Original Investigation

Stereotactic Radiosurgery With or Without Whole-Brain Radiotherapy for Brain Metastases
Secondary Analysis of the JROSG 99-1 Randomized Clinical Trial

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IMPORTANCE It remains uncertain whether treatment with stereotactic radiosurgery (SRS) alone can be safely applied to all patient populations with 1 to 4 brain metastases (BMs) exhibiting heterogeneous prognoses.

OBJECTIVE To investigate the feasibility of SRS alone for patients with different prognoses determined by the diagnosis-specific Graded Prognostic Assessment (DS-GPA).

DESIGN, SETTING, AND PARTICIPANTS A secondary analysis (performed in September 2014) of the Japanese Radiation Oncology Study Group (JROSG) 99-1, a phase 3 randomized trial, comparing SRS alone and whole-brain radiotherapy (WBRT) + SRS conducted in 1999 to 2003. Among a total of 132 patients, 88 with non–small-cell lung cancer (NSCLC) and 1 to 4 BMs were included and poststratified by DS-GPA scores to avoid potential bias from BMs from different primary cancer types. The median follow-up time was 8.05 months.

INTERVENTIONS The WBRT schedule was 30 Gy in 10 fractions over 2 to 2.5 weeks. The mean SRS dose was 21.9 Gy in SRS alone and 16.6 Gy in WBRT + SRS.

MAIN OUTCOMES AND MEASURES The primary end point was overall survival (OS), and the secondary end points included brain tumor recurrence (BTR), salvage treatment, and radiation toxic effects.

RESULTS Forty-seven patients had a favorable prognosis, with DS-GPA scores of 2.5 to 4.0 (26 SRS-alone and 21 WBRT + SRS [DS-GPA 2.5-4.0 group]), and 41 had an unfavorable prognosis, with DS-GPA scores of 0.5 to 2.0 (19 SRS-alone and 22 WBRT + SRS [DS-GPA 0.5-2.0 group]). Significantly better OS was observed in the DS-GPA 2.5-4.0 group in WBRT + SRS vs the SRS alone, with a median survival time of 16.7 (95% CI, 7.5-72.9) months vs 10.6 (95% CI, 7.7-15.5) months (P = .04) (hazard ratio [HR], 1.92; 95% CI, 1.01-3.78). However, no such difference was observed in the DS-GPA 0.5-2.0 group (HR, 1.05; 95% CI, 0.55-1.99) (P = .86). This benefit could be explained by the differing BTR rates, in that the prevention against BTR by WBRT had a more significant impact in the DS-GPA 2.5-4.0 group (HR, 8.31; 95% CI, 3.05-29.13) (P < .001) vs the DS-GPA 0.5-2.0 group (HR, 3.57; 95% CI, 1.02-16.49) (P = .04).

CONCLUSIONS AND RELEVANCE Despite the current trend of using SRS alone, the important role of WBRT for patients with BMs from NSCLC with a favorable prognosis should be considered. Our findings should be validated through appropriately designed prospective studies.

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Brain metastases (BMs) are a serious and increasingly common complication in patients with solid cancers. Lung cancer represents the most common primary tumor linked to BMs, accounting for 40% to 50% of BM cases, followed by breast cancer, which accounts for 10% to 20%.[1] Historically, the prognosis of patients with BMs has been considered uniformly poor, with a median survival in the 2- to 4-month range. However, it has become evident that not all patients with BMs have the same poor prognosis, and the use of an identical management strategy for all patients is no longer appropriate.[2]

In the initial 2006 report of the Japanese Radiation Oncology Study Group (JROSG) 99-1 phase 3 randomized clinical trial comparing up-front whole-brain radiation therapy (WBRT) combined with stereotactic radiosurgery (SRS) (WBRT + SRS arm) and SRS without up-front WBRT (SRS-alone arm) for patients with 1 to 4 BMs, we reported that adding WBRT to SRS significantly reduced brain tumor recurrence (BTR) at both initial and distant sites in the brain.[3] The impact on overall survival (OS) was not significant, but the trial was prematurely closed before reaching the accrual goal.[3] When we designed that trial in the late 1990s, the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) was the only well-established prognostic index for patients with BMs.[4]

