Gamma Knife Radiosurgery for Brainstem Metastasis

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Objective: Brainstem metastases are rarely operable and generally unresponsive to conventional radiation therapy or chemotherapy. Recently, Gamma Knife Radiosurgery (GKRS) was used as a feasible treatment option for brainstem metastasis. The present study evaluated our experience of brainstem metastasis which was treated with GKRS.

Methods: Between November 1992 and June 2010, 32 patients (23 men and 9 women, mean age 56.1 years, range 39-73) were treated with GKRS for brainstem metastases. There were metastatic lesions in pons in 23, the midbrain in 6, and the medulla oblongata in 3 patients, respectively. The primary tumor site was lung in 21, breast in 3, kidney in 2, and other locations in 6 patients. The mean tumor volume was 1,517 mm$^3$ (range, 9-6,000), and the mean marginal dose was 15.9 Gy (range, 6-23). Magnetic Resonance Imaging (MRI) was obtained every 2-3 months following GKRS. Follow-up MRI was possible in 24 patients at a mean follow-up duration of 12.0 months (range, 1-45). Kaplan-Meier survival analysis was used to evaluate the prognostic factors.

Results: Follow-up MRI showed tumor disappearance in 6, tumor shrinkage in 14, no change in tumor size in 1, and tumor growth in 3 patients, which translated into a local tumor control rate of 87.5% (21 of 24 tumors). The mean progression free survival was 12.2 months (range, 2-45) after GKRS. Nine patients were alive at the completion of the study, and the overall mean survival time after GKRS was 7.7 months (range, 1-22). One patient with metastatic melanoma experienced intratumoral hemorrhage during the follow-up period. Survival was found to be associated with score of more than 70 on Karnofsky performance status and low recursive partitioning analysis class (class 1 or 2), in terms of favorable prognostic factors.

Conclusion: GKRS was found to be safe and effective for management of brainstem metastasis. The integral clinical status of patient seems to be important in determining the overall survival time.

Key Words: Brainstem tumor · Gamma knife radiosurgery · Metastasis · Stereotactic radiosurgery.
Clinical and radiological follow-up

Follow-up MRI was performed at every 2 or 3 months after GKRS. Radiological follow-up was available for twenty-four of 32 patients and mean follow-up duration was 12.0 months (range, 1-45). Follow-up MRI was not available for 8 patients due to survival of less than 3 months after GKRS (7 patients), and loss to follow-up (1 patient).

For statistical analysis, we constructed Kaplan-Meier plots for survival and progression free survival using the dates of diagnosis, first GKRS, follow-up MRIs, and death or last follow-up. Progression free survival and overall survival times were calculated from the day of the first GKRS, using the Kaplan-Meier method with a p value of <0.05 set as significant. Primary site, age (<65 years vs. >65 years), KPS (<70 vs. >70), single vs. multiple brain metastases, active vs. absent or controlled extracranial disease, RPA classification were assessed for influence on survival. Standard statistical processing software (SPSS, version 12.0) was used.

RESULTS

Tumor control

MRI was available for 24 patients. Follow-up MRI showed tumor disappearance in 6 patients (25.0%), tumor shrinkage in 14 patients (58.3%), no change in tumor size in 1 patient (4.2%), and an increase in tumor size in 3 patients (12.5%). This translated into a local tumor control rate of 87.5% (21 of 24 tumors). In three cases, tumor progression was observed at 6, 8, and 16 months, respectively. The mean progression free survival (PFS) was 12.2 months after GKRS.

Patient survival

At the time of the assessment, 9 (28.1%) patients were alive at a mean of 20.5 months (ranged 2 to 45 months) and 22 (68.8%) patients had died after GKRS. The overall mean survival time was 7.7 months (ranged 1 to 22 months). For one patient, follow-up data was not available due to loss to follow-up.

