Defining the Interval between the Development of New Lesion on Follow Up Study and 1st Gamma Knife Radiosurgery without Whole-Brain Radiation Therapy in the Management of Brain Metastases

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The aim of this retrospective study is to define the interval between the development of new lesion on follow up study and 1st gamma knife radiosurgery (GKS) without whole brain radiation therapy (WBRT) in the management of brain metastases. Between May 1992 and January 2006, 378 patients (207 males and 174 females) with brain metastases were treated with radiosurgery at the Yonsei University Medical Center. Reviewing the follow up study was available in 357 (81.7%) cases, and new lesions were found in 83 (23.2%) cases. We classified the development of new lesions after 1st GKS as missed, invisible, true new and undetermined lesions ; *missed lesions* are those which were visible on MRI at the time of 1st GKS retrospectively, but omitted ; *invisible lesions*, too small to be visualized on MRI at the time of 1st GKS, may be less than 1mm in size at that time and will be new lesions, visible on MRI within 4months after 1st GKS ; *true new lesions*, newly metastasized to brain after GKS, developed 8 months after 1st GKS ; *undetermined lesions*, new lesions developed 5 to 7 months after 1st GKS. There were 12 patients (18.18%) of *missed lesions*, and the number of those lesions was 17 ; 10 patients (15.15%) of *invisible*, and the number, 51 ; 25 patients (37.88%) of *undetermined*, and the number, 166 ; 19 patients (28.79%) of *true new lesions*, and the number, 100. The incidence of new lesion development was high between 5th and 7th months after GKS, and after that, it decreased suddenly. And that low incidence was even after 7th months. GKS without adjuvant WBRT showed good effect, however, strict MRI follow up at 4 and 7months after GKS is necessary to detect and treat the invisible and missed lesions.

KEY WORDS: Brain metastases · Gamma knife radiosurgery · Follow up.

INTRODUCTION

In the last 15 years, radiosurgery (RS) as a therapeutic option was also considered for patients with brain metastases who had controlled systemic disease and/or a good prognosis because of systemic therapies that are more effective.[15] But after many studies have shown that RS is effective at controlling brain metastases and prolonging survival,[9][10][14][17][18] radiosurgical treatment has gained increasing therapeutic relevance for selected patients with small, circumscribed metastases in any location in the brain.

However, many treatment issues still remain unresolved, such as the use of RS with or without whole-brain radiotherapy (WBRT) and its value compared with other treatment modalities. Especially RS has been used as a boost to WBRT or a primary modality followed by adjuvant WBRT with the mind that there may be distant micrometastases that would not be irradiated with radiosurgery alone.[10] On the other hand, there are some reports about withholding WBRT until the time of further progression because of an increased risk of late complications from WBRT, such as radiation-induced dementia.[6][11][25]

The purpose of this study is to define the interval between the development of new lesion on follow up study and 1st gamma knife radiosurgery (GKS) without WBRT in the management of brain metastases, so the additional treatment modalities can be chosen properly after that study.

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MATERIALS AND METHODS

Patient population

Between May 1992 and January 2006, 378 patients (207 males and 174 females) with brain metastases were treated with radiosurgery at the Yonsei University Medical Center. The mean age was 61-year-old (range 24 to 90). Four