The RPA index divided patients into 3 classes using the following 4 factors: age, Karnofsky Performance Status (KPS), primary tumor status, and extracranial metastases. One of the weaknesses of this system was that the majority of patients eligible for the clinical trials (KPS score ≥70) tended to be classified into RPA class II; in fact, in JROSG 99-1, 86% of the patients were classified into RPA class II. Another weakness is that the RPA system is not diagnosis specific. In 2012, Sperduto et al[5] refined the "original" RPA and proposed a new index, namely the diagnosis-specific Graded Prognostic Assessment (DS-GPA).[5] In the DS-GPA index, different scoring systems were prepared for 6 different primary tumor sites. The significant factors used for scoring were KPS, age, the presence of extracranial metastases, and the number of BMs for non–small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC); tumor subtype, KPS, and age for breast cancer; KPS only for gastrointestinal (GI) cancer; and KPS and number of BMs for both renal cell cancer and melanoma. A score of 4.0 correlates with the best prognosis, whereas 0.0 correlates with the worst prognosis.

One of the realities of this index is that patients with different primary cancers and different pathological diagnoses have different prognoses even with the same DS-GPA score. For example, the median survival times (MSTs) of patients with NSCLC with GPA scores of 2.5 to 3.0 and 3.5 to 4.0 are 9.4 and 14.8 months, respectively, compared with 15.1 and 25.3 months, respectively, for breast cancer; 11.3 and 14.8 months, respectively, for renal cell cancer; and 6.9 and 13.5 months, respectively, for GI cancer.

After the initial report of JROSG 99-1,[3] other groups reported results of similarly designed randomized clinical trials (RCTs).[6,7] All 3 trials showed that the omission of up-front WBRT significantly increased the incidence of BTR at both the original and distant sites[3,6,7]; however, the impact on OS was not significant in the 2 largest trials,[3,7] whereas in the smallest trial, the omission of WBRT was associated with improved OS.[6] On the basis of these findings, the current trend for limited BMs has shifted toward SRS without up-front WBRT when the number of BMs is up to 4 (and increasingly for even a larger number of tumors).[8] It remains uncertain, however, whether a policy of treatment with SRS alone could be safely applied to all patient populations with BMs, recognizing that they exhibit heterogeneous prognoses. Herein, we report the results of a secondary analysis of the JROSG 99-1 data post-stratified by the patients' DS-GPA scores.

At a Glance

- To investigate the feasibility of stereotactic radiosurgery (SRS) alone compared with whole-brain radiotherapy (WBRT) + SRS for patients with brain metastases exhibiting different prognoses determined by the diagnosis-specific Graded Prognostic Assessment (DS-GPA).
- A secondary analysis of a randomized trial comparing SRS alone with WBRT + SRS (Japanese Radiation Oncology Study Group [JROSG] 99-1) for 88 patients with non–small-cell lung cancer with 1 to 4 BMs.
- In a favorable prognosis group, with DS-GPA score of 2.5 to 4.0 (DS-GPA 2.5-4.0 group), the median survival time of the WBRT + SRS arm was significantly longer (16.7 months) than that of the SRS-alone arm (10.6 months; $P = .04$). In an unfavorable prognosis group, with DS-GPA scores of 0.5 to 2.0 (DS-GPA 0.5-2.0 group), such a difference was not observed ($P = .86$).
- This benefit could be explained by the difference in brain tumor recurrence rate, in that the prevention effect of brain tumor recurrence by WBRT had a greater impact in the DS-GPA 2.5-4.0 group ($P < .001$) than in the DS-GPA 0.5-2.0 group ($P = .04$).
- Despite the current trend of preferring SRS alone, we need to carefully consider the important role of WBRT, especially for patients with BMs from non–small-cell lung cancer with a favorable prognosis.

