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CLINICAL STUDY

Single-fraction versus hypofractionated stereotactic radiosurgery for medium-sized brain metastases of 2.5 to 3 cm

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Abstract

Purpose Given recently suggested utility of hypofractionated stereotactic radiosurgery (SRS) in treating large brain metastases (BMs) > 3 cm, we sought to prospectively control tumor size variable to investigate the efficacy and safety of hypofractionated SRS for medium-sized BMs (2.5 to 3 cm) compared with single-fraction SRS.

Methods Between 2011 and 2015, a total of 100 patients with newly diagnosed BMs (n = 105) of 2.5 to 3 cm had been treated with either single-fraction (n = 67; median dose 20 Gy) or hypofractionated SRS (n = 38; median cumulative dose 35 Gy in 5 daily fractions). No patients received any prior or upfront whole brain radiotherapy. In each patient, treatment outcome was measured by local tumor control (LTC), overall and progression-free survival (OS and PFS), and the occurrence of radiation necrosis (RN).

Results With a median follow-up of 14 months, significant differences were observed between the single-fraction versus hypofractionated SRS groups in the incidence of RN (29.9% vs. 5.3%, $P < 0.001$) and LTC (1-year LTC rates 66.6% vs. 92.4%, $P = 0.028$). There were no differences in PFS (median 6 months vs. 6 months, $P = 0.381$) and OS (median 13 months vs. 18 months, $P = 0.239$). Treatment-related adverse events (≥ grade 2 toxicity by CTCAE ver. 4.0) occurred more frequently in single-fraction group, although the difference did not reach statistical significance (56.3% vs. 36.1%, $P = 0.084$).

Conclusions Our results suggest a better safety and efficacy profile of hypofractionated SRS for medium-sized BMs compared with single-fraction SRS. Further prospective studies are needed to confirm these results.

Keywords Stereotactic radiosurgery · Hypofractionation · Brain metastases · Radiation necrosis

Introduction

Brain metastases (BMs) are drawing greater attention in the field of neuro-oncology in terms of patient quality of life as well as survival with their growing incidence and advanced cancer therapeutics. Treatment options include radiation treatment such as stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT), surgery, and pharmacotherapy such as targeted agents. SRS has been expanding its role in the treatment of BMs over the past decades [1], which employs highly conformal dose of radiation to the target typically delivered in a single fraction. It is usually indicated for tumors less than 2 to 3 cm in diameter, because the risk of radiation toxicity such as radiation necrosis (RN) substantially increases as the tumor size increases thereover [1–4]. For larger tumors, radiation dose to tumor should be reduced to maintain the risk of radiation toxicity, which may compromise tumor control probability conversely. As a matter of fact, the incidence of RN has been reported as high as 17.2% to 38.8% in recent studies employing single-fraction SRS with reduced dose approach for the treatment of large BMs, while local tumor control (LTC) rates at 1 year were 58% to 84.6% [5–9].

In recent years, hypofractionated SRS (2 to 5 fractions) has been used for the treatment of large BMs based on the theoretical advantages of fractionation radiobiology, and the

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data in the literature suggest a promise of this approach in terms of both efficacy and safety compared with single-fraction SRS [6, 8, 10–15]. However, previous studies on this topic are all retrospective in nature with a huge heterogeneity in study design, SRS modality and technique, and dose/fractionation protocol, especially in tumor size the major confounding variable affecting the treatment outcomes. Here we sought to prospectively control tumor size to investigate the efficacy and safety of hypofractionated SRS specifically for medium-sized BMs (2.5 to 3 cm) at the border zone of tumor size for treatment with conventional single-fraction SRS and compared its outcomes with those of single-fraction SRS.

Materials and methods

Eligibility

This retrospective study with prospectively managed clinical data was approved by our institutional review board. Between January 2011 and December 2015, a total of 100 patients with 105 BMs of 2.5 to 3.0 cm were entered into the study according to the inclusion and exclusion criteria below.

