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Therapeutic effectiveness and safety of sequential ICIs with radiotherapy for symptomatic brain and bone metastases in NSCLC patients

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Abstract

In advanced non-small cell lung cancer (NSCLC), the brain and bones are common metastatic sites, and the disease seriously affects the survival time and quality of life. For metastatic lesions with symptoms, local treatment often precedes systemic treatment. However, in clinical trials, patients with symptomatic brain or bone metastases are often excluded. Therefore, limited data are available on the efficacy of immune checkpoint inhibitors (ICIs) in those patients. We aimed to evaluate the effectiveness and safety of local radiotherapy followed by ICIs in driver gene-negative NSCLC patients with symptomatic local metastasis in the brain and bone. This is a 29-month 2 centered retrospective cohort study performed in China between March 2019 and August 2021. A total of 22 patients with advanced NSCLC were included. All patients received radiotherapy in the brain or bone before the administration of ICIs. For all patients, the overall response rate was 59.09%, the median progression-free survival (PFS) was 7.5 months, the PFS rate at 6 months was 72.73%, and the PFS rate at 1 year was 13.64%. Waterfall plots showed that tumor size was mostly reduced compared with baseline. The spider map showed that the tumor continued to shrink. In terms of symptom improvement, 100% pain control and 83.33% improvement were observed in epilepsy and neurological function. Sequential ICIs with local radiotherapy is effective for the treatment of patients with symptomatic brain and bone metastases of driver gene-negative NSCLC, which will benefit patients and improve their symptoms.

Abbreviations: CCRT = concurrent radiochemotherapy, CR = complete response, CT = computed tomography, ICIs = immune checkpoint inhibitors, irAEs = immune-related adverse reactions, mPFS = median progression-free survival, NSCLC = non-small cell lung cancer, ORR = overall response rate, OS = overall survival, PD = progression disease, PD-1 = programmed cell death-1, PFS = progression-free survival, PR = partial response, PS = performance status, SD = stable disease, SREs = skeletal related event, SRS = stereotactic radiotherapy, WBRT = whole-brain radiotherapy.

Keywords: bone metastasis, brain metastasis, ICIs, NSCLC, radiotherapy

1. Introduction

Immunotherapy is another effective cancer treatment after surgery, chemoradiotherapy, and targeted drug therapy. Immune checkpoint inhibitors (ICIs) are one of the most successful treatments and have been used to treat multiple tumors including non-small cell lung cancer (NSCLC),[1,2] liver cancer,[3] melanoma, and Hodgkin's lymphoma because of their definite efficacy and long-term durable response. In the field of advanced NSCLC treatment, Keynote, Checkmate, and Impower series of studies have successively achieved positive results; programmed cell death-1 (PD-1) and programmed cell death-ligand1 inhibitors have been approved by the US Food and Drug Administration for the first-line clinical application of advanced NSCLC. Multiple ICIs in China have been approved by the National Medical Products Administration for the first-line clinical application of advanced NSCIC.

In advanced NSCLC, the brain and bones are common metastatic sites. For example, in NSCLC patients, brain metastases are as high as 20% at initial diagnosis,[4] and about 44% of NSCLC patients eventually develop brain metastases in the subsequent course of the disease.[5] In clinical trials, patients with symptomatic brain or bone metastases are often excluded. A subset of patients with brain metastasis was enrolled in a series of studies of first-line immunotherapy or combination immunotherapy for NSCLC. However, patients with brain metastasis were asymptomatic, had stable brain metastasis with no neurological symptoms associated with brain metastasis at least 2

YH and QL contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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weeks before enrollment, had no systemic cortisol treatment at least 2 weeks before enrollment, or were stable and received less than 10 mg of prednisolone or equivalent hormone therapy.[6] In the clinical setting, for patients with obvious local symptoms, local treatment often precedes systemic treatment, whereas radiotherapy is the preferred treatment among several local treatments. Systemic treatment is administered after local symptoms are under control. However, for advanced NSCLC, especially driver gene mutation-negative NSCLC, the effect and extent of local radiotherapy on systemic therapy are unclear.

