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Whole brain radiotherapy plus erlotinib for the treatment of non-small cell lung cancer patients with brain metastases: A meta-analysis and network pharmacology mechanisms

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Abstract: *The apparent increase in the incidence of non-small cell lung cancer (NSCLC) with brain metastases is due to the employment of advanced diagnostic methods and increased public health consciousness. The chief treatment for multiple brain metastases is whole-brain radiotherapy (WBRT), erlotinib is permitted as first line of therapy for terminal NSCLC patients at present. However, no comprehensive statistical and systematic analysis has been performed to verify the clinical effectiveness and security of this treatment. Consequently, we conducted a meta-analysis to assess effectiveness and safety of WBRT plus erlotinib in the cure of brain metastases from NSCLC. To investigate the mechanism of erlotinib in the treatment of brain metastases from NSCLC by network pharmacology. The results of this meta-analysis indicated that WBRT combined with erlotinib is an effective and safe treatment of brain metastases from NSCLC. WBRT combined with erlotinib can remarkably improve the overall response rate and disease control rate, and extend the 1-year survival rate, the progression-free survival, the median survival time and medium PFS. This study reveals the mechanism of multi-target and multi-pathway action of erlotinib in the treatment of brain metastases from NSCLC, and provides a basis for the study of clinical anti-tumor action mechanism of erlotinib.*

Keywords: *Whole-brain radiotherapy, Erlotinib, Brain metastases, Non-small cell lung cancer, Meta-analysis, Network pharmacology*

1. Introduction

Lung cancer is the most common cancer worldwide , and 85% of these cancers are pathologically diagnosed as non-small cell lung cancer (NSCLC). Approximately 15–30% of patients with NSCLC develop brain metastases (BM), and symptoms include headache, vomiting, and visual impairment[1]. The 5-year survival rate of patients with NSCLC is very low, whereas the median survival time of patients with untreated brain metastases is less than 3-6 months[2]. The main treatments for NSCLC patients include radiotherapy, chemotherapy, and surgery; nevertheless, these conventional treatments are less effective in treating brain metastases[3]. Thus, new strategies for the treatment of brain metastases from NSCLC need to be developed urgently.

For a long time, the standard treatment for NSCLC with multiple brain metastases has been whole-brain radiotherapy (WBRT), which can alleviate symptoms and prolong survival to some extent survival[4]. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective treatments for lung adenocarcinomas. Erlotinib is a small molecule TKI with a good lipid-water distribution coefficient, easy absorption, strong permeability, and can cross the cell membrane and the blood-brain barrier. Furthermore, the concentration of erlotinib in the cerebrospinal fluid was higher than that of the other TKIs. Therefore, the intrinsic properties of erlotinib make it the drug of choice for the treatment of lung adenocarcinoma with brain metastasis[5].

This study compared the efficacy and safety of WBRT plus erlotinib versus WBRT alone in the treatment of NSCLC with brain metastases by meta-analysis and investigated the mechanism of erlotinib in the treatment of brain metastases from NSCLC by network pharmacology.

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2. Methods

2.1 Meta-analysis

2.1.1 Search Strategy and Literature Selection

Two researchers independently conducted a comprehensive search of relevant articles using eight databases: PubMed, Cochrane Library, EMBASE, Web of Science, Clinical Trials.gov, Wanfang Database, China National Knowledge Infrastructure (CNKI), and China Science and Technology Journal Database (VIP). The search details were as follows (English database): (("carcinoma, non-small-cell lung"[MeSH Terms] OR "carcinoma non small cell lung"[Title/Abstract]) OR "carcinomas non small cell lung"[Title/Abstract]) OR "lung carcinoma non small cell"[Title/Abstract]) OR "lung carcinomas non small cell"[Title/Abstract]) OR "Non-Small-Cell Lung Carcinomas" [Title/Abstract]) OR "Nonsmall Cell Lung Cancer"[Title/Abstract]) OR "Non-Small-Cell Lung Carcinoma" [Title/Abstract]) OR "carcinoma non small cell lung"[Title/Abstract]) OR "Non-Small Cell Lung Cancer"[Title/Abstract]) AND ((((("Brain Neoplasms"[MeSH Terms] OR "brain tumor" [Title/Abstract]) OR "brain carcinoma"[Title/Abstract]) OR "brain cancer"[Title/Abstract]) OR "brain metastasis"[Title/Abstract])) AND ((((((("Radiotherapy"[MeSH Terms] OR "Radiation Therapy" [Title/Abstract]) OR "therapies radiation"[Title/Abstract]) OR "Radiation Treatment"[Title/Abstract]) OR "whole-brain radiotherapy"[Title/Abstract]) OR "WBRT"[Title/Abstract]) OR "Targeted Radiation Therapy"[Title/Abstract])) AND ((((((("Erlotinib Hydrochloride"[MeSH Terms] OR "hydrochloride erlotinib"[Title/Abstract]) OR "Erlotinib HCl"[Title/Abstract]) OR "hcl erlotinib"[Title/Abstract]) OR "Erlotinib"[Title/Abstract]) OR "n 3 ethynylphenyl 6 7 bis 2 methoxyethoxy quinazolin 4 amine" [Title/Abstract]) OR "Tarceva"[Title/Abstract]) lung Chinese databases(CNKI,etc.)searches: “feixiaoxibaofeiainaozhuanyi"("carcinoma,non-small- cell lung" and "Brain Neoplasms") AND (“eluotini” ("Erlotinib Hydrochloride") AND “quannaofangliao” (“ whole-brain radiotherapy”).

