Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

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Summary

Background We aimed to examine whether stereotactic radiosurgery without whole-brain radiotherapy (WBRT) as the initial treatment for patients with five to ten brain metastases is non-inferior to that for patients with two to four brain metastases in terms of overall survival.

Methods This prospective observational study enrolled patients with one to ten newly diagnosed brain metastases (largest tumour <10 mL in volume and <3 cm in longest diameter; total cumulative volume ≤15 mL) and a Karnofsky performance status score of 70 or higher from 23 facilities in Japan. Standard stereotactic radiosurgery procedures were used in all patients; tumour volumes smaller than 4 mL were irradiated with 22 Gy at the lesion periphery and those that were 4–10 mL with 20 Gy. The primary endpoint was overall survival, for which the non-inferiority margin for the comparison of outcomes in patients with two to four brain metastases with those of patients with five to ten brain metastases was set as the value of the upper 95% CI for a hazard ratio (HR) of 1·30, and all data were analysed by intention to treat. The study was finalised on Dec 31, 2012, for analysis of the primary endpoint; however, monitoring of stereotactic radiosurgery-induced complications and neurocognitive function assessment will continue for the censored subset until the end of 2014. This study is registered with the University Medical Information Network Clinical Trial Registry, number 000001812.

Findings We enrolled 1194 eligible patients between March 1, 2009, and Feb 15, 2012. Median overall survival after stereotactic radiosurgery was 13·9 months [95% CI 12·0–15·6] in the 455 patients with one tumour, 10·8 months [9·4–12·4] in the 531 patients with two to four tumours, and 10·8 months [9·1–12·7] in the 208 patients with five to ten tumours. Overall survival did not differ between the patients with two to four tumours and those with five to ten (HR 0·97, 95% CI 0·81–1·18 [less than non-inferiority margin], p=0·78; $p_{non\text{-}inferiority}$<0·0001). Stereotactic radiosurgery-induced adverse events occurred in 101 (8%) patients; nine (2%) patients with one tumour had one or more grade 3–4 event compared with 13 (2%) patients with two to four tumours and six (3%) patients with five to ten tumours. The proportion of patients who had one or more treatment-related adverse event of any grade did not differ significantly between the two groups of patients with multiple tumours (50 [9%] patients with two to four tumours *vs* 18 [9%] with five to ten; p=0·89). Four patients died, mainly of complications relating to stereotactic radiosurgery (two with one tumour and one each in the other two groups).

Interpretation Our results suggest that stereotactic radiosurgery without WBRT in patients with five to ten brain metastases is non-inferior to that in patients with two to four brain metastases. Considering the minimal invasiveness of stereotactic radiosurgery and the fewer side-effects than with WBRT, stereotactic radiosurgery might be a suitable alternative for patients with up to ten brain metastases.

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Introduction

Brain metastases are a common, life-threatening neurological problem for patients with cancer, in the absence of effective treatment. Previously, outcomes in patients with brain metastases were uniformly poor, and palliative treatments—eg, steroids and whole-brain radiotherapy (WBRT)—have dominated management recommendations.[1,2] However, mainly due to recent advances in systemic cancer treatment, an appropriately selected subgroup of patients with brain metastases can now achieve longer survival with maintenance of good neurological function if their brain metastases are well controlled. Since Lindquist[3] first reported that a patient with a brain metastasis had been successfully treated with stereotactic radiosurgery, evidence of the effectiveness of this treatment has been accumulating, for both stereotactic radiosurgery alone and in combination with WBRT.[4,5] Compared with WBRT, stereotactic radiosurgery has several benefits: it can be done in 1 day; more than 80% of patients will have their tumour controlled by this treatment, which can lead to early symptom palliation, even if the lesion is radioresistant; it can be repeated and

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can be done after WBRT; it does not prevent radiation therapy for other parts of the body, chemotherapy, or major surgery for another lesion; the incidence and magnitude of deterioration of neurocognitive function are much lower than with WBRT;[6] and the amount of radiation hair loss is minimal compared with WBRT.

Because many factors affect outcomes in patients with brain metastases, a one-size-fits-all treatment framework in which four or more tumours are automatically recommended for WBRT is not appropriate. On the basis of results from randomised controlled studies,[4,5] stereotactic radiosurgery alone for patients with four or even five or more tumours is not standard, and WBRT is still strongly recommended in most industrialised nations.[7,8] However, evidence that patients with five or more or even ten or more tumours might be potential candidates for stereotactic radiosurgery alone has been building since the early 21st century.[9] Since Yamamoto and colleagues[10] reported that two patients with brain metastases with ten or more tumours were successfully treated with stereotactic radiosurgery,[10] retrospective studies of patients with many brain metastases who have been successfully treated with stereotactic radiosurgery have been reported.[11–22] Nevertheless, the role of stereotactic radiosurgery for patients with five or more brain metastases is not fully understood. Therefore, reliable criteria still need to be developed to select patients for stereotactic radiosurgery of brain metastases.

The Japanese Leksell Gamma Knife (JLGK) Society planned this prospective observational study (JKGK0901) in February, 2009. Our study goals, based on observations of our patients with brain metastases who have received stereotactic radiosurgery, were to reappraise whether treatment results in patients with five to ten tumours were truly inferior to results in those with one to four tumours, and to those with two to four tumours in particular (because patients with just one tumour survive far longer than those with several[11–15,18]), and to identify factors affecting inferiority or non-inferiority. If our findings showed that stereotactic radiosurgery in patients with five to ten brain metastases was non-inferior to stereotactic radiosurgery in those with two to four tumours (which is regarded as the optimal number of tumours for stereotactic radiosurgery according to cumulative evidence and major guidelines), we hypothesised that stereotactic radiosurgery might be superior to WBRT for patients with five to ten brain metastases, because of the benefits that stereotactic radiosurgery has over WBRT.

