Stereotactic Radiosurgery Plus Whole-Brain Radiation Therapy vs Stereotactic Radiosurgery Alone for Treatment of Brain Metastases: A Randomized Controlled Trial

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Stereotactic Radiosurgery Plus Whole-Brain Radiation Therapy vs Stereotactic Radiosurgery Alone for Treatment of Brain Metastases

A Randomized Controlled Trial

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Context In patients with brain metastases, it is unclear whether adding up-front whole-brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) has beneficial effects on mortality or neurologic function compared with SRS alone.

Objective To determine if WBRT combined with SRS results in improvements in survival, brain tumor control, functional preservation rate, and frequency of neurologic death.

Design, Setting, and Patients Randomized controlled trial of 132 patients with 1 to 4 brain metastases, each less than 3 cm in diameter, enrolled at 11 hospitals in Japan between October 1999 and December 2003.

Interventions Patients were randomly assigned to receive WBRT plus SRS (65 patients) or SRS alone (67 patients).

Main Outcome Measures The primary end point was overall survival; secondary end points were brain tumor recurrence, salvage brain treatment, functional preservation, toxic effects of radiation, and cause of death.

Results The median survival time and the 1-year actuarial survival rate were 7.5 months and 38.5% (95% confidence interval, 26.7%-50.3%) in the WBRT + SRS group and 8.0 months and 28.4% (95% confidence interval, 17.6%-39.2%) for SRS alone ($P=.42$). The 12-month brain tumor recurrence rate was 46.8% in the WBRT + SRS group and 76.4% for SRS alone group ($P<.001$). Salvage brain treatment was less frequently required in the WBRT + SRS group (n = 10) than with SRS alone (n = 29) ($P<.001$). Death was attributed to neurologic causes in 22.8% of patients in the WBRT + SRS group and in 19.3% of those treated with SRS alone ($P=.64$). There were no significant differences in systemic and neurologic functional preservation and toxic effects of radiation.

Conclusions Compared with SRS alone, the use of WBRT plus SRS did not improve survival for patients with 1 to 4 brain metastases, but intracranial relapse occurred considerably more frequently in those who did not receive WBRT. Consequently, salvage treatment is frequently required when up-front WBRT is not used.

Trial Registration umin.ac.jp/ctr Identifier: C000000412

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BRAIN METASTASES OCCUR IN 20% to 40% of all patients with cancer and are generally associated with a poor prognosis.[1,2] The most common route of metastatic dissemination resulting in brain metastases is hematogenous, and it is therefore presumed that the entire brain is "seeded" with micrometastatic disease, even when only a single intracranial lesion is detected. Consequently, whole-brain radiation therapy (WBRT) has been a mainstay of treatment.[1,2]

Recently, the assumption that the entire brain is seeded with micrometastases in all patients with overt brain metastases has been questioned, prompting

For editorial comment see p 2535.

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a contrarian philosophy that in some patients, the intracranial disease is truly limited—the so-called oligometastases situation. For patients who truly have limited intracranial disease, the potential exists that WBRT could be replaced by focal therapeutic options such as resection or stereotactic radiosurgery (SRS), which delivers high-dose, focal radiation.[1-4]

The adverse effects of WBRT require a further examination of its role. Acute adverse effects are generally limited in severity and duration; however, the long-term risks of serious and permanent toxic effects, including cognitive deterioration and cerebellar dysfunction, are poorly understood.[5,6] In the attempt to minimize potential long-term morbidity following WBRT, treatments initially relying on focal therapeutic options are being used with increasing frequency. Although there have been several retrospective reports,[7-14] only 1 prospective randomized study compared the outcome of conventional surgery alone and surgery followed by WBRT.[6] Sneed et al[7] collected raw data on 983 patients from 10 institutions and suggested that there was no survival difference between patients treated with SRS alone and those treated with WBRT plus SRS. Flickinger et al[8] reviewed 116 patients with solitary brain metastases who underwent SRS with or without fractionated large-field radiotherapy and found improved local control, but not improved survival, with the addition of fractionated large-field radiotherapy. Regine et al[9] suggested that SRS alone is associated with an increasingly significant risk of brain tumor recurrence and neurologic deficit with increasing survival time. Pirzkall et al[10] showed a trend for superior local control and survival when SRS was combined with WBRT in 236 patients with 311 brain metastases. Aoyama et al,[11] Chidel et al,[12] and Shirato et al[13] have all shown that omission of WBRT from initial management was not detrimental in terms of overall survival, but brain tumors recurred in more than 50% of patients treated in this manner. Patchell et al[6] have shown that patients with cancer and single metastases to the brain who receive treatment with surgical resection and postoperative WBRT have fewer recurrences of cancer in the brain and are less likely to die of neurologic causes than are similar patients treated with surgical resection alone.

