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Original Article

Normal Brain-Sparing Radiotherapy versus Whole Brain Radiotherapy for Multiple Brain Metastasis from Non–Small Cell Lung Cancer

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Purpose The efficacy and lower neurotoxicity of normal brain-sparing radiotherapy (NBS-RT) with systemic therapy in treating multiple brain metastases from non–small cell lung cancer (NSCLC) is underexplored. This study compares whole brain radiotherapy (WBRT) and NBS-RT for multiple brain metastases in NSCLC, focusing on treatment outcomes and leukoencephalopathy.

Materials and Methods This retrospective study included 503 patients with NSCLC with multiple brain metastases at a single center, treated with either WBRT or NBS-RT. Post-RT treatments included chemotherapy, targeted therapy, or immunotherapy. Main outcomes measured were intracranial control, overall survival (OS), and leukoencephalopathy incidence.

Results In this study, 441 patients received WBRT and 62 received NBS-RT, with median ages of 62 and 61 years, respectively. A significant portion of both groups, 77.3% in WBRT and 80.6% in NBS-RT, received post-RT systemic therapy. The median number of brain metastases was 10 for WBRT and 12 for NBS-RT, with median maximal diameters of 11.7 mm in WBRT and 14.4 mm in NBS-RT. After a median follow-up of 10.9 months for WBRT and 11.8 months for NBS-RT, there were no significant differences in intracranial progression (p=0.516) or OS (p=0.492) between the groups. However, WBRT patients had a higher incidence of leukoencephalopathy than NBS-RT patients (p=0.013).

Conclusion NBS-RT combined with systemic therapy was as effective in treating multiple brain metastases as WBRT and was less toxic. NBS-RT-based strategies deserve further investigation in a prospective setting.

Key words Brain neoplasms, Leukoencephalopathies, Non-small-cell lung carcinoma, Radiotherapy

Introduction

Recently developed treatments for non–small cell lung cancer (NSCLC), including molecular targeted agents, immunotherapy, and cytotoxic chemotherapy, have significantly improved patient outcomes [1,2]. Despite a limited ability to cross the blood-brain barrier (BBB) [3], some research has suggested that these agents may be useful for treating brain metastases in patients with NSCLC [4].

While whole brain radiotherapy (WBRT) has long been the standard therapy for brain metastases in NSCLC, the steep cognitive decline that typically ensues has led to a shift towards treating patients with 1-3 small lesions (< 3 cm) with localized therapies such as stereotactic radiosurgery (SRS). While this has inspired many high-quality trials comparing WBRT to normal brain-sparing radiotherapy (NBS-RT) like SRS [5-12], large (≥ 3 cm) and multiple (≥ 4) lesions (henceforward referred to as multiple metastatic disease) have been ignored in such trials. WBRT is still preferred for multiple metastatic disease due to its expected benefit in enhancing intracranial control. However, the feasibility and outcomes of NBS-RT in such patients have remained inadequately investigated [13-15], despite its potential for intracranial tumor control with effective systemic therapy, particularly in the era of advanced NSCLC treatments.

To evaluate the feasibility of NBS-RT as a treatment for multiple brain metastases in NSCLC, we aimed to compare the treatment outcomes and the risk profiles of NBS-RT and WBRT in the previously underexplored cohort of patients having NSCLC with multiple metastatic disease involving the brain. These patients were treated with either WBRT or NBS-RT in multiple fractions, a treatment paradigm that has rarely been attempted before.

Materials and Methods

1. Patient eligibility

We retrospectively analyzed medical records from 819 patients diagnosed with NSCLC and treated for brain metastases from August 2016 to June 2023. After exclusions (fewer than 4 metastases and maximum diameter < 3 cm [n=107],

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previous WBRT [n=16], incomplete radiotherapy [RT; n=12], and absence of post-treatment magnetic resonance imaging [MRI] data [n=181]), 503 patients were eligible for analysis (S1 Fig.).

2. Radiotherapy

For each patient, the radiation dose administered to the whole brain and bilateral hippocampi was calculated. All patients underwent either fractionated WBRT or NBS-RT (Supplementary Methods). WBRT was delivered using 2D/3D conformal techniques or intensity-modulated radiotherapy (IMRT), with a standard dose of 20-30 Gy over 5-10 fractions, plus a possible gross tumor volume (GTV) boost of 5-9 Gy in select cases (S2A Fig.). IMRT involved a single prescription dose to the whole brain or a simultaneous integrated boost (SIB) around the GTV, over a total of 5-15 fractions (S2B Fig.). Hippocampus-sparing WBRT was applied when feasible, considering patient survival and planning parameters (S2C Fig.). For NBS-RT, the planning target volume (PTV) was delineated with a 3-5-mm margin around the GTV, prescribing 25-30 Gy to the PTV or an additional SIB-administered boost of 3-12.5 Gy to the GTV, delivered over 5-15 fractions (S2D Fig., S3 Table).

