pISSN 1598-2998, eISSN 2005-9256
https://doi.org/10.4143/crt.2024.223
Cancer Res Treat. 2025;57(1):47-56

Original Article

Upfront Stereotactic Radiosurgery or Fractionated Stereotactic Radiotherapy in Elderly Patients with Brain Metastases from Non–Small Cell Lung Cancer: A Retrospective Analysis of a 10-Year Bi-institutional Experience

Myungsoo Kim[1,2], **Jihye Cha**[3], **Hun Jung Kim**[4], **Woo Chul Kim**[4], **Jeongshim Lee**[4,5]

[1]Department of Radiation Oncology, Incheon St. Mary Hospital, College of Medicine, The Catholic University of Korea, Incheon, [2]Department of Radiation Oncology, College of Medicine, The Catholic University of Korea, Seoul, [3]Department of Radiation Oncology, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, [4]Department of Radiation Oncology, Inha University Hospital, Inha University School of Medicine, Incheon, [5]Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

Purpose Stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) are increasingly used as initial therapies for brain metastases (BM). We aimed to assess the outcomes of SRS/FSRT in patients aged ≥ 65 years who had 1-10 BM from non–small cell lung cancer (NSCLC).

Materials and Methods We retrospectively reviewed 91 elderly NSCLC patients with 222 BM who were treated with SRS/FSRT at two institutions between 2010 and 2020. The primary endpoint was overall survival (OS) after SRS/FSRT. In addition, in-field local control (IFLC) within the treated field was evaluated. Statistical analysis was performed to identify the prognostic factors affecting OS and IFLC.

Results During a median follow-up of 18 months, the median OS was 32 months. The 1- and 2-year survival rates were 69.8% and 56.1%, respectively. In multivariate analysis, the NSCLC-specific graded prognostic assessment (GPA) score (p=0.007) and administration of systemic therapy (p=0.039) were defined as prognosticators affecting OS. The median IFLC period was 31 months, and the 1- and 2-year IFLC rates were 75.9% and 57.6%, respectively. The total BM volume (p=0.042) significantly affected IFLC. No severe adverse events were reported after SRS/FSRT.

Conclusion SRS/FSRT is an effective upfront treatment option for BM arising from NSCLC in elderly patients, with a good OS without severe side effects. Higher GPA score and active systemic treatment were associated with improved OS, indicating that elderly patients are significant candidates for SRS/FSRT.

Key words Brain neoplasms, Non-small cell lung carcinoma, Radiosurgery, Treatment outcomes

Introduction

The aging population has led to an increasing number of elderly patients with cancer. In the future, it is estimated that 70% of newly diagnosed cancers annually will be among the elderly [1]. These aging cohorts have multiple comorbidities and poor performance, which are associated with the low tolerance and high toxicity of anti-cancer treatments. Consequently, since treatment-related toxicity is an important concern in such patients, the demand for less toxic management is increasing in clinical geriatric oncology [2-8].

Brain metastases (BM) developed in 20%-40% of patients with malignancy [9,10]. Its incidence continuously increases during their lifetime as their survival rate improves owing to the advancement of anti-cancer therapies, such as cytotoxic agents, targeted agents, and immunotherapies [9]. In patients with non–small cell lung cancer (NSCLC), which accounts for 85% of lung cancers, the brain is one of the most frequent organs with distant metastasis, which results in poor prognosis. About 20%-40% of these patients with NSCLC experience BM, and up to 10% already have BM at diagnosis [11]. Subsequently, BM management in this cohort poses a robustness issue.

Therapeutic approaches for BM include surgery, whole-brain radiotherapy, and stereotactic radiotherapy, including stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) [12]. Among them, SRS/FSRT is the emerging standard treatment for patients with 1-3 BM, and the favored treatment for patients with ≤ 10 BM owing to its acceptable tumor control and neurotoxicity reduction [2,5,7,12-14]. However, regarding the management of geriatric cancer patients with BM, the efficacy of SRS/FSRT was

Correspondence: Jeongshim Lee
Department of Radiation Oncology, Inha University Hospital, Inha University School of Medicine, 27 Inhang-ro, Jung-gu, Incheon 22332, Korea
Tel: 82-32-890-3078 Fax: 82-32-890-3082 E-mail: jshimlee@inha.ac.kr
Received February 29, 2024 **Accepted** July 2, 2024 **Published Online** July 3, 2024

unclear, as not only most physicians consider geriatric cancer patients with BM as unfavorable candidates for active treatment due to the inhomogeneity associated with diverse comorbidities, but also many trials involving BM treatment underrepresented older patients.

Our previous study examining small cohorts showed that CyberKnife-based SRS/FSRT is an effective option for elderly NSCLC patients with BM regarding prolonged survival and good tolerability [15]. In the current study, we aimed to reappraise the efficacy of SRS/FSRT for BM in elderly NSCLC patients through a bi-institutional experience with more patients, focusing on the survival of these vulnerable older patients and local control status of BM following SRS/FSRT.

