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The usefulness of stereotactic radiosurgery for recursive partitioning analysis class II/III lung cancer patients with brain metastases in the modern treatment era

In Bong Ha, MD[a], Jin Ho Song, MD[b], Bae Kwon Jeong, MD, PhD[a,c], Hojin Jeong, PhD[a,c], Yun Hee Lee, MD[d], Hoon Sik Choi, MD[e], Ki Mun Kang, MD, PhD[c,e,*]

Abstract

Stereotactic radiosurgery (SRS) is considered the initial treatment for lung cancer patients with small-sized and limited number of brain metastases. The objective of this study was to assess clinical outcomes of SRS treatment using CyberKnife (CK) for recursive partitioning analysis (RPA) class II/III patients with 1 to 3 brain metastases from lung cancer and identify which patients in the high RPA class could benefit from SRS.

A total of 48 lung cancer patients who received CK-based SRS for their metastatic brain lesions from 2010 to 2017 were retrospectively analyzed. Radiographic response was evaluated during follow-up period. Overall survival (OS) and intracranial progression-free survival (IPFS) were calculated and prognostic variables associated with OS and IPFS were evaluated.

Median follow-up time was 6.6 months. Local control rates at 6 months and 1-year following SRS were 98% and 92%, respectively. The median OS of all patients was 8 months. One-year and 2-year OS rates were 40.8% and 20.9%, respectively. In multivariate analysis, uncontrolled primary disease ($P = .01$) and Eastern Cooperative Oncology Group performance status of 2 or 3 ($P = .001$) were independent prognostic factors for inferior OS. These 2 factors were also significantly associated with inferior IPFS. In subgroup analysis according to RPA class, primary disease status was the only prognostic factor, showing statistically significant OS differences in both RPA class II and III (controlled vs uncontrolled: 41.1 vs 12.3 months in RPA class II, $P = .03$; 26.9 vs 4.1 months in RPA class III, $P = .01$).

Our results indicated that SRS could be an effective treatment option for RPA class II/III patients with brain metastases from lung cancer in the modern treatment era. SRS might be particularly considered for patients with controlled primary disease.

Abbreviations: CK = cyberknife, CNS = central nervous system, CT = computed tomography, ECOG = eastern cooperative oncology group, GTV = gross tumor volume, IICP = increased intracranial pressure, IPFS = intracranial progression-free survival, LC = local control, MRI = magnetic resonance imaging, NSCLC = non-small cell lung cancer, OS = overall survival, RC = regional control, RECIST = response evaluation criteria in solid tumors, RPA = recursive partitioning analysis, SCLC = small cell lung cancer, SRS = stereotactic radiosurgery, WBRT = whole-brain radiation therapy.

Keywords: brain metastases, lung cancer, prognostic factors, stereotactic radiosurgery

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[a] Department of Radiation Oncology, Gyeongsang National University School of Medicine, and Gyeongsang National University Hospital, Jinju, [b] Department of Radiation Oncology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [c] Institute of Health Science, Gyeongsang National University, Jinju, [d] Department of Radiation Oncology, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [e] Department of Radiation Oncology, Gyeongsang National University School of Medicine, and Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea.

[*] Correspondence: Ki Mun Kang, Department of Radiation Oncology, Gyeongsang National University School of Medicine, and Gyeongsang National University Changwon Hospital, 13 Samjungja-ro, Changwon 51472, Republic of Korea (e-mail: jsk92@gnu.ac.kr).

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1. Introduction

Lung cancer has currently the highest incidence in the world. It is the leading cause of cancer-related deaths.[1] Brain metastases from lung cancer also have a high incidence rate of 20%.[2] As this disease progresses, brain metastases occur more often. Among all cases of brain metastases, those from lung cancer account for 40% to 50%.[3] Therefore, appropriate management of brain metastases is a very important issue in treatment of lung cancer patients.