3. Evaluation of RT-related leukoencephalopathy

Leukoencephalopathy evaluation was based on MRI examinations performed > 1 month after the completion of RT. The diagnostic process included the clear identification of characteristic diffuse hyperintensities in the periventricular white matter on T2/fluid-attenuated inversion recovery imaging (S4 Fig.) [16]. RT-related leukoencephalopathy was defined by the appearance of new lesions observed when comparing MRI scans conducted before and after RT. Pre-existing changes in the T2 white-matter signal were not considered indicative of leukoencephalopathy. Leukoencephalopathy was diagnosed only when these findings were consistently observed in at least two consecutive follow-up imaging studies. All evaluations were performed by board-certified neuroradiologists. Details of the number of follow-up MRI scans and the follow-up intervals are provided in S5 Table.

4. Statistical analysis

The interval from the initiation of RT to intracranial failure (local and distant) and the occurrence of leukoencephalopathy was used to estimate the time-to-intracranial failure and the time-to-leukoencephalopathy, and the cumulative incidences were analyzed with the competing risks model [17]. Overall survival (OS) was defined as the period from the start of treatment to either any cause of death or the last observation. Univariable and multivariable analyses were conducted using Fine and Gray regression and Cox proportional hazards regression (Supplementary Methods). To adjust for differences in characteristics between groups, propensity score matching (PSM) was employed (Supplementary Methods). Statistical was 10.8 months (interquartile range [IQR], 7.4 to 17.8 months). Further significance was established for two-sided p-values < 0.05. All analysis was performed using R software ver. 4.3.1 (R Foundation for Statistical Computing).

Results

1. Patient characteristics

In this study, 441 and 62 patients were enrolled in the WBRT and NBS-RT groups, respectively. Baseline patient and treatment characteristics for both cohorts are detailed in Table 1.

A comparative analysis of the groups revealed no significant differences in intracranial tumor burden or tumor characteristics, including the total number of parenchymal metastases (median, 10; IQR, 5 to 28 in WBRT group vs. 12; IQR, 6 to 32 in NBS-RT group) and the maximal diameter of metastases (mm) (median, 11.7; IQR, 6.7 to 20.1 in WBRT group vs. 14.4; IQR, 8.2 to 26.1 in NBS-RT group). An exception was the lower incidence of leptomeningeal seeding (LMS) (37.6% vs. 21.0% in WBRT and NBS-RT groups, respectively; p=0.015) and a greater total prescription dose (biologically effective dose in Gy) in the NBS-RT group compared to the WBRT group (median, 39; IQR, 37.5 to 47.2 in WBRT group vs. 43.9; IQR, 43.9 to 47.2 in NBS-RT group; p < 0.001). Given these significant differences, PSM was implemented. Following PSM, there were no significant differences in characteristics between the two groups (S6 Table). Most patients in both groups underwent systemic therapy after RT, with 77.3% (341 out of 441) in the WBRT group and 80.6% (50 out of 62) in the NBS-RT group receiving any type of systemic therapy after RT.

2. Intracranial tumor control and OS

The median (IQR) follow-up duration in this study was 10.9 (6.4-21.0) and 11.8 (7.3-23.2) months for the WBRT and NBS-RT groups, respectively. There was no significant difference in the cumulative incidence of intracranial progression between the groups (1-year cumulative incidence, 47.4%; 95% confidence interval [CI], 42.5% to 52.1% in WBRT group vs. 49.0%; 95% CI, 35.8% to 60.9% in NBS-RT group; p=0.581 for competing risk) (Fig. 1A). In the final multivariable Cox model, older age (hazard ratio [HR], 0.68; 95% CI, 0.52 to 0.89; p=0.004) and targeted therapy after RT (HR, 0.67; 95% CI, 0.51 to 0.89; p=0.005) were significantly associated with better intracranial tumor control. The RT type had no signifi-

