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Clinical Investigation

A Multi-institutional Prospective Observational Study of Stereotactic Radiosurgery for Patients With Multiple Brain Metastases (JLGK0901 Study Update): Irradiation-related Complications and Long-term Maintenance of Mini-Mental State Examination Scores

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Summary

We continued observing our JLGK0901 study (Lancet

Purpose: The JLGK0901 study showed the noninferiority of stereotactic radiosurgery (SRS) alone as initial treatment of 5 to 10 brain metastases (BMs) compared with 2 to 4 BMs in terms of overall survival and most secondary endpoints (Lancet Oncol

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Oncol 2014;15:387-95) patients, focusing on mini-mental state examination (MMSE) results and complications, for two additional years to confirm the long-term safety of stereotactic radiosurgery (SRS) in those with 5-10 brain metastases. Neither MMSE maintenance nor post-SRS complication incidences differed among groups with 1, 2-4 and 5-10 tumors. We conclude that the already-reported non-inferiority hypothesis of SRS alone for patients with 5-10 versus 2-4 tumors gains further support.

2014;15:387-95). However, observation periods were not long enough to allow confirmation of the long-term safety of SRS alone in patients with 5 to 10 BMs.

Methods and Materials: This was a prospective observational study of Gamma Knife SRS-treated patients with 1 to 10 newly diagnosed BMs enrolled at 23 facilities between March 1, 2009, and February 15, 2012.

Results: The 1194 eligible patients were categorized into the following groups: group A, 1 tumor (n=455); group B, 2 to 4 tumors (n=531); and group C, 5 to 10 tumors (n=208). Cumulative rates of Mini-Mental State Examination (MMSE) score maintenance (MMSE score decrease <3 from baseline) determined with a competing risk analysis of groups A, B, and C were 93%, 91%, and 92%, respectively, at the 12th month after SRS; 91%, 89%, and 91%, respectively, at the 24th month; 89%, 88%, and 89%, respectively, at the 36th month; and 87%, 86%, and 89%, respectively, at the 48th month (hazard ratio [HR] of group A vs group B, 0.719; 95% confidence interval [CI], 0.437-1.172; $P=.18$; HR of group B vs group C, 1.280; 95% CI, 0.696-2.508; $P=.43$). During observations ranging from 0.3 to 67.5 months (median, 12.0 months; interquartile range, 5.8-26.5 months), as of December 2014, 145 patients (12.1%) had SRS-induced complications. Cumulative complication incidences by competing risk analysis for groups A, B, and C were 7%, 8%, and 6%, respectively, at the 12th month after SRS; 10%, 11%, and 11%, respectively, at the 24th month; 11%, 11%, and 12%, respectively, at the 36th month; and 12%, 12%, and 13%, respectively, at the 48th month (HR of group A vs group B, 0.850; 95% CI, 0.592-1.220; $P=.38$; HR of group B vs group C, 1.052; 95% CI, 0.666-1.662, $P=.83$). Leukoencephalopathy occurred in 12 of the 1074 patients (1.1%) with follow-up magnetic resonance imaging and was detected after salvage whole-brain radiation therapy in 11 of these 12 patients. In these 11 patients, leukoencephalopathy was detected by magnetic resonance imaging 5.2 to 21.2 months (median, 11.0 months; interquartile range, 7.0-14.4 months) after whole-brain radiation therapy.

Conclusions: Neither MMSE score maintenance nor post-SRS complication incidence differed among groups A, B, and C. This longer-term follow-up study further supports the already-reported noninferiority hypothesis of SRS alone for patients with 5 to 10 BMs versus 2 to 4 BMs.

Introduction

Our recently reported prospective observational investigation of 1194 brain metastasis (BM) patients clearly demonstrated stereotactic radiosurgery (SRS) using a Gamma Knife (Elekta, Stockholm, Sweden) without whole-brain radiation therapy (WBRT) as initial treatment of 5 to 10 BMs to be noninferior to that of 2 to 4 BMs in terms of overall survival (OS) (1). The post-SRS median survival time was 10.8 months in both groups (2-4 tumors vs 5-10 tumors; hazard ratio [HR], 0.974; 95% confidence interval [CI], 0.806-1.177 [less than noninferiority margin]; $P=.78$ [noninferiority test, $P<.0001$]). Furthermore, neither crude nor cumulative incidences of neurologic death, deterioration of neurologic function, local recurrence, new lesion appearance, leukoencephalopathy, and salvage treatment (repeat SRS and WBRT) differed significantly between the 2 groups. There were no significant differences in crude incidences of decreased Mini-Mental State Examination (MMSE) scores or treatment-related adverse events. However, a weakness of our prior study was that observation periods, ranging from 0.3 to 42.9 months (median, 10.7 months; interquartile range [IQR], 5.8-18.8 months), were insufficient for confirming the long-term safety of SRS alone for 5 to 10 BMs. Therefore, we continued observing these patients, focusing mainly on MMSE score maintenance and complications, for 2 additional years until the end of 2014. We reappraised whether Gamma Knife SRS alone for 5 to 10 BMs is safe in the long term, as compared with that for 2 to 4 BMs, and even that for 1 BM, as well as reported WBRT results, because preserving neurocognitive function (NCF) and quality of life while controlling BMs is essential for end-of-life care.

