

Multicenter Prospective Randomized Controlled Phase II Clinical Study of Sequential or Simultaneous Whole-Brain Radiotherapy for a Limited Number of Brain Metastases from Non-Small Cell Lung Cancer

Lei Yu, Yu He, Wenxia Ren and Daiyuan Ma*

Department of Oncology, Affiliated Hospital of North Sichuan Medical college, No.1 Maoyuan South Road, Shunqing District, Nanchong, Sichuan, 637000, China

*Corresponding Author: Daiyuan Ma, Department of Oncology, Affiliated Hospital of North Sichuan Medical college, No.1 Maoyuan South Road, Shunqing District, Nanchong, Sichuan, 637000, China, Tel: 18781733275, E-mail: mdylx@163.com

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Abstract

Objective: This study aimed to compare the neurocognitive damage and treatment efficacy of whole-brain radiotherapy (WBRT) with sequential integrated boost (SEB) or simultaneous integrated boost (SIB) in patients with non-small cell lung cancer (NSCLC) brain metastases.

Methods: 69 NSCLC patients with brain metastases were randomly divided into two groups: group A—30 cases who received WBRT(30Gy/10Fx) + SEB (12Gy/3Fx); group B-39 cases who received WBRT(30Gy/10Fx) + SIB (40Gy/10Fx). For all patients, a mini-mental state examination (MMSE) was performed before radiotherapy, at the end of radiotherapy, and 1 to 6 months after radiotherapy, and the differences in neurocognitive function between the two groups were compared. To assess the size of intracranial lesions and compare the objective remission rate (ORR), local control rate (DCR), and 6-month progression-free survival (PFS) rate of brain metastases in the two groups, enhanced MRI was performed on all patients at 1 and 6 months following radiotherapy.

Results: Both groups showed a statistically significant ($P < 0.05$) and progressive decrease in MMSE scores after radiotherapy. For group A, the MMSE scores for 1, 3, and 6 months after radiotherapy were 23.21 ± 3.1 , 22.65 ± 3.77 , and 22.41 ± 3.43 . Group B were 22.38 ± 4.62 , 21.28 ± 4.35 , and 21.19 ± 4.13 . There was a statistically significant difference between the MMSE scores of the two groups 1 month after radiotherapy compared with 3 months after radiotherapy ($P < 0.05$). In the subgroup of patients with ≤ 3 brain metastasis, the MMSE scores of groups A and B were 23.710 ± 2.998 and 20.890 ± 4.263 in 3 months

after radiotherapy, and the difference was statistically significant compared with baseline ($P < 0.05$). The treatment efficacy was assessed at 1 and 6 months after radiotherapy, and there was no significant difference in the ORR, DCR, and 6-month PFS rates between the two groups.

Conclusion: Both WBRT+SEB and WBRT+SIB negatively affect neurocognitive function in NSCLC patients with brain metastases 1 to 6 months after radiotherapy, and the most severe effects were observed 3 months after radiotherapy. In patients with ≤ 3 brain metastases, WBRT+SEB was less detrimental to neurocognitive function than WBRT+SIB. The treatment efficacy of the two approaches did not significantly differ.

Keywords: Brain metastases; Non-small cell lung cancer; Neurocognitive function; Simultaneous boost; Sequential boost; Whole-brain radiotherapy

Introduction

Lung cancer is the deadliest cancer in the world [1], with non-small cell lung cancer (NSCLC) accounting for the majority. NSCLC frequently metastasizes to the central nervous system, with 10% of patients present with brain metastases (BM) at the time of initial diagnosis and $>25\%$ of patients having BM during treatment [2]. Patients with BM often have a poor prognosis, and the survival of patients with symptomatic BMs is $\sim 1\text{--}3$ months if left untreated [3]. Currently, the treatment of BM mainly includes radiotherapy, surgery, chemotherapy, targeted therapy, immunotherapy, and palliative therapy [4]. Since surgery is mainly applicable to patients with a single BM lesion [5], and chemotherapy drugs have limited efficacy due to penetration of the blood-brain barrier [6], radiotherapy remains the primary treatment option for patients with BM. However, the neurocognitive decline caused by radiation brain injury also seriously affects the quality of survival of patients. Whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) are currently the main treatments for unresectable brain metastases (BM). WBRT has a better local control rate but has a detrimental effect on patients' neurocognitive function [7]. Even though SRS has less impact on neurocognitive function than WBRT, it also has less intracranial tumor control rate [8]. Therefore, combining the two may bring double benefits. At present, there are two primary boost schemes: sequential integrated boost (SEB), in which the boost dose is delivered after WBRT, and simultaneous integrated boost (SIB), in which the boost dose is delivered within a fraction but varied throughout the course the treat-