In the era of immunotherapy, the combination of radiotherapy and immunotherapy has a profound theoretical basis. Theoretically, radiotherapy can induce immunogenic death of tumor cells and activate T lymphocytes. Radiotherapy can reshape the tumor microenvironment; hence, radiotherapy combined with radiotherapy has garnered immense research interest, and its combination mode and timing have been explored. In the clinical setting, the analysis of KEYNOTE-001 found that patients who received radiotherapy before PD-1 monoclonal antibody treatment had better progression-free survival (PFS) and overall survival (OS) than those of patients who did not receive radiotherapy.[7] Thus, radiotherapy combined with PD-1 monoclonal antibody therapy can further improve the prognosis of patients. For patients with advanced NSCLC with brain and bone metastases, brain metastases and bone metastases are responsible for poor prognosis. In these patients, if the driver gene does not have a mutation, sequential immunotherapy is performed after radiotherapy, but relevant clinical study on its efficacy and safety is not available. Based on this, we aimed to retrospectively analyze the efficacy and safety of local radiotherapy followed by immune combination chemotherapy in patients with driver gene-negative NSCLC with symptomatic local metastasis (brain and bone) to investigate the best treatment modality for such patients.

2. Materials and methods

2.1. Patients

We retrospectively reviewed 22 patients with symptomatic brain metastasis or bone metastasis of NSCLC who had received radiotherapy and immunotherapy at The Second Affiliated Hospital of Chongqing Medical University and the Xinqiao Hospital Army Medical University between March 2019 and August 2021. The main inclusion criteria were as follows: patients aged ≥ 18 years, with an Eastern Cooperative Oncology Group Performance Status (PS) of ≤ 2, all patients had at least 1 measurable lesion for imaging evaluation according to the Response Evaluation Criteria in Solid Tumors guidelines (version 1.1), each subject had pathologically confirmed NSCLC and diver gene negative, tumor staging was assessed based on the 8th edition of the American Joint Committee on Cancer staging manual. All patients with symptomatic brain metastasis or bone metastasis, including epilepsy, intracranial hypertension, nerve dysfunction, and pain, all patients who had not received systemic anti-tumor therapy previously, follow-up after treatment for ≥ 3 months and adequate hematological and organ function, tolerant and voluntary agreed to the treatments and provided signed informed consent of routine medical documents.

2.2. Treatment

The brain or bone metastasis lesions received hypofractionated stereotactic radiotherapy[8] and 6 Mv X-ray therapeutic beams. The PD-1 inhibitor was administrated with chemotherapy within 1 week of radiotherapy. In bone metastases, including cervical vertebra (1, 7.69%), the rib (3, 23.08%), thoracic vertebra (2, 15.38%), lumbar vertebra (4, 30.76%), femur (2, 15.38%), and ilium (1, 7.69%), radiotherapy was 30 Gy in 10 fractions to indicate the dose, and radiotherapy administered for metastatic brain tumors was 51 Gy in 17 fractions or 45 Gy in 15 fractions to the indicated dose.

Different drugs were selected according to the different pathological types of patients. Patients with adenocarcinoma were administered PD-1 inhibitor with pemetrexed (500 mg/m^2)-carboplatin (AUC 5) chemotherapy every 21 days. The patients with squamous cell carcinoma were administered the PD-1 inhibitor with paclitaxel (135 mg/m^2)/albumin paclitaxel (260 mg/m^2)-carboplatin (AUC 5) chemotherapy every 21 days. After 4 cycles, the patients received maintenance therapy until the progression of the disease or unacceptable toxic effects manifested in accordance with the guidelines.

Informed patient consent was obtained before their participation, and the patient-related protocols were approved by ethics committee of the second affiliated hospital of Chongqing Medical University.

2.3. Follow-up

The baseline evaluation included imaging with computed tomography (CT) of the chest and abdomen, brain magnetic resonance imaging, symptomatic brain metastasis, and bone metastasis assessment, including epilepsy, nerve dysfunction, intracranial hypertension, and pain. Ninety percent of the patients in our study received radiographic evaluation every 6 weeks and the remaining 10% every 8 weeks. All patients were followed up for disease progression or were unable to tolerate the treatment. All surveillance scans were evaluated by an experienced radiologist for the status of initial lesions, the optimal response to therapy, and disease progression, based on the response evaluation criteria in solid tumors v1.1 criteria. The PFS, overall response rate (ORR), and the disease control rate were evaluated, and the PFS rates were counted at 3, 6, and 9 months and then at 1 year.

Safety was evaluated by assessing vital signs and clinical laboratory test results, including hematology, blood histochemistry, blood electrolyte, urinalysis, coagulation function, and serum tumor markers concentration at the same frequency as that in imageology examination. The incidence and severity of adverse events were monitored and assessed from the beginning of radiation according to the National Cancer Institute Common Terminology Criteria for adverse events (version 4.0).

2.4. Statistical analysis

PFS was estimated by the Kaplan–Meier method, and the log-rank test was applied for further analysis of PFS between the response groups. All analysis was performed according to the Statistical Package for the Social Science (version 22.0). Each test was performed at the 0.05 significance level, and all *P* values were 2-sided.

