Clinical Outcomes and Prognostic Factors of Fractionated Stereotactic Radiation Therapy for Large Brain Metastases as a Potential Alternative to Surgery

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Abstract

Introduction: We investigated the outcomes and prognostic factors for fractionated stereotactic radiation therapy (FSRT) for large brain metastases and evaluated whether FSRT could negate the need for surgery, which is the mainstream treatment for large brain metastases.

Methods: Patients with brain metastases measuring ≥ 2 cm treated with FSRT were retrospectively examined. Patients undergoing FSRT postoperatively were excluded. Local failure, intracranial failure, and adverse events were evaluated.

Results: Overall, 106 lesions in 98 patients were evaluated. Performance status was 0–1, 2–4, and unknown in 79, 25, and 2 patients, respectively. The median maximum tumor diameter was 25 mm, and the median prescription dose was 35 Gy in 3 fractions. The median follow-up period after FSRT was 7 months. The 1-year rates of local failure, intracranial failure, and overall survival were 13.0%, 57.8%, and 48.0%, respectively. In multivariate analysis, the maximum dose for target ≥ 135 Gy (biological equivalent dose of a/b of 10 Gy) and good performance status were independent positive prognostic factors for local failure. Sixteen patients (16.3%) were treated with whole-brain radiotherapy after FSRT owing to multiple intracranial recurrences, while surgery was performed for three patients (3.1%) owing to local recurrence.

Conclusions: FSRT for large brain metastases achieved good local control and only 3% of patients needed surgery after FSRT, suggesting that FSRT is a potential alternative to surgery. In FSRT, a higher maximum tumor dose was useful for local control.

Introduction

Brain metastases (BMs) affect up to 30% of all patients with cancer and cause various neurological complications [1]. The incidence of BM is expected to increase further because of expanded screening efforts using magnetic resonance imaging (MRI) and improved systemic therapies [2]. The standard of care for BM is multimodality treatment including whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and surgical resection [3, 4]. SRS provides good local control and is associated with lower cognitive dysfunction rates for intact BM [5, 6]. By contrast, the risk of radiation toxicity increases with tumor size and target volume in SRS [7]; thus, the SRS dose for a large BM is typically forced to be lowered for safety [8]. Therefore, SRS treatment has been less effective in controlling large BMs than small tumors [9].

Surgery is usually performed particularly for large BMs because of the advantages of fast resolution of peritumoral edema and immediate reduction in tumor volume [10, 11]. However, surgery has some disadvantages. Some cases involve a long postoperative recovery time, which adds to the burden of the surgery, resulting in delays in systemic therapy. Moreover, complications of surgery, such as infection and bleeding, although rare, can be fatal.

Fractionated stereotactic radiation therapy (FSRT) is an expansion technique of frameless SRS and is typically delivered using a linear accelerator. FSRT has the radiobiological advantage of fractionation of normal brain tissues, resulting in possible administration of higher doses to tumors than it can be achieved with single-fraction SRS. Therefore, FSRT is expected to reduce the risk of radiation necrosis (RN) while maintaining or improving local control for intact large BMs [2, 12–15]. Furthermore, FSRT is an effective and minimally invasive treatment for large BMs and can be a therapeutic option to facilitate the avoidance of surgery. In this study, we evaluated the treatment outcomes and investigated the prognostic factors for FSRT to identify cases where surgery could be avoided.

Patients And Methods

Patients

We retrospectively reviewed the medical records of patients who received FSRT for BM between February 2012 and December 2019 in a single Japanese institution. Patients were included if they met the following criteria: (i) diagnosed with BMs on MRI (or computed tomography [CT] in some patients), (ii) maximum diameter of BM ≥ 2 cm, (iii) treated with FSRT with three or five fractions, and (iv) tumor images of the targeted tumor were evaluated at least once after FSRT. We excluded patients who underwent surgery for the target lesion before FSRT. We performed surgery for cases with an expected prognosis ≥ 6 months and a tumor with extensive edema or neurologic symptoms.

This study was approved by our institutional ethical review board (approval number 2487), and written informed consent was obtained from all patients.

Treatments

Patients were immobilized in the supine position and wore a thermoplastic mask. Treatment planning images were obtained with contrast-enhanced CT with a 1-mm slice thickness and contrast-enhanced T1 volumetric MRI sequences with a 1.3-mm slice thickness. The gross tumor volume (GTV) was defined as an abnormal contrast-enhanced lesion on CT and MRI. The clinical target volume was equal to GTV. A 1-mm margin was added to the clinical target volume to create the planning target volume (PTV). We prescribed an optimal prescription isodose line of approximately 70% before August 2014. From September 2014 onward, a 60% isodose line was used for dose prescription. The prescribed dose covered 95% of the PTV. We aimed to prescribe 35 Gy in three fractions or 41.5 Gy in five fractions, provided that the surrounding brain tissue satisfied the dose constraints. The dose constraint was set for the surrounding brain tissue so that the volume received 23.1 Gy in three fractions or 28.8 Gy in five fractions was < 7 cc by reference to a single-fraction dose equivalent of 14 Gy calculated in biological equivalent dose (BED) of a/b of 2 Gy (BED₂) [16, 17]. All treatments were delivered using CyberKnife® (Accuray Inc., Sunnyvale, CA).

