Clinical significance of conformity index and gradient index in patients undergoing stereotactic radiosurgery for a single metastatic tumor

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OBJECTIVE Although the conformity index (CI) and the gradient index (GI), which were proposed by Paddick and colleagues, are both logically considered to correlate with good posttreatment results after stereotactic radiosurgery (SRS), this hypothesis has not been confirmed clinically. The authors' aim was to reappraise whether high CI values correlate with reduced tumor progression rates, and whether low GI values correlate with reduced complication incidences.

METHODS This was an institutional review board–approved, retrospective cohort study conducted using a prospectively accumulated database including 3271 patients who underwent Gamma Knife SRS for brain metastases (BMs) during the 1998–2016 period. Among the 3271 patients, 925 with a single BM at the time of SRS (335 women and 590 men, mean age 66 [range 24–93] years) were studied. The mean/median CIs were 0.62/0.66 (interquartile range [IQR] 0.53–0.74, range 0.08–0.88) and the mean/median GIs were 3.20/3.09 (IQR 2.83–3.39, range 2.27–11.4).

RESULTS SRS-related complications occurred in 38 patients (4.1%), with a median post-SRS interval of 11.5 (IQR 6.0–25.8, maximum 118.0) months. Cumulative incidences of post-SRS complications determined by a competing risk analysis were 2.2%, 3.2%, 3.6%, 3.8%, and 3.9% at the 12th, 24th, 36th, 48th, and 60th post-SRS month, respectively. Multivariable analyses showed that only two clinical factors (i.e., peripheral doses and brain volume receiving ≥ 12 Gy) correlated with complication rates. However, neither CIs nor GIs impacted the incidences of complications. Among the 925 patients, post-SRS MRI was performed at least once in 716 of them, who were thus eligible for local progression evaluation. Among these 716 patients, local progression was confirmed in 96 (13.4%), with a median post-SRS interval of 10.8 (IQR 6.7–19.5, maximum 59.8) months. Cumulative incidences of local progression determined by a competing risk analysis were 7.7%, 12.6%, 14.2%, 14.8%, and 15.3% at the 12th, 24th, 36th, 48th, and 60th post-SRS month, respectively. Multivariable analyses showed neurological symptoms, extracerebral metastases, repeat SRS, and CIs to correlate with incidences of local progression, whereas GIs had no impact on local tumor progression. Particularly, cumulative incidences of local progression were significantly lower in patients with CIs < 0.65 than in those with CIs ≥ 0.65 (adjusted hazard ratio 1.870, 95% confidence interval 1.299–2.843; $p = 0.0034$).

CONCLUSIONS To the authors' knowledge, this is the first analysis to focus on the clinical significance of CI and GI based on a large series of patients with BM. Contrary to the majority opinion that dose planning with higher CI and lower

ABBREVIATIONS BM = brain metastasis; CI = conformity index; GI = gradient index; GK = Gamma Knife; HR = hazard ratio; IQR = interquartile range; KPS = Karnofsky Performance Scale; NSCLC = non-small cell lung cancer; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.
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GI results in good post-SRS outcomes (i.e., low local progression rates and minimal complications), this study clearly showed that the lower the CIs were, the lower the local progression rates were, and that the GI did not impact complication rates.

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KEYWORDS brain metastases; radiosurgery; Gamma Knife; conformity index; gradient index; stereotactic radiosurgery; oncology

FOR dose planning in stereotactic radiosurgery (SRS), the conformity index (CI; the coverage ratio multiplied by the selectivity ratio) and the gradient index (GI; the brain volume receiving 50% of the planned peripheral dose divided by the target volume), which were proposed by Paddick and colleagues,^{10,11} are generally believed to be essential for obtaining good treatment results. Namely, either higher CIs (i.e., closer to 1.0) or lower GIs are expected to achieve good tumor growth control and to reduce irradiation-related complications. Although this hypothesis is generally accepted as being logically correct, surprisingly little information is available regarding its clinical significance. Our aim is to reappraise whether the above-mentioned hypothesis is actually clinically valid in patients with a single brain metastasis (BM) undergoing SRS.

