Gamma Knife Radiosurgery after Stereotactic Aspiration for Large Cystic Brain Metastases

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Objective: Several treatment options have proven effective for metastatic brain tumors, including surgery and stereotactic radiosurgery. Tumors with cystic components, however, are difficult to treat using a single method. We retrospectively assessed the outcome and efficacy of gamma knife radiosurgery (GKRS) for cystic brain metastases after stereotactic aspiration of cystic components to decrease the tumor volume.

Methods: The study population consisted of 24 patients (13 males, 11 females; mean age, 58.3 years) with cystic metastatic brain tumors treated from January 2002 to August 2008. Non-small cell lung cancer was the most common primary origin. After Leksell stereotactic frame was positioned on each patient, magnetic resonance images (MRI)- guided stereotactic cyst aspiration and GKRS were performed (mean prescription dose: 20.2 Gy). After treatment, patients were evaluated by MRI every 3 or 4 months.

Results: After treatment, 13 patients (54.2%) demonstrated tumor control, 5 patients (20.8%) showed local tumor progression, and 6 patients (25.0%) showed remote progression. Mean follow-up duration was 13.1 months. During this period, 10 patients (41.7%) died, but only 1 patient (4.2%) died from brain metastases. The overall median survival after these procedures was 17.8 months.

Conclusion: These results support the usefulness of GKRS after stereotactic cyst aspiration in patients with large cystic brain metastases. This method is especially effective for the patients whose general condition is very poor for general anesthesia and those with metastatic brain tumors located in eloquent areas.

KEY WORDS: Cystic brain metastases · Gamma knife radiosurgery · Stereotactic cyst aspiration.

INTRODUCTION

Many different treatments have proven effective for brain metastases, including surgery, stereotactic radiosurgery, whole brain radiation therapy (WBRT) and chemotherapy. Although no standard therapy has been defined, some general guidelines are available. The median survival is 1 month without treatment, with the administration of steroids increasing median survival to 2 months. Median survival improves to about 4 months after WBRT, to 6 months after gamma knife radiosurgery (GKRS) boost, and to 1 year in patients with surgery prior to WBRT. With either of the latter interventions, however, the survival benefit is attained only by patients with a single brain metastasis.

Radiosurgery has gained increasing relevance for treatment of brain metastases and offers several advantages over resection. For example, radiosurgery can be used to treat multiple metastatic lesions and allows treatment of metastases in deep locations that would be considered surgically inaccessible. Radiosurgery can also be used for patients with other major medical problems considered contraindications for general anesthesia and surgery.

Some brain metastases have large volumes because of cystic components. Sometimes complete control of the cystic component of the tumor may be a challenge for surgical removal. But, patient functional status, tumor multiplicity, and lesion location can be the real limitations for surgery. On the other hand, radiosurgery is not suitable for cystic metastatic tumors because of large volume. To treat such lesions by radiosurgery, it is necessary to decrease the volume of the cystic components.

We assessed the outcomes and efficacy of GKRS used to
treat cystic brain metastases after stereotactic aspiration of
cystic components to decrease the tumor volume.

MATERIALS AND METHODS

Between January 2002 and August 2008, 24 patients
with large cystic brain metastases were referred for GKRS.
Twenty-three of these patients had single large cystic brain
metastases, whereas one patient had two large cystic lesions.
All patients had a confirmed primary malignancy, based on
pathologic examination of specimens obtained from primary
extracranial sites. During the initial consultation, a detailed
general and neurologic history was obtained, and physical
and neurologic examinations were performed. The diagnosis
of brain metastases were confirmed using magnetic resonance
(MR) imaging. All patients were classified according to the
recursive partitioning analysis (RPA) classification system of
the Radiation Therapy Oncology Group (RTOG).

Of the 24 included patients, 13 were male and 11 female,
with a mean age of 58.3 years (range: 39-71 years). Primary
tumors included non-small cell lung cancer (11 patients,
45.8%), small cell lung cancer (2 patients, 8.3%), breast
cancer (7 patients, 29.2%), colorectal cancer (2 patients,
8.3%), hepatocellular carcinoma (1 patient, 4.2%) and
malignant melanoma (1 patient, 4.2%). Initial symptoms
of brain metastasis included motor weakness (10 patients,
41.7%), headache (9 patients, 37.5%), gait disturbance (2
patients, 8.3%), visual disturbance (1 patient, 4.2%),
seizure (1 patient, 4.2%), and incidental discovery (1
patient, 4.2%). The mean number of brain metastases was
2.7 (range: 1-13). Twenty-one lesions were located within
the supratentorial area and 4 at the infratentorial area. The
mean KPS score was 72.9 (range: 50-100). Thirteen
patients (54.2%) were categorized as RPA class 1, 6
(25.0%) as RPA class 2, and 5 (20.8%) as RPA class 3.
Patient characteristics are summarized in Table 1.

