Brain injury after cranial radiotherapy combined with immunotherapy for brain metastases in lung cancer: a retrospective study

Jiatong Li
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences
Wanhu Li
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences
Shuhui Xu
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences
Yuying Li
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences
Shuangqing Lu
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences
Feihu Chen
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences
Jinming Yu (sdyujinming@163.com)
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences
Hui Zhu
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences

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Research Article

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Abstract

Background: For patients with brain metastasis (BM) from lung cancer, whether cranial radiotherapy (CRT) combined with immune checkpoint inhibitors (ICIs) will increase the risk of radiation-induced brain injury (RBI) remains inconclusive. This retrospective study was performed with the aim of analyzing the incidence of RBI of CRT combined with ICIs and revealing the risk factors forRBI.

Methods: We retrospectively reviewed the medical records of patients with BM from lung cancer who underwent CRT between January 2019 and December 2020 at Shandong Cancer Hospital and Institute. According to whether systemic treatment was used within 6 months before and after CRT, all patients were divided into theCRT+ICIs group and the CRT+non-ICIs group respectively. The diagnosis of brain radiation-induced necrosis (RN) and white matter lesions (WML) was evaluated by brain enhanced MRI. The Fazekas scale and CTCAE v5.0 were used to grade the injury. The risk factors for RBI were identified using univariate and multivariate analyses.

Results: Overall, 210 BM patients undergoing CRT were included in our study. Within 6 months before and after CRT, 56 patients received ICIs, and 154 patients received other systemic therapeutic drugs, including tyrosine kinase inhibitors (TKIs) and chemotherapy. Seventeen (8.1%) patients developed RN, and 142 (67.6%) patients developed WML. The incidence of RN in theCRT+ICIs group vs. the CRT+non-ICIs group was 14.3% vs. 5.8% (p=0.090). However, if ICIs were used within three months of CRT, the incidence of RN in the CRT+ICIs group was significantly higher than that in the CRT+non-ICIs group (18.5% vs. 5.4%, p=0.045).

Multivariate analysis revealed that the maximum diameter of BM > 3.3 cm (p = 0.023) and the total cumulative radiation dose of metastatic lesions > 75.7 Gy (p = 0.018) were risk factors for RN. Additionally, re-radiotherapy was also a trend factor in the development of RN (OR 3.40; 95% CI 0.99-11.67, p=0.051).

Conclusions: ICIs could increase the risk of RN, especially when used within three months of CRT. The total cumulative radiation dose of metastatic lesions is closely related to the development of RN, and re-radiotherapy is also a trend factor in the development of RN.

Background

The incidence of brain metastasis (BM) accounts for approximately 20–40% of adult malignant tumors, and approximately half of BMs originate from lung cancer[1, 2]. BM has the characteristics of high mortality and poor prognosis. The combination of local treatment and systemic treatment are the main treatment modalities.

Cranial radiotherapy (CRT) is the most important local treatment for BM, including whole brain radiotherapy (WBRT), partial brain radiotherapy (PBRT) and WBRT with simultaneous integrated boost (WBRT-SIB). CRT brings higher local control (LC) and survival benefit to patients. Because of the blood–

brain barrier (BBB), it is difficult for chemotherapeutic drugs with large molecular weights to enter the brain to exert their antitumor effects. In recent years, with the proposal of abscopal effects in radioimmunotherapy[3] and the exploration of the BM immune microenvironment[4, 5], CRT combined with immune checkpoint inhibitors (ICIs) has provided the possibility for BM patients with negative driving genes. A large number of studies have shown that CRT combined with ICIs could result in significant progression-free survival (PFS), overall survival (OS) and LC for BM patients with NSCLC[6, 7].

Radiation-induced brain injury (RBI), mainly including cranial radiation necrosis (RN) and white matter lesions (WML), is a delayed irreversible radiation injury. It seriously affects the quality of life of patients, such as cognitive dysfunction and intracranial hypertension, and even leads to death in severe cases. The incidence of RBI is 8%-20% at one year after CRT for BM[8], mainly due to a series of pathophysiological changes after the damage of nerve cells and intracranial vessels after CRT. In the era of immunotherapy, whether the synergistic effect of radioimmunotherapy will increase the risk of RBI has attracted more attention. One retrospective study showed that immunotherapy was associated with symptomatic RN (HR, 2.56; 95% CI, 1.35–4.86; $p = 0.004$), and this difference was more significant in melanoma[9]. For patients with BM from melanoma, a study showed that the incidence of RN in the SRS + ipilimumab group was significantly higher than that in the SRS alone group (6% ~ 8% vs. 0%, $p = 0.005$)[10].

However, data on RBI in lung cancer are still lacking. Therefore, we carried out a retrospective study to explore whether the addition of ICIs to CRT will increase the risk of adverse brain events in lung cancer BM and further explore the risk factors for RBI.

Patients And Methods

Study design and patients

We retrospectively reviewed the medical records of patients with BM from lung cancer who underwent CRT at Shandong Cancer Hospital and Institute (Jinan, Shandong, China) between January 2019 and December 2020. Follow-up after CRT for BM by magnetic resonance imaging (MRI) was at least 3 months. The study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute. All procedures involving patients conformed to the principles outlined in the Declaration of Helsinki.

