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A retrospective study of radiotherapy combined with immunotherapy for patients with baseline brain metastases from non-small cell lung cancer

Ruoyu Lu[1,4], Ziqi Wang[1,4], Wentao Tian[1], Wen Shi[1], Xianjing Chu[1]✉ & Rongrong Zhou[1,2,3]✉

This multi-center retrospective study aimed to evaluate the safety and efficacy of first-line immunotherapy in non-small-cell lung cancer (NSCLC) patients with brain metastases (BM). The study included 138 patients treated with immune checkpoint inhibitors (ICIs), either alone or in combination with brain radiotherapy (BRT), from 2020 to October 2023. Intracranial overall response rate (iORR), overall response rate (ORR), progression-free survival (PFS), intracranial progression-free survival (iPFS), overall survival (OS) and treatment-related toxicities were evaluated. Although patients receiving ICIs plus BRT showed a trend toward longer OS compared with ICI alone, the difference was not statistically significant (P = 0.201). Among 82 patients with available data, the iORR was 49.1% (35–63) in the ICIs alone group, and 75.9% (56–90) in the ICIs + BRT group. Notably, in patients requiring corticosteroids or mannitol, combination therapy was associated with a better prognosis (P = 0.05). We found that the iORR of patients treated with ICIs + BRT was improved and did not increase the incidence of serious adverse events (SAEs). Besides, the combination of ICIs and BRT improved the survival rate of subgroups of patients using corticosteroids.

Keywords Non-small cell lung cancer, Brain metastases, Immunotherapy, Radiotherapy

Approximately 20% of cancer patients are ultimately projected to develop brain metastases (BM)[1], with non-small cell lung cancer (NSCLC) constituting nearly half of these cases[1]. At the time of diagnosis, 25–30% of patients with advanced NSCLC present with BM, with this proportion escalating to 50% as the disease progresses[1–3]. Specific molecular subtypes of primary pulmonary neoplasms, such as EGFR mutations or ALK gene rearrangements, enables the use of targeted inhibitors[4], which demonstrate improved effectiveness due to their superior permeability and activity in the brain[5]. For NSCLC patients lacking targetable genetic alterations, the current first-line systemic therapy involves immune checkpoint inhibitors (ICIs) alone or combined with chemotherapy (CT)[6,7].

Multiple clinical trials have paved the way for the approval of ICI monotherapy or combination regimens for metastatic NSCLC[8–10]. Previous studies have assessed the safety and efficacy of systemic therapies in patients with asymptomatic BM, whether treated or untreated, within the context of metastatic NSCLC[11–13]. The safety profiles of ICI monotherapy and ICI combinations in patients with BM have been documented[14–22]. The Atezo-Brain study demonstrated the safety and efficacy of ICI combined with CT in the BM subgroup[14]. Likewise, Checkmate-227 evaluated the safety and efficacy of nivolumab plus ipilimumab and CT[19]. Nonetheless, the response rate of ICIs ranges from approximately 20% to 40%.

Considerable evidence supports the combination of radiotherapy and ICIs to improve the efficacy of treatment. Radiotherapy facilitates tumor antigen release and fosters T cell-mediated immune responses, effectively transforming irradiated tumors into in situ vaccines[23,24]. Furthermore, owing to the radio-responsiveness of endothelial cells and surrounding oligodendrocytes, radiotherapy can augment the permeability of the blood–

[1]Department of Oncology, Xiangya Hospital, Central South University, Changsha, China. [2]Xiangya Lung Cancer Center, Xiangya Hospital, Central South University, Changsha 410008, China. [3]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, People's Republic of China. [4]Ruoyu Lu and Ziqi Wang contributed equally to this work. ✉email: 2204160208@csu.edu.cn; zhourr@csu.edu.cn

brain barrier (BBB), thereby facilitating ICI penetration[25]. Radiotherapy also modulates the immune-suppressive tumor stromal microenvironment, thereby augmenting the effects of immunotherapy[26]. Simultaneously, ICIs possess the potential to amplify the radiation-induced abscopal effect, counteracting the immunosuppressive effects of radiotherapy[27]. Emerging preclinical and clinical evidence points to a synergistic effect between radiotherapy and ICIs in improving disease control and survival[28–32]. Retrospective studies by Yu et al. and Takehiro et al. have demonstrated that combining ICI with brain radiotherapy (BRT), either concurrently or sequentially, serves as a predictive factor for improved intracranial local progression-free survival (PFS), intracranial distant PFS, and overall survival (OS)[33,34]. However, both studies included patients who had progressed after developing resistance.

