International Journal of Clinical Oncology (2019) 24:161–167
https://doi.org/10.1007/s10147-018-1339-7

ORIGINAL ARTICLE

Low-dose Gamma Knife radiosurgery plus whole-brain radiation therapy for patients with 5 or more brain metastases with or without meningeal dissemination

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Received: 11 June 2018 / Accepted: 7 August 2018 / Published online: 11 August 2018

Abstract

Purpose/objective(s) Radiosurgery plus whole-brain radiotherapy (WBRT) has been reported to be useful for patients with ≤4 brain metastases (BM), but we hypothesized that similar treatment may be applicable to patients with ≥5 BM with or without meningeal dissemination. The purpose of this study was to evaluate the efficacy and toxicity of low-dose Gamma Knife (GK) followed by WBRT for patients with advanced BM.

Materials/methods Major eligibility criteria for this phase II study were: (1) ≥5 BM with or without meningeal dissemination and (2) the largest tumor diameter ≤4 cm. During 2013–2016, 40 patients (13 men and 27 women) entered the study. Nineteen had meningeal dissemination. The GK dose was 12 Gy at the periphery when the longest diameter was 3–4 cm and 14 Gy when it was <3 cm. The WBRT dose to the isocenter was 30 Gy in 10 fractions, or 37.5 Gy in 15 fractions for two patients, with an expected survival of >12 months. The median number of target BM was 17.5.

Results After GK plus WBRT for 40 patients, 31 did not develop further intracranial recurrence until death or last follow-up, whereas 9 developed recurrence. With a follow-up period up to 24 months, the overall survival rate was 36% at 12 months and median survival time was 8 months. The cumulative incidence of intracranial recurrence was 25% at 12 months. Toxicity was considered acceptable.

Conclusion Treatment with low-dose GK followed by WBRT for advanced-stage BM appeared to contribute to local control.

Keywords Brain metastasis · Gamma Knife radiosurgery · Whole-brain radiation therapy

Introduction

Various radiotherapy modalities are used for the treatment of brain metastases (BM) [1–8]. All modalities have their own advantages and disadvantages. Gamma Knife (GK) radiosurgery quickly completes treatment sessions, but GK treatment alone is unsuitable for multiple (usually ≥5) BM, BM with meningeal dissemination, and BM with a longest diameter ≥3 cm. Whole-brain radiotherapy (WBRT) is effective for treating microscopic lesions but may be inferior to stereotactic radiosurgery (SRS) in obtaining local control. Therefore, treatment with SRS plus WBRT has been sporadically tested so far. Compared with SRS alone, SRS plus WBRT seems to improve intracranial tumor control [3, 5], although overall survival may not be improved because of many deaths from extracranial metastases. Generally, this combined treatment has been applied to cases with ≤4 BM [3–5].

Regarding treatment of BM with ≥5 lesions, WBRT has been commonly employed, but the Japan Leksell Gamma Knife (JLGK) Society recently reported that overall survival did not differ between patients with 2–4 BM and those with 5–10 BM when treated using GK alone [6]. However, intracranial control is expected to be reduced by employing WBRT in combination with GK for multiple BM with ≥5

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lesions. In addition, we thought that this treatment could also be applied to BM with meningeal dissemination and BM with a diameter > 3 cm, although these conditions are not suitable for GK treatment alone. Thus, we engaged in a single institution study to test the efficacy of combining GK radiosurgery and WBRT in such patients with ≥ 5 BM. Because patients with a relatively large lesions (≤ 4 cm) could be eligible, we adopted a strategy to deliver GK first and then WBRT. The rationale for this sequence was: (1) to alleviate symptoms quickly in patients with a large BM and (2) to treat all visible lesions by GK, because small lesions may become invisible after WBRT. The purpose of this study was to evaluate the early response, efficacy, and toxicity of low-dose GK plus WBRT for patients with ≥ 5 BM with or without meningeal dissemination.