A prospective randomised trial to establish whether stereotactic radiosurgery for patients with five to ten tumours yields better, worse, or equivalent outcomes to those of WBRT would provide direct evidence for both practitioners and patients; however, at the time of planning this study, information about stereotactic radiosurgery as the sole treatment for five or more brain metastases was scarce. As a result, and as a preliminary investigation to the aforementioned prospective randomised trial, we chose the observational study design described herein. If this study failed to prove the non-inferiority hypothesis, a prospective randomised trial would be unnecessary. We also took into consideration that the importance of validating non-inferiority has come to be widely accepted.

Methods

Study design and participants

This prospective observational cohort study selected participants with several brain metastases from 23 hospitals in Japan. Patients were eligible for inclusion if, at the time that they underwent stereotactic radiosurgery, they had newly diagnosed brain metastases that were confirmed by contrast-enhanced MRI no more than 6 weeks before the procedure, they had ten or fewer tumours, their largest tumour was smaller than 10 mL in volume and smaller than 3·0 cm in longest diameter, the cumulative volume of all their tumours was 15·0 mL or smaller, they had no leptomeningeal dissemination findings, and had a Karnofsky performance status (KPS) score of 70 or higher or, in patients with a KPS score of less than 70, a reasonable expectation of neurological function improvement with stereotactic radiosurgery. Patients with all types of original malignant tumours—except sarcoma and lymphoma because they are not solid cancers—were eligible. Whether patients with small-cell lung cancer should be included in such a clinical study is debated; however, our previous findings regarding stereotactic radiosurgery for patients with brain metastases did not show that stereotactic radiosurgery in patients with small-cell lung cancer was inferior to that in patients with non-small-cell lung cancer; thus, we had no valid reasons for excluding patients with small-cell lung cancer in this study.[10,12,14,16–18,23]

Patients were excluded if they had two or more original malignant tumours, were pregnant or breastfeeding, had been previously diagnosed with any psychological disorders, had contraindications for MRI examination or gadolinium agent use, or had previous surgery or irradiation to the skull or brain. These criteria were decided on the basis of our 20 years of experience with stereotactic radiosurgery for brain metastases and were mainly derived from analyses using one investigator's (TSe) database including more than 2000 patients with brain metastases who underwent stereotactic radiosurgery, which have since been published.[16,17]

The institutional review board of each facility approved all aspects of this study, and patients provided written informed consent before enrolment. The advisory committee was responsible for the study design and scientific execution of the study.

Procedures

All lesions detected by MRI with a slice thickness of 2 mm or smaller (with no gap between the upper and lower slices) after a gadolinium injection of 0·2 mL/kg covering the whole skull, with a 1·0 T or higher

performance unit, were to be irradiated in one stereotactic radiosurgery session. The study protocol, available on the University Medical Information Network Clinical Trial Registry website (number 000001812), did not allow the use of volumetric MRI or double or triple doses of gadolinium for the imaging of tumours. Eligible patients were enrolled if stereotactic MRI for dose planning—done about 1–2 h before stereotactic radiosurgery—showed ten or fewer tumours. We did not record the number of patients that were found to have more than ten tumours at this stage (ie, those that were ineligible for study inclusion). Three types of gamma units, Models B and C (including 4C) and Perfexion (Leksell Gamma Knife, Elekta Instruments AB, Stockholm, Sweden), were used. Tumour volumes of less than 4 mL were to be irradiated with 22 Gy at the lesion periphery and volumes of 4–10 mL with 20 Gy. However, increasing or decreasing a prescribed dose by 2 Gy was allowed. Irradiation doses to the optic apparatus were not to exceed 10 Gy. For brain stem lesions, peripheral doses of 20 Gy, 18 Gy, and 16 Gy were to be used for tumour volumes of less than 1 mL, 1–4 mL, and 4–10 mL, respectively. These dose selection criteria were mainly based on our long-term experience, but we also referred to the Radiation Therapy Oncology Group (RTOG) dose escalation trials of stereotactic radiosurgery alone.[12,24,25]

After stereotactic radiosurgery, patients underwent an MRI, an assessment of their general condition and performance status (KPS), and neurological tests at 3-month intervals, or more frequently if clinical and imaging conditions required it. Other treatments—eg, radiotherapy, chemotherapy (including molecularly targeted agents), immunotherapy, and hormone therapy were reported at least every 3 months, and could be initiated as soon as required. A neurocognitive function assessment with the Mini-Mental State Examination (MMSE) was recommended 4 months and 12 months after stereotactic radiosurgery and at 12-month intervals thereafter. Although debate continues as to whether neurocognitive function can be correctly assessed with the MMSE, as compared with the Hopkins Verbal Learning Test-Revised for example, we chose to use the MMSE on the basis of findings from Aoyama and colleagues.[5] After stereotactic radiosurgery, referring physicians and patients could choose any type of cancer treatment. Unmasked treating physicians assessed MRI findings and systemic and neurological status. For all patients who died, the causes of death were determined by referring physicians.

Data on secondary outcomes and adverse events were obtained at 3-month intervals or more frequently depending on the clinical circumstances; severe complications were reported immediately. Interim safety monitoring was done every year after initiation of the study to assess both the adverse events and treatment safety. The data and safety monitoring committee consisted of three members; one (YH, committee chair) was masked to any information relating to study group, and assessed and graded each adverse event (according to the Common Terminology Criteria for Adverse Events [CTCAE][26]) to recommend early termination of the study for safety, scientific, or ethical reasons, if necessary. We only recorded the number of adverse events of each grade, rather than specific details of event types.