3. Results

3.1. Patient characteristics

The clinical factors including age, gender, smoking history, PS score, pathological type, best response, brain metastasis, bone metastasis, number of metastases, the expression status of programmed cell death-ligand1, and primary complaint are shown in Table 1. Among all the subjects, 21 were male and 1 was female. The median age of all patients was 61 years (range, 39–77 years). A total of 27% of patients were nonsmokers. The best response of all 22 subjects was as follows: no patients had a complete response (CR), 13 (59.09 %) had a partial response (PR), 7 (31.82%) had stable disease (SD), and 2 (9.09%) had progressive disease (PD), as shown in Table 1.

Table 1

Characteristics of 22 NSCLC patients.

Characteristics	Subset	No	%
Gender	Male	21	95.45
	Female	1	4.55
Age (yr)	Median	61	
	Range	39-77	
Smoking history	Former	16	72.72
	Never	6	27.27
ECOG performance status score	0	6	27.27
	1	16	72.73
Pathological type	Adenocarcinoma	16	72.73
	Squamous cell carcinoma	6	27.27
Number of metastases per patient	< 5	10	45.45
	≥ 5	12	54.55
PD-L1 express	< 1%	10	45.45
	1-49%	10	45.45
	> 50%	2	9.10
Brain metastasis	Yes	13	59.09
	1-5 brain metastases	8	61.54
	6-10 brain metastases	4	30.77
	> 10 brain metastases	1	7.69
	No	9	40.91
Bone metastasis	Yes	13	59.09
	No	9	40.91
Primary complaint	Pain	17	77.28
	Epilepsy and Neurofunction Deficit	6	27.27
	Intracranial Hypertension	6	27.27
Best response	CR	0	0.00
	PR	13	59.09
	SD	7	31.82
	PD	2	9.09
PD-1 inhibitor	Pebolizumab	2	9.09
	Sintilimab	7	31.82
	Camrelizumab	13	59.09

CR = complete response, ECOG = Eastern Cooperative Oncology Group, NSCLC = non-small cell lung cancer, PD = progression disease, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand1, PR = partial response, SD = stable disease.

3.2. Response to therapy

The PFS curves of all patients are shown in Figure 1; the median PFS (mPFS) was 7.5 months. The PFS curves in both brain metastasis and bone metastasis groups are shown in Figure 2, and those in adenocarcinoma and squamous cell carcinoma groups are shown in Figure 3. mPFS in the bone metastasis group was 8 months, and mPFS in the brain group was 6 months. It was 6 months in the adenocarcinoma group and 8 months in the squamous cell carcinoma group. PFS rates at 3 months, 6 months, 9 months, and 1 year in all patients and response evaluation, ORR, and disease control rate are shown in Table 2.

The waterfall plot and spider map of tumor recession for all patients based on resist 1.1 criteria are shown in Figures 4 and 5. The waterfall plot showed the best regression of all 22 patients, no one had a CR, 13 (59.09 %) had PR, 7 (31.82%) had SD, and 2 (9.09%) had PD. The spider map showed tumor recession or growth after every follow-up time in 22 patients.

Primary complaint remission in bone and brain metastasis were as follows: pain (17, 100%), dyskinesia (2, 100%), intracranial hypertension (5, 83.33%), and neurological signs (3, 75.00%). The symptom remission rate was greater than 75% in total.

3.3. Safety

All grades of immune-related adverse events (irAEs) were assessed in 22 cases, and irAEs occurred in 19 patients. A total of 5 (26.31%) cases had ≥ 3 grades according to WHO criteria for evaluating the efficacy of adverse reactions, resulting in permanent termination of treatment in 1 case, treatment adjustment in 6 cases, and death of 1 case because of massive hemoptysis. In the case of irAEs, immune-related dermatitis had the highest incidence in 8 cases (42.10%), followed by immune-related hypothyroidism in 6 cases (31.58%). A total of 5 patients developed therapy-related grade ≥ 3 toxicities, among which 1 case had immune-related pneumonia with severe new symptoms, involving more than 50% of lung parenchyma with limited self-care ability and required oxygen and hospitalization. Another case of immune-related dermatitis had papules area > 30% of the whole body skin, accompanied by erythema, and limited daily self-care. The third case had immune-related dermatitis with intense persistent skin itching and disrupt sleep. The fourth case had an immune-related liver injury with alanine aminotransferase that increased 8 times and aspartic transaminase that increased 5 times. The fifth case had massive hemoptysis with death after immunotherapy. Refer to Table 3.

