



Fractionated versus staged gamma knife radiosurgery for mid-to-large brain metastases: a propensity score-matched analysis

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Abstract

Purpose To compare treatment results between fractionated gamma knife radiosurgery (f-GKRS) and staged gamma knife radiosurgery (s-GKRS) for mid-to-large brain metastases (BMs).

Methods We retrospectively analyzed data of patients with medium (4–10 mL) to large (> 10 mL) BMs who underwent s-GKRS or f-GKRS between March 2008 and September 2022. Patients were treated with (i) s-GKRS before May 2018 and (ii) f-GKRS after May 2018. Patients who underwent follow-up magnetic resonance imaging at least once were enrolled. Case-matched studies were conducted by applying propensity score matching to minimize treatment selection bias and potential confounding. Local control (LC) was set as the primary endpoint and overall survival (OS) as the secondary endpoint.

Results This study included 129 patients with 136 lesions and 70 patients with 78 lesions who underwent s-GKRS and f-GKRS, respectively. Overall, 124 lesions (62 lesions in each group) were selected in the case-matched group. No differences were observed in the 6-month and 1-year cumulative incidences of LC failure between the s-GKRS and f-GKRS groups (15.6% vs. 15.9% at 6 months and 25.6% vs. 25.6% at 1 year; $p=0.617$). One-year OS rates were 62.6% (95% confidence interval [CI]: 45.4–75.7%) and 73.9% (95% CI: 58.8–84.2%) in the s-GKRS and f-GKRS groups, respectively. The post-GKRS median survival time was shorter in the s-GKRS group than in the f-GKRS group (17 vs. 36 months), without significance ($p=0.202$).

Conclusions This is the first study to compare f-GKRS and s-GKRS in large BMs. Fractionation is as effective as staged GKRS for treating mid-to-large BMs.

Keywords Brain metastasis · Fractionated radiosurgery · Gamma knife · Propensity score-matched analysis · Oncology · Staged radiosurgery

Introduction

Gamma knife radiosurgery (GKRS) was originally designed as a single-fraction irradiation with the Leksell frame fixation system, which contributes to treatment accuracy. It is a less invasive and safer treatment for brain metastases than surgical procedures. However, Leksell frame fixation

is considered relatively invasive compared to conventional radiation therapy equipment with mask fixation, and its therapeutic effect is limited to large brain metastases, rather than smaller lesions [1]. In studies reporting treatment results for large metastases, the 1-year local control (LC) is reported to be 66.6–84.6%, with a high frequency of radiation necrosis (38.8–48.0%) [2–5]. Therefore, radiation-induced toxicity is a challenge in increasing tumor control rates. As a result, staged GKRS (s-GKRS) has been established to maintain therapeutic efficacy and reduce the risk of adverse events [6–8].

The Leksell Gamma Knife® Icon™ is designed with optional thermoplastic mask fixation. This novel technique allows frameless fractionated GKRS (f-GKRS) to be applied to larger lesions. Hypofractionated radiotherapy (HFRT) involves delivery of high cumulative radiation

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doses to large lesions while minimizing exposure to normal brain tissue. Pre-existing treatment equipment has been used to treat larger brain metastases using HFRT, and its efficacy and safety have been demonstrated [9]. Theoretically, this technique is expected to be adaptable with frameless f-GKRS for large brain metastases. However, only few publications have reported the preliminary outcomes of single-center studies [10–12], with small sample sizes and limited follow-up durations. While s-GKRS uses the tentative volume shrinkage of the preceding irradiation, f-GKRS uses the biological benefits of inter-fraction tissue repair in normal tissue injuries. Although these two different methods were designed to treat large brain metastases, their treatment outcomes have not been compared yet. This retrospective single-center study compared the treatment outcomes of s-GKRS and f-GKRS for large brain metastases using propensity score matching.

Methods

Data source and study population

An institutional database was used to investigate patient information and clinical outcomes. Patients with medium (4–10 mL) to large (> 10 mL) brain metastases who underwent s-GKRS or f-GKRS between March 2008 and September 2022 were identified. Patients were treated with (i) s-GKRS before Icon™ was installed in May 2018, and with (ii) f-GKRS after May 2018. Patients who underwent follow-up magnetic resonance imaging (MRI) at least once were included. Patients with (i) recurrent lesions previously treated with GKRS, (ii) a history of whole-brain radiotherapy, (iii) post-surgical lesions (tumor bed lesions), and (iv) those without post-GKRS follow-up images were excluded.