In the last several decades, whole-brain radiation therapy (WBRT) is a standard treatment for patients with multiple brain metastases. However, many clinical studies have shown that the quality of life of patients is deteriorated by the neurotoxicity caused by WBRT.[3,4] Although median survival of patients with brain metastases treated with WBRT has been reported to be less than 6 months, the number of patients with long term survival as well as median survival of patients has increased recently due to the development of systemic therapies and choice of appropriate local treatment strategies, for example, stereotactic radiosurgery (SRS) alone, SRS plus WBRT and surgical resection.[5,6] Treatment for 4 or fewer oliogometastatic lesions has been gradually replaced by SRS or surgical resection, instead of WBRT which reduces neurotoxicity while

not affecting survival.[7,8] In addition, some studies have reported that SRS alone is an effective treatment for patients with 5 or more brain metastases.[9–11]

When determining whether patients with brain metastases should receive radical local treatment, recursive partitioning analysis (RPA) classification has been widely used.[5] Although it is a readily available prognostic tool to select candidates, it lacks other important prognostic factors such as histology of tumor, number of brain metastases, and molecular features of tumor.[3,12,13] To perform treatment for brain metastases based on individual assessment of prognostic factors, it is necessary to consider all significant prognostic factors for survival. Considering median survival of patients with brain metastases, it is desirable to try aggressive treatment strategy for RPA class I patients. However, the number of such patients is very limited because most patients belong to class II and III in clinical practice.[14] Although some studies have reported SRS results in lung cancer patients with limited number of brain metastases, few studies have reported the treatment outcomes of SRS for patients with only RPA class II/III.

Thus, the aim of this study was to analyze clinical outcomes of SRS using CyberKnife (CK) (Accuray Inc, Sunnyvale, CA) for RPA class II/III patients with 1 to 3 brain metastases from lung cancer and identify which patients in the high RPA class could benefit from SRS.

2. Material and methods

2.1. Patient selection

This retrospective study was approved by the Institutional Review Board (IRB) of the Gyengsang National University Hospital (IRB number: 2018-05-015).

A total of 106 patients with brain metastases were treated with SRS using CK at the Gyengsang National University Hospital between February 2010 and May 2017. Patients were selected for this study utilizing the following criteria:

(1) pathologically proven lung cancer;
(2) RPA class II or III;
(3) completed planned schedule of SRS;
(4) a maximum diameter of each brain lesion was less than 5 cm;
(5) no apparent leptomeningeal disease.

Finally, 48 lung cancer patients eligible for RPA class II/III were retrospectively analyzed. SRS was performed in patients with less than 3 metastatic brain lesions in our institutional protocol.

2.2. Patient characteristics

The median age of the 48 patients analyzed in this study was 68.5 years (range, 48–82 years). The median follow-up time was 6.6 months (range, 0.6–89.7 months). Of these 48 patients, 37 (77.1%) were previously diagnosed with non-small cell lung cancer (NSCLC) and 11 (22.9%) were diagnosed with small cell lung cancer (SCLC). Of these NSCLC patients, 23, 9, 2, and 3 patients were diagnosed with adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and "not otherwise specified," respectively. The Eastern Cooperative Oncology Group (ECOG) performance status was 0–1 in 28 (58.3%) patients and 2–3 in 20 (41.7%) patients. Our study only included patients with RPA class II and III. The factor that determines these 2 classes is only Karnofsky performance status. When assessing the clinical performance status of patients, patient's ability to perform certain activities of daily living without help of others is regarded as up to 1 according to the ECOG scale and up to 70 according to Karnofsky performance status. We excluded RPA class from the analysis because groups categorized by ECOG (0–1 vs 2) were perfectly matched with groups categorized by RPA class (2 vs 3). At the time of the initial radiosurgery, 9 (18.8%) patients were asymptomatic, 26 (54.2%) patients had headache, 9 (18.8%) patients had unilateral weakness, 6 (12.5%) patients had seizure, 4 (8.3%) patients had dysarthria, and 2 (4.2%) patients had ataxia. Furthermore, 10 (20.8%) patients had uncontrolled primary disease and 31 (64.6%) patients had extracranial metastases. Of the total of 48 patients, 20 (41.7%) previously received WBRT, including 5 patients with SCLC who underwent prophylactic cranial irradiation. Nine of these 20 patients who received WBRT underwent SRS for salvage treatment for recurrent brain metastases while the other 11 patients underwent SRS as boost treatment for WBRT. Planning target size ranged from 0.5 to 5.0 cm (median 2.0 cm) and target volume ranged from 0.2 to 78.9 mL (median 2.6 mL). Of the total 48 patients, 41 patients (85.4%) received systemic therapies before SRS. Thirty-six patients received cytotoxic agents, 15 patients received tyrosine kinase inhibitors such as erlotinib, gefitinib and 2 patients received checkpoint inhibitors such as nivolumab. Patient characteristics are detailed in Table 1.

