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ORIGINAL ARTICLE

Predictive Factors of Micrometastases in Metastatic Brain Tumors Treated with Gamma Knife Radiosurgery

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Objective: Whether to administer or omit adjuvant whole brain radiotherapy (WBRT) in conjunction with stereotactic radiosurgery (SRS) in the initial management of patients with newly diagnosed brain metastases is still up for debate. The ability to predict micrometastases will aid in the decision making process for these patients. In this study, we analyzed factors predictive of micrometastases after gamma knife radiosurgery (GKRS).

Materials and Methods: We retrospectively reviewed clinical and imaging data of 172 patients with metastatic brain tumors who underwent GKRS from July 2012 to July 2013. The study included patients with MRIs taken at both the time of GKRS and 3 months after GKRS. The overall distant brain failure (newly detected metastatic lesions) observed on MRIs taken 3 months after SRS was estimated. Factors such as the primary origin of metastases, CCRTx, EGFR (in lung cancer), volume and number of metastases, status of systemic disease, and delayed MRI were analyzed.

Results: A total of 128 patients were enrolled in this study. Lung cancer was most common as a primary disease (80 patients, 62.5%). Among the patients enrolled, 76 patients (95%) were NSCLC and four patients (5%) were SCLC. In NSCLC patients (76), 30 patients were EGFR mutation positive and 42 patients were negative. Status of the primary disease was stable in 73 patients (57.0%), progressive in 55 patients (42.9%). Eighty-nine patients (62.1%) underwent combined systemic chemotherapy. Mean number of metastatic brain lesions at the time of planning the MRI was 3.67 (from 1 to 22) and mean total tumor volume at planning was 9.05cm^3. For brain tumors originating from lung cancer, a greater number of metastatic lesions suggested a tendency towards micrometastases 3 months after GKRS, with statistically significant differences ($p < 0.05$). Factors such as CCRTx, EGFR (in lung cancer), volume of brain metastases, status of systemic disease, and delayed MRI were not statistically significant.

Conclusions: This study shows predictive factors associated with micrometastases of metastatic brain tumors previously treated with GKRS. Patients with brain metastases originating from lung cancer, more than four metastases should be taken into consideration in the decision making of initial treatment and follow-up management.

KEY WORDS: Brain tumor · Gamma knife radiosurgery · Metastasis · Micrometastases · Stereotactic radiosurgery.

INTRODUCTION

Since the first use of gamma knife radiosurgery (GKRS) at Karolinska Hospital in 1975, GKRS has been a principal treatment modality for cerebral metastasis.[9] GKRS is a non-invasive, fast, and efficient treatment for cerebral metastases and is able to target lesions deep in the brain. Recent studies reported high local control rate (80−90%) and prolonged survival after GKRS for patients with metastatic brain tumors.[1)3)6)7)10)12)] Meanwhile, whole brain radiation therapy (WBRT) is often considered a first line treatment modality for patients with multiple brain metastases because WBRT has been traditionally believed to control micrometastases. However, with respect to the side effects of WBRT including radiation-induced dementia and decline of neurocognitive function, questions have been raised as to whether routine application of WBRT is necessary.

If one can identify the predictive factors for micrometastases after GKRS, it will be helpful in making the proper choice of treatment modality at the beginning of treatment such as GKRS alone, WBRT alone, or GKRS+WBRT, and consequently beneficial to the patients with multiple metastases. In this study, we analyzed each predictive factor suggestive of micrometastases by retrospectively reviewing clinical data of patients with brain metastases who were treated with GKRS at our institute.

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MATERIALS AND METHODS

We retrospectively reviewed clinical and imaging data of 172 patients with metastatic brain tumors who were treated with GKRS between July, 2012 and July, 2013 at Yonsei Gamma Knife center.

In all patients, brain metastases were diagnosed by magnetic resonance imaging (MRI). Patients with MRIs both at the time of GKRS and 3 months after GKRS were included (Fig. 1). After excluding 44 patients without follow up MRI 3 months after GKRS, a total of 128 patients were enrolled in this study. For all patients, T1-weighted MR images with and without the addition of gadobutrol (Gd, Gadovist ; Bayer Schering Pharma AG) and T2-weighted MR images with 1-mm slices (TR25, FOV 250mm, Matrix : 256×256mm) were obtained. Delayed T1 Gd enhanced images were taken 20 minutes after the initial Gd injection. Stereotactic radiosurgery (SRS) was performed using Gamma Knife Perfextion® (Elekta Instruments AB, Stockholm, Sweden).