For the **University Medical Information Network Clinical Trial Registry** see http://www.umin.ac.jp/ctr/index.htm

	Total (n=1194)	1 tumour (n=455)	2–4 tumours (n=531)	5–10 tumours (n=208)	p value
Tumour number					
Median (IQR)	2 (1–4)	1 (1–1)	2 (2–3)	6 (5–8)	..
Mean (SD)	3 (2)	1 (0)	3 (1)	7 (2)	..
Age, years					
Mean (SD)	65·8 (10·2)	65·9 (10·7)	65·8 (9·9)	65·4 (9·9)	0·55
Range	30–91	30–91	36–91	37–89	..
≥65	693 (58%)	270 (59%)	310 (58%)	113 (54%)	0·46
Sex					0·37
Female	471 (39%)	177 (39%)	203 (38%)	91 (44%)	..
Male	723 (61%)	278 (61%)	328 (62%)	117 (56%)	..
Primary cancer					0·35
Lung	912 (76%)	348 (76%)	400 (75%)	164 (79%)	..
Breast	123 (10%)	42 (9%)	57 (11%)	24 (12%)	..
GI tract	85 (7%)	35 (8%)	41 (8%)	9 (4%)	..
Kidney	36 (3%)	15 (3%)	19 (4%)	2 (1%)	..
Other	38 (3%)	15 (3%)	14 (3%)	9 (4%)	..
Extracerebral diseases					0·075
Controlled	811 (68%)	325 (71%)	355 (67%)	131 (63%)	..
Not controlled	383 (32%)	130 (29%)	176 (33%)	77 (37%)	..
KPS					0·92
≥80 points	1036 (87%)	395 (87%)	459 (86%)	182 (88%)	..
≤70 points	158 (13%)	60 (13%)	72 (14%)	26 (13%)	..
RPA class					0·76
1	334 (28%)	134 (29%)	141 (27%)	59 (28%)	..
2	819 (69%)	304 (67%)	371 (70%)	144 (69%)	..
3	41 (3%)	17 (4%)	19 (4%)	5 (2%)	..
Neurological symptoms					0·085
No	835 (70%)	335 (74%)	357 (67%)	143 (69%)	..
Yes	359 (30%)	120 (26%)	174 (33%)	65 (31%)	..
MMSE score					
Median (IQR)	28 (25–30)	28 (25–30)	28 (25–30)	28 (25–30)	0·66
Range	7–30	7–30	17–30	9–30	..
≥27 points	750 (63%)	279 (61%)	339 (64%)	132 (64%)	0·74
Cumulative tumour volume, mL					
Mean (SD)	2·84 (2·91)	2·27 (2·38)	3·07 (3·08)	3·54 (3·25)	<0·0001
Range	0·01–14·96	0·01–9·90	0·02–14·96	0·02–13·90	..
≥1·9 mL	601 (50%)	195 (43%)	279 (53%)	127 (61%)	<0·0001
Maximum diameter of the largest tumour (cm)					
Mean (SD)	1·63 (0·68)	1·60 (0·69)	1·66 (0·68)	1·62 (0·64)	0·49
Range	0·08–2·99	0·11–2·98	0·11–2·99	0·08–2·97	..
≥1·6 cm	600 (50%)	221 (49%)	273 (51%)	106 (51%)	0·65

Data are number (%), unless otherwise specified. Clinical characteristics were measured mainly on the day of stereotactic radiosurgery, or uncommonly on the day before. GI=gastrointestinal. KPS=Karnofsky performance status. RPA=recursive partitioning analysis.[29] MMSE=Mini-Mental State Examination.

***Table 1*: Clinical characteristics of patients, measured immediately before stereotactic radiosurgery**

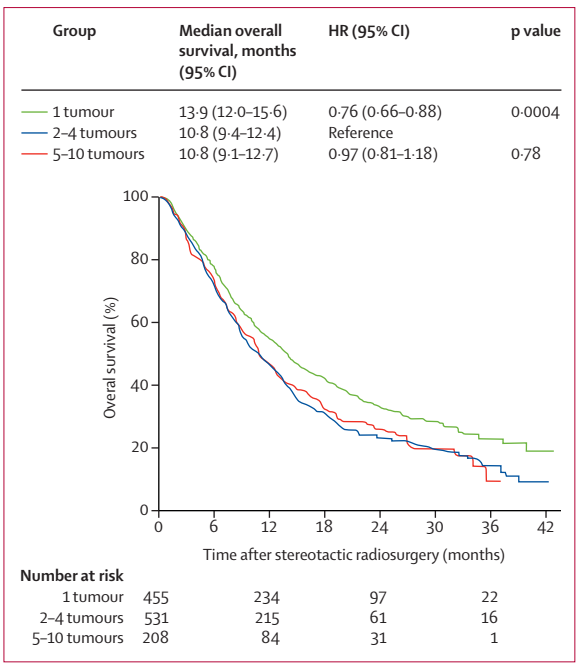

Figure: **Kaplan-Meier curves of overall survival**
HR=hazard ratio.

Outcomes

We split the patients into groups based on the number of tumours observed on initial MRI. The primary endpoint was overall survival, defined as the interval between stereotactic radiosurgery and death due to any cause, or the day of the last follow-up. Secondary endpoints were neurological death (all patients with uncertain causes of death were categorised into the neurological death group), neurological deterioration, local recurrence of the treated tumour, appearance of new lesions, leptomeningeal dissemination and leukoencephalopathy, repeat stereotactic radiosurgery, salvage WBRT, stereotactic radiosurgery-induced major complications, and maintenance of neurocognitive function. For each endpoint, failure to achieve the endpoint was regarded as an event, any other outcome was censored. Criteria for each secondary endpoint have been previously described.[16,17]

Statistical analysis

Based on one investigator's (TSe) database including more than 2000 patients with brain metastases who underwent stereotactic radiosurgery, we predicted 12-month overall survival for patients with five to ten brain tumours to be 33% and for those with two to four tumours to be 37%.[16,17] We calculated that enrolment of 1200 patients would provide power of at least 80% to show non-inferiority for patients with five to ten tumours compared with those with two to four, on the basis of the estimated proportion of patients expected to survive for 1 year, with a non-inferiority margin as the value of the upper 95% CI for a hazard ratio [HR] of 1·30, which we considered to be a clinically acceptable margin. Additional assumptions in sample-size calculations were that the ratio of the number of patients enrolled into each group (one tumour; two–four tumours; or five–ten tumours) would be 2:1:1, that follow-up would continue for at least 12 months after enrolment of the last patient, and that 10% of patients would be lost to follow-up. Non-inferiority would be established if the upper limit of the two-sided 95% CI for the between-group difference in mortality was less than the margin, at an α level of 0·05.

