

Outcome of Stereotactic Radiosurgery for Patients with Non-Small Cell Lung Cancer Metastatic to The Brain

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Stereotactic radiosurgery/Brain metastases/Non-small cell lung cancer/Retreatment/Survival.

We evaluated the treatment outcome of stereotactic radiosurgery (SRS) alone, allowing for salvage with repeat SRS or fractionated radiotherapy, for managing patients with brain metastases from non-small cell lung cancer (NSCLC). From October 1998 through November 2008, 84 patients with NSCLC metastatic to the brain were treated with linac SRS. The marginal dose of SRS ranged from 12 to 20 Gy. Twenty-one patients underwent salvage radiotherapy and repeat SRS was used for 12. The 1- and 5-year overall survival rates were 38% and 11%, respectively, and the median survival time was 9 months. The 1- and 2-year local control rates were 77% and 52%, respectively, and the median time of local control was 9 months. The most common cause of death was active extracranial disease, and central nervous system (CNS) failure was determined in 16%. Chronic CNS toxicity of grade 4 was observed in 2 patients. Uni- and multivariate analyses revealed that factors significantly affecting overall survival were the presence of active extracranial disease ($P < 0.0001$ and $P = 0.003$, respectively), performance status ($P = 0.001$ and $P = 0.009$, respectively), and number of brain metastases ($P = 0.0003$ and $P = 0.019$, respectively). There were 15 long-term survivors, surviving more than 2 years. A large proportion (87%) had a single brain metastasis initially and few intracranial distant metastases afterwards (20%). SRS alone allowing for salvage radiotherapy was effective for managing brain metastases and avoiding CNS failure from NSCLC. In consideration of appropriate prognostic factors and the so-called oligometastases situation for patient selection, the use of upfront whole brain radiotherapy might improve outcome.

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of patients with primary lung cancer, and is both the leading cause of death from cancer and the most common source of brain metastases.¹⁻⁴ It is reported that, in 30 to 50% of patients with NSCLC, brain metastases occur at some time during the course of their disease,³⁻⁵ and, if untreated, the median survival time (MST) of the patients with brain metastases is approximately 1 month.⁶

Radiation therapy is one of the most available treatment options for these patients. Historically, whole brain radiation therapy (WBRT) has been the mainstay of treatment for many years, prolonging patient survival.³ When treated with

WBRT, the MST for patients with brain metastasis from lung cancer including NSCLC is approximately 3 to 6 months.⁶⁻⁸ In addition, the use of upfront WBRT following surgical resection decreases intracranial recurrences and suppresses neurological deaths, although limited in patients with a single and surgically-accessible brain metastasis.⁹ Moreover, stereotactic radiosurgery (SRS), a noninvasive technique delivering a single large fraction of ionizing radiation to a well-defined small intracranial target with a very sharp peripheral dose falloff and resulting in minimal exposure of normal surrounding brain,¹⁰ has had a big impact on control of brain metastases and patient survival.^{11,12} Employing SRS, the MST has been extended to approximately 7 to 14 months.¹³⁻¹⁵

However, treatment results for brain metastases from NSCLC are not yet satisfactory. In fact, while there is a small proportion of patients surviving long due to effective therapy including SRS despite harboring multiple brain tumors, most patients still have a limited survival. In the current study, we evaluated the outcomes of SRS performed in our hospital for managing patients with NSCLC metastatic to the brain, and based on a detailed analysis of these out-

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comes, we sought new ways to improve treatment outcomes for our patients.

MATERIALS AND METHODS

Materials

Eighty-four patients with histo- or cytopathologically proven NSCLC metastatic to the brain underwent SRS at Iwate Prefectural Central Hospital from October 1998 through November 2008. Written informed consent was obtained before treatment from each patient. They consisted of 16 patients (19%) with previously untreated Stage IV disease and 68 (81%) recurrent or relapsed ones once definitely treated with surgery or radiochemotherapy. There were 59 men and 25 women, and the median age was 68 years (range, 42–85). The number of patients with baseline performance status (PS) 0, 1, 2 and 3 was 26, 32, 15 and 11, respectively. Histopathological subtype distribution for the lung primary included the following: 52 adenocarcinomas, 16 squamous cell carcinomas, 14 large cell carcinomas, 1 undifferentiated carcinoma, and 1 unclassified NSCLC. The number of patients harboring single, 2, 3, 4, and more than 4 brain metastases on Gadolinium enhanced T1-weighted MR imaging was 44 (52%), 27 (32%), 8 (10%), 2 (2%), and 3 (4%), respectively. The location of brain metastasis as target of SRS was supratentorial in 119 tumors: frontal lobe (42), parietal lobe (33), temporal lobe (23), occipital lobe (17), and the basal ganglia and thalamus (5), and infratentorial (cerebellum) in 19 tumors. The longest diameter of the metastatic tumor ranged from 0.3 to 4 cm (median, 1.3 cm). The number of patients with active extracranial disease, including previously untreated Stage IV disease, and that

without active extracranial disease was 63 (75%) and 21 (25%), respectively. The patients were classified according to the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification system.¹⁶⁾ This provides a prognostic index integrating 3 important prognostic factors, age, Karnofsky performance scale (KPS), and presence or absence of extracranial metastases and control status of primary tumor. According to this system, 6 patients were in Class 1, 52 in Class 2, and 26 in Class 3. Here, PS 0-1 was considered as KPS 70 or more. The characteristics of the patients are listed in Table 1.

