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ORIGINAL ARTICLE

Clinical research on stereotactic radiosurgery combined with epithermal growth factor tyrosine kinase inhibitors in the treatment of brain metastasis of non-small cell lung cancer

Feng Jia, Xiangming Cheng, Hongsheng Zeng, Juncheng Miao, Meiying Hou

Department of Oncology, Jinxiang People's Hospital, Jining, China.

Summary

Purpose: *To compare the clinical efficacy and safety of stereotactic radiosurgery (SRS) combined with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) versus whole-brain radiation therapy (WBRT) combined with EGFR-TKIs in the treatment of brain metastasis of non-small cell Lung cancer (NSCLC).*

Methods: *The clinical data of patients with brain metastatic NSCLC who had EGFR-sensitive mutation and followed between January 2014 and January 2016 was retrospectively analyzed. Patients were divided into two groups according to their treatment types. Fifty seven patients were treated with SRS combined with EGFR-TKIs, while another 57 patients were treated with WBRT combined with EGFR-TKIs. The clinical efficacy, intracranial progression-free survival (iPFS), systemic progression-free survival (sPFS), overall survival (OS,) and adverse reactions were compared between the two groups. Computed tomography (CT) or magnetic resonance imaging (MRI) were used for imaging evaluation in both groups and all patients underwent symptomatic treatment such as dehydration or hormone therapy according to the patient's condition. The efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.1) and adverse reactions were assessed based on the criteria for toxic reaction of anti-cancer drugs of WHO.*

Results: *There were no statistically significant differences in general conditions between the two groups of patients. The median iPFS and median sPFS were similar between the two groups (12.2 months vs. 11.5 months and 10.7 months vs. 9.8 months respectively, p>0.05). The median OS of patients treated with SRS + EGFR-TKIs was significantly longer than in those treated with WBRT + EGFR-TKIs (25.1 months vs. 22.0 months, respectively, p=0.042). No statistically significant differences were found in the objective response rate (ORR), disease control rate (DCR), the incidence rates of cytopenia, gastrointestinal reaction and liver dysfunction between the two groups (p>0.05). There were 8 cases with radiotherapy-associated grade 3 or higher brain damage in SRS + EGFR-TKIs group compared to 19 cases in those treated with WBRT + EGFR-TKIs, suggesting that the incidence rate of radiation-induced brain injuries in SRS + EGFR-TKIs group was remarkably lower than those in WBRT + EGFR-TKIs group (p=0.026).*

Conclusion: *The clinical efficacy of SRS combined with EGFR-TKIs is comparable to that of WBRT combined with EGFR-TKIs in the treatment of NSCLC patients with ≤3 brain metastases and EGFR-sensitive mutation and the OS of patients is longer, with lower toxic side effect and higher safety, hence SRS combined with EGFR-TKIs should be used as the preferred therapeutic regimen.*

Key words: *brain metastasis, EGFR-TKIs, NSCLC, SRS, WBRT*

Introduction

At present, the brain metastasis of NSCLC is often treated with comprehensive therapy modality, including the surgery, WBRT, SRS, chemotherapy, targeted therapy, adrenocortical hormone and anticonvulsant symptomatic treatment [1]. WBRT has long been a basis of treatment for brain metasta-

Correspondence to: Meiying Hou, BM. Department of Oncology, Jinxiang People's Hospital, No. 117, Jinfeng East Rd, 272200 Jinxiang County, Jining, Shandong, China.
Tel: +86 013953732656, E-mail: Sdjxxrmyyjf1117@sina.com
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sis of lung cancer, which can increase the survival time and reduce the local recurrence rate. However, WBRT alone can prolong the median OS of most patients only to 3-6 months [2,3]. Currently, the optimal mode based on different radiation doses remains controversial and the radiotherapy dose of WBRT fails to be curative due to its brain toxicity, therefore the local control rate is still unsatisfactory. The advent of small-molecule TKIs and other oral targeted drugs opened a new direction for the treatment of EGFR-positive patients with brain metastasis of lung cancer. A lot of studies have proved that TKIs can prolong the OS and iPFS of NSCLC patients with brain metastasis and EGFR-sensitive mutation and TKIs have gradually become the first-line therapeutic regimen for patients with brain metastasis [4-7]. In China and other countries, EGFR-TKIs combined with WBRT have been applied in the treatment of NSCLC accompanied with brain metastasis, however, its efficacy remains controversial [8].