Materials and methods

Study design

This Phase II study was approved by the Institutional Review Board at Fujieda Heisei Memorial Hospital (No. 25-4). This study is registered with the University Medical Information Network (UMIN) Clinical Trial Registry, number 000027361. Informed consent was obtained from all patients before entry. Eligibility criteria were: (1) ≥ 5 BM with or without meningeal dissemination; (2) tumor diameter ≤ 4 cm; (3) a Karnofsky performance status (KPS) score of ≥ 70 or, in patients with a KPS score of < 70, a reasonable expectation of neurological function improvement with SRS; and (4) patients with any type of original malignant solid tumors except for sarcoma and lymphoma. Even when patients fulfilled these eligibility criteria, 43 patients with 5–10 BM, all < 3 cm in diameter, were treated with GK alone and thus excluded, based on the results of the JLGK study [6] and patient's denial of entry into this study. The primary endpoint of the study was the overall survival (OS) rate. Secondary endpoints were the intracranial control rate and incidence of acute and late toxicities. In our previous study, the OS rate at 1 year was 32% after GK plus WBRT in patients with 1–43 BM (median 11) (unpublished data, October 2013). The Radiation Therapy Oncology Group reported a 1-year OS of 15% for recursive partitioning analysis (RPA) class II patients undergoing several different doses of WBRT schemes and radiation sensitizers [9]. The RPA class I represented patients with KPS ≥ 70, < 65 years of age with controlled primary and no extracranial metastases, and class III represented KPS < 70. Class II included all others cases. We estimated that most patients in our study would be in RPA class II, because of their advanced-stage BM. So, when the desirable and undesirable 1-year OS rates were assumed to be 0.32 (P1) and 0.15 (P0), respectively, the number of patients required for this study was estimated to be 38 patients using single-stage phase II designs ($\alpha = 0.05$, $\beta = 0.2$, P0 = 0.15, P1 = 0.32) [10]. Therefore, we designed to accrue 40 patients into this study, assuming a 5% loss from evaluation.

Patient characteristics

From November 2013 to March 2016, 40 patients entered the study. All patients had ≥ 5 BM, and 6 patients had a tumor diameter 3–4 cm. Nineteen patients had meningeal dissemination and 21 did not. Thirty-six patients had ≥ 11 BM. Thirteen were men and 27 were women. Their median age was 65 years. Organs of primary cancers were the lung in 24, breast in 13, and other in 3 patients. Characteristics of the patients and tumors are summarized in Table 1.

Treatment protocol

As soon as patients were judged as eligible, GK was delivered first, and after 2 or 3 days usually, WBRT was started. This interval between GK and WBRT was adopted to allow reoxygenation of the tumors while keeping the overall treatment time reasonably short [11]. In patients starting treatment at the year end or before the Golden Week holiday period in Japan (late April to early May), the longest interval allowed was 10 days.

Our GK method has been described previously [12, 13]. Briefly, contrast-enhanced magnetic resonance imaging (MRI) was carried out for treatment planning using a

Table 1 Patients and tumor characteristics

Characteristics	
Patient number	40
Age (years), range (median)	43–81 (65)
Gender, male/female	13/27
Performance status (0/1/2/3)	0/12/26/2
RPA (I/II/III)	1/33/6
Primary tumor site	
Lung (NSCLC/small cell)/breast/stomach/pharynx/unknown	24(22/2)/13/1/1/1
Extracranial lesions	
Yes/no	36/4
BM with meningeal dissemination	
Yes/no	19/21
Number with ≤ 10 BM	
Yes/no	4/36
Tumor diameter ≥ 3, ≤ 4 cm	
Yes/no	6/34

RPA recursive partitioning analysis, *NSCLC* non-small cell lung cancer, *BM* brain metastases