Treatment Techniques

Radiation therapy for brain metastasis was performed initially with SRS alone. SRS was administered with a linear accelerator (CLINAC 2100C, Varian Medical Systems, Palo Alto, CA, USA) and 10 MV X-ray was employed. Also an F.L. Fischer Stereotactic Radiosurgery System (Leibinger, Heidelberg, Germany), consisting of rigid head immobilization devices including a stereotactic head frame, a set of collimators of various aperture sizes, a CT localizer, target positioner for the linear accelerator, and a computerized system for stereotactic treatment planning and target point verification using portal films, was employed. Attachment of the head frame to the skull was done by a neurosurgeon under local anesthesia and mild sedation. For SRS planning patients had a contrast-enhanced CT scan, and gross target volume (GTV, equaling clinical target volume) was defined as the contrast enhancing tumor volume, in consideration of Gadolinium enhanced T1-weighted studies of diagnostic MR imaging. Planning target volume (PTV) was defined as the volume, GTV with a 1 to 2 mm margin of surrounding

Table 1. Baseline Patient Characteristics

Characteristics	
Age (years)	Range 42-85, Median 66
Gender	Male 59, Female 25
Performance status	0: 26, 1: 32, 2: 15, 3-4: 11
Histopathological status	ADCA: 52, SCC: 16, Large: 14, Undiff: 1, NSCLC: 1
Number of brain metastases	1: 44, 2: 27, 3: 8, 4: 2, 5-: 3
Diameter of the largest lesion	<15 mm: 41, 16-30 mm: 33, 31 mm-: 10
Presence of active extracranial lesion	Yes 63, No 21
Location of brain metastases	F: 42, P: 33, T: 23, O: 17, C: 19, Th & BG: 5
RTOG RPA Classification*	Class 1: 6, Class 2: 52, Class 3: 26

Abbreviations: ADCA, adenocarcinoma; SCC, squamous cell carcinoma; Large, large cell carcinoma; Undiff, undifferentiated carcinoma; NSCLC, non-small cell carcinoma; F, frontal lobe; P, parietal lobe; T, temporal lobe; O, occipital lobe; C, cerebellum; Th, thalamus; BG, basal ganglia; RTOG, Radiation Therapy Oncology Group; RPA, recursive partitioning analysis. *Class 1: KPS \geq 70, aged < 65 years, and no active extracranial disease; Class 3: KPS < 70, Class 2: all others.¹⁶⁾

brain tissue. In most cases, convergent dose distribution was obtained by beam arrangement using 6 non-coplanar arcs with a single isocenter. SRS dose was delivered in a single fraction and prescribed to the isocenter, ranging from 15 to 33 Gy (median, 25 Gy). The dose to PTV margin or peripheral dose, corresponding to about 80% of the isocenter dose, ranged from 12 to 20 Gy (median, 20 Gy). For 3 target lesions, which were ellipsoidal and large, a two-isocenter plan was used. In this scheme, an SRS dose of 16 to 18 Gy was prescribed to the isodose shell of around 60% of global maximum dose, covering PTV. Dose selection was based on various factors including the size, number and location of target lesions. When there were multiple target lesions, independent SRS was planned and delivered to each of them within the same treatment day. The maximum number of target lesions that received SRS in a single session was 5 for 3 patients. Only one patient underwent an upfront adjuvant whole brain radiation therapy (WBRT) of 30 Gy in 10 fractions against small distributed metastases after an initial SRS toward the 3 main tumors. When SRS alone was employed, hospitalization was needed for only 3 days. Patients were usually discharged home or, if necessary, transferred to another hospital on the following day, after overnight observation.

Twenty-four patients (29%) underwent salvage therapy, 21 (25%) with radiotherapy and 3 (4%) with surgery. As salvage radiotherapy, repeat SRS and fractionated external beam irradiation were employed. Repeat SRS was used for 12 patients (14%), 6 associated with progression of the original tumor uncontrolled by initial SRS and 6 with newly developed distant brain metastasis outside the initial SRS volume. For the former 6 patients, a second SRS was delivered using a reduced isocenter dose of 18 to 25 Gy (median, 20 Gy). For the latter 6 patients a second SRS was delivered in the same manner as the initial one with an isocenter dose of 25 Gy, and later half of them received a third SRS for the other newly developed metastases. In 2 patients (3%) with large locally-relapsed lesions, 3-dimensional conformal radiotherapy was used with the respective total target dose, prescribed to the isocenter, of 45 Gy in 15 fractions and 50.4 Gy in 21 fractions. WBRT with a total target dose of 30 Gy in 10 fractions or 40 Gy in 16 fractions was employed for 7 patients (8%), as salvage therapy to both locally relapsed and newly developed brain metastases. Three patients (4%) underwent surgical procedures as salvage. Two of them received craniotomy for resection after repeat SRS at the original site. The remaining one received ventricle-peritoneum shunting after SRS because of progressive hydrocephalus due to the mass effect from an infratentorial tumor.