Methods and Materials

This prospective observational study involved 1194 patients who were enrolled at 23 Gamma Knife facilities in Japan; a randomized technique was not used. Patients provided written informed consent prior to enrollment, and the institutional review board of each facility had already approved all aspects of this study. Before patient recruitment began, this study was registered with the University Medical Information Network Clinical Trial Registry (http://www.umin.ac.jp/ctr/index.htm, ID; 000001812). The study protocol was described in our previous publications (2, 3).

The eligibility criteria, SRS techniques, follow-up protocol and evaluation items, clinical outcomes, and study management were described previously (1, 2, 3) and are not

repeated in this article. In brief, all patients were categorized into groups A, B, and C with 1 tumor, 2 to 4 tumors, and 5 to 10 tumors, respectively. For NCF assessment, the MMSE was used (fourth and 12th months after SRS and at 12-month intervals thereafter). MMSE maintenance was defined as score decrease <3 from baseline. SRS-induced complications were graded by use of the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (4). Of the secondary endpoints, crude and cumulative incidences of leukoencephalopathy were reanalyzed. However, our study protocol did not include a grading system for leukoencephalopathy. The criteria for each endpoint regarding complications and leukoencephalopathy are detailed in our previous reports (1, 2, 3).

Statistical analysis

Issues regarding statistical analysis were also detailed in our previous article (1) and are not repeated in this report. In brief, the endpoint analyses used the Cox proportional hazards model with prognostic factors serving as covariates. For the aforementioned endpoint analyses of time-to-event outcomes, competing risk analysis was performed with the Fine-Gray generalization of the proportional hazards model accounting for death as a competing risk (5, 6). Death is a competing risk for loss to follow-up. Therefore, patients who die can no longer become lost to follow-up. Competing risks are defined as events that prevent the outcome of interest from occurring. The standard Kaplan-Meier method assumes that the follow-up of those patients in whom a competing event develops is simply censored. However, this assumption is invalid because the outcome of interest can no longer occur in those in whom the competing event develops, and such analyses will therefore overestimate the probability of the outcome of interest. Because considerable subsets of patients lacked MMSE follow-up data, we applied 4 different methods to assess the MMSE data: (*1*) complete-case analysis; (*2*) last observation carried forward (LOCF); (*3*) worst observation carried forward; and (*4*) mixed-effects model for repeated-measures analysis for sensitivity analyses.

All statistical analyses were performed by a statistician (Y.S.) not involved in either SRS treatment or patient follow-up, using SAS software (version 9.4; SAS Institute, Cary, NC) and the R statistical program (version 3.1.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

As described in our previous article, we recruited 1194 eligible patients for this study from March 1, 2009, through February 15, 2012 (1). Additional follow-up was continued through December 31, 2014, and the database was finalized on January 12, 2015. During the same period, 12 additional cases were enrolled but not included. In 2 of these 12 patients, pathology was verified to be glioblastoma after enrollment, necessitating exclusion as these were not BM cases. The other 10 patients withdrew and, therefore, could not be included in the analysis. Clinical characteristics overall and for the 3 tumor number groups are presented in Table 1 of our previous article (1).

The median post-SRS follow-up time among censored observations (155 patients) was 46.3 months (range, 30.4-67.5 months; IQR, 38.6-54.4 months), and 1039 patients (87.0%) were confirmed to be deceased. The median survival time determined after SRS by the Kaplan-Meier method was 12.0 months (95% CI, 10.9-13.0 months). Actuarial post-SRS survival rates were 50%, 27%, 19%, 12%, and 10% at the 12th, 24th, 36th, 48th, and 60th month after SRS, respectively. Among the 1039 deceased patients, the cause of death was confirmed to be non-brain disease in 942 (91%) and brain disease in 97 (9%).

Preservation of MMSE scores

Of the 1132 patients undergoing the pre-SRS MMSE (95%; mean, 27; median, 28; minimum, 7), the score was 27 or better in 750 (66%) and 26 or worse in 382 (34%). In the other 62 patients, the MMSE was not performed because of dysphasia, difficulty writing, and so on. The MMSE was performed in 66% (657 of 1003), 62% (366 of 597), 57% (185 of 326), 50% (100 of 199), and 49% of surviving patients (38 of 77) at the fourth, 12th, 24th, 36th, and 48th month after SRS, respectively. One-third to approximately one-half of patients (34%-51%) lacked MMSE follow-up data because these patients were managed outside of the investigators' facilities (eg, hospice care). As shown in Table 1, proportions with better MMSE scores (≥27) did not differ significantly among groups A, B, and C at the fourth, 12th, 24th, 36th, and 48th month after SRS. In addition, the MMSE score was maintained (score decrease <3) in 91% overall and in 92%, 91%, and 89% of groups A, B, and C, respectively, at the 12th month after SRS ($P = .84$ for group A vs group B, $P = .69$ for group B vs group C, and $P = .44$ for group A vs group C). The results were very similar at the 24th, 36th, and 48th month after SRS. Because considerable patient subsets lacked MMSE follow-up data, for sensitivity analyses, we applied the 4 aforementioned methods to assess the MMSE data (Table 2). With these 4 methods, mean MMSE scores at baseline and at the fourth, 12th, 24th, 36th, and 48th month after SRS differed minimally among the 3 tumor number groups.