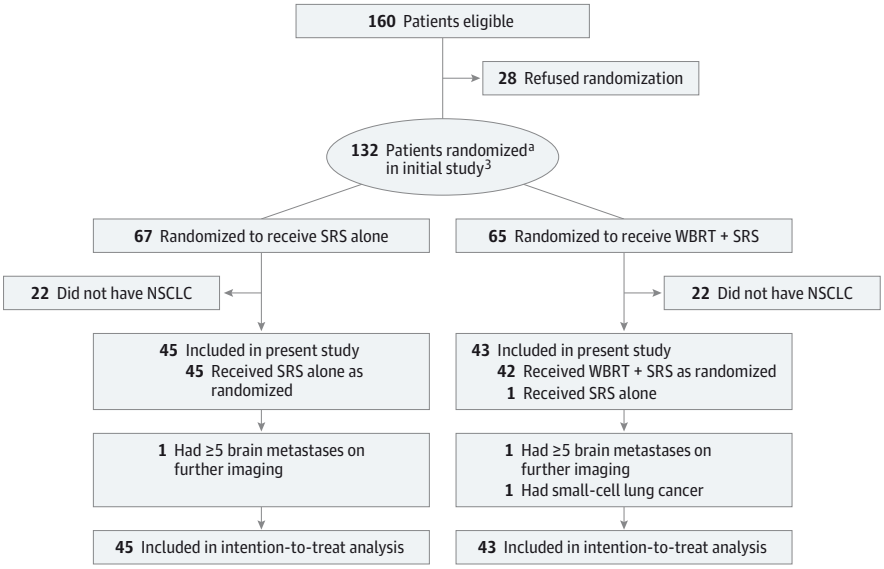
Methods

Study Design

This secondary post hoc analysis was based on an RCT, the JROSG 99-1 trial comparing SRS alone with WBRT + SRS for up to 4 BMs. Eligible patients were required to have a KPS score of 70 or more, age 18 years or older, and 1 to 4 BMs with a maximum diameter of 3 cm or smaller on contrast-enhanced magnetic resonance images, derived from a histologically confirmed systemic cancer. Patients with BMs from small-cell carcinoma, lymphoma, germinoma, and multiple myeloma were excluded. Before randomization, the patients were stratified based on the following criteria: primary tumor site (lung vs other sites), number of BMs (single vs 2-4), and the status of extracranial disease (controlled vs uncontrolled).

The research protocol was approved by the relevant institutional review boards or ethics committees, and all participants gave written informed consent. The recruitment period was from October 1999 to December 2003. The data were updated in July 2014, and the secondary analysis was performed in September 2014. The median follow-up time of the

Figure 1. CONSORT Diagram of the 88 Patients With Non–Small-Cell Lung Cancer (NSCLC)



BMs indicates brain metastases; ITT, intention-to-treat; SRS, stereotactic radiosurgery; and WBRT, whole-brain radiotherapy.

[a] Patients were stratified by number of BMs 1 vs 2-4); primary tumor (lung vs others); systemic disease (controlled vs uncontrolled).

88 patients with NSCLC included in this analysis was 8.05 months (range, 0.5-163.8 months). There were 160 eligible patients, and after excluding 28 patient because of various reasons, as described in the original publication,[3] 132 (83%) were randomized (65 to the WBRT + SRS arm and 67 to the SRS-alone arm). Patient accrual was prematurely terminated before the planned accrual number was reached.

For DS-GPA-based secondary analysis in the present study, only patients with NSCLC were included because of the lack of the tumor subtype information for patients with breast cancer and also to diminish the potential bias caused by the BMs from different primary types.[5] The details of the DS-GPA classification system for NSCLC are described in eTable 1 in the Supplement.

Treatments

The WBRT schedule was 30 Gy in 10 fractions over 2 to 2.5 weeks. For the patients assigned to the WBRT + SRS arm, WBRT was followed by SRS. The SRS dose was prescribed to the tumor margin. Metastatic tumors with a maximum diameter of up to 2 cm were treated with 22 to 25 Gy, and those diameters larger than 2 cm were treated with 18 to 20 Gy. The dose was reduced by 30% when the treatment was combined with WBRT.

Statistical Analyses

The primary end point of the original study was the patients' OS. Secondary end points included BTR, salvage treatment, and radiation toxic effects. All analyses were conducted on an intention-to-treat basis. End points were measured from the date of randomization. For time-to-event outcomes, the Kaplan-Meier method was used to estimate the median time to the event, and the differences were compared using a log-rank test. To identify significant variables associated with OS, multivariate analysis by Cox proportional hazards model was performed to calculate hazard ratios (HRs) and 95% CIs. A forward stepwise regression procedure with a cutoff of $P = .05$ was used. Candidate variables included KPS score (70-80 vs 90-100), extracranial metastases (present vs absent), the status of primary tumor (uncontrolled vs controlled), and the DS-GPA score. The DS-GPA score was categorized to 4 groups (0-1.0, 1.5-2.0, 2.5-3.0, and 3.5-4.0) and then transformed to a design variable. The Fisher exact test was used for the comparison of categorical variables, and the Wilcoxon rank-sum test was used for the comparison of continuous variables. $P < .05$, 2 sided, was considered statistically significant. All statistical analyses were performed one of the authors (H.A.) using JMP 11 software (SAS Institute Inc) and verified by a statistician (K.A.) using SPSS version 20 (IBM Corp).