Treatment modalities for lung primary tumor of the 16 patients (19%) with previously untreated Stage IV disease were the following: 2, surgery followed by postoperative radiation therapy; 4, combined chemotherapy and radiation therapy; and 10, chemotherapy alone. Chemotherapy was

used chiefly with platinum-based regimens. In all cases, SRS was carried out at the beginning of a series of anti-cancer therapies.

Follow-up and Evaluation of Local Tumor Control

The patients were followed clinically and by serial MR imaging and CT scanning, periodically whenever possible. Imaging studies were performed to assess changes in tumor size and the development of new intracranial tumors. Contrast enhancement defined the tumor margin. Local tumor control was evaluated in consideration of the response evaluation criteria in solid tumors (RECIST).¹⁷⁾ When the local status at the target site of initial SRS was assessed to be a complete response, partial response or stable disease according to the criteria, the tumor was defined as being controlled. When an increase of more than 20% in the longest diameter of the target tumor compared with the baseline value before initial SRS was observed, the tumor was defined as being progressive or relapsed.

The median follow-up period after initial SRS was 8.5 months (range, 1 to 79 months). However, sufficient records and images for evaluating the serial status of primary and systemic disease including brain tumor were obtained in 61 out of 84 patients (73%). For 15 patients (18%), although outcomes and cause of death could be determined from their records, imaging follow-up was carried out infrequently, which was insufficient for evaluating serially local control of brain tumor. They were introduced or transferred to other hospitals at some time during the course of treatment. In the remaining 8 patients (9%), records and images were insufficient. Survival or death could be determined; however, cause of death could not. They were introduced or transferred to other distant hospitals after a short period following initial SRS.

Time in months of survival and that of local tumor control were computed from the date of the patient's initial SRS. Curves of survival and local tumor control and MST were calculated using the Kaplan-Meier method. Factors potentially affecting survival were assessed with the log-rank test and the Cox proportional hazards model. All analyses were carried out with the statistical software package SPSS 11.0J for Windows (SPSS Japan Inc., Tokyo). Significance was set as $P < 0.05$.

RESULTS

Patient Survival

The 1-, 2-, and 5-year overall survival (OS) rates for all patients were 38%, 24%, and 11%, respectively (Fig. 1-a). The MST for all patients was 9 months. For previously untreated patients with Stage IV disease ($n = 16$), the 1-, 2-, and 5-year OS rates were 25%, 8%, and 0%, respectively (Fig. 1-b), and the MST was 4 months. On the other hand, the 1-, 2-, and 5-year OS rates for the relapsed or recurrent

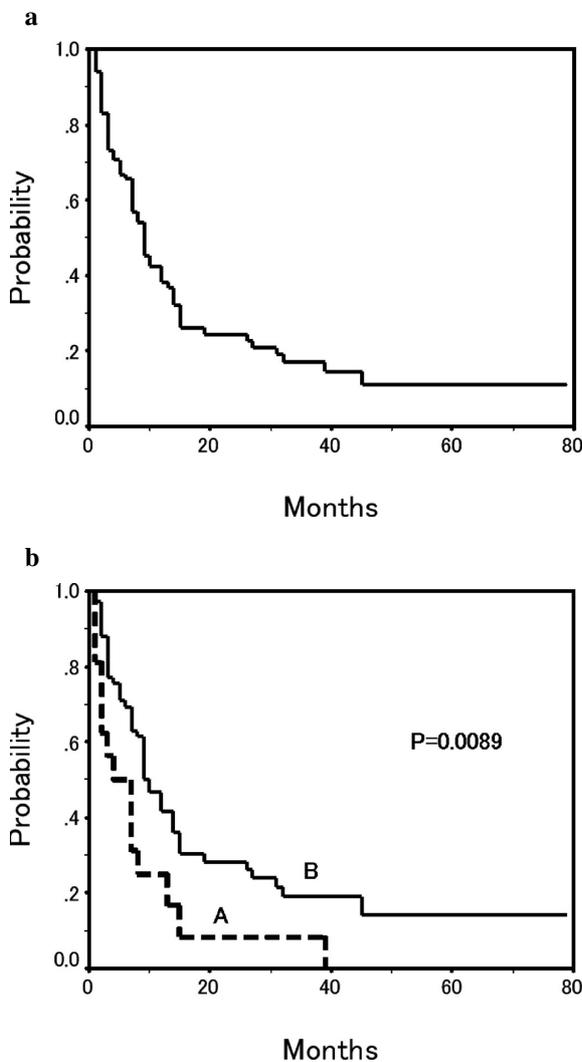


Fig. 1. a. Kaplan-Meier curve of overall survival rate for all of 84 patients. b. Kaplan-Meier curves of survival rates in previously untreated patients (A: $n = 16$) and relapsed or recurrent patients once definitely treated (B: $n = 68$).

patients once definitely treated ($n = 68$) were 42%, 28%, and 14%, respectively (Fig. 1-b, $p = 0.0089$). Their MST was 10 months.