The primary end-point was pure distant brain failure (newly detected metastatic lesions) observed on MRIs taken 3 months after GKRS. Factors such as the primary origin of metastases, CCRTx, EGFR (in lung cancer), volume and number of metastases, status of systemic disease, and delayed MRI were analyzed. These were estimated using the Student's t test for comparing mean values of the number and total volume of intracranial lesions. To compare the progression free rate according to each factor, the Kaplan-Meier plot was used. Statistical analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

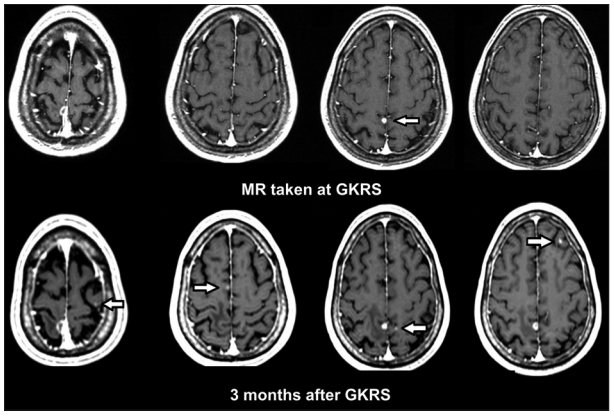

Fig. 1. Images in the upper row are pre-GKRS MR images of brain metastases from lung cancer (adenocarcinoma). Small round enhanced mass in the right parietal area. Those in the lower row are MR images 3 months after GKRS. Newly developed multiple enhanced lesions scattered in the bilateral hemisphere, suggesting micrometastases.

RESULTS

Patient's characteristics

The mean age of patients was 59.3 (25−86). Of the 128 patients, 73 (57 %) were male and 55 (42.9 %) were female. Lung cancer was most common as a primary disease (80 patients, 62.5%). Among them, 76 patients (95%) were NSCLC and 4 patients (5%) were SCLC. In NSCLC patients (76), EGFR mutations were positive in 30 patients and negative in 42 patients (Four patients were not tested for EGFR mutations). Other primary diseases included breast cancer (n=13), renal cell carcinoma (n=7), colon cancer (n=5), rectal cancer (n=4), stomach cancer (n=2), melanoma (n=3) and others (n=8). Status of the primary disease was stable in 73 patients (57.0%), and progressive in 55 patients (42.9%). Eighty-nine patients (62.1%) underwent combined systemic chemotherapy (e.g., Tarceva, Iressa, Alimta, Carbo/Taxol, etc.). Mean number of metastatic brain lesions at the time of planning the MRI was 3.67 (from 1 to 22) and mean total tumor volume at planning was 9.05cm^3. Karnofsky Performance Status ranged from 50 to 100 (mean of 89), and all patients were Recursive Partitioning Analysis Class II (Table 1).

Table 1. Patient demographics

Characteristic		No. of patients (%)
Mean age (year, range)		59.3 (25−86)
Gender		
Male	73 (57.1)	
Female	55 (42.9)	
Primary disease		
Lung cancer	80 (62.5)	
Small cell lung cancer	4	
Non-small cell lung cancer	76	
EGFR Positive	30	
EGFR Negative	42	
Other cancers	48 (37.5)	
Primary disease state		
Stable	73 (57)	
Progressive	55 (42.9)	
Combined systemic chemotherapy		
Yes	89 (69.5)	
No	39 (30.4)	
Karnofsky performance status ; median (score, range)		89 (50−100)

Factors associated with tumor recurrence vs. stability (Table 2)

Among 80 patients with lung cancer as the primary lesion of metastatic brain tumors, 55 patients (68.7%) were stable and 25 patients showed newly developed metastases. Of 48 patients with other primary lesions, 41 (85.4%) were stable and seven patients showed newly developed metastases. These results suggest that primary lesions are associated with the outcome of metastatic brain tumors after GKRS (p=0.035)(Fig. 2A).

In a total of 128 enrolled patients, 89 patients underwent concurrent chemotherapy and 63 (70.7%) of them were stable. Of the 39 patients who did not undergo concurrent chemotherapy, 33 (84.6%) were stable. Patients without concurrent chemotherapy showed slightly more stability after GKRS. However, there was no statistically significant difference (p=0.096)(Fig. 2B).