ment [9-11]. Today, there is a growing concern about the quality of patient survival. A previous study [12] showed that compared with WBRT+SIB, WBRT+SEB showed improved survival for NSCLC patients with BM, especially in cohorts of male patients, patients <60 years old, and patients with oligometastatic disease. Both treatments led to a marked reduction of neurocognitive function 3 months after radiotherapy compared with baseline. However, this effect was less pronounced in patients receiving WBRT+SEB. The results from this study are limited due to the small sample size and retrospective nature of the study from a single center. To address these limitations, we performed a multicenter, prospective, randomized controlled study to compare neurocognitive function and therapeutic efficacy of WBRT combined with SEB or SIB in NSCLC patients with BM.

Different criteria have been proposed to evaluate BM prognosis. In 1997, Gaspar proposed a recursive partitioning analysis (RPA) to evaluate the prognosis of patients with BM according to the patient's Karnofsky Performance Status (KPS) score, age, primary tumor control or not, and whether there is metastasis outside the central nervous system [13]. Patients are categorized into three grades based on RPA, and the median survival time decreases as the RPA grade increases [13]. In 2004, Lorenzoni et al. [14] proposed a simplified version of the basic score for brain metastases (BS-BM) for BM patients treated with stereotactic radiosurgery (SRS) (Table 1). More recently, Sperduto et al. [5] put forward a more detailed grading prognostic assessment (GPA) index. Patients with $\text{GPA} > 4$ have the best prognosis (Table 2).

Table 1: Basic score for brain metastases

Program	Scores	Scores
	0	1
KPS	50~70	80~100
Primary lesion control	no	yes
Extracranial metastasis	yes	no

Table 2: Grading prognostic assessment

Program	Scores	Scores	Scores
	0	0.5	1
Age (y)	>60	50~59	<50
KPS	<70	70~80	90~100
Number of lesions	>3	2~3	1
Extracranial metastasis	yes	-	no

Methods

Clinical Information

This retrospective study was approved by the Review Board of the Affiliated Hospital of North Sichuan Medical College (No. 2018ER(R)054). From October 2018 to December 2020, 69 patients with symptomatic NSCLC with BM admitted to the Affiliated Hospital of North Sichuan Medical College, Mianyang Central Hospital, Guangyuan Central Hospital, Suining Central Hospital, Dazhou Central Hospital, and Nanchong Central Hospital were enrolled into the study. Inclusion criteria were as follows: (1) the patient's condition was stable and could complete radiotherapy; (2) no contraindication to radiotherapy and ability and willingness to sign the radiotherapy consent form; (4) <10 intracranial metastases were confirmed by imaging; (5) age 18–80 years, ECOG score standard 0-2 points/KPS≥70 points, estimated survival time>1 month; (6) the maximum diameter of intracranial lesions≤5cm; (7) extracranial lesions received systematic treatment as planned; (8) ability to cooperate in MMSE scoring.

Exclusion criteria were as follows: (1) history of other malignant tumors except for NSCLC BM; (2) pregnancy or lactation; (3) participation in other clinical trials; (4)

serious complications, including severe heart rate arrhythmia, severe cerebrovascular disease, and psychosis; (5) no regular follow-up conditions, poor compliance; (6) inability to receive MRI or CT examination; (7) the dose requirement of radiotherapy prescription could not be met.

Treatment plan

A total of 69 patients were randomly divided into group A (WBRT+SEB) or group B (WBRT+SIB). Before radiotherapy, skull-enhanced CT was used for localization. The target area was delineated after the localization image was fused with the skull-enhanced MRI image through the MIM Software Beijing Co., Ltd. The clinical target volume (CTV) was the whole brain, and the planning target volume (PTV) was defined as a 5 mm margin to the CTV; the gross tumor volume (GTV) was the metastasis, and P-GTV was defined as a 2 mm margin to the GTV. The prescription dose of WBRT in group A was 30Gy/10Fx(5 fractions per week), followed by repositioning; for metastatic focus, the dose was 12Gy/3Fx (Figure 1-2). The prescription dose of WBRT in group B was 30Gy/10Fx (5 fractions per week), and the corresponding dose for metastatic focus was 40-Gy/10Fx (Figure 3). All treatments were delivered using intensity-modulated RT (IMRT) by 6MV X-ray medical linear accelerators (Elekta Synergy).

