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Clinical Article

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 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.

INTRODUCTION

Metastasis to the brain is a frequent complication of malignant tumors of the lung, breast, kidney, and of malignant melanoma[2]. Metastatic brain lesions are estimated to eventually develop in 15 to 40% of patients with cancer[31], and autopsy studies show brain metastases in 24% of cancer patients. However, brainstem metastases are uncommon, and account for only 3 to 5% of all brain metastases[8,17,30]. Brainstem metastases are generally not treated surgically due to the risk of causing neurological damage. Whole brain radiation therapy (WBRT) and stereotactic radiosurgery have been reported to provide benefits in brain metastases patients[3,4,9,10,14,19,29]. However, the benefits of such treatment in brainstem metastasis patients remain unclear.

Since the first report of Huang et al. series[15], there were some small case series for the management of brainstem metastases using Gamma Knife Radiosurgery (GKRS)[12,16,18,22,26,35]. The present study assessed outcomes following our use of GKRS for the management of brainstem metastasis, and we investigated the effect of treatment on tumor size and survival time.

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MATERIALS AND METHODS

Patient characteristics

From November 1992 to June 2010, a total of 32 patients underwent GKRS for local control of brainstem metastasis at our institute. The clinical characteristics of the 32 patients are summarized in Table 1. The study population consisted of 23 men and 9 women, with a mean age of 56.1 years (range, 39-73). The primary malignancy was lung cancer in 21 patients, breast cancer in 3, renal cell cancer in 2, prostate cancer in 2, and hepatocellular carcinoma, colorectal cancer in 1, gastric cancer in 1, and melanoma in 1. Fourteen patients had score of more than 70 on the Karnofsky performance status (KPS), and 18 had scores of less than 70. Lesions were located in the pons in 23 patients, the midbrain in 6 and the medulla oblongata in 3 patients. Fifteen patients presented with brainstem signs which

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

comprised long tract signs in 11, ataxia in 1, and diplopia in 3 patients. Six patients had a single brainstem metastasis, and the remainder had multiple intracranial deposits (range 2-15). Eighteen patients presented with active extracranial systemic disease.

Radiosurgery technique

All radiosurgical procedures in this study were carried using a Leksell Gamma Knife (B. and C. Elekta, Stockholm, Sweden). A Leksell stereotactic coordinate frame was applied to the patient's head under local anesthesia and stereotactic gadolinium-enhanced MR imaging was then performed for target coordinate determination and dose planning. The mean tumor volume at the time of GKRS was 1,517 mm^3 (range, 9-6,000). The mean marginal radiation dose was 15.9 Gy (range, 6-23). In most patients, the 50% isodose line was selected. The marginal dose was selected on the basis of histology, lesion size, lesion location and previous radiotherapy.

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 classificiation[13] were assessed for influence on survival. Standard statistical processing soft ware (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 5 patients who had a mean survival of 22 months, and RPA class 3 comprised 15 patients who had a mean survival of