As the utilization of ICIs in NSCLC continues to expand, evaluating the safety and efficacy of combining ICIs with radiotherapy remains of paramount importance. However, limited data exist regarding the combination of BRT and ICIs in NSCLC patients with BM. Therefore, our study specifically included NSCLC patients with an initial diagnosis of BMs to exclude confounding factors related to disease progression following treatment and aims to assess the safety and effectiveness of first-line ICIs in NSCLC patients with BM, providing real-world insights into diagnosis and treatment strategies.

Result

Table 1delineates the baseline characteristics of the 138 patients enrolled in this study. Baseline clinical data reveal median age of 61.6 and 61.1 years for patients in the respective cohorts, with ranges of 54.2–69.0 and 52.4–69.8 years. The majority of patients were male (n = 121, 87.7%). Histopathologically, 87 patients were diagnosed with adenocarcinomas, 41 with squamous cell carcinomas, 2 with adenosquamous carcinomas, 5 with large cell neuroendocrine carcinomas, and 3 with NSCLC- not otherwise specified (NOS). None of the patients harbored targetable mutations in EGFR, ALK, or ROS1. In both cohorts, 52 patients exhibited PD-L1 expression levels exceeding 1% (37.7%), 132 had Eastern Cooperative Oncology Group (ECOG) performance status scores of 0 to 1 (95.7%), 107 had multiple BMs (77.5%), 133 received PD-1 ICIs (96.4%), and 133 underwent combination CT (96.4%). The diameter of brain lesions varied from 4 to 60 mm. Sixty patients presented with symptomatic BMs. 99 patients (71.7%) did not receive BRT, whereas 39 (28.3%) received ICIs combined with radiotherapy, including stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT). 49 patients (44.4%) in the ICIs group and 26 patients (66.7%) in the ICIs plus BRT group received corticosteroid or mannitol treatment. Corticosteroid types included dexamethasone, prednisone, and methylprednisolone sodium succinate, administered over 2 to 4 days. Both peak doses (the highest daily dose) and cumulative doses (the total of all daily doses) were calculated as prednisolone equivalents. Peak doses ranged from 0.5 to 2 mg/kg, and the maximum cumulative dose reached 1310 mg. Building upon recent findings indicating that the neutrophil-to-eosinophil ratio (NER) and other hematological parameters hold significant predictive value in ICIs for NSCLC, we collected and compared these indicators[35]. As presented in Table 1, no meaningful differences were observed in the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), or lymphocyte-to-monocyte ratio (LMR) between patients receiving ICIs in combination with BRT and those treated with ICI monotherapy. The Kaplan–Meier (KM) curve for OS is depicted in Fig. 1. Although some evidence suggests that patients receiving ICIs plus BRT exhibited improved OS compared to those treated with ICIs alone, the difference between the two groups was not significant (HR = 0.652, 95%CI: 0.339–1.258, P = 0.201).

Table 2 summarizes the intracranial objective response rate (iORR) for the 82 evaluable patients, with an overall iORR of 58.5% (47–69), comprising 49.1% (35–63) in the ICIs group, and 75.9% (56–90) in the ICIs plus BRT group. Six patients (6.1%) in the ICIs group experience severe adverse events (SAEs), including myelosuppression, elevated amylase, and myocarditis, with each event occurring in a single patient. Analysis of brain lesions in patients from both cohorts demonstrated a significant improvement in iORR without a concomitant increase in SAEs.

Table 3 presents the univariate and multivariate analyses for the entire cohort. Given the limited sample size and the substantial loss to follow-up in this retrospective study, only two independent prognostic factors were identified: the presence of extracranial metastases (HR 3.74, 95% CI 1.28–10.94) and combination CT (HR 0.06, 95% CI 0.01–0.34). A forest plot was generated to assess the benefits of ICIs + BRT (Fig. 2). For patients receiving corticosteroids or mannitol, OS with ICIs + BRT is superior to ICIs alone (HR = 0.16, 95%CI: 0.03–1.01, P = 0.05). However, among the remaining patients, there was no statistically significant difference in prognosis between the two treatment regimens.

Discussion

In the era of immunotherapy, this study presents compelling real-world evidence elucidating the potential benefits of integrating ICIs with brain radiotherapy in the management of NSCLC patients with BMs, accentuating its favorable impact on OS despite the absence of statistical significance in our findings.