MR imaging was performed after positioning of a Leksell
stereotactic frame. MR T1-weighted images with gadolinium
contrast were obtained, and slices were reconstructed
every 2 mm in the axial plane. The SurgiPlan Electa
Instruments system was used to plan surgical trajectory.
Stereotactic cystic drainage, with or without Ommaya
reservoir insertion, was performed aseptically in the operating
room. At that time of stereotactic aspiration, the mean
tumor volume was 23.2 cc (range: 7.9-100.9 cc). Twelve
lesions (48.0%) were treated with additional Ommaya
reservoir insertion after stereotactic drainage. All patients
showed good reduction in cyst volume after stereotactic
drainage.

After cystic drainage, a second set of MR images were
obtained. GammaPlan Electa Instruments software was
used to plan GKRS. At GKRS, mean tumor volume was
reduced from 23.2 cc (range: 7.9-100.9 cc) to 4.3 cc (range:
0.2-19.0 cc) and mean tumor volume reduction rate was
77.9% (range: 31.4-98.3%). The mean prescription
radiation dose to the tumor margin was 20.2 Gy (range:
13-25 Gy). GKRS was also performed to other multiple
lesions without large cyst.

MR imaging was scheduled every 3 or 4 months (Fig. 1,
2). Tumor control was defined as a decrease in tumor size
or little change after treatment. Local tumor progression
was defined as an increase in size of a previously treated
tumor, whereas remote tumor progression was defined as
the appearance of new brain metastasis.

RESULTS

After treatment, 13 patients (54.2%) showed tumor
Table 1. Clinical characteristics of the 24 study patients and the 25
study lesions

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (%)</th>
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<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (54.2)</td>
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<tr>
<td>Female</td>
<td>11 (45.8)</td>
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<tr>
<td>Initial symptom</td>
<td></td>
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<tr>
<td>Motor weakness</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Seizure</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Incidental finding</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Primary tumor</td>
<td></td>
</tr>
<tr>
<td>Non small cell lung cancer</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Number of metastases</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>2</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>3</td>
<td>1 (4.2)</td>
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<tr>
<td>&gt;4</td>
<td>5 (20.8)</td>
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<tr>
<td>RPA Classification</td>
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</tr>
<tr>
<td>Class 1</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Class 2</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Class 3</td>
<td>5 (20.8)</td>
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<tr>
<td>Location of cystic lesions</td>
<td></td>
</tr>
<tr>
<td>Supratentorial</td>
<td>21 (84.0)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>4 (16.0)</td>
</tr>
</tbody>
</table>

RPA: recursive partitioning analysis
symptoms of brain metastasis (Table 2). The overall median survival after GKRS was 17.8 months (range: 1-39 months); 17.8 months for patients in RPA class 1, 10.9 months for patients in RPA class 2, and 6.1 months for patients in RPA class 3. One patient died 1 month after GKRS because of disseminated intravascular coagulation during chemotherapy. Median progression-free survival after treatment was 14.1 months (Fig. 3).

There was no procedure-related mortality or morbidity at the surgery and GKRS or during follow-up periods.

**DISCUSSION**

Primary and metastatic brain tumors often have associated cystic components, but the cause of cyst formation was not established clearly yet. Stem suggested that the relatively large amounts of protein in brain cyst fluid resembled that present in inflammatory exudates, which could be the result of increased permeability of pathologic vessels and mesodermal reactive processes. Cummings also suggested that formation of cyst fluid could be explained by tumor degeneration followed by transudation of fluid from blood vessels. Alternatively, Gardner et al. suggested that fluid accumulating in brain tumors is merely interstitial fluid without its normal drainage route because of the absence of lymphatics in the surrounding brain.

Conventionally, the presence of a single, large, and cystic brain tumor has been regarded as an indication for surgery. Yoshida and Mori advocated surgical treatment for patients with large cystic lesions, providing rapid relief of neurological symptoms caused by mass effect. However, if the lesions are deep within the brain or located adjacent to eloquent areas, surgical procedures may result in severe neurologic deficits. In addition, surgical procedures are not effective or safe for patients in poor general condition or those with multiple lesions.