Table 1. Patient characteristics

Characteristic	WBRT (n=441)	NBS-RT (n=62)	p-value
Age (yr)	62 (54-68)	61 (51-70)	0.903
Sex			
Male	201 (45.6)	27 (43.5)	0.869
Female	240 (54.4)	35 (56.5)	
Previous GKS			
No	337 (76.4)	41 (66.1)	0.110
Yes	104 (23.6)	21 (33.9)	
Previous surgery			
No	415 (94.1)	59 (95.2)	> 0.99
Yes	26 (5.9)	3 (4.8)	
No. of parenchymal metastasis	10 (5-28)	12 (6-32)	0.189
Max diameter of metastasis	11.7 (6.7-20.1)	14.4 (8.2-26.1)	0.070
Leptomeningeal seeding			
Absent	275 (62.4)	49 (79.0)	0.015
Present	166 (37.6)	13 (21.0)	
Pathology			
Adenocarcinoma	425 (96.4)	59 (95.2)	0.718
Others	16 (3.6)	3 (4.8)	
EGFR			
Negative	132 (29.9)	20 (32.3)	0.798
Positive	290 (65.8)	39 (62.9)	
Unknown	19 (4.3)	3 (4.8)	
ALK			
Negative	324 (73.5)	41 (66.1)	0.763
Positive	26 (5.9)	4 (6.5)	
Unknown	91 (20.6)	17 (27.4)	
ROS1			
Negative	263 (59.6)	30 (48.4)	0.227
Positive	50 (11.3)	10 (16.1)	
Unknown	128 (29.0)	22 (35.5)	
PD-L1 expression (%)	1.0 (0.0-15.0)	3.5 (0.0-50.0)	0.253
BED (Gy)	39 (37.5-47.2)	43.9 (43.9-47.2)	< 0.001
Pre-RT cytotoxic chemotherapy			
No	363 (82.3)	47 (75.8)	0.289
Yes	78 (17.7)	15 (24.2)	
Pre-RT targeted therapy			
No	280 (63.5)	44 (71.0)	0.313
Yes	161 (36.5)	18 (29.0)	
Pre-RT immunotherapy			
No	400 (90.7)	56 (90.3)	> 0.99
Yes	41 (9.3)	6 (9.7)	
Post-RT cytotoxic chemotherapy			
No	323 (73.2)	39 (62.9)	0.122
Yes	118 (26.8)	23 (37.1)	
Post-RT targeted therapy			
No	228 (51.7)	36 (58.1)	0.422
Yes	213 (48.3)	26 (41.9)	

(Continued to the next page)

Table 1. Continued

Characteristic	WBRT (n=441)	NBS-RT (n=62)	p-value
Post-RT immunotherapy			
No	396 (89.8)	54 (87.1)	0.669
Yes	45 (10.2)	8 (12.9)	
Systemic regimen change			
No	394 (89.3)	54 (87.1)	0.754
Yes	47 (10.7)	8 (12.9)	
Intrathecal chemotherapy			
No	430 (97.5)	62 (100)	0.375
Yes	11 (2.5)	0	

Values are presented as median (IQR) or number (%). ALK, anaplastic lymphoma kinase; BED, biologically effective dose; EGFR, epidermal growth factor receptor; GKS, gamma knife radiosurgery; IQR, interquartile range; NBS-RT, normal brain-sparing radiotherapy; PD-L1, programmed death-ligand 1; ROS1, c-ros oncogene 1; RT, radiotherapy; WBRT, whole brain radiotherapy.

cant impact on intracranial tumor progression (Table 2).

There was no significant difference in OS between the WBRT (median, 12.1 months [95% CI, 10.9 to 13.8]) and NBS-RT (median, 12.3 months [95% CI, 10.0 to 22.5]; p=0.491 for log-rank) groups (Fig. 1B). Multivariable Cox regression analysis identified older age (HR, 1.28; 95% CI, 1.08 to 1.52; p=0.004) and previous gamma knife surgery (GKS) (HR, 1.36; 95% CI, 1.04 to 1.79; p=0.025) as being associated with poorer OS. Conversely, anaplastic lymphoma kinase (*ALK*) mutation (HR, 0.49; 95% CI, 0.29 to 0.81; p=0.006), a higher total prescribed RT dose (HR, 0.84; 95% CI, 0.71 to 1.00; p=0.047), and undergoing targeted therapy after RT (HR, 0.66; 95% CI, 0.52 to 0.83; p < 0.001) were associated with improved OS. The presence of LMS showed a borderline-significant association with poorer OS (HR, 1.27; 95% CI, 0.98 to 1.64; p=0.069). The RT type was not a significant factor for OS (Table 2).

Post-PSM, the comparison between the groups showed no significant difference in the cumulative incidence of intracranial progression (1-year cumulative incidence, 44.2% [95% CI, 31.0% to 56.5%] vs. 48.1% [95% CI, 34.9% to 60.2%] in the WBRT and NBS-RT group, respectively; p=0.398 for competing risk) (S7A Fig.). OS (median, 12.3 [95% CI, 9.9 to 22.6] months vs. 12.3 [95% CI, 10.0 to 22.5] months in the WBRT and NBS-RT groups, respectively; p=0.758) showed no significant difference between the groups (S7B Fig.).

