

# Hypofractionated stereotactic radiotherapy with or without whole-brain radiotherapy for patients with newly diagnosed brain metastases from non–small cell lung cancer

## Clinical article

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**Object.** This study was undertaken to analyze outcomes in patients with newly diagnosed brain metastases from non–small cell lung cancer (NSCLC) who were treated with hypofractionated stereotactic radiotherapy (HSRT) with or without whole-brain radiotherapy (WBRT).

**Methods.** One hundred seventy-one patients comprised the study population. Fifty-four patients received HSRT alone, and 117 patients received both HSRT and WBRT. The median survival time (MST) was determined using the Kaplan-Meier method. Recursive Partitioning Analysis (RPA) and Graded Prognostic Assessment (GPA) were also used to evaluate the results. Univariate and multivariate analyses were performed to determine significant prognostic factors for overall survival. Tumor control, radiation toxicity, and cause of death in the HSRT and HSRT+WBRT groups were evaluated.

**Results.** The MST for all patients was 13 months. According to the Kaplan-Meier method, the probability of survival at 1, 2, and 3 years was 51.2%, 21.7%, and 10.1%. The MSTs for RPA Classes I, II, and III were 19, 12, and 5 months, respectively; and the MSTs for GPA Scores 4, 3, 2, and 1 were 24, 14, 12, and 6 months, respectively. The MSTs in the HSRT+WBRT and HSRT groups were 13 and 9 months ( $p = 0.044$ ), respectively, for all patients, 13 and 8 months ( $p = 0.031$ ), respectively, for patients with multiple brain metastases, and 16 and 15 months ( $p = 0.261$ ), respectively, for patients with a single brain metastasis. The multivariate analysis showed that HSRT+WBRT was a significant factor only for patients with multiple brain metastases ( $p = 0.010$ ). The Kaplan-Meier–estimated tumor control rates at 3, 6, 9, and 12 months were 92.2%, 82.7%, 79.5%, and 68.3% in the HSRT+WBRT group and 73.5%, 58.4%, 51.0%, and 43.3% in the HSRT group, respectively, in all 165 patients ( $p = 0.001$ ). The estimated tumor control rates at 3, 6, 9, and 12 months were 94.3%, 81.9%, 79.6%, and 76.7%, respectively, in the HSRT+WBRT group and 77.8%, 61.4%, 52.6%, and 48.2%, respectively, in the HSRT group in the 80 patients harboring a single metastasis ( $p = 0.009$ ). The estimated tumor control rates at 3, 6, 9, and 12 months were 90.5%, 83.5%, 79.5%, and 60.9%, respectively, in the HSRT+WBRT group and 68.2%, 54.5%, 48.5%, and 36.4%, respectively, in the HSRT group in the 85 patients with multiple metastases ( $p = 0.010$ ). The toxicity incidences of Grade 3 or worse were 6.0% (7 of 117 patients) in the HSRT+WBRT group and 1.9% (1 of 54 patients) in the HSRT group ( $p = 0.438$ ). The differences in neurological death rates between the HSRT+WBRT group and the HSRT group were not statistically significant (34.4% vs 44.7%,  $p = 0.125$ , in all patients; 30.0% vs 52.0%,  $p = 0.114$ , in patients with a single metastasis; and 38.0% vs 36.4%,  $p = 0.397$ , in patients with multiple metastases).

**Conclusions.** The overall survival results in the present study were similar to those in other studies. Hypofractionated stereotactic radiotherapy provides an alternative method to traditional stereotactic radiosurgery. We suggest that WBRT should be combined with HSRT in patients with single or multiple newly diagnosed brain metastases from NSCLC.

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**KEY WORDS** • brain metastasis • non–small cell lung cancer • prognostic index • hypofractionated stereotactic radiotherapy • whole-brain radiotherapy

**B**RAIN metastases are common brain malignant neoplasms that remain a major problem in clinical oncology. Non–small cell lung cancer is a common source of brain metastases; the cumulative incidence

of brain metastases after 5 years has been found to be 4.3%–10.8% among patients with Stage I–IV NSCLC.<sup>13</sup> With advances in treatment, SRS with or without WBRT offers a minimally invasive alternative to surgical removal of the tumors. Two types of devices are commonly used for brain SRS: the Gamma Knife (Elekta AB) and the specially modified or dedicated LINAC.<sup>14</sup> The SRS dose is delivered in a single fraction and patients need to be stabilized in a head frame with local anesthesia and mild sedation. To compare different treatment methods and make patients feel more comfortable, we used an-

*Abbreviations used in this paper:* GKS = Gamma Knife surgery; GPA = Graded Prognostic Assessment; GTV = gross tumor volume; HSRT = hypofractionated stereotactic radiotherapy; KPS = Karnofsky Performance Scale; LINAC = linear accelerator; MST = median survival time; NSCLC = non–small cell lung cancer; PTV = planning target volume; RPA = Recursive Partitioning Analysis; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.

other treatment method: HSRT. The purpose of the present study was to analyze outcomes in patients with newly diagnosed brain metastases from NSCLC who were treated by HSRT at our institution. Because the RPA<sup>6,7</sup> and GPA<sup>17,18</sup> (Table 1) are widely used prognostic indices and have been confirmed to be useful in patients with NSCLC,<sup>9,12,17,18</sup> we used these two indices to compare our results with those of other reports.