As shown in Figure 1A, cumulative rates of MMSE score maintenance were 91.8%, 89.9%, 88.3%, 86.8%, and 86.2% at the 12th, 24th, 36th, 48th, and 60th post-SRS months, respectively. Cumulative rates of MMSE score maintenance determined by competing risk analysis did not differ between groups B and C (HR, 1.280; 95% CI, 0.696-2.508; $P = .43$) or between groups A and B (HR, 0.719; 95% CI, 0.437-1.172; $P = .18$), as shown in Figure 1B. Among various factors potentially reducing rates of MMSE score maintenance, univariate analyses showed that none contributed significantly to unfavorable outcomes.

Table 1 Treatment outcomes after stereotactic radiosurgery

Category	Total (N=1194)	Group A: 1 tumor (n=455)	Group B: 2-4 tumors (n=531)	Group C: 5-10 tumors (n=208)	*P* value: group B vs group C
Had MMSE score at baseline	1134 (95%)	430 (95%)	506 (95%)	198 (95%)	
Score ≥27					
Baseline	750 (66%)	279 (65%)	339 (67%)	132 (67%)	.78
4 mo	517 (78%)	196 (76%)	219 (77%)	102 (84%)	.26
12 mo	305 (79%)	127 (80%)	129 (83%)	49 (71%)	.13
24 mo	164 (87%)	73 (90%)	61 (84%)	30 (88%)	.47
36 mo	88 (88%)	43 (90%)	31 (81%)	14 (88%)	.92
48 mo	34 (89%)	17 (89%)	14 (87%)	3 (100%)	>.99
Maintained NCF					
4 mo	620 (94%)	243 (95%)	260 (93%)	117 (96%)	.39
12 mo	334 (91%)	141 (92%)	137 (91%)	56 (89%)	.69
24 mo	170 (92%)	71 (90%)	69 (96%)	30 (88%)	.25
36 mo	94 (94%)	45 (94%)	33 (92%)	16 (100%)	.75
48 mo	34 (89%)	18 (95%)	13 (81%)	3 (100%)	.51
Original tumor site					
Lung (n=511)	444 (87%)	177 (88%)	180 (86%)	87 (87%)	>.99
Breast (n=74)	66 (89%)	20 (87%)	32 (86%)	14 (100%)	.31
GI tract (n=40)	38 (95%)	18 (95%)	17 (94%)	3 (100%)	>.99
Kidney (n=19)	17 (89%)	8 (100%)	9 (82%)	0	
Others (n=16)	16 (100%)	4 (100%)	7 (100%)	5 (100%)	>.99
Treatment-related complications					
None	1049 (88%)	399 (88%)	468 (88%)	182 (87.5%)	.80
Yes	145 (12%)	56 (12%)	63 (12%)	26 (12.5%)	
CTCAE grade 1	46 (4%)	18 (4%)	21 (4%)	7 (4%)	
CTCAE grade 2	54 (5%)	21 (5%)	22 (4%)	11 (5%)	
CTCAE grade 3	29 (2%)	9 (2%)	15 (3%)	5 (2%)	
CTCAE grade 4	11 (1%)	5 (1%)	4 (1%)	2 (1%)	
CTCAE grade 5	5 (0.4%)	3 (0.7%)	1 (0.2%)	1 (0.5%)	
Original tumor site					
Lung (n=912)	97 (11%)	39 (11%)	39 (10%)	19 (12%)	.54
Breast (n=123)	18 (15%)	6 (14%)	9 (16%)	3 (13%)	>.99
GI tract (n=85)	18 (21%)	7 (20%)	10 (24%)	1 (11%)	.66
Kidney (n=36)	6 (17%)	3 (20%)	3 (16%)	0	
Others (n=38)	6 (16%)	1 (7%)	2 (14%)	3 (33%)	.34
Leukoencephalopathy*	12 (1%)	4 (1%)	6 (1%)	2 (1%)	.80

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; MMSE = Mini-Mental State Examination; NCF = neurocognitive function.

* Based on 1071 patients (90%) (413 in group A [91%], 472 in group B [89%], and 186 in group C [89%]; $P=.90$) because magnetic resonance imaging results were not available owing to early death or remarkable deterioration of the clinical state soon after stereotactic radiosurgery in the other 123 patients (10%).

After the exclusion of 2 of the original tumor categories (kidney and others) because of small patient numbers, crude rates of MMSE score maintenance did not differ significantly between groups B and C for any of the 3 original tumor categories, that is, lung ($P>.99$), breast ($P=.31$), and gastrointestinal tract ($P>.99$).