Age, sex, Karnofsky performance status scores, primary cancer site and status, extracranial metastases, neurological symptoms, tumor location, target volume, target maximum diameter, marginal dose, maximum dose, follow-up MRI images, adverse events, and status at the last visit were inspected.

radiosurgical indications and techniques

As treatment equipment model, f-GKRS was performed using Icon™ and s-GKRS using Perfexion™.

For s-GKRS, in principle, two-staged GKRS was selected for medium tumors and three-staged GKRS for large tumors. However, this was not always the case, depending on the patient's condition and treatment schedule of the primary lesion. On the day before treatment, gadolinium-enhanced thin-slice T1-weighted and T2-weighted

MRI images were obtained. The Leksell frame G (Elekta Instruments AB) was applied for patient immobilization. The frame was placed on the patient's head under local anesthesia. Stereotactic contrast-enhanced MRI covering the whole brain was routinely used as a reference. This study followed the radiosurgical technique criteria of the study conducted by the Japanese Leksell Gamma Knife Society (JLGK1601) [7]. The prescription dose of each fraction was set to 11.8–14.2 Gy for two-staged GKRS and to 9.0–11.0 Gy for three-staged GKRS. The treatment intervals were completed within 6 weeks, with ≥ 12 days between each fraction (Supplemental Digital Content 1a). The planning target volume was designed to corresponded with the gross total volume defined on gadolinium-enhanced thin-slice T1-weighted images. For f-GKRS, in principle, more than five fractions (3.0–5.0 Gy/fraction) were selected for patients with relatively large tumors and five or fewer fractions (6.0–9.5 Gy/fraction) for mid-sized tumors. The number of fractions was adjusted according to the patient's condition and treatment schedule. The Icon™-specific thermoplastic mask was molded 1 day before the first fraction and used for patient immobilization during treatment. MRI (gadolinium-enhanced thin-slice T1-weighted and T2-weighted MRI images) was performed within 3 days before the first fraction and used to plan the treatment. Irradiation was performed on consecutive days. The threshold of high definition motion management was set to 1.0–1.5 mm in all cases. Interfractional evaluation by MRI was performed when the treatment continued for > 1 week or more than five fractions, and the treatment plan was modified if necessary, as reported previously [13]. According to a previous report of large brain metastases treated using linear accelerator (LINAC)-based devices [14], the prescribed doses were determined within 40.0–60.0 Gy in biologically effective doses (BED), using a linear-quadratic model with an alpha-beta ratio of 10 (BED₁₀) [15]. The treatment was fractionated into 3–15 fractions (Supplemental Digital Content 1b). The planning target volume was determined by adding 0.5–2.0 mm margin to the gross total volume defined on gadolinium-enhanced thin-slice T1-weighted images. All treatment plans were meticulously created and revised using Leksell GammaPlan (Elekta Instruments AB) by the same senior physician (A.A.).

Endpoints and post-GKRS follow-up

Follow-up MRI was performed 1–3 months after treatment and every few months thereafter. LC was set as the primary endpoint, and radiological deterioration of the treated lesion was considered LC failure. LC failure was defined as $\geq 20\%$ enlargement of the targeted lesion's diameter on contrast-enhanced areas on T1-weighted images.

The secondary endpoint was overall survival (OS). Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Radiation necrosis was defined as LC failure with additional neuroimaging confirmation, such as positron emission tomography, single-photon emission computed tomography, specific MRI sequences (magnetic resonance perfusion or arterial spin label), and pathological confirmation.

Statistical analysis

Participants' baseline characteristics are summarized as frequencies and proportions for categorical data and as medians and ranges for continuous variables. The baseline characteristics of the two groups were compared using Fisher's exact test. LC and OS were analyzed using Kaplan–Meier curves, and OS rates were compared using the log-rank test. Case-matched studies were conducted by applying propensity score matching to minimize treatment selection bias and potential confounding. A one-to-one nearest neighbor matching algorithm was used without replacement within caliper widths of 0.2. Based on clinical knowledge and previous reports, 11 possible covariates were selected for their potential association. In addition, the Fine and Gray test was performed to calculate the cumulative incidences of LC failure, and death was considered a competing risk factor. As subgroup analysis, cumulative incidences of LC

failure of s-GKRS vs. f-GKRS (≤ 5 fraction), and s-GKRS vs. f-GKRS (> 5 fraction) were inspected using propensity score matching for each subgroup.

All statistical analyses were performed using the R statistical software (R version 4.1.0; The R Foundation for Statistical Computing; Vienna, Austria). Statistical significance was set at p-values of < 0.05 .