2.3. SRS

All patients underwent SRS using CK. During treatments, all patients were immobilized with a thermoplastic head mask in supine position. Contrast-enhanced computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) for brain were taken with slice thickness of 1.0 mm and 2.5 mm, respectively. CT and MRI images were then rigidly fused with respect to each other using CK planning system (Multiplan ver. 3.5.4). Gross tumor volume (GTV) was defined as enhanced lesion observed by any of both images. First, GTV was delineated on a CT image. It was then modified to include clearly contrast-enhancing regions seen in MRI images. Clinical target volume was set to the same as GTV, assuming no microscopic invasion outside the GTV. Planning target volume was generated by adding 1-mm margin from the GTV. Organs at risk including lenses, optic nerves, optic chasm, brainstem, and spinal cord were also contoured. If 2 lesions were close to 1 cm or less, they were planned as 1 target. Seven patients had multiple brain metastatic lesions corresponding to this condition. For this reason, although the number of brain metastatic lesions in all patients treated was 70, the actual number of planning targets was 63. Inverse treatment planning was performed for all patients using Multiplan version 3.5.4 (Accuray Inc). SRS treatment plans were basically designed so that the entire GTV and at least 95% PTV were covered by the prescription dose surface. The prescription dose was normalized median 80% isodose line (range, 75%–85%) relative to the maximal dose. The prescription dose was basically determined based on volume-dependent dose regimen suggested in the Radiation Therapy Oncology Group 95-05 trial.[5] It was partly revised according to the judgment of clinicians considering the tumor size and location, the timing of SRS, and prior radiation therapy dose. Details in the prescription dose actually delivered are summarized in the Table 2 along with dose schedules and biologic equivalence dose for $\alpha/\beta = 10$.

Table 1

Patient characteristics.

Variables	Number of patients (%)	
Age, yr		
Median (range)	68.5	(48–82)
<65	18	(37.5)
≥ 65	30	(62.5)
Gender		
Male	39	(81.3)
Female	9	(18.8)
Histological type		
NSCLC	37	(77.1)
SCLC	11	(22.9)
ECOG performance status		
0–1	28	(58.3)
2–3	20	(41.7)
Neurologic status		
Symptomatic	39	(81.3)
Asymptomatic	9	(18.8)
Primary disease status		
Controlled	10	(20.8)
Uncontrolled	38	(79.2)
Extracranial metastases		
Present	31	(64.6)
Absent	17	(35.4)
RPA class		
2	28	(58.3)
3	20	(41.7)
Number of brain lesions		
1	35	(72.9)
2	5	(10.4)
3	8	(16.7)
Prior WBRT (include PCI)		
No	28	(58.3)
Yes	20	(41.7)
Systemic therapy		
Cytotoxic agents	36	(75.0)
Target agents	15	(31.3)
Immunotherapy	2	(4.2)
Target size, cm		
Median (range)	2.0	(0.5–5.0)
Target volume, mL		
Median (range)	2.6	(0.2–78.9)

ECOG = Eastern Cooperative Oncology group, NSCLC = non-small cell lung cancer, PCI = prophylactic cranial irradiation, RPA = recursive partitioning analysis, SCLC = small cell lung cancer, WBRT = whole-brain radiation therapy.

Table 2

Dose schedules for stereotactic radiosurgery (n = 63).

CyberKnife dose (BED_{10})	Number of plans (%)	
Single fraction		
16 Gy (41.6 Gy)	1	(1.6)
18 Gy (50.4 Gy)	4	(6.3)
20 Gy (60 Gy)	19	(30.2)
22 Gy (70.4 Gy)	6	(9.5)
24 Gy (81.6 Gy)	1	(1.6)
Multiple fractions		
18 Gy/3 fx (28.8 Gy)	1	(1.6)
21 Gy/3 fx (35.7 Gy)	4	(6.3)
24 Gy/3 fx (43.2 Gy)	10	(15.9)
27 Gy/3 fx (51.3 Gy)	7	(11.1)
28 Gy/4 fx (47.6 Gy)	1	(1.6)
30 Gy/3 fx (60 Gy)	8	(12.7)
35 Gy/5 fx (59.5 Gy)	1	(1.6)

BED_{10} = biologic equivalence dose for α/β=10, fx = fraction, Gy = gray.

2.4. Response and outcome assessment

After SRS, follow-up MRI (or CT if ineligible for MRI) was performed every 2 to 3 months, or when clinically indicated. Tumor response was evaluated based on Response Evaluation Criteria in Solid Tumors criteria (version 1.1).[15] In the case of multiple lesions, the sum of the 2 largest lesions was used to evaluate the response. Complete response, partial response, and stable disease were classified as local control (LC) while progressive disease was classified as local failure.

