

Efficacy and safety of WBRT+EGFR-TKI versus WBRT only in the treatment of NSCLC patients with brain metastasis: An updated meta-analysis

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Abstract

Background: To investigate the efficacy and safety of whole brain radiotherapy (WBRT) combined with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) versus WBRT only in the treatment of brain metastasis in non-small cell lung cancer (NSCLC) patients by pooling open published data.

Methods: Prospective clinical studies relevant to WBRT+EGFR-TKI versus WBRT only in the treatment of NSCLC brain metastasis were electronically searched in the Pubmed, Embase, Cochrane, Wangfang, CNKI and Google scholar databases. The treatment response, 1-year survival and treatment-associated toxicity were pooled and expressed by odds ratio (OR) under a fixed or random effect model. The publication bias was evaluated by Begg's funnel plot and Egger's line regression test.

Results: Eighteen prospective clinical studies were included in the study. The combined results indicated that the objective response rate (ORR) in the WBRT+TKI group was superior to WBRT only with a statistical difference (OR = 2.67, 95% CI: 2.10–3.38, $p < 0.05$) under a fixed effect model. Ten studies reported the 1-year survival rate between the WBRT+TKI and WBRT only groups. The combined results showed that 1-year survival rate in the WBRT+TKI group was higher than that of the WBRT only group with a statistical difference (OR = 2.70, 95% CI: 1.95–3.74, $p < 0.05$). For treatment-associated toxicity, the combined data indicated that the treatment-related rash in the WBRT+TKI group was significantly higher than that of the WBRT only group with a statistical difference (OR = 2.72, 95% CI: 1.53–4.84, $p < 0.05$). However, the incidence of nausea/vomiting (OR = 0.84, 95% CI: 0.60–1.17, $p > 0.05$), diarrhea (OR = 1.31, 95% CI: 0.83–2.07, $p > 0.05$), fatigue (OR = 1.40, 95% CI: 0.70–2.81, $p > 0.05$) and myelosuppression (OR = 0.86, 95% CI: 0.56–1.32, $p > 0.05$) were not statistically different between the two groups.

Conclusions: Based on the current publications, WBRT+EGFR-TKI can improve the treatment response and 1-year survival rate but not increase the toxicity except for rash compared to WBRT alone in the treatment of brain metastasis in NSCLC patients.

KEYWORDS

epidermal growth factor receptor-tyrosine kinase inhibitor, meta-analysis, non-small cell lung cancer, whole brain radiotherapy

[†]Kai Zhou and Xiaoping Cai contributed equally to this work

INTRODUCTION

Lung cancer, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), is known globally as one of the leading causes of malignant tumor-associated death.¹ It has previously been reported that most NSCLC (75%) cases are at an advanced stage when first diagnosed and the opportunity of surgery as a result of metastatic brain disease has been lost.² The general prognosis for NSCLC patients with metastatic brain disease is poor with an extremely low long-term survival rate.³ At present, whole brain radiotherapy (WBRT) is generally used for controlling metastatic lesions of the brain in NSCLC patients, especially those patients with multiple brain lesions.⁴ However, the treatment response or prognosis of patients with metastatic brain disease is unsatisfactory with a median survival time of 3–6 months. Therefore, improving the treatment efficacy of NSCLC patients with brain metastasis is important in order to improve their overall survival.⁵

Tyrosine kinase inhibitors (TKIs) are small molecular targeted drugs that can inhibit tyrosine kinases. Tyrosine kinases are enzymes responsible for the activation of many proteins by signal transduction cascades. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), such as erlotinib and gefitinib, are commonly clinically used in the treatment of patients with advanced NSCLC, especially those with *EGFR/KRAS* mutation. Several studies have previously evaluated the efficacy and safety of WBRT+EGFR-TKI versus WBRT only in brain metastasis cases of NSCLC.^{6,7} However, the conclusion of these studies was different due to different treatment modality

and patients clinical heterogeneity. Therefore, we performed this meta-analysis to further evaluate the efficacy and safety of WBRT+EGFR-TKI versus WBRT only in the treatment of brain metastasis of NSCLC with an up-to-date meta-analysis.