Results

Overall, 2,887 patients underwent GKRS for metastatic brain tumors between March 2008 and December 2022; 2,002 patients were treated before Icon™ was installed in May 2018 and 885 were treated afterward. Lesions with mid-to-large (volume: > 4 mL) brain metastases treated using s-GKRS or f-GKRS were identified. This study included 129 patients with 136 lesions and 70 patients with 78 lesions who underwent s-GKRS and f-GKRS, respectively.

The baseline characteristics of the s-GKRS and f-GKRS groups are summarized in Table 1. The median volumes of the treated target were 9.6 (range: 4.1–47.1) mL and 7.4 (4.0–55.8) mL ($p < 0.001$), and the median maximum diameters were 30 (range: 10–54) mm and 28 (19–54) mm ($p = 0.0012$) in s-GKRS and f-GKRS, respectively. There were 63 (46.3%) and 21 (26.9%) large metastases in the s-GKRS and f-GKRS groups, respectively ($p = 0.006$). The

Table 1 Clinical characteristics of the main 214 lesions and the case-matched 124 lesions

	s-GKRS	f-GKRS	p value	s-GKRS	f-GKRS	p value
No. of lesions	136	78		62	62	
Median age in years [range]*	67.0 [36.0–87.0]	64.5 [32.0–83.0]	0.224	67.0 [44.0–87.0]	67.0 [42.0–83.0]	0.881
Sex, no (%)*						
Female	55 (40.4)	29 (37.2)	0.665	21 (33.9)	20 (32.3)	1.000
Male	81 (59.6)	49 (62.8)		41 (66.1)	42 (67.7)	
Median KPS [range]*	80 [20–90]	80 [50–90]	0.386	80 [20–90]	80 [50–90]	0.423
Primary cancer, no (%)*						
Lung	63 (46.3)	41 (52.6)	0.305	36 (58.1)	33 (53.2)	0.849
Breast	22 (16.2)	6 (7.7)		4 (6.5)	6 (9.7)	
GI	31 (22.8)	21 (26.9)		15 (24.2)	14 (22.6)	
Others	20 (14.7)	10 (12.8)		7 (11.3)	9 (14.5)	
Stable primary cancer, no (%)*	53 (39.0)	40 (51.3)	0.087	26 (41.9)	31 (50.0)	0.471
Extracranial lesion, no (%)*	119 (87.5)	58 (74.4)	0.023	47 (75.8)	47 (75.8)	1.000
Modified RPA class, no (%)						
I + IIa	30 (22.1)	27 (34.6)	0.090	18 (29.0)	21 (33.9)	0.667
IIb	40 (29.4)	15 (19.2)		14 (22.6)	10 (16.1)	
IIc + III	66 (48.5)	36 (46.2)		30 (48.4)	31 (50.0)	
Single lesion, no (%)*	74 (54.4)	30 (38.5)	0.033	29 (46.8)	27 (43.5)	0.857
Supratentorial lesion, no (%)*	111 (81.6)	64 (82.1)	1.000	51 (82.3)	50 (80.6)	1.000
Symptomatic, no (%)*	93 (68.4)	38 (48.7)	0.006	36 (58.1)	34 (54.8)	0.856
Tumor vol, (mL) [range]*	9.6 [4.1–47.1]	7.4 [4.0–55.8]	< 0.001	8.5 [4.3–47.1]	7.2 [4.0–55.8]	0.07
Large tumor, no (%)	63 (46.3)	21 (26.9)	0.006	23 (37.1)	17 (27.4)	0.337
Follow-up period (months) [range]*	7.0 [1.0–110.0]	7.0 [1.0–42.0]	0.254	6.0 [1.0–57.0]	7.5 [1.0–42.0]	0.132

s-GKRS; staged gamma knife radiosurgery, f-GKRS; fractionated gamma knife radiosurgery, No.; number, KPS; Karnofsky performance status, GI; gastrointestinal, RPA; recursive partitioning analysis, vol; volume

* : The eleven covariates chosen for propensity score matching

median follow-up times after GKRS were 7.0 (range: 1.0–110.0) months and 7.0 (1.0–42.0) months in the s-GKRS and f-GKRS groups, respectively ($p=0.254$).

In the s-GKRS group, 81 (59.6%) and 55 (40.4%) lesions underwent two- and three-staged GKRS, respectively. The median prescription doses of each fraction were 13.0 (10.0–14.0) Gy and 14.0 (13.0–15.0) Gy in two-staged GKRS and were 10.0 (8.0–10.0) Gy, 10.0 (8.0–10.0) Gy, and 10.0 (8.0–12.0) Gy for each fraction in three-staged GKRS, respectively. The target volumes of each fraction were 8.3 (4.1–26.0) mL and 6.9 (1.2–23.3) mL in two-staged GKRS and 10.9 (4.8–47.1) mL, 8.7 (1.6–52.7) mL, and 6.5 (0.9–54.5) mL in three-staged GKRS, respectively. In the f-GKRS group, 51 (65.4%) lesions received more than five fractions. The median target volume was 7.4 (4.0–55.8) mL. The median prescription dose was 35.0 (27.0–45.0) Gy, and the median BED₁₀ was 51.6 (39.0–59.5) Gy. The treatment parameters of the 214 lesions are summarized in Table 2.