Treatment Protocol

All patients were treated with cranial intensity-modulated radiotherapy (IMRT), including WBRT, PBRT and WBRT-SIB. In our study, WBRT was used for multiple BMs (> 3), and PBRT was mainly applied to patients with 1–3 BMs. On the basis of WBRT, WBRT-SIB can be considered to improve LC. Prescription doses were based on tumor size and number. Radiotherapy parameters were extracted from the radiotherapy planning system, such as total cumulative dose, fraction times and dose per fraction.

We recorded the details of the systemic therapy by reviewing the medical records, including therapy before CRT, during CRT and after CRT. Systemic therapy includes traditional chemotherapy, tyrosine kinase inhibitors (TKIs), and ICIs. According to whether systematic treatment was used within six months before and after CRT, all patients were divided into CRT + ICIs and CRT + non-ICIs groups.

Diagnosis And Classification Of Rbi

Because of the particularity of BM, RBI and intracranial tumor responses were mainly evaluated by clinical symptoms and imaging changes obtained by contrast-enhanced MRI after CRT. We followed up the patients with MRI one month after CRT and then every two to three months thereafter. To reduce subjective differences, follow-up MRI images were evaluated by three senior imaging specialists. We divided the imaging changes of RBI into two categories, RN and WML.

1.1 RN

The performance of the RN on MRI is as follows[11]: The lesion was composed of a central low signal of the necrotic area and a surrounding high signal of the enhanced area (T1-weighted (T1WI) showed the shape of a soap bubble and garland). The edema around the lesion was obvious, showing a large range of high signals on T2 fluid-attenuated inversion recovery (FLAIR). If the diagnosis is not clear, the lesion quotient (LQ) can help us judge whether the lesions are RN. LQ was defined as the ratio of the maximum diameter of a well-defined measurable lesion on T2-weighted (T2WI) to T1WI images[8, 12] Studies have shown that the LQ of pathologically confirmed RN is 0.3 or less. LQ ≥ 0.6 indicates the possibility of tumor recurrence. According to the current research results, LQ > 0.3 had a specificity of 80%, a sensitivity of 96% and a negative predictive value of 96% for distinguishing RN from tumor recurrence[8].

1.2 WML

WML are mainly identified by the scalloped appearance of the enhancement on T2 FLAIR images and high-signal lesions in the periventricular white matter on T2WI images. The grade and score of WML were estimated by the Fazekas scale[13] **(**Table 1**).** By evaluating the signal characteristics of periventricular and deep white matter, imaging experts scored and graded the follow-up images of each patient, and then we recorded the first occurrence time of WML and graded the most serious WML.

Based on the imaging changes, RBI was diagnosed and graded according the Common Terminology Criteria for Adverse Events v5.0 (CTCAE v5.0) standard[14]. Central nervous system necrosis is divided into 5 grades: Grade 1 RN is asymptomatic or only clinical diagnosis, and this does not require treatment; Patients with grade 2 RN have clinical symptoms such as dizziness, headache and mental disorders, and their activities of daily living are limited mild; The patients with grade 3 RN have more severe symptoms and need treatment; Patient with grade 4 RN have life threatening, urgent intervention indicated; Patients die from grade 5 RN.

Statistical analysis

All statistical analyses were performed by using GraphPad Prism software version 8.0 and SPSS statistical software version 25. The comparisons of patients' baseline characteristics and the incidence of RN and WML in the two groups were analyzed by using the chi-square test and continuity correction test. The Kaplan–Meier method was used to calculate OS.

Univariate and multivariate analyses using binary logistic regression were conducted to analyze the risk factors for RN and WML. The factors analyzed included categorical variables and continuous variables. For meaningful continuous variables, we further generated receiver operating characteristic (ROC) curves to obtain the optimal cut-off value according to the maximum Youden index after considering sensitivity and specificity. Two-sided p values < 0.05 were considered statistically significant.

Results

Patient characteristics

As a result, 210 patients with BM who underwent CRT between January 2019 and December 2020 were reviewed in the present study. According to the therapeutic modality, 26.7% (56/210) of patients used chemotherapy, 44.3% (93/210) used TKIs and 29.0% (61/210) used ICIs during treatment. There were 56 patients in the CRT + ICIs group and 154 patients in the CRT + non-ICIs group.

The median follow-up time was 27.4 months (range, 1.0-50.4 months), and the median imaging follow-up time was 12.6 months (range, 1.0-43.2 months). The baseline characteristics of the patients in the two groups are summarized in Table 2. Except for gender and pathology, the baseline characteristics of patients with BM who did and did not receive ICIs were generally well balanced. In the two groups, the median age of all patients was 57 years, ranging from 32 to 78 years. There were 52.9% (111/210) males and 47.1% (99/210) females in our study. A total of 91.0% (191/210) of patients had a Karnofsky performance status (KPS) score greater than 70 (KPS > 70), and 83.3% of the patients had no history of hypertension. There were 51.4% (108/210) of patients with 1–3 BMs and 48.6% (102/210) patients with more than three BMs (> 3). In addition, 146 (69.5%) patients had adenocarcinoma. Only 11 patients had leptomeningeal metastases. Among all patients, the proportion of patients with symptomatic BM was 58.6% (123/210). CRT modes include WBRT, PBRT and WBRT-SIB. The choice of mode is related to the number and size of BMs, pathological types, general conditions and so on. In the CRT + ICIs group, the ratio of the three radiotherapy modes was 26.8% vs. 35.7% vs. 37.5%. In addition, WBRT-SIB was the main treatment mode in the CRT + non-ICIs group, and the ratio of the three radiotherapy modes was 29.2% vs. 28.6% vs. 42.2%. During the whole course of treatment, twenty (9.5%) patients received re-radiotherapy.