Inclusion criteria

(1) Age of ≥ 18 years, with histologically proven solid cancer and fewer than 10 BMs, any of which is 2.5 to 3 cm in maximum diameter on brain magnetic resonance images (MRI)
(2) Patients who had been treated with either single-fraction SRS using the Gamma Knife (GK; Elekta AB, Stockholm, Sweden) or hypofractionated (3 to 5 fractions) SRS using the Cyberknife (CK; Accuray Inc., Sunnyvale, CA) for their medium-sized BMs

Exclusion criteria.

(1) Previous history of cranial irradiation including WBRT and SRS
(2) Prior surgical resection of the targeted lesions
(3) Absence of follow-up data at least 3 months after treatment

Demographic data and tumor variables

Baseline characteristics of the patients and tumors are summarized in Table 1. A total of 105 BMs had been treated with either single-fraction (n = 67) or hypofractionated SRS (n = 38). There were no differences between the two groups in gender, age, number of lesions, tumor volume (median 9.7 cc and 11.0 cc, respectively), location, origin and status of primary cancers, patient performance, the Radiation Therapy Oncology Group-recursive partitioning analysis (RTOG-RPA) class and the diagnosis-specific graded prognostic assessment (DS-GPA) score except for extracranial metastases.

Stereotactic radiosurgery and dosimetric parameters

The Leksell Gamma Knife Perfexion System was used for single-fraction SRS and the Cyberknife Robotic Radiosurgery System Version 9.0 was used for hypofractionated SRS. All GK plans were generated using the Elekta GammaPlan system (version 9.0) based on gadolinium-enhanced axial three-dimensional T1-magnetization-prepared rapid acquisition gradient echo (3D-T1-MPRAGE) MRI (1.5 mm slice thickness) fused with computed tomography (CT) images (1.25 mm slice). The optimal plan was produced by adjustment of the sectors and collimators such that optimal dose coverage of the target while minimizing dose to surrounding normal tissues was achieved. The prescription isodose percentage was applied to 50% of the maximum dose and the median prescription dose was 20 Gy (range 18–22 Gy). For CK plans, planning CT images were fused with gadolinium-enhanced 3D-T1-MPRAGE images in the Accuray MultiPlan system (version 4.5) to facilitate delineation of the gross tumor volume (GTV; equal to the planning target volume). The prescription isodose percentage was applied to around 80% with planning objectives of GTV coverage > 99% and the conformity index (CI) < 1.2. The median prescription dose was 35 Gy (range 27–41 Gy). Doses were administered in 3 or 5 daily fractions.

Tumor coverage, the homogeneity index (HI), CI, and the gradient index× (GI) were calculated in each plan to compare dosimetric quality between the two groups. HI was measured as the ratio of the maximum dose over the prescription dose. CI was defined as the ratio of prescription isodose volume (PIV) to the volume of tumor receiving the prescription dose or more. GI was the ratio of the isodose volume receiving 50% of the prescription dose to PIV. Table 2 summarizes comparison of dosimetric parameters.

Follow-up, outcome measures, and statistics

Follow-up clinical examinations and MRIs were performed at 3 month intervals after treatment. LTC was defined as complete or partial response and stable disease using the criteria of MacDonald et al. [16]. Significant increase of tumor size (> 25%) on interval MRIs was defined as local failure. Progression was defined as local failure and/or development of a new lesion. RN was assessed objectively using MRI or confirmed pathologically after surgical resection. The following criteria were considered for RN: (1) increased T1 contrast enhancement in treated volume with

Table 1 Summary of baseline patient characteristics based on stereotactic radiosurgery modality

