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Clinical Study of Stereotactic Radiosurgery Combined with Osimertinib in the Treatment of EGFR-Positive Lung Cancer Brain Metastases

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Abstract

Background: To observe the safety and efficacy of stereotactic radiosurgery synchronous osimertinib compared with osimertinib alone in the treatment of patients with brain metastasis of EGFR-positive non-small cell lung cancer. **Methods:** EGFR-positive non-small cell lung cancer patients with brain metastasis admitted to our hospital from January 2018 to January 2020 were selected. The experimental group: 30 patients were treated with SRS combined with osimertinib. SRS treatment: prescription dose (d = 0 - 40 mm, 27 Gy/3f); targeted treatment scheme: osimertinib, 80 mg/day, taken orally after SRS treatment; control group: 30 patients were treated with osimertinib alone; osimertinib was maintained until disease progression (PD) or adverse reactions were intolerable. PFS, ORR, DCR and AEs of intracranial lesions were observed. **Results:** This study included 60 patients, with a median age of 54.8 (35 - 79) years, included 41 males and 19 females, with a median follow-up time of 34.5 (30 - 42) months. There were 30 cases in the experimental group and 30 cases in the control group, respectively. The ORR of intracranial lesions in the two groups were 96.67% and 66.67%, respectively, with significant statistical difference between the two groups ($p = 0.003$). The DCR of intracranial lesions was 100% and 96.67%, respectively, and there was no significant difference between the two groups ($p = 0.313$). The median PFS of intracranial lesions was 26.5 months and 16.5 months, respectively. There was a significant difference between the two groups ($p < 0.001$). The most common adverse event of radiotherapy was radioactive brain edema. The incidence of grades I - II in the experimental group was 43.33%. After treatment of intracranial pressure reduc-

tion, it improved, and no grades III - IV radioactive brain edema occurred. The second adverse event was osimertinib I - II, mainly including diarrhea, rash, oral ulcer, etc. **Conclusions:** SRS synchronous osimertinib therapy is more effective than simple osimertinib in the treatment of brain metastasis of EGFR-positive non-small cell lung cancer patients, and the side effects are tolerable. We look forward to further large phase III clinical studies to confirm it.

Keywords

Stereotactic Radiosurgery, Osimertinib, Advanced Non-Small Cell Lung Cancer, Brain Metastasis

1. Introduction

Lung cancer is the malignant tumor with the highest incidence rate and mortality rate in the world at present [1], which more than 80% is non-small cell lung cancer (NSCLC), 10% - 15% of non-small cell lung cancer has brain metastasis at the time of initial diagnosis, about 50% of patients will have brain metastasis in the whole disease course, and the incidence of brain metastasis in lung cancer patients with positive driving genes is higher [2] [3]. Targeted therapy is the first choice for first-line treatment of gene-positive advanced lung adenocarcinoma in clinical practice both domestically and internationally [4] [5], or a combination of surgery, proton radiation therapy, spiral tomographic radiation therapy (TOMO), stereotactic radiosurgery (SRS), and whole brain radiation therapy (WBRT). At present, there is no clinically controlled study comparing the efficacy differences between the two treatment methods of first receiving brain metastasis radiotherapy combined with epidermal growth factor receptor (EGFR) Tkis treatment or first receiving EGFR Tkis treatment. The aim of this study is to explore the safety and efficacy of SRS synchronous osimertinib compared to simple osimertinib in the treatment of EGFR-positive non-small cell lung cancer patients with brain metastasis.

2. Method

2.1. Study Subjects

Advanced lung adenocarcinoma patients admitted to our oncology department from January 2018 to January 2020 were selected. Inclusion criteria: 1) Pathological and cytological examination confirmed lung adenocarcinoma; 2) Head plain scan + enhanced MRI indicates brain metastases with ≤4 lesions and a diameter of ≤40mm; 3) Age ≥ 18 years old; 4) Gene testing (including pathological tissue and blood samples): EGFR positive (mutations in exons 19 and 21); 5) There were no abnormalities in blood routine, blood biochemistry, electrocardiogram, and bone scan before treatment; 6) KPS score ≥ 60 points; 7) The expected survival period is >3 months. Exclusion criteria: 1) Previous use of anti-tumor therapy; 2)

Poor compliance; 3) People with serious basic diseases (including uncontrolled hypertension and diabetes). A total of 72 patients were screened, according to inclusion and exclusion criteria, and 60 patients were included after screening. They were included and randomly divided into the SRS synchronous osimertinib treatment group (Group A: 30 cases) and the simple osimertinib treatment group (Group B: 30 cases) according to the case follow-up system of the oncology department of our hospital.