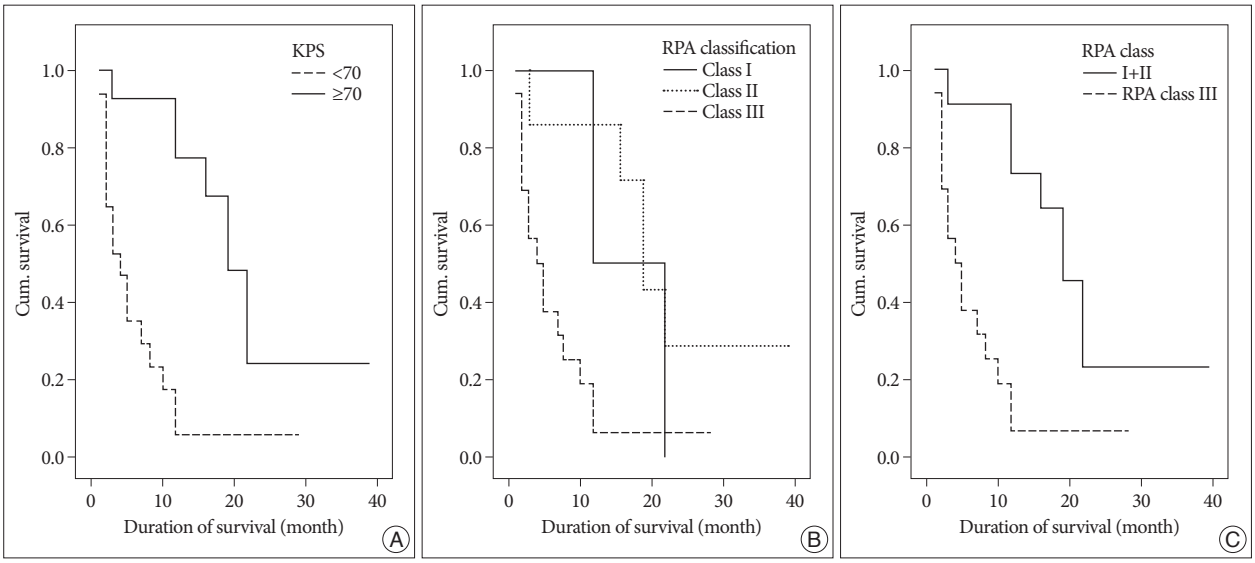

Fig. 1. A : There is a significant association between survival time and KPS score at the time of GKRS for brainstem metastasis (mean survival time 22 months among 15 patients in score more than 70 on KPS vs. 6 months for 17 in score less than 70 on KPS, p=0.0001). B : RPA Kaplan-Meier survival curve 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.

7 months (p=0.0057) (Fig. 1B). Due to the small patient population in RPA class 1 (3 patients), we compared RPA class 3 with RPA class 1 and 2 together. RPA class 1 and 2 showed better overall survival (p=0.0014) (Fig. 1C).

However, survival curves for sex, primary tumor, lesion location, and extracranial metastases did not demonstrate significant difference among subsets.

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 MRI revealed a pontine and multiple supratentorial tumors with hemorrhage. GKRS was performed at 14.8 Gy on the pontine deposit. The next day, the patient presented with swallowing difficulty and progressive impairment of consciousness. Brain CT demonstrated an increase in the extent of multifocal hemorrhagic mass lesions, and that the lesions were compressing the brainstem. The patient died of hemorrhagic tumor increase.

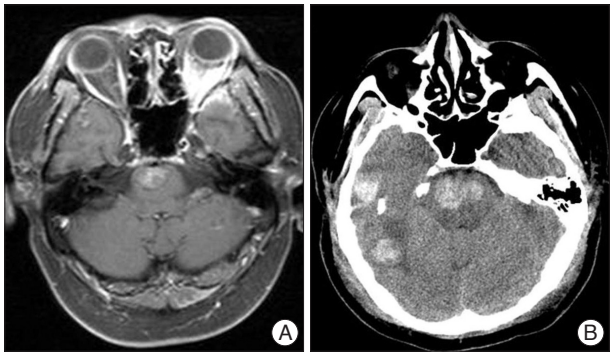

Fig. 2. Axial enhanced T1-weighted MR image demonstrating metastatic deposits with hemorrhage involving the pons (A). CT image revealing aggravation of hemorrhagic mass lesions in the right temporal lobe and pons with brain stem compression (B).

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[21,23]. 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[7,20,25,33]. Smalley et al. reported a median survival of 11.7 months after resection of a solitary brain metastasis[28]. Stereotactic radiosurgery has been reported to be as effective as open surgery in local tumor control[24,27]. GKRS is reported to result in local control rates of 83 to 94%, and median survival times ranging from 7 to 12 months[1,5,6,10,11,15].

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

Table 2. Summary of published series on brainstem metastasis treated with stereotactic radiosurgery

Series	Year	Patient no.	Mean tumor volume (mL)	Mean marginal dose (Gy)	Median survival (mo)	Tumor control (%)
Huang et al.[15]	1999	26	1.1	16.0	9.0	95
Shuto et al.[26]	2003	25	2.1	13.0	4.9	77
Fuentes et al.[12]	2006	28	2.1	19.6	12.0	92
Yen et al.[35]	2006	53	2.8	17.6	11.0	87
Hussain et al.[16]	2007	22	0.9	16.0	8.5	100
Kased et al.[18]	2007	42	0.26	16.0	9.0	92
Lorenzoni et al.[22]	2009	25	0.6	20.0	11.1	95
Valery et al. [32]	2011	30	2.8	13.4	10.0	90
Present study	2011	32	1.5	15.9	7.7	87

reported for brain metastases in other locations[3,9,22,29,34]. 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[15,16,18]. 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[15]. The current study used a mean prescribed dose of 15.9 Gy, had a local control rate of 87.5%, 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.[16] 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.[32] 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[32].

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.

Common GKRS complications include headache, nausea, vomiting, brain edema, and seizure due to radiation-induced injury or intratumoral hemorrhage. GKRS complications related to brainstem include ataxia, dysequilibrium, paresthesia and hemiparesis[18]. The reported morbidity rate after GKRS for brainstem metastasis is 5.5 to 10%[24,27,30]. Shuto et al. reported 2 of 25 patients experienced radiation-induced damage. In the study of Fuentes et al, a higher marginal dose (19.6 Gy), compared with 13 Gy in the study of Shuto et al., was administered, and no radiation-induced complication was documented. Huang et al. reported one case of vomiting and three cases of seizure among 26 patients. In the present study, a dose of 15.9 Gy was administrated. During the follow-up period, one patient with metastatic melanoma experienced intratumoral hemorrhage after GKRS.

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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