Materials and Methods

1. Study design

This retrospective study was conducted at two institutions between 2010 and 2020. We identified 91 elderly patients with NSCLC aged ≥ 65 years with 222 BM who had a Karnofsky performance status (KPS) of ≥ 70 and received upfront SRS/FSRT without whole brain radiation therapy (WBRT) at BM diagnosis, regardless of systemic drug administration. We chose 65 years as the threshold for old age because Gaspar et al. [4] classified this age as the cutoff value using recursive partitioning analysis (RPA). We collected data on tumor and patient characteristics regarding primary lung disease status, BM, extracranial disease status, treatment details included chemotherapy and SRS/FSRT, clinical outcomes, local control in the treated SRS/FSRT field, survival, and treatment-related toxicity. Moreover, we calculated the graded prognostic assessment (GPA) scores associated with NSCLC, including age, KPS, presence of extracranial metastases, and BM number [3].

2. Treatment

All patients underwent SRS/FSRT using a CyberKnife (Accuray Inc., Sunnyvale, CA) and Novalis Tx system linear accelerator (Varian, Palo Alto, CA). During SRS/FSRT, each patient was placed in a supine position and fitted with a thermoplastic mask for immobilization. Subsequently, computed tomography with a 1-mm slice thickness was performed and fused with contrast-enhanced magnetic resonance imaging (MRI). The clinical target volume (CTV) was defined based on the area of contrast enhancement on MRI, and the planning target volume was generated by adding a 2-mm margin to the CTV. Organs at risk, including the brain, eyes, lenses, optic nerves, optic chiasm, pons, brainstem, and spinal cord, were contoured. The dose-fractionation prescription of SRS was adapted and modified based on the guidelines of Radiation Therapy Oncology Group (RTOG) 90-05 as follows: 24-28 Gy for tumors ≤ 20 mm in maximum diameter, 16-18 Gy for tumors 21-30 mm, and ≤ 15 Gy for tumors 31-40 mm. For FSRT, we prescribed 26-30 Gy delivered in 2-4 fractions. Practice variation at the physician's discretion was allowed in clinical scenarios associated with the location of the tumor or adjacent critical organs, such as the pons, brainstem, or inner ear. The administered systemic therapy was assessed, including the type of systemic agent used and systemic therapy sequence.

Table 1. Patient characteristics

Variable	No. (%) (n=91)
Age (yr)	
Median (range)	70 (65-89)
65-70	49 (53.8)
> 70	42 (46.2)
Sex	
Male	52 (57.1)
Female	39 (42.9)
KPS	
70-80	52 (57.1)
90-100	39 (42.9)
Pathology	
Adenocarcinoma	11 (12.1)
Squamous cell carcinoma	75 (82.4)
Others	5 (5.5)
No. of BM	
Median (range)	2 (1-10)
1	44 (48.4)
2-4	36 (39.6)
> 5	11 (12.1)
Total BM volume (mm^3)	
Median (range)	1,275 (24-81,842)
Mean±SD	4,389±10,970
≤ 1,300	46 (50.5)
> 1,300	45 (49.5)
Primary controlled	
No	28 (30.8)
Yes	63 (69.2)
Extracranial metastases	
No	30 (33.0)
Yes	61 (67.0)
GPA score	
Median (range)	1.5 (0.5-3.0)
0.5	15 (16.5)
1.0-2.5	68 (74.7)
3	8 (8.8)

BM, brain metastasis; GPA, graded prognostic assessment; KPS, Karnofsky performance status; SD, standard deviation.

Table 2. Details regarding treatment (91 patients, 222 BM)

Variable	No. (%)
Systemic therapy (n=91)	
No	12 (13.2)
Cytotoxic agent (n=49, 53.8%)	
Docetaxel	7 (7.7)
Alimta	10 (11.0)
Gemcitabine	1 (1.1)
Docetaxel/Platinum	3 (3.3)
Alimta/Platinum	13 (14.3)
Gemcitabine/Platinum	13 (14.3)
Others	2 (2.2)
Targeted agent (n=30, 33.0%)	
EGFR inhibitor	25 (27.5)
ALK inhibitor	5 (5.5)
Lines of systemic therapy (n=91)	
None	12 (13.2)
1st	39 (42.9)
2nd	25 (27.5)
3rd	8 (8.8)
4th	7 (7.7)
Immunotherapy (n=91)	
No	72 (79.1)
Yes (n=19, 20.9%)	
Pembrolizumab	6 (6.6)
Nivolumab	8 (8.8)
Atezolizumab	5 (5.5)
RT type according per BM (n=222)	
SRS	203 (91.4)
FSRT	19 (8.6)
SRS/FSRT prescription dose (BED, Gy) per BM (n=222)	
12 Gy in 1 fx (26.4)	1 (0.5)
13 Gy in 1 fx (29.9)	1 (0.5)
15 Gy in 1 fx (37.5)	4 (1.8)
16 Gy in 1 fx (41.6)	3 (1.4)
18 Gy in 1 fx (50.4)	45 (20.3)
20 Gy in 1 fx (60.0)	54 (24.3)
22 Gy in 1 fx (70.4)	17 (7.7)
23 Gy in 1 fx (75.9)	15 (6.8)
24 Gy in 1 fx (81.6)	49 (22.1)
25 Gy in 1 fx (87.5)	10 (4.5)
28 Gy in 1 fx (106.4)	4 (1.8)
26 Gy in 2 fx (59.8)	8 (3.6)
32 Gy in 2 fx (83.2)	1 (0.5)
21 Gy in 3 fx (35.7)	2 (0.9)
24 Gy in 3 fx (43.2)	2 (0.9)
27 Gy in 3 fx (51.3)	4 (1.8)
28 Gy in 4 fx (47.6)	1 (0.5)
30 Gy in 4 fx (52.5)	1 (0.5)