We analysed all data by intention to treat. For the baseline variables, we constructed summary statistics, with frequencies and proportions for categorical data, and means and SDs for continuous variables. We compared patient characteristics using the Fisher's exact test for categorical outcomes and *t* tests or the Wilcoxon rank sum test for continuous variables, as appropriate.

We analysed the primary endpoint with the Cox proportional hazards model with prognostic factors as covariates, and generated Kaplan-Meier curves to display event distributions over time. For the aforementioned secondary endpoint analyses of time-to-event outcomes, we did a competing risk analysis with the Fine–Gray generalisation of the proportional hazards model accounting for death as a competing risk.[27,28] 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 follow-up of participants who develop a competing event is merely censored. However, this assumption is invalid because the outcome of interest can no longer occur in participants who develop the competing event, and such analyses will therefore overestimate the probability of the outcome of interest.

All statistical analyses were done by our statistician (YS), who was not involved in either stereotactic radiosurgery treatment or patient follow-up, using SAS software version 9.3 and the R statistical program, version 2.13.

This study is registered with the University Medical Information Network (UMIN) Clinical Trial Registry, number 000001812.

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the final responsibility for the decision to submit for publication.

Results

We recruited 1194 eligible patients between March 1, 2009, and Feb 15, 2012, from 23 participating facilities (appendix). Follow-up ended on Dec 31, 2012, and the database was finalised on Jan 5, 2013. We did not attempt to do an interim analysis for the primary endpoint. 12 additional patients who had been enrolled were not included in the

See Online for appendix

	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)*	p value
Age, years (≥65 *vs* <65)	1·412 (1·229–1·622)	<0·0001	1·351 (1·174–1·554)	<0·0001
Sex (male *vs* female)	1·427 (1·242–1·655)	<0·0001	1·377 (1·179–1·608)	<0·0001
KPS (≤70 *vs* ≥80)	2·079 (1·729–2·500)	<0·0001	1·529 (1·240–1·886)	<0·0001
Number of tumours				
2–4 *vs* 1	1·313 (1·131–1·525)	0·0001	1·328 (1·141–1·546)	0·0003
5–10 *vs* 2–4	0·974 (0·806–1·177)	0·78	0·993 (0·819–1·204)	0·94
Maximum diameter of largest tumour (≥1·6 cm *vs* <1·6 cm)	1·431 (1·249–1·638)	<0·0001	1·006 (0·771–1·314)	0·92
Cumulative tumour volume (≥1·9 mL *vs* <1·9 mL)	1·503 (1·313–1·721)	<0·0001	1·172 (0·899–1·530)	0·24
Primary tumour category				
Breast *vs* lung	0·743 (0·584–0·945)	0·014	0·881 (0·673–1·153)	0·36
GI *vs* lung	1·750 (1·373–2·231)	<0·0001	1·407 (1·087–1·822)	0·0094
Renal cell *vs* lung	1·063 (0·718–1·573)	0·76	0·964 (0·648–1·434)	0·13
Others *vs* lung	1·572 (1·096–2·255)	0·021	1·333 (0·922–1·927)	0·86
Extracerebral disease status (not controlled *vs* controlled)	1·385 (1·200–1·589)	<0·0001	1·272 (1·101–1·469)	0·0011
Neurological symptoms (yes *vs* no)	1·779 (1·541–2·053)	<0·0001	1·334 (1·117–1·594)	0·0013

Clinical factors were measured before stereotactic surgery. HR=hazard ratio. KPS=Karnofsky performance status. GI=gastrointestinal. *HR adjusted for all clinical factors listed in this table.

***Table 2*: Clinical factors affecting survival after stereotactic radiosurgery**

	Median overall survival, months (95% CI)				HR (95% CI); p value	
	Total (n=1194)	1 tumour (A) (n=455)	2–4 tumours (B) (n=531)	5–10 tumours (C) (n=208)	A *vs* B	B *vs* C
Lung	12·5 (11·2–13·4)	13·4 (11·7–15·5)	11·4 (9·5–13·1)	12·5 (10·3–14·9)	0·796 (0·671–0·945); p=0·0090	1·045 (0·842–1·297); p=0·69
Breast	14·8 (11·9–24·4)	27·2 (8·2–NE)	13·7 (10·9–23·6)	10·5 (5·2–NE)	0·761 (0·449–1·290); p=0·31	0·806 (0·441–1·475); p=0·48
GI tract	6·7 (5·7–8·7)	14·4 (6·7–18·2)	5·7 (4·7–7·9)	5·7 (1·5–7·9)	0·409 (0·244–0·685); p=0·0006	0·673 (0·306–1·484); p=0·33
Kidney	13·7 (6·0–17·0)	16·3 (6·0–NE)	13·7 (5·1–17·0)	3·8 (2·3–5·4)	0·511 (0·221–1·183); p=0·12	0·207 (0·040–1·082); p=0·10
Others	8·4 (6·1–10·3)	7·3 (3·3–24·3)	8·6 (1·0–14·8)	9·0 (2·9–27·3)	0·779 (0·335–1·811); p=0·56	1·263 (0·495–3·215); p=0·63

HR=hazard ratio. NE=not estimable. GI=gastrointestinal.