Table 2
Baseline characteristics of patients

Characteristics	Total (n = 210)	No. (%)		
		CRT + ICIs (n = 56)	CRT + non-ICIs (n = 154)	P Value[a]
Gender	111	42 (75.0)	69 (44.8)	**0.000**
Male	99	14 (25.0)	85 (55.2)	
Female				
Age (median, range) (y)	57 (32–78)	59 (32–78)	57 (32–77)	0.731
< 65	161	14 (25.0)	35 (22.7)	
≥ 65	49	42 (75.0)	119 (77.3)	
Hypertension history	175	47 (83.9)	128 (83.1)	0.889
No	35	9(16.1)	26 (16.9)	
Yes				
KPS score	19	5 (8.9)	14 (9.1)	0.971
≤ 70	191	51 (91.1)	140 (90.9)	
> 70				
Pathology	14	6 (10.7)	8 (5.2)	**0.030**
Squamous cell carcinoma	146	30 (53.6)	116 (75.3)	
Adenocarcinoma	43	17 (30.4)	26 (16.9)	
Small cell lung cancer	7	3 (5.4)	4 (2.6)	
Other				
Basic cerebral ischemic lesion	87	28 (50.0)	57 (37.0)	0.090
Yes	124	28 (50.0)	97 (63.0)	
No				

Abbreviations: CRT:cranial radiotherapy, ICIs: immune checkpoint inhibitors, WBRT: whole brain radiotherapy, PBRT: partial brain radiotherapy, WBRT-SIB: WBRT with simultaneous integrated boost.

Characteristics	Total (n = 210)	No. (%)		
		CRT + ICIs (n = 56)	CRT + non-ICIs (n = 154)	P Value[a]
Symptomatic brain metastases	123	31 (55.4)	91 (59.1)	0.628
Yes	88	25 (44.6)	63 (40.9)	
No				
Maximum diameter of lesion (median, range) (cm)	1.7 (0.2–6.4)	1.8 (0.5–6.4)	1.7 (0.2-5.0)	
Number of brain metastases	108	33 (58.9)	75 (48.7)	0.190
≤ 3	102	23 (41.1)	79 (51.3)	
> 3				
Leptomeningeal metastases	199	54 (96.4)	145 (94.2)	0.513
No	11	2 (3.6)	9 (5.8)	
Yes				
Radiotherapy mode	60	15 (26.8)	45 (29.2)	0.608
WBRT	64	20 (35.7)	44 (28.6)	
PBRT	86	21 (37.5)	65 (42.2)	
WBRT-SIB				
Re-radiotherapy	20	5(8.9)	15 (9.7)	0.859
Yes	190	51 (91.1)	139 (90.3)	
No				
Abbreviations: CRT:cranial radiotherapy, ICIs: immune checkpoint inhibitors, WBRT: whole brain radiotherapy, PBRT: partial brain radiotherapy, WBRT-SIB: WBRT with simultaneous integrated boost.				

Incidence Of Rbi

Overall, we first analyzed the follow-up MRI of 210 patients and found that 17 (8.1%) patients developed RN and 142 (67.6%) patients developed WML after CRT.

1. RN

The median time of development of RN was 13.3 months (range 0.53–34.8 months). The typical imaging images from patients with RN are shown in Fig. 1. All RNs occurred at the location of the BM, which has no location correlation with the white matter area of WML occurrence. Among 17 patients with RN in the two groups, 12 (70.6%) patients received PBRT, four (23.5%) patients received WBRT-SIB, and only one (5.9%) patient received WBRT. A total of 76.5% (13/17) of patients with RN received secondary CRT, and 70.6% (12/17) of patients with RN developed WML at different times during treatment. Moreover, the median cumulative radiation dose of patients with RN was 50 Gy (range 40–110 Gy).

As a result, eight patients developed RN in the CRT + ICIs group, and nine patients developed RN in the CRT + non-ICIs group. The rate of RN was relatively higher in the CRT + ICIs group than that in CRT + non-ICIs group (14.3% vs. 5.8%, $p = 0.090$), but the difference was not significant. However, if ICIs were used within three months of CRT, the incidence of RN in the CRT + ICIs group was significantly higher than that in the CRT + non-ICIs group (18.5% vs. 5.4%, $p = 0.045$). Therefore, in this study, when ICIs were applied within three months before and after CRT, the incidence of RN was 3.43 times that of the CRT group. Then, we took three months before and after CRT as the cut-off time and divided the patients who used ICIs in the whole treatment process into two groups: the group using ICIs in combination within three months and the group using ICIs in combination beyond three months. By analyzing the incidence of RN, we found that the difference was not statistically significant ($p > 0.05$).

