Three-stage Gamma Knife treatment for metastatic brain tumors larger than 10 cm³: a 2-institute study including re-analyses of earlier results using competing risk analysis

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OBJECTIVE The results of 3-stage Gamma Knife treatment (3-st-GK-Tx) for relatively large brain metastases have previously been reported for a series of patients in Chiba, Japan (referred to in this study as the C-series). In the current study, the authors reappraised, using a competing risk analysis, the efficacy and safety of 3-st-GK-Tx by comparing their experience with that of the C-series.

METHODS This was a retrospective cohort study. Among 1767 patients undergoing GK radiosurgery for brain metastases at Mito Gamma House during the 2005–2015 period, 78 (34 female, 44 male; mean age 65 years, range 35–86 years) whose largest tumor was > 10 cm³, treated with 3-st-GK-Tx, were studied (referred to in this study as the M-series). The target volumes were covered with a 50% isodose gradient and irradiated with a peripheral dose of 10 Gy at each procedure. The interval between procedures was 2 weeks. Because competing risk analysis had not been employed in the published C-series, the authors reanalyzed the previously published data using this method.

RESULTS The overall median survival time after 3-st-GK-Tx was 8.3 months (95% CI 5.6–12.0 months) in the M-series and 8.6 months (95% CI 5.5–10.6 months) in the C-series ($p = 0.41$). Actuarial survival rates at the 6th and 12th post-3-st-GK-Tx months were, respectively, 55.1% and 35.2% in the M-series and 62.5% and 26.4% in the C-series (HR 1.175, 95% CI 0.790–1.728, $p = 0.42$). Cumulative incidences at the 12th post-3-st-GK-Tx, determined by competing risk analyses, of neurological deterioration (14.2% in C-series vs 12.8% in M-series), neurological death (7.2% vs 7.7%), local recurrence (4.8% vs 6.2%), repeat SRS (25.9% vs 18.0%), and SRS-related complications (2.3% vs 5.1%) did not differ significantly between the 2 series.

CONCLUSIONS There were no significant differences in post-3-st-GK-Tx results between the 2 series in terms of overall survival times, neurological death, maintained neurological status, local control, repeat SRS, and SRS-related complications. The previously published results (C-series) are considered to be validated by the M-series results.

<https://thejns.org/doi/abs/10.3171/2018.7.GKS181392>

KEYWORDS brain metastases; stereotactic radiosurgery; Gamma Knife; three-stage; oncology

LARGE brain metastases with a clinically relevant mass effect should be removed surgically, as 2 prospective randomized trials found significantly improved survival and functionally independent survival after resection as compared with whole-brain radiotherapy

(WBRT) alone.^{25,30} Furthermore, as compared with resection alone, better treatment results can reportedly be anticipated with the addition of WBRT.^{13,24} Although stereotactic radiosurgery (SRS) in a single fraction is generally used for treating cancer patients with brain metastases, this

ABBREVIATIONS C-series = Chiba series; fSRT = fractionated stereotactic radiotherapy; GK = Gamma Knife; HR = hazard ratio; IQR = interquartile range; KPS = Karnofsky Performance Status; LINAC = linear accelerator; MRI = magnetic resonance imaging; M-series = Mito series; MST = median survival time; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy; 2-st-GK-Tx = 2-stage GK treatment; 3-st-GK-Tx = 3-stage GK treatment.

SUBMITTED May 19, 2018. **ACCEPTED** July 11, 2018.

INCLUDE WHEN CITING DOI: 10.3171/2018.7.GKS181392.

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strategy is generally not recommended for patients with larger brain metastases, due to the increased risk of later edema development with associated delayed side effects. Instead, fractionated stereotactic radiotherapy (fSRT) has been widely used for such conditions, employing a linear accelerator (LINAC) system. However, because frame placement is necessary in Gamma Knife (GK) SRS, fSRT is difficult to perform. Therefore, the herein-described staging technique was introduced. Higuchi et al. reported on 43 patients who underwent a novel procedure, 3-stage GK treatment (3-st-GK-Tx) with a 2-week interval between stages.⁶ A new GK system, Icon (Elekta AB), recently became available. With this system, not only frame-based but also mask-based fixation can be used. Therefore, oligo-fractionated irradiation can now be performed more easily than was previously possible.

