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Original Article

Prognostic Factors and Scoring Systems for Non-Small Cell Lung Cancer Patients Harboring Brain Metastases Treated with Gamma Knife Radiosurgery

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Background: The survival of non-small cell lung cancer (NSCLC) patients with brain metastases is reported to be 3～6 months even with aggressive treatment. Some patients have very short survival after aggressive treatment and reliable prognostic scoring systems for patients with cancer have a strong correlation with outcome, often supporting decision making and treatment recommendations.

Methods: A total of one hundred twenty two NSCLC patients with brain metastases who received gamma knife radiosurgery (GKRS) were analyzed. Survival analysis was calculated in all patients for thirteen available prognostic factors and four prognostic scoring systems: score index for radiosurgery (SIR), recursive partitioning analysis (RPA), graded prognostic assessment (GPA), and basic score for brain metastases (BSBM).

Results: Age, Karnofsky performance status, largest brain lesion volume, systemic chemotherapy, primary tumor control, and medication of epidermal growth factor receptor tyrosine kinase inhibitor were statistically independent prognostic factors for survival. A multivariate model of SIR and RPA identified significant differences between each group of scores. We found that three-tiered indices such as SIR and RPA are more useful than four-tiered scoring systems (GPA and BSBM).

Conclusion: There is little value of RPA class III (most unfavorable group) for the same results of 6-month and 1-year survival rate. Thus, SIR is the most useful index to sort out patients with poorer prognosis. Further prospective trials should be performed to develop a new molecular- and gene-based prognostic index model.

Key Words: Carcinoma, Non-Small-Cell Lung; Neoplasm Metastasis; Brain; Radiosurgery; Prognosis

Introduction

Lung cancer is the leading cause of cancer mortality. About 30～50% of patients with advanced lung cancer have brain metastases during the course of their illness[1,2]. In autopsy of patients with non-small cell lung cancer (NSCLC), brain metastases were identified in approximately 30～55% of cases[3]. The survival of NSCLC patients with brain metastases is reported to be 3～6 months following medical therapies, radiotherapy or chemotherapy, compared with 6～10 months in advanced NSCLC patients without brain metastases[4]. The fact that a certain percentage of these patients have very short survival times after aggressive treatment suggests that accurate survival prediction models might help to avoid overtreatment[5]. Furthermore, reliable prognostic scoring systems for patients with cancer strongly correlates with outcome, often supporting decision-making and treatment recommendations[6,7].

Recent advances in the multi-modality treatment protocols for lung cancer have led to improvement in thoracic control of the primary disease and have made

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the treatment of brain metastases a more clinically relevant issue[2,4]. Recently, gamma knife radiosurgery (GKRS) has yielded results that appear superior to those obtained with other treatment options for single or multiple brain metastases from lung cancer. It provides relatively effective tumor control and prolongs survival with a low morbidity rate[8].

Several scoring systems can be applied to patient with brain metastases for assessment of prognosis. The best known are the score index for radiosurgery (SIR), recursive partitioning analysis (RPA) classes, graded prognostic assessment (GPA) score, and basic score for brain metastases (BSBM); these have been used for understanding the natural history of cancer, predicting results of therapeutic interventions, comparing treatment results, identifying subsets of patients with poor outcomes, and planning follow-up strategies[6,7,9-11]. For these various scoring systems, it is necessary to establish the clinical significance regarding pathology and treatment modalities. The purpose of this study was to analyze the predictive power of 13 previously-identified important prognostic factors[6-11] and four scoring systems after GKRS in patients with brain metastases from NSCLC.