## Methods

### Patient Population

We reviewed the files of patients who were treated with HSRT for brain metastases from pathologically confirmed NSCLC between April 2001 and September 2011. Those patients whose brain metastases were newly diagnosed and had not previously received radiotherapy, surgery, or other treatments were included in this study. One hundred and seventy-one patients were included. Ninety-eight patients (57.3%) were male and 73 (42.7%) were female. Their ages ranged from 25 years to 80 years (median 59 years), and their KPS scores ranged from 60% to 100% (median 80%). The time between diagnosis of primary cancer and diagnosis of brain metastasis ranged from 0 to 67 months (median 8 months). Synchronous brain metastasis was defined as related brain lesions that are identified within 1 month after diagnosis of the primary disease.<sup>13</sup> There were 33 patients with synchronous brain metastasis and 138 with asynchronous brain metastasis. The status of the primary tumor and extracranial metastases were evaluated by performing chest and abdominal CT scanning, ultrasonography to detect a liver echo pattern, bone scans, and other available results found in the patients' medical records. The primary lung cancer had been controlled by surgery, radiotherapy, chemotherapy, or a combination of these treatments in 120 patients. Fifty-one patients had uncontrolled lung cancer (in 18 patients the lesions were newly diagnosed, and in 33 patients the primary tumor remained uncontrolled, although treatments had been performed). One hundred twenty-six patients had no signs of extracranial metastases and 45 patients had at least one organ metastases outside the brain (in 15 patients the extracranial metastases had been controlled by treatment; in 28 patients the extracranial metastases were still uncontrolled, although treatments

had been performed; and in 2 patients no treatment had been given to the extracranial metastases). There were 92 patients with adenocarcinoma and 79 patients without adenocarcinoma; those patients who could not be classified as having NSCLC were excluded from the study population. The number of brain metastases confirmed by enhanced CT and MRI in each patient ranged from 1 to 8 (median 2 metastases). Among all 171 patients, 101 patients received at least 1 cycle of chemotherapy (1 cycle in 12 patients, 2–4 cycles in 31 patients, and  $\geq 4$  cycles in 58 patients) and 9 patients received molecular targeted therapy with or without chemotherapy. All patients could be classified by the RPA and the GPA indices. The characteristics of these patients are presented in Table 2.

### Hypofractionated Stereotactic Radiotherapy and Whole-Brain Radiotherapy

The HSRT process was as follows. Patients were immobilized using a noninvasive mask. Helical CT images with a slice thickness of 3 mm were obtained, and were fused with MR images with the aid of image fusion software. The MR images were obtained 1–2 days before or after the positional CT scan. The GTV was defined as the contrast-enhancing tumor and the PTV was defined by adding a 1-mm margin to the GTV. Brainlab's stereotactic treatment planning system and SCAN 4.05 version of the 3D positioning and target system were applied for dose calculations. The prescribed dose was delivered to the 80%–90% dose line, which included more than 98% of the PTV. The most common dose was 32 Gy administered in 4 fractions (for 295 [83.3%] of 354 lesions in 171 patients) delivered every other day. This method of dose administration was mainly based on an in vitro fractionation schedule model that was equivalent to SRS. The method was provided by Brenner et al.,<sup>3</sup> who found that 33 Gy administered in 4 fractions was equivalent to a single 20-Gy fraction with respect to both an early effect and the lower toxicity of a late effect. Aoyama et al.<sup>1</sup> reported their results in using HSRT alone for patients with solitary and oligo brain metastases using a LINAC-based stereotactic system. The median dose to the periphery of the PTV was 32 Gy in 4 fractions, and HSRT achieved tumor control and survival equivalent to those achieved by SRS in the

TABLE 1: Details of the RPA and GPA for NSCLCs\*

Prognostic Index	Parameter Details	Class/Score
RPA	patient age: <65 yrs, KPS score: $\geq 70\%$ , controlled primary tumor, no extracranial metastases	I
	all others not in Class I or III	II
	KPS score: <70%	III
GPA	patient age in yrs: $\geq 60/50$ –59/<50	0/0.5/1
	KPS score: <70%/70%–80%/90%–100%	0/0.5/1
	no. of brain metastases: >3/2–3/1	0/0.5/1
	extracranial metastases: present/none	0/1