The 6-month and 1-year LC rates were 83.3% (95% confidence interval [CI]: 74.3–89.4%) and 75.2% (95% CI: 64.1–83.3%) in the s-GKRS group, and 82.4% (95% CI: 68.6–90.6%) and 72.0% (95% CI: 56.1–83.0%) in the f-GKRS group, respectively ($p=0.241$) (Fig. 1a). The 1-year OS rate and median survival time (MST) in the s-GKRS and f-GKRS groups were 68.7% (95% CI: 58.5–76.9%) and 25 months, and 77.2% (95% CI: 63.4–86.3%) and 36 months, respectively ($p=0.375$) (Fig. 1b). The overall incidence rates of adverse events were 2.9% and 7.7% in

the s-GKRS and f-GKRS groups, respectively ($p=0.175$). None of the patients in either treatment group experienced adverse events associated with CTCAE grade5 toxicity. Three lesions were diagnosed with radiation necrosis (2.2%) and one with hemorrhage in the s-GKRS group. One of the radiation necroses was defined as CTCAE grade4 toxicity. Five lesions (6.4%) were diagnosed with radiation necrosis and one with hemorrhage in the f-GKRS group. There was no lesion defined as CTCAE grade 4 in this group.

Propensity score matching selected 124 lesions (62 lesions in each group). The 124 case-matched lesions are summarized in Table 1, and the treatment parameters of the 124 case-matched lesions are summarized in Table 2. No differences were observed in the 6-month and 1-year cumulative incidences of LC failure between the s-GKRS and f-GKRS matched groups (15.6% vs. 15.9% at 6 months, and 25.6% vs. 25.6% at 1 year; $p=0.617$) (Fig. 1c). The post-GKRS MST was shorter in the s-GKRS matched group than in the f-GKRS matched group (17 months vs. 36 months) without significance ($p=0.202$), and the 1-year OS rates were 62.6% (95% CI: 45.4–75.7%) and 73.9% (95% CI: 58.8–84.2%) in the s-GKRS and f-GKRS matched groups, respectively (Fig. 1d). Adverse events were fewer in the s-GKRS matched group (1.6%) than in the f-GKRS matched group (9.7%), without significance ($p=0.114$). No differences were observed in the 6-month and 1-year cumulative incidences of LC failure between s-GKRS and f-GKRS (≤ 5 fraction) matched groups (10.1% vs. 5.7% at 6

Table 2 Summary of treatment parameters of the main 214 lesions and the 124 case-matched lesions

	s-GKRS	matched s-GKRS	f-GKRS	matched f-GKRS
No. of lesions	136	62	78	62
Two-staged (%)	81 (59.6)	39 (62.9)	27 (34.6)	27 (43.5)
Three-staged (%)	55 (40.4)	23 (37.1)	10 [3-15]	8 [3-15]
Large lesion (%)	63 (46.3)	23 (37.1)	21 (26.9)	17 (27.4)
Median initial tumor diameter (cm) [range]	30.0 [10.0–54.0]	29.0 [10.0–54.0]	28.0 [19.0–54.0]	28.0 [19.0–54.0]
Median tumor vol.(mL) [range]			7.4 [4.0-55.8]	7.2 [4.0-55.8]
1st session	9.6 [4.1–47.1]	8.5 [4.3–47.1]		
2nd session	7.5 [1.2–52.7]	6.9 [1.2–36.3]		
3rd session	6.5 [0.9–54.5]	6.5 [1.1–31.7]		
Median prescription dose (Gy) [range]			35.0 [27.0–45.0]	35.0 [27.0–45.0]
1st session	13.0 [8.0–14.0]	13.0 [9.0–14.0]		
2nd session	14.0 [8.0–15.0]	14.0 [10.0–14.0]		
3rd session	10.0 [8.0–12.0]	10.0 [10.0–10.0]		
Median max dose (Gy) [range]			48.6 [38.0-60.8]	49.1 [38.0-60.8]
1st session	18.7 [12.9–23.6]	18.8 [13.9–23.5]		
2nd session	19.2 [11.6–25.5]	19.3 [14.0-25.5]		
3rd session	15.2 [11.9–18.4]	15.4 [14.1–16.8]		
BED10 (Gy) [range]			51.6 [39.0-59.5]	52.2 [39.0-59.5]

s-GKRS; staged gamma knife radiosurgery, f-GKRS; fractionated gamma knife radiosurgery, No.; number, BED10; biologically effective dose ($\alpha/\beta=10$ Gy)