Local Tumor Control and Local Relapse Free Survival

Sufficient images and records for serially evaluating local tumor control were obtained in 61 of 84 patients (73%) as aforementioned. For the available patients ($n = 61$), the 1- and 2-year local control rates of brain tumor treated with initial SRS were 77 and 52%, respectively (Fig. 2-a). The median time of local tumor control after initial SRS was 9 months. The 1- and 2-year local relapse free survival rates for the available patients ($n = 61$) were 35 and 20%, respectively (Fig. 2-b). The median time of local relapse free survival after initial SRS was 9 months.

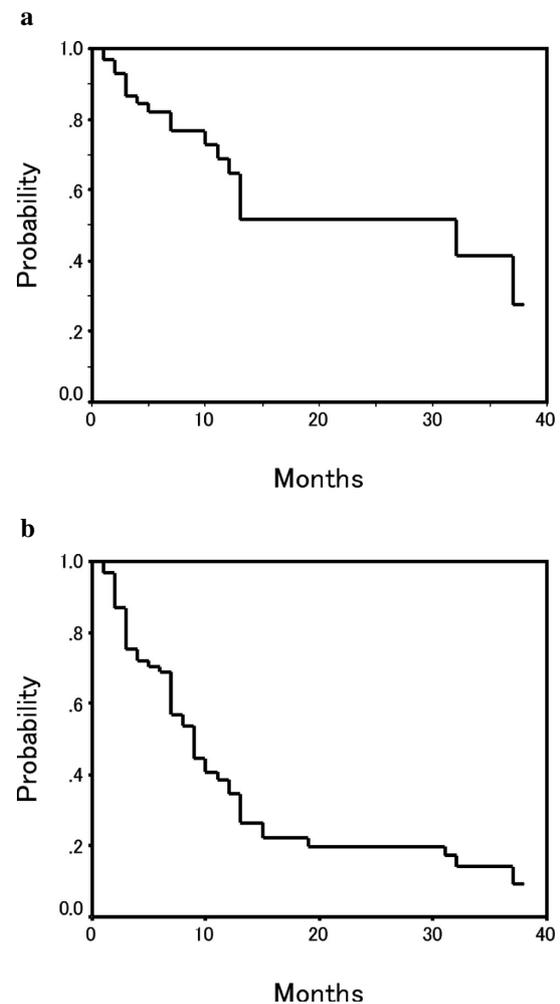


Fig. 2. a. Kaplan-Meier curve of local tumor control rate for the 61 patients evaluated. b. Kaplan-Meier curve of local relapse free survival rate for the 61 patients evaluated.

Cause of Death and CNS Failure

Sixty-six patients out of the total number of 84 died. The cause of death could not be clarified in 8 patients due to insufficient follow-up records as noted above. In the available 76 patients excluding the 8 patients, the most common cause of death was active extracranial disease (44/58, 76%). There were 2 patients who died of suicide (2/58, 3%). If the patient died from direct complications of progressive brain tumor, either within or out of the SRS volume, cause of death was considered neurologic or CNS failure. Neurologic death or CNS failure was determined in 12 patients (12/58, 21%; 12/76, 16%). The 1-, 2-, and 5-year rates of CNS failure free were 80, 73, and 48%, respectively (Fig. 3). The median time of CNS failure free after initial SRS was 45 months.

Prognostic Factors for Survival

Univariate and multivariate analyses were performed on 9

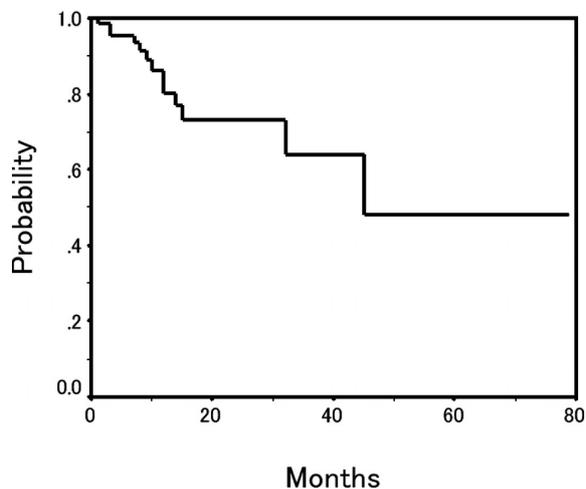


Fig. 3. Kaplan-Meier curve of central nervous system (CNS) failure free rate for the 76 patients evaluated.

