Neurocognitive function of patients with brain metastasis who received either whole-brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone

Hidefumi Aoyama, M.D., Ph.D.[1], Masao Tago, M.D.[2], Ph.D., Norio Kato, M.D.[1], Tatsuya Toyoda, M.D., PhD.[3], Masahiro Kenjyo, M.D., Ph.D.[4], Saeko Hirota, M.D, Ph.D. [5], Hiroki Shioura, MD, Ph.D. [6], Taisuke Inomata, MD, Ph.D. [7], Etsuo Kunieda, MD, Ph.D. [8], Kazushige Hayakawa, M.D, Ph.D. [9], Keiichi Nakagawa, M.D., Ph.D.[2], Gen Kobashi, M.D., Ph.D.[10], Hiroki Shirato, M.D., Ph.D.[1]

1. Department of Radiology, Hokkaido University Graduate School of Medicine, Sapporo, Japan
2. Department of Radiology, University of Tokyo Hospital, Tokyo, Japan
3. Department of Radiology, Kanto Medical Center NTT EC, Tokyo, Japan
4. Department of Radiology, Hiroshima University School of Medicine, Hiroshima, Japan
5. Department of Radiology, The Hyogo Medical Center for Adults, Akashi, Japan
6. Department of Radiology, Izumisano General Hospital, Izumisano, Japan
7. Department of Radiology, Osaka Medical College, Osaka, Japan
8. Department of Radiology, Keio University School of Medicine, Tokyo, Japan
9. Department of Radiology, Kitasato University School of Medicine, Sagamihara, Japan
10. Department of Global Health and Epidemiology, Division of Preventive Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Corresponding author:

Hidefumi Aoyama, M.D., Ph.D.

Department of Radiology, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan

Telephone: 81-11-716-1161, Facsimile: 81-11-706-7876

E-mail: hao@radi.med.hokudai.ac.jp

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ABSTRACT

PURPOSE

It is not well known how the omission of whole-brain radiotherapy (WBRT) affects the neurocognitive function of patients with 1-4 brain metastases who are treated with stereotactic radiosurgery (SRS).

MATERIALS AND METHODS

In a prospective randomized trial between WBRT+SRS and SRS-alone in patients with 1-4 brain metastases, neurocognitive function was assessed by the Mini-Mental Score Examination (MMSE). Among 132 enrolled patients, MMSE scores were available for 110 patients.

RESULTS

In the baseline MMSE analyses, statistically significant differences were observed for total tumor volume, extent of tumor edema, age, and KPS. Among 92 patients who received follow-up MMSE, 39 patients had a baseline MMSE of 27 or lower (17 in the WBRT+SRS group, 22 in the SRS-alone group). Improvements of >=3 points in the MMSEs of 9 WBRT+SRS patients and 11 SRS-alone patients (P=0.85) were observed. Among 82 patients who had baseline MMSEs >=27 or whose baseline MMSEs were <=26 but improved to >=27 after the initial brain treatment, the 12-, 24-, and 36-month actuarial free

rates of the 3-point drop in MMSE were 76.1%, 68.5%, and 14.7% in the WBRT+SRS group, and were 59.3%, 51.9%, and 51.9% in the SRS-alone group. The average duration until deterioration was 16.5 months in WBRT+SRS and 7.6 months in SRS-alone patients (P=0.05).

CONCLUSIONS

The current study revealed that, for the majority of brain metastatic patients, control of the brain tumor is the most important factor for stabilizing neurocognitive function. However, the long-term adverse effect of WBRT on neurocognitive function may not be negligible.

KEYWORDS

Brain metastasis, Radiosurgery, Whole-brain radiation therapy, Neurocognitive function, Leukoencephalopathy

INTRODUCTION

Whole-brain radiation therapy (WBRT) has long been a mainstay in the treatment of brain metastases. The role of WBRT is to control radiologically visualized tumors as well as nonvisualized micrometastases. Stereotactic radiosurgery is a method of delivering high doses of focal irradiation to a tumor while minimizing the irradiation to the adjacent normal tissue [**1, 2**]. Beginning in the 1990s, it has come to be increasingly used worldwide for patients with no more than a few brain metastases. A recent prospective randomized trial from the Radiation Therapy Oncology Group (RTOG) showed a small but significant improvement in the survival of patients that had up to 3 metastases with good prognostic factors when SRS was used in conjunction with WBRT [**2**].

However, WBRT has several adverse effects. Acute adverse effects include nausea and headache, but they are generally limited in severity and duration. On the other hand, the late adverse effects are severe, progressive, and irreversible. They are caused by a syndrome called leukoencephalopathy, which is a structural alteration of cerebral white matter in which myelin suffers the most damage. Mild cases are typified by a chronic confusional state with inattention, memory loss, and emotional dysfunction. More severe cases

produce major neurologic sequelae such as dementia, abulia, stupor, and coma. These symptoms usually develop 6-24 months after cranial radiation. The degree of neurotoxicity resulting from WBRT correlates with the total dose received and with the time-dose-fractionation scheme [**3**]. Because of the concern about leukoencephalopathy resulting from WBRT, treatment strategies relying on SRS alone have been increasingly used [**4-7**]. On the other hand, it has been pointed out that the omission of WBRT from the initial brain management results in a significant increase in brain tumor recurrence [**6, 7**]. It is noteworthy that Regine et al. reported that brain tumor recurrence could also be a cause of neurocognitive functional deterioration [**8**].