	Single-fraction SRS (n = 67)	Hypofractionated SRS (n = 38)	*P* value[a]
Male sex (%)	28 (43.8%)	19 (52.8%)	0.510
Age ≥ 65 years (%)	18 (28.1%)	16 (44.4%)	0.152
Number of metastases			0.329
Total	154	73	
Mean per patient	2.41	2.03	
Median (range)	2 (1–9)	1 (1–7)	
Tumor volume (cc), median (range)	9.7 (6.8–15.9)	11.0 (6.0–14.8)	0.178
Location of metastases			0.200
Cerebral hemisphere	49 (73.1%)	23 (60.5%)	
Cerebellum	16 (23.9%)	11 (29.0%)	
BG and diencephalon	2 (3.0%)	4 (10.5%)	
Primary cancers (%)			0.821
Lung	36 (53.7%)	20 (52.6%)	
Breast	14 (20.9%)	8 (21.1%)	
GI tract	10 (14.9%)	4 (10.5%)	
Others	7 (10.5%)	6 (15.8%)	
Status of primary cancer (%)			0.417
Controlled	34 (53.1%)	18 (50.0%)	
Uncontrolled	11 (17.2%)	10 (27.8%)	
Newly diagnosed	19 (29.7%)	8 (22.2%)	
Extracranial metastases (%)			0.016
Present	47 (73.4%)	17 (47.2%)	
Absent	17 (26.6%)	19 (52.8%)	
KPS score (%)			1
≥ 70	61 (95.3%)	34 (94.4%)	
< 70	3 (4.7%)	2 (5.6%)	
RTOG-RPA class (%)			0.665
I	13 (20.3%)	10 (27.8%)	
II	48 (75.0%)	24 (66.7%)	
III	3 (4.7%)	2 (5.6%)	
DS-GPA score (%)			0.123
≤ 1.0	10 (17.0%)	3 (9.7%)	
1.5–2.5	33 (55.9%)	13 (41.9%)	
≥ 3.0	16 (27.1%)	15 (48.4%)	

SRS stereotactic radiosurgery, *BG* the basal ganglia, *GI* gastrointestinal, *KPS* the Karnofsky performance status, *RTOG* the Radiation Therapy Oncology Group, *RPA* recursive partitioning analysis, *DS-GPA* diagnosis-specific graded prognostic assessment

[a]Chi-square test for categorical variables and Student's t-test for continuous variables

Table 2 Dosimetric parameters of Gamma Knife (single-fraction) and Cyberknife (hypofractionation) treatments

	Gamma Knife (mean ± SD)	Cyberknife (mean ± SD)	*P* value[a]
Tumor coverage (%)	98.29 ± 2.05	99.0 ± 1.44	0.048
Homogeneity index	2.01 ± 0.04	1.3 ± 0.07	< 0.001
Conformity index	1.21 ± 0.09	1.16 ± 0.09	0.031
Gradient index	2.82 ± 0.26	3.12 ± 0.49	0.001

SD standard deviation

[a]Student's t-test

central hypointensity and increased peripheral edema [17] (2) substantial regression or stability (for at least 3 months) of enhancing areas on serial follow-up MRIs without additional treatment [18], or (3) absence of perfusion within the contrast-enhancing lesion on dynamic susceptibility contrast perfusion MRI [19]. Treatment-related clinical toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Event (version 4.0) (CTCAE ver. 4.0).

Differences in baseline patient characteristics were compared using the Student's t-test for continuous variables and

the chi-square or Fisher's exact test for categorical variables. Dosimetric parameters were compared using the Student's t-test. LTC, the overall and progression-free survival (OS and PFS), and RN were estimated using the Kaplan–Meier method. The Cox proportional hazards model was used to adjust for the baseline imbalances in gender, age (≥ 65 years vs. < 65), number of tumors (single vs. multiple), location, primary cancer type, status of primary cancer, presence of extracranial metastases, KPS score (≥ 70 vs. < 70), RTOG-RPA class, and DS-GPA score. Multivariate analysis was performed by backward elimination with candidate variables of $P < 0.15$ on univariate analysis. The cumulative incidences of local failure, progression, and RN were compared using the Gray's test. The Fine and Gray method was used on modeling the hazard of sub-distribution accounting for death as a competing risk. All statistical tests were conducted using the SPSS Version 21.0 (SPSS Inc., Chicago, IL) and the R software Version 3.1.1. Statistical significance was set at $P < 0.05$.

Results

Local tumor control

With a median follow-up of 14 months (3–59 months), the estimated LTC rates at 6 months, 1 year, and 1.5 years were 92.9%, 66.6%, and 57.2% in single-fraction SRS group, and 100%, 92.4%, and 88.2% in hypofractionated SRS group, respectively ($P = 0.028$, Fig. 1a). In multivariate Cox regression analysis (Table 3), positive predictive factors for LTC included hypofractionation ($P = 0.022$), primary cancers of non-gastrointestinal origin ($P = 0.003$), and newly diagnosed primary cancers ($P = 0.038$). In the Fine and Gray analysis accounting for death as a competing risk, the statistical significance of treatment modality appeared to decline ($P = 0.093$).