Subgroup analysis revealed no significant difference in intracranial tumor control or OS between patients without and with LMS (S8 Fig.), while patients receiving NBS-RT without post-RT systemic therapy exhibited significantly worse intracranial tumor control than the patients receiving WBRT without post-RT systemic therapy (S9A Fig.). Conversely, in patients who received systemic therapy post-RT, there was no significant difference in intracranial tumor control between the NBS-RT and WBRT groups (S9C Fig.). There were no significant differences in OS between NBS-RT and WBRT groups, regardless of post-RT systemic therapy (S9B and S9D Fig.). A subgroup analysis of patients with extensive brain metastases, defined as having more than 10 parenchymal metastases, also showed no significant differences in intracranial tumor control or OS between the WBRT and NBS-RT groups (S10A and S10B Fig.).

3. Incidence of leukoencephalopathy

The incidence of leukoencephalopathy was significantly higher in the WBRT group than in the NBS-RT group (1-year cumulative incidence, 12.5%; 95% CI, 9.5% to 15.9% in WBRT vs. 6.9%; 95% CI, 2.2% to 15.5% in NBS-RT; p=0.006 for competing risk) (Fig. 1C). In patients who developed leukoencephalopathy, the median time to radiographic diagnosis was 10.8 months (IQR, 7.4-17.8 months). Further detailed analysis by RT technique demonstrated significant differences in leukoencephalopathy incidence between the conventional WBRT, hippocampus-sparing WBRT, and NBS-RT groups (1-year cumulative incidence, 11.9%; 95% CI, 8.3% to 16.3% with conventional WBRT vs. 13.4%; 95% CI, 8.6% to 19.3% with hippocampus-sparing WBRT vs. 6.9%; 95% CI, 2.2% to 15.5% with NBS-RT; p=0.017 for competing risk) (Fig. 1D). Patients receiving NBS-RT showed a significantly lower incidence of leukoencephalopathy than those receiving conventional WBRT (p=0.011 for competing risk) or hippocampus-sparing WBRT (p=0.004 for competing risk). However, there was no significant difference in the incidence of leukoencephalopathy between the conventional WBRT and hippocampus-sparing WBRT groups (p=0.450 for competing risk).

In the final multivariable competing risk regression model, WBRT was associated with an increased risk of developing leukoencephalopathy (HR, 3.51; 95% CI, 1.27 to 9.71; p=0.016) compared to NBS-RT, while post-RT immunotherapy was associated with a decreased risk of developing leukoenceph-