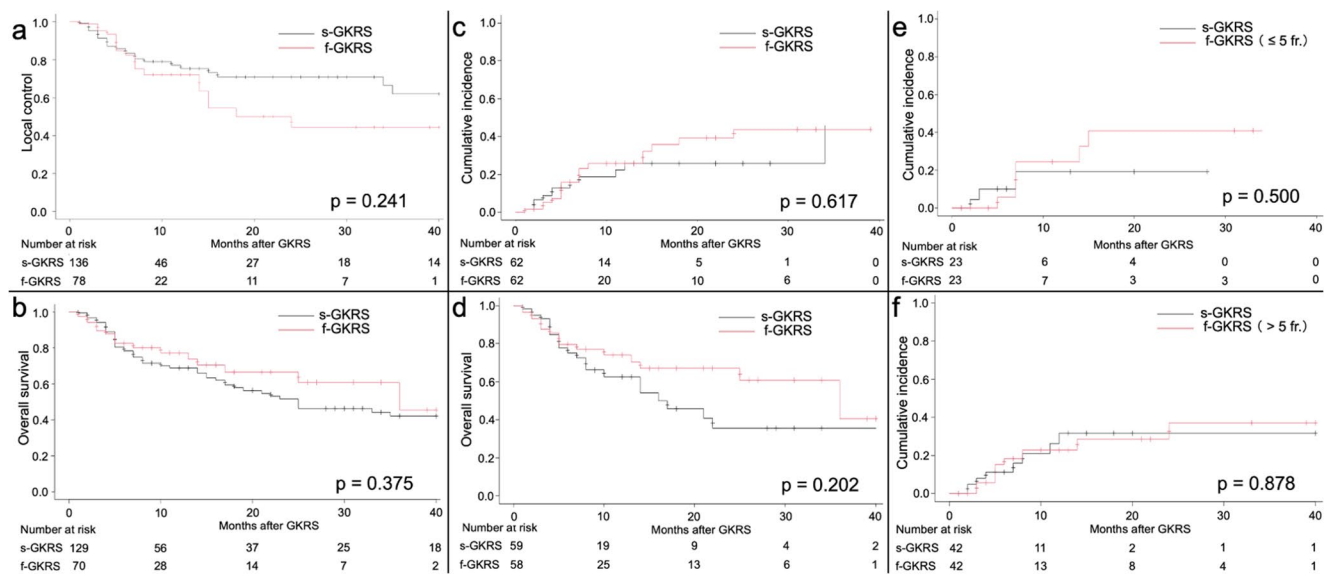


Fig. 1 (a) Local control: s-GKRS vs. f-GKRS in the main cohort of 214 lesions. The 6-month and 1-year local control rates were 83.3% (95% CI: 74.3–89.4%) and 75.2% (95% CI: 64.1–83.3%), respectively for s-GKRS. The 6-month and 1-year local control rates were 82.4% (95% CI: 68.6–90.6%) and 72.0% (95% CI: 56.1–83.0%), respectively, for f-GKRS. (b) Overall survival: s-GKRS vs. f-GKRS in the main cohort of 199 patients. The 1-year overall survival rate and median survival time in the s-GKRS and f-GKRS groups were 68.7% (95% CI: 58.5–76.9%) at 25 months and 77.2% (95% CI: 63.4–86.3%) at 36 months, respectively ($p=0.375$). (c) Cumulative incidence of local control failure: s-GKRS vs. f-GKRS in 124 case-matched lesions. No difference was observed in the 6-month and 1-year cumulative incidences of local control failure between the s-GKRS and f-GKRS groups (15.6% vs. 15.9% at 6 months and 25.6% vs. 25.6% at 1 year; $p=0.617$). (d) Overall survival: s-GKRS vs. f-GKRS in 117 case-matched patients. The post-GKRS median survival time was shorter in the s-GKRS group (17

months and 19.1% vs. 24.4% at 1 year; $p=0.500$) (Fig. 1e), and s-GKRS vs. f-GKRS (>5fraction) matched groups (11.4% vs. 18.4% at 6 months and 31.7% vs. 22.8% at 1 year; $p=0.878$) (Fig. 1f). The details of the subgroup analyses are described in Supplemental Digital Content 2.