different factors to determine their potential prognostic value with respect to overall survival (OS). Investigated were patient characteristics (age, gender, and baseline PS), tumor characteristics (histopathological subtype, number of brain metastases, the longest diameter of the largest brain metastasis in each patient, and presence of active extracranial disease), and treatment characteristics (with or without WBRT, and with or without repeat SRS). The most significant prognostic factor for OS was the presence of active extracranial disease ($P < 0.0001$ and $P = 0.0004$ for uni- and multivariate analyses, respectively). The MST with active extracranial disease was 7 months and without it was 32 months. Significant, too, were baseline PS ($P = 0.002$ and $P = 0.0049$ for uni- and multivariate analyses, respectively) and number of brain metastasis ($P = 0.0003$ and $P = 0.029$ for uni- and multivariate analyses, respectively). The MST with a good baseline PS (0-1) was 10 months and that with a poor one (2-4) was 7 months. The MST with a single brain metastasis was 13 months and that with multiple metastases, 2 or more, was 5 months. The other 6 factors did not correlate with OS. The results are summarized in Table 2 and 3 and are shown in Fig. 4 (a-c). In addition, applying the stratification by RTOG-RPA class revealed significant differences among the classes (1-3) and survival times ($P = 0.038$ between class 1 and 2, $P = 0.012$ between class 2 and 3; Fig. 5). The median survivals for RTOG-RPA classes 1, 2, and 3 were 22, 9 and 7 months, respectively.

Long-term Survivors

There were 15 long-term survivors, surviving more than 2 years. The longest survival time was 79 months, and the patient is still alive without active disease. The characteristics of long-term survivors are shown in Table 4. A large part of them had a good baseline PS (0-1, 14/15, 93%), a single

Table 2. Univariate Survival Analysis

Variables	MST(months)	P-value
PS (0-1/2-4)	10/7	0.0010
Age ($\leq 68 / > 68$)	9/9	0.7725
Gender (Male/Female)	8/12	0.1764
Number of brain metastases (Single/Multiple)	13/5	0.0003
Diameter of the largest lesion		
(-15 mm/16-30 mm)	7/12	0.7363
(16-30 mm/31 mm-)	12/9	0.1718
Histopathology (ADCA/Others)	9/8	0.2585
Active extracranial disease (No/Yes)	32/7	< 0.0001
WBRT (With/Without)	9/9	0.5253
Repeat SRS (With/Without)	9/12	0.2669

Abbreviations: PS, Performance status; ADCA, Adenocarcinoma; WBRT, Whole brain radiation therapy; SRS, Stereotactic radiosurgery.

Table 3. Multivariate Survival Analysis

Variables*	Hazard Ratio (95% CI)	P-value
PS (0-1)	2.21 (1.22-4.01)	0.009
Age (≤ 68)	0.87 (0.52-1.46)	0.601
Gender (Female)	1.01 (0.51-2.02)	0.969
Number of brain metastases (Single)	2.00 (1.12-3.55)	0.019
Diameter of the largest lesion (≤ 15 mm)	0.92 (0.61-1.40)	0.701
Histopathology (ADCA)	1.11 (0.63-1.96)	0.708
Active extracranial disease (No)	3.58 (1.56-8.21)	0.003
WBRT (Without)	0.96 (0.42-2.17)	0.912
Repeat SRS (Without)	0.68 (0.35-1.32)	0.258

Abbreviations: PS, Performance status; ADCA, Adenocarcinoma; WBRT, Whole brain radiation therapy; SRS, Stereotactic radiosurgery; CI, Confidence interval.

*Referents appear in parentheses.

brain metastasis (13/15, 87%) and absence of active extracranial disease (10/15, 67%), and underwent definitive therapy for lung primaries in the initial treatment (14/15, 93%). Treatment modalities for lung primaries in the 15 patients included the following: 11 (73%) surgery, 3 (20%) combination of radiation therapy and chemotherapy, and 1 (7%) chemotherapy alone. Intracranial retreatment was needed in 6 out of 15 patients (40%), and repeat SRS was used for 5 out of 15 (33%). Three patients with locally relapsed tumor received a second SRS at the original site and 2 of the 3 had a third SRS and, moreover, salvage surgery. Of 2 patients with new distant brain metastases, one received a second SRS for new metastases outside the initial SRS volume and another for both new metastasis and local relapse. Salvage