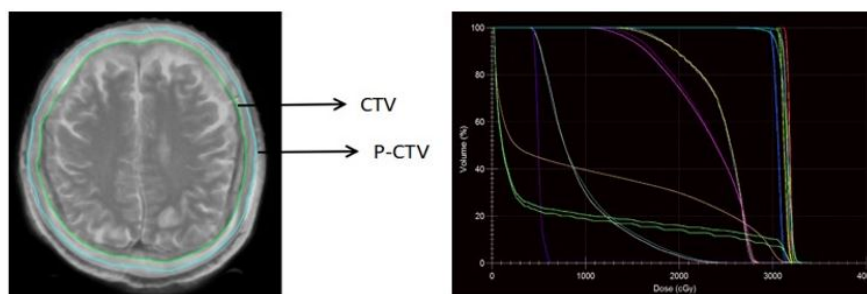


Figure 1: Target area map (left) and DVH diagram of group A at the first stage

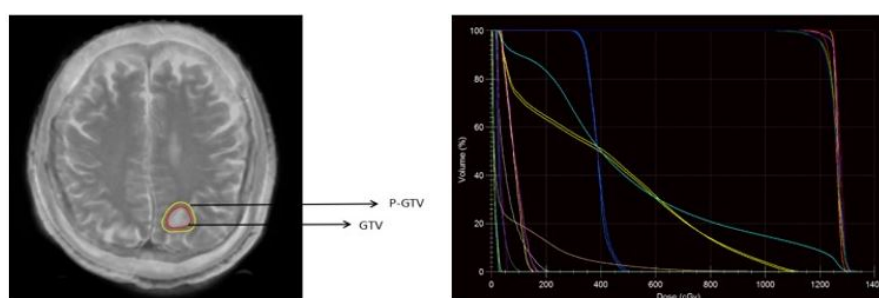


Figure 2: Target area diagram (left) and DVH diagram (diagram) of group A at the first stage

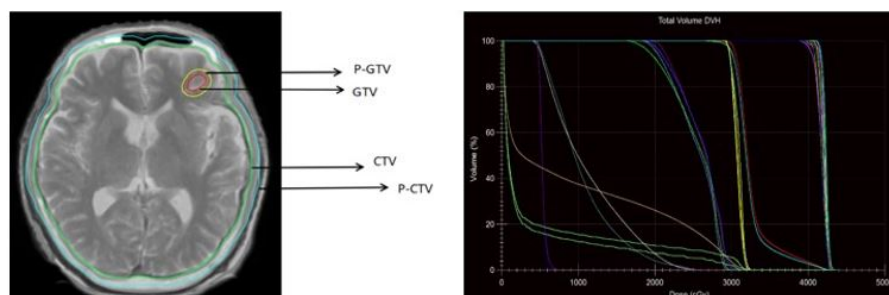


Figure 3: Target area map (left) and DVH diagram (right) of group B

Observations

We performed MMSE scoring before radiotherapy, at the end of radiotherapy, and 1, 3, and 6 months after radiotherapy to evaluate patients' neurocognitive function. In addition, the patients were subjected to brain-enhanced MRI 1 and 6 months after radiotherapy, using WHO standards. CR: complete disappearance of lesions can be seen for at least 1 month; PR: the product of the two paths of tumor decreased by more than 50%, and other lesions did not increase significantly, at least 1 month; SD: tumor two-diameter product shrinkage of less than 50% or enlargement of less than 25%, at least 1 month; PD: one or more lesions with a two-path product increase of more than 25% or new

lesions. The overall response rate (ORR) was defined as $(PR+CR)/\text{total number of cases} \times 100\%$. The disease control rate (DCR) was defined as $(SD+CR+PR)/\text{total number of cases} \times 100\%$. The progression-free survival (PFS) rate of intracranial lesions in June was defined as $(SD+CR+PR)/\text{total number of cases} \times 100\%$.