METHODS

Identification of studies via electronic databases

Prospective clinical studies on the efficacy and safety of WBRT+EGFR-TKI versus WBRT only in the treatment of NSCLC patients with brain metastasis were electronically searched in the Pubmed, EMBase, Cochrane, Wangfang, CNKI and Google scholar databases. The electronic database searching words were: Epidermal growth factor receptor-tyrosine kinase inhibitors/EGFR-TKI, lung cancer, carcinoma of the lung, non-small cell lung cancer, whole brain radiotherapy/WBRT, and gefitinib, erlotinib. The references of the identified studies were also reviewed to determine potentially suitable publications.

Study inclusion and exclusion criteria

Inclusion criteria: (i) Prospective clinical studies relevant to WBRT+EGFR-TKI versus WBRT only in the treatment of NSCLC patients with brain metastasis. (ii) Patients included in original studies were those with NSCLC confirmed by

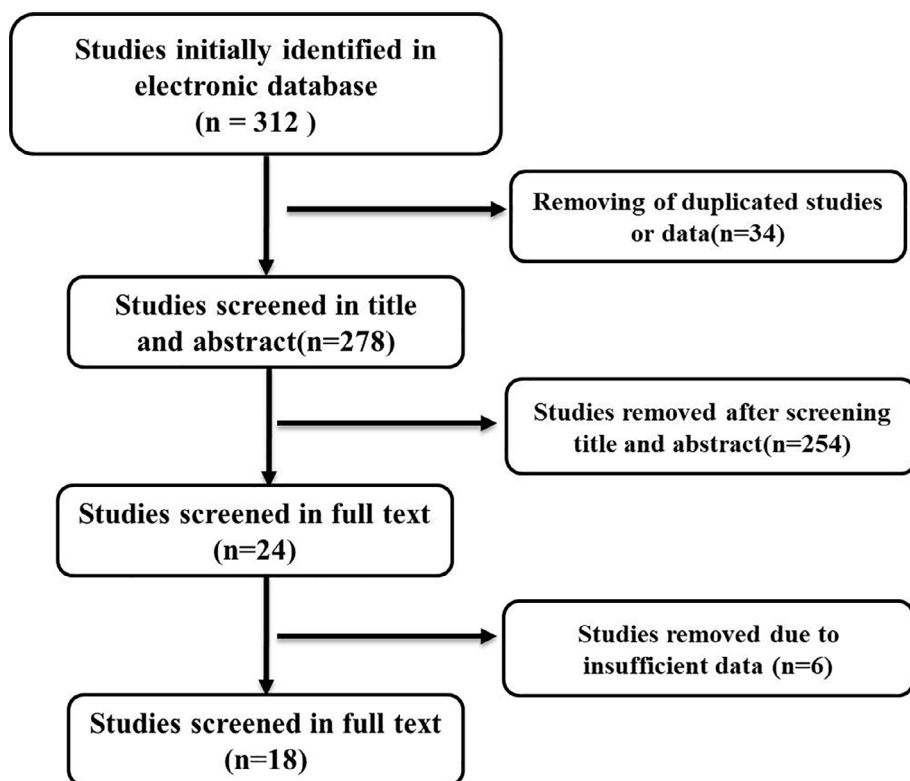


FIGURE 1 Flow-chart of electronic searching and inclusion procedure of studies included

T A B L E 1 Main features of the included studies of WBRT+EGFR-TKI versus WBRT only for non-small cell lung cancer patients with brain metastasis

