Gamma Knife Radiosurgery Results for Patients With 10-19 Versus ≥20 Brain Metastases: Retrospective Studies of 1482 Cohort and 936 Matched Patients (JLGK2107 Study)

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Abstract

Background and purpose

The role of stereotactic radiosurgery (SRS) for patients with ≥20 brain metastases (BMs) is not fully understood as yet. We compared SRS treatment results for ≥20 versus 10-19 BMs.

Materials and methods

This IRB-approved, retrospective cohort study used our prospectively accumulated database including 1482 patients (906 with 10-19 BMs, 576 with ≥20 BMs) treated with gamma knife SRS during a 20-year period (1998-2018).

Results

Because there was considerable bias in pre-SRS clinical factors between the two groups, a case-matched study was conducted and 936 (468 in each of the two groups) patients were selected for this study. The post-SRS median survival time in patients with ≥20 BMs, 5.9 (95% CI; 5.1-6.8) months, was the same as that in patients with 10-19 BMs, 5.9 (95% CI; 5.2-7.2) months. Crude and cumulative incidences of neurological death, neurological deterioration, local recurrence, repeat SRS, salvage whole brain radiotherapy and SRS-related complications, as determined by competing risk analyses, did not differ significantly between the two tumor number groups. Univariable analyses of these 1482 patients demonstrated female gender, Karnofsky Performance Status ≥80%, neurologically asymptomatic, synchronous presentation, controlled primary cancer and no extra-cerebral metastases to be factors significantly favoring longer survival in both the 10-19 and the ≥20 BM groups. To minimize the complication risk, either cumulative or the largest BM volume ≤10 mL and minimum dose ≤20.00 Gy should be taken in consideration when planning treatment.

Conclusions

We conclude that carefully-selected patients with ≥20 tumors are not unfavorable candidates for SRS alone.

Introduction

Until the middle of the second decade of the 21st century, whole brain radiotherapy (WBRT) was the standard treatment for patients with three or four, or even more, brain metastases (BMs). After we published our JLGK0901 study in which stereotactic radiosurgery (SRS) treatment results for patients with 5-10 BMs were shown to not be inferior to those for patients with 2-4 BMs [1], the tumor number barrier for SRS was eliminated from the major treatment guidelines currently in use, i.e., the National Comprehensive

Cancer Network Clinical Practice Guideline in Oncology (NCCN Guidelines), Central Nervous System Cancers, Version 2.2018, and the guideline of the Congress of Neurological Surgery (CNS) [2, 3]. Very recently, patients with 10, or even more BMs, some of whom actually had 20 or slightly more, have reportedly been treated with SRS [4–9].

The next questions are whether patients with 20 or more BMs can routinely be treated with SRS and which patients with ≥20 BMs are good candidates for SRS. Therefore, we conducted this retrospective cohort study, based on our SRS-treated cohort of 1482 BM patients with ≥10 BMs, 906 with 10-19 and 576 with ≥20 BMs, to reappraise whether treatment results were truly inferior for ≥20, as compared to 10-19, BMs. We also aimed to identify factors determining the inferiority and/or non-inferiority of this approach.

Methods

Patient Population

We carried out this retrospective cohort study employing our prospectively accumulated database comprised of 7355 consecutive patients who had undergone gamma knife (GK) SRS alone, without WBRT, for BMs during the 20-year-period spanning 1998 through 2018. Among the 7355 patients, 3558 were treated by the first author (MY) and the other 3797 by the second author (TS). Either the Institutional Review Board of Tokyo Women's Medical University (No. 1981) or that of the Tsukiji Neurological Clinic provided approval for this study (No. 2021-07). Of the 7355 patients, we selected a total of 1482 (20.2%) with ≥10 BMs (689 females, 793 males, median age; 65 [range; 25-91] years). Both pre-SRS clinical characteristics and radiosurgical parameters are presented in Table 1. The number of tumors was determined using thin slice magnetic resonance (MR) images with gadolinium enhancement at the time of SRS. As to primary cancers, the only patient with melanoma (0.1%) was included in the "Others" category.

Table 1
(Online only) Summary of clinical characteristics of 1482 patients with >10 brain metastases according to two tumor number groups*

		Cohort	Tumor number		
Characteristics			**10-19**	**≥20**	**p value**
No. of patients		1482	906	576	
Gender	Female	689 (46.5)	394 (43.5)	295 (51.2)	0.0039
	Male	793 (53.5)	512 (56.5)	281 (48.8)	
Age	<65 years	717 (48.4)	416 (45.9)	301 (52.3)	0.019
	≥65year	765 (51.6)	490 (54.1)	275 (47.7)	
Karnofsky performance status	≥80%	1106 (74.6)	684 (75.5)	422 (73.3)	0.36
	≤70%	376 (25.4)	222 (24.5)	154 (26.7)	
Modified-RPA class**	1+2a	101 (6.8)	64 (7.1)	37 (6.4)	0.0100
	2b	369 (24.9)	249 (27.5)	120 (20.8)	
	2c+3	1012 (68.3)	593 (65.5)	419 (72.7)	
Neurological symptoms	No	770 (52.0)	487 (53.8)	283 (49.1)	0.088
	Yes	712 (48.0)	419 (46.2)	293 (50.9)	
Presentation	Metachronous	1038 (70.0)	626 (69.1)	412 (71,5)	0.32
	Synchronous	444 (30.0)	280 (30.9)	164 (28.5)	
Primary cancer sites	Lung	1077 (72.7)	666 (73.5)	411 (71.4)	0.0047
	GI tract	69 (4.7)	53 (5.6)	16 (2.8)	
	Breast	222 (15.0)	114 (12.6)	108 (18.8)	
	Kidney	22 (1.5)	14 (1.6)	8 (1.4)	
	Others	92 (6.2)	59 (6.5)	33 (5.7)	
Primary cancer status	Controlled	389 (26.3)	247 (27.3)	142 (24.7)	0.28
	Not Controlled	1093 (73.7)	659 (72.7)	434 (75.3)	

RPA; Recursive Partitioning Analysis, GI, Gastro-intestinal, p Values; Fisher's exact test was used for pairs of categorical variables while Pearson p-value was used for Modified RPA and primary cancer sites.