***Table 3*: Median overall survival for five primary cancer sites**

study; two had pathological abnormalities that were verified to be glioblastoma rather than brain metastases after enrolment and the other ten patients requested withdrawal from the study and were subsequently excluded on ethical grounds. Table 1 summarises clinical characteristics, measured immediately before stereotactic radiosurgery, overall and for the three study groups. Although cumulative tumour volumes were larger in patients with a greater number of tumours (p<0·0001), all other clinical factors did not significantly differ between study groups (table 1).

Median follow-up after stereotactic radiosurgery in the 344 (29%) surviving patients was 20·9 months (IQR 12·6–29·5; 95% CI 20·8–22·8), and 850 patients (71%) died. Median overall survival after stereotactic radiosurgery in all patients was 12·0 months (95% CI 10·8–13·0). Post-stereotactic radiosurgery survival was 73·8% (95% CI 71·4–75·6) at 6 months, 50·0% (47·6–52·4) at 12 months, 27·5% (25·1–29·9) at 24 months, and 17·2% (15·1–19·4) at 36 months. Causes of death were confirmed to be non-brain diseases in 779 (92%) patients and brain diseases in 71 (8%) patients.

Median overall survival after stereotactic radiosurgery was significantly longer in patients with one tumour than in those with two to four tumours (13·9 months [95% CI 12·0–15·6] *vs* 10·8 months [9·4–12·4]; HR 0·76 [95% CI 0·66–0·88]; p=0·0004) and those with five to ten tumours (10·8 months [9·1–12·7]; HR 0·78 [95% CI 0·65–0·96]; p=0·019; figure). However, median overall survival for the two groups of patients with more than one tumour were the same (HR 0·97 [95% CI 0·81–1·18]; p=0·78; $p_{non\text{-}inferiority}$<0·0001). Of the various clinical factors measured before stereotactic radiosurgery, results of multivariable analyses showed that a solitary tumour, female sex, age younger than 65 years, KPS 80 points or higher, stable extracranial disease, and no neurological symptoms significantly favoured longer survival (table 2). Although univariable analyses showed that volume-related factors—ie, maximum diameter of the largest tumour (<1·6 cm) and cumulative tumour volume

	Total (n=1194)	1 tumour (A) (n=455)	2–4 tumours (B) (n=531)	5–10 tumours (C) (n=208)	p value (B *vs* C)
Died	850 (71%)	310 (68%)	392 (74%)	148 (71%)	0·46
Neurological death*	71 (8%)	32 (10%)	25 (6%)	14 (9%)	0·27
Deterioration of neurological function	146 (12%)	56 (12%)	62 (12%)	28 (13%)	0·53
Local recurrence†	138 (13%)	65 (16%)	54 (11%)	19 (10%)	0·78
New lesions†	625 (58%)	199 (48%)	297 (63%)	129 (69%)	0·12
Leptomeningeal dissemination†	144 (13%)	48 (12%)	61 (13%)	35 (19%)	0·067
Leukoencephalopathy†	9 (1%)	3 (1%)	4 (1%)	2 (1%)	0·68
Salvage SRS procedures	459 (38%)	148 (33%)	221 (42%)	90 (43%)	0·74
1	256 (21%)	76 (17%)	129 (24%)	51 (25%)	0·92
2	113 (9%)	45 (1%)	47 (9%)	21 (10%)	
≥3	90 (8%)	27 (6%)	45 (8%)	18 (9%)	
Salvage WBRT	107 (9%)	36 (8%)	54 (10%)	17 (8%)	0·48
Salvage surgery	23 (2%)	12 (3%)	8 (2%)	3 (1%)	1·00
Systemic anticancer agents	861 (72%)	308 (68%)	387 (73%)	166 (70%)	0·059
Molecularly targeted agents	356 (30%)	123 (27%)	157 (30%)	76 (37%)	0·078

Data are number (%), unless otherwise specified. SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy. *Percentages based on the number of patients who died. †Based on 1074 (90%) patients (414 [91%] in group A, 474 [89%] in group B, and 186 [89%] in group C; differences between proportions of patients with data, p=0·64), because MRI results were not available for 120 (10%) patients who had an early death or had remarkable deterioration of clinical state soon after stereotactic radiosurgery.

Table 4: **Treatment outcomes after stereotactic radiosurgery**

(1·9 mL)—significantly affected patient survival, none were significant predictors of longer survival on multivariable analysis. Survival duration did not differ between patients with two to four tumours compared with those with five to ten tumours (adjusted HR 0·99 [95% CI 0·82–1·20], p=0·94; $p_{non\text{-}inferiority}$<0·0001). Therefore, non-inferiority for efficacy was proven even after adjusting for prognostic factors.

In each of the five major sites of primary cancer, median overall survival of patients with five to ten tumours did not differ significantly from those with two to four (table 3); however, except for those for lung and breast cancers, the sample sizes did not provide adequate statistical power—ie, fewer than ten patients with five to ten tumours had each of the three other primary cancers (table 1).

Incidences of neurological death, deterioration of neurological function, local recurrence, appearance of new lesions, leptomeningeal dissemination, leukoencephalopathy, and use of salvage stereotactic radiosurgery, WBRT, and surgery did not differ significantly between patients with two to four tumours and those with five to ten tumours (table 4). Of the 850 deceased patients, the number of deaths caused by brain disease progression were similar between groups (table 4). Cumulative incidences of neurological death at 6 months, 12 months, and 24 months after stereotactic radiosurgery did not significantly differ between patients with two to four tumours, and those with five to ten, nor did cumulative incidences of neurological deterioration after stereotactic radiosurgery (table 5).