(Continued)

Table 2. Continued

ALK, anaplastic lymphoma kinase; BED, biological equivalent dose; BM, brain metastasis; EGFR, epidermal growth factor receptor; FSRT, fractionated stereotactic radiotherapy; fx, fraction; RT, radiotherapy; SRS, stereotactic radiosurgery.

3. Outcome assessment

The primary endpoint of this study was overall survival (OS) following SRS/FSRT for BM. Secondary endpoints were in-field local control (IFLC) within the CTV and treatment-related toxicities. The OS and IFLC periods were calculated from the last SRS/FSRT to the development of related events, including death, due to any cause or local progression, respectively, or the day of the last follow-up. We evaluated the local control status using the Response Assessment in Neuro-Oncology criteria based on enhanced lesions on follow-up MRI [16]. Furthermore, we used the nervous system disorders of the Common Terminology Criteria for Adverse Events ver. 5.0 to report treatment-related adverse events and focused on assessing to xicities of higher than grade 2.

4. Statistical analysis

OS and IFLC were analyzed using the Kaplan-Meier method. Univariate analysis was performed using log-rank tests to identify the prognostic factors associated with OS or IFLC. Multivariate Cox regression analyses were performed to assess risk factors for IFLC or OS. All statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Corp., Armonk, NY), and statistical significance was set at $p < 0.05$.

Results

1. Patient and treatment characteristics

The patient characteristics are summarized in Table 1. The median age was 70 years (range, 65 to 89 years), and 39 patients (42.9%) had a KPS of ≥ 90. Of the 91 patients, 47 (51.6%) had multiple lesions. The median total volume of BM per patient was 1,275 mm^3 (24-81,842 mm^3), and at the time of SRS/FSRT, 63 patients (69.2%) had a controlled primary tumor and 61 (67.0%) had metastases outside the brain. Furthermore, regarding the GPA scores associated with NSCLC, 15 (16.5%), 68 (74.7%), and eight (8.8%) patients had GPA scores of 0.5, 1.0-2.5, and 3.0, respectively.

Table 2 summarizes the details of the systemic drugs and SRS/FSRT administration. At the time of SRS/FSRT referral, 49 patients (53.8%) had received cytotoxic chemotherapy

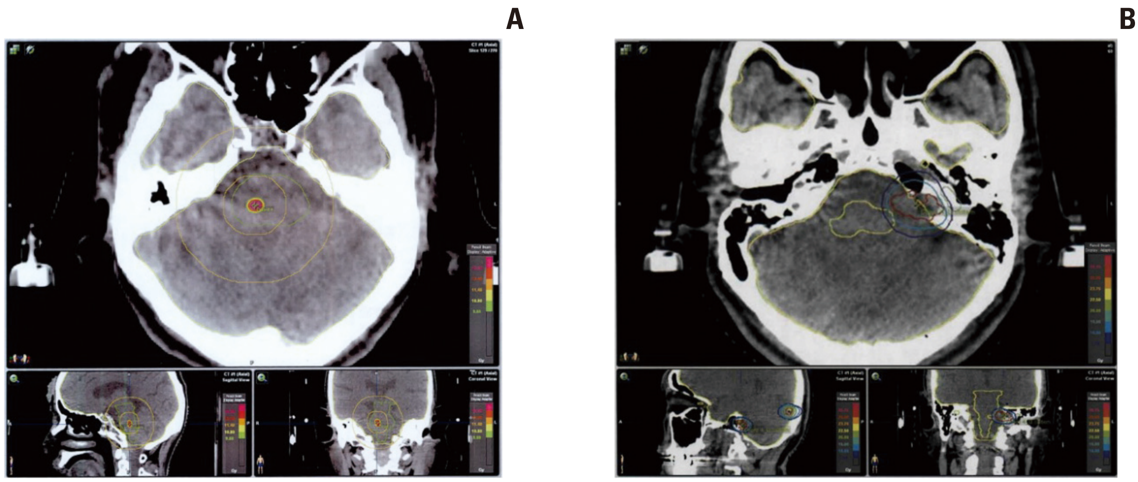

Fig. 1. Radiation therapy plans for both non–small cell lung cancer patients with a single brain metastasis (BM) who received < 15 Gy by a single fraction (biological equivalent dose, 37.5 Gy). For one patient, a stereotactic radiosurgery (SRS) of 12 Gy was administered because the BM was located in the pons (A). Another patient received an SRS of 13 Gy due to the BM being located close to the brain stem and inner ear (B).