2.2. Grouping and Methods

This study protocol was registered with the China Clinical Trial Registration Center (identifier: ChiCTR1900025626, Reg Date: 2019/09/03) and approved by the Medical Ethics Committee of Yueyang Central Hospital (identifier: 20190901). SRS was conducted by four oncologists (Weng Jie with 28 years of experience, Xiao Jia with 10 years of experience, Xie Wangti with 12 years of experience, and Yu Wu with 20 years of experience, all had the latest professional certificates). According to the Declaration of Helsinki (revised in 2013), all patients voluntarily participated in this clinical trial. All patients were informed of the current standard treatment protocol and alternative treatment protocol before treatment and signed an informed consent form. Randomly divided into the experimental Group A (n = 30) and the control Group B (n = 30). Group A received synchronous treatment with osimertinib for SRS. SRS treatment: Prescription dose (d = 0 - 40 mm, 27 Gy/3f); targeted treatment plan: osimertinib, 80 mg/day, orally administered on the day of SRS treatment; Group B: 30 patients were treated with simple osimertinib. Osimertinib is maintained until disease progression (PD) or adverse reactions are intolerable. If there are adverse events related to grades III - IV osimertinib, osimertinib will be temporarily discontinued.

2.3. Observation Indicators

The main outcome measure of this study is progression-free survival (PFS), while the secondary outcome measures are overall response rate (ORR), disease control rate (DCR) and adverse events (AEs). The efficacy evaluation refers to RECIST version 1.1, which includes complete response (CR), partial response (PR), disease stability (SD), and disease progression (PD); ORR = (CR + PR)/Total number of cases × 100%; DCR = (CR + PR + SD)/total number of cases × 100%, review head MRI, neck chest abdominal CT, and bone scan every 2 months for efficacy evaluation. Adverse reactions refer to the evaluation criteria for adverse reactions specified by the National Cancer Institute (NCI) in CTCAE version 4.0. Our department is one of the national clinical drug trial bases, and patient data is collected based on our registration and follow-up system. All patients were followed up by returning to the hospital for follow-up or phone calls.

2.4. Statistical Analysis

All data were analyzed using SPSS 22.0, qualitative data were analyzed using Chi-

square test, quantitative data were compared between groups using t-test, survival analysis was performed using Kaplan Meier method, and survival time was compared between groups using Log rank method. $p < 0.05$ was the significant difference.

3. Results

The patient characteristics are listed in Table 1. The two groups had the same baseline characteristics. The efficacy analysis is listed in Table 2.

Table 1. Patient characteristics.

Patient characteristics		Control group ($n = 30$)	Experimental group ($n = 30$)	p
Sex				
	man	22	19	0.405
	female	8	11	
Age				
	Median age (range)	53 (40 - 68)	55 (41 - 70)	
ECOG				0.573
	0 - 1	20	22	
	2 - 3	10	8	
Smoking (Y/N)				0.605
	Y	13	15	
	N	17	15	
Symptoms of brain metastasis (Y/N)				0.605
	Y	15	13	
	N	15	17	
Number of brain metastases				0.606
	1 - 2	16	14	
	3 - 4	14	16	
EGFR mutation				0.284
	Exon 19	17	14	
	Exon 21	13	16	
Extracranial metastasis (Y/N)				0.417
	Y	21	18	
	N	9	12	

3.1. Efficacy Analysis

The ORR of intracranial lesions in the two groups of patients was 96.67% and

66.67%, respectively, with a significant statistical difference between the two groups (p = 0.003). The DCR of intracranial lesions was 100% and 96.67%, respectively, with no statistically significant difference between the two groups (p = 0.313).

3.2. Adverse Event Analysis

The most common adverse event of radiation therapy is radiation-induced brain edema. The incidence rates of grade I and grade II in the experimental group were 26.67% and 16.67%, respectively. After receiving intracranial pressure reduction treatment, the improvement was observed, and no grade III or grade IV radiation-induced brain edema occurred. Next are adverse events of osimertinib, mainly including diarrhea, rash, oral ulcers, etc. (Table 2).

Table 2. Comparison of adverse reactions between two groups of treatment.

Groups	Grade	Adverse reactions			
		Radiation-induced brain edema	Diarrhoea	Oral ulcer	Erythra
Control group, n (%)	I - II	0	8 (26.67%)	9 (30.00%)	18 (60.00%)
	III - IV	0	0	0	0
Experimental group, n (%)	I - II	13 (43.33%)	9 (30.00%)	7 (23.33%)	22 (73.33%)
	III - IV	0	0	0	1 (0.33%)

3.3. Follow up and PFS

This study was followed up until June 2022, with a median follow-up of 34.5 months. There were no treatment-related deaths in both groups of patients. The median PFS of intracranial lesions was 26.5 months and 16.5 months, respectively. There was a significant statistical difference between the two groups (p < 0.001) (Figure 1).