*Values are presented as the number of patients (%) except for tumor numbers.

**Refers to the studies by Yamamoto et al.[11,14]

		Cohort	Tumor number		
Characteristics			**10-19**	**≥20**	**p value**
Extra-cerebral metastases	No	512 (34.6)	338 (37.3)	174 (30.2)	0.0051
	Yes	970 (65.4)	568 (62.7)	402 (69.8)	
Prior surgery	No	1311 (88.5)	789 (87.1)	522 (90.6)	0.054
	Yes	171 (11.5)	117 (12.9)	54 (9.4)	
Prior whole brain radiotherapy	No	1323 (89.3)	814 (89.9)	509 (88.4)	0.39
	Yes	159 (10.7)	92 (10.1)	67 (11.6)	
Tumor numbers	Mean	20	13	31	
	Median	16	13	28	
	Range	10-100	10-19	20-100	
	IQR	12-25	11-15	23-35	
Cumulative tumor volume	<10 mL	895 (60.4)	583 (64.4)	312 (54.2)	0.0001
	≥10 mL	587 (39.6)	323 (35.6)	264 (45.8)	
Largest tumor volume	<5 mL	1021 (68.9)	611 (67.4)	410 (71.2)	0.13
	≥5 mL	461 (31.1)	295 (32.6)	166 (28.8)	
Peripheral dose	<20 Gy	540 (36.4)	231 (25.5)	309 (53.7)	<0.0001
	≥20 Gy	942 (63.6)	675 (74.5)	267 (46.3)	
Single or 2/3-stage	Single	1413 (95.3)	862 (95.1)	551 (95.7)	0.89
	2/3 stage	69 (4.7)	44 (4.9)	25 (4.3)	

RPA; Recursive Partitioning Analysis, GI, Gastro-intestinal, p Values; Fisher's exact test was used for pairs of categorical variables while Pearson p-value was used for Modified RPA and primary cancer sites.

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Prior to referral to us for SRS, most of the patients had been advised to receive SRS by their primary physicians because our clinics specialize in GK SRS. It should be noted that patient selection criteria may have differed among the referring physicians. Therefore, one of the first two authors (either MY or TS) decided whether or not a patient could be treated with SRS. We did not perform SRS on patients with low Karnofsky Performance Status (KPS) scores (<70%) due to systemic diseases, a non-cooperative state due to poor neurocognitive function, diffuse meningeal dissemination, or an anticipated survival period of no

more than three months. Each patient, along with at least one adult relative, received a detailed explanation of our treatment strategies. Written informed consent was thereby obtained from each patient by one of the two main treating neurosurgeons (either MY or TS) prior to all SRS procedures.

Radiosurgical techniques

Our radiosurgical techniques were described in detail in our previous publication and are thus not repeated herein [10, 11]. Briefly, we performed standard, single-session GK SRS with frame placement in most cases. Selected doses delivered to the tumor periphery ranged from 10.00 Gy to 25.00 Gy (median; 20.00 Gy, inter-quartile range [IQR]; 18.00-21.00 Gy). However, in 69 patients, a two-/three-stage treatment protocol was selected because there was only one or a few relatively large BMs [12, 13]. Among these 69 patients, 35 underwent two-stage treatment; peripheral doses of 14.00 Gy were delivered at a three-week interval, and the other 34 underwent 3-stage treatment; peripheral doses of 9.00-10.00 Gy were administered at a two-week interval. Although, in patients with multiple BMs, one or a few relatively large BMs were irradiated with 2-/3- stage SRS, the majority of smaller BMs were irradiated in a single SRS session. Therefore, these 69 patients were not excluded from the data analysis for the present study.

Before June of 2003, in the Yamamoto series, SRS was performed using a Leksell GK Model B unit (1988-2003, Elekta, Sweden), later a Leksell GK Model C unit (2003-2013, Elekta, Sweden) was employed and, thereafter, a Leksell GK Perfexion unit (Elekta, Sweden). In the Serizawa series, the switch from the GK Model B to C was in 2003 and from the Model C to Perfexion in 2011.

Post-SRS, all patients were routinely managed by their referring physicians and were recommended to receive clinical and neuro-imaging examinations at an interval of approximately 2-3 months. However, in 244 (16.5%) of the 1482 patients, neuro-imaging follow-up could not be performed due to early post-SRS death or severe deterioration of general condition.

Case-matching

Because there was bias and a large patient number discrepancy between the two groups, i.e., patients with 10-19 BMs and those with ≥20 BMs, a case-matched study was carried out by one of the authors (YS) not participating in other aspects of this study. YS was also blinded to final outcomes. Patients were selected employing the propensity score matching method for clinical factors, i.e., age, sex, primary tumor sites, primary tumor status, extra-cerebral metastases, KPS, presentation, neurological symptoms, prior procedures (surgery and WBRT), cumulative BM volume, volume of the largest BM, peripheral doses and procedure numbers. Ultimately, 936 (468 had 10-19 BMs, the other 468 had ≥20) patients were selected. Clinical characteristics and radiosurgical parameters of matched cases are summarized in Table 2. It should be noted that clinical factors were well balanced between the two tumor number groups.