Three of the four secondary endpoints based on follow-up MRI—ie, post-stereotactic radiosurgery cumulative incidences of local recurrence, new lesion appearance, and leukoencephalopathy—did not differ significantly between the two groups of patients with more than one tumour (table 5). MRI-detected leukoencephalopathy occurred in nine (1%) of the 1074 patients in whom follow-up MRI was available (three patients who had one tumour, four patients who had two to four tumours, and two patients who had five to ten tumours). This complication was detected after salvage WBRT in eight of these nine patients. In the other patient, leukoencephalopathy was reported by the referring physician to have probably been caused by several courses of systemic anticancer treatment. Although cumulative incidences of leptomeningeal dissemination at 12 months after stereotactic radiosurgery were similar in patients with more than one tumour, the incidence became significantly higher in patients with five to ten tumours than in those with two to four after month 12 (table 5). Regarding salvage treatment, the cumulative incidences of repeat stereotactic radiosurgery or salvage WBRT did not differ significantly between patients with two to four tumours and those with five to ten (table 5). Results of univariable and multivariable analyses into the effect of clinical factors measured before stereotactic radiosurgery on secondary endpoints are presented in the appendix.

Stereotactic radiosurgery-induced adverse events occurred in 101 (8%) patients (table 6), and the proportion of patients who had one or more event of any grade did not differ between the groups of patients with multiple tumours (50 [9%] patients with two to four tumours *vs* 18 [9%] patients with five to ten tumours; p=0·89). Distributions of CTCAE grades were much the same in the two groups (table 6). Four patients died (two patients with one tumour and one each in the other two groups), mainly due to adverse events; two patients (one with one tumour and one with two to four tumours) had tumour bleeding (1·2 months and 14·8 months after stereotactic radiosurgery), one (with one tumour) had expansion of stereotactic radiosurgery-induced necrosis (6·3 months after SRS), and the other (with five to ten tumours) had status epilepticus (16·6 months after stereotactic radiosurgery).

Of the 1132 (95%) patients who were assessed by MMSE before stereotactic radiosurgery (mean score 27 points [SD 3]; median score 28 points [IQR 25–30]), 750 (66%) patients had a score of 27 points or better and 382 (34%) patients had a score of 26 or worse. MMSE was done in 662 (66%) of 1003 surviving patients at month 4 after stereotactic radiosurgery, 366 (69%) of 533 at month 12, 128 (68%) of 189 at month 24, and 36 (92%) of 39 at month 36. Neurocognitive function (defined in table 6) was maintained in 136 (91%) of 152 patients with two to four tumours and 53 (88%) of 60 patients with five to ten tumours 12 months after stereotactic radiosurgery (p=0·60; table 6). Results were also very similar between groups at month 24 and month 36 after stereotactic radiosurgery (table 6).

Discussion

Our findings suggest that stereotactic radiosurgery without WBRT as the initial treatment for patients with five to ten brain metastases is non-inferior to stereotactic radiosurgery without WBRT in those with two to four brain metastases, in terms of overall survival and most of the secondary endpoints. The American Society of Radiation Oncology guideline[8] states that level 1 evidence only supports stereotactic radiosurgery without concurrent WBRT for patients with up to four brain metastases. However, debate continues as to how many tumours can or should be treated by stereotactic radiosurgery alone. In Karlsson and colleagues' study[15] of 1921 patients with brain metastases who received stereotactic radiosurgery, median overall survival did not significantly differ in patients with two, three to four, five to eight, or more than eight metastases, despite patients with just one tumour surviving longer than those with several tumours.[15] Additionally, results of Chang and colleagues' study[30] of 323 patients with brain metastases who received stereotactic radiosurgery showed that median overall survival did not significantly differ between patients with one to five, six to ten, 11–15, or more than 15 brain metastases. Yamamoto and colleagues[21] did a case-matched study to reappraise whether treatment results of stereotactic radiosurgery alone for patients with five or more tumours differ from those for patients with one to four tumours (548 patients each in group). Although the difference in median overall survival after stereotactic radiosurgery (0·9 months) between the two groups was statistically significant, this difference is not clinically meaningful. The patients with five or more tumours had non-inferior results to those with one to four tumours, in terms of neurological death, local recurrence, repeat stereotactic radiosurgery for new tumours, maintenance of good neurological state, and stereotactic radiosurgery-related complications. Particularly because, as Yamamoto and colleagues[12,14,31] previously reported, carefully selected patients with multiple brain metastases are not at excessively high risk for stereotactic radiosurgery-related complications. Nevertheless, these studies inevitably have limitations—eg, biases involving patient selection and information in studies done in only one or a few institutes. Our prospective study, in which such biases were greatly minimised by enrolling patients from 23 institutes, might provide more powerful information when existing treatment guidelines are revised in the near future (panel).

The central criticism of stereotactic radiosurgery without WBRT, for patients with multiple brain tumours, is that microscopic tumours might go untreated, and might need to be treated with salvage stereotactic radiosurgery or another treatment. Thus, WBRT is widely advocated. However, Aoyama and colleagues[5] showed that WBRT is only able to prevent new tumours arising for a maximum of 6 months after treatment. Many patients with brain metastases can survive for more than 1 year, outliving the effects of WBRT. Hanssens and colleagues[32] reported that stereotactic radiosurgery alone, which was based on high-resolution MRI, decreased the incidence of and prolonged the time to distant recurrences. In fact, in our study, cumulative incidences of both new lesion appearance and repeat stereotactic radiosurgery were nearly the same for both groups of patients who had more than one tumour (tables 4 and 5). Therefore, the availability of an alternative treatment for patients with multiple brain metastases allows WBRT to be reserved for subsequent treatment attempts—ie, for leptomeningeal dissemination or miliary