Overall survival (OS), intracranial progression-free survival (IPFS), LC, and regional control (RC) were evaluated. OS was defined as the length of time from the date of diagnosis of brain metastases to death or the last follow-up. IPFS was defined as the length of time from the date of diagnosis of brain metastases to intracranial progression or death from any cause or the last follow-up. However, in the case of salvage SRS, the survival time was calculated from the time of diagnosis to recurrent brain metastases in MRI. LC was defined as freedom from development of new lesions within the field treated with SRS or progression in preexisting metastases. RC was defined as freedom from development of new distant brain metastases.

Adverse effects such as increased intracranial pressure (IICP) signs, neurocognitive defect, and radiation necrosis were also evaluated. Quantitative evaluation such as questionnaire on neurocognitive function was not made. However, a clear clinical record of patient's symptoms was obtained through a simple clinical interview with the clinician.

2.5. Statistical analysis

All statistical analyses were performed using SPSS software Version 21.0 for Windows. Actuarial OS, IPFS, LC rates, and RC rates were calculated using the Kaplan–Meier method. Log-rank test was used for univariate analysis to assess prognostic factors associated with OS and IPFS. Cox proportional hazard models were performed for multivariate analysis. A 2-sided P-value $< .05$ was considered statistically significant.

3. Results

LC rates at 6 months and 1-year following SRS were 98% and 92%, respectively. A representative case of good response after CK-based SRS for brain lesion is shown in Figure 1. RC rates at 6 months and 1-year following SRS were 88% and 78%, respectively. SRS site failure occurred in 5 patients while distant brain failure occurred in 12 patients during the follow-up period after SRS.

At the time of analysis, 41 (85.4%) patients died, including 26 (54.2%) patients due to cancer progression, 4 (8.3%) due to intracranial progression, 2 (4.2%) due to noncancerous cause, and 9 (18.8%) due to unknown reason. The median OS of all patients was 8 months. One-year and 2-year OS rates were 40.8% and 20.9%, respectively (Fig. 2A). In univariate analysis for OS, primary disease status (controlled vs uncontrolled: 31 vs 6.7 months; $P = .007$), ECOG performance status (0–1 vs 2–3: 12.3 vs 4.2 months; $P = .006$), extracranial metastases (absent vs present: 17.3 vs 6.7 months; $P = .04$), and primary histology (NSCLC vs SCLC: 9.9 vs 5.3 months; $P = .04$) were significant

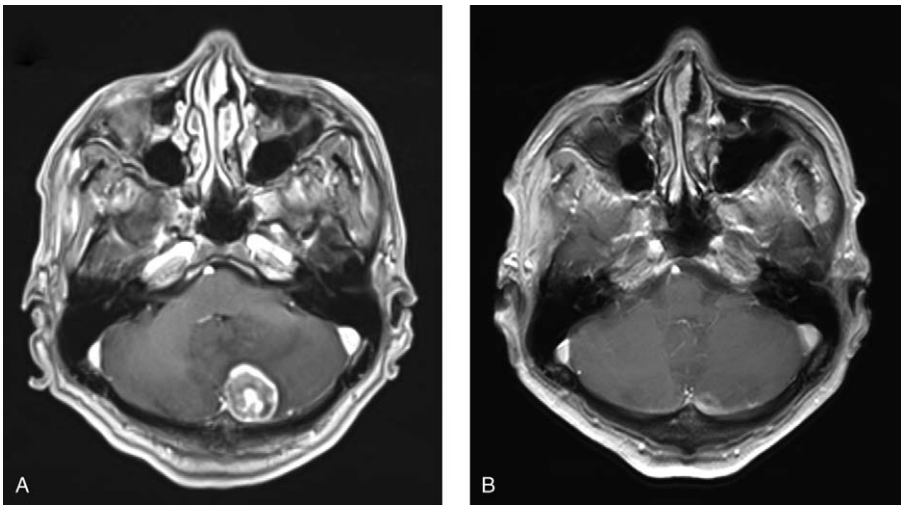

Figure 1. An example of the MRI response after CyberKnife (Accuray Inc, Sunnyvale, CA) based SRS. (A) Pre-SRS axial T1-weighted MRI with gadolinium illustrates a 2.5 cm sized enhancing mass on the left side of the cerebellum. (B) Post-SRS axial T1-weighted MRI with gadolinium at 5 months shows a partial response in which the initial mass almost disappeared. MRI = magnetic resonance imaging, SRS = stereotactic radiosurgery.

prognostic factors (Table 3). Multivariate analysis showed that uncontrolled primary disease ($P = .01$) and ECOG performance status of 2–3 ($P = .001$) were independent prognostic factors for inferior OS (Table 4).