Overall and progression-free survival

The Kaplan–Meier curves for OS are shown in Fig. 1b. There were no differences in OS between the single-fraction versus hypofractionated SRS groups (the estimated OS rates at 6 months, 1 year, and 1.5 years of 92.2%, 53.1%, and 32.8% vs. 86.1%, 69.4%, and 52.8%,

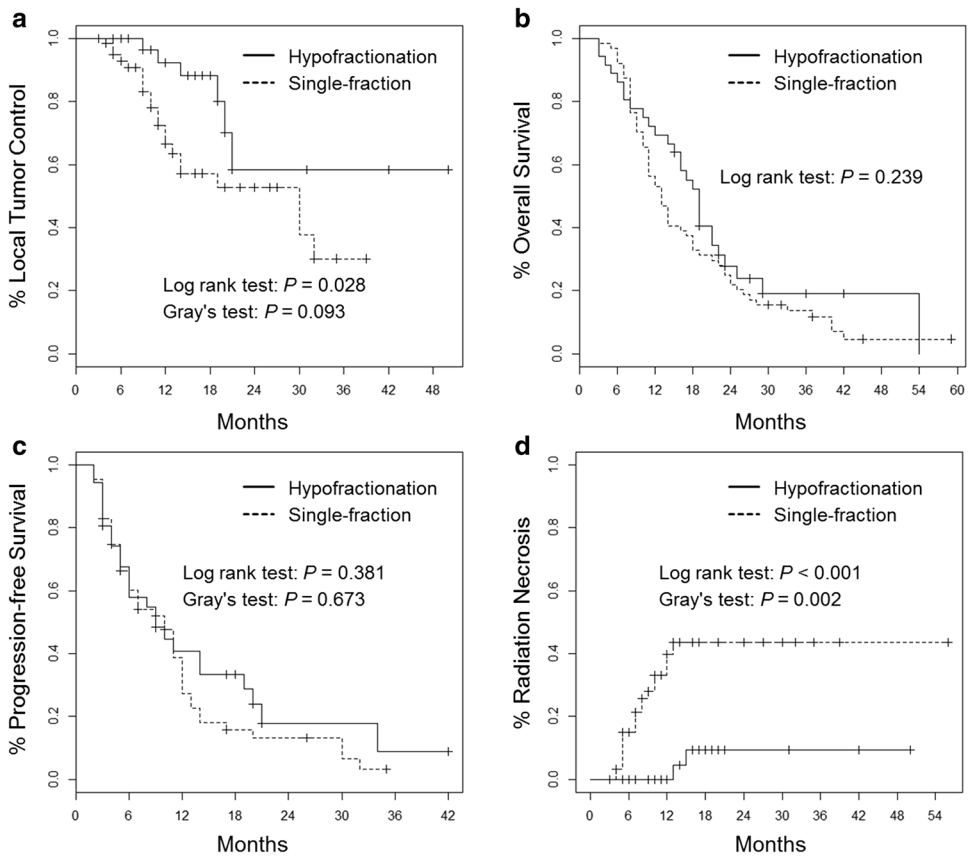

Fig. 1 The Kaplan–Meier curves for local tumor control (**a**), overall survival (**b**), and progression-free survival (**c**), and cumulative incidence curves for radiation necrosis (**d**)

Table 3 Predictive factors for local failure (Cox proportional hazards regression)