In recent years, SRS has become a very important therapeutic method for intracranial metastatic disease, especially unresectable brain metastasis. Compared with WBRT, SRS can accurately locate the high-dose radioactive ray to the metastatic lesion in the brain, with a less damage to surrounding normal brain tissues, thereby alleviating the radiotherapy-induced adverse reactions [9,10]. Studies have demonstrated that the treatment of intracranial metastatic disease with SRS can damage the blood-brain barrier and enhance the intracranial local blood circulation, thus resulting in an increase in the intracranial concentration of targeted drugs and improving the local control rate [11]. SRS can quickly control the tumor development, reduce the tumor burden, and stimulate the body's immune response in the treatment of primary lung lesion or oligometastatic disease. At the same time, it can remove the TKI-resistant subsets and prolong the effective time of EGFR-TKIs, thus extending the survival of patients.

This study aimed to compare the clinical efficacy and safety of SRS combined with EGFR-TKIs versus WBRT combined with EGFR-TKIs in the treatment of NSCLC accompanied with brain metastasis, hoping to provide references for the selection of individualized therapeutic regimen for patients with NSCLC brain metastasis.

Methods

Patients

A total of 114 lung cancer patients with brain metastasis, who were treated in our hospital from January 2014 to January 2017, were enrolled. All patients were histologically diagnosed with NSCLC and the EGFR-sensitive mutation was confirmed via molecular pathological examination. There were 64 males and 50 females, with age ranging between 27 to 80 years. In terms of pathological type of primary tumor, there were 91 cases with of adenocarcinoma, 8 cases with squamous cell carcinoma, 7 cases with adeno-squamous carcinoma, and 8 cases with unclassified NSCLC. There was one intracranial metastasis in 64 cases, 2 to 3 intracranial metastases in 50 cases, and no case with more than 3 metastases. In terms of Karnofsky performance score (KPS), there were 49 cases with ≥ 60 points and 65 cases with < 60 points. The volume of intracranial metastatic tumor was ≥4.5 cm^3 in 45 cases and <4.5 cm^3 in 69 cases. This study was approved by the ethics committee of Jinxiang People's Hospital. Signed written informed consents were obtained from the patients and/or their guardians.

Inclusion criteria: 1) patients histologically diagnosed with NSCLC; 2) patients with brain metastatic lesion confirmed via CT or MRI; 3) patients with single brain metastasis ≤5 cm, or ≤ 3 brain metastatic lesions and the diameter of each metastatic tumor ≤3 cm; and 4) patients with EGFR-sensitive mutation confirmed via molecular pathological detection, including exon-18 mutation, exon-19 deletion, and exon-21-L8585R mutation. Results of the routine blood cell and blood biochemical examinations were within normal values. The KPS reached 60 points and over after symptomatic treatment. Before treatment, patients or their families were informed of the precautions and risks of treatment and they agreed and signed the informed consent. All patients had complete follow-up data.

Exclusion criteria: 1) patients undergoing full-dose radiotherapy in the treatment target; 2) pregnancy or lactation; 3) patients recently prepared for childbearing; 4) patients receiving previous anti-tumor drug; 5) patients with obvious dysfunction in the liver, kidney, bone marrow, or other vital organs; 6) uncontrolled infections, or patients with uncontrolled cardiovascular diseases, including congestive heart failure, unstable angina, malignant pericardial effusion, or severe arrhythmia.

Treatment methods

WBRT: Patients were treated with WBRT using the 6MVX line accelerator for parallel double-field whole-brain radiation. The radiotherapy mode was DT3000-4000 cGy/10-20 times and the local dose could be increased by 1000-1500 cGy/3-5 times based on the condition.