Herein, we report the results of a prospective, multi-institutional, randomized controlled trial comparing WBRT plus SRS vs SRS alone for patients with limited (defined as ≤4) brain metastases. Through a literature search and examination of clinical trial registries, we confirmed that this is the first multi-institutional, prospective, randomized comparison of WBRT plus SRS vs SRS alone.

METHODS

Eligibility Criteria

Patients were eligible who were aged 18 years or older with 1 to 4 brain metastases, each with a maximum diameter of no more than 3 cm on contrast-enhanced magnetic resonance imaging (MRI) scans, derived from a histologically confirmed systemic cancer. Patients with metastases from small cell carcinoma, lymphoma, germinoma, and multiple myeloma were excluded. Eligible patients had a Karnofsky Performance Status (KPS) score of 70 or higher. The protocol was approved by the institutional review boards of Hokkaido University, Sapporo, Japan, and of 10 other institutions that participated in the trial through the Japanese Radiation Oncology Study Group (JROSG 99-1). Written informed consent was obtained from each patient before entry into the study.

Randomization and Treatment

Randomization was performed at the Hokkaido University Hospital Data Center. A permuted-blocks randomization algorithm was used with a block size of 4. A randomization sheet was created for each institution. After written informed consent was obtained, eligible patients were randomly assigned to receive either up-front WBRT combined with SRS or SRS without up-front WBRT. Prior to randomization, the patients were stratified based on number of brain metastases (single vs 2-4), extent of extracranial disease (active vs stable), and primary tumor site (lung vs other sites). Extracranial disease was considered to be stable when the tumor had been clinically controlled for 6 months or longer prior to the detection of brain metastases.

The WBRT dosage schedule was 30 Gy in 10 fractions over 2 to 2.5 weeks. The WBRT treatment visit proceeded to SRS when patients were assigned to the WBRT + SRS group. The SRS dose was prescribed to the tumor margin. Metastases with a maximum diameter of up to 2 cm were treated with doses of 22 to 25 Gy and those larger than 2 cm were treated with doses of 18 to 20 Gy. The dose was reduced by 30% when the treatment was combined with WBRT because the optimal combination of WBRT and SRS had not been studied in well-conducted, prospective, phase 1 dose escalation trials. In the 1990s, the Radiation Therapy Oncology Group (RTOG) initiated a phase 1 dose escalation trial of SRS alone in patients who had previously undergone radiation treatment.[14] This trial was stopped early without reaching the maximum tolerance dose, and tumor size–dependent dose recommendations for SRS alone were described. No phase 1 trial has ever tested the combination of WBRT and SRS doses. Therefore, there is no well-known or scientifically recommended dose for the combination of WBRT and SRS. There are clearly concerns that the combination could be potentially deleterious. Therefore, various studies have adopted different approaches for selection of the dose combinations to be tested. Several retrospective data suggested that the RTOG dose guidelines might be associated with a higher frequency of late radiation toxic effects when used with WBRT.[10,15] Our preexisting experience of SRS with a 30% reduced SRS dose

combined with WBRT indicated that there is not a significant difference in local tumor control (data not shown) compared with SRS with the dose suggested in the RTOG protocol. Therefore, we decided to use a 30% reduced SRS dose in the WBRT + SRS group in this study.

Follow-up Protocol

We performed clinical evaluations and MRI scans 1 and 3 months after treatment and every 3 months thereafter. In cases in which a recurrence was detected, further treatment was administered at the discretion of the attending physician. The size of the treated lesions was measured in 3 dimensions, and this size, the development of new brain metastases, and the development of leukoencephalopathy associated with radiological findings (according to the National Cancer Institute's Common Toxicity Criteria version 2.0[16]) were scored based on serial MRI scans. Local tumor progression was defined as a radiographic increase of 25% or more in the size of a metastatic lesion (bidimensional product). If an MRI result showed central or heterogeneous low intensity and if the lesion size decreased on serial studies, brain necrosis was scored; positron emission tomography or surgical resection was encouraged as appropriate to confirm MRI findings.