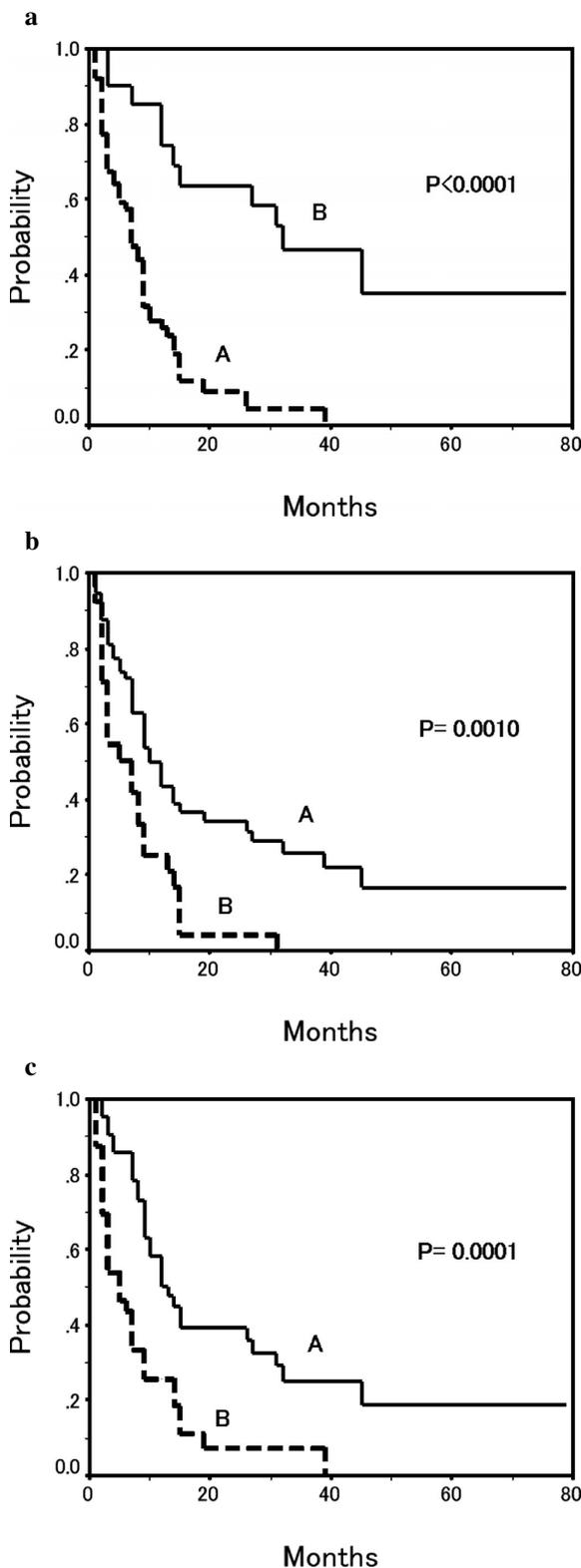


Fig. 4. a. Kaplan-Meier curves of survival rates with (A: $n = 63$) and without (B: $n = 21$) active extracranial disease. b. Kaplan-Meier curves of survival rates in patients with PS 0-1 (A: $n = 58$) and PS 2-4 (B: $n = 26$). c. Kaplan-Meier curves of survival rates in patients with single (A: $n = 44$) and multiple (B: $n = 40$) brain metastases.

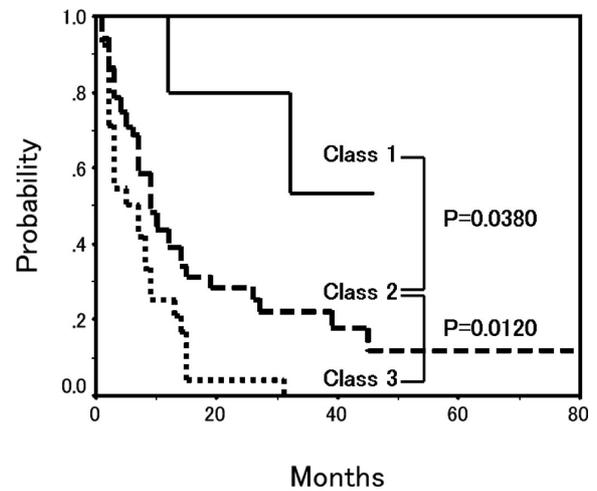


Fig. 5. Kaplan-Meier curves of survival rates in the 3 classes according to Radiation Therapy Oncology Group recursive partitioning analysis classification.¹⁶⁾ Class 1 ($n = 6$): KPS ≥ 70 , aged < 65 years, and no active extracranial disease; Class 3 ($n = 26$): KPS < 70 , Class 2 ($n = 52$): all others.

WBRT was applied to a patient with newly developed numerous brain metastases. Only 2 out of 15 (13%) long-term survivors died of CNS failure.

Complications

No major acute toxicity occurred. Although one patient had transient general seizures on the treatment day of SRS, he was soon managed with an administration of an anticonvulsant and a corticosteroid. This was considered to be acute CNS toxicity of grade 2 according to RTOG criteria.¹⁸⁾ As to chronic toxicity, one patient underwent surgical resection for localized radiation necrosis after 3 sessions of SRS, initial SRS and 2 salvage ones thereafter, at an original target site. Another patient with a similar course of treatment also underwent surgical resection, but in that case the radiation necrosis-suspected lesion revealed histopathologically to be tumor growth with necrosis. Both two cases were recognized as chronic CNS toxicity of grade 4 according to the RTOG/EORTC scoring schema,¹⁹⁾ and the latter associated with tumor relapse. Except for the 2 patients, no other major chronic CNS toxicity was recorded in the 76 patients evaluated.

DISCUSSION

In the current study, we chiefly evaluated survival parameters and probability of avoiding neurologic death or CNS failure for patients that were accompanied with NSCLC metastatic to the brain treated with SRS. As a result, they were better than what we expected and comparable with the other reports previously published.²⁰⁻²²⁾ There were 15 long-term survivors, surviving more than 2 years, and the longest