\* Information about the RPA is from Gaspar et al.<sup>6,7</sup> and information on the GPA is from Sperduto et al.<sup>17,18</sup>

## HSRT for newly diagnosed brain metastases from NSCLC

**TABLE 2: Demographic and clinical characteristics in 171 patients with single or multiple metastases from NSCLC\***

Characteristic	No. of Patients
M/F ratio	98:73
age (yrs)	
≤60	88
>60	83
KPS score	
<70%	32
≥70%	139
Dx of primary cancer & brain metastases	
synchronous	33
asynchronous	138
control of primary tumor	
yes	120
no	51
extracranial metastases	
absent	126
present	45
type of tumor	
ADCA	92
squamous cell carcinoma	49
large-cell carcinoma	10
other	20
no. of brain metastases	
single	83
multiple	88
RPA class	
I	47
II	92
III	32
GPA score	
1 (0–1 points)	16
2 (1.5–2.5 points)	104
3 (3 points)	28
4 (3.5–4 points)	23

\* Values represent number of patients unless otherwise indicated. Abbreviations: ADCA = adenocarcinoma; Dx = diagnosis.

literature.<sup>1</sup> In accordance with these reports, the HSRT dose of 32 Gy administered in 4 fractions was commonly used at our institution, although, of course, it was adjusted according to the size, number, and location of lesions as well as to whether WBRT was given. Irradiation of the lesions was performed by directing 6-MV photons from a LINAC (Siemens PRIMUS-M) using multiple noncoplanar converging arcs. Fifty-four patients (31.6%) received HSRT alone. In these patients the median prescribed dose was 32 Gy in 4 fractions (range 16 Gy in 4 fractions–54 Gy in 6 fractions) for 105 lesions. One hundred seventeen patients (68.4%) received HSRT+WBRT. In these patients the median prescribed dose was 32 Gy in 4 fractions (range 18 Gy in 4 fractions–42 Gy in 6 fractions) for 249 lesions.

In the 83 patients harboring a single brain metastasis, 29 received HSRT alone and 54 received HSRT+WBRT. In the 88 patients who harbored multiple brain metastases, 25 patients (76 lesions) received HSRT alone and 63 patients (195 lesions) received HSRT+WBRT. For patients with multiple brain metastases their brain lesions were all treated by HSRT. The time interval between the diagnosis of brain metastases and beginning treatment was within 1 week. For those patients who were also treated with WBRT (planning dose 40 Gy in 20 fractions, 5 fractions/week) the timing of WBRT was within 1 week before or after HSRT. There was no well-known or scientifically recommended dose for combined HSRT and WBRT, so we used the traditional WBRT dose of 40 Gy administered in 20 fractions. The details were as follows: 40 Gy in 20 fractions for 109 patients; 30 Gy in 10 fractions for 2 patients; and 32–38 Gy in 16–19 fractions for 6 patients.

### *Prognostic Factors for Overall Survival*

Factors in the RPA and GPA indices were analyzed as were other potential factors. Additional potential factors included the sex of the patient, histological characteristics of the tumors, treatment method, total tumor volume, and time between diagnosis of the primary cancer and diagnosis of brain metastases. Because most studies continue to demonstrate that the systemic disease status significantly affects survival, we also included this factor. Systemic disease was considered controlled only if both the primary tumor and the extracranial metastases had been controlled before the brain metastases were diagnosed. One hundred three patients had controlled systemic disease and 68 patients had uncontrolled systemic disease (38 patients had only uncontrolled primary tumor, 17 patients had only uncontrolled extracranial metastases, and 13 patients had both uncontrolled primary lung cancer and extracranial metastases). Since 52 patients received WBRT before HSRT and 65 patients received WBRT after HSRT, to confirm the consistency of the effects of prognostic factors between these two subgroups, their overall survival was compared using the Kaplan-Meier method. There was no statistically significance between these 2 patient groups (data not shown), and thus the groups were combined for subsequent analyses.

### *Tumor Control, Cause of Death, and Radiation Toxicity*

Tumor control, cause of death, and radiation toxicity in the HSRT+WBRT and HSRT groups were analyzed.

Because local tumor control may be more important than overall survival in an evaluation of the impact of radiotherapy on brain metastases, it was necessary to analyze local tumor control in this study. We did not distinguish local progression of the disease from new brain metastases during follow-up; therefore, both are included together in our evaluation of tumor control.

The cause of death was considered neurologically related if the patient died of a direct complication from locally progressive lesions or died of new brain metastases. The cause of death was considered systemically related if the patient died of a direct complication of the extracranial disease.