Table 2
Summary of clinical characteristics of 936 matched patients with >10 brain metastases according to two tumor number groups*

		Total	Tumor number		
Characteristics			**10 -19**	**≥20**	**p value**
No. of patients		936	468	468	
Gender	Female	448 (47.9)	215 (45.9)	233 (49.8)	0.27
	Male	488 (52.1)	253 (54.1)	235 (50.2)	
Age	<65 years	479 (51.2)	238 (50.9)	241 (51.5)	0.90
	≥65year	457 (48.8)	230 (49.1)	227 (48.5)	
Karnofsky performance status	≥80%	688 (73.5)	345 (73.7)	343 (73.3)	0.94
	≤70%	248 (26.5)	123 (26.3)	125 (26.7)	
Modified-RPA class**	1+2a	62 (6.6)	30 (6.4)	32 (6.8)	0.73
	2b	216 (23.1)	113 (24.2)	103 (22.0)	
	2c+3	658 (70.3)	325 (69.4)	333 (71.2)	
Neurological symptoms	No	486 (51.9)	244 (52.1)	242 (51.7)	0.95
	Yes	450 (48.1)	224 (47.9)	226 (48.3)	
Presentation	Metachronous	646 (69.0)	322 (68.8)	324 (69.2)	0.94
	Synchronous	290 (31.0)	146 (31.2)	144 (30.8)	
Primary cancer sites	Lung	698 (74.6)	356 (76.1)	342 (73.1)	0.86
	GI tract	24 (2.6)	10 (2.1)	14 (3.0)	
	Breast	145 (15.5)	70 (15.0)	75 (16.0)	
	Kidney	12 (1.3)	5 (1.1)	7 (1.5)	
	Others	57 (6.1)	27 (5.8)	30 (6.4)	
Primary cancer status	Controlled	220 (23.5)	109 (23.4)	111 (23.7)	0.94
	Not Controlled	716 (76.5)	359 (76.6)	357 (76.3)	

RPA; Recursive Partitioning Analysis, GI, Gastro-intestinal, p Values; Fisher's exact test was used for pairs of categorical variables while Pearson p-value was used for Modified RPA and primary cancer sites.

*Values are presented as the number of patients (%) except for tumor numbers.

**Refers to the studies by Yamamoto et al. [11,14]

		Total	Tumor number		
Characteristics			**10 -19**	**≥20**	**p value**
Extra-cerebral metastases	No	305 (32.6)	154 (32.9)	151 (32.3)	0.89
	Yes	631 (67.4)	314 (67.1)	317 (67.7)	
Prior surgery	No	838 (89.5)	421 (90.0)	417 (89.1)	0.75
	Yes	98 (10.5)	47 (10.0)	51 (10.9)	
Prior whole brain radiotherapy	No	814 (87.0)	404 (86.3)	410 (87.6)	0.63
	Yes	122 (13.0)	64 (13.7)	58 (12.4)	
Tumor numbers	Mean	22	14	30	
	Median	20	13	26	
	Range	10-100	10-19	20-100	
	IQR	12-26	11-15	22-32	
Cumulative tumor volume	√	642 (68.9)	275 (58.8)	269 (57.5)	0.74
	≥10 cc	392 (31.4)	193 (41.2)	199 (42.5)	
Largest tumor volume	<5 cc	642 (68.6)	323 (69.0)	319 (68.2)	0.83
	≥5 cc	294 (31.4)	145 (31.0)	149 (31.8)	
Peripheral dose	<20 Gy	403 (43.1)	202 (43.2)	201 (43.0)	1.0000
	≥20Gy	533 (57.1)	266 (56.8)	267 (57.0)	
Single or 2/3-stage	Single	885 (94.6)	440 (94.0)	445 (95.1)	0.64
	2/3 stage	51 (5.4)	28 (6.0)	23 (4.9)	

RPA; Recursive Partitioning Analysis, GI, Gastro-intestinal, p Values; Fisher's exact test was used for pairs of categorical variables while Pearson p-value was used for Modified RPA and primary cancer sites.

*Values are presented as the number of patients (%) except for tumor numbers.

**Refers to the studies by Yamamoto et al. [11,14]

Table 3
Multivariable analyses of survival after stereotactic radiosurgery (SRS)

Variables		Tumor number 10-19		Tumor number ≥20	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Sex	Male vs. Female	1.485 (1.278-1.726)	<0.0001	1.606 (1.323-1.951)	<0.0001
Age (years)	≥65 vs. <65	1.095 (0.949-1.265)	0.21	1.087 (0.911-1.298)	0.35
KPS (%)	≤70 vs. ≥80	2.184 (1.823-2.616	<0.0001	1.781 (1.467-2.207)	<0.0001
Neurological symptoms	Yes vs. No	1.325 (1.123-1.562)	0.0008	1.323 (1.073-1.632)	0.0088
Presentation	Synchronous vs metachronous	0.766 (0.654-0.900)	0.0011	0.799 (0.645-0.989)	0.039
Tumour volume (mL)	Cumulative ≥10.0 vs. <10.0	1.147 (0.920-1.434	0.23	0.826 (0.655-1.041)	0.11
	Largest tumour ≥5.0 vs. <5.0	1.109 (0.882-1.394)	0.38	1.259 (0.974-1.628)	0.078
Dose (Gy)	Minimum <20 vs. ≥20	1.111 (0.907-1.361	0.31	1.193 (0.964-1.477)	0.10
	Maximum <36 vs. ≥36	0.945 (0.872-1.090)	0.28	1.031 (0.836-1.273)	0.77
Primary cancer	Non-lung vs Lung	0.938 (0.775-1.137)	0.52	1.124 (0.864-1.464	0.38
Primary cancer status	No vs. Good	1.738 (1.451-2.082)	<0.0001	1.602 (1.275-2.012)	<0.0001
Extra-cranial metastases	Yes vs. No	1.552 (1.335-1.802	<0.0001	1.460 (1.194-1.784)	0.0002