SRS-induced complications

SRS-induced complications occurred in 145 patients (12%): 46, 54, 29, 11, and 5 with CTCAE (version 3.0) grades 1, 2, 3, 4, and 5, respectively, including 30 asymptomatic cases receiving steroid treatment based on magnetic resonance imaging (MRI) findings of radiation injury. As shown in Table 1, there were no significant differences in crude incidences of SRS-induced complications: 56 patients in group A (12%), 63 in group B (12%) and 26 in group C (12.5%) ($P=.85$ for group A vs group B, $P=.80$ for group B vs group C, and $P>.99$ for group A vs group C). In addition, distributions of CTCAE grades were very similar among the 3 groups (Table 1). After the exclusion of 2 of the original tumor categories (kidney and others) because of small patient numbers, crude incidences of complications did not differ significantly between groups B and C for the lung category ($P=.54$), breast category ($P>.99$), or gastrointestinal tract category ($P=.66$). Cumulative incidences of SRS-induced complications were almost the same in these 3 groups (A, B, and C) (HR of group A vs group B, 0.850; 95% CI, 0.592-1.220; $P=.38$;

Table 2 Sensitivity analyses of missing data for Mini-Mental State Examination scores

		Complete-case analysis				Last observation carried forward				Worst observation carried forward			MMRM		
Period	Group	n	Mean	SD	*P* value	n	Mean	SD	*P* value	Mean	SD	*P* value	LS mean	SE	*P* value
Baseline	Group A	430	27.0	3.6	.43	430	27.0	3.6	.43	27.0	3.6	.43	27.0	0.2	.22
	Group B	506	27.1	3.0	Ref	506	27.1	3.0	Ref	27.1	3.0	Ref	27.1	0.1	Ref
	Group C	198	26.9	3.6	.42	198	26.9	3.6	.42	26.9	3.6	.42	26.9	0.3	.16
4 mo after SRS	Group A	256	28.0	2.9	.36	433	27.4	3.4	.59	27.4	3.4	.39	27.8	0.2	.28
	Group B	284	27.9	2.7	Ref	511	27.5	2.9	Ref	27.4	3.0	Ref	27.8	0.2	Ref
	Group C	122	28.3	2.7	.47	199	27.4	3.5	.95	27.4	3.6	.86	27.9	0.2	.48
12 mo after SRS	Group A	159	28.4	2.5	.40	436	27.4	3.4	.59	27.1	3.6	.16	27.8	0.2	.5
	Group B	156	28.2	2.9	Ref	516	27.4	3.2	Ref	27.0	3.3	Ref	27.6	0.2	Ref
	Group C	69	27.3	3.9	.021	201	27.2	3.8	.56	26.9	3.7	.39	27.2	0.4	.027
24 mo after SRS	Group A	77	28.7	2.2	.13	436	27.4	3.4	.55	26.8	3.6	.35	27.9	0.2	.43
	Group B	73	28.5	2.1	Ref	516	27.4	3.2	Ref	26.8	3.3	Ref	27.7	0.2	Ref
	Group C	34	28.4	2.2	.12	201	27.2	3.8	.58	26.7	3.8	.7	27.6	0.4	.11
36 mo after SRS	Group A	47	29.2	1.5	.52	436	27.4	3.4	.37	26.7	3.6	.21	28.2	0.3	NA
	Group B	36	28.7	2.5	Ref	516	27.3	3.2	Ref	26.7	3.3	Ref	27.7	0.2	Ref
	Group C	15	29.3	1.6	.64	201	27.2	3.8	.62	26.6	3.8	.64	28.3	0.3	NA
48 mo after SRS	Group A	19	29.2	2.1	.077	436	27.4	3.4	.26	26.6	3.6	.44	28.7	0.4	NA
	Group B	16	28.1	3.5	Ref	516	27.3	3.2	Ref	26.6	3.3	Ref	28.2	0.6	Ref
	Group C	2	29.0	1.4	.45	201	27.2	3.8	.56	26.4	3.8	.61	29.3	0.4	NA

Abbreviations: LS = least square; MMRM = mixed-effects model for repeated measures; Ref = reference category; SE = standard error; SRS = stereotactic radiosurgery.

HR of group B vs group C, 1.052; 95% CI, 0.666-1.662; $P = .83$) (Fig. 2A). Five patients died mainly of complications: 3 in group A and 1 each in groups B and C. Two had tumor bleeding (1.2 and 14.8 months after SRS), one had expansion of SRS-induced necrosis (6.3 months after SRS), and the other two had status epilepticus (16.6 and 17.4 months after SRS). Symptomatic complications occurred in 86 of the 145 patients (59%). The most common symptom was motor dysfunction (43 patients, 30%), followed by seizure (14, 10%), decreased NCF (9, 6%), disturbed consciousness (6, 4%), cerebellar ataxia (6, 4%), speech disturbance (5, 3%), visual field defect (4, 3%), and others (6, 4%). MRI findings of complications in 140 patients (97%) were localized intensity changes of the normal brain surrounding the SRS-irradiated lesions (121 patients, 86%), leukoencephalopathy (11, 8%), bleeding (8, 6%), and cyst formation (3, 2%). Among the 121 patients with intensity changes, steroid treatment was required in 90 (74%) and surgical intervention in 7 (6%). Treatment outcomes for complications were reported for 120 patients (83%), with improvement in 33, no changes in 77, and deterioration in 10 (death in 5, as described earlier).

Applying multivariate analyses to all factors found to be statistically significant on univariate analyses (age, Karnofsky Performance Status, tumor size and volume, primary tumor, neurologic symptoms, peripheral dose, and skull volume receiving >5 Gy) revealed age <65 years (HR, 1.455; 95% CI, 1.045-2.035; $P = .027$), large tumor (maximum diameter of largest tumor ≥1.6 cm; HR, 0.375; 95% CI, 0.217-0.667; $P = .0011$), and neurologic symptoms (HR, 0.413; 95% CI, 0.279-0.614; $P < .0001$) to be significantly unfavorable in terms of complications (Table 3).