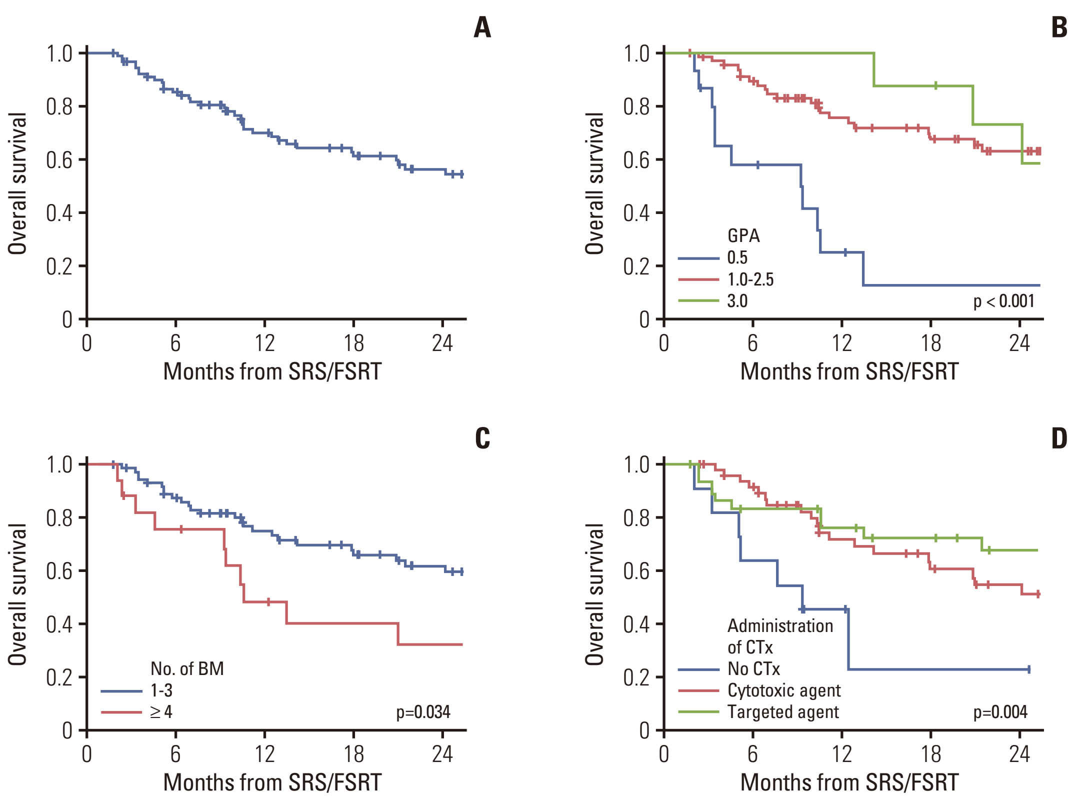

Fig. 2. Overall survival following stereotactic radiosurgery (SRS)/fractionated stereotactic radiotherapy (FSRT) for brain metastasis (BM) in the cohort (A), according to the non–small cell lung cancer–specific graded prognostic assessment (GPA) score (B), number of BM (C), and administration of systemic chemotherapy (D). CTx, chemotherapy.

Table 3. Prognostic factors related to OS

Variable	Univariate analysis			Multivariate analysis[a)]	
	1-Year OS (%)	2-Year OS (%)	p-value	Hazard ratio (95% CI)	p-value
Age (yr)					
65-70	77.2	65.0	0.499	-	-
> 70	63.9	41.0		-	-
GPA score					
0.5	24.8	12.4	< 0.001	Ref	< 0.001
1.0-2.5	75.5	62.9		0.127 (0.047-0.344)	< 0.001
3	87.5	72.9		0.083 (0.020-0.338)	0.001
Total BM volume (mm³)					
≤ 1,300	72.0	60.4	0.258	-	-
> 1,300	67.4	51.5		-	-
No. of BM					
1-3	74.9	61.7	0.034	Ref	0.103
≥ 4	48.1	32.1		0.385 (0.122-1.215)	-
Primary controlled					
Controlled	76.7	64.1	0.335	-	-
No controlled	66.7	52.2		-	-
Systemic therapy					
No	45.5	22.7	0.004	Ref	0.015
Cytotoxic agent	71.7	54.5		0.449 (0.179-1.131)	0.089
Targeted agent	76.1	67.8		0.215 (0.074-0.622)	0.005
Immunotherapy					
No	69.0	53.2	0.744	-	-
Yes	73.0	65.7		-	-
BED (Gy)					
< 60.0	70.5	57.5	0.735	-	-
≥ 60.0	68.9	54.6		-	-

BED, biological equivalent dose; BM, brain metastasis; CI, confidence interval; GPA, graded prognostic assessment; OS, overall survival; Ref, reference. [a)]Variables were entered into the multivariate regression model in a stepwise method if $p \le 0.10$ and were removed at any point if $p > 0.10$.

and 30 (33.0%) received targeted agents. Moreover, in the pre-SRS/FSRT period, 40 patients (44.0%) had administrated second-line or more systemic agents and 19 (20.9%) had received immunotherapy. Regarding SRS/FSRT, 203 BM (91.4%) were delivered single-fraction SRS/FSRT and 19 (8.6%) were delivered multiple-fraction SRS/FSRT. SRS was delivered at a dose of 12-28 Gy, which is equal to the biologically equivalent dose (BED) of 26.4-106.4 Gy. Among them, two patients received < 15 Gy in a single fraction (BED, 37.5 Gy). In one patient, an SRS dose of 12 Gy in a single fraction was applied because the tumor was located in the pons (Fig. 1A). Another patient delivered 13 Gy in a single fraction due to the tumor location being close to the brainstem and inner ear (Fig. 1B).