HR; hazard ratio, 95% CI; 95% confidence intervals, KPS; Karnofsky Performance Status, SRS; stereotactic radiosurgery

Variables		Tumor number 10-19		Tumor number ≥20	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Pre-SRS whole brain radiotherapy	Yes vs. No	1.210 (0.936-1.563)	0.15	1.028 (0.775-1.363)	0.85
Pre-SRS surgery	Yes vs. No	0.896 (0.721-1.113)	0.32	0.925 (0.672-1.273)	0.63

HR; hazard ratio, 95% CI; 95% confidence intervals, KPS; Karnofsky Performance Status, SRS; stereotactic radiosurgery

Table 4
Post-treatment crude and cumulative incidences of the secondary endpoints determined using competing risk analysis

	Tumor Number group	Crude incidences (%)	Fisher p value	Cumulative Incidences (post-SRS months), %					HR (95% CI)/ ChiSq p value
				12	24	36	48	60	
Neurological death	10-19	63 (13.6)	0.57	10.4	13.6	14.6	15.0	15.0	1.092 (0.777-1.536)/0.61
	≥20	69 (15.0)		10.5	13.8	15.4	15.4	15.8	
Neurological deterioration*	10-19	76 (16.2)	0.49	12.9	16.2	16.8	17.7	17.7	1.121 (0.823-1.526)/0.47
	≥20	85 (18.2)		13.6	17.8	19.1	19.1	19.6	
Local recurrence**	10-19	16 (3.58)	0.61	2.7	4.2	4.8	4.8	4.8	1.220 (0.633-2.352)/0.55
	≥20	20 (4.4)		3.9	4.8	5.3	5.3	5.3	
Repeat SRS	10-19	138 (29.5)	0.77	26.4	30.6	31.5	31.5	31.5	0.951 (0.750-1.206)/0.68
	≥20	133 (28.4)		26.3	29.6	29.6	29.8	29.8	
Salvage WBRT	10-19	30 (6.4)	0.79	5.6	6.6	6.9	6.9	6.9	1.099 (0.671-1.800)/0.71
	≥20	33 (7.1)		6.0	6.9	7.5	7.5	7.5	
SRS-related complications	10-19	16 (3.4)	1.00	1.1	3.4	3.4	4.1	4.1	1.050 (0.531-2.077)/0.88
	≥20	17 (3.6)		1.8	3.0	3.7	3.7	3.7	

SRS; stereotactic radiosurgery, WBRT; whole brain radiotherapy□ChiSq; chi square

*See text.

**Based on 911 (454 [97.0%] in the 10-19 brain metastasis (BM) group and 457 [97.6%] in the ≥20 BM group) patients in whom neuro-imaging results were available.

Table 5
Univariable and multivariable analyses of stereotactic radiosurgery (SRS)-related complications

Variables		Uni-variable analyses		Multi-variable analyses	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Sex	Male vs. Female	0.630 (0.341-1.163)	0.14		
Age (years)	continuous variable	0.898 (0.187-4.676)	0.90		
	≥65 vs. <65	0.970 (0.552-1.705)	0.92		
KPS (%)	≤70 vs. ≥80	2.047 (0.939-4.462	0.072		
Neurological symptoms	Yes vs. No	2.093 (1.181-3.708)	0.011	2.265 (0.624-8.2173)	0.21
Presentation	Synchronous vs metachronous	1.224 (0.679-2.206)	0.50		
Tumor number	continuous variable	3.723 (0.382-22.231)	0.20		
	≥20 vs 10-19	1.681 (0.934-2.963)	0.073		
Cumulative tumor volume (mL)	continuous variable	12.534 (2.110-51.870	0.0077		
	≥10.0 vs. <10.0	2.059 (1.158-3.662	0.014	1.729 (0.370-8.078)	0.49
Largest tumor volume (mL)	continuous variable	33.182 (1.140-503.309)	0.043		
	≥10.0 vs. <10.0	2.441 (1.080-5.516)	0.032	2.888 (0.692-12.047)	0.15
Minimum dose (Gy)	continuous variable	0.195 (0.048-0.876)	0.034		
	<20 vs. ≥20	1.827 (0.999-3.337)	0.050	0.780 (0.251-3.018)	0.83

HR; hazard ratio, 95% CI; 95% confidence intervals, KPS; Karnofsky Performance Status, SRS; stereotactic radiosurgery

Variables		Uni-variable analyses		Multi-variable analyses	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Maximum dose (Gy)	continuous variable	0.525 (0.945-35.471)	0.058		
	<36 vs. ≥36	0.634 (0.359-1.123)	0.12		
12-Gy brain volume (mL)	continuous variable	25.696 (1.290-320.523	0.035		
	<43 vs. ≥43	0.302 (0.084-1.083)	0.066	0.585 (0.130-2.627)	0.48
Primary cancer	Non-lung vs Lung	1.687 (0.942-3.020)	0.079		
Primary cancer status	No vs. Good	1.155 (0.643-2.074)	0.63		
Extra-cranial metastases	Yes vs. No	1.389 (0.779-2.475	0.27		
Pre-SRS whole brain radiotherapy	Yes vs. No	1.920 (0.895-4.120)	0.094		
Pre-SRS surgery	Yes vs. No	0.426 (0.132-1.377)	0.15		

HR; hazard ratio, 95% CI; 95% confidence intervals, KPS; Karnofsky Performance Status, SRS; stereotactic radiosurgery

Outcomes

The primary endpoint of this study was overall survival. Secondary endpoints were maintenance of neurological condition, neurological death, recurrence of the irradiated BMs, SRS-related complications and salvage treatments, i.e., repeat SRS and/or WBRT. The primary and secondary endpoints were defined in detail in our previous publication [10]. For time-to-event outcomes, intervals were defined as being from the day of SRS to the day of the event or the most recent follow-up.