Results

Patients' Distributions According to the DS-GPA

The CONSORT diagram of patients with NSCLC is provided in **Figure 1**.[9] Among the 132 randomized patients, 88 (67%) had NSCLC (45 SRS-alone arm and 43 WBRT + SRS arm). Seventy-five patients (85%) were male and 13 were female (15%). Forty-seven patients had a favorable prognosis (defined as DS-GPA score of 2.5-4.0; 26 in the SRS-alone arm and 21 in the WBRT + SRS arm [DS-GPA 2.5-4.0 group]) and 41 had an unfavorable prognosis (DS-GPA score of 0.5-2.0; 19 patients in the SRS-alone arm and 22 in the WBRT + SRS arm [DS-GPA 0.5-2.0 group]). The baseline characteristics of the treatment arms were well balanced in regard to KPS, age, number of BMs, status of primary tumor, and the existence of extracranial metastases (**Table 1**).

OS, Brain Tumor Recurrence, and Toxic Effects

As a result of Cox analysis, it was suggested that a dose-dependent DS-GPA score (Reference: DS-GPA 3.5-4.0; DS-GPA

Table 1. Distribution of Patients in Each Treatment Group According to the DS-GPA and Associated Factors

DS-GPA and Associated Factors	All (N = 88)	Treatment Group		*P* Value
		SRS Alone (n = 45)	WBRT + SRS (n = 43)	
DS-GPA group				
0.5-2.0/2.5-4.0	41/47	19/26	22/21	.40
0.5-1.0/1.5-2.0/2.5-3.0/3.5-4.0	8/33/37/10	5/14/23/3	3/19/14/7	.17
KPS: 70-80/90-100	31/57	14/31	17/26	.41
Age, y: <50/50 to 60/>60	6/55/27	2/31/12	4/24/15	.40
No. of BMs: 1/2-3/4	51/29/8	26/14/5	25/15/3	.77
Status of primary tumor: Controlled/uncontrolled	34/54	16/29	18/25	.54
Extracranial metastases: Absent/present	42/46	22/23	20/23	.84

Abbreviations: BMs, brain metastases; DS-GPA, diagnosis-specific Graded Prognostic Assessment; KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

Table 2. Outcomes in Each Treatment Group According to the DS-GPA Score

DS-GPA	Treatment Arm, Median (95% CI), mo		WBRT + SRS, HR (95% CI)	*P* Value
	SRS-Alone	WBRT + SRS		
Overall Survival				
All	8.6 (6.1-10.5)	7.9 (4.9-13.7)	1.33 (0.85-2.08)	.20
0.5-2.0	6.5 (3.7-8.6)	4.75 (2.7-9.1)	1.05 (0.55-1.99)	.86
2.5-4.0	10.6 (7.7-15.5)	16.7 (7.5-72.9)	1.92 (1.01-3.78)	.04
BTR-Free Time				
All	6.2 (3.4-6.7)	25.5 (10.6-68.3)	5.01 (2.44-11.11)	<.001
0.5-2.0	5.3 (2.0-6.7)	10.6 (3.0-N/A)	3.57 (1.02-16.49)	.04
2.5-4.0	6.2 (2.9-10.2)	37.5 (10.0-68.3)	8.31 (3.05-29.13)	<.001
Pattern of BTR, Total No. (Local/Distant/Both)				
All	27 (4/19/4)	13 (2/9/2)	...	...
0.5-2.0	8 (0/6/2)	6 (0/5/1)	...	...
2.5-4.0	19 (4/13/2)	7 (2/4/1)	...	...
Salvage Brain Treatment for BTR, No. (%)				
All	18 (40)	6 (14)	...	.006
0.5-2.0	4 (21)	2 (9)	...	.38
2.5-4.0	14 (54)	4 (19)	...	.01
Grade 3 or 4 Late Radiation Toxic Effects, No. (%)				
All	1 (2.2)	2 (4.7)	...	.61
0.5-2.0	0	0	...	NA
2.5-4.0	1 (3.8)	2 (9.5)	...	.57