The median IPFS of all patients was 5.3 months. One-year and 2-year IPFS rates were 23.9% and 15.2%, respectively (Fig. 2B). Similar to the analysis for OS, primary disease status and ECOG performance status were significant prognostic factors for IPFS (Table 4).

We also analyzed OS according to primary disease status and the presence of extracranial metastases in each RPA class II and III group. In RPA class II group, median OS time of patients with controlled primary disease was significantly higher than that of patients with uncontrolled primary disease (41.1 vs 12.3 months; $P = .03$; Fig. 3A). Patients without extracranial metastases had significantly higher median OS than those with extracranial metastases (29.1 vs 8.5 months; $P = .03$; Fig. 3B). In the RPA class III group, only OS according to primary disease status showed statistically significant difference (controlled vs uncontrolled: 26.9 vs 4.1 months; $P = .01$; Fig. 4A). OS according to the presence of extracranial metastases also showed a large difference of 5.1 months (absent vs present: 9.3 vs 4.2 months; $P = .07$; Fig. 4B), although the difference was marginally significant.

No symptoms or signs caused by radiation-induced necrosis were observed during follow-up period after SRS. In addition, there was no case showing significant neurocognitive dysfunction. Other complications included seizure in 2 patients and IICP signs in 3 patients due to cerebral edema.

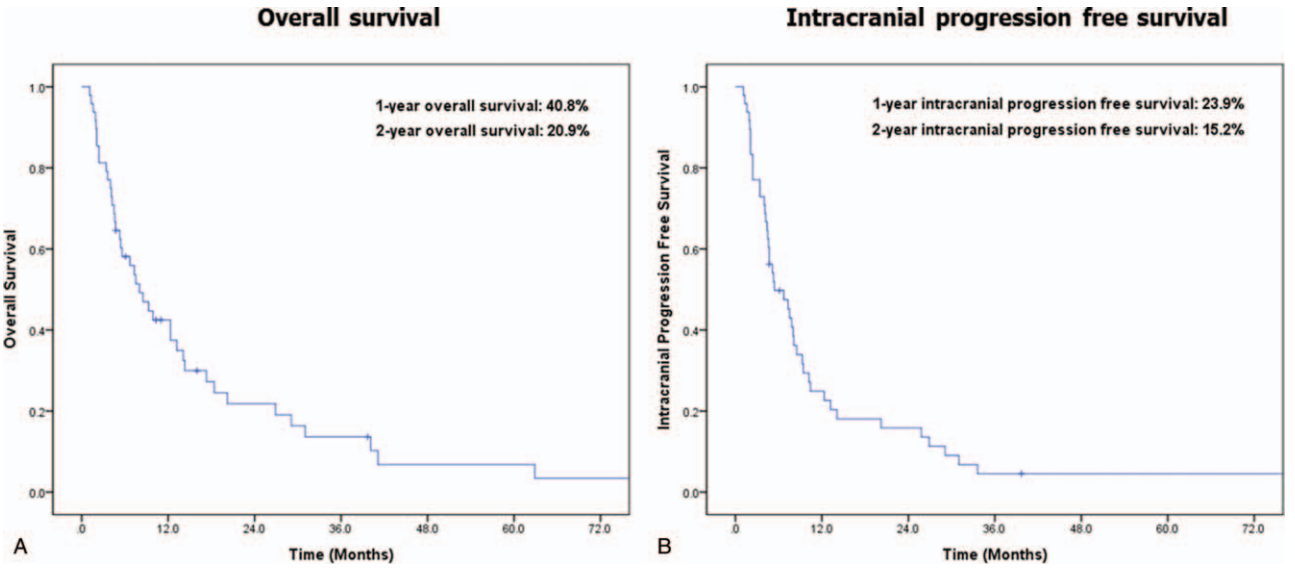

Figure 2. Overall survival (A) and intracranial progression-free survival (B) of recursive partitioning analysis class II/III lung cancer patients with brain metastases.

Table 3

Results of univariate analysis of overall survival and intracranial progression-free survival.