Statistical Analysis

The Kaplan-Meier method was applied to assess overall survival and competing risk analysis was applied for time-to-event outcome analyses of all of the secondary endpoints. The Cox Proportional Hazard model was used for the multivariable analyses identifying factors favoring longer survival. All statistical analyses were carried out by the aforementioned experienced statistician (YS) using SAS software version 9.4 (SAS Institute, Cary, NC, USA). Before the statistical analyses, the entire database was cleaned by one of the co-

authors (YH). These two authors were not involved in administering the SRS treatments nor in any aspects of patient follow-up.

Results

The median post-SRS follow-up period for 124 censored observations (8.4%) was 6.5 (IQR; 1.1-20.6) months, with 1358 patients (91.6%) having died as of the end of June 2020. The overall median survival time (MST) after SRS was 6.2 (95% CI; 5.8-6.8) months. The respective actuarial post-SRS survival proportions were 27.7%, 10.9%, 4.6%, 2.5% and 1.6% at the 12th, 24th, 36th, 48th and 60th post-SRS months. Among the 1358 deceased patients, the causes of death could not be determined in 26, but were confirmed in the remaining 1332 to be non-brain diseases in 1136 (85.3%) and brain diseases in 196 (14.7%) patients. Among the total 1482 patients, follow-up MR imaging was performed at least once in 1238 (83.5%). Among the 1482 patients, 553 (37.3%) underwent salvage SRS, generally for newly-appearing lesions (499 patients, 92.3%) and, less commonly, for recurrence of a treated lesion (54 patients, 3.7%), while salvage WBRT was administered to 98 (6.6%).

Cohort study

The post-SRS MST was slightly longer in the group with 10-19 BMs (6.7 [95% CI; 5.9-7.3] months) than in that with ≥20 BMs (5.7 [95% CI; 5.0-6.4] months), as shown in Fig. 1, A. Although the post-SRS MST difference reached statistical significance (hazard ratio [HR]; 1.121, 95% CI; 1.005-1.250, p=0.040), the actual MST difference was only 1.0 month. The respective actuarial post-SRS survival proportions in the patients with 10-19 BMs were 29.0%, 11.6%, 5.2%, 2.2% and 1.4% at the 12th, 24th, 36th, 48th and 60th post-SRS months, while the corresponding percentages in patients with ≥20 BMs were 25.6%, 9.7%, 3.5%, 2.6% and 1.5%. In patients with 10-19 BMs, MSTs were 16.6 months for Modified Recursive Partitioning Analysis (M-RPA) 1+2a, 11.2/2b and 4.7/2c+3, respectively (p<0.0001) (Figure 2, A) [11,14]. Also, in patients with ≥20 BMs, the MSTs were 31.0, 9.5 and 4.5 months for M-RPA 1+2a, 2b and 2c+3, respectively (p<0.0001) (Fig. 2).

Among various pre-SRS clinical factors examined, univariable analysis demonstrated female gender, KPS ≥80%, neurologically asymptomatic, synchronous presentation, controlled primary cancer and no extra-cerebral metastases to be factors significantly favoring longer survival in both of the number groups, i.e., 10-19 BMs and ≥20 BMs, as shown in Table 3. For all clinical factors significantly impacting survival, both HRs and p-values were similar in the two groups. No impacts, on survival, of age, cumulative BM volume, the volume of the largest BM, minimum and maximum irradiation doses, or the primary cancer and prior treatments, i.e., pre-SRS, WBRT or surgery, were detected.

Case-matched study

As shown in Fig. 1, the post-SRS MSTs were the same in the two BM number groups, 5.9 (95% CI; 5.2-7.2) months for those with 10-19 BMs and also 5.9 (95% CI; 5.1-6.8) months for the group with ≥20 BMs. The respective actuarial post-SRS survival proportions in the patients with 10-19 BMs were 26.7%, 10.5%, 5.2%,

1.9% and 0.9% at the 12th, 24th, 36th, 48th and 60th post-SRS months, while the corresponding values in patients with ≥20 BMs were 27.0%, 11.0%, 4.1%, 2.9% and 1.5% (HR; 1.017, 95% CI; 0.890-1.164, p=0.80).

The crude and cumulative incidences of neurological death, neurological deterioration, local recurrence, repeat SRS, salvage WBRT and SRS-related complications did not differ significantly between the two BM number groups (Table 4).

Factors relating to high incidences of SRS-related complications

Univariable analyses of the cohort dataset (1482 patients with ≥10 BMs) showed the presence of neurological symptoms, the cumulative and largest BM volumes, minimum dose and 12 Gy-brain volume to be significantly related to higher incidences of SRS-related complications, as shown in Table 5. Nevertheless, none of these five clinical factors reached statistical significance on multivariable analyses. For this study on SRS-related complications, we used receiver operating characteristics analysis to determine the cut-off value for dividing the continuous variables into two groups, i.e., 4.15 mL (area under the curve [AUC]; 0.536)/cumulative volume, 9.94 mL (AUC; 0.461/the largest BM volume, 20.00 Gy (AUC; 0.538)/minimum dose and 42.8 mL (AUC; 0.563)/12 Gy-brain volume. For convenience, the nearest integers were applied. The cut-off value for the cumulative volume of 4 mL was incompatible with the largest BM volume of 10 mL. Therefore, we also used 10 mL as the cut-off value for the cumulative BM volume.