The current study from the Japanese Radiation Oncology Study Group Protocol 99-1 (JROSG 99-1) is the first prospective randomized trial comparing SRS alone and WBRT combined with SRS. The details of the results have been published elsewhere [**1**]. In brief, it was a multi-institutional prospective randomized trial comparing WBRT+SRS and SRS alone conducted in Japan between 1999 and 2003. Patients were randomized to receive WBRT+SRS (65 patients) or SRS alone (67 patients) for brain metastases. The primary endpoint was survival. No significant difference between the groups was observed in

survival or cause of death; however, patients in the SRS-alone group experienced brain tumor recurrence significantly more frequently than those in the WBRT+SRS group. No difference in the functional observation rate (Karnofsky Performance Status; KPS => 70) was observed.

We also monitored neurocognitive function serially by the Mini-Mental Score Examination (MMSE) [**8-12**]. Herein, we present the results of detailed analysis of neurocognitive function for this trial. This is the first report to compare neurocognitive function in patients receiving either SRS alone or WBRT+SRS.

MATERIALS AND METHODS

Randomization and Treatment

Eligible patients had 1-4 brain metastases detected on enhanced MRI, each less than 3 cm, and good systemic performance status (KPS of 70 or more). A total of 132 patients were randomized to receive WBRT+SRS (65 patients) or SRS alone (67 patients) for brain metastases. Written informed consent was obtained from each patient before entry into the study. 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. Prior to randomization, the patients were stratified based on the following criteria: number of brain metastases (single vs. 2-4), extent of extracranial disease (active vs. stable), and primary tumor site (lung vs. other sites). The 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 schedule was 30 Gy in 10 fractions over 2 to 2.5 weeks. WBRT proceeded to SRS in patients 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 22-25 Gy, and those larger than 2 cm were treated with 18-20 Gy. The dose was reduced by 30% when the treatment was combined with WBRT [**1**].

Assessment of neurocognitive function

Neurocognitive function was assessed by the MMSE [**8-12**]. The MMSE is a short, standardized tool to grade cognitive function. The examination begins with an assessment of orientation to place and time. A maximum of 10 points can be obtained in this section. A test of memory has the subject immediately repeat the name of three objects presented orally. The subject then subtracts sevens

serially from 100 and is subsequently asked to recall the three items previously repeated. The final section evaluates aphasia and apraxia by testing naming, repetition, compliance with a three-step command, comprehension of written words, writing, and copying a drawing, for a total of 9 points in this section. The maximum score that can be obtained for the entire MMSE is 30 points [**10-12**]. Physicians administered MMSE before or during the brain treatment and gave it again at 1 month, 3 months and, if possible, every 3 months thereafter. The factors included in the analyses were the number of brain metastases on contrast-enhanced magnetic resonance imaging (MRI), the total volume of brain metastases, and the degree of brain edema on T2-weighted MRI. Brain edema was scored from grade 0 to grade 2. Patients with Grade 0 had no edema; those with Grade 1 had edema limited to less than half of one hemisphere, and those with Grade 2 had edema exceeding half of one hemisphere.

For the analysis of post-treatment change in MMSE, patients for whom no follow-up MMSEs were available were excluded. A statistically meaningful change is defined as a three-point change in MMSE score [**8, 12**]. While this criterion is felt to be potentially less conservative, due to the possibility of missing a “meaningful” change in MMSE score [**13**], it may be a more reliable change

index [**8, 12**]. In addition, a score of 26 or less was defined as abnormal [**8**]. MRI findings regarding leukoencephalopathy were also assessed according to the criterion in NCI-CTC version 2.0 and correlated to the change in MMSE score [**14**]. Tumor progression was scored when there was an increase in tumor size of at least 25%, based on the measurement of perpendicular diameters [**1**].

Statistical analysis

The MMSE score was summarized as an average. Due to a ceiling effect and the clustering of values at 30, the data were not normally distributed. The Wilcoxon rank-sum test was used to compare the means. The χ^2 test was used to determine the relationship between two categorical variables, and the Fisher exact test was used when small cell sizes were encountered in 2 x 2 contingency tables. Univariate analyses were carried out by the Kaplan and Meier method, and we used the log-rank test to compare differences between the groups. A two-sided P value of less than or equal to 0.05 was considered to reflect statistical significance. All statistical analyses were initially performed by a physician (HA) using a commercial statistical software package (StatView 5.0J; SAS Institute Inc., Cary, NC, USA), and all results were verified by a statistician

(GK) using a different software package (SAS version 9.1; SAS Institute Japan Ltd., Tokyo, Japan).

RESULTS

Baseline MMSE

The pre-treatment MMSE was obtained in 99 patients. MMSE data during the treatment were obtained in 11 additional patients. Those data, from 110 of 132 (83%) patients enrolled the study, constituted the “baseline” MMSEs and were used for the analysis (**Figure 1**). The characteristics of those 110 patients are listed in **Table 1** by treatment group. There was no statistically significant difference between the groups. A comparison of MMSE according to the patients’ characteristics is summarized in **Table 2**. The average baseline MMSE did not differ significantly between treatment groups (P=0.47). Statistically significant differences were observed in the total tumor volume of brain metastases (<3 cc vs. >=3 cc), extent of tumor edema (Grade 0-1 vs. Grade 2), age (<65 vs. >=65), and KPS (70-80 vs. 90-100). The number of brain metastases was not a significant factor.