2. OS and factors related to survival

During a median follow-up period of 18 months (range, 2 to 104 months), the median OS period was 32 months, with an OS of 69.8% at 1 year and 56.1% at 2 years (Fig. 2A). Univariate analysis identified the NSCLC-specific GPA score (0.5 vs. 1.0-2.5 vs. 3, $p < 0.001$) (Fig. 2B), BM number (1-3 vs. ≥ 4, p=0.034) (Fig. 2C), and systemic therapy administration (no administration vs. cytotoxic agent vs. targeted agent, p=0.004) (Fig. 2D) as significant factors related to OS, whereas the total BM volume (p=0.258), primary tumor control (p=0.335), and immunotherapy administration (p=0.744) did not affect OS. In detail, the median OS for patients with NSCLC-specific GPA scores of 0.5, 1.0-2.5, and 3.0 were 9.2, 33.0, and 47.0 months, respectively. We found a median OS of 9.3 months for patients without chemotherapy and 27 and 47 months for those receiving cytotoxic and targeted agents, respectively. In the multivariate analysis, both the NSCLC-specific GPA score (p=0.007) and systemic therapy administration (p=0.039) were confirmed to be prognostic factors

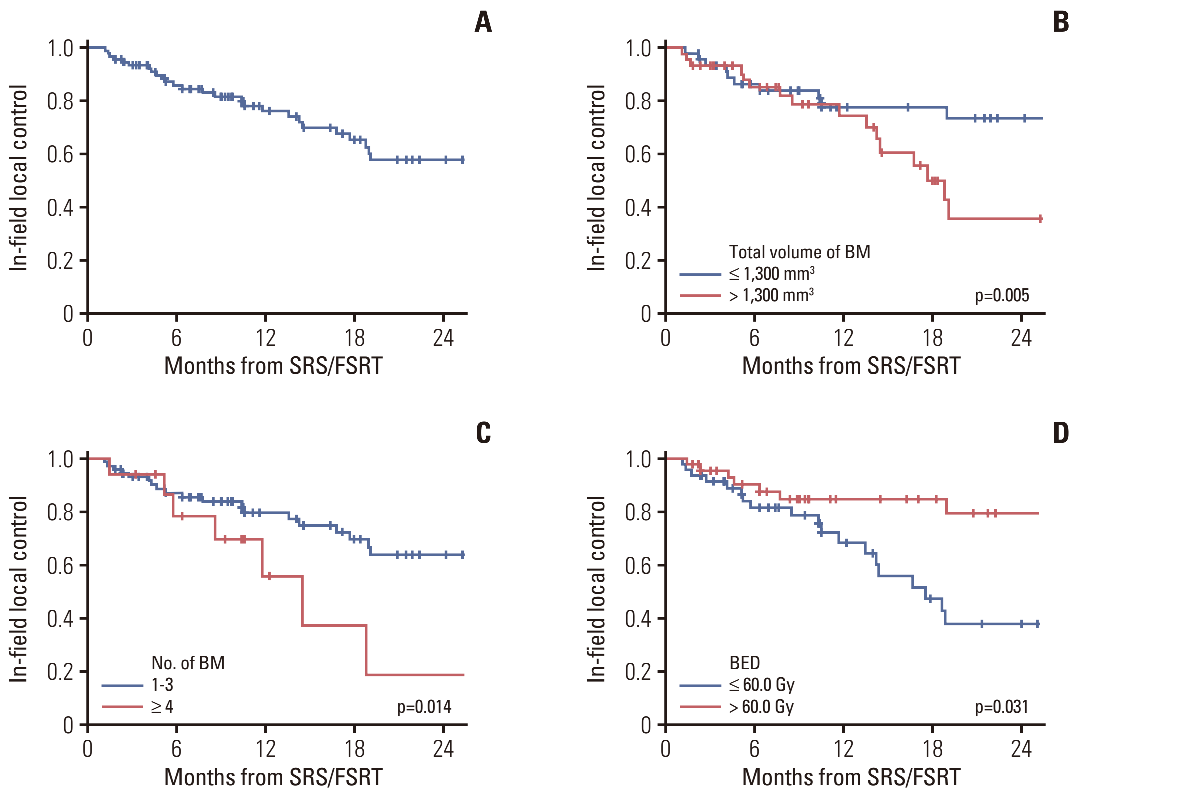

Fig. 3. In-field local control of brain metastasis (BM) treated with stereotactic radiosurgery (SRS)/fractionated stereotactic radiotherapy (FSRT) in the cohort (A), according to the total volume of BM (B), number of BM (C), and biologically effective dose (BED) (D).

affecting OS. The results of the analysis of the variables correlated with OS are shown in Table 3.