1.5-T scanner (EXCELART Pianissimo, Toshiba Medical Systems, Otawara, Japan) and a Leksell frame under local anesthesia. Treatment planning was performed using Leksell GammaPlan (Elekta AB, Stockholm, Sweden). The planning target volume was defined as the contrast-enhanced tumor region plus a 1-mm margin. GK was performed with a Leksell Gamma Knife unit (Model C, Elekta AB). Tumors with a longest diameter of 3–4 cm were irradiated with 12 Gy, and those < 3 cm were irradiated with 14 Gy. Increasing or decreasing a prescribed dose by 2 Gy was allowed. All BM were treated by GK in one fraction. However, when treating all BM was considered difficult because of time or safety, tiny lesions were allowed to be left untreated by GK. The median prescribed dose of GK was 14 Gy at the periphery (50% isodose line). The median number of target BM was 17.5 (range 5–34).

WBRT was performed using a linear accelerator (Synergy S, Elekta AB, Stockholm, Sweden) equipped with 4-mm multileaf collimators. Treatment planning was carried out using Pinnacle^3 (Philips, Amsterdam, The Netherlands). The standard WBRT dose to the isocenter was 30 Gy in 10 fractions. In patients with expected long-term survival (> 1 year), 37.5 Gy in 15 fractions was allowed. The WBRT dose to isocenter was 30 Gy in 10 fractions for 38 patients and 37.5 Gy in 15 fractions for 2 patients. The median interval between GKS and starting WBRT was 2 days (range 1–10 days). The GKS and WBRT treatments are summarized in Table 2.

Evaluation

All patients were scheduled to undergo contrast-enhanced MRI or computed tomography (CT) before and at 3-month intervals (± 1 month) after GK. In patients with poor health conditions, follow-up imaging studies were performed whenever possible. Local recurrence was suspected when enlargement of the contrast enhancement of the irradiated region (> 20% in the longest diameter compared with that before GK) was detected on MRI or CT images. Intracranial recurrence was defined as local recurrence or appearance of new BM. Time to intracranial recurrence was evaluated based on the follow-up imaging. Toxicities were evaluated using the Common Terminology Criteria for Adverse Events Version 4.0.

Table 2 Parameters for GKS and WBRT

Number of brain tumors[a]	
Range (median)	5–34 (17.5)
Median total dose at GK (Gy)	
Range (median)	12–14 (14)
Total dose (Gy) and fraction at WBRT	
30/10	38
37.5/15	2

GK Gamma Knife, *WBRT* whole-brain radiotherapy

[a]Brain tumors treated GK

Statistical analysis

OS was calculated from the start of GK using the Kaplan–Meier method. The log-rank test was used to compare survival curves. The time to intracranial recurrence was calculated from the start of GK. A Fine and Gray competing risks regression model was used to estimate and compare cumulating incidences of intracranial recurrence, thereby considering patient death as a competing risk. All statistical analyses were carried out using R version 3.4.1 for Windows (The R Foundation for Statistical Computing, Vienna, Austria). P values of < 0.05 were defined as significant.

Results

All 40 patients were evaluable. Of the 40 patients, 14 were alive and 26 were dead at the time of this analysis. Seventeen patients died of systemic disease, 2 patients died due to the progression of brain lesions, 1 patient died of another disease, and the cause of death was unclear in 6 patients. Thirty-one did not develop further recurrence until death or last follow-up, whereas 9 developed recurrence. After GK plus WBRT, the median follow-up period was 7 months (range 1–24 months) for all patients, and 12 months (range 1–24 months) for living patients. The OS rate was 36% at 12 months and median OS time was 8 months (Fig. 1a). For all patients, the cumulative incidence of intracranial recurrence was 25% at 12 months (Fig. 1b).