Studies	Year	WBRT+EGFR-TKI			WBRT only			Outcome	EGFR mutation
		Sample size	Age	Treatment	Sample size	Age	Treatment		
Cai et al. ⁶	2013	65	Na	WBRT + erlotinib/gefitinib	92	Na	Whole brain radiotherapy	ORR, 1-year survival, toxicity	27.4%
Zhuang et al. ⁷	2013	23	60	WBRT	31	63	WBRT	ORR	20.4%
Fu et al. ⁸	2012	38	56	Radiotherapy + gefitinib	123	56	Radiotherapy	ORR, 1-year survival, toxicity	Na
Zhang ⁹	2014	20	52 (32–78)	Radiotherapy + gefitinib/erlotinib	27	51 (33–75)	Radiotherapy	ORR, 1-year survival, toxicity	Na
Yi & Qin ¹⁰	2012	21	Na	Radiotherapy + gefitinib	21	Na	Radiotherapy	ORR, DCR, toxicity	Na
Xiao et al. ¹¹	2011	24	Na	3D-CRT + gefitinib	22	Na	3D-CRT	ORR, DCR, toxicity	Na
Wu et al. ¹²	2012	35	Na	WBRT + gefitinib	18	Na	WBRT	ORR, 1-year survival rate	Positive
Liu ¹³	2013	52	54 (28–74)	WBRT/3D-CRT + erlotinib	52	51(30–72)	WBRT/3D-CRT	ORR, DCR, toxicity, PFS	Positive
Liu et al. ¹⁴	2015	35	75.8 (65–80)	Radiotherapy + gefitinib	35	74.8 (65–80)	Radiotherapy	ORR, DCR, toxicity	Nm
Zou et al. ¹⁵	2016	30	64.12 (20–70)	WBRT + gefitinib	30	64.32 (22–7-)	WBRT	ORR, DCR, KPS, 1-year survival, toxicity	Positive
Liang et al. ¹⁶	2017	35	52.5 (45–60)	WBRT + erlotinib	35	61.5 (55–68)	WBRT	ORR, DCR, toxicity	Positive
Yuan et al. ¹⁷	2017	23	58.4 (45–73)	WBRT + erlotinib	23	58.5 (44–72)	WBRT	ORR, DCR, 1-year survival, toxicity	Na
Yang ¹⁸	2017	40	59.4 (43–75)	WBRT + erlotinib	40	59.8 (45–73)	WBRT	ORR, DCR, 1-year survival	Mixed
Lu ¹⁹	2018	45	67.45 (52–83)	WBRT/3D-CRT + erlotinib	45	68.06 (55–85)	WBRT/3D-CRT	ORR, DCR, 1-year survival	Na
Xu et al. ²⁰	2018	31	54.47 (36–69)	WBRT + gefitinib	30	53.52 (35–70)	WBRT	ORR, DCR, toxicity	Positive
An et al. ²¹	2020	30	39–78	WBRT + gefitinib	30	39–78	WBRT	ORR, DCR, toxicity	Na
Shen ²²	2021	36	57.43 (35–67)	WBRT + gefitinib	36	58.52 (37–64)	WBRT	ORR, DCR, toxicity	Na
Liang ²³	2021	41	68.2 (41–82)	WBRT + erlotinib	41	68.9 (53–83)	WBRT	ORR, DCR, toxicity, 1-year survival	Na

pathology or cytology. (iii) Studies were published in English or Chinese. (iv) Brain metastasis was confirmed by CT or MRI. (v) Treatment associated response and toxicity could be extracted from the original studies.

Exclusion criteria: (i) Review or case report relevant to WBRT+EGFR-TKI or WBRT in the treatment of NSCLC patients with brain metastasis. (ii) Animal studies. (iii) Brain metastases of other carcinoma not NSCLC. (iv) Studies without enough data to calculate the ORR or treatment toxicity.