4. Discussion

Before the advent of targeted therapy drugs for lung cancer, once NSCLC experienced brain metastasis, the traditional standard treatment regimen included surgery, chemotherapy, and radiation therapy, with a median OS of approximately 3 - 14.8 months [6]. Surgery is suitable for lung cancer patients with brain metastases who have good control of extracranial lesions, severe intracranial hypertension symptoms, and good physical condition [7]. Chemotherapy drugs (such as pemetrexed, paclitaxel, and platinum) have poor blood-brain barrier permeability and poor efficacy in patients with NSCLC and brain metastasis [8]. Radiotherapy for NSCLC patients with brain metastasis includes proton radiotherapy [9], TOMO radiotherapy [10], WBRT [11], and SRS [12]. Previous research results suggest that radiotherapy can open the blood-brain barrier and improve the

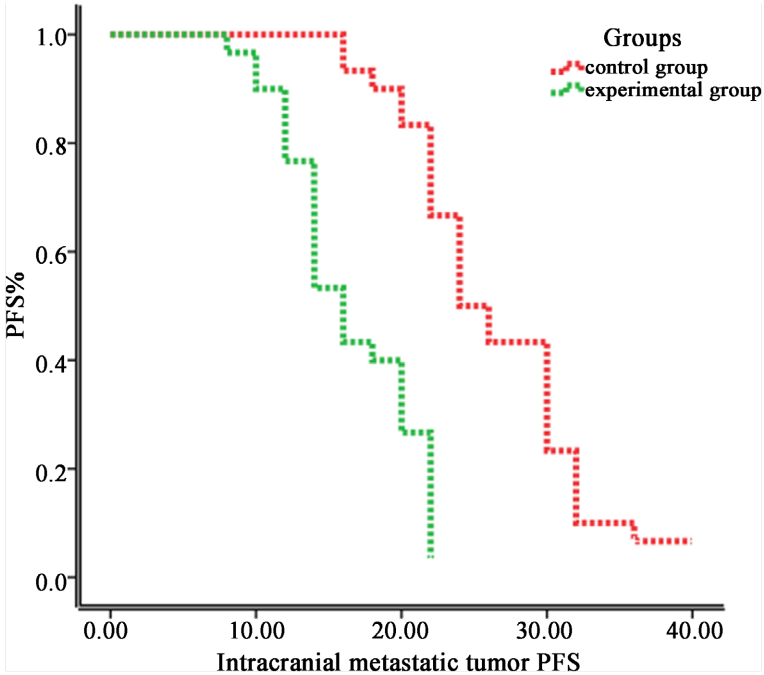

Figure 1. Intracranial progression-free survival in the experimental and control groups.

efficacy of EGFR driven gene positive advanced NSCLC patients [13]-[17]. The RTOG-9505 study [18] summarized the tolerable doses of SRS for the treatment of recurrent primary brain tumors or brain metastases. The maximum tolerable doses of SRS were 24 Gy, 18 Gy, and 15 Gy when the maximum diameter of the tumor was ≤2.0 cm, 2.1 - 3.0 cm, and 3.0 - 4.0 cm, respectively. However, the data from this center's study showed that the incidence of acute and chronic radiation-induced brain edema was as high as 60% when the diameter of the brain metastases was ≤20 mm and the SRS dose (24 Gy/1f). Based on previous studies, therefore, this study used the SRS (27 Gy/3f) regimen to treat T790M positive non-small cell lung cancer patients with brain metastasis. The efficacy of the patients was no less than that of a single SRS regimen (24 Gy/1f), and the incidence of radiation-induced brain edema was about 15%.

The emergence of lung cancer-targeting drugs has significantly prolonged the survival period of advanced lung cancer and improved the quality of life of patients. The mutation rate of lung adenocarcinoma driving gene in Asian population is about 60%, of which EGFR mutation is the most common. The FLAURA study results showed that osimertinib showed significant benefits in treating median PFS in EGFR-positive NSCLC patients compared to the first-generation EGFR Tkis drug (19.1 months and 10.9 months, respectively) [19]. The AURA3 study results showed that the median intracranial PFS of T790 positive NSCLC patients with brain metastasis treated with the osimertinib group and pemetrexed combined with cisplatin group was 11.7 and 5.6 months, respectively, and the intracranial ORR was 70% and 31%, respectively [20]. In 2017, Magnuson *et al.* [21] retrospectively analyzed 351 patients with EGFR-positive NSCLC accompa-