	Post-SRS cumulative rates (95% CI)			HR (95% CI)	p value
	6 months	12 months	24 months		
Neurological death*					
1 tumour	0·9% (0–1·7)	4·2% (2·4–6·1)	7·0% (4·5–9·5)	1·17 (0·69–1·97)	0·56
2–4 tumours	0·4% (0–0·9)	1·7% (0·6–2·9)	5·3% (3·2–7·3)	Reference	NA
5–10 tumours	1·4% (0–3·1)	4·3% (1·6–7·1)	7·1% (3·3–11·0)	1·47 (0·76–2·85)	0·25
Deterioration of neurological function†					
1 tumour	5·1% (3·0–7·1)	8·4% (5·8–10·9)	11·9% (8·8–15·0)	0·85 (0·59–1·22)	0·38
2–4 tumours	4·9% (3·1–6·7)	8·0% (5·7–10·4)	11·6% (8·8–14·5)	Reference	NA
5–10 tumours	5·2% (2·2–8·3)	8·7% (4·9–12·6)	13·0% (8·0–18·1)	1·15 (0·76–2·85)	0·54
Local recurrence‡§					
1 tumour	6·5% (4·1–8·9)	12·7% (9·5–15·9)	15·5% (11·9–19·2)	1·15 (0·80–1·65)	0·45
2–4 tumours	3·0% (1·4–4·5)	7·0% (4·6–9·3)	12·1% (8·9–15·3)	Reference	NA
5–10 tumours	4·3% (1·4–7·3)	6·5% (2·9–10·1)	9·8% (5·1–14·6)	0·90 (0·53–1·53)	0·70
New lesions§					
1 tumour	23·9% (19·8–28·0)	36·7% (32·0–41·4)	47·9% (43·0–53·0)	0·55 (0·46–0·66)	<0·0001
2–4 tumours	40·0% (35·5–44·4)	54·5% (50·0–59·0)	65·5% (60·9–70·1)	Reference	NA
5–10 tumours	45·9% (38·7–53·1)	63·8% (56·8–70·9)	72·0% (64·7–79·4)	1·22 (0·99–1·50)	0·067
Leptomeningeal dissemination§					
1 tumour	3·6% (1·8–5·4)	7·1% (4·6–9·6)	11·0% (7·8–14·2)	0·71 (0·48–1·04)	0·087
2–4 tumours	5·1% (3·1–7·1)	8·8% (6·2–11·3)	13·2% (9·9–16·5)	Reference	NA
5–10 tumours	4·9% (1·8–8·0)	11·7% (6·9–16·4)	21·9% (15·0–28·7)	1·58 (1·04–2·40)	0·035
Leukoencephalopathy§					
1 tumour	0·0%	1·1% (NE–2·4)	1·1% (NE–2·4)	0·55 (0·12–2·46)	0·43
2–4 tumours	0·0%	1·2% (0·0–2·4)	1·2% (0·0–2·4)	Reference	NA
5–10 tumours	0·0%	1·5% (NE–3·7)	1·5% (NE–3·7)	1·47 (0·27–8·13)	0·66
Repeat SRS					
1 tumour	12·1% (9·1–15·1)	23·1% (19·3–27·1)	31·9% (27·5–36·4)	0·57 (0·46–0·71)	<0·0001
2–4 tumours	22·8% (19·3–26·4)	34·6% (30·5–38·6)	43·1% (38·7–47·5)	Reference	NA
5–10 tumours	23·1% (17·3–28·8)	38·3% (31·6–45·1)	45·4% (38·0–52·7)	1·12 (0·88–1·44)	0·36
Whole-brain radiotherapy					
1 tumour	2·1% (0·8–3·5)	5·1% (3·1–7·1)	7·8% (5·2–10·4)	0·62 (0·41–0·95)	0·053
2–4 tumours	3·6% (2·0–5·2)	7·0% (4·9–9·3)	10·4% (7·6–13·1)	Reference	NA
5–10 tumours	1·4% (0–3·1)	5·4% (2·3–8·6)	9·1% (4·7–13·5	0·78 (0·45–1·34)	0·36

Detections of new lesions, meningeal dissemination, or leukoencephalopathy were regarded as events, any other outcomes were censored. Either repeat SRS or salvage WBRT was regarded as an event, any other outcomes were censored. SRS=stereotactic radiosurgery. HR=hazard ratio. NA=not applicable. NE=not estimable. *Death caused by any intracranial disease—ie, tumour recurrence, carcinomatous meningitis, cerebral dissemination, or progression of other untreated intracranial tumours. †A decrease in Karnofsky performance status score to less than 70 points due to neurological worsening. ‡Increased size of an enhanced area on post-contrast T1-weighted MRI and enlarged tumour core on T2-weighted MRI (more than 10% increase in the maximum diameter). §Based on 1074 (90%) patients (414 [91%] in group A, 474 [89%] in group B, and 186 [89%] in group C; differences between proportions of patients with data, p=0·64), because MRI results were not available for 120 (10%) patients because they had an early death or had remarkable deterioration of clinical state soon after.