Extensive prior studies have investigated the efficacy and safety of combining ICIs and radiotherapy. However, consensus on the efficacy of this combination therapy remains elusive. Certain studies contend that ICIs combined with brain radiotherapy significantly prolong patient prognosis. For instance, a retrospective study by Lee et al. demonstrated that gamma knife treatment administered 14 days post-treatment of NSCLC-BM patients with ICIs markedly improved OS[36]. The prospective study by Mehmet et al. in 2023 included 13 patients with BMs from NSCLC and assessed the safety and efficacy of nivolumab and ipilimumab alongside concurrent SRS, concluding that dual ICIs plus SRS exhibited a manageable safety profile[37]. Nevertheless, the study was constrained by a small cohort size and a single-arm design. A recent study by Lu et al. involving 113 patients evaluated the efficacy of ICIs plus CT versus ICIs plus CT combined with brain radiotherapy for the

	Immunotherapy (*N* = 99)	Immunotherapy + radiotherapy (*N* = 39)	p.value
Sex			0.779
Female	13 (13.1%)	4 (10.3%)	
Male	86 (86.9%)	35 (89.7%)	
Age	61.6 ± 7.43	61.1 ± 8.70	0.771
Smoking			1.000
No	25 (25.3%)	10 (25.6%)	
Yes	74 (74.7%)	29 (74.4%)	
Drinking			0.641
No	60 (60.6%)	26 (66.7%)	
Yes	39 (39.4%)	13 (33.3%)	
Antecedent chronic illnesses			1.000
No	74 (74.7%)	29 (74.4%)	
Yes	25 (25.3%)	10 (25.6%)	
Histology			0.058
Adenocarcinoma	58 (58.6%)	29 (74.4%)	
Others	10 (10.1%)	0 (0.00%)	
Squamous cell	31 (31.3%)	10 (25.6%)	
T stage			0.188
T1	12 (12.1%)	5 (12.8%)	
T2	19 (19.2%)	14 (35.9%)	
T3	19 (19.2%)	3 (7.69%)	
T4	45 (45.5%)	15 (38.5%)	
N stage			0.978
N0	13 (13.1%)	6 (15.4%)	
N1	7 (7.07%)	2 (5.13%)	
N2	24 (24.2%)	8 (20.5%)	
N3	52 (52.5%)	22 (56.4%)	
PD-L1 expression			0.869
1–49%	26 (26.3%)	10 (25.6%)	
< 1%	12 (12.1%)	5 (12.8%)	
≥ 50%	13 (13.1%)	3 (7.69%)	
ECOG			1.000
< 2	95 (96.0%)	37 (94.9%)	
≥ 2	4 (4.04%)	2 (5.13%)	
The number of BMs			0.431
Multiple	76 (76.8%)	33 (84.6%)	
Single	23 (23.2%)	6 (15.4%)	
The number of EMs			0.742
No	51 (51.5%)	22 (56.4%)	
Yes	48 (48.5%)	17 (43.6%)	
Bone			0.454
Yes	39 (39.4%)	12 (30.8%)	
Liver			0.292
Yes	6 (6.06%)	5 (12.8%)	
Adrenal			0.781
Yes	19 (19.2%)	6 (15.4%)	
Types of ICIs			1.000
PD-1	95 (96.0%)	38 (97.4%)	
PD-L1	4 (4.04%)	1 (2.56%)	
Chemotherapy			0.321
No	5 (5.05%)	0 (0.00%)	
Yes	94 (94.9%)	39 (100%)	
Targeting angiogenesis			1.000
No	64 (64.6%)	25 (64.1%)	
Yes	35 (35.4%)	14 (35.9%)	
Thoracic surgery			0.193
Continued			

	Immunotherapy (*N* = 99)	Immunotherapy + radiotherapy (*N* = 39)	p.value
No	98 (99.0%)	37 (94.9%)	
Yes	1 (1.01%)	2 (5.13%)	
Brain surgery			0.711
No	82 (82.8%)	34 (87.2%)	
Yes	17 (17.2%)	5 (12.8%)	
Corticosteroid or mannitol			**0.031***
No	55 (55.6%)	13 (33.3%)	
Yes	44 (44.4%)	26 (66.7%)	
Thoracic radiotherapy			0.053
No	97 (98.0%)	35 (89.7%)	
Yes	2 (2.02%)	4 (10.3%)	
Symptomatic BMs			0.332
No	59 (59.6%)	19 (48.7%)	
Yes	40 (40.4%)	20 (51.3%)	
SII	1243 ± 1244	1183 ± 1019	0.772
NLR	4.14 ± 2.41	4.72 ± 3.47	0.344
PLR	203 ± 127	202 ± 131	0.968
LMR	2.81 ± 1.58	2.62 ± 1.22	0.468