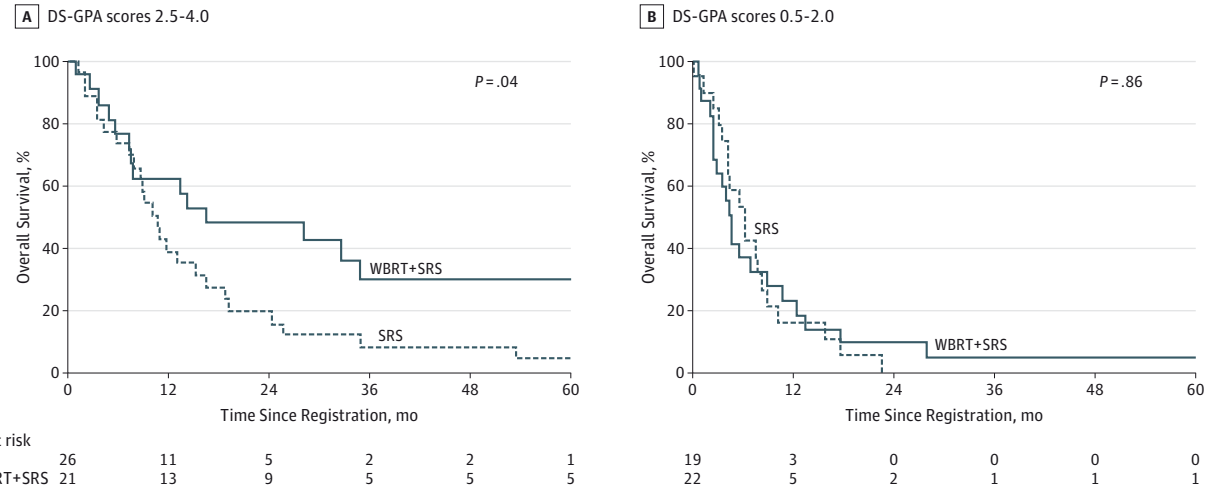
Abbreviations: BTR, brain tumor recurrence; DS-GPA, diagnosis-specific Graded Prognostic Assessment; ellipsis (...), not applicable; HR, hazard ratio; NA, not available; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

0.0-1.0: HR, 7.48 [95% CI, 2.13-26.33] $P = .002$; DS-GPA 1.5-2.0: HR, 3.04 [95% CI, 1.10-8.39] $P = .03$; DS-GPA 2.5-3.0: HR, 1.77 (95% CI, 0.65-4.77] $P = .26$) and the status of the primary tumor (HR, 1.90, 95% CI, 1.11-3.23; $P = .02$) were selected as the independent and significant variables for OS. The OS values of each treatment group according to the DS-GPA are summarized in **Table 2**. Significantly better OS was observed in the patients with a favorable prognosis (DS-GPA 2.5-4.0) in the WBRT + SRS arm vs the SRS-alone arm, with the MST values of 16.7 (95% CI, 7.5-72.9) months vs 10.6 (95% CI, 7.7-15.5) months ($P = .04$) with an HR of 1.92 (95% CI, 1.01-3.78) in favor of WBRT + SRS (**Figure 2**A). However, this survival differential was not observed in the patients with an unfavorable prognosis (DS-GPA 0.5-2.0) (HR, 1.05; 95% CI, 0.55-1.99) ($P = .86$) (Figure 2B).

The frequency and the pattern of BTR, median BTR-free time, and the number of patients requiring salvage brain therapy are summarized in Table 2. The omission of WBRT increased BTRs at both the initial and distant sites in the brain. The preventive effect of WBRT was most prominent in the DS-GPA 2.5-4.0 group (HR, 8.31; 95% CI, 3.05-29.13) ($P < .001$) (**Figure 3**A) compared with the DS-GPA 0.5-2.0 group (HR, 3.57; 95% CI, 1.02-16.49) ($P = .04$) (Figure 3B).

As a result, salvage brain treatment for BTR was more frequently required in the patients in the DS-GPA 2.5-4.0 stratum who received SRS alone (54%) compared with both the DS-GPA 2.5-4.0 patients who were allocated to the WBRT + SRS arm (19%) and the DS-GPA 0.5-2.0 patients with unfavorable prognoses (SRS alone, 21%; and WBRT + SRS arm, 9%). Regarding radiation-

Figure 2. Overall Survival of Patients With Non–Small-Cell Lung Cancer, With DS-GPA Scores of 2.5 to 4.0 and 0.5 to 2.0