SRS: The Leksell stereotactic instrument was installed under local anesthesia, during which the lesion should be located in the center of headstock as far as possible. GE 1.5 Tesla MRI thin-slice scan was performed (slice thickness: usually 2-3 mm) under Gd-DTPA enhancement. MRI was performed to obtain the MRI scan image data under normal magnetic field homogeneity. The treatment plan was completed using the Leksell Gamma plan-TPS software system, the MRI scan image sequence was input, and the lesion scope and surrounding organs at risk were accurately delineated. At the same time, the tumor site, size and surrounding organs

at risk were noticed, and only 5-15 mm collimator was used, while 20 mm and 25 mm collimators were seldom used. Finally, the treatment was completed using the HO-LY-SRRS CNC full-automatic gamma ray SRS treatment system.

In the treatment plan developed by our hospital, the peripheral dose was 12-20 Gy, the 50% isodose curve was most commonly used and the coordinate position was comprehensively considered from the three-dimensional perspective when the target was designed. The crystalline lens is the most sensitive tissues to radiation and its tolerance dose is 4-5 Gy. Sometimes it is needed to block the lead using the cribriform foramina and the ray should be avoided passing through the eyeball when the treatment plan was designed. The corresponding therapeutic dose was given according to the number and volume of metastatic tumor and whether it was in the functional area. After treatment, symptomatic treatments, such as dehydration or hormone therapy, were performed, and anti-epileptic therapy was conducted if necessary, followed by close observation for 1 week.

Gefitinib (250 mg/d) or erlotinib (150 mg/d) was orally administered in both groups and the efficacy was evaluated after 1 month. The treatment was maintained for responders until the disease progression or unacceptable toxicity.

Observation indexes

After treatment for 4 weeks, routine biochemical tests including liver and renal functions were reviewed and patients were followed up once every month and underwent imaging examinations of the chest and brain every other month. The therapeutic effect was divided into complete response (CR, disappearance of all known lesions), partial response (PR, decline in the sum of products of the largest diameter and the largest vertical diameter by 50% and above), stable disease (SD, no other changes in the lesion) and progressive disease (PD, increase in the sum of products of the largest diameter and the largest vertical diameter by 25% and above, or appearance of new lesion(s)) according to the Response Evaluation Criteria in Solid Tumors (RECIST) [12].

Objective response rate (ORR): CR + PR, and disease control rate (DCR): CR + PR + SD. iPFS: the duration from the treatment of intracranial metastasis to the progression of intracranial lesion or death. Systematic progression-free survival (sPFS): the duration from the treatment to the progression of other non-intracranial lesions, or death. OS: the duration from the brain metastasis to the death of patients or the last follow-up. The adverse reactions were evaluated according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (version 3.0).

Statistics

SPSS 19.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Numerical variables were expressed as the mean, and classified variables were expressed as [n (%)]. Chi-square test was adopted for the comparison of difference of two or more unordered categorical data. Survival analysis was performed using the Kaplan-Meier method, and the survival difference was detected using the Log-rank test. $P<0.05$ suggested that the difference was statistically significant.

Table 1. Baseline characteristics of the studied patients

Characteristics	*SRS group n (%)*	*WBRT group n (%)*	*p value*
Age (years), mean±SD	53.5±12.9	51.8±11.3	0.456
Gender			
Male	34 (59.6)	30 (52.6)	0.572
Female	23 (40.4)	27 (47.4)	
Histological type			0.743
Squamous cell carcinoma	3 (5.3)	5 (8.8)	
Adenocarcinoma	47 (82.4)	44 (77.1)	
Adenosquamous carcinoma	4 (7.0)	3 (5.3)	
Not classified	3 (5.3)	5 (8.8)	
Numbers of intracranial metastatic tumor			0.257
1	35 (61.4)	29 (50.9)	
2-3	22 (38.6)	28 (49.1)	
Size of intracranial metastatic tumor, cm^3			0.565
≥4.5	24 (42.1)	21 (36.8)	
<4.5	33 (57.9)	36 (63.2)	
Intracranial symptoms	48/57 (84.2)	52/57 (91.2)	0.254
KPS score			0.344
≥60	27 (47.4)	22 (38.6)	
<60	30 (52.6)	35 (61.4)	

SRS: stereotactic radiosurgery, WBRT: whole-brain radiation therapy, KPS: Karnofsky performance status

Results

Patient baseline data

Patients were followed up from the diagnosis with NSCLC with brain metastasis to the death or the last follow-up. All patients were followed-up via outpatient clinic, admission, and telephone till January 2018, with a median follow-up time of 17 months (range 2-48). The baseline characteristics of patients in both groups are shown in Table 1. There were no statistically significant differences in the gender, age, pathological type, number and size of brain metastasis, central nervous system symptoms, and KPS between the two groups (p>0.05).