Methods

Patient Population

This retrospective study was approved by the institutional review board of the Tokyo Women's Medical University, Tokyo. Our prospectively accumulated data set consisted of 3271 consecutive patients with BM treated with Gamma Knife (GK) SRS at the Mito GammaHouse during the 18-year period between July 1998 and June 2016. Among the 3271 patients, excluding 4 who were lost to follow-up, 925 with a single BM at the time of treatment (335 women and 590 men, mean age 66 [range 24–93] years) who underwent SRS were studied (Fig. 1). Pre-SRS clinical characteristics are summarized in Table 1. Prior to referral to us for SRS, treatment selections had generally been made by the patients' primary physicians, such that different patient selection criteria had been applied. Therefore, the second author (M.Y.) judged whether or not SRS was indicated for each patient. The treatment strategies were explained in detail to each patient, as well as to

at least one adult relative, and written informed consent was obtained from all patients by the second author before SRS procedures were performed. Prior to SRS, surgical removal had been performed in 189 patients (20.4%) and whole-brain radiotherapy (WBRT) had been done in 27 (2.9%).

Radiosurgical Techniques

A stereotactic coordinate frame (Leksell Model G frame; Elekta Instruments AB) was applied under local anesthesia, supplemented with mild sedation in some cases. For target coordinate determination and dose planning, stereotactic Gd-enhanced T1-weighted axial MR images with a slice thickness of 2 mm, multiple slices of which covered the entire brain, were obtained. For dose planning, the Leksell GammaPlan (Elekta) was used. GK SRS was performed using a Leksell GK Model B unit (Elekta) from July of 1991 through June of 2003, a Leksell GK Model C unit (Elekta) from July of 2003 through November of 2013, and thereafter, a Leksell GK Perfexion (Elekta) through June of 2016. Standard, single-session GK SRS was performed. However, in 35 patients (3.8%) in whom the tumor volume was large, a 3-stage treatment was applied.³ Our dose selection was based on our experiences accumulated during the 7-year period between 1992 and 1998 in Japan. The median dose at the tumor periphery was 22.00 (interquartile range [IQR] 20.00–24.00, maximum 25.00) Gy. In this series, peripheral doses of 15.00–25.00 Gy were used in more than 99% of patients. Radiosurgical parameters are summarized in Table 2. The mean/median CIs were 0.62/0.66 (IQR 0.53–0.74, range 0.08–0.88) and the mean/median GIs were 3.20/3.09 (IQR 2.83–3.39, range 2.27–11.4).

Clinical Outcomes

Local progression and SRS-related symptomatic complications were analyzed in relation to the CIs and the GIs. Patients were recommended to undergo post-SRS MRI follow-up at a 2- to 3-month interval. Criteria for local progression (i.e., progression of the SRS-irradiated lesion) were usually an increase in the size of the enhanced area on post-Gd T1-weighted MR images and an enlarged tumor core on T2-weighted MR images as well as detection of a high choline peak on proton MR spectrograms.⁵ However, in some cases in which MRI raised suspicion of progression, methionine PET was also used to confirm whether or not the tumor had progressed.^{7,9}

Regarding SRS-related symptomatic complications, treatment was considered to have failed in those with worse than Radiation Therapy Oncology Group (RTOG) grade 2 neurotoxicity.¹² However, treatments in 4 patients with RTOG grade 0 and 1 patient with grade 1 were clas-

FIG. 1. Flow diagram outlining patient selection for this study.

TABLE 1. Summary of preradiosurgical demographic characteristics

Characteristic	Value
No. of patients	925
Age (yrs)	
Median	67
Range	24–93
IQR	59–74
Sex	
Male	590 (63.8)
Female	335 (36.2)
Neurological symptoms	
Yes	490 (53.0)
No	435 (47.0)
KPS score	
≥80%	736 (79.6)
<70%	189 (20.4)
Modified RPA class*	
1 + 2a	446 (48.2)
2b	295 (31.9)
2c + 3	184 (19.9)
Primary cancer	
NSCLC	497 (53.7)
SCLC	61 (6.6)
Breast	78 (8.4)
Gastrointestinal tract	147 (15.9)
Kidney	51 (5.5)
Others	91 (9.8)
Presentation	
Synchronous	140 (15.1)
Metachronous	785 (84.9)
Primary cancer status	
Controlled	372 (40.2)
Uncontrolled	553 (59.8)
Extracranial metastases	
Yes	415 (44.9)
No	510 (55.1)
Prior surgery	
Yes	189 (20.4)
No	736 (79.6)
Prior WBRT	
Yes	27 (2.9)
No	898 (97.1)

RPA = recursive partitioning analysis; SCLC = small cell lung cancer. Values are presented as the number of patients (%) unless otherwise indicated.