Materials and Methods

1. Patients

Between March 2003 and June 2010, we treated 203 patients with brain metastases from lung cancer with Leksell Gamma Knife B (Elekta Instruments AB, Stockholm, Sweden) radiosurgery. Retrospective analysis of the NSCLC patients who underwent GKRS was performed after approval of the institutional review board at the Pusan National University School of Medicine. Survival time was measured from the date of GKRS until death or last clinical evaluation updated to June 2011. The minimum follow-up period was 12 months from GKRS. Exclusion criteria included: 1) number of brain metastases >10; 2) largest brain lesion volume >30 cm^3; 3) Karnofsky performance status (KPS) score <50; 4) very poor overall prognosis due to progressive systemic disease; 5) unknown status of extracranial metastases due to incomplete evaluation; 6) pathologically unconfirmed case; 7) double primary cancer; and 8) patients who underwent only GKRS in our center during follow-up at another hospital for lung cancer.

2. GKRS protocol

As previously described, GKRS was delivered with a Leksell Gamma Knife B using collimators of 4, 8, 14, or 18 mm, alone or in combination. The Leksell stereotactic frame was applied to the head, and then images for dose planning were obtained from magnetic resonance imaging (MRI). The scanned images were exported to treatment planning system, Leksell Gamma Plan version 5.34 (Elekta Instruments AB) running on a Hewlett-Packard workstation. All treatments were guided with a stereotactic MRI scanning. The mean prescribed dose was 20 Gy, calculated at 50% of the maximum dose in the matrix.

3. Study design

The first part of this study was a retrospective survival analysis for 13 prognostic factors and four scoring systems. The second part of the study was a multivariate Cox proportional-hazard analysis for prognostic factors and scoring systems.

Survival analysis was calculated in all patients for the following 13 prognostic factors: 1) gender; 2) age (for statistical purposes, we classified into two age groups, ≤ 65 vs. >65); 3) KPS ($50\sim70$ vs. $80\sim100$); 4) number of brain metastases (1 vs. ≥ 2); 5) extracranial disease status (controlled vs. uncontrolled primary tumor); 6) largest brain lesion volume (<2 vs. ≥ 2 cm^3); 7) presence of extracranial metastases; 8) number of extracranial metastases (1 vs. ≥ 2); 9) specific sites of extracranial mestastases (liver, lung, bone, adrenal gland, kidney, alimentary tract, spleen, pancreas, pleura, pericardium, peritoneum, distant lymph node, meninx, pulmonary lymphangitic carcinomatosis, and soft tissue); 10) histopathology; 11) systemic chemotherapy (received chemotherapy vs. supportive care); 12) whole brain

Table 1. Score index for radiosurgery in brain metastases (SIR), graded prognostic assessment (GPA) and basic score for brain metastases (BSBM)

	SIR score*			GPA score†			BSBM score‡	
	0	1	2	0	0.5	1	0	1
Age, yr	≥60	51～59	≤50	≥60	50～59	<50	-	-
KPS	≤50	60～70	80～100	<70	70～80	90～100	50～70	80～100
Number of lesions	≥3	2	1	>3	2～3	1	-	-
Extracranial metastases	-	-	-	Present	-	None	Present	None
Control of primary tumor§	PD	PR-SD	CR-NED	-	-	-	No	Yes
Largest lesion Volume, cm^3	>13	5～13	<5	-	-	-	-	-

*The sum of scores ranged from 0～10 and score index for radiosurgery was divided into three groups according to their marks (0 to 3, 4 to 6, and 7 to 10). †The sum of scores was divided into four classes: I (3.5～4 points, most favorable group), II (3 points), III (1.5～2.5 points), and IV (0～1 points, most unfavorable group). ‡The sum of scores was divided into four classes: I (3 points, most favorable group), II (2 points), III (1 point), and IV (0 points, most unfavorable group). §Control of primary tumor was estimated using RECIST (response evaluation criteria in solid tumors), except for metastatic brain lesions.
KPS: Karnofsky performance status; PD: progressive disease; PR: partial response; SD: stable disease; CR: complete response; NED: no evidence of disease.

radiation therapy (WBRT); and 13) medication of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI).