Table 2. The clinical effective rates in the two studied groups

	SRS group	*WBRT group*	x^2	*p value*
CR	7	9	2.418	0.490
PR	38	30		
SD	9	13		
PD	3	5		
ORR (%)	78.9	68.4		
DCR (%)	94.7	91.2		

SRS: stereotactic radiosurgery, WBRT: whole-brain radiation therapy, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: objective response rate, DCR: disease control rate

Table 3. The median iPFS, median sPFS and median OS of the two studied groups

	SRS group	*WBRT group*	*p value*
Median iPFS	12.2	11.5	0.487
Median sPFS	10.7	9.8	0.115
Median OS	25.1	22.0	0.042

SRS: stereotactic radiosurgery, WBRT: whole-brain radiation therapy, iPFS: intracranial progression free survival, sPFS: systematic progression free survival, OS: overall survival

Clinical efficacy

In terms of efficacy, there were 7 cases of CR, 38 cases of PR, 9 cases of SD and 3 cases of PD in the SRS + EGFR-TKIs group, with ORR of 78.9%, DCR of 94.7% versus 9 cases of CR, 30 cases of PR, 13 cases of SD, and 5 cases of PD in the WBRT + EGFR-TKIs group with ORR of 68.4% and DCR of 91.2%. No statistically significant differences were found in the ORR and DCR between the two groups (p>0.05) (Table 2).

Survival analysis

The median iPFS and median sPFS had no statistically significant differences between the SRS + EGFR-TKIs and WBRT + EGFR-TKIs group (12.2 months *vs.* 11.5 months, 10.7 months *vs.* 9.8 months, p=0.487 and p=0.115). The median OS of patients in the SRS + EGFR-TKIs group was significantly longer than that in WBRT + EGFR-TKIs group (25.1 months *vs.* 22.0 months, p=0.042), showing a statistically significant difference (Table 3 & Figure 1).

Adverse reactions

The grade 3 or higher adverse reactions in both groups are shown in Table 4. There were 12 versus 9 cases of rash, 2 versus 4 cases of neutropenia, 1 versus 0 cases of thrombocytopenia, 4 versus 7 cases of gastrointestinal reaction, 6 versus 4 cases of liver dysfunction, and 8 versus 19 cases of radiation-induced brain injuries in both groups, respectively. The incidence rates of rash, neutropenia, thrombocytopenia, gastrointestinal reaction, and liver dysfunction showed no statistically significant differences between the two groups (p>0.05) and the incidence rate of radiation-induced brain injuries in the SRS + EGFR-TKIs group was significantly lower than that in the WBRT + EGFR-TKIs group (p=0.026).

Table 4. The comparison of adverse reaction in the two studied groups

Parameters	*SRS group n (%)*	*WBRT group n (%)*	*p value*
Rash	13 (22.8)	9 (15.8)	0.477
Neutropenia	2 (3.5)	4 (7.0)	0.679
Thrombocytopenia	1 (1.8)	1 (1.8)	1.000
Gastrointestinal AR	4 (7.0)	7 (12.3)	0.528
Liver function damage	6 (10.5)	4 (7.0)	0.742
Radiation induced brain injuries	8 (14.0)	19 (33.3)	0.026

SRS: stereotactic radiosurgery, WBRT: whole-brain radiation therapy, AR: adverse reaction