3. IFLC and factors related to local control

The median IFLC period was 31 months. The 1- and 2-year IFLC rates were 75.9 and 57.6%, respectively (Fig. 3A). Upon univariate analysis, the NSCLC-specific GPA score (0.5 vs. 1.0-2.5 vs. 3, p=0.030), total BM volume (≤ 1,300 vs. > 1,300 mm^3, p=0.005) (Fig. 3B), BM number (1-3 vs. ≥ 4, p=0.014) (Fig. 3C), and BED (< 60 vs. ≥ 60 Gy, p=0.031) (Fig. 3D) were found to influence IFLC. In the multivariate analysis, both the total BM volume (p=0.042) and BM number (p=0.014) were significant factors influencing IFLC. The results of the analysis of factors affecting the IFLC are shown in Table 4.

No acute or late toxicities of higher than grade 2 were observed during or after SRS/FSRT.

Discussion

Several landmark studies involving radiotherapy for BM have reported SRS/FSRT as a standard practice for cancer patients with BM, contributing to a shift in the radiation approach from WBRT to SRS/FSRT in limited BM scenarios [7,13,17]. Current guidelines recommend SRS/FSRT as an upfront treatment for patients with limited BM, whereas WBRT is selectively indicated for those with extended multiple or innumerable BM and/or large-volume intracranial metastases [14,18,19].

Age is considered a key component of RPA [4] and GPA [2,3] when analyzing the prognosis of cancer patient with BM. Considering the vulnerability of elderly patients with BM to neurological toxicity post-treatment, it may be better to administer SRS/FSRT instead of WBRT. Chen et al. [5] compared elderly patients with BM treated using SRS with those treated using WBRT, focusing on grade 2-4 toxicity, and concluded that SRS was associated with lower toxicity than WBRT. Gregucci et al. [6] observed no moderate or severe adverse effects, including neurological complications, after SRS in elderly patients with BM. With early diagnosis and appropriate interventions, elderly patients can return to a healthy state [20,21]. Therefore, instead of being subjected to palliative care, elderly patients with BM should receive standard treatment equal to that administered to non-elderly patients with BM. However, most clinical trials have underrepresented older patients and have not shown sufficient

Table 4. Prognostic factors related to IFLC

Variable	Univariate analysis			Multivariate analysis[a]	
	1-Year IFLC (%)	2-Year IFLC (%)	p-value	Hazard ratio (95% CI)	p-value
Age (yr)					
65-70	73.8	54.1	0.308	-	-
> 70	80.2	64.8		-	-
GPA score					
0.5	31.2	31.2	0.030	-	-
1.0-2.5	77.7	54.2		-	
3	100	100		-	
Total BM volume (mm³)					
≤ 1,300	77.6	73.5	0.005	Ref	0.040
> 1,300	74.4	35.8		2.410 (1.042-5.576)	
No. of BM					
1-3	79.6	63.8	0.014	Ref	0.022
≥ 4	55.8	18.6		2.962 (1.169-7.504)	
Primary controlled					
Controlled	77.0	57.0	0.890	-	-
No controlled	75.2	57.9		-	
Systemic therapy					
No	69.4	69.4	0.630	-	-
Cytotoxic agent	72.4	51.7		-	
Targeted agent	84.5	67.3		-	
Immunotherapy					
No	74.5	53.5	0.162	-	-
Yes	80.8	70.7		-	
BED (Gy)					
< 60.0	68.3	37.7	0.031	-	-
≥ 60.0	84.5	79.3		-	

BED, biological equivalent dose; BM, brain metastasis; CI, confidence interval; GPA, graded prognostic assessment; IFLC, in-field local control; Ref, reference. [a]Variables were entered into the multivariate regression model in a stepwise method if p ≤ 0.10 and were removed at any point if p > 0.10.

outcomes in elderly patients with BM following SRS/FSRT although two-thirds of patients with cancer are aged > 65 years. To address this gap in research, our study analyzed the results of elderly patients with NSCLC and 1-10 BM who were treated using SRS/FSRT and had a KPS score of ≥ 70 without combined WBRT.

Regarding survival, we found that OS at 12 and 24 months after SRS/FSRT were 69.8 and 56.1%, respectively, with a median OS of 32 months. JLGK0901-Elderly trial by Higuchi et al. [22] reported a median OS of 10 months after SRS for BM from various primary sites in 693 elderly patients (aged ≥ 65 years), which was shorter than the median OS of 14 months in 501 younger patients (aged < 65 years). Moreover, Yamamoto et al. [23] showed that the median OS after SRS was 9 months in elderly patients (aged ≥ 65 years) with BM from NSCLC among 2,441 patients during a 20-year duration from 1998 to 2018. This disparity between our study and the above trials may have originated from our carefully selected patients with healthy aging condition, such as a good performance status (KPS ≥ 70) and active treatment application including systemic treatment.