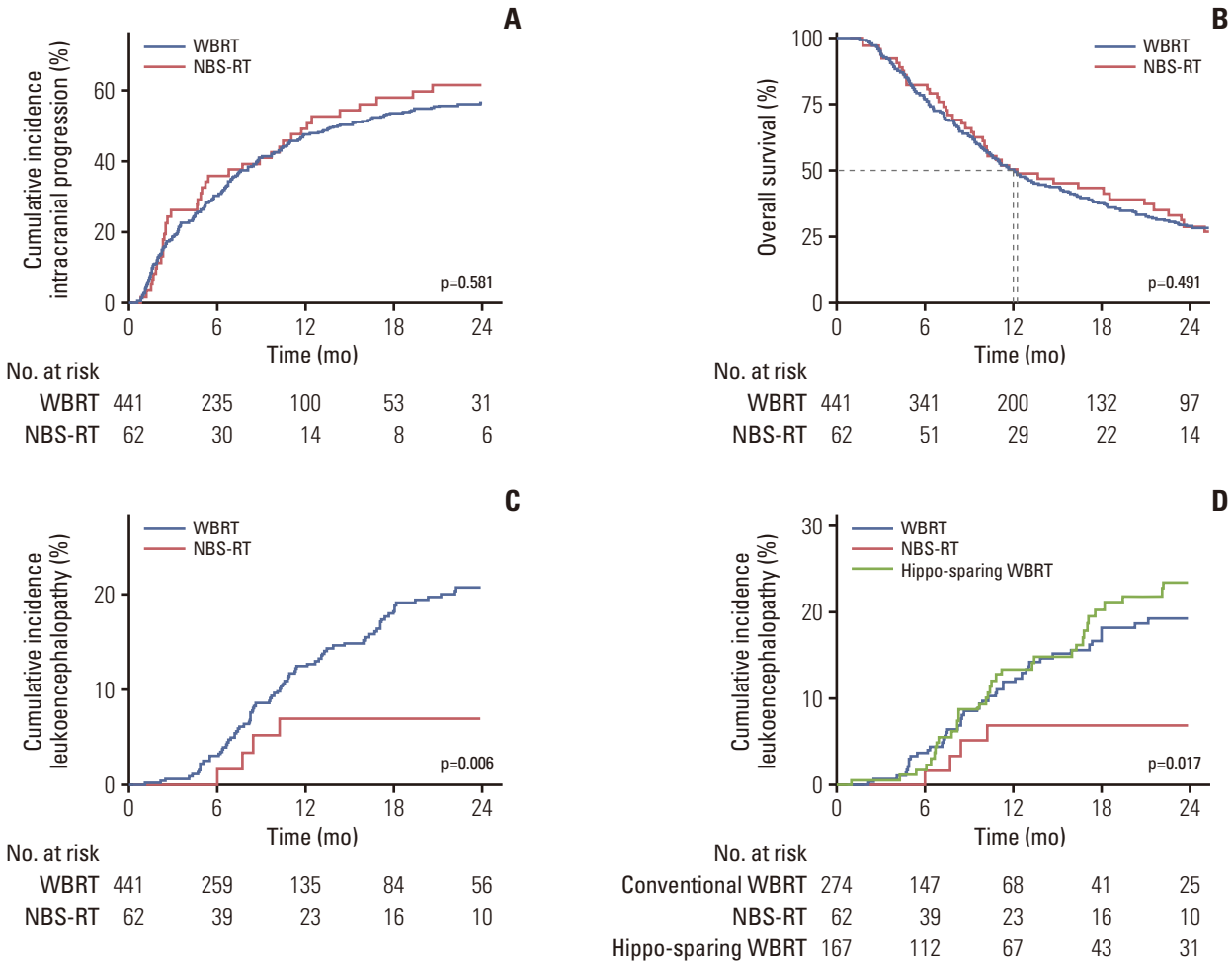

Fig. 1. Treatment outcomes and cumulative incidence of leukoencephalopathy according to radiotherapy (RT) group. Cumulative incidence of intracranial tumor progression (A), overall survival (B), and cumulative incidence of leukoencephalopathy (C) according to RT group. Cumulative incidence of leukoencephalopathy by detailed RT technique (D). NBS-RT, normal brain-sparing radiotherapy; WBRT, whole brain radiotherapy.

alopathy (HR, 0.17; 95% CI, 0.04 to 0.66; p=0.011) (Table 3).

In the subgroup analysis focused on assessing the risk of leukoencephalopathy associated with WBRT, older patients, those without prior GKS, those without LMS, and those who did not receive pre-RT systemic therapy showed an increased risk of developing leukoencephalopathy (S11 Table).

Discussion

To the best of our knowledge, this study is the first to compare outcomes in patients receiving NBS-RT in multiple fractions to those achieved in patients undergoing WBRT for multiple brain metastases in NSCLC. This patient population has historically been treated exclusively with WBRT and the potential benefits of lower-toxicity RT have been largely unexplored. Our findings demonstrated that NBS-RT can achieve outcomes in NSCLC (OS and intracranial tumor control) comparable to those of WBRT, when combined with improved systemic therapy. We observed a significantly lower risk of leukoencephalopathy with NBS-RT, which appears to be associated with the reduced brain dose identified in the dosimetric analysis (Supplementary Results, S12 and S13 Tables).

Historically, poor survival rates led to treatments for patients with distant metastases, including brain metastases, that primarily emphasized survival outcomes, often at the expense of quality of life (QoL). However, recent advancements in NSCLC therapies, especially targeted therapies for specific cancer genes and proteins [18,19], as well as immunotherapies involving checkpoint inhibitors [20,21], have significantly improved survival outcomes, thus elevating the

Table 2. Competing risk regression for intracranial progression and Cox proportional hazards regression analysis for overall survival