* Categorized according to Yamamoto and colleagues.^{21,23}

sified as failures because either steroid administration or surgical intervention was required to prevent possible neurological deterioration during further observation.

All of these criteria for local progression and complications have remained consistent for more than 20 years at

TABLE 2. Summary of radiosurgical parameters

Characteristic	Value
Tumor vol (cm ³)	
Median	4.6
Range	0.01–126.2
IQR	1.21–9.62
Min absorbed dose to the tumor (Gy)	
Median	22.00
Range	5.80–25.00
IQR	20.00–24.00
Max absorbed dose to the tumor (Gy)	
Median	36.00
Range	20.00–60.00
IQR	30.00–40.00
Total absorbed energy to the whole skull (Joules)	
Median	2.7
Range	0.2–11.7
IQR	1.25–3.9
Mean absorbed dose to the whole skull (Gy)	
Median	0.7
Range	0.1–3.2
IQR	0.3–1.1
Whole skull vol receiving ≥5 Gy (cm ³)	
Median	69.0
Range	0.7–857.6
IQR	19.3–119.3
Whole skull vol receiving ≥12 Gy (cm ³)	
Median	18.5
Range	0.1–169.4
IQR	5.1–32.7
CI	
Median	0.66
Range	0.08–0.88
IQR	0.53–0.74
GI	
Median	3.09
Range	2.27–11.4
IQR	2.83–3.39

Max = maximum; min = minimum.

our facilities and have also been widely confirmed based on our previous publications.^{6,16,18–20,22,24}

Statistical Analysis

All data were analyzed according to the intention-to-treat principle. For baseline variables, summary statistics were constructed that used frequencies and proportions for categorical data and means or median and IQR for continuous variables. For the time-to-event outcome analyses of the aforementioned end point, a competing risk analysis was applied because death is a competing risk for this end point.^{1,2}

We performed univariable analyses of the CIs and GIs

TABLE 3. Cumulative incidences of complications after SRS

Cumulative Incidences	No.	Mos After SRS					Adjusted HR	95% Confidence Interval	p Value
		12	24	36	48	60			
Overall	925	0.022	0.032	0.036	0.038	0.039			
CI <0.65	420	0.017	0.020	0.023	0.026	0.026	1.477	0.766–2.847	0.240
CI ≥0.65	505	0.027	0.043	0.048	0.048	0.051			
GI <3.1	470	0.019	0.022	0.024	0.027	0.030	1.486	0.781–2.827	0.23
GI ≥3.1	455	0.026	0.044	0.049	0.049	0.049			
Single shot	199	0.005	0.010	0.010	0.022	0.022			
CI <0.65	168	0.006	0.006	0.012	0.020	0.020	3.764	0.631–22.45	0.14
CI ≥0.65	31	0.000	0.036	0.036	0.036	0.036			
GI <3.1	252	0.025	0.030	0.030	0.030	0.030	1.079	0.525–2.271	0.83
GI ≥3.1	474	0.029	0.043	0.049	0.049	0.052			
Multiple shots	726	0.027	0.039	0.042	0.042	0.045			
CI <0.65	254	0.025	0.030	0.030	0.030	0.030	1.079	0.525–2.217	0.83
CI ≥0.65	474	0.029	0.043	0.049	0.049	0.052			
GI <3.1	322	0.025	0.029	0.029	0.029	0.034	1.449	0.713–2.943	0.31
GI ≥3.1	404	0.029	0.047	0.053	0.053	0.053			
Vol <5.0 cm ³	484	0.013	0.022	0.027	0.030	0.030			
CI <0.65	309	0.010	0.013	0.017	0.021	0.021	1.675	0.649–4.235	0.28
CI ≥0.65	175	0.018	0.038	0.046	0.046	0.046			
GI <3.1	228	0.014	0.014	0.019	0.024	0.024	1.297	0.496–3.395	0.59
GI ≥3.1	256	0.012	0.030	0.035	0.035	0.035			
Vol ≥5.0 cm ³	441	0.033	0.044	0.047	0.047	0.050			
CI <0.65	111	0.039	0.039	0.039	0.039	0.039	1.064	0.391–2.891	0.90
CI ≥0.65	330	0.032	0.045	0.049	0.049	0.053			
GI <3.1	242	0.025	0.030	0.030	0.030	0.035	1.733	0.731–4.112	0.21
GI ≥3.1	199	0.044	0.062	0.069	0.069	0.069			

to identify clinical factors associated with the incidences of complications and local progression. Also, to identify baseline and clinical variables associated with local progression and complications, competing risk analyses were performed with the Fine-Gray generalization of the proportional hazards model.^{1,2} The adjusted hazard ratio (HR), 95% confidence intervals, and p values were initially calculated with multivariable analyses. A p value of less than 0.05 was regarded as indicating a statistically significant difference.