Radiation toxicities (≥ Grade 3) according to the Ra-



diation Therapy Oncology Group central nervous system toxicity criteria<sup>15</sup> were evaluated.

#### *Follow-Up and Statistical Analysis*

Follow-up examinations were performed 1–3 months after treatment, every 3 months during the 1st year, and every 6 months thereafter. Enhanced MR or CT imaging was used to evaluate tumor control and radiation toxicity.

Overall survival for each factor and each level of the RPA and GPA was determined using the Kaplan-Meier method in a univariate analysis. Survival time was calculated from the date brain metastasis was diagnosed to the date the patient died. Patients who were still alive or lost to follow-up were classified as censored as of the last known date they were alive. The log-rank test was used to compare levels of each prognostic factor. A multivariate stepwise Cox regression analysis was performed to evaluate the prognostic factors selected by the univariate analysis ( $p \leq 0.10$ ). The evaluation and comparison of tumor control rates was also based on the Kaplan-Meier method and the log-rank test. The relationship of variables of different groups was also tested using the Wilcoxon rank sum test for continuous variables and the Chi-square test (or Fisher exact test when small sizes were encountered in tables) for categorical variables. All analyses were performed using SPSS version 13.0 (SPSS Inc.) A  $p$  value  $\leq 0.05$  was considered statistically significant. To determine the role of WBRT in patients with different numbers of brain metastases, two subgroups (patients with a single metastasis and patients with multiple metastases) were also analyzed.

### **Results**

As of the last follow-up date in February 2012, 150 patients (87.7%) had died. The median follow-up time was 12 months (range 1–75 months) for all 171 patients and 22 months (range 8–75 months) for the 21 patients (12.3%) who were censored. The MST for all 171 patients was 13 months (95% CI 11.128–14.872 months). The survival probability at 1 year was 51.2% (95% CI 43.8%–58.6%); at 2 years it was 21.7% (95% CI, 15.2%–28.2%), and at 3 years it was 10.1% (95% CI 5.0%–15.2%). The MSTs for RPA Classes I, II, and III were 19, 12, and 5 months, respectively. The MSTs for GPA Scores 4, 3, 2, and 1 were 24, 14, 12, and 6 months, respectively.

The univariate analysis showed some different prognostic factors in the three patient groups (Table 3). The treatment method (HSRT alone vs HSRT+WBRT) was a significant factor for all patients and for patients with multiple brain metastases, but not for patients with a single brain metastasis. The MSTs in the HSRT+WBRT and HSRT alone groups were 13 and 9 months ( $p = 0.044$ ), respectively, for all patients (Fig. 1A); 13 and 8 months ( $p = 0.031$ ), respectively, for patients with multiple brain metastases (Fig. 1C); and 16 and 15 months ( $p = 0.261$ ), respectively, for patients with a single brain metastasis (Fig. 1B).

Because the status of systemic disease was not independent of the status of the primary tumor and extracranial metastases, we developed two multivariate models to analyze these factors. One model was used to evaluate the impact of the primary tumor and extracranial metastases (the systemic disease was excluded) if they met the

entering criterion (Table 4). The other model was used to evaluate the impact of systemic disease (the primary tumor and extracranial metastases were excluded) if it met the entering criterion (Table 5).

The multivariate analysis showed that there were also some different prognostic factors in these groups (Table 4 and Table 5). The treatment method (HSRT alone vs HSRT+WBRT) was a significant factor only for patients with multiple brain metastases (HR 2.036, 95% CI 1.189–3.488,  $p = 0.010$ ), not for all patients or patients with a single brain metastasis.

Six patients died before follow-up could be performed and thus are not included in the evaluation of tumor control. The Kaplan-Meier–estimated tumor control rates at 3, 6, 9, and 12 months were 92.2%, 82.7%, 79.5%, and 68.3%, respectively, in the HSRT+WBRT group and 73.5%, 58.4%, 51.0%, and 43.3%, respectively, in the HSRT group in all 165 patients ( $p = 0.001$ ) (Fig. 2A). The estimated tumor control rates at 3, 6, 9, and 12 months were 94.3%, 81.9%, 79.6%, and 76.7%, respectively, in the HSRT+WBRT group and 77.8%, 61.4%, 52.6%, and 48.2%, respectively, in the HSRT group in the 80 patients harboring a single metastasis ( $p = 0.009$ ) (Fig. 2B). The estimated tumor control rates at 3, 6, 9, and 12 months were 90.5%, 83.5%, 79.5%, and 60.9%, respectively, in the HSRT+WBRT group and 68.2%, 54.5%, 48.5%, and 36.4%, respectively, in the HSRT group in the 85 patients with multiple metastases ( $p = 0.010$ ) (Fig. 2C).