Four scoring systems were developed with various compositions of the prognostic factors (Table 1). SIR is a pure number that results from the association of five major prognostic factors: 1) age; 2) KPS; 3) extracranial disease status; 4) number of brain lesions; and 5) largest brain lesion volume[9]. In accordance with RPA grouping, survival curves were classified into three classes: I (KPS ≥70, controlled primary tumor, age <65 years, and only intracranial metastases); II (all patient not in class I or III); and III (KPS <70)[7]. Components of GPA are age, KPS, extracranial metastases, and number of brain metastases[10]. BSBM is the sum of scores for three prognostic factors: 1) KPS; 2) control of primary tumor; and 3) extracranial metastases[11].

4. Statistical analyses

Survival curves for each prognostic factor and scoring system were obtained by the Kaplan-Meier method using SPSS software version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Demographic and clinical data were described by medians, means, frequencies, range, and percentages. The log-rank test was used for univariate analysis and multivariate regression was conducted using the Cox proportional hazard model. A p-value <0.05 was considered statistically significant.

Results

1. Study population

Among the 203 enrolled NSCLC patients, 81 were excluded. At the time of analysis, there are 21 patients (17.2%) alive with a median follow-up of 605 days (range, 371～2,164 days). Table 2 shows the demographics and baseline characteristics of the 122 patients. The median overall survival (OS) of the entire cohort was 278.5 days (range, 31～2,164 days).

Fifteen patients who were surgically managed for primary lung cancer (12.3%) and 23 patients (18.9%) received WBRT during some phase of their treatment. Five patients (4.1%) underwent surgical resection of a brain metastases before GKRS and eight patients (6.6%) received GKRS as a boost after WBRT. In the case of repeated GKRS for later development of new brain metastases (13 patients), survival was calculated from the date of the first GKRS.

Using clinical and pathologic information, the initial stage of all patients were I, II, IIIa, IIIb, or IV in 3, 3,

Table 2. Patient demographics and baseline clinical characteristics

Variable	Evaluable patients (n=122)
Median age, yr (range)	64.5 (28～83)
Female sex, n (%)	49 (40.2)
Median KPS (range)	80 (50～100)
Median time from lung cancer diagnosis to GKRS, day (range)	16.5 (0～2,596)
Median survival after GKRS, day (range)	278.5 (31～2,164)
Median number of brain metastases (range)*	2.0 (1～10)
Median volume of largest target lesion, cm^3 (range)	2.10 (0.05～29.5)
Histopathology, n (%)	
Adenocarcinoma	91 (74.6)
Squamous cell carcinoma	20 (16.4)
Neuroendocrine carcinoma	3 (2.5)
Large cell neuroendocrine carcinoma	2 (1.6)
Unclassified non-small cell lung cancer	6 (4.9)
Systemic disease status, n (%)	
Controlled primary tumor	54 (44.3)
Uncontrolled primary tumor	68 (55.7)
Median total number of GKRS per patient (range)	1.0 (1～3)
Presence of ECM at performing GKRS, n (%)	90 (73.8)
Median number of ECM at performing GKRS (range)	1.0 (0～7)
Frequent sites of ECM, n (%)	
Lung to lung	50 (41.0)
Bone	43 (35.2)
Pleura or malignant pleural effusion	34 (27.9)
Distant lymph node	19 (15.6)
Lymphangitic carcinomatosis	15 (12.3)
Patients received chemotherapy, n (%)†	91 (74.6)
Received EGFR TKI	59/91
Received platinum doublet	62/91
Received single agent	60/91
Patients received WBRT, n (%)	23 (18.9)

*80 (65.6%) of 122 patients had multiple brain metastases. †Six (6.6%) of 91 patients received neoadjuvant or adjuvant chemotherapy. KPS: Karnofsky Performance Status; GKRS: gamma knife radiosurgery; ECM: extracranial metastases; EGFR TKI: epidermal growth factor receptor tyrosine kinase inhibitor; WBRT: whole brain radiation therapy.

11, 3, and 102 patients, respectively (classified by the seventh edition of the TNM classification for NSCLC)[12].