Variable	Intracranial progression				Overall survival			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)								
< 60	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥ 60	0.77 (0.65-0.91)	0.002	0.68 (0.52-0.89)	0.004	1.17 (1.01-1.35)	0.034	1.28 (1.08-1.52)	0.004
Sex								
Male	1 (reference)		-		1 (reference)		-	
Female	1.13 (0.89-1.42)	0.318	-	-	0.98 (0.80-1.19)	0.813	-	-
Previous GKS								
No	1 (reference)		-		1 (reference)		1 (reference)	
Yes	0.95 (0.72-1.27)	0.751	-	-	1.50 (1.19-1.88)	< 0.001	1.36 (1.04-1.79)	0.025
Previous surgery								
No	1 (reference)		-		1 (reference)		1 (reference)	
Yes	1.35 (0.85-2.15)	0.201	-	-	0.53 (0.34-0.85)	0.008	0.67 (0.38-1.17)	0.157
No. of parenchymal metastasis								
< 10	1 (reference)		-		1 (reference)		-	
≥ 10	1.05 (0.89-1.24)	0.535	-	-	1.09 (0.94-1.25)	0.241	-	-
Max diameter of metastasis (mm)								
< 20	1 (reference)		-		1 (reference)		-	
≥ 20	1.04 (0.83-1.32)	0.726	-	-	0.71 (0.57-0.88)	0.002	-	-
Leptomeningeal seeding								
No	1 (reference)		-		1 (reference)		1 (reference)	
Yes	1.07 (0.84-1.37)	0.575	-	-	1.34 (1.09-1.66)	0.006	1.27 (0.98-1.64)	0.069
Pathology								
Adenocarcinoma	1 (reference)		-		1 (reference)		-	
Others	0.81 (0.39-1.68)	0.569	-	-	1.35 (0.81-2.27)	0.253	-	-
EGFR								
Negative	1 (reference)		-		1 (reference)		-	
Positive	1.05 (0.82-1.36)	0.687	-	-	1.05 (0.82-1.36)	0.687	-	-
ALK								
Negative	1 (reference)		-		1 (reference)		1 (reference)	
Positive	0.94 (0.59-1.50)	0.797	-	-	0.94 (0.59-1.50)	0.797	0.49 (0.29-0.81)	0.006
ROS1								
Negative	1 (reference)		-		1 (reference)		-	
Positive	1.27 (0.88-1.84)	0.204	-	-	1.27 (0.88-1.84)	0.204	-	-
PD-L1 expression (%)								
< 1	1 (reference)		1 (reference)		1 (reference)		-	
≥ 1	0.89 (0.74-1.07)	0.199	0.80 (0.61-1.06)	0.116	0.89 (0.74-1.07)	0.199	-	-
Radiotherapy								
NBS-RT	1 (reference)		-		1 (reference)		-	
WBRT	0.89 (0.64-1.25)	0.516	-	-	1.11 (0.82-1.51)	0.492	-	-
BED (Gy)								
≤ 39	1 (reference)		-		1 (reference)		1 (reference)	
> 39	0.98 (0.83-1.16)	0.824	-	-	0.77 (0.67-0.89)	0.001	0.84 (0.71-1.00)	0.047
Pre-RT cytotoxic chemotherapy								
No	1 (reference)		-		1 (reference)		-	
Yes	0.82 (0.59-1.14)	0.246	-	-	1.68 (1.30-2.16)	< 0.001	-	-

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Table 2. Continued

Variable	Intracranial progression				Overall survival			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Pre-RT targeted therapy								
No	1 (reference)		-		1 (reference)		-	
Yes	0.78 (0.61-0.99)	0.044	-	-	0.80 (0.65-0.99)	0.042	-	-
Pre-RT immunotherapy								
No	1 (reference)		1 (reference)		1 (reference)		-	
Yes	0.70 (0.44-1.11)	0.126	0.68 (0.42-1.12)	0.130	1.91 (1.36-2.66)	< 0.001	-	-
Post-RT cytotoxic chemotherapy								
No	1 (reference)		-		1 (reference)		-	
Yes	0.96 (0.74-1.25)	0.761	-	-	1.28 (1.03-1.60)	0.025	-	-
Post-RT targeted therapy								
No	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Yes	0.75 (0.59-0.94)	0.014	0.67 (0.51-0.89)	0.005	0.64 (0.52-0.78)	< 0.001	0.66 (0.52-0.83)	< 0.001
Post-RT immunotherapy								
No	1 (reference)		-		1 (reference)		-	
Yes	0.88 (0.59-1.31)	0.528	-	-	1.25 (0.90-1.74)	0.188	-	-
Systemic regimen change								
No	1 (reference)		-		1 (reference)		1 (reference)	
Yes	0.93 (0.63-1.37)	0.715	-	-	1.52 (1.12-2.08)	0.008	1.39 (0.96-2.02)	0.081
Intrathecal chemotherapy								
No	1 (reference)		-		1 (reference)		-	
Yes	1.50 (0.76-2.98)	0.245	-	-	1.58 (0.87-2.88)	0.135	-	-

ALK, anaplastic lymphoma kinase; BED, biologically effective dose; CI, confidence interval; EGFR, epidermal growth factor receptor; GKS, gamma knife radiosurgery; HR, hazard ratio; NBS-RT, normal brain-sparing radiotherapy; PD-L1, programmed death-ligand 1; ROS1, c-ros oncogene 1; RT, radiotherapy; WBRT, whole brain radiotherapy.

importance of QoL in patient care.

For over half a century, WBRT has been the standard treatment for brain metastases. However, a significant proportion of patients undergoing WBRT develop leukoencephalopathy on long-term follow-up [22,23], often accompanied by cognitive decline. The advent of sophisticated RT techniques has prompted more investigation of localized gross tumor-targeted approaches like SRS as potential alternatives to WBRT for patients with a limited number of small brain metastases. This shift in approach has resulted in a multitude of randomized controlled trials, aimed at investigating various treatment combinations, including WBRT alone, SRS alone, and combined WBRT/SRS [5-12,24-26]. These trials have consistently demonstrated that while survival outcomes with SRS alone and WBRT are not significantly different, cognitive decline is significantly less pronounced with SRS alone and intracranial tumor control is significantly better with WBRT. The latter benefit is commonly attributed to the effective management of presumed micrometastases, which would have otherwise led to intracranial failure.

