the quality of daily life. Therefore, the control of peritumoral edema is clinically important.

Edema control around brain metastases from RCC by GKS has not been well described. In a previous study, peritumoral edema improved in eight of 16 patients after GKS, but the details were not reported. In the current study, peritumoral edema disappeared in 27 of 60 tumors, decreased in 13, was unchanged in 16, and progressed in four. From our experience, edema disappeared after GKS in less than one-half of treated tumors. We think this difficulty in edema control is a characteristic of GKS for brain metastases from RCC. The presence of pretreatment edema has not been correlated with postradiosurgical complication rates. Therefore, the marginal dose should not be decreased even for tumors associated with severe peritumoral edema at the time of GKS. In our study, results of univariate and multivariate analyses showed that the delivered peripheral dose was significantly correlated with control of peritumoral edema, with a delivered peripheral dose of more than 20 Gy significantly correlated with better control of peritumoral edema. Therefore, we recommend a marginal dose of 20 Gy or more, if possible, although 18 Gy may be enough to achieve a high tumor control rate.

Newly developed peritumoral edema after GKS was observed in only three of 72 tumors not associated with peritumoral edema at the time of GKS. In a previous study, worsening of peritumoral edema on follow-up imaging after GKS was reported in 4.3% of cases. The relatively short survival time after GKS may be involved in this low incidence of GKS-related edema and in the absence of apparent radionecrosis in our study.

The prognostic factors in patients with brain metastases treated by GKS include systemic disease, age, KPS score, Radiation Therapy Oncology Group grade, time from occurrence of brain metastases until diagnosis of RCC, radiosurgical dose to tumor margin, and maximum radiosurgical dose. In our study, the number of treated lesions at the first GKS, KPS score, RPA classification, and an interval from diagnosis of RCC to brain metastasis were...
significant factors for survival. We found no significant correlation between survival and age or radiosurgical dose to the tumor margin, although such correlations have been reported.25

The median interval from the diagnosis of RCC to brain metastases has been reported to range from 12 to 19 months.14,31 In our study, the interval ranged from 1 month to 20 years (mean 5.2 years). The results of multivariate analysis suggested that an interval from diagnosis of RCC to brain metastasis of less than 1 year was correlated with worse survival time. Patients treated with a combination of WBRT and radiosurgery have been reported to survive longer than patients treated with radiosurgery only.11 Better local control has been achieved with a combination of

WBRT and radiosurgery.3,9,16 However, because of the high tumor growth control rate associated with GKS, GKS alone is appropriate for treatment of brain metastases from RCC.18

The optimum treatment for patients with multiple metastatic brain tumors from RCC remains controversial. Gamma Knife surgery has been recommended for patients with up to three or four metastases.9,16,21,25 As many as 10 brain metastases from RCC can be treated by GKS in one session.17 The upper limit of the daily skull internal dose should be less than 10,000 mJ.24 Therefore, 20–25 lesions are treatable with GKS if all tumors are less than 1 cm in diameter.34 The maximum number of treatable tumors with GKS may be 25 if the tumors are small and the maximum doses are less than 40 Gy.32 When GKS alone was used for patients with 10 or more metastatic brain tumors, the cumulative irradiation dose to the whole brain was within the threshold level for brain necrosis.30

Development of new metastases after GKS is common. We usually recommend repeated GKS for these patients.27 The radioresistant nature of RCC and the good results with use of GKS have encouraged us to use GKS repeatedly.17 The preventive effect of WBRT on the development of new metastases from RCC remains unclear.10 Evolving extracranial disease is an important factor in the reseeding of brain metastases, and repeated GKS is recommended.18 In a previous study, distant metastasis to the brain occurred in 27 (39%) of 69 patients, and 16 of 69 patients received repeated GKS (two or three procedures).25 In another study, GKS was used to treat subsequent new brain metastases from RCC in 8 (36%) of 22 patients.1 In our study, 18 patients received repeated GKS (from two to eight procedures) for further metastases after the first GKS. Of these, 12 patients had died by the end of the study. Nine of the 12 patients who received repeated GKS died of systemic disease, regardless of recurrent brain metastases. In another study, late distant failure occurred in about one half of cases, but death from progression of brain disease was avoided in most cases.16 Based on our experience and the findings of previous studies, we recommend repeated GKS for further metastases after initial GKS. Radiosurgery alone has been used for patients with as many as ten brain metastases at initial presen-

**TABLE 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>male sex</td>
<td>0.49</td>
<td>0.97</td>
</tr>
<tr>
<td>age &gt;60 yrs</td>
<td>0.13</td>
<td>0.67</td>
</tr>
<tr>
<td>multiple metastases at 1st GKS†</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>history of craniotomy</td>
<td>0.36</td>
<td>0.76</td>
</tr>
<tr>
<td>presence of other systemic metastases</td>
<td>0.06</td>
<td>0.14</td>
</tr>
<tr>
<td>KPS score &lt;70 at 1st GKS†</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>interval &lt;1 yr from diagnosis of RCC to brain metastases†</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>poor RPA classification†</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>lower delivered marginal dose at 1st GKS</td>
<td>0.10</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* Survival analysis using the Cox proportional-hazards model.
† Significantly correlated with a shorter survival time.
tation. On the other hand, for patients with numerous metastases, WBRT should be considered, although its efficacy remains controversial. Further study is needed to determine the efficacy of WBRT in combination with GKS for metastatic brain tumors from RCC.

Conclusions

Gamma Knife surgery is effective for the treatment of metastatic brain tumors from RCC. The rate of complete response on follow-up MR imaging is relatively low, but the tumor growth control rate is high. For control of tumor growth and peritumoral edema, we recommend 20 Gy or more, if possible, as the delivered marginal dose. Gamma Knife surgery should be used as the initial treatment modality if possible, even for patients with multiple metastases. Repeated GKS is recommended for newly developed brain metastases because of the low sensitivity of RCC to conventional radiation therapy.

Acknowledgment

We thank Dr. Naoki Hasegawa, Department of Pathology, Yokohama Rosai Hospital; Dr. Daisuke Suyama, Department of Neurosurgery, Yokohama Shintoshi Neurosurgical Hospital (Yokohama, Kanagawa, Japan); and Dr. Koji Yamamura, Department of Neurosurgery, Yokohama Minami Kyosai Hospital (Yokohama, Kanagawa, Japan) for their helpful suggestions.

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Manuscript received December 15, 2005.
Accepted in final March 2, 2006.
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