Subsequently, we manually searched the annual meetings of the ASCO, ASTRO, and ESMO for lung cancer. The last search date was January 20, 2021. References to the included studies were reviewed to identify other relevant studies. Any dispute was resolved through discussion and consensus among researchers.

2.1.2 Inclusion and Exclusion Criteria

Studies that met the following criteria were included: (1) Participants: The patient was diagnosed histologically or cytologically with NSCLC and was confirmed with BM by CT or MRI; (2) Intervention: the experimental group was treated with WBRT combined with erlotinib; (3) comparator: the control group was treated with WBRT alone; (4) Outcome: such as risk ratio (RR), or necessary raw data with 95% confidence intervals (CIs); (5) Study design: from an original study randomized controlled trials (RCTs), non-randomized clinical trials, observational studies; (6) the full text of the article is in English or Chinese.

Studies were excluded for the following reasons: (1) duplicate publications; (2) case reports, reviews, and animal experiments; and (3) publication in a language other than English or Chinese.

2.1.3 Data Extraction

Two researchers extracted the following information from each study: name of the first author, publication year, study period, sample size, intervention, controls, outcomes, and adverse events.

2.1.4 Quality Assessment of Included Studies

The methodological quality was assessed independently by two investigators, with RCT studies using the Cochrane Collaboration tool [6] and studies using the Newcastle-Ottawa Scale (NOS), and studies that obtained six or more stars on the modified NOS were considered to be of high quality[7], which were then used to describe the information.

2.1.5 Statistical Analysis

Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and SPSS 21.0 was used for data analysis[8]. For dichotomous variables, results were reported as relative risk ratios (RRs) and 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$. Inconsistency index (I^2) was used to test for heterogeneity. If the results were found to have good homogeneity ($P > 0.1$; $I^2 \leq 50\%$), they were analyzed using a fixed-effect model; if there was no good homogeneity ($P < 0.1$; $I^2 > 50\%$), then the random effects model was used. I^2 was used as the chief evaluation method when the outcomes

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of the two heterogeneity tests were inconsistent.

2.2 Network pharmacology

2.2.1 Targets acquisition of erlotinib and NSCLC with brain metastases

DrugBank was used to identify the targets of erlotinib. GeneCards (https://www.genecards.org/) was used to screen the targets of brain metastases from NSCLC taking "brain metastases from non-small cell lung cancer" as the keyword.

2.2.2 PPI network construction of erlotinib in the treatment of NSCLC with brain metastases

Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/) was used to intersect the selected drug targets and disease targets to obtain a Venn diagram. To clarify the relationship between targets, the common targets of drugs and diseases were submitted to the STRING 11.0 database (https://string-db.org) to construct the protein-protein interaction (PPI) network. The species was set as "Homo sapiens" the threshold was set as "medium confidence" (0.400), and the rest were set to default settings.

The PPI network was visualized using Cytoscape 3.8.0. CytoHuabba, the built-in tool of Cytoscape, was used to analyze the network topology parameters of each node, including degree, betweenness, and closeness, and to judge the core targets of drugs to exert therapeutic effects. The greater the degree of connectivity of a node, the more important it is. The core targets of drug therapy were determined according to the network topology parameters.

2.2.3 GO biological process and KEGG pathway analysis

DAVID was used for GO enrichment and KEGG enrichment analysis, and the processes or pathways with $P < 0.05$ were screened and visualized using the online mapping platform Weishengxin. GO analysis explained and annotated three aspects: biological process, molecular function, and cellular location.

The Kyoto Encyclopedia of Genes and Genomes Pathway (KEGG) was used for KEGG pathway analysis, which can directly detect the pathways involved in the target.

2.2.4 Drug-target-pathway-disease network construction

A drug-target-pathpath-disease network was constructed via Cytoscape 3.8.0.

3. Results

3.1 Meta-analysis

3.1.1 Description of Included Trials

We found 359 potentially relevant articles from eight databases: 38 from PubMed, 26 from Cochrane Library, 101 from EMBASE, 65 from Web of Science, 36 from CNKI, 62 from Wan Fang, 24 from VIP, and 7 from hand searched relevant studies. Of these studies, 117 were excluded because of duplication. After verifying the relevant terms in the titles and abstracts, we excluded 176 unrelated articles. After reading the full text, another 48 articles were excluded, of which 20 did not report the original data, 24 had a different comparison, and four did not find the full text. Finally, 18 studies were included in this meta-analysis. Fifteen of the 18 studies were RCTs and the other three were non-RCTs. Figure 1 shows a flowchart of study selection.