At each visit, functional status and neurologic toxic effects were scored. Systemic functional status was evaluated by using the KPS score. Neurologic function was evaluated according to the criteria listed in TABLE 1.[17] Neurosurgeons or radiation oncologists specializing in neuro-oncology measured the neurologic status as well as the KPS score at the clinic. We did not attempt to blind the investigators with regard to patients' treatment assignments. Systematic functional status and neurologic function were scored by the physicians who treated the patients. An acute toxic effect was identified as an event that arose within 90 days of the initiation of radiotherapy and a late toxic effect was considered as an event that occurred thereafter, according to the central nervous system toxicity criteria listed among the RTOG Late Radiation Morbidity Scoring Criteria.[18] For all patients who died, the cause of death was determined. The cause of death was determined by autopsy in 1 patient and by clinical evaluation based on the definition proposed by Patchell et al[6] in all other patients. Patients were considered to have died of neurologic causes if they had stable systemic disease and

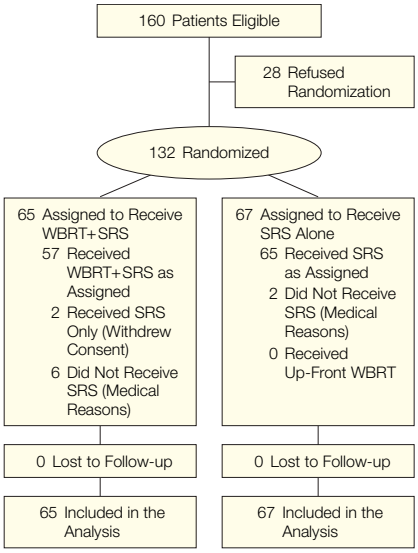
Table 1. Baseline Characteristics*

Characteristics	WBRT + SRS (n = 65)	SRS Alone (n = 67)
Age at diagnosis, mean (range), y	62.5 (36-78)	62.1 (33-86)
<65	32 (49)	34 (51)
≥65	33 (51)	33 (49)
Men	46 (71)	53 (79)
No. of brain metastases		
1	31 (48)	33 (49)
2-4	34 (52)	34 (51)
Primary tumor site		
Breast	6 (9)	3 (4)
Lung	43 (66)	45 (67)
Colorectal	5 (8)	6 (9)
Kidney	5 (8)	5 (7)
Other	6 (9)	8 (12)
Primary tumor status		
Stable	30 (46)	33 (49)
Active	35 (54)	34 (51)
Extracranial metastases		
Stable	41 (63)	38 (57)
Active	24 (37)	29 (43)
RPA		
Class 1 (aged <65 years; no active extracranial disease)	11 (17)	8 (12)
Class 2 (aged ≥65 years; active extracranial disease)	54 (83)	59 (88)
Histological status		
Squamous cell	11 (17)	11 (16)
Adenocarcinoma	43 (66)	43 (64)
Large cell	2 (3)	4 (6)
Other	9 (14)	9 (13)
KPS score†		
70-80	31 (48)	23 (34)
90-100	34 (52)	44 (66)
Neurologic function		
No symptoms (grade 0)	38 (59)	47 (70)
Minor symptoms, fully active without assistance (grade 1)	12 (18)	13 (19)
Moderate symptoms; fully active but requires assistance (grade 2)	8 (12)	4 (6)
Moderate symptoms; less than fully active, requires assistance (grade 3)	7 (11)	3 (5)
Severe symptoms; totally inactive (grade 4)	0	0
Chemotherapy after brain treatment	18 (38)	19 (40)
Maximum diameter of brain metastases, cm		
Mean (SD)	1.53 (0.78)	1.42 (0.79)
Median (range)	1.40 (0.2-3.0)	1.30 (0.2-3.0)
SRS dose at the tumor margin, mean (SD), Gy	16.6 (3.6)	21.9 (2.7)

Abbreviations: KPS, Karnofsky Performance Status; RPA, recursive partition analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*Data are expressed as No. (%) of participants unless otherwise noted.
†A higher score indicates better performance.

progressive neurologic dysfunction. Patients with severe neurologic disability who died of intercurrent illness were also included among neurologic deaths, as were patients with both rapidly progressive systemic disease and advancing neurologic dysfunction, because these patients also represent brain treatment failures.