Patients with multiple metastases have not traditionally been considered candidates for NBS-RT. WBRT was considered appropriate in such circumstances. However, advancements in systemic therapies for NSCLC change the context to highlight the potential benefits of NBS-RT in these patients, and paradoxically challenge the orthodox view that good intracranial control is attainable only with WBRT. It suggests that NBS-RT for multiple metastases combined with effective systemic therapy could be sufficient for intracranial tumor control comparable to WBRT. In this context, we employed NBS-RT, targeting the GTV to spare normal brain tissue, similar to SRS, while incorporating the benefits of multifractionation, as in WBRT, to reduce treatment-related toxicity. Central to this strategy is the focus on gross tumor (like SRS) to reduce the risk of cognitive impairment commonly associated with WBRT, while simultaneously facilitating the multi-fraction treatment of multiple lesions that often pose significant challenges in conventional SRS. The recent use of fractionated SRS for large metastases shares conceptual similarities with our approach [15]. However, it primarily targets larger tumors and is not specifically designed for treating multiple brain metastases.

Table 3. Competing risk regression analysis for leukoencephalopathy

Variable	Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)				
< 60	1 (reference)		1 (reference)	
≥ 60	1.26 (0.94-1.68)	0.118	1.37 (0.92-2.06)	0.126
Sex				
Male	1 (reference)		-	
Female	1.29 (0.87-1.93)	0.208	-	-
Previous GKS				
No	1 (reference)		-	
Yes	0.87 (0.54-1.38)	0.551	-	-
Previous surgery				
No	1 (reference)		1 (reference)	
Yes	0.43 (0.14-1.37)	0.155	0.40 (0.13-1.28)	0.122
No. of parenchymal metastasis				
< 10	1 (reference)		-	
≥ 10	0.87 (0.66-1.15)	0.323	-	-
Max diameter of metastasis (mm)				
< 30	1 (reference)		-	
≥ 30	0.76 (0.48-1.20)	0.235	-	-
Leptomeningeal seeding				
No	1 (reference)		-	
Yes	0.88 (0.57-1.34)	0.54	-	-
Pathology				
Adenocarcinoma	1 (reference)		-	
Others	0.23 (0.03-1.59)	0.136	-	-
EGFR				
Negative	1 (reference)		-	
Positive	1.13 (0.74-1.75)	0.567	-	-
ALK				
Negative	1 (reference)		-	
Positive	0.85 (0.38-1.91)	0.701	-	-
ROS1				
Negative	1 (reference)		-	
Positive	0.77 (0.39-1.52)	0.456	-	-
PD-L1 expression (%)				
< 1	1 (reference)		-	
≥ 1	1.00 (0.74-1.36)	0.989	-	-
Radiotherapy				
NBS-RT	1 (reference)		1 (reference)	
WBRT	3.63 (1.31-10.03)	0.013	3.51 (1.27-9.71)	0.016
BED (Gy)				
≤ 39	1 (reference)		-	
> 39	0.90 (0.68-1.19)	0.461	-	-
Pre-RT cytotoxic chemotherapy				
No	1 (reference)		-	
Yes	0.74 (0.42-1.30)	0.298	-	-
Pre-RT targeted therapy				
No	1 (reference)		-	
Yes	1.41 (0.95-2.10)	0.088	-	-

(Continued to the next page)

Table 3. Continued

Variable	Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Pre-RT immunotherapy				
No	1 (reference)		-	
Yes	0.51 (0.21-1.24)	0.136	-	-
Post-RT cytotoxic chemotherapy				
No	1 (reference)		-	
Yes	0.97 (0.62-1.52)	0.898	-	-
Post-RT targeted therapy				
No	1 (reference)		-	
Yes	1.52 (1.02-2.26)	0.039	-	-
Post-RT immunotherapy				
No	1 (reference)		-	
Yes	0.17 (0.04-0.67)	0.012	-	-
Systemic regimen change				
No	1 (reference)		1 (reference)	
Yes	0.84 (0.20-3.47)	0.812	0.17 (0.04-0.66)	0.011
Intrathecal chemotherapy				
No	1 (reference)		-	
Yes	0.89 (0.47-1.69)	0.715	-	-

ALK, anaplastic lymphoma kinase; BED, biologically effective dose; CI, confidence interval; EGFR, epidermal growth factor receptor; GKS, gamma knife radiosurgery; HR, hazard ratio; NBS-RT, normal brain-sparing radiotherapy; PD-L1, programmed death-ligand 1; ROS1, c-ros oncogene 1; RT, radiotherapy; WBRT, whole brain radiotherapy.