Table 1. Enrolled patients' characteristics in the overall cohort. Abbreviation: **PD-1**: Programmed Cell Death Protein 1; **PD-L1**: Programmed Cell Death Ligand 1; **ECOG**: Eastern Cooperative Oncology Group; **BMs**: Brain Metastases; **EMs**: Extracranial Metastases; **ICIs**: Immune Checkpoint Inhibitors; **SII**: Systemic Immune-Inflammation Index; **NLR**: Neutrophil-to-Lymphocyte Ratio; **PLR**: Platelet-to-Lymphocyte Ratio; **LMR**: Lymphocyte-to-Monocyte Ratio.

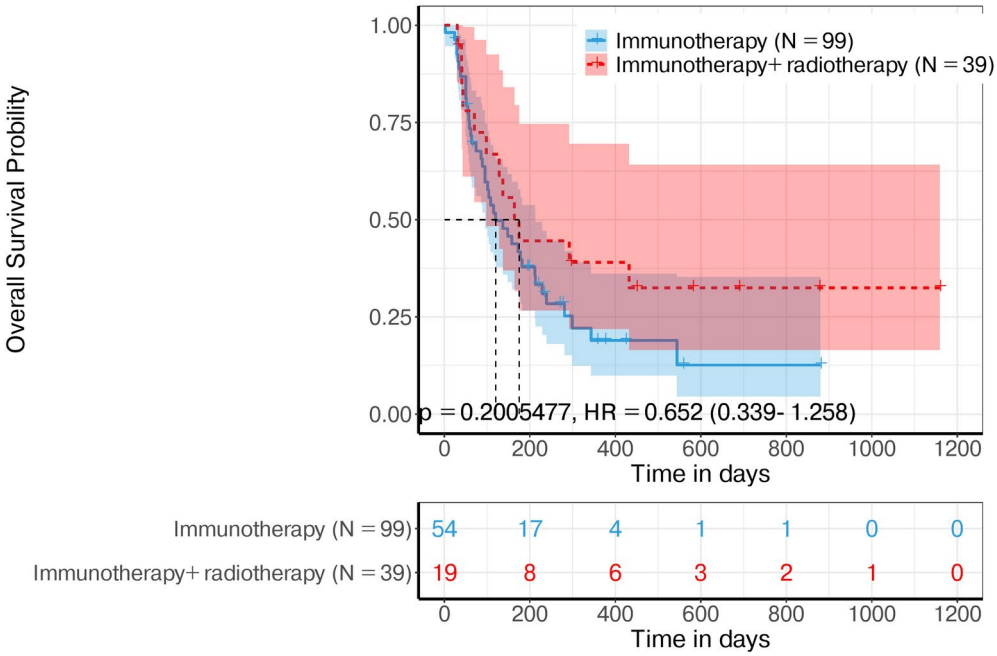

Fig. 1. Kaplan–Meier curves of OS for the two groups according to the receipt of brain radiotherapy.

treatment of BMs in NSCLC patients. Their findings indicated that immune-based therapies, when paired with brain radiotherapy conferred statistically significant survival benefits[38]. Conversely, other studies align with our findings. The results of our survival data showed that patients treated with ICIs plus BRT had better OS compared to ICIs alone, with an HR of 0.652 (95%CI: 0.339–1.258). However, our results were not statistically significant due to the limited number of patients enrolled in the study, which is a limitation of our study. Watanabe et al. observed that BMs patients who had undergone prior radiotherapy exhibited prolonged PFS compared to those without radiotherapy, albeit without statistical significance[39]. A meta-analysis revealed that ICIs combined with radiotherapy did not improve PFS or OS compared to ICIs alone[40]. Teixeir et al.'s meta-analysis also failed to

	Overall	Immunotherapy	Immunotherapy + radiotherapy	P.value
	N = 138	*N = 99*	*N = 39*	
Objective response rate, % (95% CI)	58.5(47–69)	49.1(35–63)	75.9(56–90)	**0.034***
Best overall response				
CR	11	7 (13.2%)	4 (13.8%)	1.00
PR	37	19 (35.8%)	18 (62.1%)	**0.04****
SD	28	24 (45.2%)	4 (13.8%)	**0.09****
PD	6	3 (5.8%)	3 (10.3%)	0.66
Serious adverse events				
Discontinuation of ICIs	6	6 (6.1%)	0 (0.0%)	0.184

Table 2. Intracranial objective response and adverse events in the overall cohort. Abbreviation: **CR**: Complete Response; **PR**: Partial Response; **SD**: Stable Disease; **PD**: Progressive Disease.

reveal a significant difference in the efficacy of ICIs in BMs patients treated with or without radiotherapy[41]. Similarly, a study by Hendriks et al. found that prior brain radiotherapy was not associated with PFS in univariate analysis (HR = 0.80, 95% CI: 0.60–1.08, p = 0.144), which corroborates our results[42].