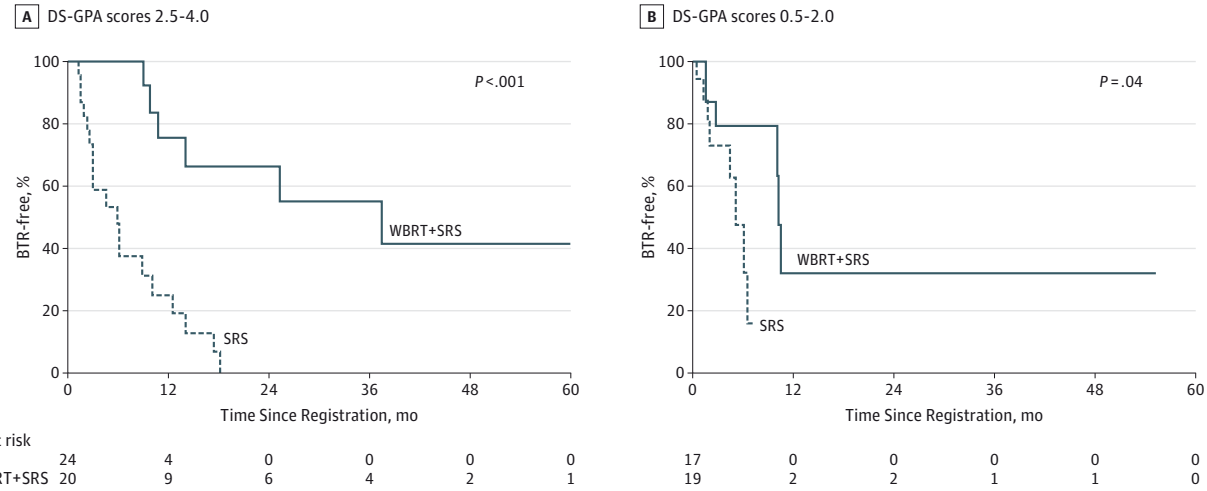


No. at risk

SRS	26	11	5	2	2	1	19	3	0	0	0	0
WBRT+SRS	21	13	9	5	5	5	22	5	2	1	1	1

DS-GPA indicates diagnosis-specific Graded Prognostic Assessment; SRS, stereotactic radiosurgery; and WBRT, whole-brain radiotherapy.

Figure 3. Brain Tumor Recurrence-Free Rate of Patients With Non–Small-Cell Lung Cancer, With DS-GPA Scores of 2.5 to 4.0 and 0.5 to 2.0



No. at risk

SRS	24	4	0	0	0	0	17	0	0	0	0	0
WBRT+SRS	20	9	6	4	2	1	19	2	2	1	1	0

DS-GPA indicates diagnosis-specific Graded Prognostic Assessment; SRS, stereotactic radiosurgery; and WBRT, whole-brain radiotherapy.

induced late toxic effects, all 3 of the patients who developed grade 3 or 4 toxic effects belonged to the DS-GPA 2.5-4.0 group.

Neurocognitive Function

Neurocognitive function was assessed by the Japanese version of the Mini-Mental State Examination (MMSE), and the results are summarized in eTable 2 in the Supplement. Baseline data were available in 70 patients. At baseline, the MMSE score in the GPA 2.5-4.0 group was significantly better than that in the GPA 0.5-2.0 group (28.0 vs 27.0; $P = .01$). When the 2 prognostic groups (DS-GPA 0.5-2.0 and 2.5-4.0) were considered separately, there was no significant difference in baseline MMSE scores between the 2 treatment arms in either group. Follow-up MMSE data were available in 57 patients (81%). Among the 24 patients in the DS-GPA 0.5-2.0 group, the median duration until the last follow-up MMSE was 3.6 (range, 1.3-14.5) months in the SRS-alone arm and 3.6 (range, 1.3-49.5) months in the WBRT + SRS arm ($P = .86$). Among the 33 patients in the DS-GPA 2.5-4.0 group, these values were 8.5 (range, 1.4-49.8) months and 9.5 (1.8-58.7) months, respectively ($P = .81$). Regarding the score at the last follow-up, no significant difference between the treatment arms was observed in either the DS-GPA 0.5-2.0 group (SRS-alone arm, 27.5; and WBRT + SRS arm 28.0; $P = .77$) or DS-GPA 2.5-4.0 group (SRS-alone arm, 28.0; and WBRT + SRS arm, 26.5; $P = .40$).