The cause of death was documented in 15 patients. Death was related to brainstem metastasis in one patient (increase in hemorrhagic tumor with clinical worsening), development of other brain metastases in five, and aggravation of primary cancer in nine patients.

Prognostic factors for survival

KPS score and recursive partitioning analysis (RPA) classification were shown to have affected survival. Patients with scores more than 70 on KPS group had better overall survival than those with less than 70 (Fig. 1A). RPA class 1 comprised 3 patients who had a mean survival of 17 months, RPA class 2 comprised 3 patients who had a mean survival of 22 months, and RPA class 3 comprised 15 patients who had a mean survival of

Table 1. Summary of patients and tumor characteristics

| Characteristic                      | No. of patients (n=32) |
|-------------------------------------|------------------------|
| Sex (male/female)                   | 23/9                   |
| Mean age in years (range)           | 56.1 (39-73)           |
| Location                            |                        |
| Midbrain                            | 6                      |
| Pons                                | 23                     |
| Medulla                             | 3                      |
| No. of intracranial metastases      |                        |
| Single brainstem                    | 6                      |
| Multiple brain metastases           | 26                     |
| Symptoms related to brainstem deposit before GKRS |                  |
| None                                | 17                     |
| Long tract signs                    | 11                     |
| Ataxia                              | 1                      |
| Diplopia                            | 3                      |
| KPS core                            |                        |
| >70                                 | 14                     |
| <70                                 | 18                     |
| RPA classification                  |                        |
| Class 1                             | 6                      |
| Class 2                             | 10                     |
| Class 3                             | 16                     |
| Primary cancer                      |                        |
| Lung cancer                         | 21                     |
| Breast cancer                       | 3                      |
| Renal cell carcinoma                | 2                      |
| Hepatocellular carcinoma            | 1                      |
| Prostate cancer                     | 2                      |
| Colorectal cancer                   | 1                      |
| Advanced gastric cancer             | 1                      |
| Melanoma                            | 1                      |

GKRS : Gamma Knife Radiosurgery, KPS : Karnofsky performance status, RPA : recursive partitioning analysis

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and is even longer in patients with a single or limited numbers of metastatic tumors who undergo surgical resection. Smalley et al. reported a median survival of 11.7 months after resection of a solitary brain metastasis. Stereotactic radiosurgery has been reported to be as effective as open surgery in local tumor control and GKRS is reported to result in local control rates of 83 to 94%, and median survival times ranging from 7 to 12 months.

The advantages of GKRS are that it is minimally invasive and suitable for lesions inaccessible via surgery. To date, 8 studies have reported on outcomes following stereotactic radiosurgery for brainstem metastases, and their findings are summarized in Table 2. Even though they are small, retrospective, non-controlled studies due to rarity of this disease, they showed the usefulness of GKRS for brainstem metastasis. Those studies reported local control rates of 77 to 100%, which are similar to rates.

Complication

Complication was observed in only 1 case (Fig. 2). This patient was a 51-year-old man who had a metastatic tumor with hemorrhage from a malignant melanoma in the right temporal lobe. After tumor resection, 4 new supratentorial metastatic lesions appeared, and they were treated using GKRS. MRI at 1 month after GKRS showed that all 4 tumors had slightly decreased in size. However, 10 months after GKRS, the patient presented with headache and seizures. Brain CT revealed a pontine and multiple supratentorial metastatic lesions, and that the lesions were compressing the brainstem. The patient died of hemorrhagic tumor increase.

DISCUSSION

Brainstem metastases are relatively rare and have a poor prognosis. The median survival in patients with untreated metastasis to the brain is 1 to 2 months. Survival time is reported to be increased to 3 to 6 months following fractionated radiotherapy, and is even longer in patients with a single or limited numbers of metastatic tumors who undergo surgical resection. Smalley et al. reported a median survival of 11.7 months after resection of a solitary brain metastasis. Stereotactic radiosurgery has been reported to be as effective as open surgery in local tumor control, and GKRS is reported to result in local control rates of 83 to 94%, and median survival times ranging from 7 to 12 months.