Table 4. Long term survivors

No.	Gender	Age	PS	pathol.	U/R	Nr-BM	ECL	Prim-Tx.	RSDose	Salvage	OC	Time	CNS-F
1.	M	72	1	AD	R	1	N	Surg.	25		A	79	
2.	M	80	1	AD	R	1	N	CRT	25		A	65	
3.	F	59	0	LC	R	1	N	Surg.	25	S	A	46	
4.	M	68	1	AD	R	1	N	Surg.	25	S	D	45	Y
5.	M	73	0	AD	R	1	N	CRT	25		A	41	
6.	F	57	0	AD	R	1	N	CRT	25		A	41	
7.	M	72	1	AD	U	2	Y	Surg.	25		D	39	
8.	F	65	0	AD	R	3	N	Surg.	25	SSCS'	A	35	
9.	M	60	1	AD	R	1	N	Surg.	25	SSC	D	32	Y
10.	F	56	2	AD	R	1	Y	Surg.	33	W	D	31	
11.	M	56	1	AD	R	1	N	Surg.	25	S'S'	A	31	
12.	M	70	0	AD	R	1	N	Surg.	25		A	31	
13.	F	74	1	LC	R	1	Y	Surg.	25		D	27	
14.	M	75	0	LC	R	1	Y	Surg.	25		D	28	
15.	M	56	0	AD	R	1	N	Chemo	25		A	24	

Abbreviations: M, male; F, Female; PS, Performance Status; Pathol., Histopathological Diagnosis; AD, Adenocarcinoma; LC, Large Cell Carcinoma; U, Previously Untreated; R, Recurrent or Relapsed; Nr-BM, Number of Brain Metastases; ECL, Active Extracranial Lesion; Y, Yes; N, No; Prim-Tx, Initial Treatment of Primary; Surg., Surgery; CRT, Chemoradiation; Chemo, Chemotherapy alone; RSDose, Dose of Initial Stereotactic Radiosurgery (SRS), prescribed to isocenter; Salvage, Salvage Treatment; S, Repeat SRS at The Original Site; S', Repeat SRS outside The Initial SRS Volume; C, Craniotomy for Surgical Resection; W, Whole Brain Radiation Therapy; OC, Outcome; A, Alive; D, Dead; Time, Survival Time in Months; CNS-F, Central Nervous System-Failure.

was alive for 79 months without active disease. Although tumor progression and number of brain metastases varied among patients, our basic treatment strategy to date was to employ SRS initially and as salvage for avoiding CNS failure as much as possible. Therefore, repeat SRS was frequently employed not only for newly developed brain metastases but also for locally-relapsed tumors at an original site. Only when considered necessary from disease status, WBRT or partial-brain irradiation was used as salvage. As a result, CNS failure was determined only in 16% of the patients estimated, and the most common cause of death was active extracranial disease. Avoiding CNS failure, by stabilization or improvement of clinical symptoms, enhancing survival, and reducing risk, is the goal of SRS for treating brain metastases. From this viewpoint, our results were satisfactory although intracranial retreatment was unavoidable with considerable frequency.

Assessment of prognostic factors for survival revealed the impact of presence of active extracranial disease, baseline PS, and number of brain metastasis upon OS. The former two have been emphasized as important factors to predict prognosis of NSCLC metastatic to the brain in a number of

previous reports.^{12,15,20,21,23-25)} RTOG-RPA classification, too, based on 3 prognostic factors including the two mentioned above, has been known as a clinically useful prognostic index.^{16,26)} In the current study, RTOG-RPA classification represented the prognostic potential which could clearly discriminate survival times between the classes. Those studies including ours show that the selected patients, with a good baseline PS and the predominant problem being brain disease rather than extracranial disease, would have a favorable prognosis when SRS was applied. Meanwhile, the remaining significant factor, number of brain metastases is also important. Recently, Hu *et al.* stated that American Joint Committee on Cancer (AJCC) thoracic Stage I NSCLC patients associated with solitary brain metastasis had a comparable outcome with Stage I without brain metastasis, when treated using thoracic radiation therapy, chemotherapy, and craniotomy or SRS to the brain.²⁷⁾ Flannery *et al.* reported an excellent outcome, an MST of 18 months and a 5-year OS of 21%, in patients with synchronous, solitary brain metastasis from NSCLC treated with gamma knife SRS.²⁸⁾ Also in our study, a large proportion of the long-term survivors (13/15, 87%) had only a single brain metastasis. Number of brain

metastases appears an important prognostic factor comparable with the other two. With knowledge of the significant factors and indices, it seems possible to a degree to predict the prognosis of NSCLC patients metastatic to the brain, leading to an optimized and efficient therapeutic strategy with SRS.

More importantly, we should pay attention to the fact that 25% (21/84) of the patients finally needed salvage radiation therapy. Long-term survivors received intracranial retreatment with a higher rate of 40% (6/15), probably because of the increasing possibility of local relapse and distant metastases with prolonged survival. In this context, we would like to refer to the use of upfront WBRT with SRS. However, there has been a controversy concerning the effects of WBRT as an adjuvant treatment to SRS. For example, in the retrospective analysis by Sneed *et al.* omission of WBRT in the initial management of patients treated with SRS for up to 4 brain metastases did not appear to compromise survival or intracranial control when allowing for salvage therapy.²⁹⁾ A multi-institutional review by Sneed *et al.* demonstrated that omission of upfront WBRT did not seem to compromise length of survival in patients treated with SRS for newly diagnosed brain metastases.¹⁴⁾ Pirzkall *et al.* found no difference in overall survival for 236 patients treated with SRS alone in comparison with SRS and WBRT, whereas in the subset of patients without extracranial disease omitting WBRT resulted in a survival decrease.³⁰⁾