Discussion

To our knowledge, this is the first investigation, based on a large series, i.e., nearly 1500 patients in whom GK SRS alone was performed by two highly experienced neurosurgeons (T.S. and M.Y.), to clarify treatment results of SRS alone for patients with ≥20 BMs as compared to those with 10-19 BMs. In this cohort study, the post-SRS MSTs differed significantly between the two groups. This difference is explained by the larger number of patients in the M-RPA 2c+3 category in the BM ≥20 versus the BM 10-19 group (Table 1) [11,14]. Nevertheless, this difference, only one month, can be regarded as having little clinical impact. It should be noted that, in the case-matched study, MSTs were the same in the two groups. Furthermore, the two BM number groups did not differ significantly in either crude or cumulative incidences of neurological death, neurological deterioration, local recurrence, repeat SRS, salvage WBRT or SRS-related complications, as determined employing competing risk analyses (Table 4). Also, it should be noted that crude and cumulative incidences of SRS–related complications were almost the same as or slightly lower than those in previous reports of SRS results in patients with 1-4 or ≤10 BMs [1,5,8,10].

In 1998, the first author (MY) reported two lung cancer patients in whom more than 30 BMs were successfully controlled with no additional radiotherapy to the brain for 4.5 and 5.5 months, the respective remaining survival periods, after SRS alone [15]. Since then, several retrospective studies on SRS for ≥10 BMs have been published [16-24]. However, in five of these studies, the patient numbers were not large enough to allow meaningful statistical analysis, i.e., the maximum was only 103 patients. The first author (MY) previously found, based on 720 (360 in each group) case-matched patients with 2-9 vs ≥10 BMs, that

the post-SRS MST difference between these two groups did not reach statistical significance [23]. Furthermore, the two groups did not differ significantly in cumulative incidences, as determined using competing risk analyses, of neurological deterioration, neurological death, local recurrence, re-SRS for new lesions or SRS-related complications.

Recently, Hughes et al reported that MSTs were 8.0, 6.3 and 4.7 months for patients with 1, 2-4, and 5-15 BMs, respectively (p=0.14), and that salvage SRS and WBRT rates did not differ among these three tumor number groups [5]. According to their results, however, one-year distant failure in the brain occurred in 27%, 44% and 40% of cases, respectively (p=0.01). A major weakness of their study was the rather small patient numbers, i.e., 190 patients with 2-4 and 68 with 5-15 BMs, yielding insufficient statistical power. Therefore, we performed a retrospective cohort study using our prospectively accumulated database including 1515 patients with 5-10 BMs and 804 with 11-20 BM, undergoing GK SRS. The post-SRS MST was slightly longer in the group with 5-10 (7.7 months) than in that with 11-20 (6.5 months, p<0.0001) BMs [23]. Crude and cumulative incidences of local recurrences were significantly lower in the group with 11-20 than in that with 5-10 BMs, while those of other secondary endpoints were similar to or slightly lower in the 11-20 than in the 5-10 tumor number group.

The next question we tackled was the best approach to selecting patients with ≥20 BMs who would likely benefit from SRS alone. As described above, KPS ≥80%, the absence of neurological symptoms, well controlled primary cancer and no extra-cranial metastases were factors associated with longer survival. According to the CNS Guidelines published in 2019, the use of SRS alone is recommended for improving the overall survival of patients with more than four BMs having a cumulative volume <7 mL [3]. We consider this criterion to be overly strict, however. Our JLGK0901 Study clearly demonstrated cumulative tumor volume ≤15.0 mL to be an acceptable cut-off value [1]. If patient selection criteria require simplification, patients with either M-RPA class 1+2a or 2b would be better candidates for SRS alone treatment even if they have ≥20 BMs (Fig. 2) [11,14]. In our experience, for minimizing incidences of SRS-related complications, patients with either cumulative or a largest BM volume of ≤10 mL, being irradiated with a minimum dose of ≤20.00 Gy, are good candidates for GK SRS alone.

In a Rando phantom experiment, the first author (MY) analyzed cumulative whole brain irradiation doses based on the treatment protocol for a patient with 48 lesions [15]. The estimated cumulative irradiation doses were 2.60 Gy to 6.69 Gy at sites located some distance from the targets. Also, in 2002, the first author (MY) determined the total dose absorbed by the normal brain using a treatment protocol for 92 patients who underwent SRS for 10 or more BMs and reported single-session GK SRS for ≥10 BMs to be safe, i.e., the median cumulative absorbed dose to the normal brain was 7.71 (range; 2.16-8.51) Gy [24]. These earlier results are highly consistent with those described in the recent studies reported by Yang et al [25] and Boone et al [26]. Varlotto et al reported that a brain volume receiving >12 Gy correlated with higher incidences of SRS-related complications [27]. We previously reported, based on a study of nearly 3000 patients, that multivariable analysis demonstrated the 12-Gy brain volume to have no impact on complication rates [28]. As described herein, we did not find that the 12-Gy brain volume clearly corelates with higher complication rates in the present study (Table 5).