During the past decade, stereotactic radiosurgical procedure, particularly GKRS, have gained increasing relevance in the combined treatment of cerebral metastatic disease. The rise in use of this technique is attributable to minimal invasiveness, a substantial reduction in hos-
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Fig. 3. Kaplan-Meier survival plot shows the overall patient survival rate over 38 months after cyst aspiration and gamma knife radiosurgery. Surviving patients (n = 13) were censored.

Inpatientization time and cost, an excellent local tumor control rate (even in putatively radioresistant oncotypes), and a very low associated morbidity were demonstrated. Moreover, although there have been no direct randomized clinical comparisons of GKRS with other surgical-radiotherapy protocols, the results of GKRS in patients with solitary lesions were similar or superior to those obtained using other methods.

Large cystic brain metastases do not appear suitable for radiosurgery. Because the volume of the lesion is the limiting factor for radiosurgery given that it correlates with radionecrosis risk. Because the cystic component of a metastatic lesion is unresponsive to radiation, the therapeutic effect of GKRS is reduced. Pan et al. reported that tumors with large cystic components (>10 mL) were not effectively controlled by GKRS alone. Microsurgical resection or a combination of stereotactic cyst aspiration and GKRS, applied to the solid component of the tumor, was shown to result in a 1-year survival rate of 60%.

Frenzit et al. reported that 39.1% of the patients did not experience local or remote tumor progression, the overall median survival was 15 months, and 26.3% of patients died from neurological progression after stereotactic drainage and GKRS of cystic brain metastases. In our study, 54.2% of patients showed tumor control, the overall median survival was 17.8 months and 4.2% of the patient died from progression of the brain metastases after treatment. But, Tendulkar et al. reported that median survival was reported to be 8.7 months after subtotal resection for single brain metastasis and 10.6 months after gross total resection of a single brain metastasis. Although it is difficult to directly compare these findings, the results of GKRS after stereotactic cyst aspiration of large cystic metastases were as good as that of gross total surgical resection. If the tumors locate in the eloquent areas or in the deep locations, or have large cystic volume, it is difficult to remove the tumor completely. In such situations, GKRS after stereotactic cyst aspiration could be the better treatment modality than surgical resection.

Among patients with unresectable brain metastases classified into RPA classes 1, 2, and 3, the median survival time was 7.1 months, 4.2 months, and 2.3 months, respectively. We observed long-term median survival of 17.8 months, 10.9 months, and 6.1 months in RPA classes 1, 2 and 3, respectively. Moreover, patients in RPA class 3 were too weak to permit general anesthesia. But, this modality does not require general anesthesia. These findings further reinforce the efficacy of GKRS after stereotactic cyst aspiration for unresectable cystic brain metastases.

Stereotactic cyst aspiration is a safe and effective procedure. Possible complications include hemorrhage, neurosurgical deficits, seizures, and infection. The mortality rate in several large series has been less than 1%, and complication rates vary from 0% to 7%. The complications of stereotactic radiosurgery are related to the effects of radiation on the brain and structures in proximity to the lesions. Significant early complications include seizures and worsening neurological deficits, but they are very rare. Approximately one-third of patients experience mild transient symptoms, including headache, nausea, and dizziness. Late complications occur 6 to 9 months after the procedure and can include facial palsy, trigeminal neuropathy, and visual symptoms. Patients may become symptomatic from radiation necrosis or local brain edema. Frenzit et al. reported that there was no acute complication and 7.6% of the patients experienced radio- necrosis after stereotactic aspiration and GKRS of cystic brain metastases. In our study, there were no procedure related mortality or morbidity.

This treatment method is composed of two stereotactic procedures with a single frame application. Stereotactic cyst aspiration with or without Ommaya reservoir insertion and GKRS are performed with a single frame application on the same day. So, GKRS after stereotactic cyst aspiration can contribute to a substantial reduction in hospitalization time, cost, and inconvenience of patients.

CONCLUSION

Cyst aspiration reduced tumor volume, permitting increase in radiation dose and decreasing the associated risks of radiation necrosis and post-radiation complications. Our findings support the usefulness and safety of GKRS after
stereotactic cyst aspiration in patients with large cystic brain metastases. This method is especially applicable in patients whose overall condition is too poor to permit general anesthesia and in those with metastatic lesions deeply located.

References