Statistical analysis

The primary endpoint of the present retrospective study was local failure (LF). Other endpoints were best tumor response, intracranial failure (ICF), overall survival, surgery for targeted lesion, and toxicities. Time to event date was calculated in months from the start date of FSRT. Tumor response was evaluated according to the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) [18]. Initial response was recorded on MRI at 1–3 months after FSRT. LF was defined as a progressive disease of the target lesion according to RANO-BM. LF was estimated using the cumulative incidence function adjusted for the competing risk of death and compared using Gray's test for equality. For the multivariate analysis of LF, the Fine–Gray competing risks model was used for deriving the hazard ratio for all variables identified as significant in the univariate analysis. The overall survival rate was estimated using the Kaplan–Meier method. The results were considered significant for p values < 0.05 . All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [19].

Results

Patient characteristics

Among 821 lesions treated with stereotactic radiation therapy in our institution, 106 lesions in 98 patients were eligible for this study. The patient and tumor characteristics are shown in Table 1. Fifteen (15.3%) patients underwent WBRT before FSRT. Twenty-one (19.8%) lesions were larger than 30 mm in terms of the maximum tumor diameter. The median prescribed dose was 35 Gy in three fractions (range, 22.5–41.5 Gy in three to five fractions). Details of the dose characteristics are summarized in Table 2.

Table 1
Patient characteristics

Characteristic	106 cases from 98 patients
Age (years)	
Median (range)	68 (39–93)
Sex	
Male/Female	57/41
PS	
0–1/2–4 /unknown	79/25/2
Primary lesion	
Lung	72
Breast	15
Colorectal	8
Others	11
Number of brain metastases	
1/2–	40/66
Tumor maximum diameter (mm)	
Median (range)	25 (20–50)
Tumor volume (cc)	
Median (range)	7.2 (1.6–39.1)
History of whole brain radiotherapy	
Yes/No	19/87
Systemic therapy after FSRT	
Yes/No/Unknown	78/27/1
<i>PS</i> , performance status, <i>FSRT</i> ; fractionated stereotactic radiotherapy	

Table 2
Dose and dosimetric characteristics

	Median (range)
Prescription dose/fraction	35 Gy in 3 fr. (25-41.5 Gy in 3–5 fr.)
Prescription dose, BED ₁₀	76 Gy (38–76 Gy)
Tumor marginal isodose line	60% (50–95%)
Maximum dose, BED ₁₀	148 Gy (49–188 Gy)
Mean dose, BED ₁₀	103 Gy (43–125 Gy)
Normal tissue V _{14 Gy} equivalent	6.2 cc (0–22 cc)
Normal tissue V _{12 Gy} equivalent	8.9 cc (1.8–30 cc)
<i>BED₁₀</i> ; biological equivalent dose of a/b of 10 Gy	

Clinical outcomes

The median follow-up period was 7 months (range, 1–48 months). All patients completed the planned treatment without respite. No patients treated in the hospital required an extension of their hospital stay. Complete response, partial response, stable disease, and progressive disease occurred in 14, 74, 17, and 1 case(s), respectively. LF was observed in 13 lesions during follow-up. The 6- and 12-month LF rates were 5.4% and 13.0%, respectively (Fig. 1). The 12-month LF rate for BMs ≥ 3 cm was 25.1%. ICF was confirmed in 54 patients. The median ICF time was 10.4 months, and the 6- and 12-month ICF rates were 30.1% and 57.8%, respectively (Fig. 1). The median overall survival was 11.5 months (Fig. 2). Three patients (3.1%) underwent surgery because of local recurrence 5–10 months after FSRT and 16 patients (16.3%) underwent WBRT owing to the occurrence of multiple BMs after FSRT.

Univariate analysis showed that the factors associated with better prognostic factors for LF were maximum dose for PTV ≥ 135 Gy in BED of α/β of 10 Gy (BED₁₀) and good performance status (PS). Neither maximum diameter nor prescribed dose correlated with LF in the univariate analysis (Table 3). In the multivariate analysis, a maximum dose for PTV ≥ 135 Gy with BED₁₀ (Fig. 3) and a good PS were independent positive prognostic factors for LF (Table 4).