Post-treatment change in MMSE

Post-treatment improvement in MMSE

Follow-up MMSEs were given to 92 patients a median of 2.5 times (range 1-17). The median follow-up period was 5.3 months (average, 11.0; range, 0.7-58.7). Among those 92 patients, 39 patients (17 in the WBRT+SRS group, 22 in the SRS-alone group) had baseline MMSEs of 27 or lower. Fifty-three patients who had baseline MMSEs of 28-30 were excluded from this analysis because an improvement of 3 points or more could not be expected (ceiling effect). The mean (standard deviation) MMSE value was 24.9 (3.3) in the WBRT+SRS group and 25.3 (2.1) in the SRS-alone group (P=0.65). An improvement in MMSE of 3 or more points was observed in 20 of the 39 patients (51%) after the initial brain treatment. There was no statistical difference between the two treatment groups: 9 of 17 in the WBRT+SRS group and 11 of 22 in the SRS-alone group (χ^2=0.03, P=0.85). The improvement was observed at the mean of 6.0 (5.9) months in the WBRT+SRS group and 3.6 (2.8) months in the SRS-alone group (P=0.24). Three patients experienced worsening of MMSE (deterioration by 3 points or more) without improvement. The remaining 16 patients did not show a change of 3 points or more in their MMSE scores.

Post-treatment deterioration of MMSE

Included in this analysis were patients who had baseline MMSE of 27 or greater (65 patients) and those whose baseline MMSE was 26 or lower but improved to 27 or greater (17 patients) after the initial brain treatment. Because we revealed that some patients experience improvement in MMSE after the initial brain treatment, we used the best MMSE score minus the deteriorated MMSE score for the change in MMSE in this analysis. The Kaplan-Meier curves of the patients who did not have 3-point MMSE deterioration in each treatment group are shown in **Figure 2a**. There was no statistical difference by log-rank test (P=0.73). Deterioration of MMSE occurred in 14 of 36 patients in the WBRT+SRS group and in 12 of 46 in the SRS-alone group (χ^2=1.52, P=0.21). However, the time until the deterioration was marginally different between the groups. Deterioration was observed at 13.6 months on average (median, 12.0 months; range, 1.8-31.1) in the WBRT+SRS group and 6.8 months (median, 6.6 months; range, 1.6-12.9) on average in the SRS-alone group (P=0.05). The deterioration was presumably attributed to brain tumor recurrence in 3 and 11 patients in the WBRT+SRS group and the SRS-alone group, respectively

(P<0.0001). The deterioration was either clinically or radiologically attributed to a toxic radiation event in 5 and 0 patients in the WBRT+SRS group and the SRS-alone group, respectively. The cause was unclear in the remaining 7 patients. A further follow-up MMSE after the 3-point drop was available in 10 of 26 patients. Of those 10, an improvement of 3 or more points was observed in 7 (5 in the WBRT+SRS group, 2 in the SRS-alone group). Of the 7, 2 subjects received salvage brain treatment (1 with SRS, 1 with surgery). The other 5 patients received only close observation or best-supportive care, including steroid administration. **Figure 2b** shows the Kaplan-Meier curves of patients free from MMSE deterioration when the first event in a drop was not counted if MMSE showed significant recovery in further follow-up. The 12-, 24-, and 36-month actuarial free rates of the second event in the 3-point drop of MMSE were 76.1% (95%CI: 58.7-93.5), 68.5% (95%CI: 47.3-89.7), and 14.7% (95%CI: 0-39.0) in the WBRT+SRS group, and 59.3% (95%CI: 37.5-81.1), 51.9% (95%CI: 28.6-75.2), and 51.9% (95%CI: 28.6-75.2) in the SRS-alone group. Although the difference was not significant by the log-rank test (P=0.79), the separation of the two curves between 12 and 24 months became wider than that in **Figure 2a**. The average duration until deterioration was 16.5 months (median,

15.8; range, 1.8-34.5) in the WBRT+SRS group and 7.6 months (median, 7.4; range, 1.6-12.9) in the SRS-alone group (P=0.05).

Figure 2c shows the actuarial rate of subjects free from a drop of MMSE to 26 or less. An event of a drop to 26 or lower was counted as an event unless MMSE recovered to 27 or more in the further follow-up. The 12-, 24-, and 36-month actuarial MMSE preservation rates (27 or above) were 78.8% (95%CI: 61.6-96.0), 78.8% (95%CI: 61.6-96.0), and 22.5% (95%CI: 0-49.4) in the WBRT+SRS group. They were 53.3% (95%CI: 32.9-73.7), 42.6% (95%CI: 17.9-67.3), and 42.6% (95%CI: 17.9-67.3) in the SRS-alone group (P=0.46). The separation of the two curves between 12 to 24 months after treatment became more prominent than that in **Figure 2b**. This fact might indicate that WBRT was effective at preventing deterioration of neurocognitive function resulting from brain tumor recurrence in an early phase after treatment. However, WBRT could be a cause of continuous deterioration of neurocognitive function in long-term survivors.