Recently, however, Aoyama *et al.* reported a noteworthy randomized controlled trial of SRS alone versus SRS plus upfront WBRT from the Japan Radiation Oncologist Study Group.³¹⁾ In the trial the use of SRS plus WBRT did not improve survival for patients with 1 to 4 brain metastases, compared with SRS alone. However, in selected patients with a single brain metastasis their results suggested SRS plus WBRT improved survival. Indeed, they reported that SRS plus WBRT significantly improved local brain tumor control, compared with SRS alone. The omission of WBRT resulted in decreased tumor control and consequently salvage treatment was frequently required, both at the site of SRS and in the remaining untreated brain. An addition of WBRT to SRS did not decrease systemic and neurological function and did not increase toxic effects of radiation. From their study, at least it is confirmed that upfront WBRT added to SRS improves local control both at the site of SRS and in the remaining brain without increasing either acute or late radiation toxicities, which has an impact upon avoiding frequent intracranial retreatment and maintaining neurological function.

On the other hand, it is of concern that a large proportion of long-term survivors in our study had a single brain metastasis initially (13/15, 87%) and few intracranial distant metastases afterwards (3/15, 20%). This tendency might be related to the so-called “oligometastases situation”, which means a philosophy that in some patients the intracranial disease is truly limited, contrary to the presumption widely

accepted to date that the entire brain is seeded with micrometastatic disease even when only a single intracranial lesion is detected.³¹⁾ If the intracranial disease is truly limited and the “oligometastases situation” is identifiable, employing SRS alone initially allowing for repeat SRS as salvage, not combined with upfront WBRT, could be justified for selected patients. In this context, identification of the patient group with “oligometastases situation” is needed, or the related clinical and biological parameters of tumor should be investigated. Although the objects might be limited to some selected patients, whether SRS plus upfront WBRT or SRS alone allowing for salvage chiefly with repeat SRS is better, is still a controversial issue, because the continuous deterioration of neurocognitive function for long-term survivors who underwent WBRT cannot be neglected.³²⁾

Of course, treatment for the patients with apparently unfavorable prognostic factors or indices should be adequately individualized and optimized in view of the cost-benefit ratio. For the patients with numerous brain metastases and expectations of limited survival, WBRT alone would be a standard and superior therapy.^{11,12)} At the same time, in the previously untreated Stage IV disease, more concern should be focused on control of the primary tumor. With respect to survival, the control of systemic cancer would often outweigh the clinical course of irradiated brain tumors. Actually, it was of note that the survival times of the 16 patients with previously untreated Stage IV NSCLC in our study were unexpectedly poor, the MST being only 4 months. One of the explanations for the poor results might be that, in a large proportion of the patients (63%, 10/16), primaries were insufficiently treated with systemic chemotherapy alone irrespective of thoracic stages. From this viewpoint, it was of interest that Flannery *et al.* demonstrated definitive thoracic therapy significantly impacted overall survival in the previously untreated patients with synchronous, solitary brain metastasis from NSCLC.²⁸⁾ Likewise, Hu *et al.* suggested that aggressive treatment to the lung could be justified for newly diagnosed thoracic Stage I NSCLC patients with solitary brain metastasis managed with SRS plus WBRT or surgery.²⁷⁾ As to the untreated patients with Stage IV NSCLC metastatic to the brain, at least with early thoracic stage and metastatic only to the brain, more aggressive treatment to primary tumors should be considered as well as managing brain metastases.

Regarding neurological complication of repeat SRS, Bhatnagar *et al.* reported that repeat SRS could be performed with minimal CNS toxicity compared with baseline in 26 patients with benign and malignant tumors.³³⁾ In the final report of RTOG protocol 90-05, Shaw *et al.* revealed the feasibility of SRS as retreatment of recurrent primary and metastatic brain tumors previously irradiated, whereas they also showed the maximally tolerated SRS dose ranged from 15 to 24 Gy depending on the tumor size.³⁴⁾ Those reports demonstrated the clinical usefulness and feasibility

of repeat SRS as salvage, which is consistent with our results. It remains to be determined whether repeat SRS to the same lesion produces additional benefit for the patient or should be avoided whenever possible as Chin *et al.* recommended in their report.³⁵⁾ However, it is also suggested that the treatment strategy, intending to treat and salvage brain metastases as much as possible relying on SRS, has led to the considerably longer survivals and a low CNS failure rate in a number of reports including ours.^{14,15,22,24,36,37)}

In conclusion, SRS alone allowing for salvage with repeat SRS or fractionated radiotherapy was effective for managing brain metastases and avoiding CNS failure from NSCLC. At the same time, the use of upfront WBRT combined with SRS was reported to significantly improve local tumor control.³¹⁾ Taking into consideration significant prognostic factors and indices should help us to choose an appropriate way of treatment for each patient, and further investigation with respect to the “oligometastases situation” might offer novel findings of importance that could be incorporated in designing a new-stage treatment strategy with SRS.

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