The median OS time was 11 and 7 months for patients with and without meningeal dissemination, respectively, with no difference between the two groups ($P = 0.37$) (Fig. 2a). The cumulative incidence of intracranial recurrence was 29 and 28% at 12 months, respectively (Fig. 2b). The median OS time was 13 months for patients with 5–10 BM and 7 months for patients with > 10 BM (Fig. 2c). The cumulative incidence of intracranial recurrence was 0 and 28% at 12 months, respectively (Fig. 2d). The median OS time was 9 and 6.5 months for patients with a tumor with a longest diameter of < 3 cm and those of 3–4 cm, respectively (Fig. 2e). The cumulative incidence of intracranial recurrence was 29 and 0% at 12 months, respectively (Fig. 2f). When evaluated by the RPA class, one patient in class I died at 5 months, and 33 patients in class II had a median OS time of 7 months. In 6 patients in class III, the median OS was 13 months. The cumulative incidence of intracranial recurrence was 31% at 12 months for RPA class II and 0%

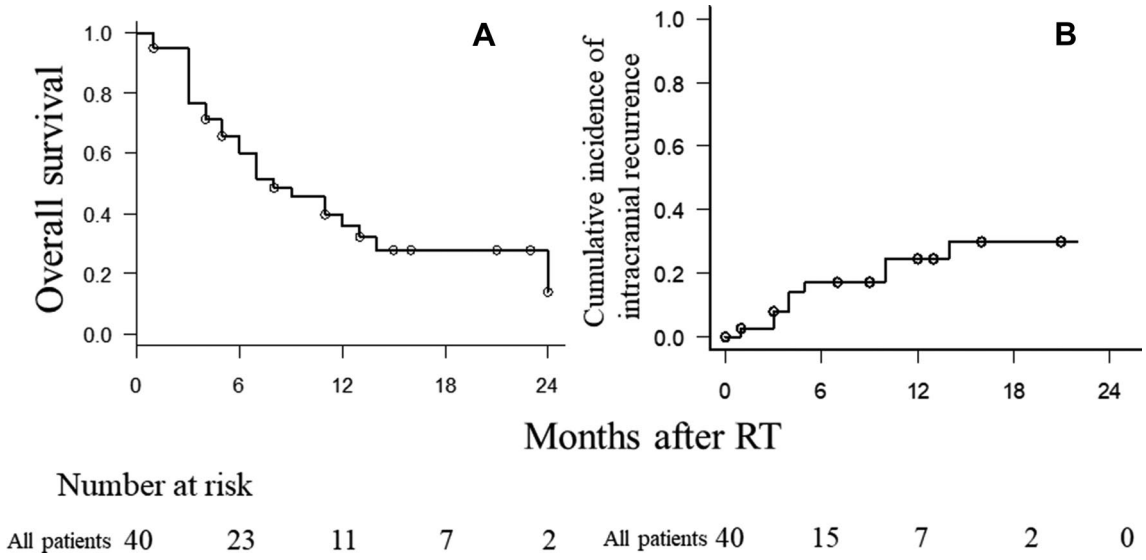

Fig. 1 **a** Overall survival curves for all patients. **b** Cumulative incidence of intracranial recurrence for all patients

for class III. The OS and the cumulative incidence of intracranial recurrence are summarized in Table 3.

Nine patients developed recurrence; 6 were re-treated by GK and 3 patients were treated conservatively. Two patients had symptomatic brain edema, but it was controlled by corticosteroids. One patient had leukoencephalopathy. One patient had radiation necrosis after radiotherapy. Two patients had middle ear inflammation, but it was controlled by surgical treatment.

Discussion

The role of radiosurgery appears to be increasing rapidly in the treatment of BM. A recent trend may be that even for multiple (≥ 5) BM, WBRT is reserved until it becomes necessary. The greatest reason for avoiding WBRT is the neurological adverse effects of WBRT, but in advanced BM with a relatively short expected survival time, neurocognitive decline after WBRT may not be frequently encountered [14]. However, advanced BM investigated in this study are not suitable for treatment with SRS alone, and the effect of WBRT alone is usually not satisfactory. Therefore, we investigated the combination of relatively low doses of GK and WBRT in patients such advanced disease. The cumulative incidence of intracranial recurrence was low (25% at 12 months using the competing risk analysis). Subgroup analyses revealed that patients with meningeal dissemination had OS and intracranial control rates similar to those of patients without dissemination. In addition, patients with ≥ 11 BM and patients with a 3–4 cm tumor had reasonable OS and intracranial control rates. Although the incidence of radiation necrosis was one of the major concerns in late toxicities of GK plus WBRT, it was only observed in one patient in our study. Overall, toxicity was judged as acceptable.