Our approach attained intracranial tumor control and OS comparable to those seen with WBRT and with significantly reduced radiation damage, as manifested by the decreased incidence of leukoencephalopathy. This finding contrasts with previous results suggesting the superiority of WBRT in intracranial control over only treating the gross tumor. We attributed this contrast to the unique patient profiles in our study compared to earlier trials. Our focus on patients with multiple metastatic disease (generally excluded in previous trials) allowed us to irradiate a substantial portion of the brain with NBS-RT. This is unattainable when treating only 1-3 small lesions with SRS; hence, such treatments crucially preclude the potential for widespread BBB disruption possible with our regimen. This led us to hypothesize that systemic therapy might be more effective for intracranial tumor control following such BBB disruption [27]. The subgroup analysis supported this hypothesis, showing that patients not receiving systemic therapy post-RT had a higher incidence of intracranial failure with NBS-RT than WBRT. In contrast, there was no significant difference in intracranial tumor control between NBS-RT and WBRT in patients who received systemic therapy post-RT. Furthermore, patients in our study, treated more recently, frequently received advanced targeted therapies for epidermal growth factor receptor (*EGFR*), *ALK*, and *ROS1* [18,19] mutations and immunotherapies [20,21], representing an improved systemic treatment regimen than those treated in earlier trials [5-12,24-26]. Combined, the use of advanced systemic therapy post-RT in our study likely played a key role in achieving intracranial tumor control with NBS-RT, comparable to WBRT. This finding aligns with prior research showing the benefits of post-RT systemic therapy over standalone systemic therapy [28,29].

A large proportion of patients with brain metastases eventually develop intracranial progression (281 out of 503 in our study). In those who have undergone WBRT, reirradiation options are frequently constrained due to accumulated high doses in the brain parenchyma, which heightens the risk of adverse effects. In contrast, NBS-RT conserves brain regions previously underexposed to radiation, allowing for the delivery of more effective doses for tumor control. This is illustrated in a representative case (S14 Fig.) where a patient initially treated with NBS-RT experienced progression in an area not previously irradiated. The patient subsequently received another round of NBS-RT at a full dose, effectively targeting the progressed area.

This study's retrospective design presents some limitations that caution against overestimating its results. Firstly, its retrospective nature resulted in an imbalance in patient numbers and characteristics between the WBRT and NBS-RT groups. Although PSM was used to address these disparities,

it led to a smaller patient cohort and diminished statistical reliability. Our study indicated no significant differences in intracranial control post-PSM, but a larger cohort might reveal significant differences. In this study, MRI-detected leukoencephalopathy was used as an objective surrogate endpoint. However, it is important to recognize that radiologically confirmed radiation-induced leukoencephalopathy does not always correlate with immediate clinical symptoms such as cognitive decline. In our cohort, only 25.3% of patients with leukoencephalopathy presented with associated symptoms (S15 Table). Despite this, long-term studies have indicated that even asymptomatic leukoencephalopathy observed on imaging can be associated with delayed cognitive deterioration and diminished QoL [30]. Therefore, imaging findings can be considered a reasonable surrogate for clinically meaningful leukoencephalopathy in the absence of immediate symptoms. A further challenge lies in distinguishing cognitive decline caused by leukoencephalopathy from that due to brain metastasis progression, particularly in patients receiving WBRT. Many patients eventually experience intracranial progression, complicating the accurate assessment of neurological symptoms related specifically to leukoencephalopathy. Due to the retrospective nature of this study, precise evaluation of symptomatology was not feasible. As such, we were compelled to rely on imaging-based surrogates, which represents a key limitation of this study. Lastly, the process of delineating all metastases for NBS-RT can be labor-intensive with numerous metastases, emphasizing the need for emerging artificial intelligence models for precise GTV contouring.

In this retrospective cohort study, NBS-RT for NSCLC with multiple brain metastases, when combined with post-RT systemic therapy, showed outcomes comparable to WBRT, with a lower leukoencephalopathy risk. However, given the study's limitations, these findings are preliminary. Prospective studies are needed to confirm the viability of NBS-RT for multiple brain metastases from NSCLC, especially when used alongside systemic therapy, in terms of patient cognitive function and QoL.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Institutional Review Board of Severance Hospital (approval number: 4-2023-0309). Due to the retrospective nature of the research, the requirement for informed consent was waived. Furthermore, this study adhered to the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Author Contributions

Conceived and designed the analysis: Park S, Lee CG.
Collected the data: Park S, Cho J, Kim KH, Yoon HI, Lee CG.
Contributed data or analysis tools: Park S, Kim KH.
Performed the analysis: Park S.
Wrote the paper: Park S, Cho J, Kim KH, Yoon HI, Lee CG.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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