Variables	No.	Median OS, mo	*P*-value	Median IPFS, mo	*P*-value
Primary disease status			**.007**		**.001**
Controlled	10	31		26.9	
Uncontrolled	38	6.7		4.7	
ECOG performance status			**.006**		**.04**
0–1	28	12.3		7.8	
2–3	20	4.2		4.1	
Extracranial metastases			**.04**		**.005**
Absent	17	17.3		10.2	
Present	31	6.7		4.7	
Histological type			**.04**		.07
NSCLC	37	9.9		7.5	
SCLC	11	5.3		2.4	
No. of brain lesions			.67		.39
1	35	6.7		5.1	
≥2	13	12.3		8.0	
Neurologic status			.27		.90
Asymptomatic	9	12.3		6.7	
Symptomatic	39	8.0		5.4	
Age			.46		.81
<65	18	12.3		7.3	
≥65	30	5.4		4.7	
Prior WBRT			.54		.78
No	28	7.5		6.7	
Yes	20	8.5		5.1	

ECOG = Eastern Cooperative Oncology group, IPFS = intracranial progression-free survival, No. = number, NSCLC = non-small cell lung cancer, OS = overall survival, SCLC = small cell lung cancer, WBRT = whole-brain radiation therapy.

4. Discussion

Recently, with the advent of novel targeted or immunotherapeutic agents, rapid development of systemic therapy has improved survival and clinical outcomes of patients with metastatic lung cancer.[16–21] Previously, SRS for brain metastases is known to be an effective alternative treatment modality for WBRT in patients with RPA class I predicted to have good prognosis.[5,22] There are not so many clinical studies on patients with RPA class II/III who are predicted to have poor prognosis. Particularly RPA class III patients were excluded from most randomized studies because of their extremely poor prognosis.[23,24] However, in the modern treatment era, when chemotherapeutic agents with acceptable toxicity and advanced supportive management are introduced, lung cancer patients with brain metastases not necessarily have lower survival rates due to old age or poor performance.[25,26] Our results also showed that, in the modern treatment era, survival benefit could be achieved through aggressive local treatment for brain lesions if primary disease is adequately controlled even if patients with old age or poor performance.

Since the publication of RPA classification system by Gaspar et al, it has been questionable whether this could be generally applied to determine the treatment strategies of patients with brain metastases.[5] A few studies have been conducted to verify this system.[14,27,28] Nieder et al have confirmed that patients with RPA class I have no disagreement with aggressive local treatment such as SRS.[14] However, considering time to non-central nervous system (CNS) death, primary disease controlled subgroups of RPA class II patients suggest that aggressive LC of brain metastases may provide survival benefit.[14] Yamamoto et al have divided RPA class II into 3 subclasses by scoring 4 prognostic factors (Karnofsky performance status, tumor numbers, primary disease status, and nonbrain metastases) and reported that prognostic factors that can determine RPA class II are diverse and very heterogeneous, showing significant

Table 4

Results of multivariate analysis of overall survival and intracranial progression-free survival.

Variables	OS			IPFS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Primary disease status (controlled vs uncontrolled)	4.49	1.41–14.34	**.01**	4.04	1.28–12.75	**.02**
ECOG performance status (0–1 vs 2–3)	3.87	1.79–8.36	**.001**	2.62	1.28–5.35	**.008**
Histological type (NSCLC vs SCLC)	1.88	0.85–4.16	.12	1.92	0.84–4.35	.12
Extracranial metastases (absent vs present)	1.46	0.61–3.52	.40	1.79	0.75–4.30	.19

ECOG = Eastern Cooperative Oncology group, IPFS = intracranial progression-free survival, NSCLC = non-small cell lung cancer, OS = overall survival, SCLC = small cell lung cancer.