Figure 1. Flow of Study Participants



SRS indicates stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

End Points and Statistical Analysis

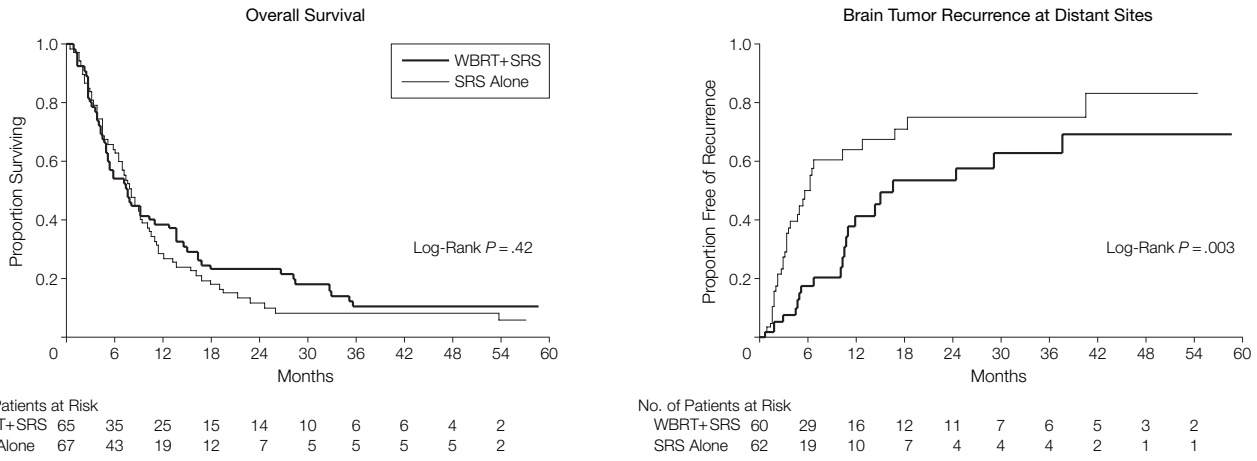
The primary end point of the study was overall survival. Secondary end points were cause of death, functional preservation, brain tumor recurrence, salvage treatment, and toxic effects of radiation. All analyses were conducted on an intention-to-treat basis. The study was designed to have 80% power to detect an absolute difference of 30% in the median survival time, with a 2-sided α level of .05. Using an estimated median survival time of 8.7 months for the group receiving SRS alone[11] and a follow-up time of 15 months, the sample size required to detect this difference was 89 patients per group. An interim analysis was planned wherein 50 patients would be assigned to each group to determine whether the sample size was large enough to show a significant difference with a 2-sided α level of .05. End points were measured beginning at the date of randomization. Univariate analyses were carried out by the Kaplan-Meier method.[19] We assumed that the survival rate was always higher in the WBRT + SRS group than in the SRS-alone group based on the suggestions in a retrospective study, and we used the log-rank test to compare differences between the groups. The χ^2 test was used to determine the relationship between 2 categorical variables, and the Fisher exact test was used when small cell sizes were encountered in 2×2 contingency tables. A 2-tailed t test was used to compare the means of continuous variables between the treatment groups. Multivariate analyses were performed to evaluate the factors selected via the univariate analyses ($P<.10$). Stratification in the randomization was taken into account in the statistical analysis. The Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals (CIs).[20] A 2-sided P value of .05 or less was considered to reflect statistical significance. Additional covariates were examined as appropriate and are noted in the "Results" section. All statistical analyses were initially performed by a physician (H.A.) using a commercial statistical software package (StatView version 5.0J, SAS Institute Inc, Cary, NC), and all results were verified by a statistician (G.K.) using a different software package (SAS, version 9.1, SAS Institute Japan Ltd, Tokyo, Japan).

RESULTS

Patients and Treatment

The recruitment period was from October 1999 to December 2003. There were

Figure 2. Overall Survival and Brain Tumor Recurrence at Distant Sites



The mean survival time was 7.5 months for patients receiving whole-brain radiation therapy (WBRT) plus stereotactic radiosurgery (SRS) and 8.0 months for patients receiving SRS alone. This difference was not significant ($P=.42$). There was a statistically significant decrease in brain tumor recurrence in the WBRT+SRS group ($P=.003$).

160 eligible patients, of whom 132 (83%) were randomized (65 to WBRT + SRS and 67 to SRS alone) (FIGURE 1). The date of last follow-up was April 2005. The interim analysis was performed with 122 patients (about 60 in each group), which takes into account the possible number of patients with protocol violations. Patient accrual was terminated before the planned final accrual number had been reached because the results of the interim analyses indicated that at least 805 patients were necessary to detect a significant difference in the primary end points. In addition, the numbers of patients appeared sufficient to detect a significant difference in brain tumor recurrence rates: 31 patients in each group were shown to be enough to detect a 30% difference in the median month of 50% brain tumor recurrence (16.2 months with WBRT + SRS vs 5.5 months with SRS alone).