2. Prognostic factors

The results of log-rank test and multivariate analysis for prognostic factors that may influence survival are summarized in Table 3. Age <65 years, KPS score ≥ 80, largest brain lesion volume <2 cm^3, absence of extracranial metastases, absence of lung-to-lung metastases, systemic chemotherapy, achievement of primary tumor control, and EGFR TKI medication were favorable factors for longer survival in univariate analysis. Gender, histopathology, number of brain metastases (one vs. two or more), number of extracranial metastases (one vs. two or more), and use of radiosurgery with WBRT were not significant predictors of survival. In multivariate analysis, age, KPS, largest brain lesion volume, systemic chemotherapy, primary tumor control, and medication involving EGFR TKI were independent prognostic factors for survival.

3. Prognostic scoring systems

Kaplan-Meier survival curves of SIR, RPA, GPA, and BSBM are illustrated in Figure 1. All four prognostic

Table 3. Univariate and multivariate analysis for prognostic factors

Variable	Univariate p-value by log-rank test	Multivariate analysis		
		HR	95% CI	p-value
Age (≤65 vs. >65), yr	0.003	1.557	1.030～2.354	0.036
Gender (female vs. male)	0.110	Not included in multivariable model		
KPS (50～70 vs. 80～100)	<0.001	2.261	1.451～3.523	<0.001
Histopathology (ADC vs. SCC)	0.134	Not included in multivariable model		
Largest brain lesion volume (<2 vs. ≥2 cm^3)	0.016	1.678	1.107～2.544	0.015
Number of brain lesions (1 vs. ≥2)	0.330	Not included in multivariable model		
Extracranial metastases (yes vs. no)	0.051	1.216	0.742～1.993	0.438
Lung to lung metastases (yes vs. no)	0.030	1.402	0.916～2.146	0.120
Number of extracranial metastases (1 vs. ≥2)	0.351	Not included in multivariable model		
Systemic chemotherapy (yes vs. no)	<0.001	3.089	1.814～5.259	<0.001
Primary tumor control (yes vs. no)	<0.001	3.643	2.199～6.037	<0.001
Whole brain radiotherapy (yes vs. no)	0.099	Not included in multivariable model		
Medication of EGFR TKI (yes vs. no)	<0.001	1.894	1.212～2.958	0.005

HR: hazard ratio; CI: confidence interval; ADC: adenocarcinoma; SCC: squamous cell carcinomaSee; KPS: Karnofsky Performance Status; EGFR TKI: epidermal growth factor receptor tyrosine kinase inhibitor.

scoring systems demonstrated statistical significance by log-rank test. There were 53 patients with high SIR marks (≥6) and no patient with a score of 0 or 10. Distributing these patients in groups based on scores of 0～3, 4～6, and 7～10 revealed 25, 67, and 30 patients, respectively. Median survival times for the SIR were: score 0～3 (most unfavorable group), 183 days; score 4～6, 247 days; and score 7～10 (most favorable group), 806 days. In univariate analysis, significant differences were found between three groups of SIR marks (SIR 7～10 vs. SIR 4～6, p<0.001; SIR 7～10 vs. SIR 0～3, p<0.001; SIR 4～6 vs. SIR 0～3, p=0.002). The adjusted hazard ratios (HRs) for SIR were 3.283 (score 7～10 vs. 4～6; 95% confidence interval (CI), 1.874～5.750; p<0.001), 7.962 (score 7～10 vs. 0～3; 95% CI, 3.959～16.011; p<0.001), and 2.185 (score 4～6 vs. 0～3; 95% CI, 1.301～3.670; p=0.003). Multivariate Cox proportional hazard model of SIR system identified significant difference between the three groups of SIR scores.