Discussion

It has been recognized that the addition of WBRT to SRS may increase the likelihood of cognitive adverse effects without in-

creasing OS for patients with up to 3 or 4 BMs, although it significantly reduces BTR at both the initial and distant sites.[6] As a result, over the last decade SRS without up-front WBRT has seen increasing use as a treatment for patients with up to 3 or 4 BMs; moreover, a recent report indicated that the SRS-alone strategy could be safely applied for up to 10 BMs.[8] However, the major flaw in this approach is the failure to recognize that improved intracranial control could translate to improved survival in patients at preferential risk of dying from intracranial as opposed to extracranial progression. There are several examples of this in the radiotherapy literature, with the 2 most notable ones being improved survival through the control of intracranial disease, when WBRT is used prophylactically for either patients with limited SCLC who have experienced a good response to chemotherapy[10] or patients with a single metastasis, for whom the only randomized data showing survival improvement were from trials that combined WBRT with SRS[11] or resection.[12] Because this survival benefit from WBRT is not observed uniformly, with the most notable examples of this being the use of prophylactic cranial irradiation in NSCLC[13] and the addition of WBRT to unselected cohorts of patients with limited BMs managed with SRS,[3,7] it has not been clear whether there are subsets embedded within these groups that may actually experience a survival benefit from WBRT.

An initial hint in this regard can be found in the study conducted by Pirzkall et al,[14] who described 236 patients treated with SRS with or without the nonrandom use of WBRT. In the subset of patients without extracranial disease, ie, the group least likely to rapidly succumb to extracranial progression, SRS + WBRT resulted in a median survival of 15.4 months, compared with 8.3 months for those treated with SRS alone (P = .08). Although this observation was not significant, it provided the hypothesis that improved intracranial control resulting from WBRT could potentially affect overall survival in selected subsets of patients. The JROSG 99-1 trial was the first RCT comparing SRS alone with WBRT + SRS. In the initial analysis, we could not extract groups for whom the combination therapy conferred a survival benefit because there was no sufficiently sensitive prognostic index available in 2006. In the present secondary post hoc analysis, however, we were indeed able to identify such a group, ie, the NSCLC patients with a favorable prognosis (DS-GPA 2.5-4.0) appeared to benefit by the addition of WBRT to SRS. This survival benefit, which did not extend to the unfavorable prognostic group, may have been attributable to the prevention of BTR by WBRT, which had more impact in the favorable than in the unfavorable group.

In this context, we note that Sperduto et al[15] recently published the results of a secondary analysis of RTOG 9508, which is an RCT comparing WBRT alone and WBRT + SRS for patients with up to 3 BMs. The initial report showed that patients had a survival benefit on post hoc analysis if they had NSCLC.[11] In the secondary analysis, patients were poststratified according to the DS-GPA score. It is of note that patients with breast cancer were excluded because of the lack of HER2 status information; as a result, NSCLC became more dominant in the secondary report (84%) than in the initial report (64%). Sperduto et al[15] found that there was no survival difference between treatments when they analyzed the overall group; however, patients with a DS-GPA score of 3.5 to 4.0 had better OS when treated with WBRT + SRS (MST, 21.0 months) than with WBRT alone (MST, 10.3 months) (P = .05).[15]

By combining the findings of the DS-GPA–based secondary analyses of JROSG 99-1 and RTOG 9508, it becomes clear that patients with BM from NSCLC with a favorable prognosis could have realized a survival benefit by the combination of WBRT and SRS compared with either SRS alone or WBRT alone; for this reason, an improved understanding of the long-term neurocognitive outcomes is increasingly important.

The impact of up-front WBRT on neurocognitive function and neurological adverse events has remained uncertain owing to the high risk of performance and detection bias and the lack of consistency in the instruments and methods used to measure and report results across studies.[16] In a trial conducted by Chang and colleagues,[6] the deterioration in learning and memory function at 4 months after treatment was significantly more frequent among the patients who received WBRT + SRS than among those who received SRS alone. However, the deterioration at 4 months is usually transient and could be reversed to baseline by 8 months[17]; therefore, neurocognitive function as measured by the Hopkins Verbal Learning Test-Total Recall (HVLT-TR) at 4 months might not be adequate for understanding the full trajectory of neurocognitive function following WBRT in patients with a favorable prognosis.[18]

It is important to note that neurocognitive function is also closely related to the brain tumor burden, and in one report, the preservation of neurocognitive function was better among the patients whose tumor burden became smaller after brain irradiation.[19] In the initial analysis of neurocognitive function in JROSG 99-1, a trend of better preservation of neurocognitive function at 12 months was observed in the WBRT + SRS arm (76%) compared with the SRS-alone arm (59%) owing to the better brain tumor control in the WBRT + SRS arm.[20] In the present analysis, no significant difference in the MMSE score at the last follow-up was observed when the patients were classified by their DS-GPA scores, implying no excess residual cognitive dysfunction in the WBRT + SRS arm. This may have been because the positive effect on neurocognitive function of the reduced frequency of BTR after WBRT and the negative impact of the late adverse effects of WBRT offset each other. Nevertheless, the deterioration of neurocognitive function as a consequence of late adverse events following WBRT is a real and serious matter of concern for long-term survivors. *N*-methyl-d-aspartate (NMDA)-receptor agonists used to treat Alzheimer disease have been shown to delay the progression of neurocognitive deterioration associated with WBRT.[21,22]