Leukoencephalopathy, detectable by MRI, occurred in 12 of the 1074 patients (1.1%) with follow-up MRI. This complication was detected after salvage WBRT in 11 of these 12 patients. In these 11 patients, leukoencephalopathy was detected by MRI 5.2 to 21.2 months (median, 11.0 months; IQR, 7.0-14.4 months) after WBRT. Follow-up MMSE scores were available in 8 of the 12 patients. MMSE scores decreased in 2 of these 8 patients (25%). As shown in Table 1 and Figure 2B, there were no significant differences in either crude or cumulative incidences of leukoencephalopathy among the group A, group B, and group C patients.

Discussion

Incidences of MMSE score deterioration and SRS-related complications were reconfirmed to be acceptably low overall and to be very similar in group A, group B, and group C patients with an additional 2-year follow-up period; that is, the median observation time among censored observations was 46.3 months (range, 30.4-67.5 months; IQR, 38.6-54.4 months) in the current report, while that in our previous report was 20.9 months (range, 7.1-42.9 months; IQR, 12.6-29.5 months) (1). Even though the observation period was nearly 2 years longer in the surviving patients, as compared with our original publication (1), complications occurred in only 44 additional patients; that is, the crude incidence increased by just 3.7%. In addition, as shown in Figure 2A, the cumulative incidence curves for complications had low slopes at the 24th post-SRS month and thereafter in all 3 groups.

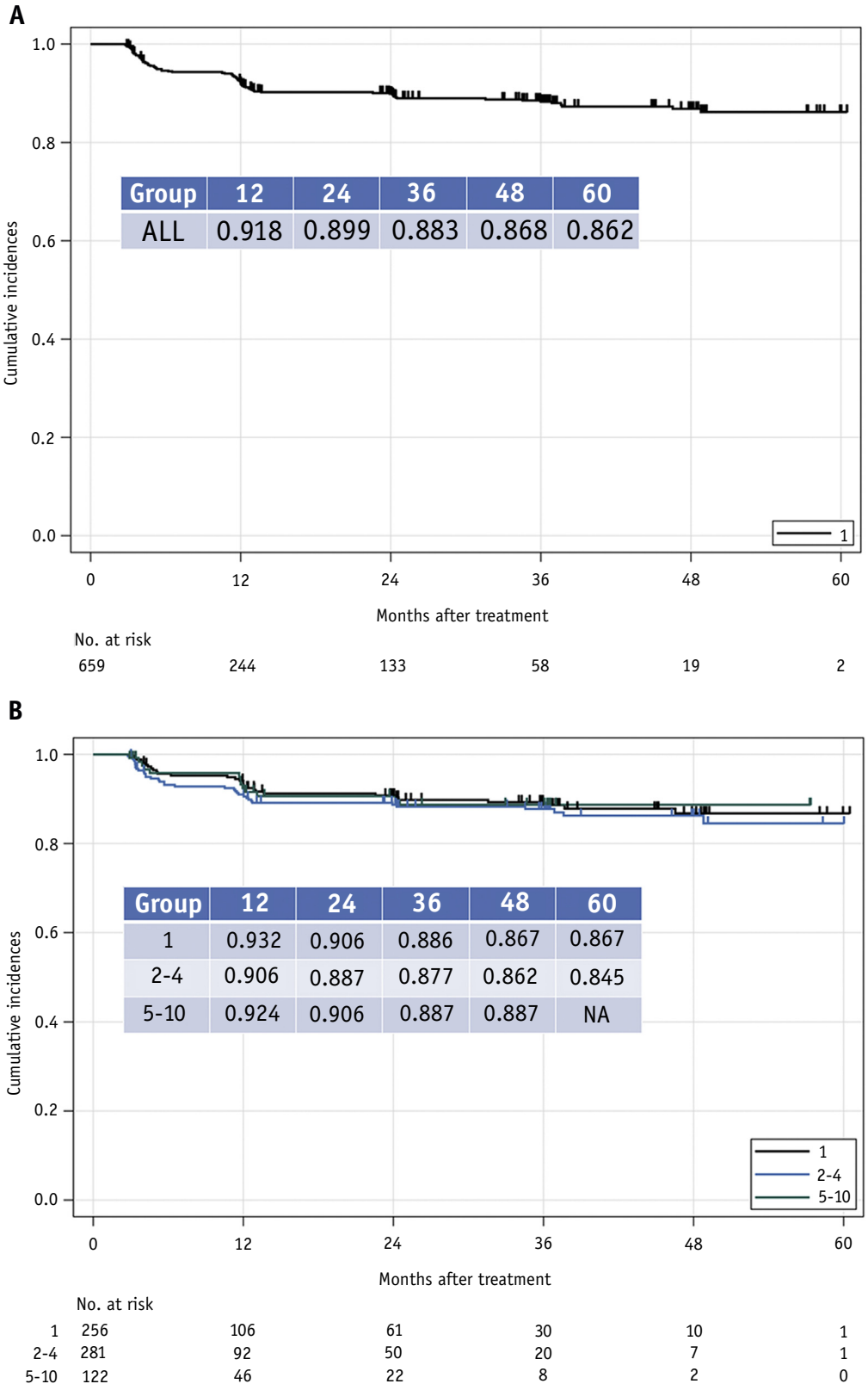

Fig. 1. Cumulative incidences of maintained Mini-Mental State Examination scores after stereotactic radiosurgery overall (A) and for the 3 tumor number groups: group A (1 tumor), group B (2-4 tumors), and group C (5-10 tumors) (B).