The radiotherapy-related adverse events in patients with bone and brain metastasis were observed in about 15 patients (68.18%) and included radiation enteritis, radioactive pharyngitis, radiation esophagitis, intracranial hypertension, and myelosuppression. Intracranial hypertension showed the highest incidence in 8 patients (36.36%) (Table 4 and graded with Common Terminology Criteria for Adverse Events) (version 5.0).

4. Discussion

Lung cancer is a malignant tumor with high morbidity and mortality worldwide. NSCLC is a common pathological type of lung cancer, accounting for about 85% of lung cancer. In NSCLC patients, the brain and bones are common sites of metastasis. About 60% of NSCLC patients will develop brain metastasis throughout the disease, and the incidence of bone metastasis is up to 40%. Once brain metastases occur, the prognosis is poor, and the survival time of untreated patients is 1 to 2 months. Even patients who received standardized radiotherapy had limited OS.[9,10] Lung cancer bone metastasis occurs in weight-bearing bone, and most lung cancer bone metastases are osteolytic, seriously affecting the quality of life. More than 40% of patients have skeletal-related events (SREs) 3 months after the diagnosis of bone metastasis.[11] Once SREs occur, it significantly shortens the survival time of patients. Studies have shown that the survival time can be shortened by half, and if combined with severe SREs such as hypercalcemia, pathological fractures, spinal cord

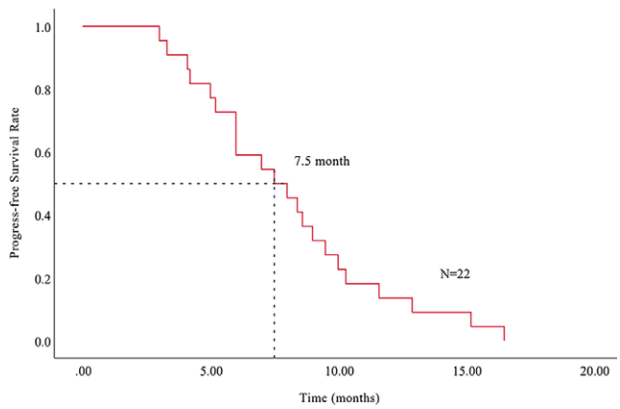

Figure 1. Progress-free survival curves of all patients.

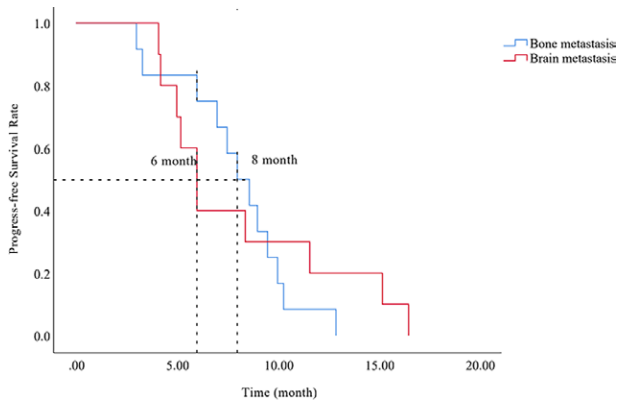

Figure 2. Progress-free survival curves in both bone and brain groups.

compression, and other complications, the survival of patients will be further shortened.[12] Therefore, in the clinical setting, once symptomatic NSCLC brain metastasis or bone metastasis is diagnosed, the lesions causing symptoms need to be treated on time.[13]

Radiotherapy is a common treatment for brain and bone metastases in NSCLC patients because of its definite efficacy. Radiotherapy is commonly used in combination with immunotherapy. Radiotherapy combined with immunotherapy has a deep theoretical basis. First, radiotherapy can block cell division through direct and indirect effects and has a direct therapeutic effect on tumors.[14] Second, radiotherapy can induce immunogenic death of tumor cells, form a "tumor vaccine," activate T lymphocytes, and produce distant effects. Third, radiotherapy can remodel the tumor microenvironment, and radiotherapy promotes the normalization of abnormal blood vessels, activates endothelial cells, upregulates the expression of vascular adhesion molecules, and increases the content of T cells in tumors.[15] Radiation injury can upregulate the expression of adhesion molecules and promote the infiltration of T cells in the tumor microenvironment. In the clinical setting, radiotherapy combined with immunotherapy can provide survival benefits to patients with advanced cell lung cancer. The PEMBRO-RT study is the first study to explore the efficacy of pembrolizumab combined with stereotactic body radiation therapy (SBRT) versus pembrolizumab in advanced lung cancer and found that pembrolizumab administration after SBRT improved the treatment response rate by more than twice and was well tolerated.[16] However, retrospective studies have reported that previous thoracic radiotherapy did not improve the efficacy but increased the incidence of immune pneumonia. At present, for