We posit that discrepancies between these studies may stem from the following factors: 1) variations in cohort sizes. Lee's study included 77 patients, while Mehmet's study featured only 13 patients. Lu's study encompassed the largest cohort with 113 patients[36–38]. 2) Differences in treatment lines. In the studies conducted by Lee, Mehmet, and Hendriks, over half of the patients exhibited metachronous BMs, and ICIs were administered as later-line treatment, potentially amplifying the radiotherapy effect[36,37,42]. Lu's study is more analogous to ours, as both included patients with synchronous BMs receiving first-line immunotherapy[38]. 3) Differences in radiotherapy regimens. In Lu's study, 31% of patients received WBRT and 41% received WBRT plus Boost[38]. Given the potential for cognitive impairment, current guidelines advocate for SRS in patients with limited metastases, which accounts for the greater proportion of SRS-treated patients in our study. In summary, methodological heterogeneity significantly influences study outcomes. Our study primarily focuses on the efficacy and safety of immunotherapy, and its combination with brain radiotherapy, in patients with synchronous NSCLC BMs and negative driver gene status, with SRS serving as the predominant radiotherapy modality. Unlike metachronous BMs, the microenvironment of synchronous BMs more analogous to the primary lesion, potentially better reflecting the synergistic effects of first-line immunotherapy and radiotherapy. Although our results showed no significant survival benefit with the addition of brain radiotherapy, analysis of the lesions in both cohorts revealed that the iORR of patients receiving ICIs plus brain radiotherapy was significantly enhanced, without a concomitant rise in severe adverse events. Furthermore, our treatment approach aligns with existing guidelines, thus we believe our study bridges a critical gap in the literature and offers valuable insights for clinical practice.

Moreover, our multivariable cox regression analysis identifies that the use of combination CT is an important independent prognostic factor for survival. Multiple phase III clinical trials underscore that ICIs in combination with CT are beneficial for all patients with advanced lung cancer, irrespective of PD-L1 expression. The results of KEYNOTE-189 revealed a mPFS of 8.8 months for combination therapy[43]. Camrelizumab plus CT also achieved a mPFS of 11.3 months in NSCLC patients with BMs[44]. Comparable efficacy was observed with the combination of CT, sintilimab and atezolizumab[45,46]. Our results further corroborate that ICI + CT improves the survival of patients with BMs from NSCLC. One plausible reason could be that CT mitigates the occurrence of hyper-progression associated with ICIs in lung cancer patients without significantly exacerbating AEs[47].

In addition, baseline patient characteristic analysis revealed that although other baseline characteristics (including symptomatic BMs) did not differ significantly between the two cohorts, a greater proportion of patients in the ICIs plus BRT group had their cranial pressure reduced by using mannitol, corticosteroids, and other therapies, and this difference was statistically significant. Our subgroup analysis further demonstrated that combined ICIs plus BRT conferred a survival benefit in the corticosteroids -treated patients. This might imply that NSCLC patients with BMs receiving ICIs combined with radiotherapy tend to experience more severe intracranial hypertension compared to those receiving ICIs alone. According to the 2021 European Association of Neuro-Oncology (EANO)–European Society for Medical Oncology (ESMO) guidelines , administering anti-edema treatment with corticosteroids in patients presenting with neurological deficits may not only alleviate mass effects, such as nausea, vomiting, and fatigue, but also improve survival[48]. Furthermore, analysis of dynamic MRI from 30 patients with BMs by Teng et al. revealed an increase in permeability in tumors with initially low permeability following brain radiotherapy[49]. This increase in permeability may exacerbate cerebral edema post-radiotherapy, which Harat et al. reported could persist for up to six months after SRS or WBRT[50]. In addition to the possibility that brain radiotherapy itself may cause brain injury after radiotherapy, some previous clinical studies have shown that ICIs have the potential to increase the occurrence of radiation-induced brain injury[51,52]. However, some recent retrospective studies have shown that immunotherapy is not significantly associated with radiation-induced brain injury, and due to the lack of prospective studies and the heterogeneity of patients included, the conclusion needs further exploration[53–55]. Even so, our study found that immunotherapy was not significantly associated with radiation-induced brain injury, which may be linked to the use of anti-edema treatments such as steroids in our cohort. Consistent with the 2022 American Society for Radiation Oncology (ASTRO) guidelines, we posit ICIs alone for asymptomatic BMs, while combining ICIs with brain radiotherapy