Data and information extraction

Two researchers independently reviewed the studies and extracted the data. If there were different opinions in data extraction, a third reviewer was consulted to discuss the divergence and make a final decision. The information extracted from the study included: (1) general data: author's name, publication date and author's country, and (2) literature features: number of cases, median age, EGFR mutation status, treatment methods and outcome indicators in the WBRT+EGFR-TIK

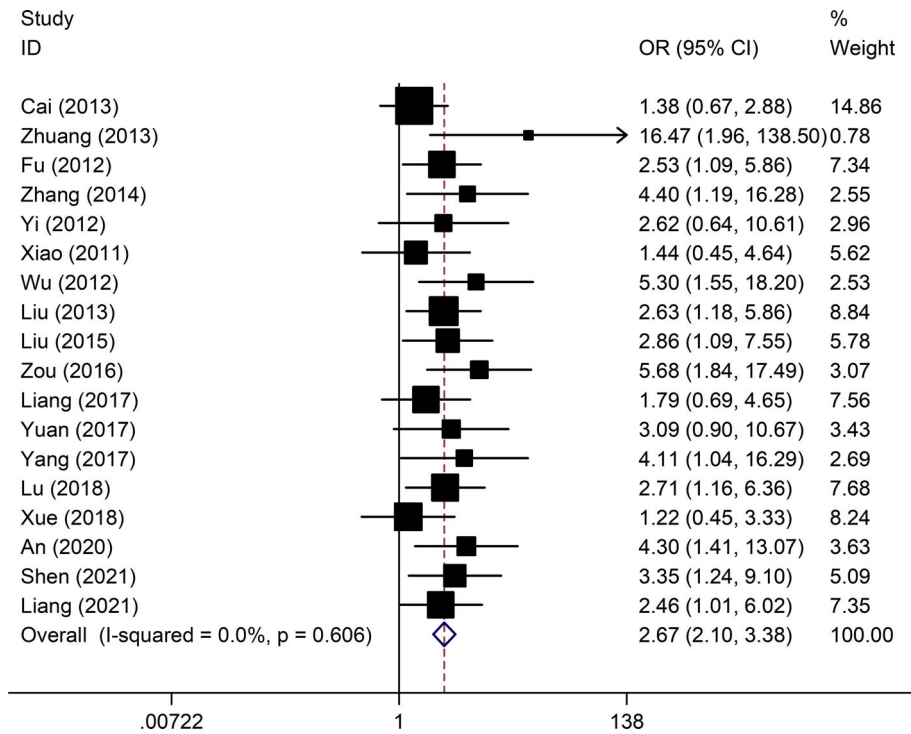


FIGURE 2 The forest plot of objective response rate between WBRT+TKI versus WBRT only for non-small cell lung cancer patients with brain metastasis