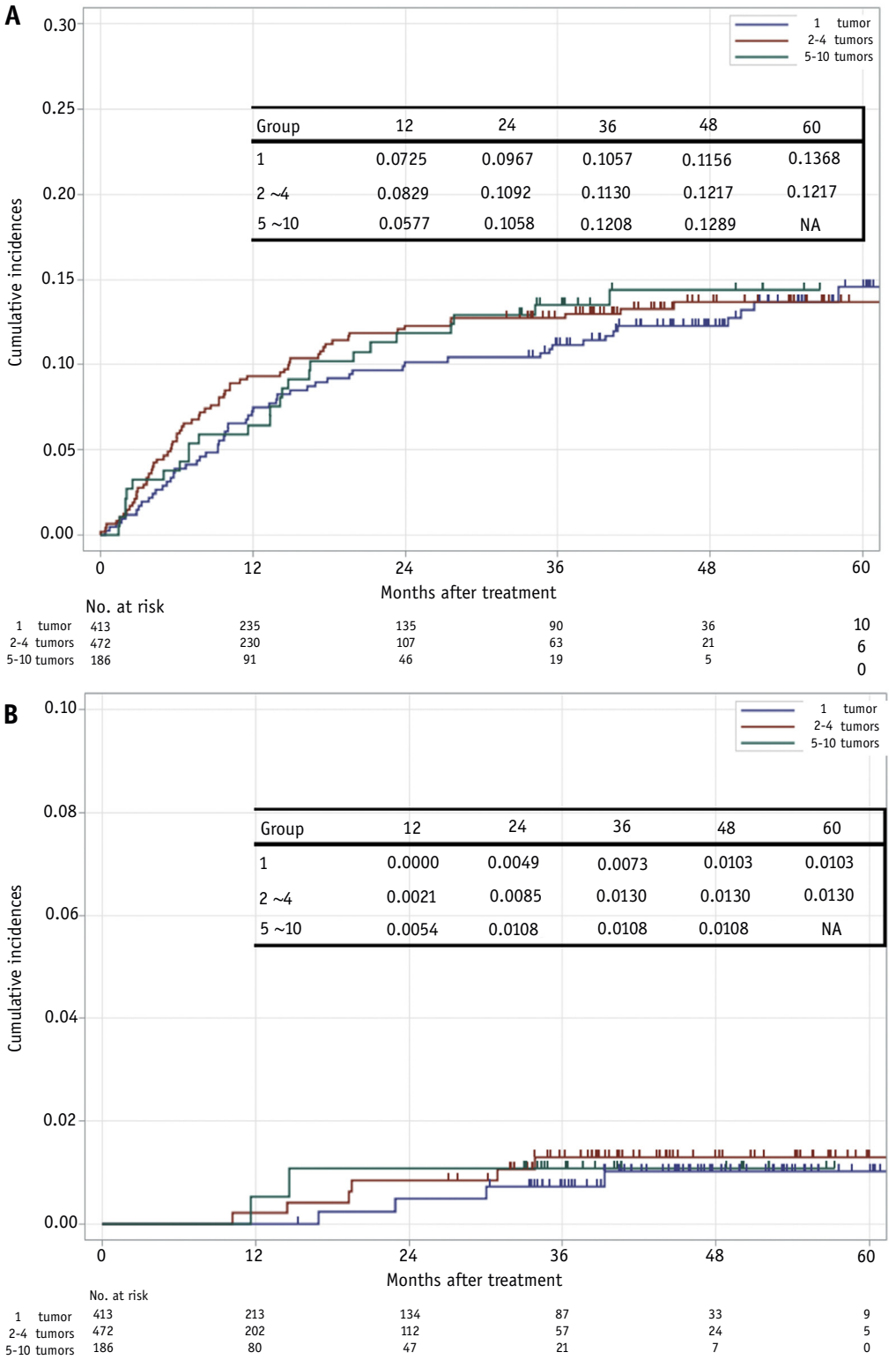

Fig. 2. Cumulative incidences of irradiation-related complications (A) and leukoencephalopathy (B) after stereotactic radiosurgery for the 3 tumor number groups: group A (1 tumor), group B (2-4 tumors), and group C (5-10 tumors). The leukoencephalopathy data are based on 1071 patients (90%) (413 in group A [91%], 472 in group B [89%], and 186 in group C [89%]; $P = .90$) because magnetic resonance imaging results were not available owing to early death or remarkable deterioration of the clinical state soon after stereotactic radiosurgery in the other 123 patients (10%).