Table 3
Univariate analysis

		1-y local failure rate (%)	p value
PS	0–1 (n = 79)	9.2	0.0422
	2- (n = 27)	31.6	
Maximum diameter	< 30 mm (n = 85)	11.6	0.530
	≥ 30 mm (n = 21)	27.6	
Number of brain metastases	< 2 (n = 40)	12.9	0.388
	≥ 2 (n = 66)	16.9	
Systemic therapy after FSRT	yes (n = 78)	11.4	0.316
	no (n = 27)	20.2	
Prescribed dose (BED ₁₀)	< 75 Gy (n = 33)	4.2	0.317
	≥ 75 Gy (n = 73)	16.3	
Mean dose (BED ₁₀)	< 100 Gy (n = 45)	23.3	0.0729
	≥ 100 Gy (n = 61)	9.5	
Maximum dose (BED ₁₀)	< 135 Gy (n = 41)	26.7	0.00402
	≥ 135 Gy (n = 65)	6.0	
PS, performance status, FSRT; fractionated stereotactic radiation therapy, BED ₁₀ ; biological equivalent dose of a/b of 10 Gy			

Table 4
Multivariate analysis

	HR	95% CI	P value
Performance status (0–1 vs. 2–4)	0.29	0.10–0.82	0.02
Maximum dose (≥ 135 Gy BED ₁₀ vs. < 135 Gy BED ₁₀)	0.16	0.041–0.60	0.007
BED ₁₀ ; biological effective dose of a/b of 10 Gy			

There was no grade 3 or higher toxicity in the present study. RN was observed in 5 (3.9%) lesions. The median time to RN was 18 months (range, 3–19 months). All RNs were clinically diagnosed by MRI based on observation over time. All patients with RN were asymptomatic and did not undergo surgery or biopsy. Grade 2 intracranial hemorrhage was identified in two (1.9%) lesions, and both had tumor hemorrhage.

Table 5

Content and results of previous studies of outcomes for fractionated stereotactic radiotherapy for large brain metastases

	Study type	n	Median f/u	Median diameter	Dose (Gy) /fractions	Isodose line	LC rate	RN rate	Prognostic factor
Navarria et al [1]	Retrospective	102	14 mos	2.9 cm	37/3, 32/4	80%	1-y 96%	5.8%	KPS, extracranial control
Jeong et al [2]	Retrospective	38	10 mos	17.6 cc (> 3 cm)	35/3 or 5	80%	1-y 87%	15.8%	Prescription dose
Inoue et al [3]	Retrospective	85	8 mos	12.6 cc	31/5	58%	8-m 92.9%	2.6%	NA
Inoue et al [4]	Retrospective	159	7 mos	6.9 cc	27/3	60%	7-m 95.8%	2.1%	NA
Murai et al [5]	Prospective	61	NA	NA (> 2.5 cm)	NA	NA	1-y 69%	NA	NA
Marcrom et al [6]	Retrospective	182	5 mos	1.68 cm	25 or 30/5	NA	1-y 86%	6%	Smaller tumor size, higher prescription dose
Minniti et al [7]	Retrospective	138	29 mos	NA (> 2 cm)	27/3	80– 90%	1-y 90%	8%	Non- melanoma
Current study	Retrospective	106	7 mos	2.5 cm	35/3	60%	1-y LF 13.0%	3.9%	PS, maximum tumor dose
<i>f/u</i> , follow up, <i>LC</i> , local control, <i>RN</i> , radiation necrosis, <i>KPS</i> , karnofsky performance status, <i>NA</i> , not applicable, <i>PS</i> , performance status, <i>LF</i> , local failure									
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Study type	n	Median f/u	Median diameter	Dose (Gy) /fractions	Isodose line	LC rate	RN rate	Prognostic factor
6. Marcrom SR, McDonald AM, Thompson JW, Popple RA, Riley KO, Markert JM, Willey CD, Bredel M, Fiveash JB (2017) Fractionated stereotactic radiation therapy for intact brain metastases. <i>Adv Radiat Oncol</i> 2: 564–571 doi:10.1016/j.adro.2017.07.006								
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Discussion

This study showed that FSRT for large BMs resulted in good local control. Only 3% of patients received surgery due to local recurrence after FSRT. No grade 3 or higher toxicities were observed, and no patients required an extension of hospital stay. These findings suggest that FSRT has the potential to be an alternative to surgery in terms of its low LF rate and low toxicity rate. In addition, a higher maximum dose for PTV was useful for local control.