According to RPA, most patients (79.5%) were in class II and 20.5% were in class I or III. RPA Kaplan-Meier survival curves showed a significant difference between the three classes (class I vs. class II, p=0.018; class I vs. class III, p<0.001; class II vs. class III, p=0.002) in univariate analysis, with the expected median survival for class I patients of 846 days, 279 days for class II, and 69 days for class III. These results suggest that the estimated survival for patients with RPA class I was longer by about 25.9 months than patients with RPA class III. In the multivariable model, RPA system showed statistical difference in RPA class I vs. class II (HR, 3.260; 95% CI, 1.390～7.648; p=0.007), class I vs. class III (HR, 9.555; 95% CI, 3.444～26.504; p <0.001), and class II vs. class III (HR, 2.953; 95% CI, 1.583～5.507; p=0.001). The characteristic finding of RPA system in the current study was that the patients with RPA class I (most favorable group) had the longest median survival time (846.0 days; range, 187～2,130 days) and those with RPA class III (most unfavorable group) had the shortest median survival time (69 days; range, 31～1,056 days).

The survival curve of the GPA system showed an improved clinical trend toward in patients with lower class of GPA (p<0.001). However, there was no statistical difference in class I vs. class II (p=0.491) and 1-year survival rate of patients with GPA class II (75%) was higher than that of class I (67%). Furthermore, there was no statistical difference in class II vs. class III (p=0.116) by log-rank test. In multivariate analysis, GPA