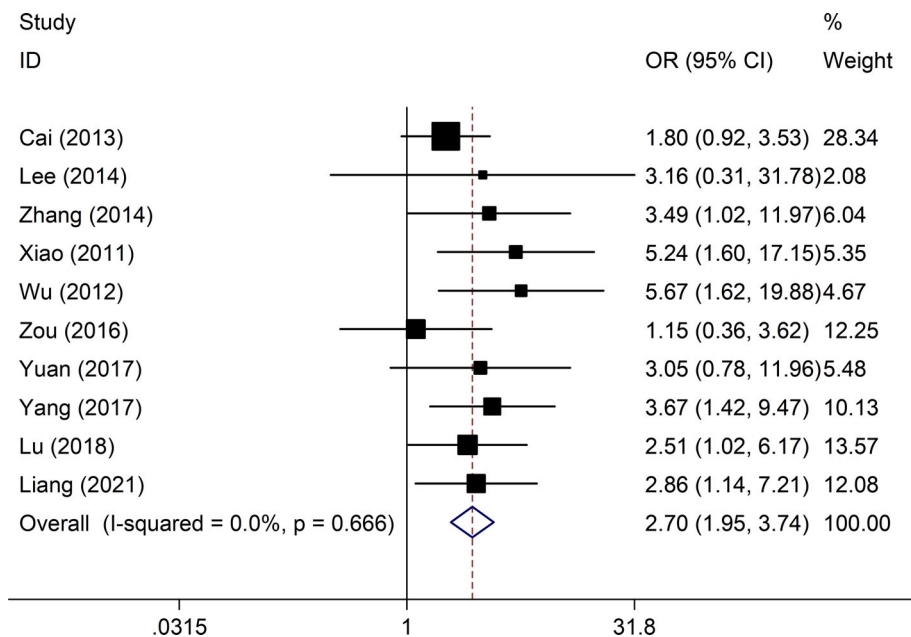


FIGURE 3 The forest plot of the 1-year survival rate between WBRT+TKI versus WBRT only for non-small cell lung cancer patients with brain metastasis