Hippocampal-avoidance WBRT was recently reported to preserve cognition compared with WBRT in a single-arm phase 2 trial, and phase 3 trials are under way.[23] Modification of the dose-fractionation schedule of WBRT combined with SRS would be another approach. Hypofractionated WBRT regimens including 30 Gy in 10 fractions or 37.5 Gy in 15 fractions became standard through RTOG trials in the 1970s and 1980s, when SRS was not widely available. In addition, the early detection of BMs was usually not possible because of the limited availability of MRI. Today, such modalities have become

a part of daily practice; therefore, the role of WBRT combined with SRS is different from that in the 1970s and 1980s.

We recently launched a clinical trial investigating the combination of reduced-dose as well as reduced dose-per-fraction WBRT (25 Gy in 10 fractions) combined with SRS (JROSG 13-1) for patients satisfying eligibility criteria similar to those used in the JROSG 99-1 trial. This dose-fractionation schedule has been commonly used in prophylactic cranial irradiation for patients with SCLC and those with NSCLC, and the degree of long-term toxic effects in neurocognitive function has been confirmed to be milder than that from the more conventionally hypofractionated schedules such as 30 Gy in 10 fractions or 37.5 Gy in 15 fractions.[24] In light of the survival benefit of the combination of WBRT and SRS, intensive efforts to reduce the cognitive effects of WBRT are now warranted.

The present study has several limitations that are common to all secondary analyses. First, the patients were not stratified by DS-GPA scores; as a result, the imbalance of patient distribution within the DS-GPA 2.5-4.0 group could not be completely eliminated, although the differences were not significant. Second, over the last decade great progress has been made in systemic therapies, including molecularly targeted therapies.[25] Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are now a standard treatment for patients with advanced NSCLC with *EGFR* mutations, and they may also be effective for controlling BMs in such patients.[26] Up-front EGFR-TKIs could be one of the treatment choices for patients with *EGFR*-mutant NSCLC with asymptomatic BMs, but it remains unsolved whether up-front EGFR-TKI treatment or radiation therapy is more appropriate owing to the absence of head-to-head comparisons.[27] Similar data and questions are now also emerging for NSCLC cases positive for echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase.[28]

Conclusions

Despite the current trend of preferring SRS alone, we need to carefully consider the important role of WBRT, especially for patients with BMs from NSCLC who have a favorable prognosis. These findings should be validated through prospective studies, not only for NSCLC but also for other primary cancers. In addition, further investigations targeting WBRT methods that result in less cognitive impairment with a reliable and durable neurocognitive end point after treatment are warranted.

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Invited Commentary

The Changing Landscape of Whole-Brain Radiation Therapy

Kevin S. Oh, MD; Jay S. Loeffler, MD

The Japanese Radiation Oncology Study Group (JROSG) 99-1 investigators[1] conducted a randomized clinical trial (RCT) of stereotactic radiosurgery (SRS) with or without whole-brain radiation therapy (WBRT) in patients with 1 to 4 brain metastases. When originally published in 2006, the data suggested that the inclusion of WBRT improved rates of 12-month brain tumor recurrence and use of salvage brain treatment but not overall survival. In the secondary post hoc analysis in this issue of *JAMA Oncology*, Aoyama and colleagues[2] conclude that treatment with WBRT plus SRS is significantly associated with improved overall survival compared with SRS alone in the cohort limited to non-small-cell lung cancer (NSCLC) with a favorable prognosis (disease-specific Graded Prognostic Assessment 2.5-4.0). In the current era of personalized medicine, this is an appropriate attempt to renew interest in a subset of patients who may derive a survival benefit from WBRT using prospectively gathered data. However, the landscape of managing multiple brain metastases is complex and rapidly changing. The decision to use WBRT revolves around its impact on 3 interrelated components: (1) overall survival, (2) intracranial control, and (3) neurocognitive sequelae.

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With respect to overall survival, there are no appropriately powered RCTs to suggest an improvement with WBRT. There are now 3 RCTs that have confirmed a lack of survival benefit, and this consensus has built considerable inertia against WBRT.[1,3,4] Intracranial control has never translated into a survival benefit, and many believe that this is explained by the availability of salvage options and/or competing risks of