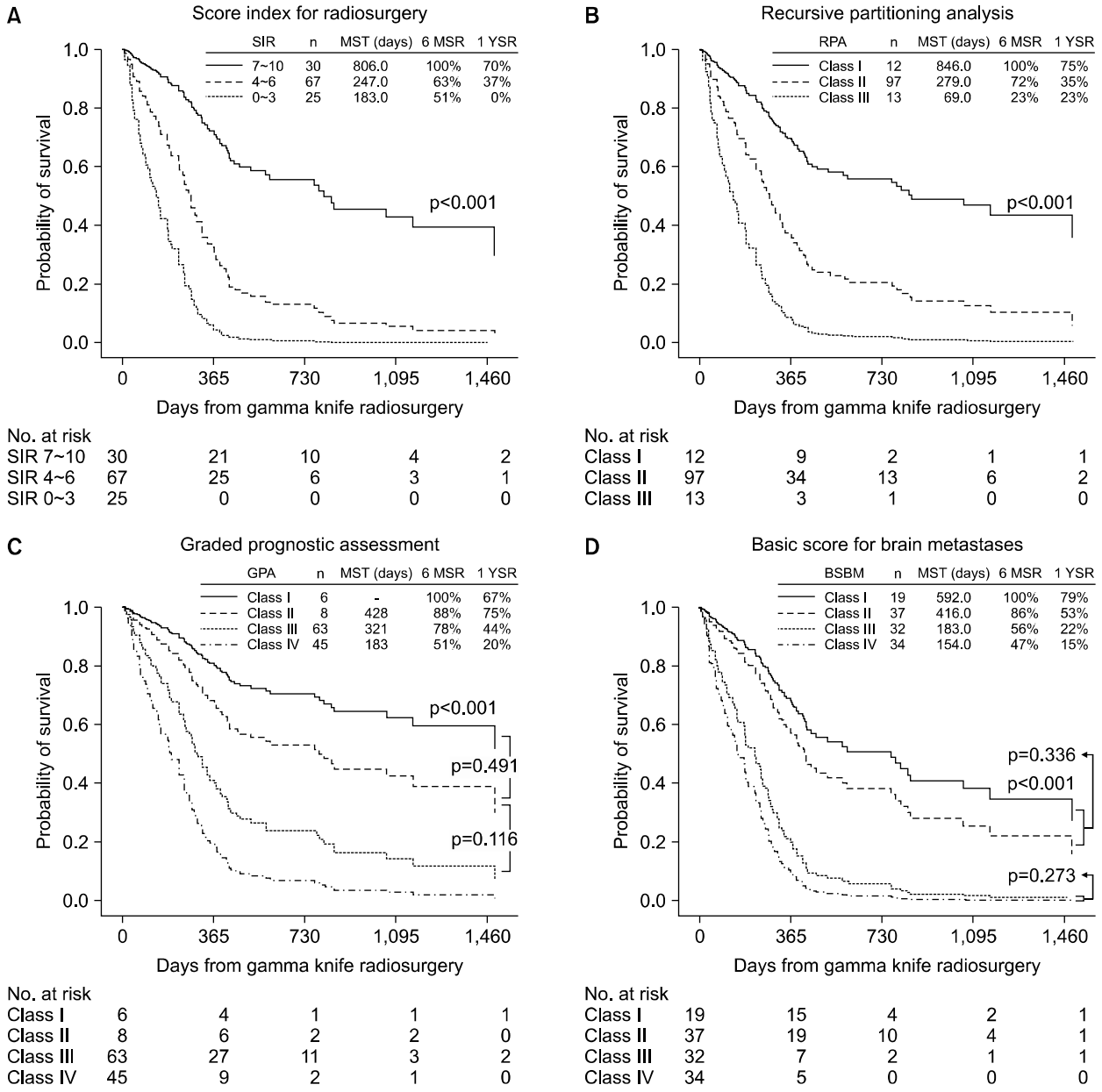

Figure 1. Kaplan-Meier survival curves for prognostic scoring systems. (A) SIR provided the most accurate prediction on survival after GKRS. (B) There was little value of RPA class III on survival model for the same results from 6 month survival rate and 1 year survival rate. (C) GPA scoring system revealed statistical differencse only in class I vs. class IV and class III vs. class IV and there were no significant differences between other classes. (D) The survival curves of BSBM were grouped with class I~II and class III~IV. There was a statistical difference in BSBM class I~II vs. class III~IV. SIR: score index for radiosurgery; RPA: recursive partitioning analysis; GPA: graded prognostic assessment; BSBM: basic score for brain metastases; MST: median survival time; 6 MSR: 6-month survival rate; 1 YSR: 1-year survival rate.

scoring system showed statistical difference only in class I vs. class IV (HR, 5.988; 95% CI, 1.379~26.000; p=0.017) and class III vs. class IV (HR, 1.617; 95% CI, 1.048~2.497; p=0.030) and there were no significant differences between other classes.

The survival analysis for BSBM demonstrated sig-

nificant difference by log-rank test, with p-values of <0.001. Actuarial median survival was 592 days for patients with class I, 416 days for class II, 183 days for class III, and 154 days for class IV. The adjusted hazard ratios of BSBM scoring system were 4.900 (95% CI, 2.384～10.074; $p<0.001$) for class I vs. class III, 7.573 (95% CI, 3.602～15.922; $p<0.001$) for class I vs. class IV, 2.431 (95% CI, 1.394～4.236; $p=0.002$) for class II vs. class III, and 3.739 (95% CI, 2.114～6.612; $p<0.001$) for class II vs. class IV. BSBM class I vs. II and class III vs. IV were not included in the multivariable model due to insignificant results of log-rank test. The Kaplan-Meier survival curves of BSBM classes were distinctively grouped with class I～II and class III～IV. There was a statistical difference in BSBM class I～II vs. class III～IV (HR, 3.801; 95% CI, 2.440～5.923; $p<0.001$).