Table 3 Clinical factors affecting posttreatment complications

Factor	Univariate		Multivariate	
	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age: <65 y vs ≥65 y	1.432 (1.032-1.995)	.032	1.455 (1.045-2.035)	.027
Sex: female vs male	1.086 (0.782-1.506)	.62		
KPS: ≤70 vs ≥80	2.134 (1.353-3.339)	.0019	1.065 (0.641-1.710)	.80
Tumor number				
2-4 (group B) vs 1 (group A)	1.186 (0.827-1.706)	.35		
5-10 (group C) vs 2-4 (group B)	1.072 (0.667-1.973)	.77		
Maximum diameter of largest tumor: <1.6 cm vs ≥1.6 cm	0.326 (0.226-0.462)	<.0001	0.375 (0.217-0.667)	.0011
Cumulative volume: <1.9 mL vs ≥1.9 mL	0.442 (0.317-0.614)	<.0001	1.748 (0.988-2.961)	.055
Primary tumor category: lung vs non-lung	0.564 (0.401-0.803)	.0017	0.831 (0.583-1.199)	.32
Extracerebral disease status: not vs controlled	0.945 (0.644-1.356)	.76		
Neurologic symptoms: no vs yes	0.288 (0.207-0.402)	<.0001	0.413 (0.279-0.614)	<.0001
Peripheral dose maximum: <22 Gy vs ≥22 Gy	1.712 (1.216-2.389)	.0023	1.232 (0.860-1.752)	.25
Global maximum dose: <40 Gy vs ≥40 Gy	1.015 (0.721-1.416)	.93		
Skull volume receiving >5 Gy: <31 mL vs ≥31 mL	0.424 (0.299-0.594)	<.0001	0.798 (0.488-1.305)	.37
Systemic anticancer agent treatment: no vs yes	1.132 (0.746-1.666)	.55		

Abbreviations: CI = confidence interval; HR = hazard ratio; KPS = Karnofsky Performance Status.

We chose the MMSE according to the report by Aoyama et al (7). At the time of designing this study in late 2008, in the field of radiation therapy for BM patients, the MMSE was the only test battery used in high-quality journals (7). The Hopkins Verbal Learning Test—Revised (HVLT-R) (PAR, Lutz, FL) and other alternatives had not yet come into widespread clinical use. At present, debate continues as to whether NCF can be correctly evaluated with the MMSE as compared with the HVLT-R or other assessment tools. Even though the measurement system used in our study is not highly scientific as compared with contemporary tests and MMSE follow-up data were not available for all of our patients, this study is the first to show the MMSE score to be well maintained in 80% to 90% of patients for 3 to 4 years after SRS for multiple BMs (Table 1, Fig. 1). Although the HVLT-R or other assessment tools might yield more meaningful data, the observation periods have not as yet exceeded 2 years after treatment in recently published articles in which post-WBRT NCF changes were evaluated using the HVLT-R. In the prospective randomized study conducted by Chang et al (8) at 4 months, total recall and HVLT-R delayed recognition were worse in patients who underwent SRS plus WBRT than in those receiving SRS alone (52% vs 24% and 22% vs 6%, respectively). Sun et al (9) reported that, on the basis of their prospective randomized study, at 6 and 12 months, the incidence of cognitive function decreases was higher in the prophylactic cranial irradiation group (35% and 41%, respectively) than in the observation group (18% and 25%, respectively). In addition, Soffietti et al (10) concluded that, on the basis of their prospective randomized study, adjuvant WBRT after surgery or radiosurgery for 1 to 3 BMs might negatively affect some aspects of health-related quality of life.

Aoyama et al (11) reported the 36-month actuarial rates of MMSE score decrease to be 85% in the SRS-plus-WBRT group and 48% in the SRS-alone group. These rates differed markedly between their results and ours (Fig. 1). However, we should note that the rates of Aoyama et al were probably overestimates because only the standard Kaplan-Meier method was used. We consider competing risk analysis to be necessary for re-evaluation of their data. While WBRT-induced NCF decline is largely untreatable and irreversible, declines developing after SRS can be caused by new BMs, local recurrence, or complications and are thus mostly treatable and generally reversible. Although considerable subsets of patients lacked MMSE follow-up data, the 3 analyses designed for dealing with missing data (LOCF, worst observation carried forward, and mixed-effects model for repeated measures) yielded results similar to those of the complete-case analysis, indicating that the missing data minimally influenced our results. Therefore, we assume our findings to be robust. However, as noted previously, in the case of not-missing-at-random data, these inferential techniques applicable to missing-at-random data typically lose validity (1). Nevertheless, the major weakness of MMSE score decreases, in both the study by Aoyama et al and our study, is that the sample sizes become very small in the later periods, that is, ≥36 months after treatment. Therefore, statistical power was clearly insufficient to allow comparisons of MMSE score decreases among our 3 groups.

A major criticism of SRS-alone treatment as compared with SRS plus WBRT is that a prophylactic effect against potential newly developing tumors cannot be expected because of the highly focused irradiation applied. WBRT is generally considered to prevent the appearance of microscopic tumors. However, Chao et al (12) showed that new tumors developed in 45% of patients >6 months after WBRT. As described in our original publication (1), the cumulative incidences of new BMs after SRS-alone treatment—that is, 24%, 40%, and 46% (1 BM, 2-4 BMs, and 5-10 BMs, respectively) at the sixth post-SRS month—are very similar

to the results of Chao et al. Aoyama et al (7) reported that, in their randomized controlled study of patients undergoing treatment of 1 to 4 BMs, the 12-month actuarial rate of new BM development was 41% in the group receiving WBRT plus SRS. As described earlier (1), the cumulative incidences of new BMs after SRS-alone treatment of 37% and 55% (1 BM and 2-4 BMs, respectively) at the 12th post-SRS month did not differ markedly from the rate reported by Aoyama et al, 41%. Therefore, WBRT is considered to prevent new BM appearance in a limited number of BM patients. Furthermore, it should be noted that WBRT can rarely be repeated for patients with meningeal dissemination or numerous BMs not treatable by SRS.