Nevertheless, there is surprisingly little information on 3-st-GK-Tx. In this study, we reappraised the efficacy of this approach, focusing especially on maintenance of neurological status, local control, and the safety of this treatment strategy, using our prospectively accumulated data set of our patients who underwent 3-st-GK-Tx for brain metastases with a volume exceeding 10 cm³. We also compared our experience at Mito Gamma House (Mito series [M-series]) with that from Chiba (Department of Neurological Surgery, Chiba University Graduate School of Medicine) reported by Higuchi et al. (Chiba series [C-series]) using a contemporary statistical method, competing risk analysis, which was not yet available when the C-series results were reported.

Methods

Patient Population

This was an IRB-approved (Tokyo Women's Medical University IRB) retrospective cohort study using our prospectively accumulated database including 3160 consecutive patients who underwent GK SRS for brain metastases during the period from 1998 through 2016. We started 3-st-GK-Tx in December of 2005. During a subsequent 10-year-period, 1767 patients with brain metastases underwent GK SRS at our facility. Among these 1767 patients, 78 whose largest tumor exceeded 10 cm³ in volume and who were treated with 3-st-GK-Tx were studied (M-series; 34 women and 44 men, mean age 65 years, range 35–86 years). Because all patients were referred to our institution by their primary physicians, the first author (M.Y.) decided whether or not SRS could be performed. Our facility performed only GK treatment (we are not equipped with other irradiation systems). Therefore, all patients referred to the first author (M.Y.) were seeking consultation regarding GK treatment. If a physician responsible for the patient had recommended another fractionated scheme using a LINAC system, a referral to the first author (M.Y.) would not have been made. Basically, we did not perform SRS on patients with low Karnofsky Performance Status (KPS) scores because of systemic diseases, a non-cooperative state due to poor neurocognitive function, meningeal dissemination, and/or an expected survival period of 3 months or less. In the series of 78 cases, SRS rather than surgery was recommended by primary neurosurgeons be-

cause of high risk with general anesthesia due to progression of non-brain diseases in 32 cases and because of the patient's relatively advanced age, 65 years or older, in 27 cases. The 19 remaining patients had anxiety regarding surgery and refused it. As mentioned above, fSRT was difficult to perform using a GK because of the need for frame-based treatment, and the herein-described staging technique was introduced instead.

Baseline characteristics of the 78 patients are shown in Table 1, along with those of the 43 C-series patients. For analyses of these C-series patients, we used the database that had been used at the time of publication,⁶ but we used an updated version for the present investigation. Because all patients had been referred to our institution, as noted above, primary physicians had already made the decision as to whether or not to perform surgery or WBRT for brain metastases. For this reason, 5 (6.4%) of the 78 M-series patients had undergone surgery and 3 (3.9%) had undergone WBRT before 3-st-GK-Tx. The modified recursive partitioning analysis was used for determining the prognostic grade.^{36,38}

Radiosurgical Techniques

The treatment strategies were explained in detail to each patient, as well as at least 1 adult relative, and written informed consent was obtained from all patients by the first author (M.Y.) before the treatments were administered. As we previously described our radiosurgical techniques in detail,^{36,38} they are not repeated herein. Briefly, SRS was performed employing a Leksell GK Model C unit (Elekta AB) before December 2013 and, thereafter, a Leksell Perfexion unit (Elekta AB). We applied 3-st-GK-Tx techniques, as reported by Higuchi et al.⁶—i.e., the target volumes were covered with a 50% isodose gradient and irradiated with a peripheral dose of 10 Gy for each procedure.⁷ The interval between procedures was 2 weeks.

Frame fixation and dose planning were performed for each procedure. In patients who also had small tumors, these were irradiated with single-session SRS (19.00–24.00 Gy at the tumor periphery) mostly at the time of the first procedure or, less commonly, at the time of the third procedure. Therefore, in the M-series, the median cumulative number of tumors was 2 (range 1–31, IQR 1–6), as shown in Table 1. In this series, the median number of tumors irradiated using 3-st-GK-Tx was 1 (range 1–31, IQR 1–2). In these subsets, the median cumulative volume was 23.2 cm³ (range 10.2–92.8 cm³, IQR 17.9–35.0 cm³). Volume changes of the largest tumors, in response to the 3 irradiation sessions, are presented as a real number (Fig. 1 left) and as a percentage against the first tumor volume (Fig. 1 right).