According to CTCAE V5.0, among 17 patients with RN, five patients were grade 1, which were observed only during the imaging follow-up; 1 patient was grade 2, and the patient had mild symptoms of dizziness and headache, and no special treatment was needed; 10 patients were grade 3, and clinicians generally used bevacizumab or a combination of mannitol and dexamethasone for symptomatic treatment, and the symptoms of patients were relieved after treatment; 1 patient was grade 4, and the patient had severe headache and limited movement of one side of the limb, so surgery had been considered to alleviate the symptoms after consultation with neurosurgery experts; and no patients died because of RN.

2. WML

The typical imaging images from patients with WML are shown in Table 1. WML mainly occurred in periventricular white matter (PVWM) and deep white matter (DWM), and the location of WML was not related to RN. Among 142 patients with WML, the numbers of patients receiving WBRT, PBRT and WBRT-SIB were 44, 33 and 65, respectively. A total of 11.3% (16/142) of patients had received re-radiotherapy. The median time of WML occurrence was 5.87 (range 0.5–30.1). According to the Fazekas scale, there were 23 (16.2%) patients with grade 1 WML, 50 (35.2%) patients with grade 2 WML and 69 (48.6%) patients with grade 3 WML.

Among 142 patients with WML, the rate of any grade WML was 62.5% (35/56) in the CRT + ICIs group and 69.5% (107/154) in the CRT + non-ICIs group. The incidence of WML between the two groups was not significantly different ($p = 0.339$). If ICIs were used within three months of CRT, the incidence of WML between the CRT + ICIs group and the CRT group was 51.9% vs. 69.8% ($p = 0.068$).

We compared brain MRI of patients before and after CRT. There were 65 patients with ischemic spots on MRI imaging before CRT, and they were assessed as grade 1 WML. Among them, 80.0% (52/65) of patients developed grade 2–3 WML after CRT. Then, we analyzed the natural risk of WML in patients before CRT and found that there was no statistical correlation between age and WML (OR 1.53; 95% CI 0.81–2.92, $p = 0.193$).

Effects Of Rn And Wml On Survival

The median OS (mOS) for the 210 patients was 28.2 months (95% CI 26.5–31.2 months). For 17 patients with RN, the mOS was significantly longer than for those without RN. The mOS for patients in the non-RN group was 26.1 months (95% CI 22.4–30.0 months), while the mOS of patients in the RN group was not reached ($p = 0.016$). In addition, there was no significant difference in mOS between the non-WML group and the WML group, which were 24.4 months and 29.1 months, respectively ($p = 0.329$). (Fig. 2)

Risk Factors For Rbi

As shown in Table 3, we first conducted a univariate analysis on the factors that may be related to the occurrence of RN and WML, and then in consideration of the collinearity of some variables, the statistically significant factors in the univariate analysis were further included in the multivariate analysis. The factors include categorical variables and continuous variables. The optimal cut-off values of statistically significant continuous variables were obtained by ROC curve analysis.

Table 3
univariate and multivariate analysis of risk of developing RN and WML

	Univariate analyses		Multivariate analyses	
Risk Factors	OR (95%CI)	p-value	OR (95%CI)	p-value
Brain necrosis				
Gender (Female)	0.98(0.36–2.64)	0.962	NA	—
Age (≥ 65)	0.19(0.02–1.46)	0.110	NA	—
KPS score (> 70)	0.72(0.15–3.44)	0.685	NA	—
BM after progression	3.50 (1.24–9.89)	**0.018**	2.96 (0.82–10.74)	0.098
Number of BM (> 3)	0.20 (0.06–0.73)	**0.015**	0.38 (0.09–1.59)	0.184
Maximum diameter(> 3.3cm)	1.51(1.04–2.19)	**0.030**	1.67 (1.08–2.60)	**0.023**
Asymptomatic BM	0.74(0.26–2.08)	0.566	NA	—
Radiotherapy mode (PBRT)	6.51(2.19–19.37)	**0.001**	2.01 (0.25–16.09)	0.512
Cumulative radiation dose of the whole brain (Gy)	0.97 (0.95–0.99)	**0.040**	1.00 (0.95–1.06)	0.982
Cumulative radiation dose of metastatic lesions(> 75.7Gy)	1.05 (1.02–1.08)	**0.001**	1.05(1.01–1.09)	**0.018**
Re-radiotherapy	3.40(0.99–11.67)	0.051	NA	—
WML	1.16(0.39–3.45)	0.785	NA	—
White matter lesions				
Gender (Female)	1.13(0.63–2.01)	0.684	NA	—
Age (≥ 65)	1.64(0.80–3.40)	0.180	NA	—
KPS score (> 70)	1.24(0.47–3.31)	0.663	NA	—

Abbreviations: WML: white matter lesion

	Univariate analyses		Multivariate analyses	
Number of BM (> 3)	2.04 (1.13–3.69)	**0.019**	1.63(0.80–3.31)	0.180
Basic cerebral ischemic lesion	1.89 (1.03–3.48)	**0.041**	3.26(1.57–6.75)	**0.002**
Maximum diameter	0.95(0.75–1.20)	0.671	NA	—
Pathology (squamous cell carcinoma)	0.33(0.11-1.00)	**0.049**	0.31(0.09–1.03)	0.057
Radiotherapy mode (PBRT)	0.36(0.20–0.67)	**0.001**	0.51(0.17–2.24)	0.373
The dose per fraction of the whole brain	1.70 (1.32–2.19)	**0.000**	1.39(0.83–2.33)	0.210
Cumulative radiation dose of the whole brain	1.04 (1.02–1.06)	**0.000**	1.04(1.00-1.08)	0.084
Cumulative radiation dose of metastatic lesions (Gy)	1.02(0.99–1.04)	0.149	NA	—
Re-radiotherapy	2.03(0.65–6.33)	0.221	NA	—
Abbreviations: WML: white matter lesion				