A confirmed cause of death was available in 137 of the 150 patients who died; the cause of death was unknown in 13 patients and they were excluded from the analysis of causes of death. Patients died of different causes: 31 of neurological disease, 55 of systemic disease, and 4 of both neurological and system disease in the HSRT+WBRT group; and 21 of neurological disease, 21 of systemic disease, and 5 of both neurological and system disease in the HSRT group ( $p = 0.125$ ) in all patients. Among the patients who harbored a single metastasis, 12 died of neurological disease, 25 of systemic disease, and 3 of both neurological and systemic disease in the HSRT+WBRT group; and 13 died of neurological disease, 9 of systemic disease, and 3 of both neurological and systemic disease in the HSRT group ( $p = 0.114$ ). Among the patients who harbored multiple metastases, 19 died of neurological disease, 30 of systemic disease, and 1 of both neurological and systemic disease in the HSRT+WBRT group; and 8 died of neurological disease, 12 of systemic disease, and 2 of both neurological and systemic disease in the HSRT group ( $p = 0.397$ ).

A total of eight cases of  $\geq$  Grade 3 toxicity occurred in 171 patients. Five patients developed reversible cerebral edema that required hospitalization (Grade 3), 1 patient developed radionecrosis that required surgery (Grade 4), and 2 patients developed fatal cerebral edema (Grade 5). The latter 2 patients refused surgery and died 1–3 months after HSRT or HSRT+WBRT, although corticosteroid medications had been administered. Among the patients suffering from radiation toxicity, 1 patient (Grade 5 toxicity) was among the 54 patients in the HSRT group (1.9%), and 7 patients (Grade 3 toxicity in 5 patients; Grade 4 in 1 patient; and Grade 5 in 1 patient) were among the 117 patients in the HSRT+WBRT group (6.0%). The toxicity

**TABLE 3: Univariate survival analysis for all patients and subgroups by number of brain metastases**

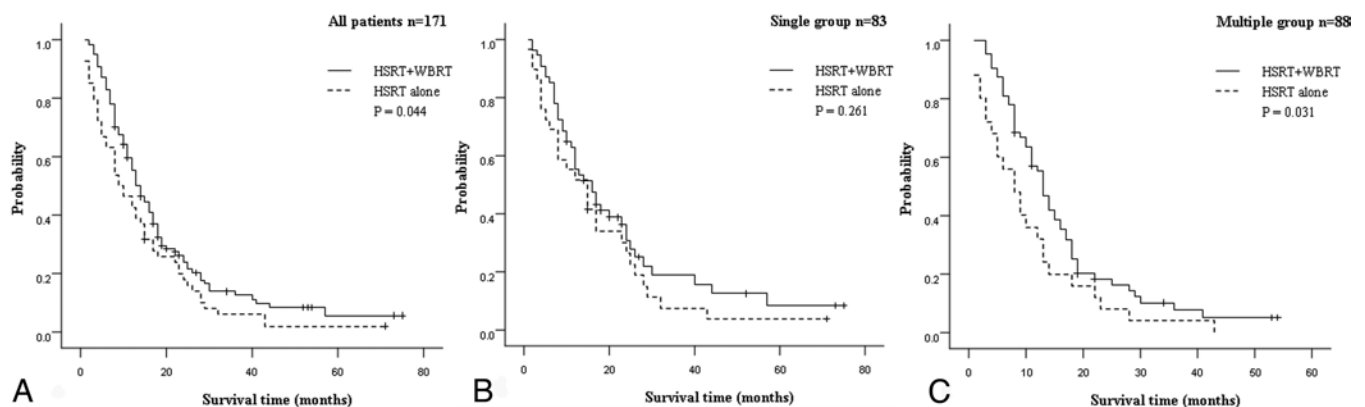
Variable	p Value		
	All Patients	Patients w/ a Single Metastasis	Patients w/ Multiple Metastases
sex			
male vs female	0.784	0.418	0.284
Dx of primary cancer & brain metastases			
synchronous vs asynchronous	0.037	0.046	0.531
age (yrs)			
≤60 vs >60	0.022	0.011	0.310
KPS score			
<70 vs ≥70	<0.001	<0.001	<0.001
control of primary tumor			
yes vs no	0.017	0.013	0.506
extracranial metastases			
absent vs present	0.001	0.009	0.044
systemic disease			
controlled vs uncontrolled	0.001	<0.001	0.276
total tumor vol			
<15 cm <sup>3</sup> vs ≥15 cm <sup>3</sup>	0.055	0.042	0.559
type of tumor			
ADCA vs non-ADCA	<0.001	0.065	<0.001
treatment			
HSRT alone vs HSRT+WBRT	0.044	0.261	0.031
no. of brain metastases			
1 vs ≥2	0.038		

incidences of Grade 3 or worse in the two groups were not statistically significant ( $p = 0.438$ ).