Varlotto et al (13) reported that, among 137 BM patients who survived for at least 1 year after Gamma Knife SRS, post-radiosurgical sequelae had developed in 11.4% by the fifth post-SRS year. Our cumulative incidences of complications of 12% at the fifth post-SRS year, 12% at the fifth post-SRS year, and 13% at the fourth post-SRS year (data at the fourth post-SRS year are given for group C because fifth-year data were not available) in groups A, B, and C, respectively, were very similar to theirs. Yamamoto and colleagues (14) found that, on the basis of 167 BM patients who survived for at least 3 years after Gamma Knife SRS, the actuarial incidence of delayed complications estimated by competing risk analysis was 4.2% at the 60th month after SRS, very low as compared with the incidences reported in our study, 12% to 13%. However, their crude incidence, 10%, was very similar to ours, 12% overall, as well as to incidences in each of our 3 groups. Williams et al (15) reported incidences of post-SRS complications and their predictive factors by comprehensively reviewing 273 patients undergoing linear accelerator (linac)—based SRS for 1 to 2 BMs and noted complications, usually seizures, to be associated with 127 of 316 treated lesions (40%). The second possible weakness of our study is that all patients with minor complications, such as seizures, might not have been surveyed comprehensively. If severe problems, not only symptomatic but also those apparent only on MRI, occurred in SRS-treated patients, every physician, without exception, consulted the investigators. Because a seizure can be caused by a brain tumor itself, most physicians did not consider seizures to be SRS related. Several authors have shown correlations of tumor volume and/or WBRT with complications (13-16). In this study, factors associated with complications were age <65 years, large tumor, and pretreatment neurologic symptoms.

The crude incidence of leukoencephalopathy was 1% (12 patients) (Table 1). Unfortunately, this complication could not be graded because our study protocol did not include a leukoencephalopathy grading system. This complication was detected after salvage WBRT in 11 of the 12 patients and after SRS alone in only 1. Monaco et al (17) recently reported that, on final MRI, leukoencephalopathy developed in 36 of 37 patients (97.3%) treated with WBRT whereas only 1 of 31 undergoing SRS alone had this complication. The cumulative incidences of leukoencephalopathy determined with competing risk analyses were 1% at the 36th and 48th month, and even at the 60th month, after SRS (Table 1). In contrast, the cumulative incidences of leukoencephalopathy after salvage WBRT were reportedly high. According to the recent report of Ebi et al (18), post-WBRT leukoencephalopathy incidences were 34% (11 of 32), 43% (6 of 14), 67% (2 of 3), and 100% (2 of 2) in patients followed up for $\geq$6, $\geq$12, $\geq$24, and $\geq$36 months, respectively.

According to a phase 3 randomized trial of WBRT in addition to SRS in patients with 1 to 3 tumors, recently presented by Brown et al (19), NCF decline, especially for immediate recall, memory, and verbal fluency, was more frequent with the addition of WBRT to SRS. They concluded that initial treatment with SRS and close monitoring should be recommended for patients with newly diagnosed BMs treatable with SRS. On the basis of our study results (1), a phase 3 randomized trial of WBRT versus SRS for 4 to 10 BMs is currently under way (ClinicalTrials.gov identifier NCT02353000, http://www.clinicaltrials.gov/). The results are anticipated to clarify the role of SRS without WBRT versus WBRT alone for 5 to 10 BMs. Nevertheless, at present, there is no evidence showing the superiority of WBRT to SRS alone for patients with 5 to 10 tumors.

It is important to note that all patients in this series were treated with single-fraction Gamma Knife radiosurgery. Confirmation of the safety and efficacy of this approach using alternative technology platforms (eg, single-isocenter linac techniques) and fractionation schemes (eg, 3- to 5-fraction schemes) remains to be demonstrated and would be desirable to make this approach more accessible across centers and less onerous for patients. In fact, Ma et al (20) reported that the volumes of normal brain receiving 4 and 12 Gy were higher for a linac-based SRS platform than with the Gamma Knife Perfexion (Elekta) in cases in which 3, 6, 9, and 12 tumors were irradiated. Although debate continues on this issue (21-23), our results reported in this article are applicable only to Gamma Knife SRS for multiple BMs.

Finally, according to the results of this longer-term follow-up study, approximately 20% of BM patients who met the JLGK0901 study criteria survived for >3 years after SRS. This means that longer-term NCF maintenance is absolutely crucial in treatment selection for BM patients.

Conclusions

This study has several weaknesses, that is, patient selection bias, observation bias, smaller sample sizes for subgroup investigations, and missing data. Nevertheless, neither the rates of decreased MMSE scores nor those of post-SRS complications differed among groups A, B, and C. The already-reported noninferiority hypothesis of SRS alone for patients with 5 to 10 BMs versus 2 to 4 BMs gains further support, in terms of treatment safety, from this longer-term follow-up study.

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