In univariate analysis, the results showed that the number and size of BMs were significantly correlated with the occurrence of RN. More than three metastatic lesions are a protective factor for the development of RN (OR 0.20; 95% CI 0.06–0.73, $p = 0.015$), and the maximum diameter of BM is a risk factor (OR 1.51; 95% CI 1.04–2.19, $p = 0.030$); in other words, the larger the maximum diameter of metastatic lesions is, the higher the risk of RN. Then, the ROC curve analysis results showed that the cut-off value of the maximum diameter of BM was 3.3 cm. Compared to patients initially diagnosed with BM, BM after progression (OR 3.50; 95% CI 1.24–9.89, $p = 0.018$) was a risk factor for the occurrence of RN. In addition, PBRT as a radiotherapy mode (OR 6.51; 95% CI 2.19–19.37, $p = 0.001$), total cumulative radiation dose of metastatic lesions (OR 1.05; 95% CI 1.02–1.08, $p = 0.001$) and total cumulative radiation dose of the whole brain (OR 0.97; 95% CI 0.95–0.99, $p = 0.040$) were significantly correlated with the occurrence of RN. The cut-off value of the cumulative radiation dose of metastatic lesions was 75.7 Gy. In consideration of the collinearity of some variables, we then included all variables identified as statistically significant in the multivariate analysis. The results showed that the maximum diameter of BM (> 3.3 cm, OR 1.67; 95% CI 1.08–2.60, $p = 0.023$) and the cumulative radiation dose of brain metastases (> 75.7 Gy, OR 1.05; 95% CI 1.01–1.09, $p = 0.018$) were significantly correlated with the occurrence of RN. Moreover, among the risk factors, re-radiotherapy (OR 3.40; 95% CI 0.99–11.67, $p = 0.051$) was also a trend factor in the development of RN, although the data in this study did not reach statistical significance.

On the other hand, univariate analysis showed that the number of BMs (> 3), the basic cerebral ischemic lesion, the dose per fraction of the whole brain and the total cumulative radiation dose of the whole brain were statistically significant risk factors for WML. The pathological type of squamous cell carcinoma (OR 0.33; 95% CI 0.11-1.00, $p = 0.049$) and CRT mode of PBRT (OR 0.36; 95% CI 0.20–0.67, $p = 0.001$) were protective factors for WML. However, we further conducted multivariate analysis and found that only basic cerebral ischemic lesions (OR 3.26; 95% CI 1.57–6.75, $p = 0.002$) were a statistically significant risk factor for the development of WML.

Discussion

CRT combined with ICIs has brought significant therapeutic efficacy for BM patients with NSCLC. RBI is the most serious event of CRT, and it can affect not only the quality of life but also the prognosis of patients. For patients with BM, whether CRT combined with ICIs will increase the risk of RBI remains inconclusive. This retrospective study showed that the incidence of RN was 8.1% when patients were treated with CRT combined with or without ICIs. The median time for the occurrence of RN was 13.3 months. Further study showed that the application of ICIs within 6 months before and after CRT tends to increase the risk of RN. If ICIs were used within three months of CRT, the risk of RN could be further improved. Additionally, the maximum diameter of the BM (> 3.3 cm) and the cumulative radiation dose of brain metastases (> 75.7 Gy) were significantly correlated with the occurrence of RN.

Whether the application of ICIs will increase the risk of RN remains inconclusive. At present, several studies have confirmed that the use of ICIs can increase the RN rate, but the correlation is significant mainly in melanoma. A meta-analysis of 16 studies (14 on melanoma, 2 on NSCLC) showed that in NSCLC BM, the reported RN rate in SRS + ICIs and SRS alone ranged from 2.9–3.4% and 0-2.9%, respectively. However, in patients with BM from melanoma, the incidence of RN was higher in SRS + ICIs than in SRS alone (16.0% vs. 6.5%; $p = 0.065$; OR, 2.35), and RN tended to occur 2.4 times more frequently in SRS + ICIs than in SRS alone in melanoma BM[15]. Additionally, Martin et al. retrospectively investigated 480 patients with newly diagnosed BM secondary to NSCLC (n = 294), melanoma (n = 145), and renal cell carcinoma (n = 41) treated with SRS and further analyzed the association between ICIs and symptomatic RN. The results showed that receipt of ICIs was associated with symptomatic RN (HR, 2.56; 95% CI, 1.35–4.86; $p = 0.004$), especially in patients with melanoma (HR, 4.02; 95% CI, 1.17–13.82; $p = 0.03$)[9]. However, this correlation is not significant in lung cancer. A matched cohort study analyzed the safety for patients with NSCLC BM treated with ICIs combined with SRS. According to whether ICIs were used within 3 months before and after SRS, 51 patients were assigned to the concurrent ICIs queues (17 patients) and ICIs naive queues (34 patients), respectively. The results showed that there was no increased rate of RN or intratumoral hemorrhage in patients receiving concurrent ICIs (5.9% vs. 2.9%, $p = 0.99$)[16]. In our research, the incidence of RN in the CRT + ICIs group was significantly higher than that in the CRT + non-ICIs group, especially when used within 3 months of CRT (18.5% vs. 5.4%, $p = 0.045$). We analyzed the reasons for the different conclusions from lung cancer, considering that it may be limited by the difference in CRT technology and the lower cumulative radiation dose of SRS. In addition, immature RN diagnosis and

identification technology also affects the analysis of results; for example, it is difficult to distinguish between RN and tumor recurrence or false progress[17–19].