To further evaluate these results, we compared the radiation dose and total tumor volume in the various patient groups.

The total volumes of tumor in the group of patients with a single metastasis and the group of patients with multiple metastases were similar. The mean and median total tumor volumes were 14.28 cm<sup>3</sup> and 7.32 cm<sup>3</sup>, respectively (range 0.16–86.00 cm<sup>3</sup>), in the single metastasis group and 13.80 cm<sup>3</sup> and 8.73 cm<sup>3</sup>, respectively (range 0.56–83.64 cm<sup>3</sup>), in the multiple metastases group ( $p = 0.521$ ). We also

analyzed the total volumes of tumor in the two treatment groups. The total volumes of tumor in the HSRT+WBRT and HSRT groups were similar in all three patient groups. The mean and median total tumor volumes were 12.48 cm<sup>3</sup> and 7.83 cm<sup>3</sup>, respectively (range 0.16–75.97 cm<sup>3</sup>), in the HSRT+WBRT group and 17.40 cm<sup>3</sup> and 9.37 cm<sup>3</sup>, respectively (range 0.84–86.00 cm<sup>3</sup>), in the HSRT group ( $p = 0.079$ ) in all patients. The mean and median total tumor volumes were 12.01 cm<sup>3</sup> and 6.96 cm<sup>3</sup>, respectively (range 0.16–67.10 cm<sup>3</sup>), in the HSRT+WBRT group and 18.50 cm<sup>3</sup> and 8.74 cm<sup>3</sup>, respectively (range 0.84–86.00 cm<sup>3</sup>), in the HSRT group ( $p = 0.166$ ) in patients harboring a single me-



**FIG. 1.** Graphs showing overall survival curves for all patients (A), patients with a single metastasis (B), and patients with multiple metastases (C) stratified by treatment (HSRT+WBRT vs HSRT alone).

**TABLE 4: Multivariate survival analysis for all patients and patient subgroups based on the status of the primary tumor and extracranial metastases**

Variable	HR	95% CI	p Value
all patients			
age in yrs (>60 vs ≤60)	1.688	1.199–2.377	0.003
KPS score (<70 vs ≥70)	4.389	2.848–6.766	<0.001
extracranial metastases (present vs absent)	1.977	1.371–2.851	<0.001
tumor type (non-ADCA vs ADCA)	1.606	1.138–2.267	0.007
no. of brain metastases (≥2 vs 1)	1.664	1.186–2.333	0.003
single-metastasis patient group			
KPS score (<70 vs ≥70)	7.348	3.804–14.191	<0.001
extracranial metastases (present vs absent)	3.179	1.762–5.736	<0.001
total tumor vol (≥15 cm <sup>3</sup> vs <15 cm <sup>3</sup> )	2.181	1.273–3.736	0.005
multiple-metastases patient group			
KPS score (<70 vs ≥70)	2.432	1.328–4.455	0.004
extracranial metastases (present vs absent)	2.307	1.338–3.980	0.003
tumor type (non-ADCA vs ADCA)	2.809	1.718–4.593	<0.001
treatment (HSRT alone vs HSRT+WBRT)	2.036	1.189–3.488	0.010

tastasis. The mean and median total tumor volumes were 12.88 cm<sup>3</sup> and 8.26 cm<sup>3</sup>, respectively (range 0.56–75.97 cm<sup>3</sup>), in the HSRT+WBRT group and 16.12 cm<sup>3</sup> and 9.77 cm<sup>3</sup>, respectively (range 2.67–83.64 cm<sup>3</sup>), in the HSRT group ( $p = 0.298$ ) in patients with multiple metastases.

The HSRT doses administered to patients with single and multiple metastases were also similar. The mean and median doses were 31.86 Gy and 32 Gy, respectively (range 18–54 Gy), in patients harboring a single metastasis and 31.44 Gy and 32 Gy, respectively (range 16–42 Gy), in patients with multiple metastases ( $p = 0.592$ ). We also analyzed the HSRT doses in the different treatment groups. The HSRT dose in the HSRT+WBRT group was lower than that in the HSRT group in all three patient groups. The mean and median doses were 31.27 Gy and 32 Gy, respectively (range 18–42 Gy), in the HSRT+WBRT group and 32.18 Gy and 32 Gy, respectively (range 16–54 Gy), in the HSRT group ( $p = 0.001$ ) in all patients. The mean and median doses were 31.20 Gy and 32 Gy, respectively (range 18–42 Gy), in the HSRT+WBRT group

and 33.07 Gy and 32 Gy, respectively (range 25–54 Gy), in the HSRT group ( $p = 0.036$ ) in patients harboring a single metastasis. The mean and median doses were 31.28 Gy and 32 Gy, respectively (range 20–40 Gy), in the HSRT+WBRT group and 31.84 Gy and 32 Gy, respectively (range 16–42 Gy), in the HSRT group ( $p = 0.014$ ) in patients with multiple metastases.