All statistical analyses were performed by a statistician (Y.S.) using SAS software version 9.4 (SAS Institute). Prior to the statistical analyses, the database was cleaned by one of the coauthors (Y.H.). These two authors were not involved in either SRS treatment or patient follow-up.

Results

As of December 2016, the median post-SRS observation time among censored observations (144 patients) was 10.0 (IQR 4.3–21.0, maximum 201.5) months and 781 patients (84.4%) had died. The overall median survival time after SRS was 11.4 (95% confidence interval 10.1–12.4, IQR 5.0–25.5) months. Actuarial post-SRS survival rates were 70.3%, 47.7%, 26.4%, 17.3%, 12.1%, and 10.7% at the 6th, 12th, 24th, 36th, 48th, and 60th post-SRS month, re-

spectively. Among the 781 patients who died, causes of death could not be determined in 27, but were confirmed in the remaining 754 to be nonbrain disease in 666 (88.3%) and brain disease in 88 (11.7%).

During a median post-SRS observation period of 9.7 (IQR 4.2–20.5, maximum 201.5) months, SRS-related complications occurred in 38 patients (4.1%), with a median post-SRS interval of 11.5 (IQR 6.0–25.8, maximum 118.0) months. Cumulative incidences of post-SRS complications determined by a competing risk analysis were 2.2%, 3.2%, 3.6%, 3.8%, and 3.9% at the 12th, 24th, 36th, 48th, and 60th post-SRS month, respectively (Table 3). Among the 925 patients, post-SRS MRI was performed at least once in 716, who were thus eligible for local progression evaluation. Among these 716 patients, local progression was confirmed in 96 (13.4%), with a median post-SRS interval of 10.8 (IQR 6.7–19.5, maximum 59.8) months. Cumulative incidences of local progression determined by a competing risk analysis were 7.7%, 12.6%, 14.2%, 14.8%, and 15.3% at the 12th, 24th, 36th, 48th, and 60th post-SRS month, respectively (Table 4).

As shown in Table 5, multivariable analyses revealed that only two clinical factors—i.e., peripheral doses and brain volume receiving ≥ 12 Gy—correlated with complication rates. However, neither CIs nor GIs impacted the incidences of complications. Cumulative incidences of

TABLE 4. Cumulative incidences of local progression after stereotactic radiosurgery

Cumulative Incidences	No.	Mos After SRS					Adjusted HR	95% Confidence Interval	p Value
		12	24	36	48	60			
Overall	718	0.077	0.126	0.142	0.148	0.153			
CI <0.65	344	0.052	0.094	0.101	0.110	0.110	1.870	1.299–2.843	0.0034
CI ≥0.65	374	0.100	0.156	0.181	0.185	0.194			
GI <3.1	355	0.102	0.148	0.163	0.167	0.176	0.693	0.463–1.037	0.074
GI ≥3.1	363	0.051	0.104	0.122	0.130	0.130			
Single shot	156	0.060	0.081	0.096	0.104	0.113			
CI <0.65	136	0.053	0.078	0.078	0.088	0.088	3.374	1.206–9.434	0.020
CI ≥0.65	20	0.105	0.105	0.222	0.222	0.295			
GI <3.1	112	0.064	0.093	0.114	0.114	0.126	0.592	0.170–2.062	0.41
GI ≥3.1	44	0.049	0.049	0.049	0.080	0.080			
Multiple shots	562	0.082	0.140	0.157	0.162	0.165			
CI <0.65	208	0.051	0.105	0.119	0.127	0.127	1.608	0.968–2.618	0.056
CI ≥0.65	354	0.100	0.159	0.178	0.182	0.187			
GI <3.1	243	0.120	0.175	0.187	0.193	0.201	0.635	0.410–0.982	0.041
GI ≥3.1	319	0.051	0.112	0.133	0.138	0.138			
Vol <5.0 cm ³	392	0.051	0.087	0.100	0.104	0.111			
CI <0.65	259	0.036	0.064	0.064	0.069	0.069	2.913	1.532–5.539	0.0010
CI ≥0.65	133	0.080	0.132	0.176	0.176	0.201			
GI <3.1	179	0.058	0.091	0.106	0.106	0.125	0.839	0.445–1.581	0.58
GI ≥3.1	213	0.045	0.083	0.095	0.102	0.102			
Vol ≥5.0 cm ³	326	0.109	0.174	0.194	0.203	0.203			
CI <0.65	85	0.101	0.189	0.223	0.242	0.242	0.835	0.478–1.456	0.52
CI ≥0.65	241	0.111	0.168	0.183	0.189	0.189			
GI <3.1	176	0.147	0.205	0.219	0.227	0.227	0.664	0.392–1.124	0.12
GI ≥3.1	150	0.061	0.135	0.163	0.173	0.173			