In terms of risk factors for RN, previous studies usually paid more attention to the CRT dose and volume[20–22]. Korytko et al. analyzed the risk of RN and showed that when the cumulative dose reached 72 Gy and the dose per fraction was 2 Gy, the rate of RN reached > 5%[23]. Similarly, another retrospective study reviewed 34 patients with primary brain tumors retreated with fractionated external beam irradiation and showed that the incidence of RN at higher doses (78–94 Gy) could reach 17%[24]. In general, the dose of CRT was limited to 50 Gy/25 f with a conventional fraction, and the incidence of RBI was significantly reduced[25]. The present results showed that the cumulative radiation dose > 75.7 Gy was significantly correlated with RN. The target volume was another risk factor for RN. A multi-institutional analysis showed that for larger lesions (≥ 2 cm in diameter), the RN rate was 12.3% in the SRS group with the median cumulative dose of 18 Gy[26]. A safety analysis for larger lesions (> 3 cm in diameter) showed that 15.8% of patients had developed grade 2–3 RN when the median cumulative dose of SRS reached 35 Gy[27]. Although CRT has been proven to be effective in treating BM, our research results indicated that it was not feasible for larger lesions, especially those > 3.3 cm, due to increased toxicity and a higher RN rate.

Several studies have evaluated the relationship between the modalities of CRT and the risk of RN. RN is uncommon in patients receiving WBRT alone, which is related to the low total cumulative dose of WBRT[28]. Several retrospective studies showed that RN was usually associated with high-dose local radiotherapy, such as SRS or brachytherapy, with or without additional WBRT added, and the RN rate was as high as 19%[25, 29, 30]. In terms of WML, a study on patients with extensive BMs showed that compared to SRS alone, the incidence of WML treated with WBRT was higher (79%); additionally, the WML rate of WBRT + SRS was as high as 97%, while that of SRS alone was only 3%[31]. In this study, only one patient suffered from RN in the WBRT group. However, in patients with WML, 76.8% of patients had received WBRT, regardless of whether they had received PBRT. This also showed that SRS or PBRT could increase the risk of RN, and WBRT was related to WML.

When patients suffered from recurrence of BM after CRT, re-radiotherapy was still an effective treatment, but it could increase the occurrence of RN. One study on RN and cognitive dysfunction in patients after radiotherapy for nasopharyngeal carcinoma showed that re-radiotherapy with a total dose > 80 Gy was significantly associated with the occurrence of RN ($p = 0.003$)[32]. The analysis of risk factors in this study showed that although there was no significant difference between RN and re-radiotherapy, there was a tendency (OR = 3.40; 95% CI 0.99–11.67, $p = 0.051$). The potential reasons may be the limited sample size and the low incidence of RN.

As the risk factors for WML, Reuck et al. conducted a comparative analysis on the severity and distribution of WML in imaging and histology in 84 people without brain tumor disease and concluded that the natural incidence of WML was significantly related to age. There was no occurrence of WML in

people under 35 years old. The incidence of middle-aged people without dementia was 11%~20% and 100% in 85-year-old individuals[33]. In this study, the risk of WML before CRT was not related to age. This may be related to the unbalanced baseline age composition of the included patients. In our research, the proportion of the elderly group (≥ 65 years old) was relatively low. Besides, the formation of BM and the use of a systemic therapeutic regimen before CRT may change the structure of brain white matter. The results suggested that the application of WBRT and the higher dose per fraction or cumulative dose of WBRT resulted in a higher incidence of WML. Therefore, for patients with higher requirements for quality of life, if they have to receive WBRT, the risk of WML could be reduced by reducing the dose per fraction and increasing the fraction times.

Regarding the impact of RN on survival, Colaco et al. conducted survival analysis on 180 patients with BM and concluded that the mOS was significantly longer for those with RN at 23.7 months (95% CI 18.3–38.5 months) than for those in the group without RN at 9.9 months (95% CI 7.9–11.7 months) ($p = 0.01$) [34]. Our survival analysis also drew similar conclusions, and the difference was statistically significant. We deemed that this might be related to the higher sensitivity of metastatic tumors to radiation in patients with better treatment effects. In addition, RN as a delayed treatment effect, the use of ICIs had prolonged the survival, resulting in a higher diagnostic rate. There was no significant correlation between the development of WML and the survival time of patients with BM.

Limitations

Limitations of our study include its retrospective nature and the small sample size, which reduced the statistical power and led to no significant difference in RN incidence between the two groups. In addition, because ICIs were incorporated into medical insurance in January 2020 in China, the number of patients using ICIs was relatively small. However, the results of our study showed that ICIs increased the risk of RN. This conclusion still needs to be proven by a study with a large sample size. Second, the lack of pathology on the subsequent lesions to distinguish RN from pseudoprogression and tumor recurrence and subjective bias in imaging evaluation cannot be completely avoided. Therefore, the imaging evaluation of this study was conducted by three imaging experts to minimize the bias caused by subjectivity. Third, during the follow-up, the cognitive function evaluation methods were limited, which makes it impossible to analyze the correlation between WML and cognitive dysfunction. The relevance needs to be explored through more prospective research.