Clinical Outcomes

All patients were recommended to receive clinical follow-up as well as magnetic resonance imaging (MRI) at 2-month intervals for 12 months following 3-st-GK-Tx and, thereafter, at 3-month intervals. After 3-st-GK-Tx, the primary endpoint was overall survival, and the secondary endpoints were neurological death, neurological deterioration, local recurrence of the treated tumor, irradiation-

induced major complications, and further salvage SRS for new or recurrent lesions. For each endpoint, failures were regarded as events and any others as censored. Overall survival time was defined as the interval between the first procedure day of the 3-st-GK-Tx and death due to any cause (progression of systemic metastases and/or brain metastases, other disease unrelated to cancer, accident, suicide, and so on) or the day of the last follow-up. Neurological death was defined as death caused by any intracranial disease, including tumor recurrence, carcinomatous meningitis, cerebral dissemination, and progression of untreated intracranial tumors. Cumulative local recurrence incidence was calculated as the interval between the first session of 3-st-GK-Tx and the day when follow-up MRI demonstrated local recurrence. Basically, local recurrence was detected by MRI (regression of enhanced area on T1-weighted MRI obtained after contrast agent administration and enlarged tumor core on T2-weighted MRI).¹¹ However, in some cases in which MRI raised suspicion of recurrence, methionine positron emission tomography was used for determining whether or not the tumor had recurred.^{20,22} All findings of recurrence on MRI were regarded as events and any others as censored.

Also, repeat SRS-free survival time was defined as the interval between the 3-st-GK-Tx and the day the repeat SRS was performed; all repeat SRS procedures for such lesions were regarded as events and any others as censored.

Neurological deterioration-free survival time was defined as the interval between the first session of 3-st-GK-Tx and the day when any neurological worsening due to brain disease manifested (that is, local recurrence, progression of new lesions, and SRS-induced complications). Decreases in KPS score due to neurological worsening in patients with scores of 20% or less were regarded as events and any others as censored. Patients with major complications included those with Radiation Therapy Oncology Group (RTOG) neurotoxicity of grade 2 or worse and, even if the grade was either 0 or 1, those in whom surgical intervention was required based on sequential MRI follow-up demonstrating progressive enlargement of a cyst and/or a mass lesion making further observation excessively high risk.²⁶ SRS-induced complications included MRI-demonstrated enlargement of a heterogeneously enhanced area without clear evidence of a tumor core on T2-weighted images and with remarkable perifocal edema. All of these conditions were regarded as events and any others as censored.

Our above-mentioned criteria for neurological death, neurological deterioration, local recurrence, and complications have been widely confirmed based on our previous publications.^{14,31–36,38}

Statistical Analysis

We analyzed all of the data according to the intention-to-treat principle. For baseline variables, summary statistics were constructed with frequencies and proportions for categorical data and with medians, interquartile ranges (IQRs), and full ranges for continuous variables. The standard Kaplan-Meier method was used for overall and neurological death-free survivals. Also, univariate and

TABLE 1. Summary of demographic characteristics in 43 C-series and 78 M-series patients

Characteristics	C-Series	M-Series	p Value
No. of patients	43	78	
Age (yrs)			0.4263
Median	64	65	
Range	41–84	38–86	
IQR	56–70	57–75	
Sex			>0.99
Male	24 (55.8%)	44 (56.4%)	
Female	19 (44.2%)	34 (43.6%)	
Neurological Sx			0.0418
Yes	40 (93.0%)	61 (78.2%)	
No	3 (7.0%)	17 (21.8%)	
KPS score			0.3407
80%	21 (48.8%)	46 (59.0%)	
≤70%	22 (51.2%)	32 (41.0%)	
Modified RPA class			0.6119
1+2a	3 (7.0%)	7 (9.0%)	
2b	14 (32.6%)	19 (24.3%)	
2c+3	26 (60.5%)	52 (66.7%)	
Primary cancer status			0.0004
Controlled	2 (4.7%)	25 (32.1%)	
Not controlled	41 (95.3%)	53 (68.0%)	
Primary cancer			0.5250
Lung	12 (27.9%)	37 (47.4%)	
Non-lung	31 (72.1%)	41 (52.6%)	
Extracranial metastases			<0.0001
Yes	41 (95.4%)	44 (56.4%)	
No	2 (4.7%)	34 (43.6%)	
Prior surgery			0.4206
Yes	1 (2.3%)	5 (6.4%)	
No	42 (97.7%)	73 (93.6%)	
Prior WBRT			0.5516
Yes	0 (0%)	3 (3.9%)	
No	43 (100%)	75 (96.2%)	
No. of tumors, total			0.7170
Median	2	2	
Range	1–14	1–31	
IQR	1–4	1–6	
No. of tumor, 3-stage			
Median	NA	1	
Range	NA	1–31	
IQR	NA	1–2	
Tumor vol, cm ³			
Cumulative, total			0.0009
Median	19.4	25.0	
Range	10.8–50.0	10.2–92.8	
IQR	14.2–27.5	19.5–38.5	