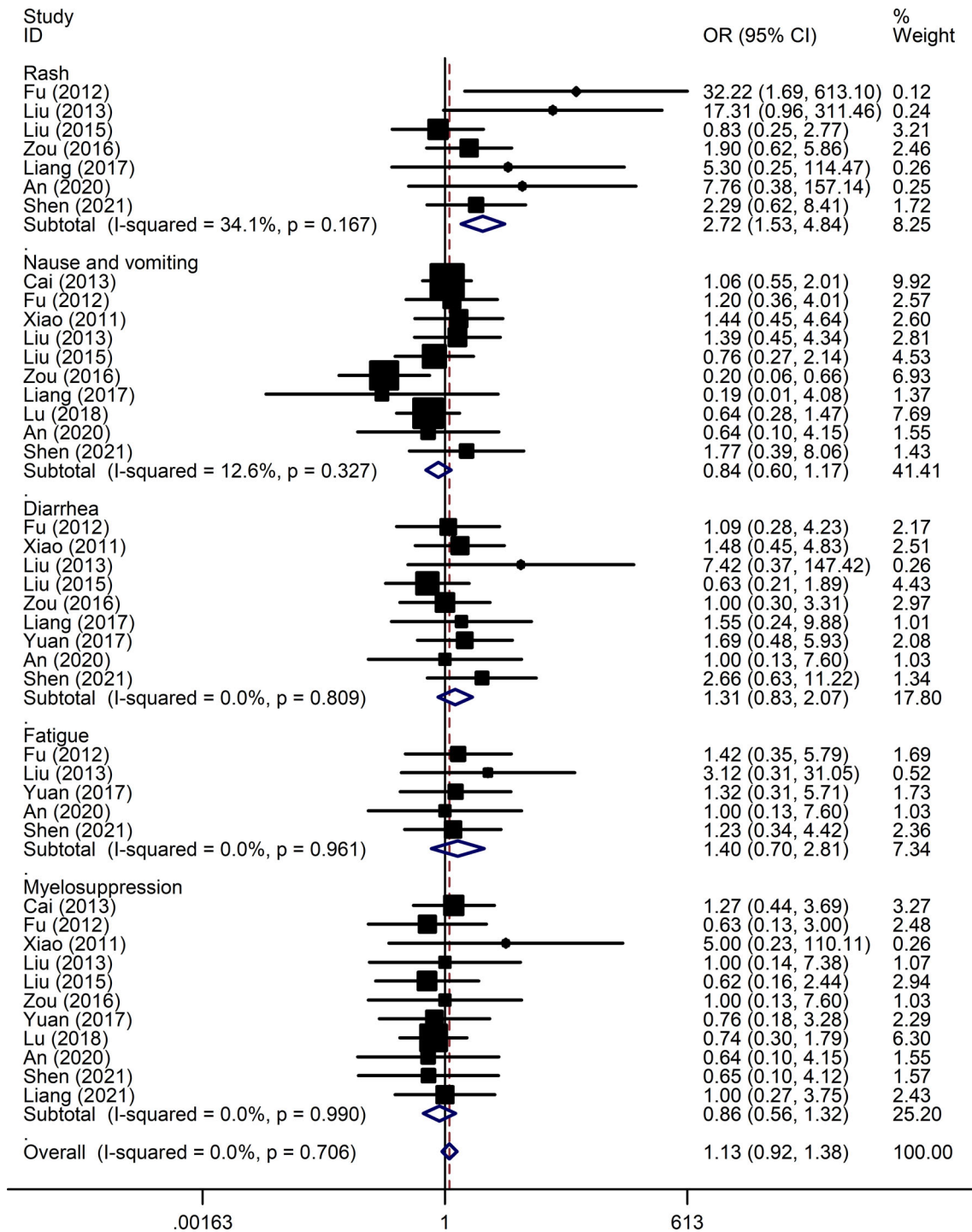


FIGURE 4 The forest plot of treatment-related toxicity between WBRT+TKI versus WBRT only for non-small cell lung cancer patients with brain metastasis

and the WBRT only group. The corresponding authors would be contacted by e-mail if the required data could not be obtained. If the required data could not be obtained finally, it would be recorded as “not available/Na”.

Publication bias evaluation

The publication bias was evaluated by Begg’s funnel plot and Egger’s line regression test. If the funnel plot was left-

right symmetrical and Egger’ test $p > 0.05$, the publication bias was considered as not significant.

Statistical analysis

STATA11.0 statistical software (<http://www.stata.com>) was used for data pooling. The treatment response was demonstrated by objective response rate (ORR) and calculated by

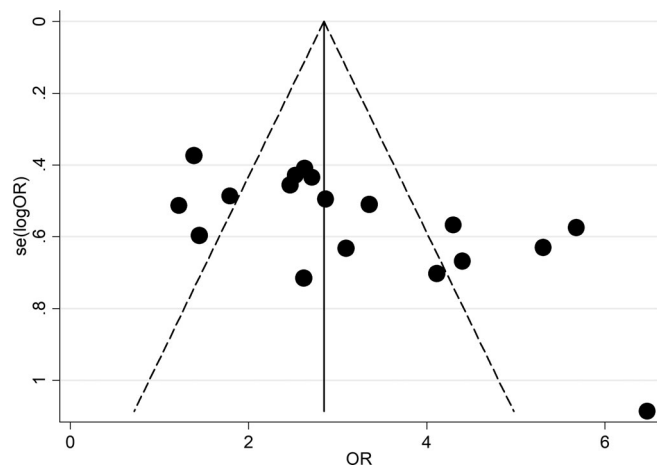


FIGURE 5 The funnel plot of treatment-related toxicity between WBRT+TKI versus WBRT only for non-small cell lung cancer patients with brain metastasis

the equation of $ORR = \text{complete response (CR)} + \text{partial response (PR)}$. The ORR and treatment associated toxicity was expressed by odds ratio (OR) and corresponding 95% confidence interval (95% CI). The statistical heterogeneity across the included 18 studies was investigated by I^2 test. Publication bias was assessed by Begg's funnel plot and Egger's line regression test (Figure 1).

RESULTS

Main features of included studies

After removing unsuitable publications, 18 prospective clinical studies were included for clinical data combination. The general features of the studies included are shown in Table 1.

Combined objective response rate between WBRT+TKI and WBRT only groups

All the 18 studies reported a response rate between the WBRT+TKI and WBRT only groups. The combined result indicated that ORR in the WBRT + TKI group was superior to WBRT only with a statistical difference ($OR = 2.67$, 95% CI: 2.10–3.38, $p < 0.05$) under a fixed effect model, Figure 2.

1-year survival analysis between WBRT+TKI and WBRT only groups

Ten studies reported the 1-year survival rate between the WBRT+TKI and WBRT only groups. The data was combined under a fixed effect mode because of nonstatistical heterogeneity ($I^2 = 0.0\%$, $p = 0.666$). The combined results showed that the 1-year survival rate in the WBRT+TKI

group was higher than that of the WBRT only group with a statistical difference ($OR = 2.70$, 95% CI: 1.95–3.74, $p < 0.05$), Figure 3.