The retrospective design of our study would likely be its major weakness. Another possible weakness is that neither original cancer phenotypes nor information on the administration of systemic anti-cancer agent treatments, both of which are regarded as correlating with survival, was included in our database. However, our two databases were contemporaneously accumulated and, therefore, lack of the above-mentioned information is considered to have little impact on the results of the present study. Furthermore, we believe that the present results support the hypothesis generated in response to publication of the JLGK Study;[1] SRS for ≥20 BMs is well tolerated and there is no evidence of associated increases in toxicity, treatment failure, and/or the need for salvage therapy. However, ongoing prospective randomized studies (NCT03075072, NCT03550391, NCT03297788, NCT02953717, and so on) will test these conclusions and may provide more robust support for this hypothesis in 2023 or thereafter.

Conclusion

Carefully-selected patients, i.e., those with either cumulative or largest tumor volumes of ≤10 mL and those with M-RPA 1+2a and 2b, even if they have ≥20 BMs, are not unfavorable candidates for receiving SRS alone. However, either a randomized controlled trial or a study based on big data should be conducted in the near future, to clarify the optimal application of SRS alone in patients with 20 or more BMs.

Declarations

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Author contribution

All of the authors contributed to this work; Dr.Serizawa performed SRS, Drs. Higuchi and Sato independently performed the statistical analyses and Dr. Kasuya was responsible for the basic study design.

Missing data availability

Not applicable

Compliance with Ethical Standards

Conflict of Interest: The authors have no conflicts of interest to declare.

Research involving human participants and/or animals: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Written informed consent was obtained from each patient by one of the two main treating neurosurgeons (either MY or TS).

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Declaration of interests: The authors have no conflicts of interest to declare.

The Institutional Review Boards of Tokyo Women's Medical University (No. 1981) and Tsukiji Neurological Clinic (No. 2021-07) gave approval for the present study.

This research was registered to the University Medical Information Network Registry website, http://www.umin.ac.jp/ctr/index.htm (number R000050686).

The academic committee of the Japanese Leksell Gamma Knife Society qualified this research (JLGK2021 Study).

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Figures

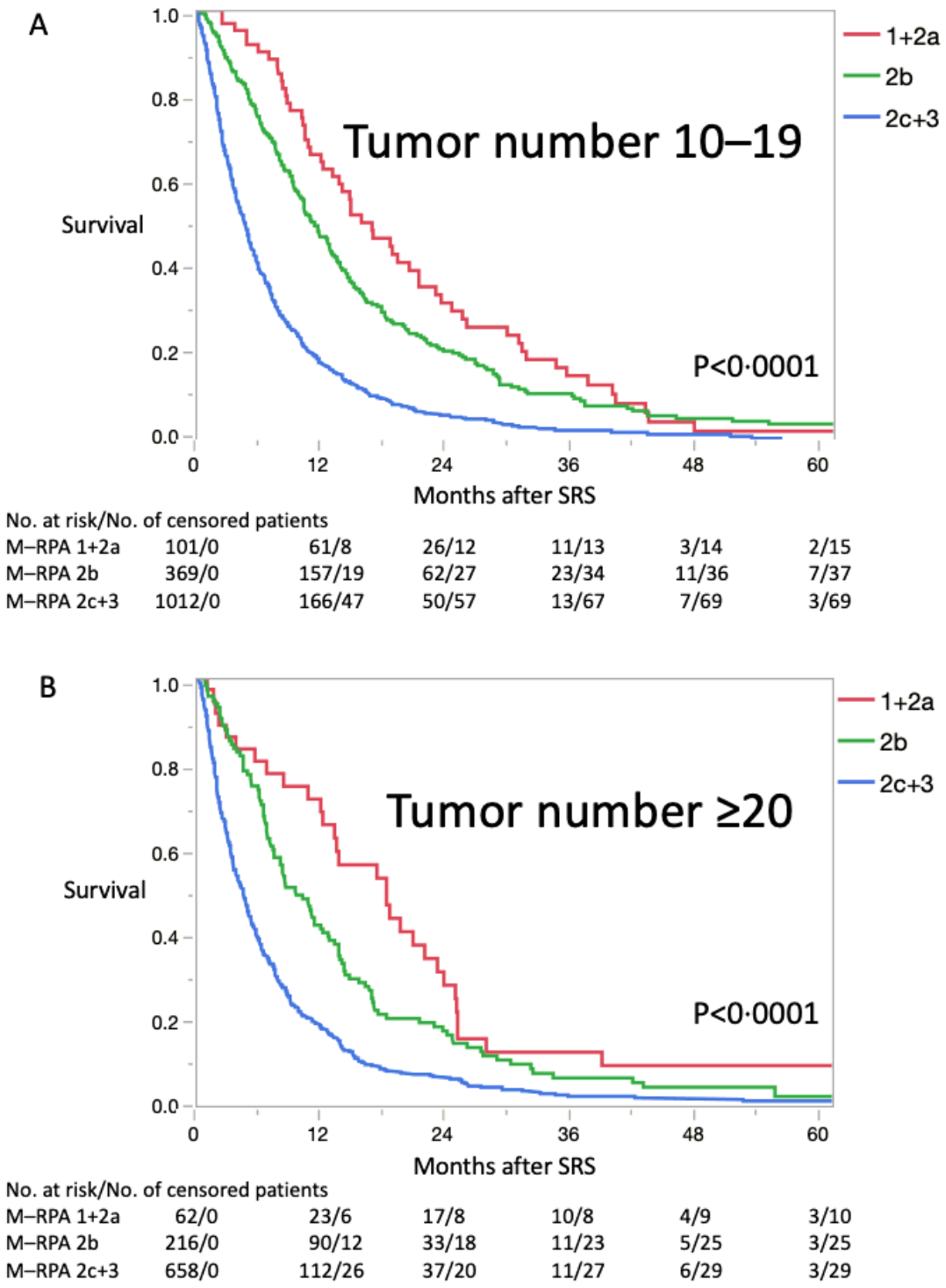
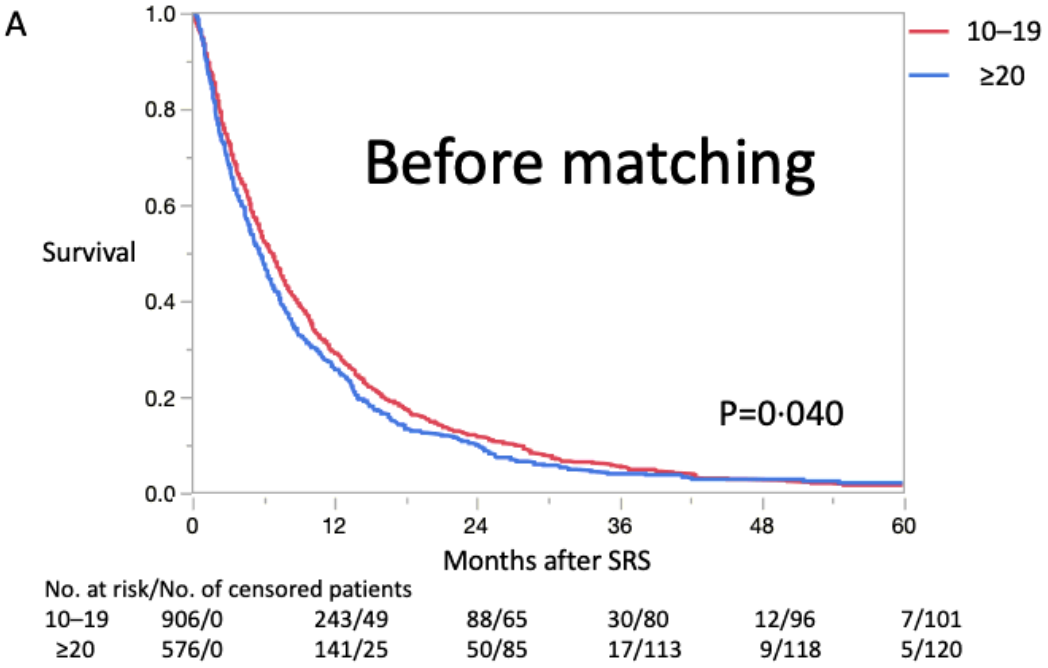