RTOG9508 reported that the median survival time in the WBRT and SRS group for patients with a single BM was 6.5 months [15]. A randomized clinical trial in patients with 1–3 BM reported that median overall survival was 10.4 months for SRS alone and 7.4 months for SRS plus WBRT [16]. Another randomized clinical trial in patients with 1–3 BM reported that median overall survival was 8.5 months for all patients [3]. In these studies, patients with 1–3 newly diagnosed BM were randomly allocated to either WBRT or WBRT followed by SRS boost. In our study with much more advanced BM, the median survival time was 8 months. Considering 36 patients in our study had extracranial lesions, our results compared very favorably with those stated above. So, GK plus WBRT may be a treatment option for advanced stage BM. It is reported that prognostic factors for BM patients vary with the type of primary cancer [17], and in the near future, we plan to evaluate the issue in advanced-stage BM for each primary tumor.

One of the issues to be further investigated is the sequence of GK and WBRT. We delivered GK first for early alleviation of symptoms in symptomatic patients and for treatment of even tiny lesions which might disappear with WBRT. However, in asymptomatic patients and those with all sizable tumors, GK after WBRT may be more reasonable, because the treatment volume for GK becomes smaller. To allow as much size reduction as possible after WBRT and not to allow repopulation of tumor cells after WBRT, a treatment strategy to deliver WBRT first (2–3 weeks) followed by GK or SRS 2–3 weeks later may be conceivable. We are