There was no statistical difference between the groups in the baseline characteristics of the patients (Table 1). The median follow-up time was 7.8 months (range, 0.5-58.7 months) for the entire study and 49.2 months (range, 19.6-58.7 months) for survivors. Ninety-two percent of the patients included in the study completed the assigned treatment (Figure 1).

Survival and Cause of Death

By the time of the last follow-up visit in April 2005, 57 patients in the WBRT + SRS group and 62 patients in the SRS-alone group had died. Death was attributed to neurologic causes in 13 patients (22.8%) in the WBRT + SRS group and in 12 patients (19.3%) in the SRS-alone group ($\chi^2 = 0.21$; $P = .64$). The median survival time was 7.5 months with WBRT + SRS and 8.0 months with SRS alone. The higher median survival time with SRS alone was discordant with the 1-year actuarial survival rates of 38.5% (95% CI, 26.7%-50.3%) for the WBRT + SRS group and 28.4% (95% CI, 17.6%-39.2%) for the SRS-alone group ($P = .42$). FIGURE 2A shows that this discordance was due to the crossing of the 2 survival curves. The results of the univariate and multivariate analyses are shown in TABLE 2 and TABLE 3. The number of patients in each institution was too small to allow for a meaningful comparison among institutions. Recursive partition analysis was not included in the multivariate analysis because it is not independent of age and extracranial metastases. Treatment group was not found to be significant in either analysis.

Posttreatment Neurologic Toxicity

A summary of posttreatment neurologic toxicity is given in TABLE 4. Symptomatic acute neurologic toxicity was observed in 4 patients receiving WBRT + SRS and in 8 patients receiv-

Table 2. Univariate Survival Analysis

	No. of Participants	Survival Time, Median (Range), mo	*P* Value
Treatment group			
WBRT + SRS	65	7.5 (0.8-58.7)	.42
SRS alone	67	8.0 (0.5-57.0)	
Age, y			
<65	66	8.9 (0.9-58.7)	.07
≥65	66	6.5 (0.5-55.6)	
Sex			
Male	99	7.1 (0.5-58.7)	.20
Female	33	10.5 (0.8-57.0)	
No. of brain metastases			
1	68	8.6 (1.4-58.7)	.02
2-4	64	7.3 (0.5-55.6)	
Primary tumor site			
Lung	88	8.1 (0.5-58.7)	.33
Other	44	7.1 (0.9-57.0)	
Primary tumor status			
Stable	69	9.2 (0.9-58.7)	<.001
Active	63	6.5 (0.5-53.8)	
Extracranial metastases			
Stable	79	13.3 (1.1-58.7)	<.001
Active	53	6.1 (0.5-55.6)	
RPA			
Class 1	19	16.0 (0.9-58.7)	<.001
Class 2	113	7.5 (0.5-55.6)	
KPS score			
70-80	54	5.0 (0.5-58.7)	<.001
90-100	78	9.2 (0.8-57.0)	
Chemotherapy after brain treatment			
Yes	37	10.1 (1.3-53.8)	.34
No	95	6.8 (0.5-58.7)	

Abbreviations: KPS, Karnofsky Performance Status; RPA, recursive partition analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

Table 3. Multivariate Survival Analysis

Variables*	Hazard Ratio (95% CI)	*P* Value
Treatment group (WBRT + SRS)	1.37 (0.93-1.98)	.11
Age (<65 y)	1.48 (1.01-2.16)	.04
No. of brain metastases (1)	1.36 (0.94-1.97)	.10
Primary tumor status (stable)	1.62 (1.11-2.36)	.01
Extracranial metastases (stable)	2.35 (1.55-3.55)	<.001
KPS score (90-100)	1.69 (1.16-2.47)	.007

Abbreviations: CI, confidence interval; KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*Referents appear in parentheses.

Table 4. Treatment-Related Neurotoxic Effects*

	No. in WBRT + SRS Group (n = 65)				No. in SRS-Alone Group (n = 67)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Acute toxic effects	2	1	1	0	3	3	2	0
Seizure	0	0	1	0	1	2	1	0
Other	2	1	0	0	2	1	1	0
Late toxic effects	3	0	2	2	1	0	0	2
Radiation necrosis	1	0	0	2	0	0	0	1
Leukoencephalopathy	1	0	2	0	0	0	0	0
Other†	1	0	0	0	1	0	0	1
Radiological leukoencephalopathy	2	3	2	0	1	1	0	0

Abbreviations: SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*From the National Cancer Institute's Common Toxicity Criteria version 2.0.[16]
†Other effects included 1 case of slight lethargy (grade 1) in the WBRT + SRS group and 1 case each of seizure (grade 4) and headache (grade 1) in the SRS-alone group.