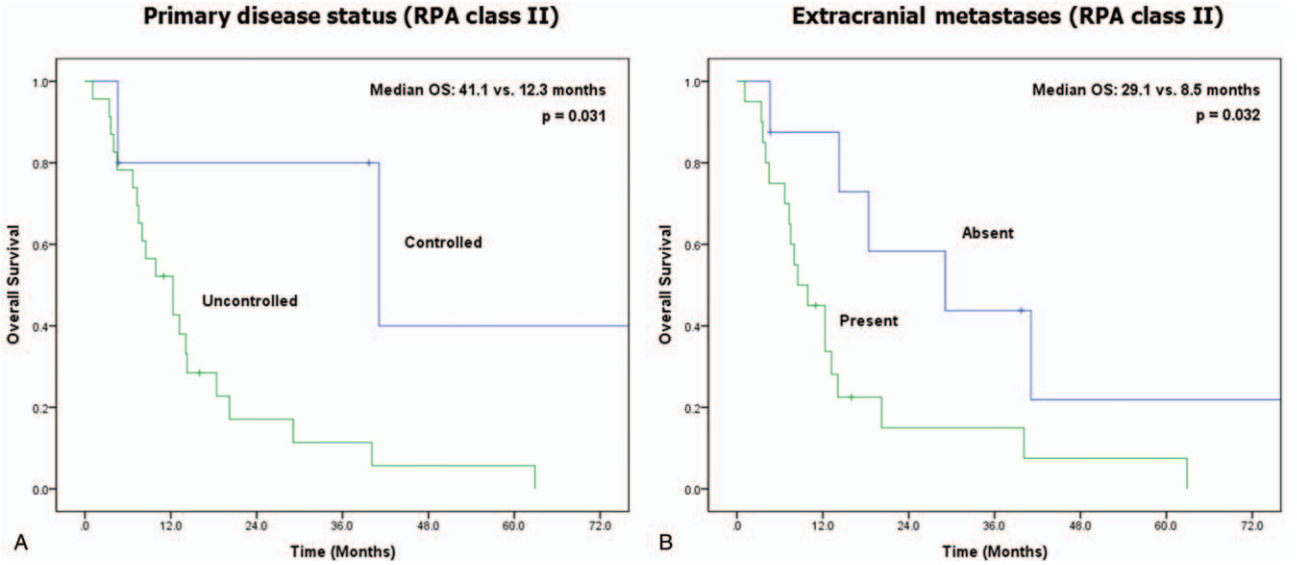

Figure 3. Overall survival difference according to primary disease status (A) and extracranial metastases (B) for recursive partitioning analysis class II patients.

differences among subclasses for OS ($P < .001$ for all subclasses).[28] In the above study, they included tumor numbers that could be associated with target volume rather than age, one of the prognostic factors that determine original RPA class, suggesting the importance of LC in the era of advanced systemic therapies.[28]

One retrospective study has shown that RPA class III patients with brain metastases have a reasonable median OS of 7.2 months when they are treated with SRS alone.[26] That study also argues that poor performance patients may be ideal candidates for SRS because low incidence of distant CNS failure during life expectancy and single faction treatment can be helpful for patients with debility and their caregivers.[26] We also believe that the convenience of short fractionation is a clear benefit for poor performance patients. In addition, SRS is more effective than WBRT in that it could be used in combination with chemotherapy without delaying systemic therapy.

According to our study results, significant prognostic factors for both OS and IPFS in multivariate analysis were primary disease status and ECOG performance status. Primary disease status has been previously identified as the strongest prognostic factor associated with survival and intracranial progression in several studies.[12,29,30] This plays a very important role in clinical decision-making, in predicting long term outcome after treatment of patients with brain metastases, and when using treatment strategies such as upfront SRS. The ECOG scale is the simplest and most commonly used performance status scale in clinical practice and was also used in our study. Because the patient group