Variable	Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P
Sex						
Female	Reference	Reference	Reference			
Male	2.35	0.31–17.54	0.406			
Age						
< 65 years	Reference	Reference	Reference			
≥ 65 years	2.15	0.89–5.18	0.088	1.45	0.55–3.83	0.451
Smoking						
No	Reference	Reference	Reference			
Yes	3.40	0.78–14.82	0.103			
Drinking						
No	Reference	Reference	Reference			
Yes	1.53	0.63–3.76	0.348			
Antecedent chronic illnesses						
No	Reference	Reference	Reference			
Yes	1.62	0.66–3.99	0.296			
Histology						
Adenocarcinoma	Reference	Reference	Reference			
Others	2.80	0.61–3.99	0.296			
T stage						
T1	Reference	Reference	Reference			
T2	1.45	0.28–7.49	0.656			
T3	1.61	0.27–9.78	0.603			
T4	1.34	0.29–6.15	0.705			
N stage						
N0	Reference	Reference	Reference			
N1	3.46	0.22–55.78	0.381			
N2	0.71	0.14–3.53	0.675			
N3	1.45	0.41–5.18	0.568			
PD-L1 expression						
< 1%	Reference	Reference	Reference			
1—49%	2.04	0.34–12.37	0.437			
≥ 50%	0.86	0.16–4.69	0.857			
ECOG						
< 2	Reference	Reference	Reference			
≥ 2	1.13	0.26–4.94	0.874			
The number of BMs						
Multiple	Reference	Reference	Reference			
Single	0.79	0.23–2.71	0.711			
The number of EMs						
No	Reference	Reference	Reference			
Yes	2.70	1.03–7.07	0.043	3.74	1.28–10.94	0.016
Chemotherapy						
No	Reference	Reference	Reference			
Yes	0.13	0.03–0.61	0.009	0.06	0.01–0.34	0.001
Targeting angiogenesis						
No	Reference	Reference	Reference			
Yes	0.79	0.32–1.94	0.608			
Thoracic Local therapy						
No	Reference	Reference	Reference			
Yes	1.61	0.57–5.51	0.450			
Combined corticosteroid						
No	Reference	Reference	Reference			
Yes	3.17	1.31–7.67	0.011	1.87	0.65–5.38	0.244
Symptomatic BMs						
No	Reference	Reference	Reference			

Continued

Variable	Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P
Yes	0.87	0.36–2.11	0.756			
SII	1.00	1.00–1.00	0.482			
NLR	0.88	0.72–1.09	0.252			
PLR	1.00	0.99–1.00	0.633			
LMR	0.96	0.71–1.30	0.787			

Table 3. The HRs (95% CI) for Overall Survival by Cox regression. Abbreviation: **PD-L1**: Programmed Cell Death Ligand 1; **ECOG**: Eastern Cooperative Oncology Group; **BMs**: Brain Metastases; **EMs**: Extracranial Metastases; **SII**: Systemic Immune-Inflammation Index; **NLR**: Neutrophil-to-Lymphocyte Ratio; **PLR**: Platelet-to-Lymphocyte Ratio; **LMR**: Lymphocyte-to-Monocyte Ratio.

remains advantageous for symptomatic patients, without increasing the likelihood of post-treatment adverse events, provided anti-edema treatment is employed when appropriate[56].

We observed that numerous studies emphasize the significance of PD-L1 expression[57,58]. Chen et al.'s meta-analysis found higher iORR and iDCR in patients with high PD-L1 expression compared to those with no or low PD-L1 expression treated with pembrolizumab[59]. However, our data did not yield similar results. Our team discovered through RNA sequencing that BMs exhibit an immunosuppressive tumor microenvironment (TME)[60]. It has also been demonstrated that BMs have different PD-L1 expression levels compared to primary lung tumors[61]. Since our study excluded patients with prior systemic therapy and focused exclusively on BMs, eliminating the confounding effect of treatment-induced resistance, we propose that the specific immunosuppressive TME of BMs, which results in divergent PD-L1 expression compared to primary lung lesions, rendered PD-L1 expression non-predictive of efficacy in our study. Additionally, as our retrospective study included patients treated with different ICIs, and the correlation between PD-L1 expression and the efficacy of various ICIs varies, this could also contribute to the findings[59–66].