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TABLE 1. Summary of demographic characteristics in 43 C-series and 78 M-series patients

Characteristics	C-Series	M-Series	p Value
Tumor vol, cm ³ (<i>continued</i>)			
Cumulative, 3-stage			
Median	NA	23.2	
Range	NA	10.2–92.8	
IQR	NA	17.9–35.0	
Largest tumor			0.0015
Median	16.2	21.5	
Range	10.8–35.5	10.2–70.0	
IQR	11.9–21.2	16.1–27.3	

NA = not available; RPA = recursive partitioning analysis; Sx = symptoms.

multivariate analyses using the Cox proportional hazard model were performed to determine pre-2nd SRS clinical factors favoring longer survival.

For time-to-event outcome analyses of the 4 aforementioned endpoints, a competing risk analysis was applied because death is a competing risk for these endpoints. The standard Kaplan-Meier method was applied, i.e., follow-up results from those developing a competing event (specifically, death) were simply censored. We consider competing risk analysis to have been necessary for meaningful evaluation of these data. Also, to identify baseline and clinical variables associated with the 4 aforementioned outcomes, competing risk analyses were applied employing the Fine-Gray generalization of the proportional hazards model accounting for death as a competing risk.^{3,4} The Fine-Gray generalization specifically makes use of the subdistribution hazard to model cumulative incidence, thereby quantifying the overall benefit or harm of an exposure.

All comparisons were planned, and the statistical tests conducted were 2-sided. A p value of less than 0.05 was considered to indicate a statistically significant difference. A statistician (Y.S.), using SAS software version 9.4 (SAS Institute), performed all analyses. Before the statistical analyses, the database was cleaned by one of the coauthors (Y.H.). Neither of these authors was involved in either the SRS treatment protocol or patient follow-up.

Results

In the M-series, the median follow-up time for 13 censored observations was 16.0 months (IQR 11.7–28.1 months, maximum 80.7 months) after the 3-st-GK-Tx, and 65 patients (83.3%) had died as of the end of September 2016. Actuarial survival proportions were 55.2%, 35.2%, 22.1%, and 7.7% at 6, 12, 24, and 36 months, respectively, after the 3-st-GK-Tx (Fig. 2). The post-3-st-GK-Tx median survival time (MST) in the M-series (8.3 months, 95% CI 5.6–12.0 months, IQR 3.8–16.8 months) was very similar to that in the C-series (8.6 months, 95% CI 5.3–10.6 months, IQR 4.6–12.4 months) (hazard ratio [HR] 1.175, 95% CI 0.790–1.728, $p = 0.42$). As shown in Table 2, multivariable analysis revealed controlled vs not-controlled primary cancer (HR 0.395, 95% CI 0.214–0.652, $p = 0.0011$), lung cancer vs non-lung cancer (HR 0.373, 95% CI 0.210–0.652, $p = 0.0005$), and largest tumor volume smaller than 20 cm³ vs 20 cm³ or larger (HR 0.490, 95% CI 0.323–0.345, $p = 0.0009$) to be significant predictive factors for longer post-3-st-GK-Tx survival.

The crude incidences of neurological death (14.3% in the C-series vs 13.8% in the M-series, $p > 0.99$), neurological deterioration (18.6% vs 18.0%, $p > 0.99$), local recurrence (7.0% vs 9.2%, $p = 0.66$), repeat SRS (25.6% vs 22.1%, $p = 0.65$), and SRS-related complications (2.3% vs 5.1%, $p = 0.36$) are compared between the 2 case series in Table 3. Salvage WBRT was necessary in 1 (2.3%) of the C-series patients but none of the M-series patients ($p = 0.35$), while salvage surgery was required in 3 (3.9%) of the M-

FIG. 1. Left: Volume of largest tumors (in cubic centimeters) at the first, second, and third procedures. **Right:** Change in volume of the largest tumors at the second and third procedures. Percentage values are relative to the volume at the first procedure. Horizontal bars near the mean values are the 95% confidence intervals and those farther from the mean values are standard deviations.