Of 76 NSCLC patients, 56 were treated with chemotherapy (56=43 patients with targeted therapy+13 patients with other chemotherapy). Among 43 patients with targeted therapy, 17 (39.5%) showed newly developed metastases, while it was observed in three out of 13 (23.0%) patients with other chemotherapy. However, there was no statistically significant difference (p=0.339)(Fig. 2C).

Among 76 patients with NSCLC as the primary tumor, 72 patients were tested for EGFR mutations [30=EGFR (+) and 42=EGFR (−)]. Newly developed metastases were found in 11 out of 42 (26.1%) patients without EGFR mutations, while 13 out of 30 (43.3%) EGFR positive patients showed newly developed metastases 3 months after GKRS. However, there was no statistically significant difference (p=0.139)(Fig. 2D).

Table 2. Factors associated with micrometastases

Factors	Stable/unstable	p value
Primary origin of tumor		0.035
Lung cancer (80)	55 (68.7%)/25 (31.3%)	
Other cancer (48)	41 (85.4%)/7 (14.6%)	
Concurrent chemotherapy		0.096
Yes (89)	63 (70.7%)/26 (29.3%)	
No (39)	33 (84.6%)/6 (15.4%)	
Combined systemic chemotherapy (NSCLC only)		0.339
Targeted CTx. (43)	26 (60.5%)/17 (39.5%)	
Other CTx. (13)	10 (77.0%)/3 (23.0%)	
EGFR status (NSCLC only)		0.139
Positive (30)	17 (56.7%)/13 (43.3%)	
Negative (42)	31 (73.9%)/11 (26.1%)	
Tumor volume (cm^3)	6.7/9.86	0.606
No. of metastatic lesions	2.94/4.69	0.021

With respect to tumor volume, the average volume of stable tumors was 6.7cm^3, larger than the average volume of progressed tumors (9.86cm^3). However, there was no statistically significant difference (p=0.606). On the other hand, the mean number of metastatic lesions was 2.94 for stable tumors and 4.69 for progressive tumors (p=0.021). These results suggest that a larger number of metastatic brain lesions are associated with distant failure after GKRS (Fig. 3).

In addition to these factors, the effect of systemic disease status (stable or progressive) and whether delayed MRIs were taken or not were also analyzed. p values for each factor were 0.098 and 0.839, respectively, suggesting that there were no significant differences between each group.

DISCUSSION

Whether to administer or omit adjuvant WBRT in conjunction with GKRS in the initial management of patients with newly diagnosed brain metastases is subject to debate. WBRT as a treatment modality to palliate symptoms can prolong median survival time and has been considered as a standard of care for the majority of patients with brain metastases.[17] The most common route of metastatic dissemination is hematogenous. Therefore, even when single intracranial lesion is detected on image, it should be assumed that the entire brain is "seeded" with micrometastases. Aoyama, et al. reported detection of fewer distant metastases after GKRS+WBRT compared to the group receiving only GKRS.[2]

However, given the marked improvement in the resolution and sensitivity of brain imaging and the potential for radiation-induced dementia, many investigators have questioned the necessity for routine application of WBRT in patients with brain metastases. Perhaps patients with good prognosis could be managed with SRS alone, reserving WBRT for salvage as needed.[18] Hasegawa, et al. evaluated outcomes and prognostic factors for survival and tumor control in patients with metastatic brain tumors who were treated with GKRS only. In this report, they advocated that WBRT should not be part of the initial treatment protocol for selected patients with one or two tumors with good control of their primary cancer, better Karnofsky Performance Scale score, and younger age.[8]

GKRS has been introduced as a treatment modality for

metastatic brain tumors since its first trial in 1975. GKRS is a non-invasive, fast, and efficient treatment for cerebral metastases and is able to target lesions deep in the brain. In contrast to WBRT, GKRS is thought to preserve cognitive function and therefore be less harmful to patients. In many studies, it has been proven that GKRS is a very useful and effective tool in the management of brain metastases, resulting in high local tumor control rate.[9] Recent studies reported high local control rate (80−90%) and prolonged survival after GKRS for patients with metastatic brain tumors.[1)3)6)7)10)12)] Furthermore, in comparison to GKRS alone versus WBRT alone, four class II evidence studies demonstrated a statistically significant survival advantage for single-dose GKRS in patients with either single or multiple brain tumors.[11)13-15)19)]