Table 5: **Secondary endpoint analyses**

metastases treatable only with WBRT. As clearly shown in this study, cumulative incidences of leptomeningeal dissemination 12 months after stereotactic radiosurgery were similar in both groups of patients with multiple tumours (table 5), such that a combination of stereotactic radiosurgery and WBRT is not thought to be warranted as the initial treatment for patients with five to ten tumours. By contrast, newer approaches such as hippocampus-sparing WBRT and combined memantine and WBRT have shown promise in the reduction of declines in memory and cognitive function.[33,34]

	Total (n=1194)	1 tumour (A) (n=455)	2–4 tumours (B) (n=531)	5–10 tumours (C) (n=208)	p value (B *vs* C)
Treatment-related adverse events*					0·89†
None	1093 (92%)	422 (93%)	481 (91%)	190 (91%)	
Grade 1 and 2	69 (6%)	22 (5%)	36 (7%)	11 (5%)	..
Grade 3	20 (2%)	6 (1%)	10 (2%)	4 (2%)	..
Grade 4	8 (1%)	3 (1%)	3 (1%)	2 (1%)	..
Grade 5	4 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	..
Had MMSE at baseline	1132 (95%)	430 (95%)	504 (95%)	198 (95%)	..
Maintained neurocognitive function‡					
4 months after SRS	623/662 (94%)	243/256 (95%)	263/284 (93%)	117/122 (96%)	0·27
12 months after SRS	333/366 (91%)	141/154 (92%)	139/152 (91%)	53/60 (88%)	0·60
24 months after SRS	120/128 (94%)	55/60 (92%)	47/48 (98%)	18/20 (90%)	0·20
36 months after SRS	28/30 (93%)	14/15 (93%)	10/11 (91%)	4/4 (100%)	1·00

Data are number of patients with one or more adverse event (%), unless otherwise specified. MMSE=Mini-Mental State Examination. SRS=stereotactic radiosurgery. *Graded according to Common Terminology Criteria for Adverse Events, version 3.0.[26] †p value is for the number of patients with no adverse events versus the number with at least one or more grade 1–5 adverse event across all three tumour number groups. ‡Number of patients whose MMSE score did not decrease by 3 points or more from baseline (ie, same day or one day before or after SRS); percentages are based on the number of patients who completed MMSE at that timepoint.[5]

Table 6: **Adverse events and maintenance of neurocognitive function**

Panel: Research in context

Systematic review

We searched PubMed for reports published from Jan 1, 1990, to Dec 31, 2013, that contained the terms "stereotactic radiosurgery", "brain metastases", "multiple tumors", and "prospective study". This search identified 24 citations, which we then manually restricted to prospective studies with more than 1000 participants. No study fulfilling these criteria was identified.

Interpretation

To our knowledge, our study of 1194 patients is the first sufficiently powered prospective observational investigation to examine whether stereotactic radiosurgery without whole-brain radiotherapy (WBRT) as the initial treatment for patients with five to ten brain metastases is non-inferior to that for patients with two to four brain metastases in terms of overall survival. Our results show the non-inferiority of stereotactic radiosurgery without WBRT for patients with five to ten brain metastases as compared with those with two to four tumours. This result challenges the practice of inconsistent use of stereotactic radiosurgery for patients with five or more brain metastases, in whom most treatment guidelines still strongly recommended WBRT, and provides evidence in favour of offering stereotactic radiosurgery to patients with multiple brain metastases. Existing treatment guidelines for the management of patients with brain metastases might need to be revised in the near future.

The major weakness of our study might be the absence of a pretreatment case-control technique—ie, each researcher arbitrarily registered patients considered to meet the inclusion criteria. Thus, the ratio of the number of patients in the three groups was 2:2:1, certainly different from the 2:1:1 we had expected at the start of this study. However, although this difference weakened the statistical power, the non-inferiority hypothesis was still clearly proven. Also, clinical factors measured before stereotactic radiosurgery were minimally biased in the three groups (table 1). Although increases in cumulative tumour volumes correlated significantly with increased tumour numbers, this bias is not considered to have reduced the quality of the present study because increased tumour volume is apparently an unfavourable factor for longer survival. In fact, multivariable analyses in this study showed that tumour size-related factors did not significantly affect survival (table 2). Nevertheless, our results showed that stereotactic radiosurgery alone for patients with five to ten brain metastases is non-inferior to that for patients with two to four brain metastases, if total intracranial tumour burdens are similar. However, some bias was apparent in systemic anticancer therapy given after stereotactic radiosurgery between groups of patients with multiple tumours—ie, more patients with five to ten tumours were given these agents than were those with four or fewer tumours (table 4). Although the differences were not statistically significant, this finding might have affected our results.

We justify the use of our study design because non-inferiority testing for our one-group treatment strategy, rather than a randomised controlled trial, is often applied in clinical studies in which a randomised controlled trial would be difficult to undertake—eg, those assessing surgery or radiotherapy.

Another potential weakness of this study is that many patients did not have MRI or MMSE follow-up data, which clearly weakens our results for cumulative incidences of new lesion appearance, local recurrence, and leukoencephalopathy, as well as MMSE outcomes. However, the robustness of our findings is, at least, not thought to affect the results for the primary endpoint. Furthermore, we used four different methods to assess the MMSE data: complete-case analysis, last observation carried forward (LOCF), worst observation carried forward (WOCF), and the pattern-mixture model (PM) for sensitivity analyses (appendix). The three missing data analyses (LOCF, WOCF, PM) yielded results similar to those of the complete-case analysis, and the missing data did not affect the results. Therefore, we assume our findings to be robust. However, in the case of data that are not missing at random, these inferential techniques that are valid for missing-at-random data are typically no longer valid.

Further research on this topic is currently ongoing. The North American Gamma Knife Consortium is undertaking a prospective randomised study into neurocognitive outcomes in patients given radiotherapy for five or more

brain metastases (NCT01731704). The results are expected to clarify the role of stereotactic radiosurgery without WBRT versus WBRT for multiple brain metastases.

Contributors

MY, TSe, TShu, AA, YH, JK, KY, KTa, NS, EK, HA, SM, and KTs participated in the design. MY, TSe, TShu, AA, HJ, SY, ON, HK, AM, SS, YKid, YI, MH, HO, MG, MS, TA, KK, YKik, TShi, TG, MT, and YM participated in data collection. MY, TSe, TShu, AA, YH, JK, KY, and YS participated in data analysis. All authors participated in data interpretation, drafting, and finalising the report.

Declaration of interests

The authors declare that they have no competing interests.

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