FIG. 2. Overall survivals after 3-stage treatment in the 2 groups, Chiba-series (C-series) and Mito-series (M-series) patients, estimated using the standard Kaplan-Meier method.

series patients but none of the C-series patients ($p = 0.55$). Also, at the 6th/12th/24th post-3-st-GK-Tx months, cumulative incidences of neurological death (0%/7.2%/9.6% in C-series vs 7.7%/7.7%/7.7% in M-series, adjusted HR 0.894, 95% CI 0.338–2.440, $p = 0.83$), neurological deterioration (6.9%/14.2%/19.0% vs 8.9%/12.8%/14.9%, adjusted HR 0.990, 95% CI 0.412–2.328, $p = 0.96$), local recurrence (0.0%/4.8%/7.2% vs 3.1%/6.2%/13.1%, adjusted HR 1.935, 95% CI 0.525–7.124, $p = 0.32$), repeat SRS (21.1%/25.9%/25.9% vs 11.5%/18.0%/22.3%, adjusted HR 0.783, 95% CI 0.365–1.683, $p = 0.53$), and SRS-related complications (2.3%/2.3%/2.3% vs 2.5%/5.1%/5.1%, adjusted HR 2.168, 95% CI 0.234–19.40, $p = 0.49$) did not differ significantly between the 2 groups (Table 3).

In 61 (78.2%) of 78 M-series patients, steroid treatment was initiated a few weeks prior to or after the first session of 3-st-GK-Tx and was continued for 3–42 weeks (median 8 weeks, IQR 8–12 weeks) after the initial session.

No neurological deficits were noted at the time of the first 3-st-GK-Tx session in 17 of the 78 patients in the M-series. In these 17 patients, no neurological worsening occurred during a median observation period of 28 weeks (range 3–151 weeks, IQR 11–109 weeks) until the day of the final follow-up or patient death. Among the 61 remaining patients, neurological symptoms showed normalization in 21 (34.4%) and improvement in 29 (47.5%) for 1–23 weeks (median 9 weeks, IQR 4–13 weeks) after 3-st-GK-Tx. However, no improvement was noted after 3-st-GK-Tx in the other 11 (18.0%) during the median observation period of 12 weeks (range 3–145 weeks, IQR 4–24 weeks).

In 172 M-series patients who underwent a single session of SRS for brain metastases of 10 cm³ or larger during the same study period, MST was 6.5 months (95% CI 5.1–7.7 months) (HR vs patients with 3-st-GK-Tx 1.285, 95% CI 0.946–1.770, $p = 0.1103$). The crude incidences of neurological death, neurological deterioration, local recurrence, repeat SRS, and SRS-related complications were 10.6%, 13.4%, 8.1%, 20.2%, and 4.1%, respectively.

Discussion

In Japan, the 3-st-GK-Tx procedure has been widely applied for patients with relatively large brain metastases or small brain metastases located in anatomically critical brain structures. However, as yet, validity testing of this technique has not been performed. Therefore, we reappraised the efficacy and safety of 3-st-GK-Tx using our own data set. Also, we compared our treatment outcomes with those of the C-series, which we reanalyzed using a competing risk analysis because only Kaplan-Meier analysis had been applied in the original publication by Higuchi and colleagues.⁶ The study periods differed between these 2 series (2002–2006 for the C-series vs 2005–2015 for the M-series). Furthermore, as shown in Table 1, there were some disproportions between the 2 series in neurological symptoms, primary cancer status, extracerebral metastases, and the cumulative and largest tumor volumes. However, this 2-institutional retrospective study demonstrated

TABLE 2. Clinical factors affecting survival after 3-stage treatment

Characteristic	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (yrs): <65 vs ≥65	0.975 (0.666–1.427)	0.8960	0.847 (0.556–1.292)	0.4407
Sex: female vs male	0.769 (0.519–1.133)	0.1846	0.896 (0.435–1.112)	0.1294
Neurological Sx: yes vs no	1.370 (0.827–2.425)	0.2316	0.858 (0.466–1.665)	0.6384
KPS score: ≥80% vs ≤70%	0.717 (0.490–1.053)	0.0895	0.858 (0.545–1.350)	0.5068
Modified RPA class				
1+2a vs 2b	0.604 (0.226–1.357)	0.2360	0.651 (0.230–1.591)	0.3611
1+2a vs 2c+3	0.364 (0.141–0.773)	0.0065	0.530 (0.182–1.334)	0.1857
2b vs 2c+3	0.603 (0.386–0.919)	0.0183	0.815 (0.467–1.391)	0.4581
Primary cancer status: controlled vs not	0.461 (0.264–0.757)	0.0017	0.395 (0.214–0.698)	0.0011
Primary cancer: lung vs non-lung	0.621 (0.411–0.926)	0.0191	0.373 (0.210–0.652)	0.0005
Extra-cranial metastases: no vs yes	0.678 (0.435–1.029)	0.0681	0.908 (0.507–1.602)	0.7421
Number of tumors: solitary vs multiple	0.846 (0.569–1.242)	0.3954	0.693 (0.443–1.074)	0.1010
Largest tumor vol (cm ³): <20 vs ≥20	0.691 (0.473–1.017)	0.0608	0.490 (0.323–0.745)	0.0009