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Modality						
Hypofractionation	1					
Single-fraction	2.675	1.074–6.662	0.035	2.940	1.172–7.377	0.022
Sex						
Female	1					
Male	0.678	0.304–1.515	0.344			
Age						
< 65 years	1					
≥ 65 years	0.860	0.363–2.040	0.733			
Location						
Cerebrum	1					
Cerebellum	2.760	1.263–6.033	0.011			
BG and diencephalon	1.162	0.152–8.906	0.885			
Number of metastasis						
Single	1					
Multiple	0.714	0.333–1.534	0.388			
Primary cancer						
Lung	1					
Breast	2.697	1.060–6.862	0.037			
GI tract	10.875	3.533–33.474	< 0.001	4.509	1.694–11.999	0.003
Others	2.801	0.706–11.123	0.143			
Status of primary cancer						
Controlled	1					
Uncontrolled	0.498	0.148–1.677	0.261			
Newly diagnosed	0.108	0.014–0.799	0.029	0.118	0.016–0.887	0.038
Extracranial metastases						
Absent	1					
Present	1.636	0.714–3.751	0.245			
KPS score						
< 70	1					
≥ 70	1.012	0.135–7.560	0.991			
RTOG-RPA score						
I	1					
II	1.239	0.494–3.104	0.648			
III	1.165	0.138–9.877	0.888			
DS-GPA score						
< 1.5	1					
1.5–2.5	1.341	0.371–4.840	0.654			
≥ 3.0	1.458	0.398–5.377	0.569			

HR hazard ratio, *CI* confidence interval, *BG* the basal ganglia, *GI* gastrointestinal, *KPS* the Karnofsky performance scale, *RTOG* the Radiation Therapy Oncology Group, *RPA* recursive partitioning analysis, *DS-GPA* diagnosis-specific graded prognostic assessment

respectively; $P = 0.239$). Primary cancer of gastrointestinal origin was the only independent predictor for OS (hazard ratio, 2.699; 95% confidence interval, 1.489–4.891; $P = 0.001$; Supplementary Table 1). Along with the OS, PFS did not differ between the two groups with the estimated PFS rates at 6 months, 1 year, and 1.5 years of 60.2%, 27.3%, and 15.9% in single-fraction group versus 58.0%, 40.9%, and 33.5% in hypofractionated group, respectively ($P = 0.381$, Fig. 1c). Multiple BMs were associated with increased risks of progression (hazard ratio, 1.692; 95% confidence interval, 1.057–2.709; $P = 0.028$; Supplementary Table 2).

Radiation necrosis and treatment-related toxicity

The incidence of RN was significantly lower in hypofractionated group than in single-fraction group: the estimated RN rates at 6 months, 1 year, and 1.5 years were 0%, 0%, and 9.3% in hypofractionated group compared with 15.1%, 39.8%, and 43.6% in single-fraction group, respectively ($P < 0.001$, Fig. 1d). The hazard ratio for RN was 8.479 in single-fraction SRS group (95% confidence interval, 1.966–36.570; $P = 0.004$; Table 4) and no other factors were associated with the occurrence of RN. Treatment-related clinical toxicity of ≥ grade 2 by CTCAE ver. 4.0 was seen

Table 4 Predictive factors for radiation necrosis (Cox proportional hazards regression)

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Modality						
Hypofractionation	1					
Single-fraction	8.479	1.966–36.570	0.004	8.479	1.966–36.570	0.004
Sex						
Female	1					
Male	0.651	0.273–1.552	0.333			
Age						
< 65 years	1					
≥ 65 years	0.312	0.092–1.056	0.061			
Location						
Cerebrum	1					
Cerebellum	0.371	0.110–1.256	0.111			
BG and diencephalon	–	–				
Number of metastasis						
Single	1					
Multiple	1.299	0.561–3.010	0.541			
Primary cancer						
Lung	1					
Breast	0.672	0.219–2.063	0.448			
GI tract	1.007	0.225–4.499	0.993			
Others	0.997	0.283–3.510	0.996			
Status of primary cancer						
Controlled	1					
Uncontrolled	1.853	0.680–5.048	0.228			
Newly diagnosed	1.250	0.434–3.602	0.679			
Extracranial metastases						
Absent	1					
Present	0.933	0.397–2.191	0.873			
KPS score						
< 70	1					
≥ 70	1.055	0.142–7.868	0.958			
RTOG-RPA score						
I	1					
II	0.808	0.313–2.085	0.659			
III	0.810	0.097–6.753	0.845			
DS-GPA score						
< 1.5	1					
1.5–2.5	3.558	0.459–27.57	0.225			
≥ 3.0	2.601	0.320–21.15	0.371			