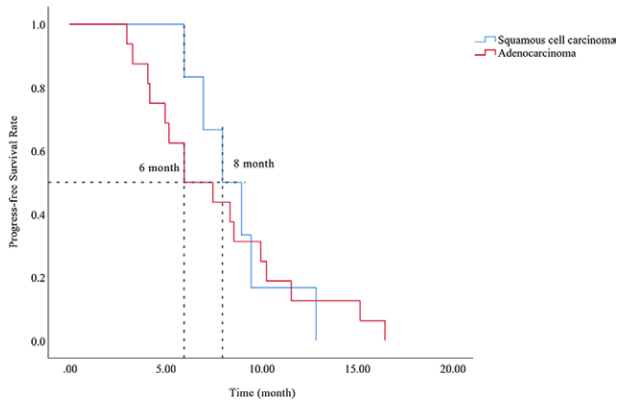

Figure 3. Progress-free survival curvesin in both squamouscell carcinoma and adenocarcinoma groups.

advanced NSCLC, radiotherapy is mostly administered before immunotherapy, and radiotherapy dose conventional fractionation, hypofractionation, and SBRT are used. A Pacific study demonstrated that durvalumab significantly improved PFS, OS, metastasis-free survival, and incidence of new lesions with tolerable toxicity compared with those treated with placebo for locally advanced NSCLC, thus making it a recommended maintenance therapy after concurrent chemoradiotherapy (CCRT) in patients with stage III unresectable lung cancer.[17] These results suggest that thoracic radiotherapy combined with immunotherapy is effective and has tolerable side effects. However, whether radiotherapy for brain and bone metastases can have high immunotherapeutic efficacy is unclear.

In the radiotherapy of brain metastases, the commonly used treatment modalities are whole-brain radiotherapy (WBRT) and stereotactic radiotherapy (SRS). The use of WBRT prolongs median overall survival in patients with brain metastases[18]; however, because of the strong association between WBRT and cognitive decline, clinical oncologists are ambiguous about the use of WBRT in patients with brain metastases.[19] Compared with WBRT, SRS can increase the dose to metastases and reduce the dose to surrounding tissues, thereby reducing adverse effects. Currently, in the clinical setting, hypofractionation or SRS alone is preferred for the treatment of NSCLC patients with brain metastases.[20] In the radiotherapy of bone metastases, the main purpose is palliative analgesia; hence, the commonly used irradiation method is 30 Gy in 10 fractions to indicate dose or 40 Gy in 20 fractions to indicate dose. As the increase in the number of irradiation may delay the systemic treatment, 30 Gy in 10 fractions to indicate dose is more commonly used. Compared with conventional fractionation, hypofractionation combined with ICIs better activates immunity.[21] Data from the literature showed that ablative versus palliative only radiotherapy yields clinical benefits for patients treated with ICIs.[22] Therefore, theoretically, radiotherapy for brain and bone metastases can induce the immunogenic death of tumor cells, reshape the tumor immune microenvironment, and activate immunity. We retrospectively studied patients with primary symptomatic brain and bone metastases, and the doses of radiotherapy were 51 Gy in 17 fractions or 45 Gy in 15 fractions to indicate dose, respectively. A single radiotherapy dose greater than 3 Gy was called hypofractionation radiotherapy. After the completion of radiotherapy, immunotherapy combined with chemotherapy was administered as recommended by the guidelines. The results revealed that for all patients, the ORR was 59.09%, mPFS was 7.5 months, the PFS rate at 6 months was 68.18%, and the PFS rate at 12 months was 13.64%. The ORR was 50% in the brain metastasis group, mPFS at 6 months, PFS rate at 6 months was 50%, and the PFS rate at 12 months was 20%. Waterfall plots showed that tumor size was mostly reduced compared with baseline. The spider map showed that the tumor continued to shrink. In terms of symptom improvement, the data showed 100% pain control and 100% improvement in neurological function. Because of the lack of similar clinical studies in the past, we compared our study with clinical studies involving asymptomatic brain metastasis. A study compared the effect of baseline brain metastases on the efficacy of first-line pembrolizumab in combination with platinum-based chemotherapy versus that with chemotherapy alone. Studies pooled data from KEYNOTE-021 cohorts G (non-squamous), KEYNOTE-189 (non-squamous), and KEYNOTE-407 (squamous) advanced NSCLC patients. All studies allowed for the stabilization of patients with brain metastases. The study showed that the ORR of pembrolizumab combined with chemotherapy was significantly higher than that of chemotherapy regardless of brain metastasis status, and the duration of response was significantly higher. In patients with brain metastases, the OS was 18.8 months and 7.6 months, and the PFS was 6.9 months and 4.1 months for pembrolizumab combined with chemotherapy and chemotherapy alone,

Table 2

Survival analysis and response evaluation of all patients.