TABLE 3. Post-treatment results: crude and cumulative incidences in C- and M-series

Result	Crude Incidence	p Value	Cumulative Incidence, 6/12/24 Mos	HR (95% CI)*	p Value
Neurological death†		>0.99		1.039 (0.341–2.927)	0.9436
C-series	0.143		0.000/0.172/0.291		
M-series	0.138		0.100/0.100/0.100		
Neurological deterioration		>0.99		0.990 (0.395–2.315)	0.9822
C-series	0.186		0.083/0.276/0.379		
M-series	0.180		0.112/0.198/0.278		
Local recurrence		0.6599		0.632 (0.138–2.200)	0.4867
C-series	0.070		0.000/0.144/0.358		
M-series	0.092		0.072/0.104/0.350		
Repeat SRS		0.6544		1.221 (0.554–2.581)	0.6088
C-series	0.256		0.266/0.365/0.365		
M-series	0.221		0.196/0.318/0.515		
SRS-related complications		0.3554		0.460 (0.024–3.109)	0.4557
C-series	0.023		0.023/0.023/0.023		
M-series	0.051		0.039/0.096/0.096		

* Adjusted hazard risk determined using a competing risk analysis.

† Based on deceased patients, i.e., 42 in the C-series and 65 in the M-series.

that the post-3-st-GK-Tx results were remarkably similar between the 2 series in terms of overall survival times, neurological death, maintained neurological status, local control, repeat SRS, and SRS-related complications. We consider this study to be the first validation of the post-3-st-GK-Tx results reported by Higuchi et al.⁶

Although MSTs did not differ significantly between the 2 patient groups, as described above, actuarial survival rates differed remarkably at 12 months after 3-st-GK-Tx (Fig. 2). We speculated that these differences were attributable to the availability of target agent treatment because of the differences in the study periods (i.e., 2002–2006 for the C-series vs 2005–2015 for the M-series). In lung cancer patients, the difference in survival rates at the 12th post-3-st-GK-Tx month or later was remarkable (28.1% in the C-series and 50.7% in the M-series). However, there were no significant differences in survival rates for non-lung cancer patients between the 2 series (25.8% in the C-series vs 22.0% in the M-series patients).

Higuchi et al. described a total dose of 30 Gy delivered in 3 stages with an interval of 2 weeks as being equivalent to a single administration of 20 Gy.⁶ The 20-Gy dose was generally used in GK radiosurgery for relatively small brain metastases and was considered to be both effective and safe, achieving 80%–90% tumor control rates with complication incidences of less than 5%.^{37,39} However, even in cases in which tumor volumes exceeded 10 cm³, our study showed crude tumor control rates to be 93.0% in the C-series and 90.8% in the M-series, and the respective crude complication rates were 2.3% and 5.1%. Although debate continues as to whether it is appropriate to apply a linear quadratic method for high dose per fraction effects in radiosurgery,^{12,29} the prescription dose of 10 Gy with an interval of 2 weeks was essentially equal to 60 Gy as the biological equivalent dose to malignant cells (alpha/beta ratio of 10) based on the linear quadratic model. The

biological equivalent dose (alpha/beta ratio of 2) was 180 Gy. Furthermore, as compared with fSRT, staged SRS for brain metastases is considered to be the most beneficial regarding reoxygenation and reduced tumor volume over the 3 procedures (Fig. 1) and, furthermore, no interruption of systemic anticancer agent treatment is necessary.