While some reports have shown good clinical outcomes of FSRT alone for large BMs (Table 5) [14, 16, 17, 20–23], surgery is regarded as the mainstay treatment strategy for large BMs [24], as surgical resection has been considered a more reliable method than radiotherapy for reversing neurological deficits [8]. Although surgical resection can lead to fast resolution of peritumoral edema and immediately reduce the tumor volume [10, 11], a surgical approach sometimes involves a waiting time for surgery and a postoperative recovery time in addition to the burden of surgery. Compared with surgery, FSRT alone has an overall shorter treatment time and is less invasive. These factors make it a good option for patients who need to receive systemic therapy following local treatment for BM. In this cohort, patients not candidates for surgery because of their prognosis or had a waiting time for surgery were included. Only three patients (3.1%) required surgery 5–10 months after FSRT. In other words, most cases in this study achieved local control and were able to avoid surgery.

Conversely, FSRT has some disadvantages such as delay in the resolution of peritumoral edema or the shrinkage of tumor volume and the characteristics of radiotherapy that induce edema. Therefore, one goal of the present study was to identify the patients suitable for surgery and those who could be allowed to receive FSRT alone. We showed that a good PS and high maximum dose for PTV were correlated with a low LF rate. However, PS is thought to be a prognostic factor but not a predictive factor; therefore, PS cannot be used as an independent decision-making criterion between surgery and FSRT.

Regarding the maximum dose for PTV, the present data suggest that a higher maximum dose is appropriate for FSRT. Although it is unclear why the maximum dose relates to local control, a few studies have reported a correlation between the maximum tumor dose and local control [25, 26]. In the report of RTOG 90–05, patients treated with a linear accelerator were more likely to have local progression than those treated by a gamma-knife procedure [27]. In gamma-knife SRS, a 50% isodose line is usually used for dose prescription, and in linear-accelerator SRS, a 60–90% isodose line is usually used for dose prescription. Compared with linear-accelerator SRS, gamma-knife SRS can typically deliver a higher maximum dose to the target. The same report mentioned that the hypoxic and more radioresistant portion of the tumor is located in the center of the tumor; hence, a higher maximum dose resulted in better local control. Even if the prescription dose is low because of the dose for the surrounding normal brain tissue, it is not a difficult technique to escalate the maximum dose in large BM; therefore, this is useful in daily clinical situations.

We used two uniform dose constraints for normal tissue of 23.1 Gy in 3 fractions or 28.8 Gy in 5 fractions < 7 cc by reference to a single dose equivalent of 14 Gy calculated in BED₂, resulting in five cases of asymptomatic (grade 1) RN (3.9%). No patients required surgery because of RN. A systematic review recommended the dose constraints for normal tissue of 23 Gy in 3 fractions and 29 Gy in 5 fractions < 20 cc and estimated the rate of grade 3 RN to be 3.4% and the rate of RN that required surgery to be 0% [28]. The dose constraints we used, therefore, are considered safe and reproducible.

The present study has some limitations. First, there were inevitable selection biases in this retrospective study. Treatment decisions of surgery or FSRT may have been affected by clinicians' intentions. Caution is needed to interpret these results, and these results might not be applicable to all large BM cases. Conversely, these results would adapt for the cases without strong edema or neurologic symptoms. Second, neither the prescription dose nor the prescription isodose line was unified. It is difficult to unify the prescription dose for large BMs owing to the prescription dose that depend on the dose constraints for normal brain tissue. However, the dose constraint for normal brain tissue was uniformed. Third, patients with BM $\geq$ 3 cm were not the majority (19.8 %) in this cohort. Because of the small sample size of patients with BMs $\geq$ 3 cm, this may have limited the detection of significant differences in clinical outcomes. Further research is required for larger BMs.

In conclusion, we showed the outcomes of FSRT for large BMs with low LF rates and acceptable toxicities in this study. Only 3% of patients needed surgery for the targeted lesion after FSRT. The study results suggest that FSRT for large BMs has the potential to be an alternative to surgery, at least as a good alternative treatment option for cases without extensive edema or neurologic symptoms. In this clinical setting, a maximum tumor dose of $\geq$ 135 Gy in BED₁₀ is important for tumor control.

Declarations

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Declarations

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Conflicts of interest/Competing Interests. The authors state that they have no conflicts of interest.

Availability of data and material: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable

Author contributions: H.O.; Designed and performed experiments, analyzed data and wrote the paper. K.I.; Designed experiments and co-wrote the paper. K.K.; Supervised the research.

Ethics approval: Approval was obtained from the ethics committee of Tokyo metropolitan Komagome hospital. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate: Individually informed consent was waived given the retrospective non-invasive nature of the study.

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Figures

Figure 1

Cumulative incidence of local and intracranial failure rates

Figure 2

Kaplan–Meier curve of the overall survival rate

Figure 3

Cumulative incidence of the local failure rate according to the maximum tumor dose