Statistical analysis

All statistical analyses were performed using the SPSS 22.0 software. Normally distributed variables were described as mean and standard deviation. Independent samples were used to test the differences between groups, and paired samples were used to test the differences within groups. Other quantities were compared by either chi-

square (χ^2) or Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics and manifestations

A total of 72 eligible cases were initially included in this study. Three patients who discontinued radiotherapy were excluded, and 69 cases were finally included in the study. Tables 3 and 4 summarize the clinical characteristics of the two groups of patients.

Differences between the two groups of patients at each treatment stage

There was no significant difference in MMSE scores between the two groups at each treatment stage ($P > 0.05$) (Table 5).

Changes in the neurocognitive function of patients in group A (WBRT+SEB) at different treatment stages

The MMSE scores at 1, 3, and 6 months after radiotherapy were significantly lower than those before radiotherapy ($P < 0.05$). There was no significant difference between the MMSE score at the end of radiotherapy and before radiotherapy ($P > 0.05$). There was a significant difference in MMSE scores between 3 months after radiotherapy and 1 month after radiotherapy ($P < 0.05$). There was no significant difference in MMSE score between 6 months after radiotherapy and 3 months after radiotherapy ($P > 0.05$). It shows that in the SEB group, the most substantial impairment of the neurocognitive function was observed 3 months after radiotherapy and that this impairment improved 6 months after radiotherapy (Table 6).

Changes in the neurocognitive function of patients in group B (WBRT+SIB) at different treatment stages

The MMSE scores at 1, 3, and 6 months after radiotherapy were significantly lower than those before radiotherapy ($P < 0.05$). There was no significant difference between the MMSE score at the end of radiotherapy and before radiotherapy ($P > 0.05$). There was a significant difference in

MMSE scores between 3 and 1 months after radiotherapy ($P < 0.05$). There was no significant difference in MMSE score between 6 and 3 months after radiotherapy ($P > 0.05$). It shows that in the SIB group, the neurocognitive function deterioration is the most pronounced at 3 months after radiotherapy and alleviates 6 months after radiotherapy (Table 7).

Changes of neurocognitive function in different treatment stages of two treatment methods in each subgroup

We found that age, gender, EGFR/ALK/ROS1 driver gene mutation, pathological type of breast cancer, and KPS score had no effect on MMSE scores between the two methods at each treatment stage ($P > 0.05$) (Tables 8, 9, 10, 11, 12).

There was no significant difference in MMSE scores among patients with ≥ 3 intracranial metastases at each treatment stage ($P > 0.05$); in patients with ≤ 3 intracranial metastases, there was a statistically significant difference in MMSE scores at the end of radiotherapy and 3 months after radiotherapy ($P < 0.05$) (Table 13). These data suggest that in patients with ≤ 3 intracranial metastases, the neurocognitive damage caused by the SEB regimen at the end of radiotherapy and 3 months after radiotherapy was lower than that caused by the SIB regimen.

DCR and ORR

The DCR of group A was 96.00%, while that of group B was 94.30%, with no significant difference between groups ($P > 0.05$) (Table 14). The ORRs of groups A and B were 84.00% and 80.00%, respectively, also without significant difference ($P > 0.05$) (Table 14). These findings indicate no difference in DCR and ORR between the two treatment regimens.

6-month PFS

The 6-month PFS rates of intracranial metastases in the two groups were 50.0% and 58.6%, respectively ($P > 0.05$). These data indicate no significant difference between the two regimens regarding treatment efficiency. (Table 15).

Table 3: Analysis of patients' clinical characteristics

		Group A	Group B	P
Age (y)	<60	16	22	0.799
	≥60	14	17	
Gender	Male	18	24	0.897
	Female	12	15	
Pathology	Non-adenocarcinoma	8	8	0.548
	Adenocarcinoma	22	31	
Number of lesions	≤3	15	23	0.458
	>3	15	16	
Gene mutation	Yes	12	17	0.765
	No	18	22	
KPS	<80	8	8	0.548
	≥80	22	31	
RPA	Level I	6	4	0.254
	Level II	24	35	

Table 4: BS-BM and GPA

	Group A (n=30)	Group B (n=39)	Z	P
BS-BM	2.00(1.00,3.00)	1.00(1.00,2.00)	-1.446	0.148
GPA	1.50(0.88,2.13)	1.50(1.00,2.00)	-0.260	0.795

Table 5: Difference analysis of two groups of patients at the same treatment stage