Discussion

The existing literature in the past decade has established the efficacy of s-GKRS for large-sized brain metastases [6–8, 16–23]. The present study's outcomes were as follows: 6-month LC, 83.3%; 1-year LC, 75.2%; MST, 25.0 months; and 1-year OS, 68.7%. According to previous reports, the 6-month and 1-year LC rates were 85.0–100% and 61.0–92.0%, and the MST and 1-year OS rates were 7.0–24.7 months and 35.2–60.0%, respectively. The latest report of s-GKRS in 2022 showed the most favorable outcome in regard to LC, but the study included small lesions and the maximum range of tumor volume was smaller than previously reported [23]. According to these factors, our study's

months) than in the f-GKRS group (36 months), without significance ($p=0.202$), and the 1-year overall survival rate was 62.6% (95% CI: 45.4–75.7%) and 73.9% (95% CI: 58.8–84.3%) in the s-GKRS and f-GKRS groups, respectively. (e) Cumulative incidence of local control failure: s-GKRS vs. f-GKRS (≤ 5 fr.) in 46 case-matched lesions. No difference was observed in the 6-month and 1-year cumulative incidences of local control failure between the s-GKRS and f-GKRS (≤ 5 fr.) groups (10.1% vs. 5.7% at 6 months and 19.1% vs. 24.4% at 1 year; $p=0.500$). (f) Cumulative incidence of local control failure: s-GKRS vs. f-GKRS (>5 fr.) in 84 case-matched lesions. No difference was observed in the 6-month and 1-year cumulative incidences of local control failure between the s-GKRS and f-GKRS (>5 fr.) groups (11.4% vs. 18.4% at 6 months and 31.7% vs. 22.8% at 1 year; $p=0.878$). f-GKRS, fractionated gamma knife radiosurgery; s-GKRS, staged gamma knife radiosurgery; CI, confidence interval; fr., fraction

outcomes were comparable with those of previous reports (Table 3).

Delivery of high doses of radiation by HFRT minimizes adverse events by maintaining LC, and LINAC-based equipment delivering HFRT for large brain metastases has been discussed in several publications. The conventional LINAC series focused on lesions sized >4 mL or >2 cm in diameter, reporting a 1-year OS of 56.0–69.0% and 1-year LC of 61.0–100% [24–27]. In comparison, the CyberKnife series in the literature reported a 1-year OS and 1-year LC of 13.0–69.4% and 63.0–92.4%, respectively [2, 28–30]. A systematic review of 1049 metastases sized >2 cm in diameter collected from 15 series concluded that HFRT showed better LC when administered safely than single-fraction GKRS [31]. Conversely, the biggest disadvantage of HFRT using LINAC is that the gradient index is inferior to that of GKRS and 10 times higher in extracranial exposure to radiation doses. It should be noted that when comparing extracranial doses of various treatment equipment, Leksell Gamma Knife® Perfexion™, the predecessor of Icon™, was superior in terms of radiation protection

Table 3 Review of large brain metastases treated by staged gamma knife radiosurgery

Author	Year	Pt.	Lesion	Med/ Mean vol. (mL)	[range]	Sessions	Med FU (m)	[range]	6m LC (%)	1y LC (%)	MST (m)	[range]	1y OS (%)	RN (%)
Higuchi et al. ⁶	2009	43	NA	17.6	[10.8–35.5]	3	7.8	NA	89.8	75.9	8.8	NA	NA	NA
Yomo et al. ¹⁶	2012	27	28	17.8	[10.0–53.3]	2	8.9	[1.0–21.0]	85.0	61.0	11.9	[4.7–15.6]	45.0	3.7
Yomo & Hayashi ¹⁷	2014	58	61	16.4	[10.0–56.1]	2	9.0	NA	85.0	64.0	11.8	[5.5–15.6]	47.0	5.2
Hasegawa et al. ¹⁸	2017	56	65	21.0	[10.0–76.0]	2, 3 [†]	6.0	[1.0–40.0]	93.0	80.0	7.0	[4.0–10.0]	42.0	NA
Angelov et al. ¹⁹	2017	54	63	10.5	[2.4–31.3]	2	NA	NA	88.0	NA	10.8	[4.9–26.9]	49.0	3.2
Dohm et al. ²⁰	2018	33	39	11.7	[0.81–60.93]	2	7.7	NA	NA	86.7	NA	NA	60.0	10.3
Yamamoto et al. ²¹	2018	78	NA	21.5	[10.2–70.0]	3	16.0	[11.7–28.1]	NA	NA	8.3	[5.6–12.0]	35.2	NA
Serizawa et al. ⁷	2018	221	NA	17.1	NA	2	11.7	[2.9–74.3]	NA	NA	12.3	[10.6–15.0]	49.5	6.8
		114	NA	19.4	NA	3							45.4	
Yomo et al. ⁸	2020	48	68 [‡]	6.1	[2.0–10.0]	2	15.2	[5.3–70.0]	90.0	84.0	24.7	[16.8–NA]	NA	NA
Ito et al. ²²	2020	178	182	16.6 [§]	NA	2	5.4	[2.5–12.4]	NA	NA	6.6	[5.3–9.3]	52.0	4.2
Cho et al. ²³	2022	NA	118	NA	[0.9–19.1]	2	NA	NA	95.0–100	90.0– 92.0	11.0	[7.0–15.0]	NA	7.0
Current report	2023	129	136	7.3	[4.0–55.8]	2, 3	7.0	[1.0–42.0]	83.3	73.5	25.0	NA	69.1	2.2