## Discussion

Gerosa et al.<sup>8</sup> reported outcomes in 504 patients with brain metastases from NSCLC who were treated by GKS. The lesions were primary in 86% and recurrent in 14% of 836 cases. Whole-brain radiotherapy was performed before GKS in 32.6% of patients and after GKS in 36.1% of patients. The overall MST in these 504 patients was 14.5 months. In the report by Frazier et al.<sup>5</sup> there were 81 NSCLC cases among a total of 237 cases of brain metastases treated by GKS. Sixty-three patients received GKS alone and 18 patients received GKS with WBRT. The overall MST for the patients with NSCLC was 9 months.

**TABLE 5: Multivariate survival analysis for all patients and patient subgroups based on the status of the systemic disease**

Variable	HR	95% CI	p Value
all patients			
age in yrs (>60 vs ≤60)	1.530	1.091–2.144	0.014
KPS score (<70 vs ≥70)	3.999	2.610–6.129	<0.001
systemic disease (uncontrolled vs controlled)	1.597	1.137–2.243	0.007
tumor type (non-ADCA vs ADCA)	1.679	1.192–2.365	0.003
no. of brain metastases (≥2 vs 1)	1.584	1.132–2.217	0.007
single-metastasis patient group			
KPS score (<70 vs ≥70)	4.900	2.643–9.085	<0.001
systemic disease (uncontrolled vs controlled)	2.650	1.541–4.556	<0.001
total tumor vol (≥15 cm <sup>3</sup> vs <15 cm <sup>3</sup> )	2.229	1.297–3.832	0.004

## HSRT for newly diagnosed brain metastases from NSCLC

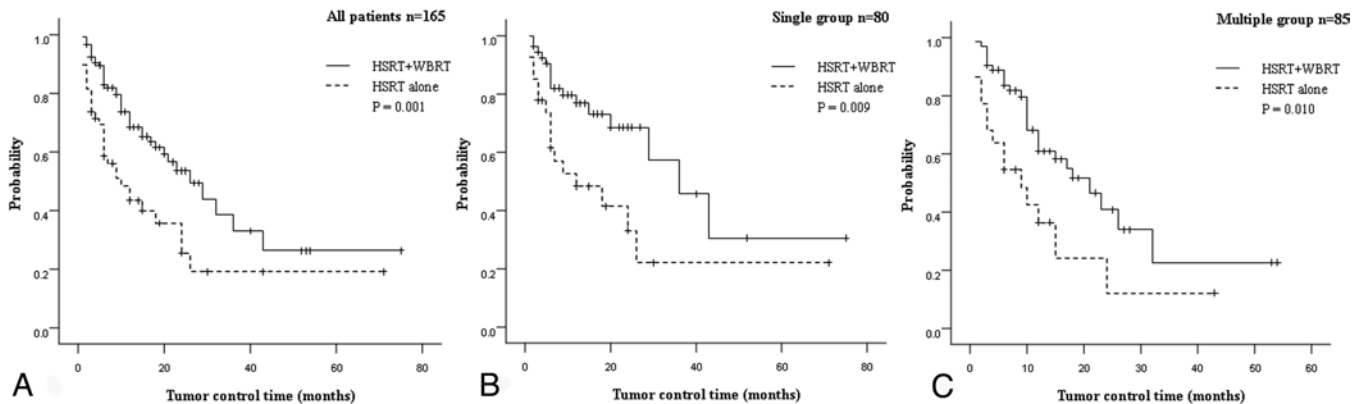


Fig. 2. Graphs showing tumor control curves for all patients (A), patients with a single metastasis (B), and patients with multiple metastases (C) stratified by treatment (HSRT+WBRT vs HSRT alone).

Mariya and colleagues<sup>10</sup> evaluated outcomes of LINAC SRS alone in 84 patients with metastatic lesions in the brain due to NSCLC. The 1- and 2-year overall survival rates were 38% and 24%, respectively, and the MST was 9 months. The MSTs for patients in RPA Classes I, II, and III were 22, 9, and 7 months, respectively. In our present study the MST for the 54 patients treated with HSRT alone was 9 months. The 1- and 2-year overall survival rates in this group were 42.6% and 17.7%, respectively; and the MSTs for patients in RPA Classes I, II, and III were 24, 12, and 4 months, respectively.