Discussion

Recent studies of NSCLC populations with brain metastases demonstrated several independent prognostic factors. Rades et al. concluded that performance status, age, and extracranial metastases have a potential effect on survival[13]. Mariya et al. revealed that the factors significantly affecting overall survival were primary tumor control, performance status, and number of brain metastases[14]. Nieder et al.[7] found that the only factors influencing survival were primary tumor control and performance status. Pan et al.[15] revealed that patient with an age <65 years, KPS score ≥ 70, no preexisting neurological deficits, multiple GKRS sessions, and a prior craniotomy survived longer. In all published studies, performance status commonly manifested as an independent prognostic factor. KPS is one of the most significant independent prognostic factors within the domain of oncology and all prognostic scoring system had KPS as an important component[7,9-11,16]. In the current study, multivariate analysis showed prognostic impact of KPS, as expected. Although KPS has recognized general accuracy for survival assessment, the measurement of KPS is somewhat subjective and based upon momentary data subject to change during the clinical evolution period. For example, a patient with brain metastases presenting with acute and severe neurological deficits resulting in a KPS of 50, after administration of high-dose steroids frequently improves his/her clinical situation to a functional status or a KPS of 80. This may result in patients, at the same illness stage, receiving a KPS of 50 or 80, depending upon whether or not they received steroids[9,17]. Therefore, making treatment decisions solely on the basis of KPS seems to be inadequate and factors such as age and primary tumor control should be considered. Many clinical trials for heterogenous group of cancers identified a prognostic role of age and extracranial disease status and the majority of prognostic scoring systems were comprised of these factors: 1) age for SIR, RPA, and GPA; and 2) extracranial disease status for SIR, RPA, and BSBM[7,9-11]. From one-half of the published literature concerning NSCLC populations with brain metastases, age and extracranial disease status (primary tumor control) were identified as independent prognostic factors and multivariate Cox regression of current study showed the same results[6,13-15]. In the subset of NSCLC patients who underwent GKRS, the present study revealed that age and extracranial disease status were also important prognostic factors.

In most studies about SIR, only a limited proportion of patients had NSCLC[9]. There has been no trial for homogeneous group of NSCLC patients. In the present study, there was a relatively even patient distribution in each SIR group and multivariate analysis revealed statistical difference between each SIR group. One-year survival rate of patients with SIR 0～3 (most unfavorable group) was 0%; this finding implies that the SIR scoring system is the most useful index to sorting out the poor prognostic group. The prognostic impact of the RPA system was previously confirmed in two NSCLC patient populations[18,19]. However, Nieder et al. identified that survival in RPA class III (most unfavorable class) is quite variable, with 40～50% of patients dying within 2 months, but 10～15% surviving for more than 6 months[6]. In the present study, although the mean survival time of patients with RPA class III (69 days) was

shortest, the 1-year survival rate (23%) was highest among the most unfavorable groups of four prognostic scoring systems, and the same survival rates were observed at 6 months and 1 year. Certain portion of patients with RPA class III might display long-term survival. As described above, prognosis estimation on the basis of KPS alone was inadequate (RPA class III was made up of only one factor, namely KPS <70). Therefore, the SIR system is better than RPA in sorting out the poor prognostic group. In the recent literature, there has been a trend toward four-tiered systems such as GPA and BSBM. Nieder et al. showed that their analysis favors the use of the GPA score in unselected patients with brain metastases from NSCLC[7]. However, our study demonstrates a lack of statistical significances in both GPA and BSBM. Thus, in the subset of patients who received GKRS, three-tiered indexes such as SIR and RPA are more useful than four-tiered scoring systems.

Recently, the gene mutation status [such as epidermal growth factor receptor (EGFR), K-ras, and EML-ALK4 fusion] has been elucidated and is widely-used in clinical practice. Especially, identifying EGFR mutations and medication of EGFR TKI improves clinical outcomes. Gow et al. revealed that the patients who receive an EGFR TKI at any time after diagnosis of brain metastases survive longer than those who do not[20]. Other prior studies about the impact of EGFR TKI in NSCLC patients harboring brain metastases demonstrated the important role of EGFR TKI on metastatic brain lesions[21-23]. There was also a significant prognostic impact of EGFR TKI medication in our study. Furthermore, Eichler et al. found that the EGFR mutation status is associated with improved survival in NSCLC patients with brain metastases, indicating that EGFR-mutant cancer may have increased radiosensitivity compared with wild-type disease[24].

The present study focused on identifying poorer prognostic patients in NSCLC patients with brain metastases who received GKRS. Several prognostic factors such as age, KPS, primary tumor control, and medication involving EGFR TKI influenced survival. However, it was insufficient to predict prognosis using only one factor. Analyzing the four available prognostic scoring systems, SIR was the most useful index to sort out patients with poorer prognosis in our cohort. Further prospective trials should aim to establish a new prognostic index model with a molecular and gene basis.

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