[†] Three patients were treated by 3 stage GKRS, [‡] Cases selected by the propensity score matching; [§] Mean volume was calculated

Pt.: patient number, Lesion: lesion number, Med: median, vol.: volume, FU: Follow-up time, m; months, 6 m; six months, 1y: one year, LC: local control, MST: median survival time, OS: overall survival, RN: radiation necrosis, NA: not available

[32]. In particular, one report compared the treatment plans with gamma knife and other LINAC-based devices for large brain metastases. Gamma knife demonstrated that the sharpest dose fell off in normal brain tissue despite having the highest dose within the tumor [33]. After introducing Leksell Gamma Knife® Icon™ in 2015, the fractionation ability was introduced for gamma knives. Icon™ was designed with optional thermoplastic mask fixation. To maintain its accuracy as high as those of its predecessors, a high-definition motion management system, which is an infrared stereoscopic camera that detects a nose marker's displacement, was installed in the equipment settings. These new features allowed the fractionation of GKRS with mask, which is considered safer and less invasive than conventional single-fraction GKRS with frame fixation. One study reported that f-GKRS distributed a higher dose to the tumor and a lower dose to the normal brain tissue than s-GKRS by comparing the BED of their treatment plans [34]. According to their report, theoretically, f-GKRS should be more effective and safer for treating large brain metastases. Additionally, Grimm et al. compared frame fixation and mask fixation GKRS, and showed that mask fixation using GKRS was safer regarding radiation necrosis [35]. One study analyzed patients who underwent frame fixation or mask fixation GKRS using a questionnaire and reported that patients were more comfortable and less likely to experience pain with mask fixation [36]. Another study compared frame fixation and mask fixation single-fraction GKRS, and reported similar outcomes between the two groups, although the mean pain scale score was higher in patients with frame fixation. Patients also experienced disadvantages of mask fixation, such as longer treatment time and higher extracranial doses due to the cone-beam computed tomography [37]. Furthermore, mask fixation has been reported to show a significantly higher degree of error variability, even though the motion error was < 1 mm in the translational direction and 1° in the rotational direction for both fixations [38]. Hence, this fact had to be considered when treating small lesions and lesions near critical structures. Conversely, this could be a negligible factor when treating large brain metastases. Only a few studies have reported the outcomes of f-GKRS. This was validated in another study that reported a 1-year LC of 84.8% with a low incidence of symptomatic adverse events, although target volumes > 4.5 mL were a significant predictor of symptomatic adverse events [39]. Kim et al. first reported f-GKRS for large brain metastases. The treatment was performed using Leksell Gamma Knife® Perfexion™, with frame fixation of 2–4 fractions on consecutive days [40]. In their study, the BED₁₀, median OS, and 1-year OS were 24.2–60.0 (median: 43.2) Gy, 16.2 months, and 66.7%, respectively. However, their study's greatest challenge was the treatment protocol involving attaching a

painful frame for every fraction during treatment. Two preliminary studies have been published on frameless f-GKRS for large metastatic brain tumors. Moreover, a prescription dose of 21–40 Gy, when administered for 3–5 consecutive days, showed median BED₁₀ of 51.3 (range: 35.7–72.0) Gy, median OS of 12.0 months, and 1-year OS of 93.3% [11]. In a study with three or five fractions at 5–9 Gy per fraction, BED₁₀ was 35.7–51.3 Gy, LC was 98.5% at 6 months and 96.0% at 1 year, and median OS and 1-year OS were 23.2 months and 63.6%, respectively (Table 4) [10]. In the present circumstances, further investigation is required in the field of frameless f-GKRS for large metastatic brain tumors.