Based on 718 patients; i.e., 207 patients were excluded because neuroimaging results were not available.

complications were assessed by dividing the patients into groups (i.e., single vs multiple shots and those with a tumor volume < 5 cm³ vs ≥ 5 cm³, along with CIs < 0.65 vs ≥ 0.65 or GIs < 3.1 vs ≥ 3.1), as demonstrated in Table 3. No statistically significant differences were detected in any of these subgroup analyses.

Also, as shown in Table 6, multivariable analyses revealed that neurological symptoms, extracerebral metastases, and CIs correlated with incidences of local progression, whereas GIs were not associated with local tumor progression. As shown in Table 4, cumulative incidences of local progression were significantly lower in patients with CIs < 0.65 than in those with CIs ≥ 0.65 (adjusted HR 1.870, 95% confidence interval 1.299–2.843; *p* = 0.0034). These results were also obtained in subgroups of patients receiving single-shot treatment (adjusted HR 3.374, 95% confidence interval 1.206–9.434; *p* = 0.020) as well as in those with tumor volumes < 5 cm³ (adjusted HR 2.913, 95% confidence interval 1.532–5.539; *p* = 0.0010). In a subgroup of patients receiving multiple-shot treatment, cumulative incidences of local progression were significantly lower in those with GIs ≥ 3.1 than in patients with GIs < 3.1 (adjusted HR 0.635, 95% confidence interval 0.410–0.982; *p* = 0.041).

Regarding neurologically qualitative survival,²⁴ there was no significant difference in maintained Karnofsky

Performance Scale (KPS) score (< 20% decrease due to neurological diseases) between the two groups with GI ≥ 3.1 and GI < 3.1 (HR 0.810, 95% confidence interval 0.562–1.161; *p* = 0.2059). Nevertheless, the cumulative rate of maintained KPS score was significantly higher in patients with CI < 0.65 than in those with CI ≥ 0.65 (HR 0.511, 95% confidence interval 0.350–0.738; *p* = 0.0003).

Discussion

In comments on our previous publication focusing on delayed cyst formation in patients with BM surviving > 3 years after SRS, Regis stated that the mean GI value in our series was quite poor (approximately 4) and noted that cyst formation might partially account for this result.^{4,13} However, we have long wondered whether either CI or GI truly impacts treatment results, despite these indexes being theoretically regarded as correlating with post-SRS outcomes. We reported that, based on 207 patients with vestibular schwannomas who were followed up for at least 10 years after SRS, CI did not correlate with good tumor control and GI had no impact on the degree of hearing preservation.¹⁵ Nevertheless, to our knowledge the present study is the first analysis to focus on the clinical significance of CI and GI based on a large patient series.