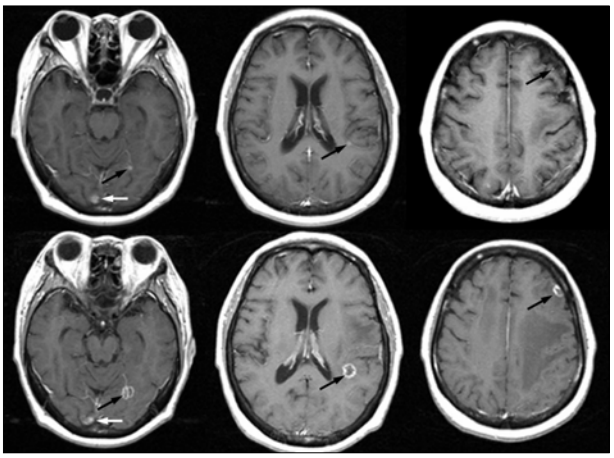

Fig. 1. Axial T1-weighted MR images with Gadolinium enhancement. Upper : At the time of 1st GKS image shows a metastatic mass less than 1cm in diameter on right occipital lobe (white arrow). Lower : Follow up image of 6 months after GKS showed reduction of previous treated lesion, but multiple new lesions were emerged (black arrow). Previous image was re-examed, and these lesions were visible, but we *missed* (black arrow on upper).

hundred and thirty seven procedures were done for 1760 lesions. Among these procedures, GKS without WBRT were 364 procedures (83.3%) and GKS with WBRT, 73 (16.7%). And 47 patients (12.4%) went repeated GKS treatment for the previous or new lesion found on follow up MRI.

Treatment protocol and follow up evaluation

The eligibility criteria for radiosurgical treatment were as followed : all patients had limited systemic disease and good Karnofsky Performance Scale (KPS) scores (more than 70). Also small (<3.5cm in maximum diameter) spherical, well-circumscribed lesions were included. Large size tumor (single or multiple) was surgically treated, and miliary or recurred multiple metastases was treated with WBRT.

The median size of the lesions treated was 0.98cm^3 (range 0.02 to 22.6cm^3). The median radiation dose at the isocenter was 27.21Gy (range 10 to 45Gy). The median radiation dose at the tumor margin was 16.31Gy (range 5 to 28.40Gy). And the median number of metastatic lesions was 8 (range 1 to 29).

MRI, with 1mm thin cut and double dose contrast enhancement, was used for follow up evaluation and was performed at every 3-month interval after 1st GKS. But when the patient had some new subjective symptoms, image scanning was done immediately. Reviewing the follow up study was available in 357 (81.7%) cases, and new

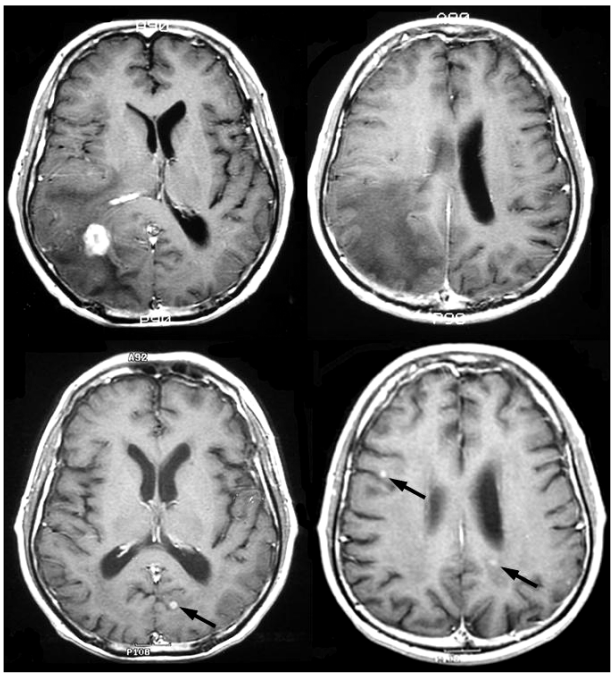

Fig. 2. Axial T1-weighted MR images with Gadolinium enhancement. Upper : At the time of 1st GKS images shows a metastatic lesion with peritumoral edema on right parietal lesion. Lower : Follow up image of 3 months after GKS showed reduction of previous treated lesion and peritumoral edema, but multiple new lesions were emerged (black arrow). May be they were too small to be visualized on MRI at the time of GKS, so we called invisible lesion.

lesions were found in 83 (23.2%) cases.