Table 5. Univariate Analysis of Development of New Metastases at Distant Brain Sites

	Actuarial Rate, %		Log-Rank *P* Value
	6 mo	12 mo	
Treatment group			
WBRT + SRS	17.5	41.5	.003
SRS alone	49.9	63.7	
Age, y			
<65	34.5	55.9	.65
≥65	33.9	49.0	
Sex			
Male	32.7	51.5	.39
Female	36.3	55.9	
No. of brain metastases			
1	27.3	39.2	.03
2-4	42.4	69.9	
Primary tumor site			
Lung	29.5	52.0	.40
Other	43.1	55.9	
Primary tumor status			
Stable	32.8	44.8	.20
Active	37.1	69.6	
Extracranial metastases			
Stable	29.5	38.4	.02
Active	37.3	69.3	
KPS score			
70-80	43.2	57.4	.05
90-100	29.9	50.8	
Chemotherapy after brain treatment			
Yes	37.1	59.0	.33
No	32.9	50.0	

Abbreviations: KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

ing SRS alone (*P*=.36), including 1 and 2 patients with grade 3 toxicity, respectively, in each group. The symptoms developed a median of 6 days after initiation of treatment (range, 1-64 days) in the WBRT + SRS group and 10 days (range, 1-86 days) in the SRS-alone group. Symptomatic late neurologic radiation toxic effects were observed in 7 patients in the WBRT + SRS group and in 3 patients in the SRS-alone group (*P*=.20). Toxic effects were experienced for a median of 15.6 months (range, 6.7-59.4 months) in the WBRT + SRS group and 6.2 months (range, 5.8-8.1 months) in the SRS-alone group. There were 3 cases of radiation necrosis (grade 1, n=1; grade 4, n=2), 3 cases of leukoencephalopathy (grade 1, n=1; grade 3, n=2), and 1 case of slight lethargy (grade 1) in the WBRT + SRS group. In patients receiving SRS alone, the following effects were observed: 1 case of radiation necrosis (grade 4), 1 of seizure (grade 4), and 1 of headache (grade 1). Radiation necrosis was diagnosed using positron emission tomography or surgical resection in all cases. Radiological findings consistent with leukoencephalopathy were observed in 7 patients in the WBRT + SRS group and in 2 patients in the SRS-alone group (*P*=.09). Three of these 9 patients also experienced symptomatic leukoencephalopathy; the other 6 patients were asymptomatic.

Brain Tumor Recurrence

Brain tumor recurrence at either distant or local sites in the brain was observed in 63 patients (23 in the WBRT + SRS group and 40 in the SRS-alone group). The 12-month actuarial brain tumor recurrence rate was 46.8% (95% CI, 29.7%-63.9%) in the WBRT + SRS group and 76.4% (95% CI, 63.3%-89.5%) in the SRS-alone group (*P*<.001).

Fifty-five patients had new brain metastases at distant sites (21 in the WBRT + SRS group and 34 in the SRS-alone group). The 12-month actuarial rate of developing new brain metastases was 41.5% (95% CI, 24.4%-58.6%) in the WBRT + SRS group and 63.7% (95% CI, 49.0%-78.4%) in the SRS-alone group (*P*=.003) (Figure 2B).

The multivariate analysis revealed that WBRT + SRS was associated with a reduced risk of recurrence (hazard ratio, 0.32; 95% CI, 0.18-0.58; $P<.001$) (TABLE 5 and TABLE 6).

During the follow-up period, 122 patients (92% of the total patients enrolled) had at least 1 follow-up MRI scan performed. In total, 581 follow-up MRI scans were performed; of these, 87 scans (15%) demonstrated new brain metastases; these 87 "event scans" were obtained in 55 patients. Sixteen percent of these "event scans" (14/87) were associated with neurologic symptoms at the time of the MRI examination.

A total of 247 metastases received initial treatment with SRS (117 in the WBRT + SRS group and 130 in the SRS-alone group). Follow-up MRI was available for 210 metastases (85%). The actuarial local tumor control rate at 12 months was 88.7% (95% CI, 80.1%-97.3%) in the WBRT + SRS group and 72.5% (95% CI, 60.3%-84.7%) in the SRS-alone group ($P=.002$) (FIGURE 3). The histopathological type (adenocarcinoma vs others) was not shown to be a significant factor ($P=.90$). The multivariate analysis also showed significantly better tumor control by WBRT + SRS treatment (hazard ratio, 4.83; 95% CI, 2.00-11.65; $P<.001$).