The relationship between MRI findings of leukoencephalopathy on NCI-CTC version 2 and clinical manifestations was also evaluated. Abnormal MRI leukoencephalopathy was seen in 7 patients (Grade 1, 2 patients; Grade 2,

4 patients; Grade 3, 1 patient). All 7 patients were in the WBRT+SRS group. Four of them (Grade 1, 1 patient; Grade 2, 2 patients; Grade 3, 1 patient) experienced a clinically significant drop of MMSE (3 points or more). The other 3 patients (Grade 1, 1 patient; Grade 2, 2 patients) did not experience a significant drop in MMSE score. **Figures 3** shows illustrative MRI images of 2 patients with different clinical courses. Patient 1 experienced Grade 3 radiological leukoencephalopathy without tumor recurrence at 47 months after WBRT+SRS (**Figure 3ab**). This patient had a baseline MMSE of 29 and a best score of 30 at 7 months after radiotherapy. She experienced a continuous drop in MMSE after a transient recovery, and her last MMSE, at 47 months, was 21. Patient 2 experienced Grade 2 radiological leukoencephalopathy at 15 months after WBRT+SRS. His baseline MMSE was 29 and his final score, at 15 months, was 29 (**Figure 3cd**).

Discussion

The Mini-Mental State Examination is the most frequently used and established tool for assessing the neurocognitive function of patients with brain tumors [**7-13**]. The importance of MMSE in the treatment of patients with brain

metastases as well as in those with low-grade glioma has been pointed out by Murray et al. [**9**] and Brown et al. [**10**]. Murray et al. assessed MMSE in 182 patients with brain metastases who were treated with WBRT of 30 Gy in 10 fractions among 445 patients who enrolled in a Radiation Therapy Oncology Group study (RTOG 91-04), in which 30 Gy in 10 fractions was compared to accelerated hyperfractionation of 54.4 Gy (1.6 Gy b.i.d.). They reported that patients who had low MMSE (23 or less) had worse prognoses compared with those with higher MMSE. In 88 patients who had baseline MMSEs of 29 or less, 48 (54.5%) demonstrated an improvement in MMSE at a follow-up visit. Regine et al. evaluated 309 patients whose MMSEs were available among 445 patients who enrolled in RTOG 91-04 [**8**]. They found that control of the brain tumor has a significant impact on the maintenance of MMSE scores. At 3 months, the average change in MMSE score was a drop of 0.5 for those whose brain metastases were radiologically controlled, as compared to a drop of 6.3 for those with uncontrolled brain metastases ($p=0.02$). One of the shortcomings of this report was that they evaluated the change in MMSE only at 3 months after brain treatment; therefore, the long-term effect of WBRT was not fully investigated. In the current study, we revealed some important factors that might affect a

patient's baseline MMSE. The number of brain metastases was not a significant factor affecting baseline MMSE, but tumor volume (3 cc or more) and degree of edema (half of a hemisphere or more) were significant factors. More importantly, 51% of patients who had MMSE scores of 27 or less experienced significant improvement of MMSE at a median of 2.7 months after the treatment, regardless of which treatment they received initially. This finding supports the findings reported by Murray et al. [**9**].

Another important finding of the current study was the continuous drop in MMSE in patients who received WBRT initially, although WBRT was not a cause of neurocognitive deterioration for the majority of brain metastatic patients. Patients who received WBRT combined with SRS experienced stable MMSE for approximately 2 years after treatment, perhaps due to the preventative effect on brain tumor recurrence compared with the SRS-alone group. Considering that the median survival of patients with brain metastases is around 7 months, this prevention effect when WBRT is included in the initial management is beneficial in the majority of brain metastatic patients. Nevertheless, the continuous deterioration of neurocognitive function for long-term survivors receiving WBRT could not be neglected.

In addition, MRI findings suggested leukoencephalopathy was useful only for patients who experienced severe neurocognitive dysfunction, and most patients who had Grade 1-2 radiological leukoencephalopathy did not show clinically meaningful signs of neurocognitive dysfunction as assessed by MMSE was used for the assessment. This is consistent with findings by Fujii O et al. [**15**]. They evaluated the white matter changes on MRI following WBRT in 24 patients. Whereas 12 patients (50%) developed radiological Grade 3 (large confluent areas) or more leukoencephalopathy, only 6 of these 12 patients showed clinical abnormalities such as dementia, depression, and speech impairment. However, the true incidence of neurocognitive deterioration is not well understood. In patients with small cell carcinoma of the lung whose primary tumor is in complete remission, prophylactic cranial irradiation (PCI) using WBRT is becoming a standard treatment [**16**]. Van de Pol M et al. assessed late neurologic toxicity in 7 patients who received PCI and survived 2 years or more. The memory decline was insidious and started within 6 months after the termination of therapy in 4 patients and after 2 years in 2 patients [**17**]. Stuschke M et al. reported that patients treated with PCI had higher-grade white matter abnormalities than patients who were not treated with PCI, as detected by T2-weighted MRI

(P=0.04). Grade 4 white matter abnormalities were detected in 2 of 9 patients treated with PCI and in 0 of 4 patients not treated with PCI [**18**]. Cull et al. reported the frequency of neurocognitive impairment in 52 patients who received PCI and survived more than 2 years. They evaluated neurocognitive function using four different methods: the Williams delayed recall test, the Digit symbol, the Complex figure test, and Trials A and B. No impairment in any of these tests was observed in 19% of patients. Impairment was observed with one test in 27%, with two tests in 22%, with three tests in 25%, and with all four tests in 7% [**19**]. These findings indicate that WBRT frequently accompanies neurocognitive impairment in long-term survivors.