nied by brain metastasis. The results showed that patients who received sequential EGFR Tkis treatment after SRS treatment had a longer OS survival benefit (46 months). Priority was given to EGFR Tkis treatment and the timing of radiotherapy was postponed, significantly leading to a decrease in OS benefit (25 months). In 2017, Magnuson *et al.* [21] studied 351 patients with EGFR-positive NSCLC accompanied by brain metastasis. Among them, 100 patients received SRS first, 120 patients received WBRT first, and 131 patients received EGFR Tkis first. The results showed that the median OS of the three groups was 46 months, 30 months, and 25 months, respectively, and the median intracranial PFS was 23 months, 24 months, and 17 months, indicating that using EGFR Tkis first in patients with EGFR-positive NSCLC accompanied by brain metastasis would reduce OS, following SRS followed by EGFR-Tkis treatment can prolong patient survival and reduce cognitive impairment in the central nervous system (CNS). In addition, multiple research results have shown that SRS is more effective than WBRT and can better preserve CNS cognitive function [22]-[25]. The SRS synchronous EGFR Tkis regimen is more effective than WBRT and EGFR Tkis alone in treating EGFR-positive NSCLC patients with brain metastasis, and the side effects are tolerable.

The preliminary research results of our center suggest that a single SRS (24 Gy/1f, diameter of metastatic lesion ≤ 20 mm) has a high incidence of acute and chronic radiation-induced brain edema of grades III - IV, reaching over 60%. The design of this study used three segmentation methods: SRS (27 Gy/3f, 9 Gy/1f). The results of this study showed that the median PFS of intracranial lesions in the experimental group and the control group were 26.5 months and 16.5 months, respectively, with significant statistical differences between the two groups ($p < 0.001$). The ORR of intracranial lesions in the two groups was 96.67% and 66.67%, respectively, with a significant statistical difference between the two groups ($p = 0.003$). The DCR of intracranial lesions was 100% and 96.67%, respectively, and there was no statistically significant difference between the two groups.

The common adverse reactions of osimertinib include diarrhea, rash, oral ulcers, and nail toxicity [26], all ranging from grade I to grade II, with no discontinuation observed. The most common adverse event of radiation therapy is radiation-induced brain edema. The incidence of grades I - II radiation-induced brain edema in the experimental group was 43.33%, and improved after treatment with intracranial pressure reduction. No grades III - IV radiation-induced brain edema occurred.

In summary, compared with the control group, SRS combined with osimertinib treatment can significantly improve the median PFS and ORR of intracranial lesions in EGFR-positive non-small cell lung cancer patients with brain metastasis. In addition, the adverse reactions of SRS combined with osimertinib treatment are controllable and worthy of clinical promotion. However, the sample size of this study is limited, and the reliability of the conclusions still needs to be further confirmed by prospective multicenter randomized controlled studies.

5. Conclusion

There has been controversy over whether patients with NSCLC and brain metastases should receive EGFR-TKI first, or receive head radiotherapy simultaneously, or receive EGFR-TKI treatment later. This study confirms that in patients without head symptoms, receiving EGFR-TKI treatment simultaneously with head SRS can improve patient survival without increasing comorbidities.

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Authors' Contributions

In 2019, our hospital established lung cancer MDT with the following members. Wangti Xie is responsible for designing research plans, implementing research, and writing papers; Yu Wu, Xiaoshan Cheng, Jianbing Hu, Jie Weng, Fang Wen, Jia Xiao, Rong Dang, Xiang Yao, Xianggan Huang, and Dunqian Liu are responsible for collecting clinical data, proposing research ideas, providing technical guidance, imaging guidance, and revising papers; Yuqi Su and Jianlong Fang are responsible for literature search and data analysis.

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Availability of Data and Materials

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

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee of Yueyang Central Hospital (20190901) on 2019/09/01.

Conflicts of Interest

This study was independently conducted by the undersigned author in accordance with the statement of contribution, and no undue position or financial interest was accepted as a result of conducting the study, thereby re-evaluating the independence of the study. Sex and scientificity are guaranteed.

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Abbreviations

SRS	stereotactic radiosurgery
TOMO	tomographic radiation therapy
WBRT	whole brain radiation therapy
EGFR	epidermal growth factor receptor
NSCLC	non-small cell lung cancer
PFS	progression free survival
ORR	overall response rate
DCR	disease control rate
AEs	adverse events
CR	complete response
PR	partial response
SD	disease stability
PD	disease progression