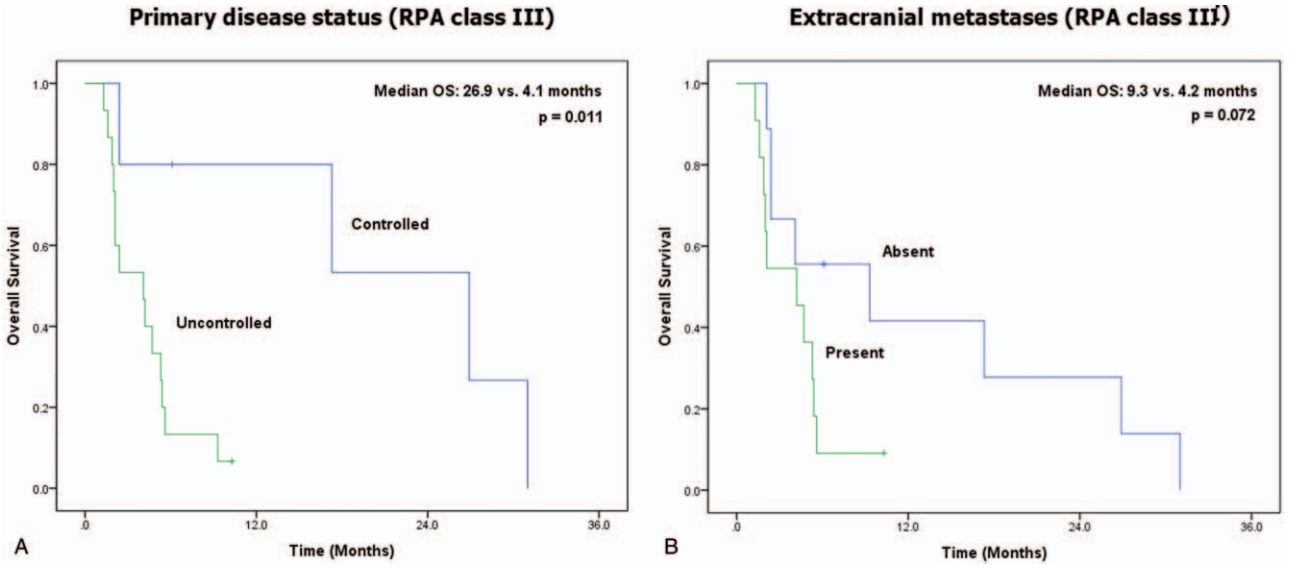

Figure 4. Overall survival difference according to primary disease status (A) and extracranial metastases (B) for recursive partitioning analysis class III patients.

divided into ECOG (0–1 vs 2) is the same group as the RPA class (2 vs 3), this shows that the RPA class also serves as a statistically significant prognostic factor for survival. The presence of extracranial metastases is known to be a significant poor prognostic factor for survival in several clinical studies, including factors that should be considered in diagnosis-specific graded prognostic assessment by stratifying based on primary cancer histology as well as RPA classification for brain metastases.[5,13,22] The presence of extracranial metastases in our study was a significant prognostic factor in univariate analysis of OS and IPFS. However, it did not show any statistically significant difference in multivariate analysis.

In each group of RPA class II and III, we further analyzed the OS for these 2 factors (primary disease status, extracranial metastases) showing significantly survival difference in univariate analysis except for age among the 3 factors determining RPA class II. As a result, controlled primary disease was associated with significantly superior OS in both RPA class II and III. The absence of extracranial metastases was also associated with significantly superior OS in RPA class II. Particularly, RPA class III patients with poor performance had a median survival time longer than 2 years if the primary disease was controlled. These results suggest that, among patients with RPA class II/III, some of them will have good prognosis depending on whether their primary tumor and extracranial metastatic lesions are controlled.

When we identified adverse effects, there were no patients with significant neurocognitive dysfunction or radionecrosis. Only 10% of patients suffered from neurologic toxicities after SRS. Side effects might have been underestimated due to evaluations without a quantitative neurocognitive test. Individual setting of dose schedules at clinician's discretion might have also affected the severity of side effects.

We acknowledge that this retrospective study has several limitations including selection bias and confounding factors. In particular, patients who previously had WBRT were included. Heterogeneous lung cancer group was formed by including both SCLC and NSCLC patients. In addition, the relatively small sample size limits the statistical power. Thus, further studies with a large number of patients are needed to validate our findings and to help determine which patients will need active local treatment or just supportive care.

5. Conclusions

In conclusion, our results showed that SRS could be a useful treatment modality for RPA class II/III patients with 1 to 3 brain metastases from lung cancer in the modern treatment era. We suggest that patients with older age or poor performance should not be unconditionally excluded from aggressive treatment for brain metastases and SRS might be considered as an initial treatment for RPA class II/III patients with well-controlled primary disease.

Author contributions

Conceptualization: In Bong Ha, Ki Mun Kang.
Data curation: In Bong Ha, Bae Kwon Jeong.
Formal analysis: In Bong Ha, Bae Kwon Jeong, Ki Mun Kang.
Funding acquisition: Ki Mun Kang.
Investigation: In Bong Ha, Hojin Jeong, Hoon Sik Choi.
Methodology: Hojin Jeong, Yun Hee Lee.
Project administration: Jin Ho Song, Yun Hee Lee, Hoon Sik Choi.
Resources: Hoon Sik Choi.
Software: In Bong Ha, Yun Hee Lee.
Supervision: Ki Mun Kang.
Validation: Jin Ho Song, Hojin Jeong, Hoon Sik Choi, Ki Mun Kang.
Visualization: In Bong Ha.
Writing – original draft: In Bong Ha, Ki Mun Kang.
Writing – review & editing: In Bong Ha, Ki Mun Kang.
Ki Mun Kang orcid: 0000-0002-6123-9635.

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