Clearly, while our findings are of interest, our report is not without limitations. First, we did not monitor the use of corticosteroid, which could be potentially influential to neurocognitive function. Second, we used MMSE as the sole measurement of neurocognitive function; however, MMSE has been criticized for having low specificity and sensitivity [**20**]. Recently, the Radiation Therapy Oncology Group started to use a “neurocognitive battery” of several assessment tools [**21-24**]. Mehta et al. suggested that this battery is feasible for use in clinical trials and could detect small changes in neurocognitive function

that MMSE alone could not detect [**21, 22**]. Nevertheless, we believe the present findings are valuable and that MMSE is still a useful tool to examine neurocognitive function in trials in which neurocognitive function is not the primary endpoint. There is no established effective treatment for neurocognitive deterioration after WBRT. Recently, Shaw EG et al. reported that donepezil, a drug developed for Alzheimer's disease, has a positive effect on cognitive function; however, further investigation is necessary to establish this drug's potential role in relation to WBRT [**25**].

In conclusion, the current study revealed that the control of brain tumors is the most important factor in stabilizing neurocognitive function for the majority of brain metastatic patients. However, the long-term adverse effect on neurocognitive function may not be negligible. Therefore, the development of a means to identify those patients who are less likely to experience brain tumor recurrence, as well as further investigation to establish an optimal schedule of WBRT when combined with SRS, would be important steps toward the refinement of the treatment of brain metastases.

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TABLE 1. Patients baseline characteristics

Characteristics	WBRT+SRS (N=51)	SRS (N=59)	
	no. of patients (%)		P-value
Age at diagnosis (median [range])(years)	65 [36-78]	64 [33-81]	
<65 years	25 (49%)	31(52%)	0.71
>=65 years	26 (51%)	28 (48%)	
Gender			
Men	36 (71%)	46 (78%)	0.37
Women	15 (29%)	13 (22%)	
KPS			
70-80	24 (47%)	21 (36%)	0.22
90-100	27 (53%)	38 (64%)	
Number of brain metastases			
1	27 (53%)	30 (51%)	0.82
2-4	24 (47%)	29 (49%)	
Status of Brain edema			
Grade 0	13 (25%)	14 (24%)	0.63
Grade 1	29 (57%)	38 (64%)	
Grade 2	9 (18%)	7 (12%)	
Total volume of brain metastases			
<3cc	23 (45%)	29 (49%)	0.67
>= 3cc	28 (55%)	30 (51%)	
Primary tumor site			
Lung	32 (63%)	39 (66%)	0.71
Others	19 (37%)	20 (34%)	
Primary tumor status			
Stable	23 (45%)	30 (51%)	0.54
Active	28 (55%)	29 (49%)	
Extracranial metastases			
Stable	35 (69%)	36 (61%)	0.40
Active	16 (31%)	23 (39%)	

WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; KPS, Karnofsky Performance Status; SD, standard deviation

TABLE 2. Analysis of baseline MMSE and associated factors

Variables	Number	Average (SD)	P-value (Mann-Whitny U test)
Treatment group			
WBRT+SRS	51	26.7 (3.3)	0.86
SRS-alone	59	27.1 (2.9)	
Age at diagnosis			
<65 years	56	27.9 (2.0)	0.001
>=65 years	54	25.9 (3.7)	
Gender			
Men	82	26.7 (3.3)	0.33
Women	28	27.6 (2.1)	
KPS			
70-80	45	25.5 (3.8)	0.0002
90-100	65	27.9 (1.9)	
Number of brain metastases			
1	57	27.4 (2.3)	0.29
2-4	53	26.4 (3.7)	
Status of Brain edema			
Grade 0-1	94	27.2 (2.8)	0.008
Grade 2	16	25.0 (4.2)	
Total volume of brain metastases			
<3cc	52	27.8 (1.9)	0.01
>= 3cc	58	26.1 (3.7)	
Primary tumor site			
Lung	71	26.9 (3.2)	0.86
Others	39	27.0 (2.9)	
Extracranial disease			
Stable	23	27.6 (2.2)	0.96
Active	87	27.2 (2.2)	

WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; KPS, Karnofsky Performance Status; SD, standard deviation