In modern-day clinical care of patients with brain metastases, maintenance of good neurological function and, ultimately, a decreased incidence of neurological death have recently been recognized as crucial goals. The JLKG0901 study showed crude incidences of neurological deterioration and neurological death to be 12% and 8%, respectively, in patients with tumor volumes smaller than 10 cm³ treated with a single session of GK radiosurgery.^{37,39} In the present study, crude incidences of neurological deterioration (18.6% in the C-series and 18.0% in the M-series) and neurological death (14.3% in the C-series and 13.8% in the M-series) were somewhat poorer than those obtained in the above-mentioned JLKG0901 study. However, in patients with relatively large brain metastases who underwent surgical removal followed by WBRT or radiosurgery, neurological death rates of 14%–33% have been reported.^{7–9,13,16,24,28} Most notably, among the 61 neurologically symptomatic patients, neurological symptoms fully resolved or showed significant amelioration in 50 (82.0%) during the relatively short post-3-st-GK-Tx intervals (median 9 weeks, IQR 4–13 weeks), although steroid treatment was necessary in 48 (78.7%) of the 61 patients.

Using a LINAC system, fSRS has generally been performed for the treatment of brain metastases. The dose selection and fractionation protocols for brain metastases with a size of 2.5–3.0 cm or larger varied from 18–53 Gy with 2–15 fractionations.^{10,15,17,19,21,23} Cumulative incidences of local tumor control were reportedly 61%–96% at the 12th post-irradiation month and crude incidences of fSRS-related complications were 6%–14%. Our herein-reported

TABLE 4. Studies on 2- or 3-stage GK treatment for patients with large brain metastases

Authors & Year	No. of Pts	No. of Tumors, Med (mean), Max	Largest Tumor Vol in cm ³ , Med (range)	Peripheral Dose in Gy, Mean or Range/Procedure	No. of Procedures (interval in wks)	Med Survival Time in Mos	Local Recur Rate (%)	Compl Rate (%)	Neurol Death Rate (%)
Higuchi et al., 2009	43	2 (3), 14	16.2 (10.8–35.5)	10	3 (2)	8.8	7.0	2.3	13.8
Yomo et al., 2014	58	2, 8	16.4 (10.0–56.1)	10–15	2 (3–4)	11.8	15.0/6 mos	5.0	17.0
Dohm et al., 2018	33	2 (2), 7	11.7 (0.8–60.9)	10–21	2 (4)	60.0%/12 mos	12.1	6.1	32.6/12 mos
Hasegawa et al., 2017	56	NA	21.0 (10.0–76.0)	10–13	2 (1–4)	7.0	15.0	1.9	7.3
Angelov et al., 2017	54	NA	10.5 (2.4–31.3)	12–18	2 (5)	10.8	14.3	6.4	11.5
Present study	78	2 (5), 31	21.5 (10.2–70.0)	10	3 (2)	8.3	9.2	5.1	13.8

Compl = complications; med = median; neurol = neurological; pts = patients; recur = recurrence.

results, i.e., cumulative incidences of local tumor control at the 12th post-3-st-GK-Tx month being 85.6% in the C-series and 89.6% in the M-series with corresponding crude incidences of complications of 2.3% and 5.1%, were not inferior to the above-mentioned post-fSRS results. Jiang et al. reported that, of 40 patients with brain metastases larger than 3 cm treated with 20–53 Gy with 4–15 fractions, neurological death occurred in 9 patients (22.5%).¹⁰ Kwon et al. reported that, of 27 patients who underwent fSRS with 20–36 Gy with 4–6 fractions, neurological death occurred in 18 patients (66.7%), although among their 27 patients, only 1 patient had a tumor larger than 3 cm.¹⁵ Our neurological death results, 14.3% in the C-series and 13.8% in the M-series, were slightly better than those of the 2 above-described series.

Because 3 procedures are regarded as placing a major burden on both patients and physicians, 2-staged GK radiosurgery (2-st-GK-Tx) was proposed by Yomo et al.^{40,41} Their treatment strategy involved total doses of 20–30 Gy being delivered in 2 sessions with an interval of 3–4 weeks. Based on data from 58 patients, they found that the MST after 2-st-GK-Tx was 11.8 (95% CI 5.5–15.6) months and that 1- and 2-year post-2-st-GK-Tx survival rates were 47% and 20%, respectively. Of 44 deceased patients, only 5 (11%) had died due to brain tumor progression and the 1- and 2-year post-2-st-GK-Tx, neurological death-free survival rates were 91% and 84%, respectively. Furthermore, the 6- and 12-month post-2-st-GK-Tx local tumor control rates were 85% and 64%, respectively. Three patients (5%) developed symptomatic radiation injury, necessitating conservative management. Therefore, Yomo and colleagues concluded that, as an alternative to 3-st-GK-Tx, 2-session GK radiosurgery should possibly be offered to patients with large brain metastases who are in poor condition or are, for any reason, ineligible for standard care. The results of 3 retrospective investigations regarding 2-st-GK-Tx were recently reported (Table 4). The local recurrence rates in these studies ranged from 12.1% to 15.0% and complication incidences from 1.9% to 6.4%, results very similar to those obtained with 3-st-GK-Tx.^{1,2,5}