Consequently, our study showed that NSCLC-specific GPA score and systemic drug administration were prognostic factors affecting OS. The disease-specific GPA score for BM is an important prognostic scoring tool [3]. Our results correspond with those of previous studies showing a significant association between the NSCLC-specific GPA score and OS, although there was a numerical difference in the OS period according to the GPA score. We found that the median OS for patients with GPA scores of 0.5, 1.0-2.5, and 3.0 were 9.2, 33.0, and 47.0 months, respectively, whereas Woody et al. [24] reported median OS periods of 2.8, 6.7, 9.8, and 13.2 months with DS-GPA scores of 0-1.0, 1.5-2, 2.5-3.0, and 3.5-4.0, respectively, in NSCLC patients with BM who were treated with SRS alone or combined SRS and WBRT. Furthermore, our results show that prolonged OS may benefit from systemic treatment administration, which our previous study [15] failed to determine owing to the small cohort size. The 2-year OS rate was 54.5% in cohorts who underwent chemotherapy and 67.8% in those who were administered a targeted agent, whereas that in patients who did not receive systemic chemotherapy was only 22.7%. Radiotherapy is the standard treatment for BM, whereas systemic therapy is effective for controlling extracranial diseases due to cytotoxic chemotherapy having limited efficacy for BM owing to low central nervous system (CNS) penetration [25], and therefore controls extracranial disease rather than intracranial disease. However, targeted therapies show more response rates owing to relatively good CNS penetration, thereby controlling intracranial and extracranial diseases [25,26]. Goldberg et al. [27] reported that patients with NSCLC and BM showed good responsiveness to systemic treatment with pembrolizumab and could benefit from such systemic treatment [27]. However, unlike these results, our study did not show any difference in OS between patients who received immunotherapy and those who did not. Further trials investigating the role of systemic treatments, including targeted agents and immunotherapy, in improving oncological outcomes in these patients are required.

Since SRS/FSRT is a local therapy, we assessed the IFLC of SRS/FSRT and its predictive factors for BM. Herein, the IFLC rates at 12 and 24 months were 75.9% and 57.6%, respectively. These results correspond with those of previous studies showing that SRS is effective in treating patients with BM, resulting in high IFLC rates (70%-90%) [18,28-31]. Among them, Noel et al. [29] and Minniti et al. [28] reported IFLC rates of 91 and 84%, respectively, at 12 months after SRS in elderly patients with BM.

In our cohort, the univariate analysis related to IFLC identified a low GPA score, larger total BM volume, BM number of ≥ 4, and low BED as risk factors for local progression. Total BM volume was the strongest factor affecting IFLC following multivariate analysis. Similarly, Bhatnagar et al. [30] identified that the total treatment volume, age, RPA, and marginal dose were significant prognostic factors when assessing outcomes following SRS in patients with ≥ 4 BM, and defined that the total tumor volume was the strongest predictor of IFLC, with 1-year IFLC rates of 97% for lesions < 2 cm^3 and 75% for lesions ≥ 2 cm^3. Therefore, the overall BM volume is an important factor affecting IFLC considering SRS/FSRT, implicating intracranial metastatic tumor burden as a significant prognosticator.

This study had several limitations. The study involved unavoidable selection bias resulting from its retrospective nature. Typically, we selected elderly patients with good performance who belonged to RPA class II, and we could not report detailed toxicity data owing to incorrect medical records. Additionally, we did not compare the outcomes of SRS/FSRT for BM between age groups or between older and younger patients. However, our research is valuable in that it provides useful data regarding SRS/FSRT in elderly patients with NSCLC-induced BM. Most previous reports have included elderly patients with BM resulting from various primary cancers, except for a few studies [15,23].

In conclusion, our study suggests that SRS/FSRT is beneficial as an initial treatment for elderly patients aged ≥ 65 years with NSCLC-induced BM, showing improved OS and suitability without severe adverse effects. Moreover, those with a high GPA who received active systemic treatment were considered better candidates for SRS/FSRT. Specifically, our findings indicate that the value of age as a decision-making factor for BM treatment has diminished owing to advanced anti-cancer therapies and the improved health of elderly patients with cancer. Future prospective studies are required to elucidate the appropriate standard treatment for elderly cancer patients with BM.

Ethical Statement

This study was approved by the Institutional Review Boards of the two institutions (2023-11-013 and OC24RIDI0015). The requirement for informed consent was waived.

Author Contributions

Conceived and designed the analysis: Kim M, Cha J, Kim HJ, Kim WC, Lee J.
Collected the data: Kim M, Cha J, Lee J.
Contributed data or analysis tools: Kim M, Lee J.
Performed the analysis: Kim M, Cha J, Lee J.
Wrote the paper: Kim M, Lee J.
Paper review: Kim HJ, Kim WC, Lee J.

ORCID iDs

Myungsoo Kim : https://orcid.org/0000-0002-0651-549X
Jeongshim Lee : https://orcid.org/0000-0002-7280-5401

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

This study was supported by the Inha University Research Grant and a National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT) (No. NRF-2018R1C1B5086265).