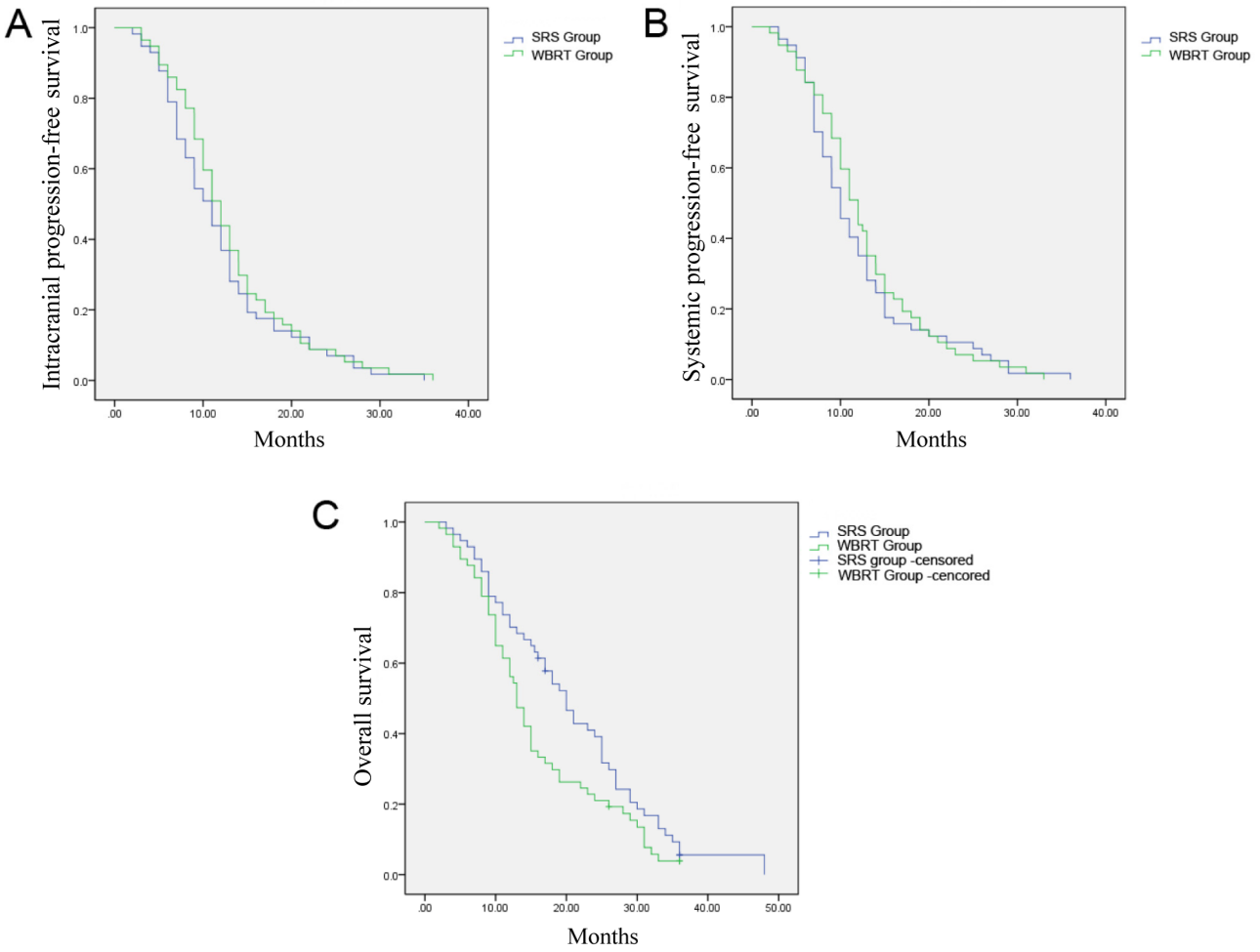

Figure 1. The survival curves in stereotactic radiosurgery (SRS) combined with EGFR-TKIs group and whole brain radiotherapy (WBRT) combined with EGFR-TKIs group, respectively. **A:** Intracranial progression-free survival (p=0.487); **B:** Systemic progression-free survival (p=0.115); **C:** Overall survival (p=0.042).