The next question is whether 3-st-GK-Tx or 2-st-GK-Tx is the better option in terms of patient outcomes. Very recently, Serizawa et al. reported a multi-institutional retrospective study designed to compare the treatment results of these 2 protocols (i.e., 3-stage or 2-stage treatment).²⁷

Based on 106 patients in each group after case matching, MST was longer in the 3-st-GK-Tx group (16.1 months [95% CI 12.0–20.0 months]) than that in the 2-st-GK-Tx group (11.3 months [95% CI 8.5–16.9 months]). However, this difference was not statistically significant (HR 1.080, 95% CI 0.776–1.502, $p = 0.65$). The cumulative incidences of tumor progression (16.1% vs 11.6% at 1 year, $p = 0.31$), neurological death (5.1% vs 6.0% at 1 year, $p = 0.58$), and serious radiation-related adverse events (3.0% vs 4.0% at 1 year, $p = 0.49$) did not differ significantly between the 2 groups.

As mentioned above, fSRS has been widely applied for managing relatively large brain metastases.^{10,15,17,19,21,23} Formerly, however, GK was rarely employed for oligo-fractionation because the standard GK radiosurgery technique required a pin-based head frame. For the past few years, the Elekta Extend bite-block palatal vacuum immobilization system has been available. This system facilitates performing oligo-fractionated GK SRS. McTyre and colleagues reported on 34 patients with meningiomas, pituitary adenomas, vestibular schwannomas, hemangiomas or brain metastases.¹⁸ Although the follow-up period in their study was brief, they concluded that fractionated GK SRS using this system was well tolerated in patients undergoing irradiation for large tumors. However, the Extend system is not as yet in widespread use due to its technical complexity.

A few years ago, an innovative GK unit, the Leksell Gamma Knife Icon (Elekta AB), became commercially available. This new model is anticipated to make fractionated GK radiosurgery more accessible because it simplifies immobilization of the patient's head by eliminating the need for a conventional pin-fixation frame or the Extend bite block, instead employing a mask fixation system.

The major weakness of our present study is that it was retrospective. There were considerable biases in patient selection and post-SRS observation. Another weakness is that meticulous follow-up neuroimaging data were lacking in some cases mainly due to early deterioration of the patient's general condition or death soon after treatment. A third, quite important, weakness of this study is that data on molecular subtypes and systemic anticancer agent treatments were lacking in most cases because, as noted above, systemic cancers were managed by referring physicians who worked at different facilities. Also, the limitations of

treatable tumor volume remain unclear. In the M-series, the largest tumor volume was 70.0 cm³. Hasegawa et al. reported that they treated a patient whose largest tumor was 76.9 cm³ in volume.⁵ Further experiences are required before we can answer questions pertaining to maximum treatable tumor volumes.

Conclusions

No significant differences in post-3-st-GK-Tx results between the C-series and the M-series, in terms of overall survival times, neurological death, maintained neurological status, local control, repeat SRS and SRS-related complications, were detected. The previously published results of Higuchi et al.⁶ are thus considered to be validated by our M-series results.

Acknowledgments

We are very grateful to Jonathan Knisely, MD, Department of Radiation Oncology, Weill Cornell Medicine, North Shore University Hospital, for his helpful advice on fractionated fSRT for large brain metastases and also to Bierta E. Barfod, MD, Katsuta Hospital Mito Gamma House, for her help with the language editing of the manuscript.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Yamamoto, Higuchi, Serizawa, Kasuya. Acquisition of data: Higuchi, Serizawa, Kawabe, Nagano, Koiso, Watanabe, Aiyama. Analysis and interpretation of data: Yamamoto, Higuchi, Serizawa. Drafting the article: Yamamoto. Critically revising the article: Yamamoto, Higuchi, Serizawa. Reviewed submitted version of manuscript: Yamamoto, Higuchi, Kawabe, Nagano, Koiso, Watanabe, Aiyama. Approved the final version of the manuscript on behalf of all authors: Yamamoto. Statistical analysis: Higuchi, Sato. Study supervision: Yamamoto, Serizawa, Kasuya.

Supplementary Information

Previous Presentations

This work was presented in oral form at the 19th Biannual Congress of the International Leksell Gamma Knife Radiosurgery Society, Dubai, United Arab Emirates, March 4–8, 2018.

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