	Group A (n=30)	Group B (n=39)	t	P
Before radiotherapy	24.33±2.96	23.74±3.67	0.719	0.475
At the end of radiotherapy	24.33±2.99	23.67±3.73	0.801	0.426
1 month after radiotherapy	23.21±3.1	22.38±4.62	0.827	0.411
3 months after radiotherapy	22.65±3.77	21.28±4.35	1.299	0.199
6 months after radiotherapy	22.41±3.43	21.19±4.13	1.098	0.278

Table 6: Cognitive Function Differences of Patients in Group A at Each Treatment Stage

	Baseline level	Different treatment stages	P
Before radiotherapy - 1 month after radiotherapy	24.33±2.96	24.33±2.99	1.000
Before radiotherapy - 3 months after radiotherapy	24.33±2.96	23.21±3.1	0.002
Before radiotherapy - 6 months after radiotherapy	24.33±2.96	22.65±3.77	0.000
1 month after radiotherapy - 3 months after radiotherapy	24.33±2.96	22.41±3.43	0.003
3 months after radiotherapy - 6 months after radiotherapy	23.21±3.1	22.65±3.77	0.032
Before radiotherapy - 1 month after radiotherapy	22.65±3.77	22.41±3.43	1.000

Table 7: Cognitive Function Differences of Patients in Group B at Each Treatment Stage

	Baseline level	Different treatment stages	P
Before radiotherapy - 1 month after radiotherapy	23.74±3.67	23.67±3.73	0.412
Before radiotherapy - 3 months after radiotherapy	23.74±3.67	22.38±4.62	0.000
Before radiotherapy - 6 months after radiotherapy	23.74±3.67	21.28±4.35	0.000
1 month after radiotherapy - 3 months after radiotherapy	23.74±3.67	21.19±4.13	0.000
3 months after radiotherapy - 6 months after radiotherapy	22.38±4.62	21.28±4.35	0.000
Before radiotherapy - 1 month after radiotherapy	21.28±4.35	21.19±4.13	0.478

Table 8: Analysis of age subgroups

Age<60	Groups	Number	Average	standard deviation	t	P
Before radiotherapy	Group A	16	25.13	2.391	1.248	0.22
	Group B	22	23.77	3.816		
At the end of radiotherapy	Group A	16	25.31	2.522	1.522	0.137
	Group B	22	23.64	3.836		
1 month after radiotherapy	Group A	15	24.27	2.631	1.657	0.107
	Group B	21	22	4.796		
3 months after radiotherapy	Group A	15	24	2.582	1.617	0.115
	Group B	20	22.05	4.293		
6 months after radiotherapy	Group A	12	23.83	3.129	1.605	0.121
	Group B	15	21.4	4.437		
Age≥60						
Before radiotherapy	Group A	14	23.43	3.368	-0.22	0.827
	Group B	17	23.71	3.584		
At the end of radiotherapy	Group A	14	23.21	3.167	-0.392	0.698
	Group B	17	23.71	3.704		

1 month after radiotherapy	Group A	13	22	3.24	-0.59	0.56
	Group B	16	22.88	4.47		
3 months after radiotherapy	Group A	11	20.73	3.977	-0.404	0.689
	Group B	16	21.38	4.161		
6 months after radiotherapy	Group A	10	20.7	3.093	-0.136	0.893
	Group B	11	20.91	3.859		

Table 9: Gender subgroup analysis

Male	Groups	Number	Average	Standard deviation	t	P
Before radiotherapy	Group A	18	25.61	1.883	1.323	0.193
	Group B	24	24.46	3.31		
At the end of radiotherapy	Group A	18	25.56	1.756	1.211	0.233
	Group B	24	24.5	3.362		
1 month after radiotherapy	Group A	16	24.56	2.337	0.981	0.333
	Group B	22	23.45	4.044		
3 months after radiotherapy	Group A	16	24	2.582	1.617	0.115
	Group B	22	22.05	4.293		
6 months after radiotherapy	Group A	12	23.25	2.958	1.038	0.31
	Group B	14	21.79	4.042		
Female						
Before radiotherapy	Group A	12	22.42	3.315	-0.127	0.9
	Group B	15	22.6	4.032		
At the end of radiotherapy	Group A	12	22.5	3.555	0.113	0.911
	Group B	15	22.33	4.012		
1 month after radiotherapy	Group A	12	21.42	3.147	0.367	0.715
	Group B	15	20.8	5.074		
3 months after radiotherapy	Group A	10	20.5	4.478	0.236	0.815
	Group B	14	20.07	4.305		
6 months after radiotherapy	Group A	10	21.4	3.836	0.513	0.613
	Group B	12	20.5	4.296		