The advantage of f-GKRS is that it increases the total radiation dose delivered to lesions, while allowing reduction of the radiation dose delivered to normal brain tissue. This should be a more effective and safer option for managing large brain metastases. The present study analyzed the differences in LC between s-GKRS and f-GKRS for mid-to-large brain metastases. Propensity score matching was performed to reduce biases and heterogeneous factors; f-GKRS was as effective as s-GKRS for mid-to-large brain metastases. OS was longer in the f-GKRS group than in the s-GKRS group, with no statistical significance. Additionally, f-GKRS should be considered a substitute for patients ineligible to undergo the entire s-GKRS treatment. The shorter treatment period of f-GKRS can be an added advantage for patients with large brain metastases. If the treatment of the brain lesion is accomplished earlier, the patient could swiftly move on to the succeeding treatment for the primary lesion.

Limitations

A limitation of this study is that the confounding factors of concurrent systemic therapy could not be eliminated. Since this was a retrospective study investigating two different treatment approaches performed in different eras, the paradigm shift of systemic therapy between both eras [41] was not considered. Targeted therapy has shown drastic advances in variety and effectiveness in recent years, potentially influencing outcomes. In the future, a well-designed multi-institutional prospective cohort study is needed to investigate accurate OS and LC. An additional limitation is that, compared to previous studies, the present study included cases treated by a relatively higher number of fractions. Conventionally, hypofraction is defined as five or fewer fractions, and previous publications concerning Leksell Gamma Knife® Icon™ are as such. However, more than half of our cases were fractionated into more than five categories, which does not meet the definition of hypofraction. This difference should be carefully considered when interpreting study data. The aim of increasing the number

Table 4 Review of large brain metastases treated by fractionated gamma knife radiosurgery

Author	Year	Pt.	Lesion	Fixation	GK Model	Mean/ Med vol. (mL) [range]	Med no. of fr. [range]	Med dose (Gy) [range]	BED10 (Gy) [range]	Mean/ Med FU (m) [range]	ly LC (%)	MST (m)	ly OS (%)	RN (%)
Kim et al. ⁴⁰	2016	36	36	frame	Perfixion	18.3 [10.0–50.3]	3 [2–4]	24 [20–30]	43.2 [24.2–60.0]	13.4 [1.0–51.9]	NA	16.2	66.7	2.7
Park et al. ¹¹	2019	15	17	mask	Icon	21.2 [11.0–38.1]	3 [3–5]	27 [21–40]	51.3 [35.7–72.0]	12.0 [2.0–24.0]	NA	12.0	93.3	0
Samanci et al. ¹⁰	2021	58	76	mask	Icon	6.2 [4.0–22.2]	3 [3–5]	27 [21–30]	51.3 [35.7–51.3]	12.0 [2.0–37.0]	96.0	23.2	63.6	0
Current report	2023	70	78	mask	Icon	7.3 [4.0–55.8]	10 [3–15]	35 [27–45]	51.6 [39.0–59.5]	7.0 [1.0–42.0]	72.0	36.0	76.7	6.4

Pt.; patient number, Lesion; lesion number, GK; gamma knife, Med; median, vol.; volume, no.; number, fr.; fraction, BED10; biologically effective dose ($\alpha/\beta=10$ Gy), FU; Follow-up time, m; months, ly; one year, LC; local control, MST; median survival time, OS; overall survival, RN; radiation necrosis, NA; not available

of fractions was to minimize the risk of radiation injury, and the results of propensity score matched analysis of s-GKRS vs. f-GKRS (>5 fraction) demonstrated the possibility of the effectiveness of more than five fraction GKRS. However, little is known about f-GKRS performed with more than five fractions. Accordingly, the choice of fractionation number should be carefully investigated in the future, and further accumulation of cases is required.

Conclusion

To the best of our knowledge, this study is the first to compare f-GKRS and s-GKRS for relatively large brain metastases. Our report showed that f-GKRS is as effective as s-GKRS, and this strategy should be considered an alternative management strategy for patients unsuitable for frame fixation.

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Author contributions All authors contributed to the study conception and design. Material preparation, and statistical analysis, figure preparation were performed by Ryuichi Noda. The first draft of the manuscript was written by Ryuichi Noda and all authors commented on previous versions of the manuscript. Statistical analysis was reviewed by Mariko Kawashima and Atsuya Akabane. Data collection was performed by Ryuichi Noda, Mariko Kawashima, Atsuya Akabane. The study was directed by Tomohiro Inoue and Atsuya Akabane. All authors read and approved the final manuscript.

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Statements & Declarations

Competing interests The authors declare no competing interests.

Ethics approval and consent to participate This study was conducted in accordance with the Declaration of Helsinki (revised version, 2013). The study protocol was approved by the Institutional Review Board of NTT Medical Center, Tokyo (approval number: 21–71).

Consent to participate Written informed consent was obtained from all patients.

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