HR hazard ratio, *CI* confidence interval, *BG* the basal ganglia, *GI* gastrointestinal, *KPS* the Karnofsky performance scale, *RTOG* the Radiation Therapy Oncology Group, *RPA* recursive partitioning analysis, *DS-GPA* diagnosis-specific graded prognostic assessment

Table 5 Treatment-related clinical toxicity

Grade (CTCAE ver. 4.0)	Single-fraction (n = 64)	Hypofractionation (n = 36)	*P* value
1	28 (43.8%)	23 (63.9%)	
2	17 (26.6%)	6 (16.7%)	
3	16 (25.0%)	6 (16.7%)	
4	3 (5.7%)	1 (2.8%)	
5	0	0	
Grade ≥ 2	36 (56.3%)	13 (36.1%)	0.084

CTCAE common terminology criteria for adverse events

in 36 patients (56.3%) in single-fraction group versus in 13 patients (36.1%) in hypofractionated group ($P = 0.084$; Table 5).

Discussion

Our current study shows the clinical advantages of hypofractionated SRS approach compared with single-fraction SRS in treating medium-sized BMs (2.5 to 3 cm) at the border zone of tumor size for conventional single-fraction SRS treatment in terms of both efficacy and safety. The key clinical relevance is focused on the superior safety profile of hypofractionation approach without compromised tumor control as shown by significantly reduced risks of RN along with clinical radiation toxicity. Moreover, a certain benefit in LTC is also suggested with this approach, although statistical significance appears to be marginal.

These observations are well in line with the theoretical advantages of fractionation radiobiology. Fractionated administration of radiation dose potentially reduces toxicity to late-responding normal tissues with a low α/β ratio compared with a single acute dose of radiation for a given level of tumor damage [3, 20]. In addition, reoxygenation and redistribution of the cell cycle between fractions render hypoxic tumor cells and cells in less responding cell cycles more radiosensitive [21, 22]. In this theoretical context, it is reasonable to assume that fractionation delivery of SRS would potentially mitigate the risks of radiation toxicity and enhance tumor control probability compared with single-fraction SRS.

Currently, few studies are available on direct comparison of the efficacy and safety between single-fraction versus hypofractionated SRS for large BMs. Minniti et al. [6] reported on 289 patients with BMs > 2 cm who had been treated with either single-fraction SRS (n = 151; median dose 18 Gy) or hypofractionated SRS (n = 138; 27 Gy in 3 fractions) and compared LTC and the risk of RN between the groups. In their series, LTC rates at 1 year were 77% in single-fraction group and 91% in hypofractionated group, while the incidences of RN were 20% and 8%, respectively. Similarly, Feuvret et al. [8], in their small series of BMs > 3 cm, reported a superior tumor control rate (LTC in 100% at 1 year) in hypofractionated group (n = 12; 23.1 Gy in 3 fractions) compared with single-fraction group (n = 24; 14 Gy; LTC in 58% at 1 year), although RN was not observed in both groups with relatively lower prescription doses used. Our study adds to these observations with a merit of prospective control of tumor size in a narrow range of 2.5 to 3 cm, which enables us to interpret the data more intuitively and clearly. One recent international meta-analysis including 15 studies on SRS for large BMs > 2 cm mostly of a single-arm treatment design, either single-fraction or hypofractionated SRS (2 comparative studies described above included) concluded hypofractionated SRS may offer a reduced risk of RN while maintaining or enhancing 1-year LTC as compared with single-fraction SRS [23], which is almost consistent with our current results. Although certain limitations do exist including the retrospective nature of all studies included, unstandardized terms and definitions, and, most of all, a vast heterogeneity in histology, SRS modality and technique, prescription dose, and fractionation protocol, the results of these studies along with ours provide a reasonable rationale for implementing prospective controlled clinical trials to move forward into a better standard of care treatment for large BMs.

Conclusions

Our results suggest a better safety and efficacy profile of hypofractionated SRS for medium-sized BMs of 2.5 to 3 cm compared with single-fraction SRS. Further prospective controlled studies are needed to confirm these results.

Compliance with ethical standards

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

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