	Bone metastasis (n = 12)	Brain metastasis (n = 10)	Adenocarcinoma (n = 16)	Squamous cell carcinoma (n = 6)	Total (n = 22)
PFS rates [n (%)]					
3 mo	12 (100.00)	10 (100.00)	16 (100.00)	6 (100.00)	22 (100.00)
6 mo	10 (83.33)	6 (60.00)	10 (62.50)	6 (100.00)	16 (72.73)
9 mo	5 (41.67)	3 (30.00)	5 (31.25)	3 (50.00)	8 (36.36)
1 yr	1 (8.33)	2 (20.00)	2 (12.50)	1 (16.67)	3 (13.64)
Response evaluation [n (%)]					
CR	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
PR	8 (66.67)	5 (50.00)	8 (50.00)	5 (83.33)	13 (59.09)
SD	3 (25.00)	4 (40.00)	6 (37.50)	1 (16.67)	7 (31.82)
PD	1 (8.33)	1 (10.00)	2 (12.50)	0 (0.00)	2 (9.09)
ORR [n (%)]	8 (66.67)	5 (50.00)	8 (50.00)	5 (83.33)	13 (59.09)
DCR [n (%)]	11 (91.67)	9 (90.00)	14 (87.50)	6 (100.00)	20 (90.91)

CR = complete response, PD = progression disease, PFS = progression-free survival, PR = partial response, SD = stable disease.
ORR: objective response rate (ORR = CR + PR).
DCR: disease control rate (DCR = CR + PR + SD).