Classification of new lesions

Reviewing follow up MRI, we classified the development of new lesions after 1st GKS as missed, invisible, true new and undetermined lesions ; *missed lesions* are those which were visible on MRI at the time of 1st GKS retrospectively, but omitted (Fig. 1) ; *invisible lesions*, too small to be visualized on MRI at the time of 1st GKS, may be less than 1mm in size at that time and will be new lesions, visible on MRI within 4 months after 1st GKS (Fig. 2) ; *true new lesions*, newly metastasized to brain after GKS, developed 8 months after 1st GKS (Fig. 3) ; *undetermined lesions*, new lesions developed 5 to 7 months after 1st GKS.

RESULTS

Incidence of new lesion development after 1st GKS without WBRT

There were 12 patients (18.18%) of *missed lesions*, and

the number of those lesions was 17 ; 10 patients (15.15%) of *invisible*, and the number, 51 ; 25 patients (37.88%) of *undetermined*, and the number, 166 ; 19 patients (28.79%) of *true new lesions*, and the number, 100. The incidence of new lesion development after 1st GKS without WBRT is summarized in Table 1.

Timing of the development of new lesions after 1st GKS without WBRT

The incidence of new lesion development was high between 5th and 7th months after GKS, and after that, it decreased suddenly. And that low incidence was even after 7th months (Fig. 4).

Table 1. Classification of new lesions

Type	No. of lesions	No. of patients (%)
Missed	17	12 (18.18%)
Invisible (<4m.)	51	10 (15.15%)
Undetermined (5-7m.)	166	25 (37.88%)
True (>8m.)	100	19 (28.79%)
Total	324	66 (100%)

No. : numbers, m. : months

DISCUSSION

Multiple treatments, such as surgery, RS, WBRT, chemotherapy, immunotherapy and others, etc., are now available for patients with brain metastases. And many studies have shown that RS is effective at controlling brain metastases and prolonging survival.[9)10)14)17)18)] Also results of well-designed studies for the treatment of single metastases have demonstrated that, for patients with a reasonable prognosis, RS plus WBRT is superior to WBRT alone.[1)] But RS plus WBRT (RS as a adjuvant therapy after WBRT) didn't show the improved survival in the management of single and multiple metastases.[3)4)7)24)] Sneed et al. reported that survival and local tumor control were

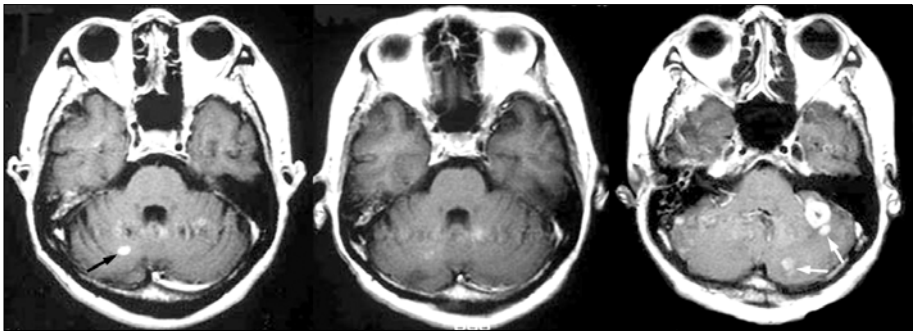

Fig. 3. Axial T1-weighted MR images with Gadolinium enhancement. Left : At the time of 1st GKS images shows a metastatic lesion on right cerebellum (black arrow). Middle : Follow up image of 10months after GKS showed well controlled previous lesion without new lesion development. Right : Follow up image of 25months after GKS showed multiple lesions (white arrow) on cerebellum, which sites were not previously treated ones and we called these, true new lesions.