TABLE 5. Multivariable analyses of complications after SRS

Variable	Comparison	HR	95% Confidence Interval	p Value
Sex	Male vs female	0.896	0.372–2.161	0.81
Age (yrs)	≥65 vs <65	1.102	0.536–2.267	0.79
KPS score (%)	≤70 vs ≥80	2.601	0.789–8.575	0.12
Modified RPA class*	2c + 3 vs 1 + 2a	1.193	0.255–5.577	0.82
	2c + 3 vs 2b	1.099	0.287–4.217	0.89
Symptomatic	Yes vs no	0.543	0.265–1.112	0.095
Pre-SRS surgery	Yes vs no	2.872	0.981–8.404	0.054
Pre-SRS WBRT	Yes vs no	0.226	0.041–1.242	0.087
Tumor vol (cm ³)	≥5.0 vs <5.0	1.158	0.397–3.381	0.79
Nos. of target points	Multiple vs single	1.535	0.362–6.505	0.56
Peripheral dose (Gy)	≥20 vs <20	0.235	0.059–0.932	0.039
Max dose (Gy)	≥35 vs <35	1.279	0.401–4.077	0.68
Brain vol receiving ≥12 Gy (cm ³)	≥30 vs <30	0.349	0.125–0.973	0.044
Original tumor status	Non- vs well-controlled	2.141	0.907–5.056	0.083
Original tumor	SCLC vs breast	2.195	0.42–11.463	0.35
	SCLC vs GI	0.143	0.011–1.781	0.13
	SCLC vs kidney	1.702	0.302–9.591	0.55
	SCLC vs NSCLC	0.887	0.246–3.206	0.86
	SCLC vs others	0.488	0.072–3.292	0.46
Extracerebral metastases	Yes vs no	1.518	0.499–4.617	0.46
GI	≥3.1 vs <3.1	1.275	0.635–2.562	0.49
CI	≥0.65 vs <0.65	0.738	0.311–1.752	0.49

* Categorized according to Yamamoto and colleagues.^{21,23}

It is widely believed that an optimal dose plan for SRS would be based on a higher CI (nearer 1.0) and a lower GI. However, the present study clarified that this assumption is not applicable to SRS for BM. Rather, we found that the lower a CI was, the lower the local progression rate was. This observation was even more remarkable in subgroups of patients with relatively small tumors (< 5.0 cm³) or in those who had received single-shot treatment. Although in GK SRS the tumor volume is the same as the planned target volume, a margin of a few millimeters may be reasonable, as is generally applied in LINAC-based SRS, particularly in GK SRS for rather small tumors (i.e., 2–3 mm in diameter), with a single isocenter. In such a case, even if a 90% or 95% isodose gradient is used, with a coverage rate of 1.0, the selectivity rate is very low. Therefore, the CI is calculated to be 0.2–0.1, or even lower. However, the absolute volume of the normal brain tissue included within the target volume is usually very small. In contrast, in the present study, GI was clearly shown to have a minimal impact in lowering the incidence of complications. Although a higher GI was shown to correlate with a lower incidence of local progression, this was only in the subset of patients receiving multiple-shot treatment. These observations appear to support the aforementioned results obtained using a margin of a few millimeters.

Nakamura et al. reported that the median CIs (the ratio of the prescription volume to the target volume) were 1.67 for all 1338 evaluable lesions and 1.40–1.43 for lesions

similar to those in two LINAC radiosurgery series that reported CIs of 1.8 and 2.7, respectively.⁸ However, they did not describe further analyses. Sneed et al. reported that, based on their analysis of 2049 lesions, the median CI was 0.5 (IQR 0.35–0.66).¹⁴ These data were slightly worse than ours—i.e., median 0.66 and IQR 0.53–0.74. Although they also noted, based on analysis of 1831 lesions, that the median GI was 3.18 (IQR 2.85–3.74), the method applied to GI determination in patients with multiple BMs was not described. Their cohort consisted of 435 patients, considerable numbers of whom had multiple BMs (Paddick's GI can be correctly calculated only in patients with a single BM). Nevertheless, Sneed et al.'s GI data were very similar to ours—i.e., median 3.09 and IQR 2.83–3.39. They concluded that there were no significant influences of either the Paddick CI or the GI on the risk of adverse radiation effect with target volumes > 1.0 cm³. In our study, CI did not significantly impact local progression rates (as a continuous variable, HR was 0.737, 95% confidence interval 0.034–18.46; *p* = 0.8485) in patients with tumor volumes > 1.0 cm³. However, CI did significantly influence local progression rates (as a continuous variable, HR was 5.626, 95% confidence interval 1.064–34.86; *p* = 0.0417) in patients with tumor volumes < 5.0 cm³.