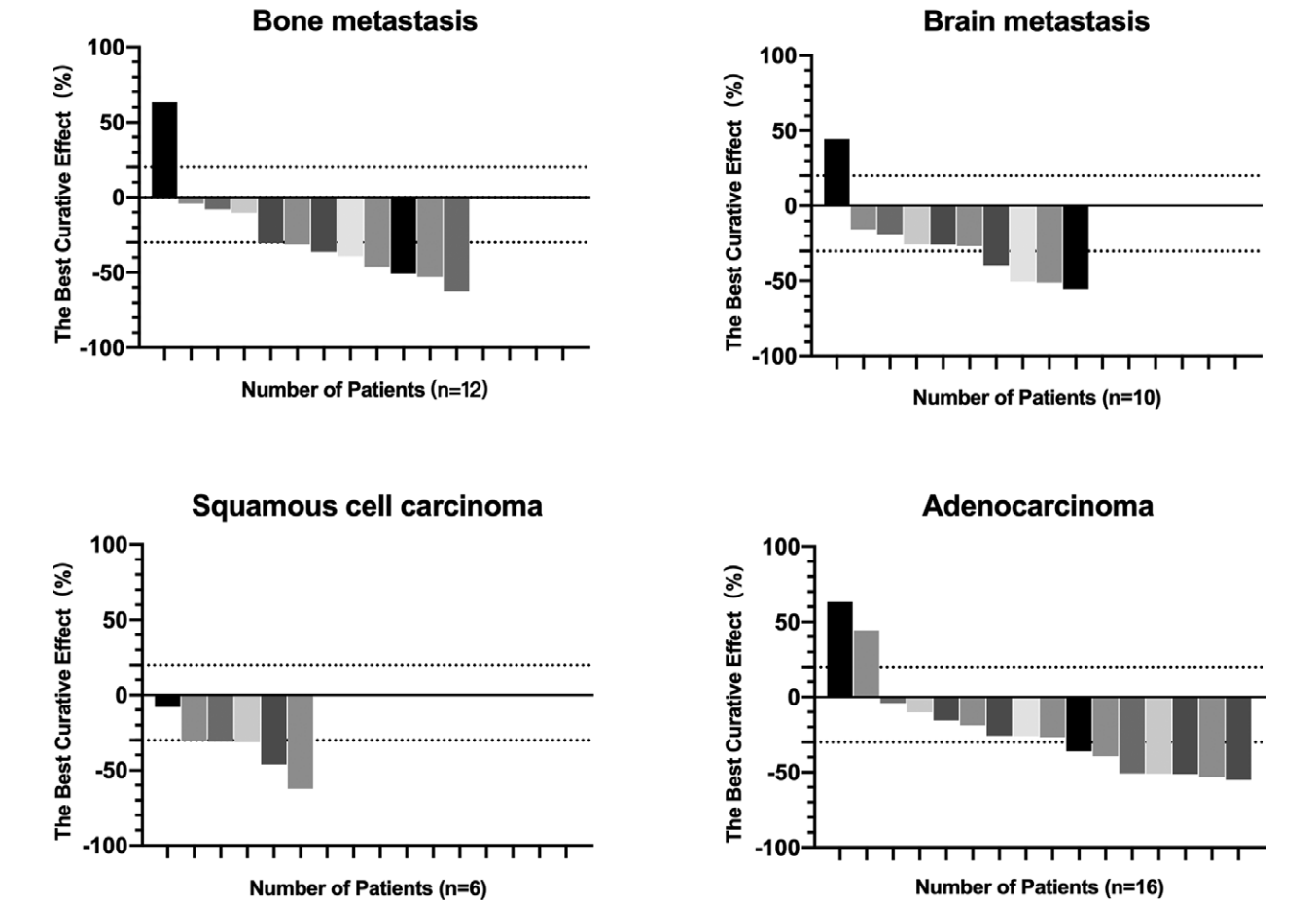

Figure 4. Waterfall plot of tumor recession for all the patients based on RECIST 1.1 criteria. RECIST = response evaluation criteria in solid tumors.

respectively.[23] Our study showed that even with symptomatic brain metastases, hypofractionated radiotherapy followed by sequential ICIs combined with chemotherapy, and patients could achieve similar short-term results, especially for symptom control such as pain and loss of brain function.

In thoracic radiotherapy sequential or combined with immunotherapy, safety is a common concern. In the PACIFIC or LUN14-179 studies, immunotherapy was started 1 to 42 days and 28 to 56 days after the end of radical CCRT, respectively. An important reason for this is to circumvent severe treatment-related pneumonia caused by the superposition of radiation pneumonitis and immune pneumonitis. The PACIFIC study showed a significant benefit in OS for patients who initiated immunotherapy within 14 days of concurrent chemotherapy compared with patients who initiated immunotherapy after 14 to 42, suggesting that a shorter interval between immunization and radiotherapy is better. The phase II clinical study KEYNOTE-799 of pembrolizumab combined with CCRT for the treatment of unresectable stage III (IIIA–IIIC) cell lung cancer showed that 72 patients (64.3%) and 30 patients (41.1%)