Conclusions

In general, in the era of immunotherapy, ICIs could increase the risk of RN for BM patients with lung cancer, especially when used within three months of CRT. The number and size of BMs were significantly correlated with RBI. The risk of RBI can be reduced through the adjustment of radiotherapy parameters. In addition, secondary radiotherapy tends to increase the risk of RN, which still needs much research to be verified.

Abbreviations

BM: brain metastases, CRT:cranial radiotherapy, ICIs: immune checkpoint inhibitors, RBI: radiation-induced brain injury, RN: radiation-induced necrosis, WML: white matter lesion, MRI: magnetic resonance imaging, CTCAE: common Terminology Criteria for Adverse Events, TKIs: tyrosine kinase inhibitors, WBRT: whole brain radiotherapy, PBRT: partial brain radiotherapy, WBRT-SIB: WBRT with simultaneous integrated boost, LC: local control, BBB: blood-brain barrier, PFS: progression free survival, OS: overall survival, NSCLC: non-small cell lung cancer, SRS: stereoscopic radiosurgery, IMRT: intensity-modulated radiotherapy, FLAIR: fluid-attenuated inversion recovery, LQ: lesion quotient, T2WI: T2-weight, ROC: receiver operating characteristic, KPS: Karnofsky performance status, PVWM: periventricular white matter, DWM: deep white matter.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Shandong Cancer Hospital and Institute and was performed in accordance with the Declaration of Helsinki.

Consent for publication

Agreed.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Authors' contributions

JL conceived and drafted the manuscript. WL, SX, YL and SL acquired the patient data. JL, SX and FC analyzed these patient data. JY and HZ edited and corrected the manuscript. All authors read and approved the fnal manuscript.

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Table

Table 1 is available in the Supplementary Files section.

Figures

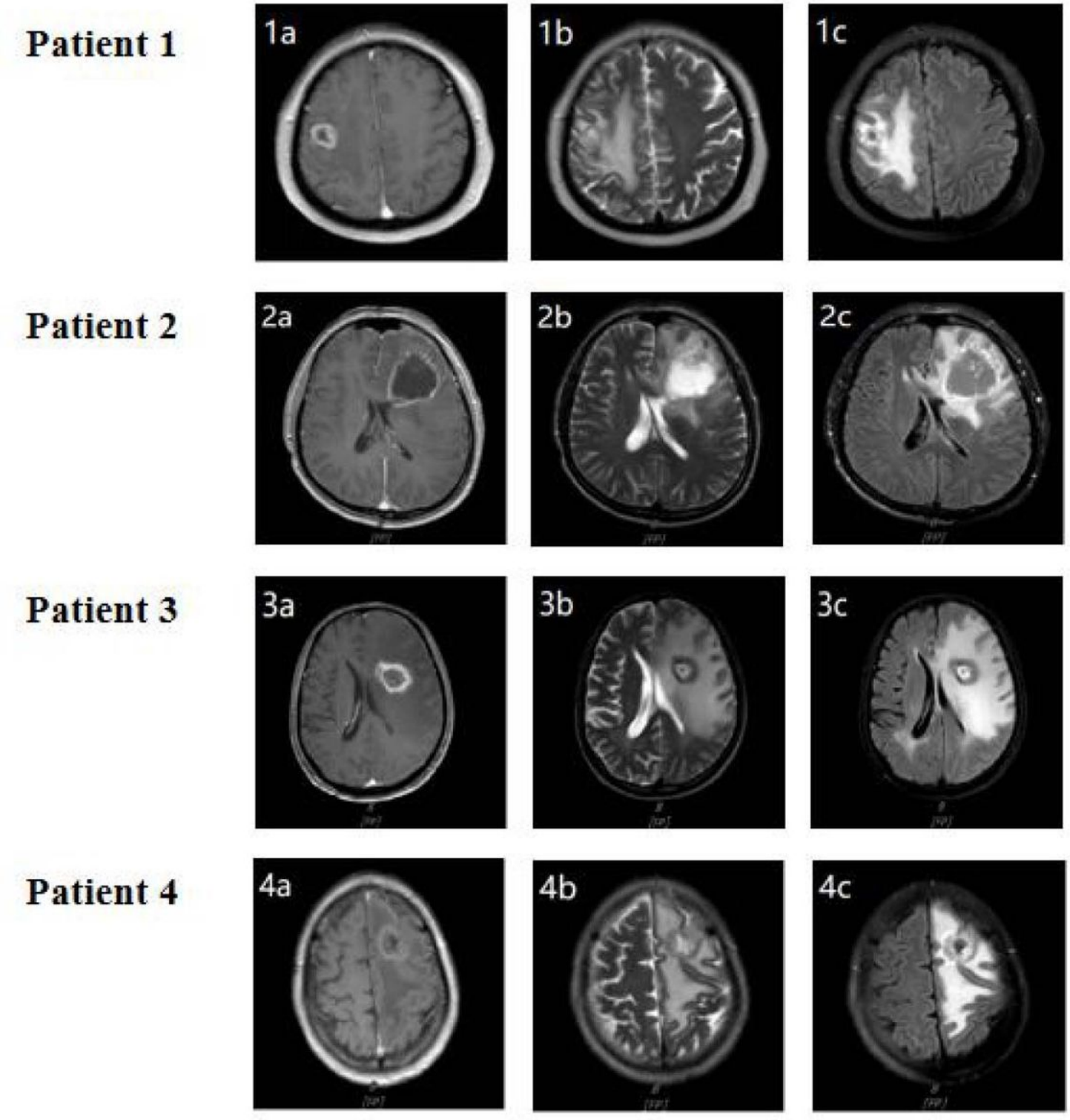
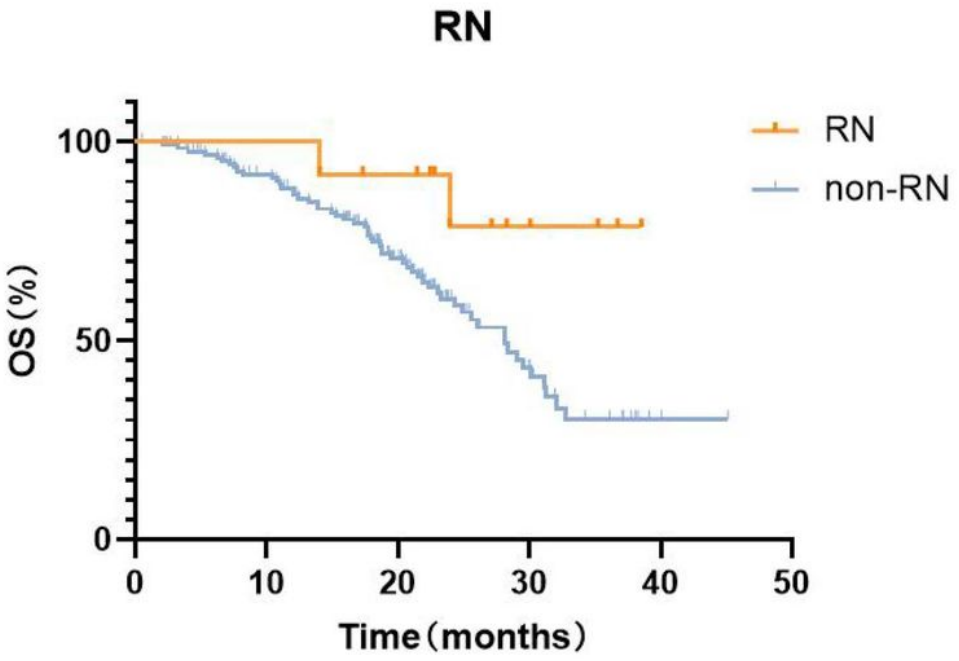