Discussion

Brain is a common site for metastasis in NSCLC and the incidence rate of brain metastasis can be up to 30-50% [13]. Currently, WBRT, SRS, hormone therapy, and surgical operation, as well as comprehensive treatment combined with molecular targeted therapy or systemic chemotherapy dominate the treatment of NSCLC with brain metastasis. WBRT is a standard therapeutic method for metastatic brain tumor, which can rapidly improve the neurological symptoms of patients with brain metastasis and control the intracranial subclinical lesion to a certain degree. However, WBRT causes irreversible damage to surrounding normal tissues due to the wide radiation range and it also leads to a variety of neurological sequelae. WBRT has a lower total dose and a higher recurrence rate, which can be performed only once and only symptomatic treatment can be performed after recurrence [14,15]. Therefore, WBRT should be applied with caution.

SRS is an emerging precision radiotherapy technique in recent years, which locates the lesion using the stereotactic technique and radiates the target region using a high-dose small-field beam once. SRS is characterized by higher single dose, fewer times of radiotherapy, and shorter course of treatment, thus increasing the local control rate, survival time, and quality of survival [16,17]. Considering the advantages of SRS, more patients have been increasingly chosen for SRS, instead of WBRT. However, the optimal therapeutic method remains controversial.

EGFR-TKIs have been used as the first-line therapeutic method for NSCLC patients with EGFR-sensitive mutation. Some studies have found a certain biological effect between EGFR-TKIs and radiotherapy. In other words, EGFR-TKIs can increase the sensitivity of tumor cells to radiotherapy through inhibiting EGFR signal transmission, blocking cell cycle, inhibiting angiogenesis, and promoting apoptosis [18]. At the same time, radiotherapy can also further increase the permeability

of blood-brain barrier, thus providing benefits for the drugs to entry into the brain with an increased concentration of EGFR-TKIs [19]. Currently, EGFR-TKIs alone or EGFR-TKIs combined with WBRT are adopted in the treatment of NSCLC with brain metastasis, but the efficacy has a certain difference in previous studies.

In this study, the efficacy of SRS combined with EGFR-TKIs versus WBRT combined with EGFR-TKIs in the treatment of NSCLC with brain metastasis was compared. The results revealed no statistically significant differences in the ORR, DCR, iPFS, and sPFS between the two groups, whereas only OS and adverse reactions were statistically significant. The median OS of patients in the SRS + EGFR-TKIs group was significantly longer than that in the WBRT + EGFR-TKIs group and the incidence rate of radiotherapy-induced brain damage was significantly lower than that in WBRT + EGFR-TKIs group, which are consistent with the literature findings reporting that SRS can prolong the OS of patients. The reason for the lower incidence rate of radiotherapy-induced brain damage in SRS versus WBRT is due to the fact that SRS can accurately locate the high-dose radioactive ray to the metastatic brain lesion, with less damage to surrounding normal brain tissues, thereby alleviating the radiotherapy-induced adverse reactions.

However, SRS is limited by the diameter of the lesion and the number of metastatic tumors. According to related literature reports, the local control rate of SRS is nearly 100% in cases with the volume of metastatic brain lesion <100 mm^3 or diameter <6 mm and SRS can prolong the OS in patients with volume of metastatic brain lesion <250 mm^3 or diameter <10 mm [20]. It is generally believed that better efficacy can be obtained in patients with largest diameter of lesion <3 cm and number of metastatic tumors <3. A recent study has proved that in patients who undergo SRS alone, the OS of those with 5-10 metastatic brain lesions is not inferior to that of those with 2-4 metastatic brain lesions, thus suggesting an indication for SRS even in case of 10 metastatic brain lesions [21]. Considering that the brain tissue invasion and the incidence rate of adverse reactions to SRS are less and lower than those in WBRT and MRI constantly increases the detection accuracy of small lesions and precise positioning of SRS, SRS combined with EGFR-TKIs has become an appropriate therapeutic choice for NSCLC patients with fewer brain metastatic lesions and EGFR-sensitive mutation.

Conclusions

The clinical efficacy of SRS combined with EGFR-TKIs is comparable to that of WBRT combined with EGFR-TKIs in the treatment of NSCLC patients with brain metastasis ≤3 and EGFR-sensitive mutation and the OS is longer with lower toxic side effect and higher safety. Thus SRS combined with EGFR-TKIs should be used as the preferred therapeutic regimen.

Conflict of interests

The authors declare no conflict of interests.

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