Figure legends

Figure 1. Flow of study participants

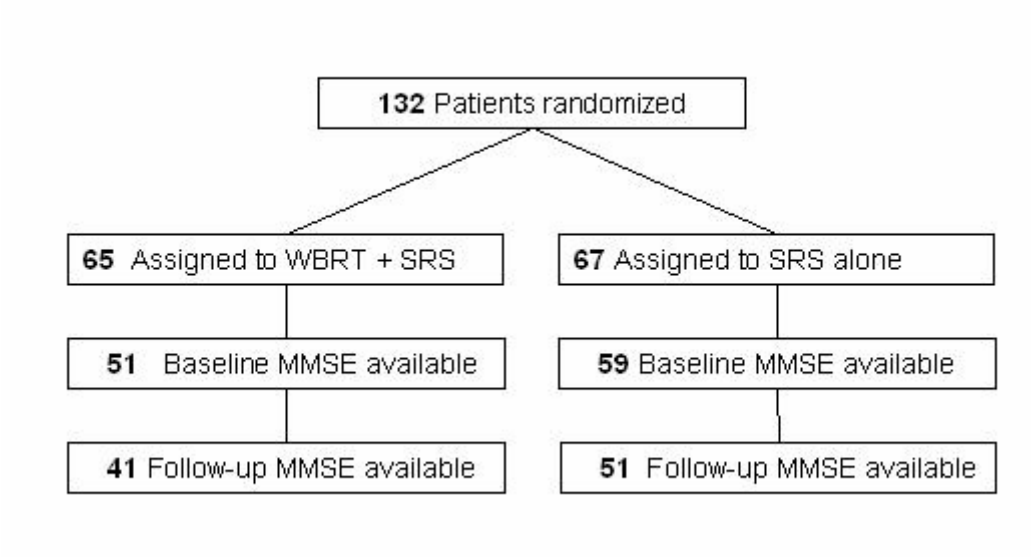
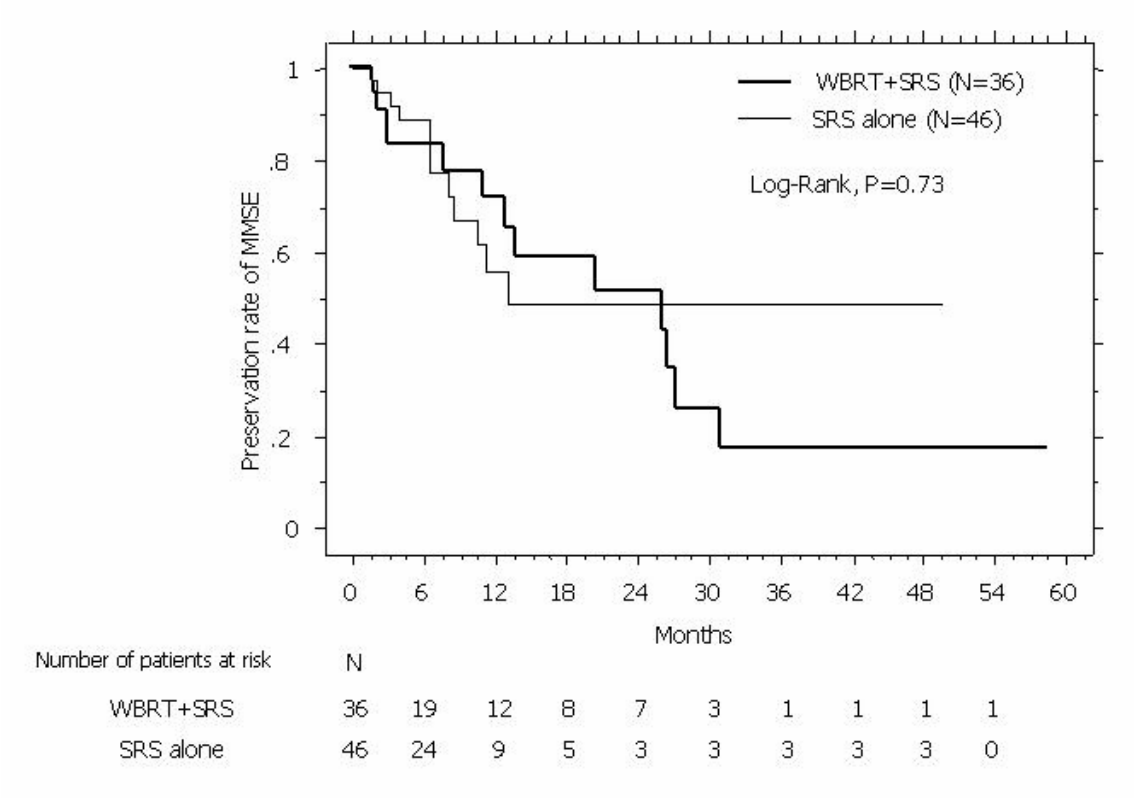
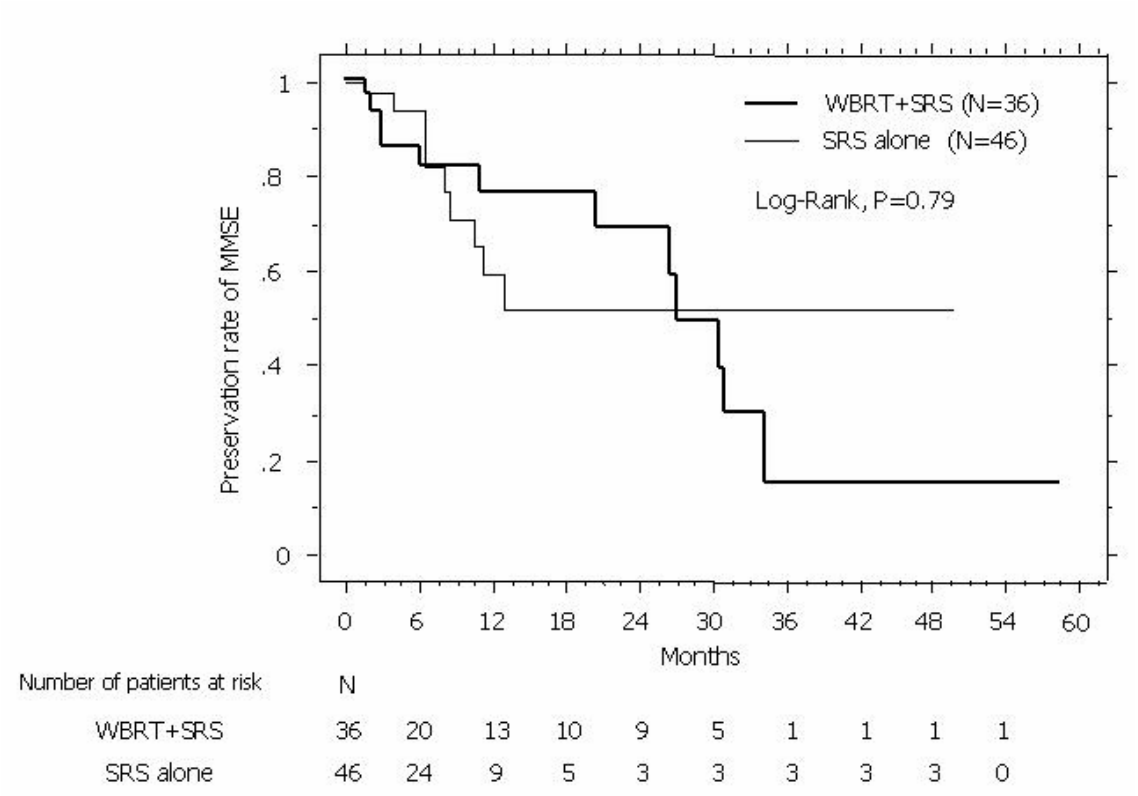