References

1. Yancik R, Ries LA. Cancer in older persons: an international issue in an aging world. Semin Oncol. 2004;31:128-36.
2. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys. 2008;70:510-4.
3. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys. 2010;77:655-61.
4. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997; 37:745-51.
5. Chen L, Shen C, Redmond KJ, Page BR, Kummerlowe M, McNutt T, et al. Use of stereotactic radiosurgery in elderly and very elderly patients with brain metastases to limit toxicity associated with whole brain radiation therapy. Int J Radiat Oncol Biol Phys. 2017;98:939-47.
6. Gregucci F, Fiorentino A, Corradini S, Figlia V, Mazzola R, Ricchetti F, et al. Linac-based radiosurgery or fractionated stereotactic radiotherapy with flattening filter-free volumetric modulated arc therapy in elderly patients: a mono-institutional experience on 110 brain metastases. Strahlenther Onkol. 2019;195:218-25.
7. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA. 2016;316:401-9.
8. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009; 10:1037-44.
9. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep. 2012;14:48-54.
10. Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, Nayak L, et al. Brain metastases. Nat Rev Dis Primers. 2019;5:5.
11. Schuette W. Treatment of brain metastases from lung cancer: chemotherapy. Lung Cancer. 2004;45 Suppl 2:S253-7.
12. Fecci PE, Champion CD, Hoj J, McKernan CM, Goodwin CR, Kirkpatrick JP, et al. The evolving modern management of brain metastasis. Clin Cancer Res. 2019;25:6570-80.
13. Scoccianti S, Ricardi U. Treatment of brain metastases: review of phase III randomized controlled trials. Radiother Oncol. 2012;102:168-79.
14. Shinde A, Akhavan D, Sedrak M, Glaser S, Amini A. Shifting paradigms: whole brain radiation therapy versus stereotactic radiosurgery for brain metastases. CNS Oncol. 2019;8:CNS27.
15. Lee J, Kim HJ, Kim WC. CyberKnife-based stereotactic radiosurgery or fractionated stereotactic radiotherapy in older patients with brain metastases from non-small cell lung cancer. Radiat Oncol J. 2023;41:258-66.
16. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015;16:e270-8.
17. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA. 2006;295:2483-91.
18. Varlotto JM, Flickinger JC, Niranjan A, Bhatnagar AK, Kondziolka D, Lunsford LD. Analysis of tumor control and toxicity in patients who have survived at least one year after radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys. 2003; 57:452-64.
19. Dhermain F, Noel G, Antoni D, Tallet A. Role of radiation therapy in brain metastases management. Cancer Radiother. 2020;24:463-9.
20. Kim HJ, Min KB, Min JY. Healthy aging predicts mortality risks: results from the Korean longitudinal study of aging (2006-2014). Arch Gerontol Geriatr. 2021;94:104333.
21. Zamudio-Rodriguez A, Dartigues JF, Amieva H, Peres K. A literature review of healthy aging trajectories through quantitative and qualitative studies: a psycho-epidemiological approach on community-dwelling older adults. J Frailty Aging. 2021;10:259-71.
22. Higuchi Y, Yamamoto M, Serizawa T, Sato Y, Shuto T, Akabane A, et al. Stereotactic radiosurgery in elderly patients with brain metastases: comparison with non-elderly patients using database of a multi-institutional prospective observational study (JLGK0901-Elderly). J Neurooncol. 2019;144:393-402.
23. Yamamoto M, Serizawa T, Sato Y, Higuchi Y, Kasuya H, Barfod BE. Stereotactic radiosurgery for brain metastases: a retrospective cohort study comparing treatment results between two lung cancer patient age groups, 75 years or older vs 65-74 years. Lung Cancer. 2020;149:103-12.
24. Woody NM, Greer MD, Reddy CA, Videtic GM, Chao ST, Murphy ES, et al. Validation of the disease-specific GPA for patients with 1 to 3 synchronous brain metastases in newly diagnosed NSCLC. Clin Lung Cancer. 2018;19:e141-7.
25. Yousefi M, Bahrami T, Salmaninejad A, Nosrati R, Ghaffari P, Ghaffari SH. Lung cancer-associated brain metastasis: molecular mechanisms and therapeutic options. Cell Oncol (Dordr). 2017;40:419-41.
26. Tan AC, Itchins M, Khasraw M. Brain metastases in lung cancers with emerging targetable fusion drivers. Int J Mol Sci. 2020;21:1416.
27. Goldberg SB, Schalper KA, Gettinger SN, Mahajan A, Herbst RS, Chiang AC, et al. Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results

and biomarker analysis from a non-randomised, open-label, phase 2 trial. Lancet Oncol. 2020;21:655-63.
28. Minniti G, Esposito V, Clarke E, Scaringi C, Bozzao A, Lanzetta G, et al. Stereotactic radiosurgery in elderly patients with brain metastases. J Neurooncol. 2013;111:319-25.
29. Noel G, Bollet MA, Noel S, Feuvret L, Boisserie G, Tep B, et al. Linac stereotactic radiosurgery: an effective and safe treatment for elderly patients with brain metastases. Int J Radiat Oncol Biol Phys. 2005;63:1555-61.
30. Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. Int J Radiat Oncol Biol Phys. 2006;64:898-903.
31. Yomo S, Hayashi M. Is upfront stereotactic radiosurgery a rational treatment option for very elderly patients with brain metastases? A retrospective analysis of 106 consecutive patients age 80 years and older. BMC Cancer. 2016;16:948.