Our cox multivariate regression analysis also identified the presence of extracranial metastases as an independent prognostic factor, aligning with DS-GPA and Lung-molGPA systems[67,68]. Therefore, we believe that adequate local therapy should be employed to control extracranial metastatic lesions.

The principal limitation of our study lies in its retrospective design, which results in missing data and selection bias. Although data from three centers were included, we acknowledge that the patient sample size was limited. Future large-scale prospective trials are warranted to evaluate brain radiotherapy combined with ICIs in the treatment of NSCLC BMs. By focusing exclusively on synchronous BMs, our study mitigates confounding factors, providing significant contributions to existing knowledge. Until further prospective data are available, we believe our findings offer critical insights and actionable guidance for clinicians managing NSCLC patients with BMs.

Method

Patients

Clinical data from NSCLC patients with BMs treated with first-line ICIs at Xiangya Hospital, Xiangya Changde Hospital and Xiangya Boai Hospital between 2020 and October 2023 were retrospectively collected. The inclusion criteria comprised: 1) diagnosis of NSCLC with BMs at initial presentation; 2) presence of at least one quantifiable brain lesion corroborated by MRI at initial diagnosis; and 3) administration of first-line ICI. Patients were excluded if they: 1) had small cell lung cancer; 2) lacked measurable BMs detected at initial diagnosis; or 3) had undergone treatment with other antineoplastic agents prior to ICIs. Patients who underwent radiotherapy for BMs either preceding or subsequent ICIs were included.

General information was compiled, encompassing demographics (name, gender, age), tobacco and alcohol consumption history, antecedent chronic illnesses, oncological history, ECOG-PS score, status of primary malignancy, and status of extracranial metastases. Clinicopathological attributes, driver gene mutations, PD-L1 tumor proportional score, and treatment regimen were recorded. Hematological parameters, including erythrocytes, platelets, neutrophils, eosinophils, and basophil counts, were collected pre- and post-ICIs administration.

Patients were stratified into two cohorts based on their receipt of BRT. Concurrent ICIs with BRT were defined as ICIs administered within two weeks before or after radiotherapy. Patients who received non-concurrent BRT and ICIs were defined as those receiving radiotherapy and ICIs more than 2 weeks apart. Radiotherapy was classified as any modality of BRT including WBRT and SRS.

To ensure the safeguarding of patient confidentiality and personal identity, and considering that the associated risks did not exceed minimal levels, the study adhered to an ethically approved alternative protocol.

Assessments

The primary endpoints were iORR and ORR. Control of intracranial and extracranial lesions was assessed by MRI and CT every 3 months. The efficacy of each assessment was categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints included PFS, iPFS, OS and treatment-related toxicity. PFS was defined as the duration from initiation of ICIs to disease progression or mortality from