Figure 2a. Actuarial curves of subjects free from a 3-point drop in MMSE



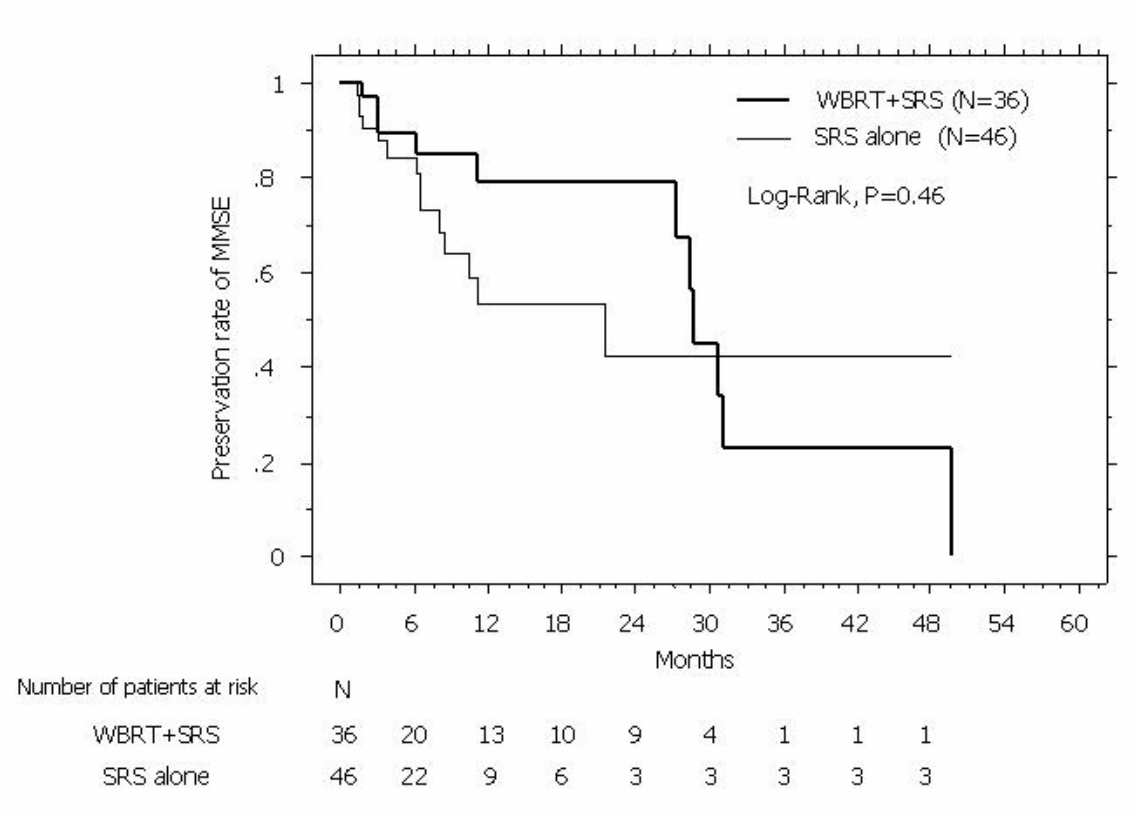
Number of patients at risk	N									
WBRT+SRS	36	19	12	8	7	3	1	1	1	1
SRS alone	46	24	9	5	3	3	3	3	3	0