Treatment-related toxicity between WBRT +TKI and WBRT only groups

The combined results demonstrated that the treatment-related rash in the WBRT+TKI group was significantly higher than that of the WBRT only group with a statistical difference ($OR = 2.72$, 95% CI: 1.53–4.84, $p < 0.05$). However, the incidence of nausea/vomiting ($OR = 0.84$, 95% CI: 0.60–1.17, $p > 0.05$), diarrhea ($OR = 1.31$, 95% CI: 0.83–2.07, $p > 0.05$), fatigue ($OR = 1.40$, 95% CI: 0.70–2.81, $p > 0.05$) and myelosuppression ($OR = 0.86$, 95% CI: 0.56–1.32, $p > 0.05$) were not statistically different between the WBRT+TKI and WBRT only groups, Figure 4.

Publication bias

The funnel plot was left–right asymmetric which indicated an obvious publication bias. The Egger's line regression test also showed statistical publication bias ($p < 0.05$), Figure 5.

DISCUSSION

Brain metastasis in NSCLC patients is common. About 30%–50% of patients with NSCLC will eventually develop brain metastasis leading to neurological dysfunction which seriously reduces their quality of life. The prognosis of NSCLC patients with brain metastatic lesions is extremely poor with a median survival time of 3–6 months. Therefore, how to determine effective treatment methods in lung cancer patients with brain metastasis is important in order to improve their prognosis. It has been reported that the prognosis of brain metastatic driver gene positive NSCLC cases can be significantly improved by gene detection and targeted drug treatment. Lung cancer driver genes usually include epidermal growth factor receptors (EGFRs), anaplastic lymphoma kinase (ALK), ROS1 fusion, HER2 mutation, BRAF mutation, neurotrophic tyrosine receptor kinase (NTRK) fusion, etc.

In recent years, with the rapid development of precision medicine, targeted drugs associated with the aforementioned driver genes play an important role in improving the prognosis of NSCLC patients with brain metastasis. The most applied targeted drugs for patients with advanced NSCLC include epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), such as gefitinib and erlotinib. EGFR targeted drugs are small molecule drugs of erlotinib and gefitinib which can pass through the blood–brain barrier and can be used in the treatment of NSCLC patients with

brain metastasis. For NSCLC patients with brain metastasis and *EGFR* mutation, the ORR has been reported to be about 60% with a median OS of 13 months, and median PFS of 11.7 months.^{24,25}

Several studies have indicated that WBRT plus target drugs may have potential survival benefit for improving the treatment response and long-term survival of NSCLC cases with brain metastasis.²⁶ However, the conclusion of these studies was different due to the different treatment modalities and clinical heterogeneity of patients. In the present study, we pooled the treatment response and toxicity of the 18 studies included and found the ORR and 1-year survival rate in the WBRT+TKI group was higher than that of the WBRT only group with a statistical difference ($p < 0.05$). However, the treatment-associated toxicity of a rash in the WBRT+TKI group was significantly higher than that of the WBRT only group (OR = 2.72, 95% CI: 1.53–4.84, $p < 0.05$). This study indicates that based on current publications, WBRT+EGFR-TKI can improve the treatment response and 1-year survival rate but not increase the toxicity except for a rash, compared with WBRT alone in NSCLC patients with brain metastasis.

In conclusion, WBRT combined with EGFR-TKIs for NSCLC patients with brain metastasis is better than WBRT only. WBRT+EGFR-TKIs can improve the treatment response and 1-year survival rate, but does not increase the treatment toxicity, except for rash. However, there are also deficiencies in the meta-analysis such as the small samples in each study included, clinical heterogeneity (age of the included cases, treatment modality, gene mutations) language restriction and publication bias. Therefore, the conclusions should be further validated by well-designed multiple center clinical trials.

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CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest.

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