Figure 1

Overall survivals of the two patient groups, i.e., 10-19 vs ≥20, according brain metastases, for the entire cohort (A) as well as in matched patients (B). SRS; stereotactic radiosurgery



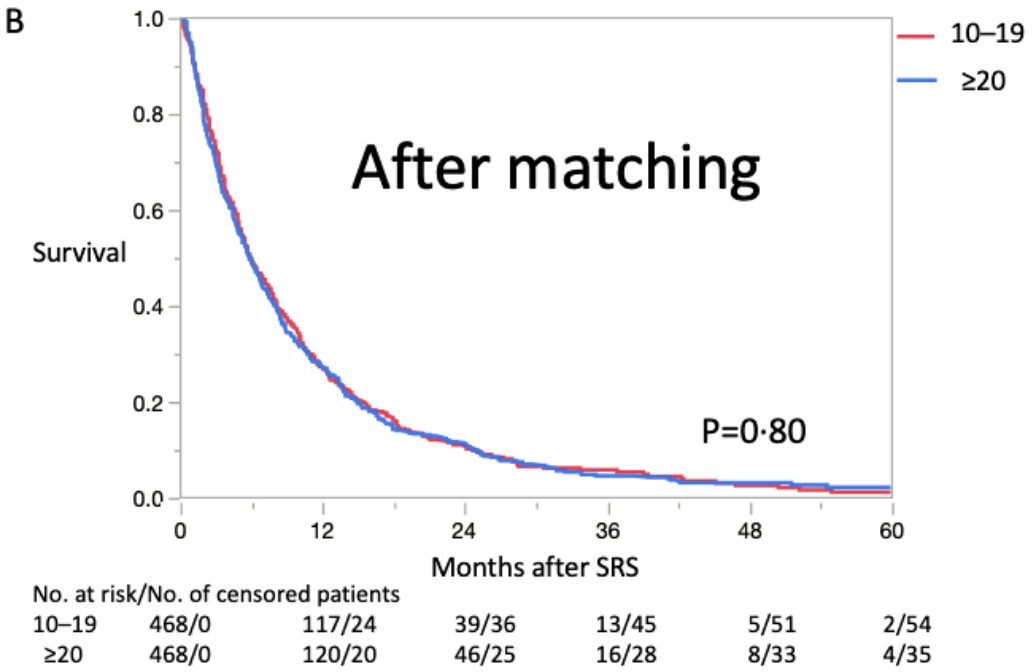


Figure 2

Overall survival according to 10-19 (A) and ≥20 (B) brain metastases (BMs) based on three Modified Recursive Partitioning Analysis (M-RPA) subclasses: 1+2a, 2b and 2c+3.19,20 Median survival times (MSTs) and their 95% confident intervals (CIs) were 16.6 (12.0-21.0) months/1+2a, 11.2 (9.9-12.8) months/2b and 4.7 (4.1-5.1) months/2c+3 in the patients with 10-19 BMs (p<0.0001) and MSTs and their

95% CIs were 18.1 (12.0-22.8) months/1+2a, 9.5 (7.4-12.0) months/2b and 4.5 (3.8-5.0) months/2c+3 in the patients with 10-19 BMs ($p<0.0001$). SRS; stereotactic radiosurgery