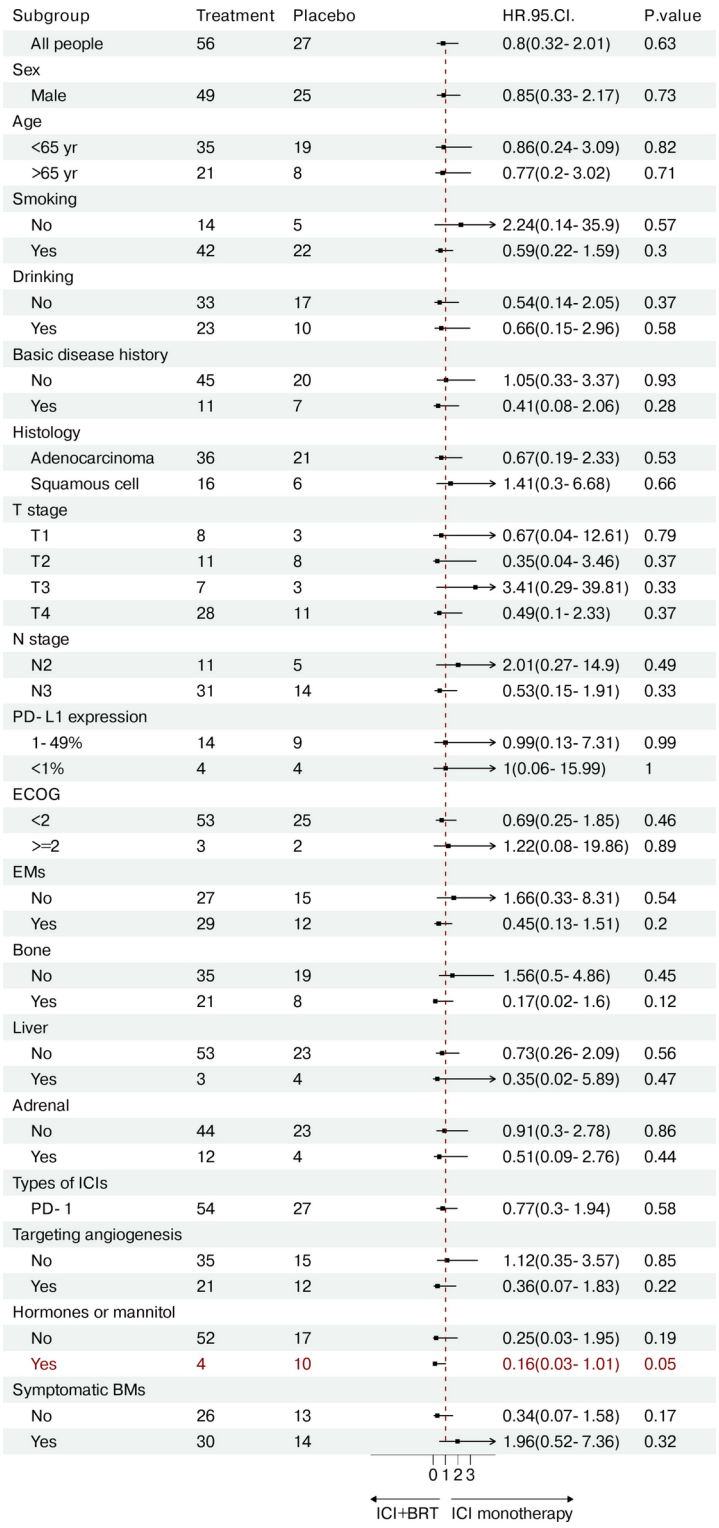

Fig. 2. Forest plot of overall survival in subgroups and overall population of patients with newly diagnosed brain metastases from non-small cell lung cancer receiving first-line immunotherapy. This forest plot reflects the comparison of the efficacy between ICI + BRT and ICI in each subgroup. An HR less than 1 indicates the superiority of ICI + BRT, while an HR greater than 1 indicates the superiority of ICI. Only in the subgroup of patients who received Hormones or mannitol, ICI + BRT was significantly superior to ICI.

any cause. iPFS was defined as the interval from initiation of ICIs to progression of intracranial lesions or death. OS was defined as the period from the initiation of ICIs until death from any cause or until the last documented follow-up. Treatment-related toxicities were assessed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis

Statistical analysis were conducted utilizing R software (4.2.3). Cox proportional hazards regression models were applied to assess factors independently associated with OS, PFS, and iPFS. The distribution of patients' baseline characteristics was summarized using frequency analysis. Fisher's exact test was utilized to evaluate the baseline characteristics of patients receiving various treatment strategies. The KM analysis was employed to estimate iPFS, PFS and OS , and the log-rank test was applied to compare survival differences between subgroups.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. Access to the data will be considered following review of a detailed research proposal to ensure appropriate use and protection of patient information.

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Author contributions

Conceptualization, R.L. and Z.W.; methodology, R.L. and Z.W.; software, R.L. and Z.W.; validation, X.C. and R.Z., formal analysis, R.L. and Z.W.; investigation, R.L. and Z.W.; resources, R.L. and Z.W.; data curation, R.L. and Z.W.; writing—original draft preparation, R.L., Z.W. and W.T.; writing—review and editing, R.L., Z.W., W.T. and W.S.; visualization, R.L. and Z.W., X.C.; supervision, X.C. and R.Z.; project administration, X.C. and R.Z.; funding acquisition, R.Z.. All authors have read and agreed to the published version of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study was conducted in accordance with the guidelines of the Declaration of Helsinki. All methods were performed in accordance with the relevant guidelines and regulations. The study protocol was approved by the ethics committee of Xiangya Hospital, Central South University (202406122). In accordance with the Ethical Review Methodology for Biomedical Research Involving Humans (2016 Edition) established by the Chinese authorities, the Ethics Committee of Xiangya Hospital, Central South University granted approval for the waiver of patient consent.

Additional information

Correspondence and requests for materials should be addressed to X.C. or R.Z.