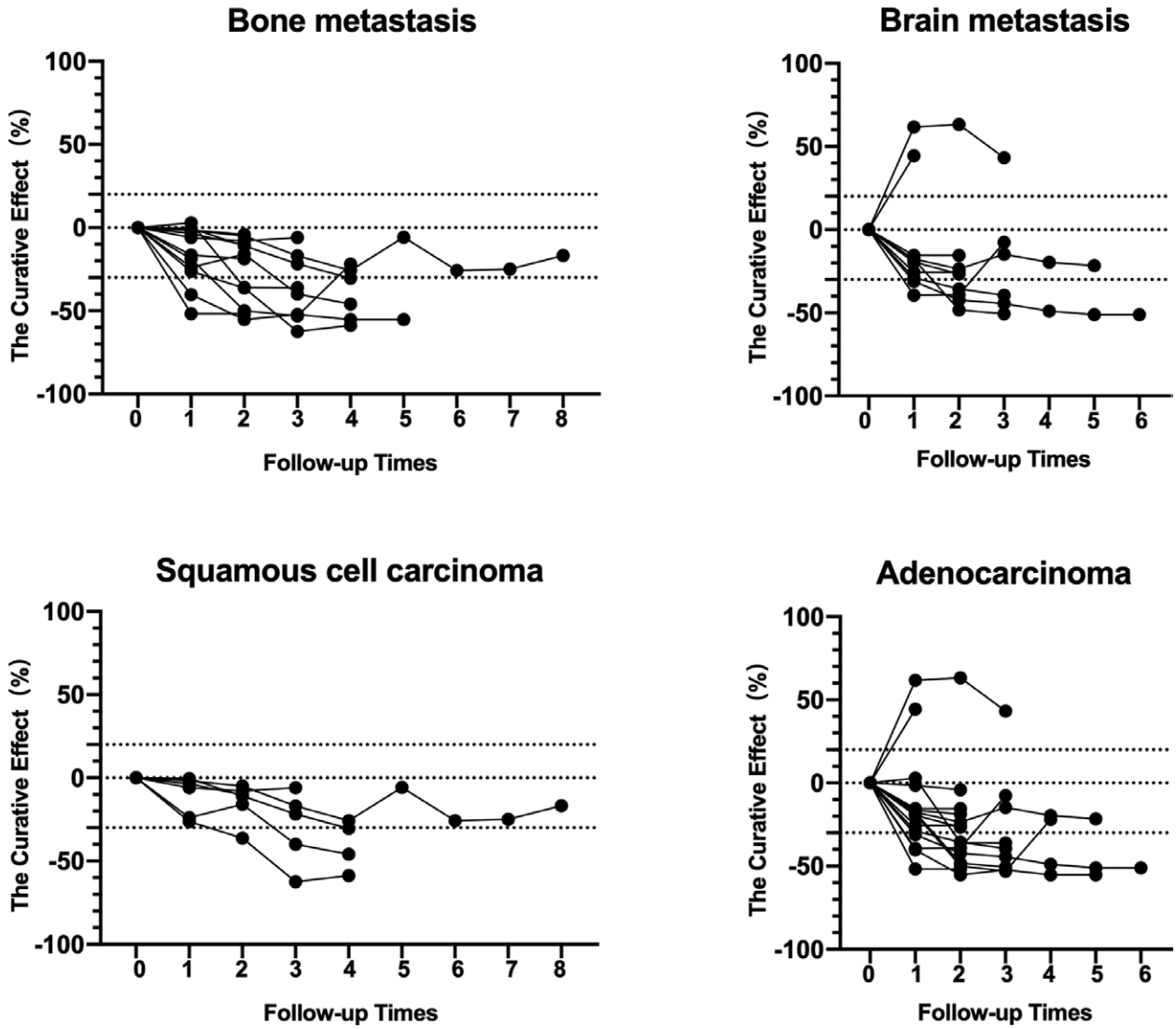

Figure 5. Spider map of tumor recession for each patients based on RECIST 1.1 Criteria. RECIST = response evaluation criteria in solid tumors.

Table 3

Immune-related adverse event and grading of all patients（n = 19）.

irAEs（n = 19）	All grades [n (%)]	≧ 3 grade [n (%)]
Pneumonia	3（15.79）	1（5.26）
Hypothyroidism	6（31.58）	0（0.00）
Liver injury	1（5.26）	1（5.26）
Death	1（5.26）	1（5.26）
Dermatitis	8（42.10）	2（10.52）
Lead to treatment adjustment	6（31.58）	—
Resulting in permanent termination of treatment	1（5.26）	—

irAEs were observed in only 19 patients of all the 22 patients.
irAEs = immune-related adverse reactions.

in cohorts A and B, respectively, had treatment-related adverse reactions of grade 3 or higher.[24] Based on these reasons, to ensure the efficacy and reduce side effects, we administered sequential immunotherapy after radiotherapy instead of synchronous therapy and controlled the administration of immunotherapy within 1 week after radiotherapy. The sites receiving radiotherapy in this study included the thoracic vertebra and lumbar vertebra. No significant occurrence of interstitial pneumonia was observed in patients receiving sequential immunotherapy with radiotherapy for thoracic metastasis, which may be related to the low dose of radiotherapy received by the patients.

5. Conclusion

Symptomatic brain and bone metastases are common accompanying symptoms of newly diagnosed NSCLC, and radiotherapy to control symptoms does not affect the efficacy due to the delay of systemic treatment before systemic immune-combined chemotherapy. On the contrary, radiotherapy can increase the efficacy of immunotherapy and improves symptoms with controllable side effects.

Author contributions

Conceptualization: Cuiping Tang, Yusheng Huang.
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Formal analysis: Cuiping Tang, Yusheng Huang.
Funding acquisition: Yusheng Huang.
Investigation: Cuiping Tang, Qian Li, Yusheng Huang.
Methodology: Cuiping Tang, Qian Li.
Project administration: Cuiping Tang.

Table 4

Primary complaint remission and radiotherapy-related adverse event in bone and brain metastasis.

Characteristics	N(%)	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)	Grade 5 (n)
Primary complaint remission（n = 22）						
Pain	17(77.27)	7	9	1	0	0
Epilepsy and Neurofunction Deficit	5(22.73)	4	1	0	0	0
Intracranial Hypertension	5(22.73)	2	2	1	0	0
Radiotherapy-related adverse event（n = 22）[n(%)]						
Any radiotherapy-related adverse event	15(68.18)	10	4	1	0	0
Radiation enteritis	3(13.64)	1	2	0	0	0
Radioactive pharyngitis	1(4.55)	1	0	0	0	0
Radiation esophagitis	2(9.09)	2	0	0	0	0
Intracranial hypertension	8(36.36)	5	2	1	0	0
Myelosuppression	1(4.55)	1	0	0	0	0

Resources: Cuiping Tang, Qian Li.
Software: Cuiping Tang, Qian Li.
Supervision: Cuiping Tang, Yusheng Huang.
Validation: Yusheng Huang.
Visualization: Yusheng Huang.
Writing – original draft: Cuiping Tang.
Writing – review & editing: Yusheng Huang.

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