Table 10: Gene mutation subgroup analysis

Gene mutation	Groups	Number	Average	Standard deviation	t	P
Before radiotherapy	Group A	18	24.500	2.956	0.701	0.487
	Group B	22	23.770	3.491		
At the end of radiotherapy	Group A	18	24.390	2.893	0.680	0.501

	Group B	22	23.680	3.551		
1 month after radiotherapy	Group A	16	22.750	3.000	0.079	0.937
	Group B	20	22.650	4.271		
3 months after radiotherapy	Group A	15	21.930	3.751	0.842	0.406
	Group B	20	20.800	4.073		
6 months after radiotherapy	Group A	12	21.580	3.528	0.417	0.681
	Group B	13	21.000	3.464		
No gene mutation						
Before radiotherapy	Group A	12	24.080	3.088	0.274	0.786
	Group B	17	23.710	3.996		
At the end of radiotherapy	Group A	12	24.250	3.251	0.426	0.673
	Group B	17	23.650	4.061		
1 month after radiotherapy	Group A	12	23.830	3.243	1.060	0.299
	Group B	17	22.060	5.105		
3 months after radiotherapy	Group A	11	23.640	3.749	1.030	0.313
	Group B	16	21.880	4.731		
6 months after radiotherapy	Group A	10	23.400	3.204	1.136	0.269
	Group B	13	21.380	4.840		

Table 11: Analysis of subgroups of different pathological types

Non-adenocarcinoma	Groups	Number	Average	Standard deviation	t	P
Before radiotherapy	Group A	8	25.500	2.268	-0.744	0.469
	Group B	8	24.380	3.623		
At the end of radiotherapy	Group A	8	25.250	2.252	-0.567	0.580
	Group B	8	24.380	3.739		
1 month after radiotherapy	Group A	6	23.000	1.789	-0.370	0.718
	Group B	8	22.250	4.683		
3 months after radiotherapy	Group A	6	21.830	2.639	-0.334	0.744
	Group B	8	20.630	4.534		
6 months after radiotherapy	Group A	4	22.250	2.872	-0.827	0.440
	Group B	4	19.750	4.924		
Adenocarcinoma						
Before radiotherapy	Group A	22	23.910	3.115	0.338	0.737
	Group B	31	23.580	3.722		
At the end of radiotherapy	Group A	22	24.000	3.192	0.523	0.603
	Group B	31	23.480	3.767		

1 month after radiotherapy	Group A	22	23.270	3.397	0.727	0.471
	Group B	29	22.410	4.679		
3 months after radiotherapy	Group A	20	22.900	4.077	1.155	0.254
	Group B	28	21.460	4.359		
6 months after radiotherapy	Group A	18	22.440	3.617	0.807	0.425
	Group B	22	21.450	4.044		

Table 12: Analysis of different KPS scoring subgroups

KPS <80	Groups	Number	Average	Standard deviation	t	P
Before radiotherapy	Group A	8	22.380	3.462	-0.388	0.704
	Group B	8	23.130	4.224		
At the end of radiotherapy	Group A	8	22.130	3.044	-0.620	0.545
	Group B	8	23.250	4.132		
1 month after radiotherapy	Group A	7	21.000	3.109	-0.228	0.824
	Group B	6	21.500	4.764		
3 months after radiotherapy	Group A	6	19.830	3.545	0.367	0.721
	Group B	6	19.000	4.290		
6 months after radiotherapy	Group A	5	20.400	3.362	0.164	0.824
	Group B	5	20.000	4.301		
KPS ≥80						
Before radiotherapy	Group A	22	25.050	2.478	1.294	0.202
	Group B	31	23.900	3.572		
At the end of radiotherapy	Group A	22	25.140	2.587	1.491	0.142
	Group B	31	23.770	3.685		
1 month after radiotherapy	Group A	21	23.950	2.783	1.240	0.221
	Group B	31	22.550	4.646		
3 months after radiotherapy	Group A	20	23.500	3.487	1.535	0.310
	Group B	30	21.730	4.283		
6 months after radiotherapy	Group A	17	23.000	3.317	1.230	0.227
	Group B	21	21.480	4.143		