Salvage treatment for progression of brain tumor was required significantly more frequently in patients receiving SRS alone (29 patients) than in the WBRT + SRS group (10 patients) ($\chi^2=12.33$; $P<.001$). Salvage WBRT was applied in 11 patients in the SRS-alone group but was not used in any patients in the WBRT + SRS group. Salvage SRS was used in 19 patients in the SRS-alone group and in 9 patients in the WBRT + SRS group.

Systemic and Neurologic Functional Preservation

Systemic functional preservation rates (KPS score ≥70) at 12 months were 33.9% (95% CI, 22.2%-45.4%) in the WBRT + SRS group and 26.9% (95% CI, 16.3%-37.5%) in the SRS-alone group ($P=.53$). The decrease in the KPS score to below 70 was attributed to neurologic causes in 17 patients (29%) in the WBRT + SRS group and 14 (22%) in the SRS-alone group.

The actuarial rates of neurologic preservation at 12 months were 72.1% (95% CI, 58.8%-85.4%) with WBRT + SRS and 70.3% (95% CI, 55.6%-85.0%) with SRS alone ($P=.99$) when neurologic preservation was defined as a lack of any worsening of the neurologic grade on follow-up examination, compared with the pretreatment grade. In total, 85 patients (38 in the WBRT + SRS group and 47 in the SRS-alone group) did not have neurologic symptoms when brain metastases were diagnosed (grade 0). Among the 47 patients who had a pretreatment grade of 1 to 3, an improvement in neurologic status was observed at least once in 9 patients and 10 patients in the respective groups ($\chi^2=1.32$; $P=.24$). Deterioration of neurologic function was observed in 43 patients, including 7 who initially experienced improvement after treatment (22 in the WBRT + SRS group and 21 in the SRS-alone group; $\chi^2=0.09$; $P=.75$). This deterioration was attributed to either original or distant brain metastases in 13 patients (59%) in the WBRT + SRS group and 18 patients (86%) in the SRS-alone group ($\chi^2=3.78$; $P=.05$). Late neurologic radiation toxic effects were the cause of deterioration in 4 and 2 patients in each group, respectively. Either meningeal dissemination or spinal cord metastases induced neurologic deterioration in 5 and 1 patient in each group, respectively.

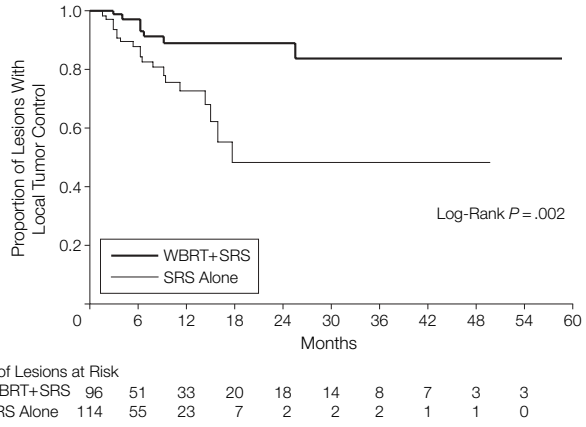
Neurocognitive function was optionally assessed using the Mini-Mental State Examination (MMSE). Among the 44 patients (25 in the WBRT + SRS group and 19 in the SRS-alone group) who lived 12 months or longer, MMSE data were available in 28 patients at least once (16 in the WBRT + SRS group and 12 in the SRS-alone group) at the median follow-up times of 30.5 months (range, 13.7-58.7 months) with WBRT + SRS and 20.7 months (range, 13.3-53.8 months) with SRS alone. The median MMSE pretreatment score was 28.0 (range, 23-30) in the WBRT + SRS

Table 6. Multivariate Analysis of Development of New Metastases at Distant Brain Sites

	Hazard Ratio (95% CI)	*P* Value
Treatment group (WBRT + SRS)	0.32 (0.18-0.58)	<.001
No. of brain metastases (2-4)	1.69 (0.97-2.93)	.06
Extracranial metastases (active)	2.06 (1.17-3.64)	.01
KPS score (70-80)	2.14 (1.17-3.93)	.01

Abbreviations: CI, confidence interval; KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

Figure 3. Local Tumor Control



There was a statistically significant increase in local tumor control in patients receiving whole-brain radiation therapy (WBRT) plus stereotactic radiosurgery (SRS) ($P=.002$).

group and 27.0 (range, 23-30) in the SRS-alone group. The median score at the final follow-up was 27.0 (range, 21-30) in the WBRT + SRS group and 28.0 (range, 18-30) in the SRS-alone group.