The major weakness of this study is the retrospective design. There were considerable biases in patient selection and post-SRS observations. The second weakness is that post-SRS neuroimaging data were lacking in 22% of

TABLE 6. Multivariable analyses of local progression after SRS

Variable	Comparison	HR	95% Confidence Interval	p Value
Age (yrs)	≥65 vs <65	0.950	0.608–1.485	0.82
Sex	Male vs female	0.791	0.501–1.248	0.31
KPS score (%)	≤70 vs ≥80	1.792	0.886–3.625	0.10
Modified RPA class*	2c + 3 vs 1 + 2a	0.829	0.283–2.431	0.73
	2c + 3 vs 2b	1.493	0.608–3.670	0.38
Symptomatic	Yes vs no	0.577	0.342–0.973	0.039
Pre-SRS surgery	Yes vs no	0.789	0.456–1.366	0.40
Pre-SRS WBRT	Yes vs no	1.855	0.332–10.368	0.48
Tumor vol (cm ³)	≥5.0 vs <5.0	0.961	0.508–1.818	0.90
Nos. of target points	Multiple vs single	0.588	0.272–1.274	0.18
Peripheral dose (Gy)	≥20 vs <20	1.086	0.579–2.035	0.80
Max dose (Gy)	≥35 vs <35	1.023	0.608–1.721	0.93
Brain vol receiving ≥12 Gy (cm ³)	≥30 vs <30	0.619	0.334–1.145	0.13
Original tumor status	Non- vs well-controlled	1.518	0.869–2.651	0.14
Original tumor	SCLC vs breast	0.978	0.330–2.895	0.97
	SCLC vs GI	1.252	0.503–3.115	0.63
	SCLC vs kidney	0.551	0.141–2.151	0.39
	SCLC vs NSCLC	0.584	0.254–1.342	0.21
	SCLC vs others	0.305	0.072–1.296	0.11
Extracerebral metastases	Yes vs no	2.640	1.424–4.895	0.0021
GI	≥3.1 vs <3.1	0.719	0.447–1.156	0.17
CI	≥0.65 vs <0.65	0.474	0.276–0.814	0.0068

Based on 718 patients; i.e., 207 patients were excluded because neuroimaging results were not available.

* Categorized according to Yamamoto and colleagues.^{21,23}

our patients, mainly because of rapid worsening of their general condition, eventually resulting in death with a relatively short survival period after SRS (median survival time was 2.7 months in this group). The third weakness is that all patients with mild and/or transient complications probably were not included because most of the patients in our cohort were managed by physicians in other hospitals, such that less serious complications probably were not reported to us. Therefore, our complication incidence was lower than those reported by Sneed et al. and by Williams et al.^{14,17} In their reported series, convulsive seizures were counted. However, convulsive seizure is regarded as one of the major symptoms caused by a BM itself. Thus, we did not count convulsive seizures as SRS-related complications. However, we are highly confident that relatively severe complications were reported to us. Thus, we assessed patients with RTOG Neurotoxicity grade 2 or worse in this study. As mentioned above, this criterion has reportedly remained consistent for many years and is widely accepted, as documented in our previous publications.^{6,16,18–20,22,24} The fourth weakness of our study is that data on systemic anticancer agent treatments were insufficient because, as mentioned above, systemic cancers were managed by referring physicians who worked at different facilities. Therefore, we could not survey whether systemic anticancer agent therapy had been administered or any potential effects of such treatments, which probably means that the results reported herein do not adhere

to the modern strategies for management of patients with BM, particularly those with non-small cell lung cancer (NSCLC).

Our results are strictly applicable only to patients with a single BM irradiated by SRS. As the next step in the process of evaluating the utility of the GI, we hope to develop a novel method by which the GI can be correctly calculated even in patients with multiple intracranial lesions. As is well known, the present method for GI calculation is applicable only to patients with a single target in the cranium. At present, we have no method of calculating the GI in patients with multiple intracranial lesions.

Conclusions

We believe this to be the first analysis focusing on the clinical significance of CI and GI based on a large series of patients with BM. Contrary to the majority opinion that dose planning with a higher CI and a lower GI produces good post-SRS outcomes (i.e., low local progression and minimal complications), this study clearly demonstrated that lower CIs are associated with lower local progression rates and that GI has no impact on complication rates.

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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: M Yamamoto, Ishikawa. Acquisition of data: Aiyama, Kawabe, Watanabe, Koiso. Analysis and interpretation of data: Aiyama. Drafting the article: Aiyama. Critically revising the article: M Yamamoto, Aiyama, Kawabe, Watanabe, Koiso, Ishikawa, Matsumura, Kasuya. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: M Yamamoto. Statistical analysis: Sato, Higuchi. Administrative/technical/material support: Matsumura, Kasuya. Study supervision: M Yamamoto, Ishikawa, T Yamamoto, Matsumura, Kasuya.

Supplemental Information

Previous Presentations

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