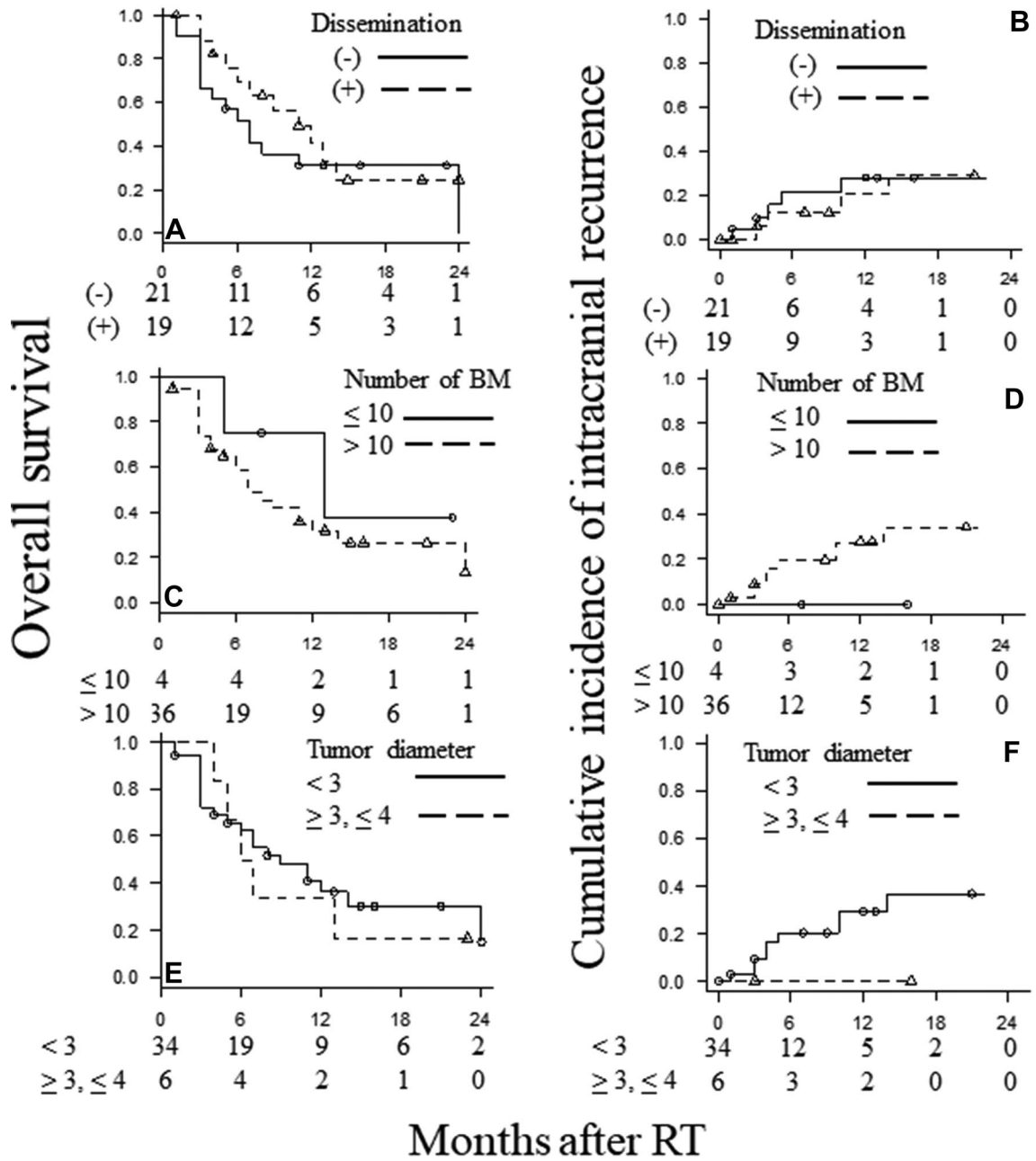

Fig. 2 Overall survival curves for patients with or without meningeal dissemination (**a**), for patients with 5–10 BM or > 10 BM (**c**), and for patients with a longest tumor diameter of < 3 or 3–4 cm (**e**). Cumulative incidences of intracranial recurrence for patients with or without meningeal dissemination (**b**), for patients with 5–10 BM or > 10 BM (**d**), or for patients with a longest tumor diameter of < 3 or 3–4 cm (**f**)

planning a study to compare the two strategies (GK first or WBRT first).

There are a few limitations in this study. The study subjects were advanced multiple BM, but they could be grouped into ≥ 11 BM, BM with meningeal dissemination, and BM with a 3–4 cm lesion. In particular, the last group had a small number of patients ($n = 6$), so evaluation of this subgroup was not satisfactory. In addition, OS, intracranial control, and toxicity were endpoints of this study, and neurogenic death and neurocognitive functions after treatment were not evaluated. Nevertheless, this study suggested feasibility and utility of GK plus WBRT in such advanced BM. These issues should be investigated in future studies.

Table 3 OS and the cumulative incidence of IR according to patients and tumor characteristics

Characteristics	MST (months)	OS at 12 months (%)	Cumulative incidence of IR at 12 months (%)
RPA			
1/2/3	5/7/13	0/31/67 $P=0.52$	0/25/0 $P=0.25$
Meningeal dissemination			
Yes/no	11/7	41/31 $P=0.37$	29/28 $P=0.78$
Number with ≤ 10 BM			
Yes/no	13/7	75/32 $P=0.41$	0/28 $P=0.23$
Tumor diameter ≥ 3, ≤4 cm			
Yes/no	6.5/9	33/36 $P=0.60$	0/29 $P=0.13$
Extracranial lesions			
Yes/no	8/14.5	34/50 $P=0.74$	28/0 $P=0.19$

MST median survival rate, *OS* overall survival, *IR* intracranial recurrence, *RPA* recursive partitioning analysis, *BM* brain metastases

Conclusion

Treatment with low-dose GK followed by WBRT for advanced-stage BM appeared to yield favorable intracranial control. Adverse events were mostly acceptable. Although survival time was not long because almost all patients had very advanced disease, this treatment may be worth further investigation by selecting patients with expected long-term survival based on age, performance status, primary cancer, etc.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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