COMMENT

Stereotactic radiosurgery is a method of delivering high doses of focal radiation to a tumor while minimizing irradiation of the adjacent normal tissue. This approach was originally developed by the Swedish neurosurgeon Lars Leksell as a substitute for direct surgical intervention.[21] Stereotactic radiosurgery is now available worldwide, and it is increasingly used to treat brain metastases because it is less invasive compared with direct surgical intervention, although a direct randomized comparison of the 2 modes has not been performed to date.

Whole-brain radiation therapy has been a standard treatment for brain metastases for several decades.[1-4,6,7,17] In more recent years, the importance of focal aggressive therapy combined with WBRT has been increasingly recognized.[3,4,22-24] Andrews et al[4] recently reported the results from RTOG 9508, a multi-institutional phase 3 trial of 333 patients with 1 to 3 brain metastases who received WBRT with or without SRS boost. A statistically significant improvement in median survival with the addition of SRS was seen in patients with a single brain metastasis.

To reduce the risk of late radiation effects,[1,2,5] WBRT is increasingly being omitted from the initial management strategy.[6-13] There is not yet a general consensus regarding the risks and benefits of omitting up-front WBRT. One study showed a trend toward improved survival among patients who received SRS alone,[12] whereas another study showed a trend toward worse survival among patients who received SRS alone.[10] A retrospective multi-institutional review of SRS alone vs SRS with WBRT in 569 patients failed to show any difference in survival between the 2 groups.[7] In a single-institution prospective randomized trial comparing WBRT with observation in patients who underwent conventional surgery,[6] a large increase in intracranial relapse and a concomitant increase in death due to neurologic causes were identified in the non-WBRT group; however, no survival difference was identified in that study. In the present study, no significant survival difference was observed between the groups receiving WBRT + SRS and SRS alone, although the number of patients was not large enough to allow detection of any differences that were smaller than we had assumed. In addition, no significant difference in the frequency of death due to neurologic causes was observed. Moreover, these results were obtained in spite of the rather large increase in intracranial failure when WBRT was omitted. A further observation of note from the present trial was the significant increase in local failure with SRS alone, even though the radiation dose in these patients was considerably higher than that administered to patients receiving WBRT + SRS. We have adapted the 30% reduced dose of SRS in the WBRT + SRS group, which could have lowered local control of the brain metastasis in the WBRT + SRS group. However, we have observed opposite results in this study; the local control rate was significantly higher in the WBRT + SRS group than in the SRS-alone group. This observation lends merit to the value of fractionation, which might help overcome some radiation resistance mechanisms, such as hypoxia.

Also of concern in this context is that higher brain recurrence rates are associated with neurologic deterioration.[9] In a previous randomized study of surgery with or without WBRT,[6] the time to neurologic deterioration was dramatically longer in the WBRT group, although no difference in functional independence was observed. In the current study, no significant difference in the preservation of neurologic function was observed. However, the present study might have less ability to detect small differences, and the present assessment of neurologic function was not conducted with sophisticated measures that might have detected differences between patient groups.

Although surgery and SRS are both focal treatments, SRS is less invasive and may be repeated more often than surgical intervention.[11] The optimal timing of these interventions is an issue that remains open for debate. Our results suggest that the early detection of a brain recurrence and early salvage brain treatment may prevent neurologic deterioration and neurologic death, even when WBRT is not included in the initial treatment. However, study participants more frequently undergo physical and radiological examinations than do patients in the community. Given that the majority of new brain metastases were initially detected in asymptomatic patients, studies assessing the benefits of scheduled imaging should be conducted in the future.

In conclusion, our findings demonstrated that SRS alone without up-front WBRT was associated with increased brain tumor recurrence; however, it did not result in either worsened neurologic function or increased risk of neurologic death. With respect to patient survival, the control of systemic cancer might outweigh the frequent recurrence of brain tumors. Therefore, SRS alone could be a treatment option, provided that frequent monitoring of brain tumor status is conducted.

Author Contributions: Dr Aoyama had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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> The only true hope for civilization—the conviction of the individual that his inner life can affect outward events and that, whether or not he does so, he is responsible for them.
> —Stephen Spender (1909-1995)