Because the reports of GPAs for patients with brain metastases from NSCLC who have been treated only with SRS are rare, we compared our results with those of patients treated with mixed methods. In the report of diagnosis-specific GPA for 4295 patients with a variety of newly diagnosed histological diseases by Sperduto et al.,<sup>18</sup> there were 1888 patients with NSCLC. The MSTs for GPA Scores 4, 3, 2, and 1 were 14.38, 11.33, 6.53, and 3.02 months, respectively. Our results (the MSTs for GPA Scores 4, 3, 2, and 1 were 24, 14, 12, and 6 months, respectively) seemed better than those in the study by Sperduto et al. One possible reason is that their report included patients treated with WBRT alone (the MST in that group was only 3.42 months). In the subgroup analyses stratified by treatment methods, their results were similar to ours. In the study by Sperduto et al., the MST of the WBRT with SRS group was 12.59 months and the MST of the SRS group was 9.92 months. In our study the MST of the HSRT+WBRT group was 13 months and the MST of the HSRT alone group was 9 months.

Debate exists about the importance of combined WBRT and SRS versus SRS alone, although many studies have been conducted. The result of a multiinstitutional review by Sneed et al.<sup>16</sup> found no survival difference between combined WBRT and SRS and SRS alone. A randomized controlled trial also showed that WBRT plus SRS did not improve survival for patients with 1 to 4 brain metastases compared with SRS alone.<sup>2</sup> Nevertheless, the results of a retrospective analysis of 236 patients showed that patients treated with WBRT and SRS had a longer survival than those treated with SRS alone in patients without evidence of extracranial disease.<sup>11</sup>

There were both similarities and differences between our results and those of other reports. In our study the

treatment method (HSRT alone vs HSRT+WBRT) was a significant factor for all patients with brain metastases from NSCLC in the univariate analysis, but it was not a significant factor in the multivariate analysis. To evaluate the role of WBRT for patients with single or multiple brain metastases, we divided 171 patients into two subgroups. The results in the single brain metastasis group showed that the combined HSRT+WBRT did not improve survival. This was consistent with the findings of Flannery et al.<sup>4</sup> In patients with multiple brain metastases, however, those in the HSRT+WBRT group had a longer MST (13 months) than those in the HSRT alone group (8 months) according to the univariate analysis; this difference in survival remained in the multivariate analysis.

Aoyama et al.<sup>2</sup> reported the results of a randomized controlled trial in which the 12-month estimated rates of brain tumor recurrence and developing new brain metastases were 46.8% and 41.5%, respectively, in the SRS+WBRT group ( $p < 0.001$ ) and 76.4% and 63.7%, respectively, in the SRS-alone group ( $p = 0.003$ ). Our results showed that the HSRT+WBRT group had a better tumor control rate than the HSRT group in three patient groups (all patients, patients harboring a single metastasis, and patients with multiple metastases). Although the tumor control rates in our study could not be directly compared with the results in that clinical trial, both studies had the same conclusion: a combined treatment could reduce the risk of recurrence compared with a single treatment alone.

The neurological death rates in the HSRT+WBRT group and the HSRT group were similar. This was because overall survival could be affected not only by brain metastases but also by systemic disease.

Although more patients in the HSRT+WBRT group (7 of 117) developed  $\geq$  Grade 3 toxicity than those in the HSRT group (1 of 54), the difference between the two treatment groups was not statistically significant ( $p = 0.438$ ).

In the present study both the total tumor volumes and the radiation doses in the single metastasis and multiple metastases patient groups were similar. The total tumor volumes in the different treatment groups were similar as well. The HSRT dose in the HSRT+WBRT group was lower than that in the HSRT group in the three patient groups (all patients, patients harboring a single metastasis, and patients with multiple metastases). The HSRT



dose reduction in the combined treatment group was consistent with that of another report,<sup>2</sup> and this was because combined treatment can be potentially deleterious.

### Conclusions

The overall survival results in this retrospective study of patients with newly diagnosed brain metastases from NSCLC who were treated with HSRT were similar to the results of previous reports. Hypofractionated stereotactic radiotherapy provides an alternative method to traditional SRS. The HSRT+WBRT group had a longer MST than the HSRT group in patients with multiple brain metastases, and the HSRT+WBRT group had a better tumor control rate than the HSRT group in all three patient groups (all patients, patients harboring a single metastasis, and patients with multiple metastases). We suggest that WBRT should be combined with HSRT in patients with both single and multiple brain metastases from NSCLC.

### Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Li, Ma. Acquisition of data: Ma, HW Zhang, Wang, Dang, S Zhang, Yao, XM Zhang. Analysis and interpretation of data: Ma, HW Zhang, Wang, Dang, S Zhang, Yao, XM Zhang. Drafting the article: Li, Ma. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Li. Statistical analysis: Ma, HW Zhang, Wang, Dang, S Zhang, Yao, XM Zhang. Administrative/technical/material support: Ma, HW Zhang, Wang, Dang, S Zhang, Yao, XM Zhang. Study supervision: Li.

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