Although the control rate of micrometastases by WBRT is high, it is assumed that the control rate of metastatic lesions will be at least as high following GKRS for micro-

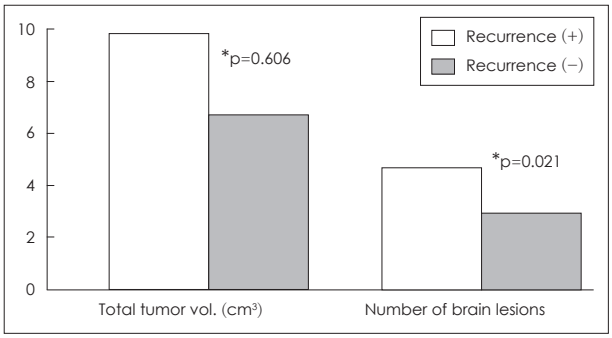

Fig. 3. Tumor volume did not affect the rate of recurrence. However, a greater number of metastatic brain lesions did result in more recurrences.

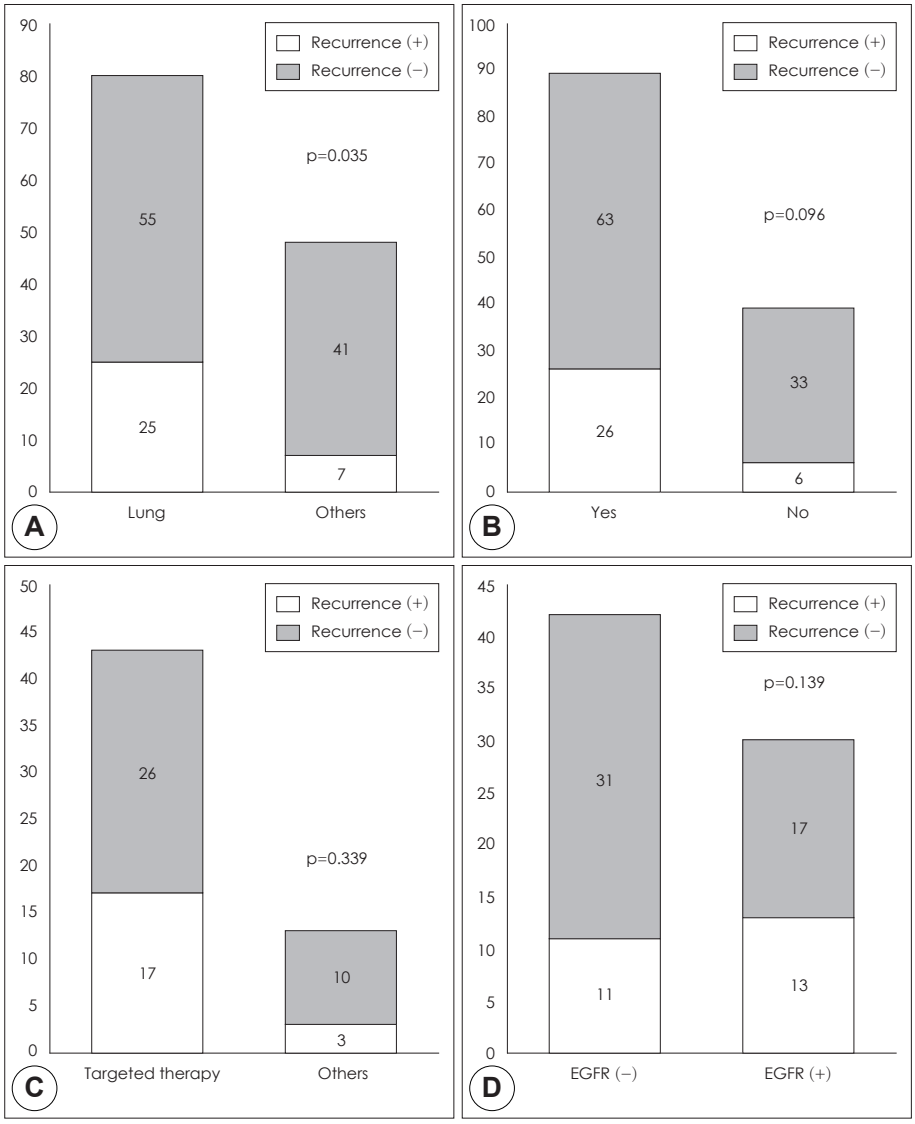

Fig. 2. Factors associated with micrometastases after GKRS. A : Metastatic brain tumors originating from lung cancer had a greater tendency to recur compared to other origins (p=0.035). B : Patients who underwent CCRTx had more recurrences ; however, there was no statistically significant difference (p=0.096). C : Among patients with NSCLC as the primary cancer, patients with targeted therapy had more recurrences ; however, there was no statistically significant difference (p=0.339). D : EGFR (+) NSCLC patients showed a greater tendency to recur ; however, there was no statistically significant difference (p=0.139).

metastases that can be visualized at the time of GKRS. Hanssens, et al. proposed that additional brain metastases can be diagnosed in 40% of patients by using high-resolution imaging ; thus, reducing the incidence of and lengthening the time to distant failures, consequently replacing prophylactic WBRT with high resolution imaging.[7)]

However, GKRS, which is based on images, has limitations in that it cannot control micrometastases. Micrometastases, too small to be visualized on any routine image scans or, travelling through the bloodstream would grow into visible recurrent tumors in the future. If distant brain failure is detected on MRIs 3 months after GKRS, surgeons should decide whether to continue with systemic chemotherapy or change the regimen and also decide whether to conduct WBRT or repeat GKRS. In any situation, it will be harmful to patients because additional cost and decline of the patient's medical condition are expected. Therefore, it is assumable that if one can predict a tendency towards micrometastases after GKRS, it will be helpful for choosing a treatment modality that is efficient and effective at the beginning of treatment (e.g., GKRS alone, WBRT alone, or GKRS+WBRT). Also, surgeons can check precisely for small and invisible metastatic lesions with the expectation of micrometastases, similar to the Hanssens, et al. study.[7)]

There are many reports demonstrating prognosis and clinical outcome such as survival time after metastatic brain tumor treatment. In contrast, there are few reports investigating factors associated with a tendency towards micrometastases of metastatic brain tumors after radiosurgical treatment. Xiao, et al. reported risk factors for distant brain failure (DBF) after GKRS alone, such as the number of metastases, uncontrolled extracranial disease, and total volume of brain metastases.