Table 13: Analysis of subgroups with different number of lesions

Number of lesions ≤3	Groups	Number	Average	Standard deviation	t	P
Before radiotherapy	Group A	15	25.270	2.219	1.965	0.056
	Group B	23	23.530	3.674		
At the end of radiotherapy	Group A	15	25.400	2.414	2.094	0.043

	Group B	23	23.470	3.730		
1 month after radiotherapy	Group A	15	24.000	2.449	1.604	0.187
	Group B	21	22.250	4.703		
3 months after radiotherapy	Group A	14	23.710	2.998	2.212	0.033
	Group B	21	20.890	4.263		
6 months after radiotherapy	Group A	12	23.170	3.186	1.764	0.088
	Group B	19	20.810	3.945		
Number of lesions>3						
Before radiotherapy	Group A	15	23.400	3.376	-0.702	0.490
	Group B	16	24.440	3.779		
At the end of radiotherapy	Group A	15	23.270	3.195	-0.732	0.472
	Group B	16	24.330	3.873		
1 month after radiotherapy	Group A	13	22.310	3.591	-0.270	0.790
	Group B	16	22.780	4.577		
3 months after radiotherapy	Group A	12	21.420	4.316	-0.595	0.560
	Group B	15	22.630	4.658		
6 months after radiotherapy	Group A	10	21.500	3.659	-0.578	0.573
	Group B	12	22.800	4.970		

Table 14: DCR and ORR

	Group A	Group B	χ^2	P
DCR	96.00%	84.00%	0.09	0.764
ORR	84.00%	80.00%	0.156	0.693

Table 15: 6-month PFS rates

	CR	PR	SD	PD	6-month PFS rates	χ^2	P
Group A	2	7	2	11	50.0%	0.375	0.371
Group B	1	13	3	12	58.6%		

Discussion

In this study, 69 patients with NSCLC BM were analyzed to compare the advantages and disadvantages of WBRT+SEB and WBRT+SIB. Our primary goal was to evaluate the effect of these therapeutic regimens on cognitive function and BM survival. Compared with baseline, the MMSE score was significantly reduced in both groups at 1, 3, and 6 months after radiotherapy ($P<0.05$), indicating that

the neurocognitive function decreased in both groups during 6 months' post-radiotherapy. However, the decline rate of the WBRT+SEB group was much less pronounced. In patients with ≤ 3 intracranial metastases, we observed that the WBRT+SIB group had a significantly lower MMSE score than the WBRT+SEB group ($P<0.05$), indicating that the SEB regimen inflicted less damage to the neurocognitive function 3 months after radiotherapy. We observed no statistically significant difference in MMSE scores between 6

and 3 months after radiotherapy. Therefore, we believe that in patients with neurocognitive impairment, it is most pronounced 3 months after radiotherapy and may recover in 1 year or more after radiotherapy. Finally, there was no difference between ORR, DCR, and 6-month PFS rates between the groups, suggesting that BM progression is not particularly vulnerable to sequential or concurrent radiotherapy regimens.

Our results are consistent with previously published research. Luo et al. [15] found no significant difference in the treatment effect, adverse reactions, and survival rate between WBRT+SEB and WBRT+SIB groups across 80 patients with NSCLC BM. However, Li [16] demonstrated better survival and treatment efficacy for the WBRT+SIB regimen compared with the WBRT+SEB treatment in 65 patients with NSCLC BM. There was no statistical difference between the two treatment methods in the incidence of acute and late radiation injury.

WBRT is closely related to neurocognitive function impairment because radiation damage to the hippocampus is associated with declining learning ability and memory [17,18]. Therefore, when BM patients are treated with

WBRT, targeting the hippocampus should be avoided to protect cognitive function. With the progress of radiotherapy technology, implementing hippocampal protective WBRT is feasible. In this study, the patients were not treated with hippocampal protective WBRT, which may have a certain impact on the assessment of neurocognitive impairment.

This study has several limitations, including a short observation time and a small sample size. Moreover, there may be a small discrepancy in MMSE scoring among participating centers. This study did not use hippocampal protection. We plan to employ hippocampal protective WBRT in future studies to further compare the advantages and disadvantages of the two treatment methods.

In conclusion, both WBRT+SEB and WBRT+SIB treatment regimens negatively affected neurocognitive function in NSCLC patients with BM. In patients with ≤ 3 BMs, WBRT+SEB had less effect on neurocognitive function than WBRT+SIB. There was no difference in treatment efficacy between the two approaches. More research is needed to identify the optimal radiotherapy treatment regimen for patients with BM.

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