Figure 1

Typical RN imaging performance of 4 patients. a. TIWI b. T2WI c. T2 FLAIR

(A) :



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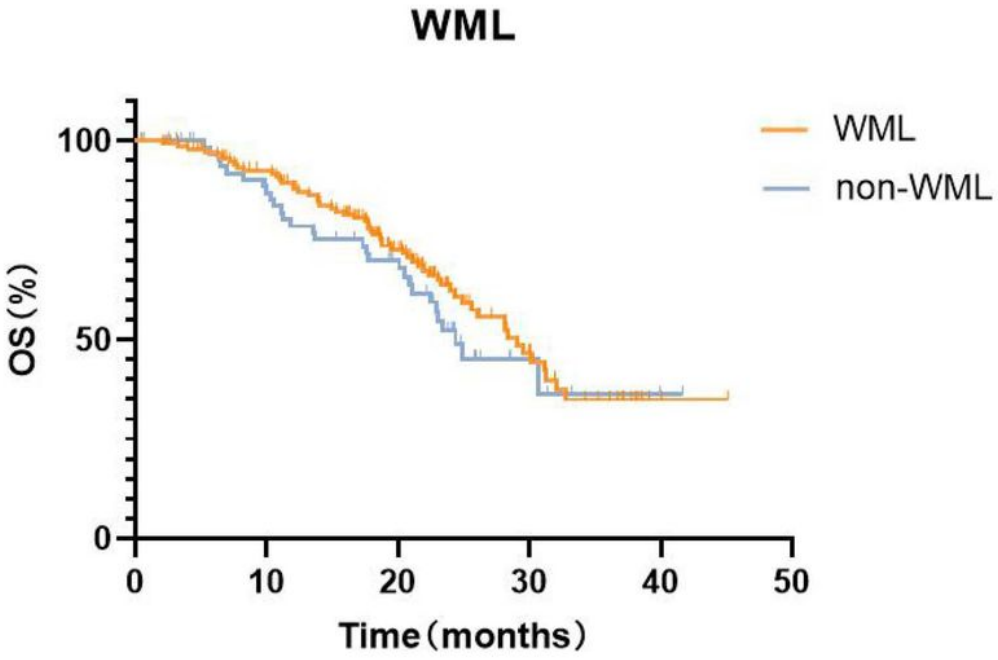

Figure 2

(A) Comparison of Survival outcomes between patients with and without brain necrosis (RN); (B) Comparison of Survival outcomes between patients with and without white matter lesion (WML).

Supplementary Files

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- Table1.docx