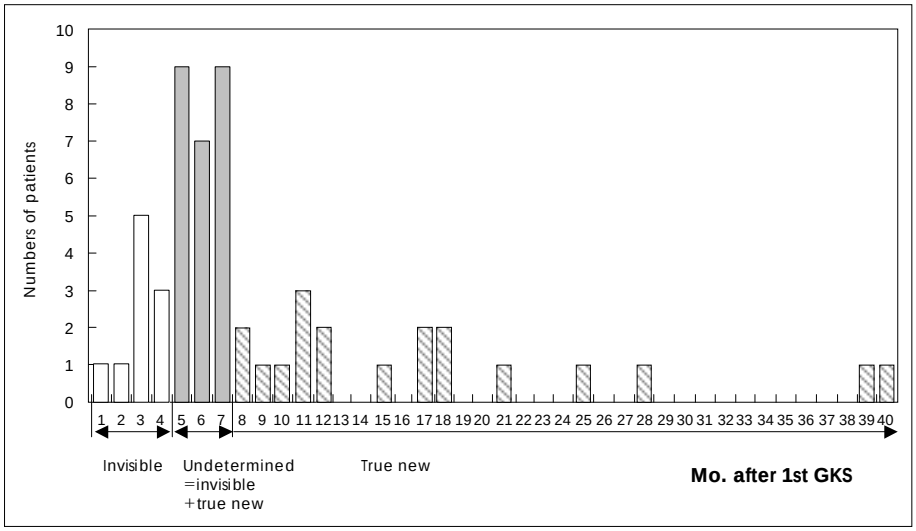

Fig. 4. The incidence of new lesion development was high between 5th and 7th months after GKS, and after that, it decreased suddenly. And that low incidence was even after 7th months. These findings suggest that the number of undetermined lesions must be the sum of the number of invisible lesions and true new lesions developed during that period.

almost the same for radiosurgery alone versus stereotactic RS and WBRT.[5)7)18)23)24)29)] It was same results in our data that WBRT was not a significant variable on the local tumor control (p=0.6555, not shown in this study).

Even though WBRT may control micrometastases not seen on MRI, there are some group withholding WBRT for the purpose of avoiding short-term toxicity and long-term cognitive problems in patients with limited brain disease.[2)5)8)10)12)13)17-24)26-28)] Especially the late toxicities, such as memory impairment, personality change and neurocognitive deficits, which occur more than 90 days after treatment, is problematic for the long term surviving patients in the point of quality of life.[1)6)16)]

Another reason for withholding WBRT is that it makes difficulty in selecting the appropriate dosage. The single dose equivalent (SDE) of fractionated WBRT is variable according to formula, and the total SDE (sum of WBRT and RS) is not clearly known. And when it is combined with WBRT, the fall-off curve of RS will be flattened. For example, when SDE of fractionated WBRT is 10Gy, 5Gy of RS (margin dose in 50% isodose) will be not enough maximum dose for the control of tumor, because total SDE of margin dose will be 15Gy and maximum 20Gy. On the other hand, 10Gy of RS will be too much for the margin dose, total SDE of margin dose will be 20Gy and maximum 30Gy, and it could raise the risk of radiation toxicity.

Hasegawa et al. suggested that periodic imaging examinations, every 3 to 4 months during the first 2 years, are required after RS for brain metastases.[10)] But there was no report suggesting follow up period with objective data in the treatment of brain metastases with RS only. This is our purpose of study to define the interval between the development of new lesion on follow up study and 1st GKS without WBRT. In our results, the incidence of new lesion development was high between 5th and 7th months after GKS, and after that, it decreased suddenly. And that low incidence was even after 7th months. These findings suggest that the number of undetermined lesions must be the sum of the number of invisible lesions and true new lesions developed during that period. So the additional treatment must be added for these lesions at that time, WBRT or RS whatever will be.

CONCLUSION

The incidence of new lesion development was high between 5th and 7th months after GKS, and after that, it decreased suddenly. And that low incidence was even after 7th months. GKS without adjuvant WBRT showed good effect on tumor control, however, strict MRI follow up at 5th and 7th months after GKS is necessary to detect and treat the invisible and missed lesions.

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