[5)] However, in this study, micrometastases and distant brain failure were not distinguished. Sawrie, et al. also reported predictors of DBF, such as more than three metastases, stable or poorly controlled extracranial disease, and histologic characteristics of melanomas, but no association between DBF and tumor volume or concurrent administration of temozolomide have been found.[16)] Our results revealed statistically significant factors predictive of micrometastases and failure of local control after GKRS. Compared to other primary cancers, lung cancer patients had a statistically significant tendency towards distant failure of brain metastases 3 months after GKRS (suggesting micrometastases)($p=0.035$). In addition, a greater number of metastatic lesions showed more distant brain failures 3 months after GKRS ($p=0.021$). Chang, et al. demonstrated that patients with more than 15 metastatic brain lesions were found to have faster development of new lesions in the brain.[4)] Whether patients received concurrent chemotherapy or not, EGFR status (in lung cancer), systemic disease state, delayed MR, etc. did not affect the distant brain failure.

The number of patient who was enrolled in this study was relatively small to make a conclusion that such factors are definitely related with distant brain failure, although it showed statistically significances. Further studies with larger number of patients and various origin of primary tumor are required for reaching more meaningful conclusion. Additionally, it would be hasty to conclude that all of the patients with such predictive factors of micrometastases should be candidate for WBRT, because WBRT related complications such as radiation-induced dementia are also able to make a serious problem affecting patient's clinical outcomes. Furthermore, because WBRT should be applied in case of leptomeningeal metastasis or military parenchymal metastasis, it would be better to save WBRT for the last treatment modality. Therefore, it is important to apply WBRT appropriately, considering each patient's clinical status.

CONCLUSION

This study shows predictive factors associated with micrometastases of metastatic brain tumors previously treated with GKRS. Factors such as lung cancer as a primary disease, more than four metastatic lesions may indicate future detection of micrometastases on MRIs 3 months after GKRS. With careful consideration of each patient's clinical status, GKRS in combination with WBRT could be one of the treatment options for these patients. We recommend that the findings of this study should be taken into consideration in the decision making process and patient selection of metastatic brain tumors for SRS or WBRT.

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