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Fig. 1. A : There is a significant association between survival time and KPS score at the time of GKRS for brainstem metastasis (mean survival time 22 months among 15 patients in score more than 70 on KPS vs. 6 months for 17 in score less than 70 on KPS, \( p = 0.0001 \)). B : RPA Kaplan-Meier survival curve shows significant a difference between the three classes (\( p = 0.0059 \)), with the expected mean survival for class 1 patients to be 17 months, 22 months for class 2, and 7 months for class 3. C : Survival of 15 patients in RPA 3 (mean survival=7 months) compared with 8 patients in RPA 1 and 2 together (mean survival=21 months), \( p = 0.0014 \).

Fig. 2. Axial enhanced T1-weighted MR image demonstrating metastatic deposits with hemorrhage involving the pons (A). CT image revealing aggravation of hemorrhagic mass lesions in the right temporal lobe and pons with brain stem compression (B).
reported for brain metastases in other locations\(^{6,8,22,29,34}\). The median survival times ranged from 4.9 to 12 months. Most series used a low radiation dose, ranging from 13 to 20 Gy, with the most common prescribed marginal dose being 16 Gy\(^{5,16,18}\). In 1999, Huang et al. reported a local control rate of 95% and a median survival time of 9 months in 26 patients with brainstem metastasis using a median prescribed dose of 16 Gy\(^{16}\). The current study used a mean prescribed dose of 15.9 Gy, had a local control rate of 87.5%, and a mean survival time of 7.7 months, all of which are comparable to previous series. No direct relationship between peripheral dose delivered and local control were observed. Hussain et al.\(^{10}\) reported a local control rate of 100% using a median prescribed dose of 16 Gy, whereas Lorenzoni et al.\(^{22}\) used a mean prescribed dose of 20 Gy, reported a local control rate of 95%.

The advantage of dose reduction is to limit severe adverse effects involving normal tissue included in the prescription isodose. Valery et al.\(^{22}\) tried to limit peripheral isodose to 13 Gy and to improve conformal dosimetry, reported a local control rate of 90.0%, a mean survival time of 10.0 months. There are possible explanations for the good local control rate compared with hemispherical locations usually treated with higher doses. Targeting or defining an intraparenchymal target is more accurate in this area; high-density brainstem white fibers surrounding the lesion may constitute a barrier against cell spread; and a combination of both may come into play\(^{22}\).

Lorenzoni et al.\(^{22}\) reported that the only patient with tumor recurrence was treated initially with a marginal dose of 18 Gy; the lesion was retreated 8 months later with a marginal dose of 20 Gy. This patient did not develop radiation-induced morbidity and lived 21.5 months after the first treatment. In the present study, two of three patients with tumor recurrence underwent a second GKRS for brainstem metastasis. At 6 and 16 months after the first treatment, they were retreated with a marginal dose of 12.5 and 10 Gy respectively, who had been treated initially with a marginal dose of 12 Gy. These patients lived 12 and 19 months after the first treatment and did not develop radiation-induced morbidity. The prescribed dose was lower compared with the study by Lorenzoni et al. This suggests that the brainstem may tolerate such doses at least for this relatively short period.

Yen et al.\(^{35}\) found that the absence of extracranial disease was the only favorable prognostic factor. Kased et al. reported that factors associated with longer survival were a single metastasis, non-melanoma histology, and extracranial disease control. As mentioned above, the present study found that Karnofsky Performance Status (KPS) and Recursive partitioning analysis (RPA) classification were factors associated with survival rate.

### CONCLUSION

Brainstem metastasis accounts for only a small proportion of brain metastases (3\%-5\%), but the prognosis is highly unfavorable. GKRS resulted in an excellent local control rate with relatively low morbidity and complication rates in patients with brainstem metastasis, indicating it is effective and safe. Patient survival was linked to systemic disease severity.

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