Figure 2b. Actuarial curves of subjects free from a second 3-point drop in MMSE



Number of patients at risk	N									
WBRT+SRS	36	20	13	10	9	5	1	1	1	1
SRS alone	46	24	9	5	3	3	3	3	3	0

Figure 2c. Actuarial rate of subjects free from a drop of MMSE to 26 or less



Number of patients at risk	N								
WBRT+SRS	36	20	13	10	9	4	1	1	1
SRS alone	46	22	9	6	3	3	3	3	3

Figure 3a. Pre-treatment T2-weighted MRI of case 1, who received WBRT+SRS

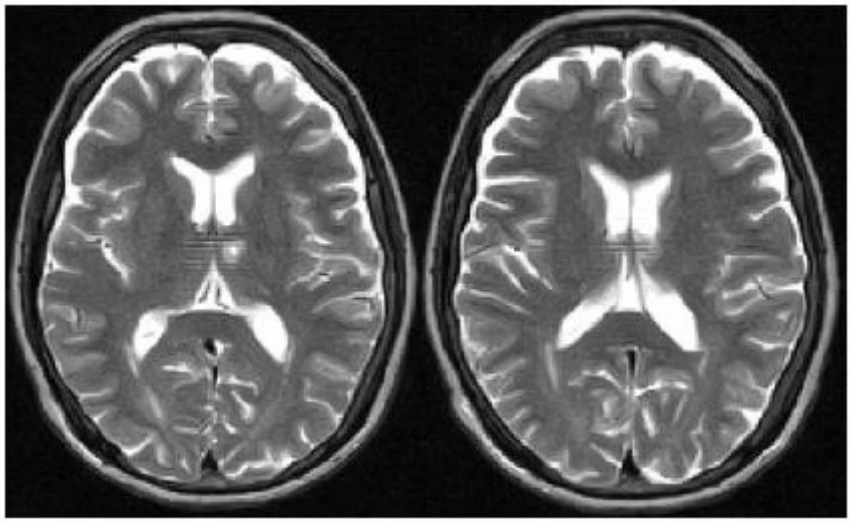


Figure 3b. T2-weighted MRI at 46.6 months after the initial brain treatment for case 1

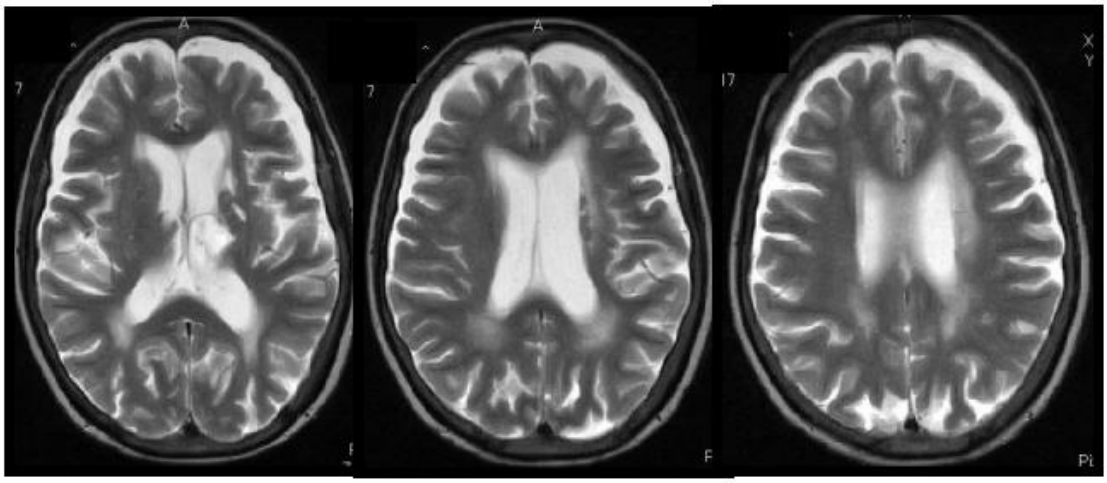


Figure 3c. Pre-treatment T2-weighted MRI of case 2, who received WBRT+SRS

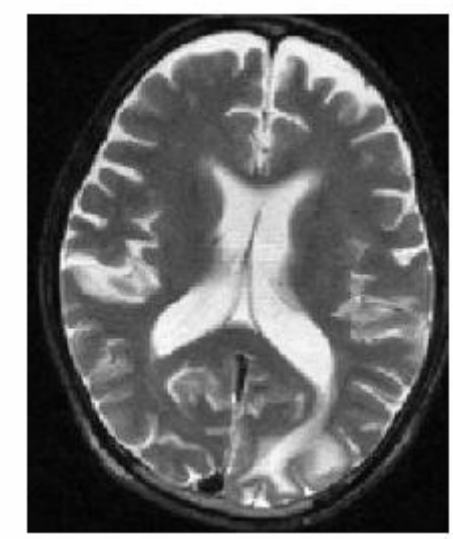


Figure 3d. T2-weighted MRI at 15 months after the initial brain treatment for case