A total of 1,743 patients with brain metastases derived from NSCLC were included in the included studies, with 834 patients receiving WBRT plus erlotinib and 909 receiving WBRT. The treatment ranged from four weeks to two months. The dosage of erlotinib administered was 150 mg/day once daily in 17 trials and 100 mg/day once a day in one trial. WBRT (29–42 Gy)/(10–12)F. Table 1 summarizes the characteristics of the studies.

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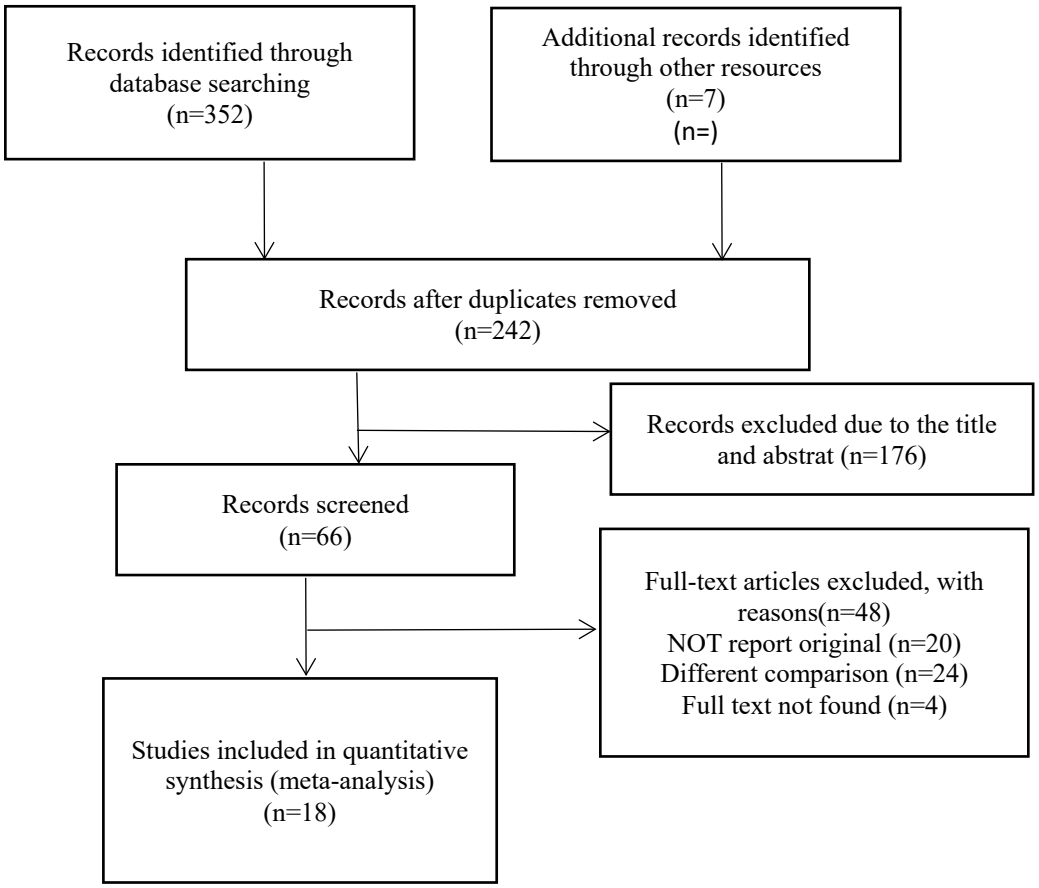

Figure 1: Flow chart of studies included in the meta-analysis.

Table 1: Summary of the characteristics of the 18 trials included in the meta-analysis.

First Author /Year	NP	MA	Female	Outcomes	AEs
Huimin Huang 2019	250/250	68/68	118/120	CR,PR,SD,PD,RR,DCR,1-year survival rates,survival time	NO
Xianbin Liang 2017	35/35	52/61	20/18	CR,PR,SD,RR,DCR	YES
Xuexiao Liu 2016	46/54	67/69	14/17	CR,PR,SD,PD,RR,DCR,medium OS,1-year survival rates	YES
Yaling Liu 2019	30/30	59/59	10/12	CR,PR,SD,PD,RR,DCR,Medium PFS,PFS	NO
Aili Lu 2018	45/45	67/68	21/22	CR,PR,SD,PD,RR,DCR,1-year survival rates	YES
Jinfeng Qi 2018	49/49	NO	NO	CR,PR,SD,PD,RR,DCR,1-year survival rates,PFS	YES
Gang Yuan 2017	23/23	58/59	9/10	CR,PR,SD,PD,RR,DCR,medium OS,1and 2 year survival rates,	YES
Xiaohong Liu 2015	28/30	62/62	10/11	CR,PR,SD,PD,RR,DCR	YES
MoLi 2015	32/35	59/54	NO	CR,PR,SD,PD,RR,DCR,PFS,Medium PFS, medium OS,1-year survival rates	YES
Meiling Yang 2016	40/40	60/59	25/23	CR,PR,SD,PD,RR,DCR,PFS,medium OS, 1-year survival rates	NO
Songbo Li 2019	31/31	58/60	15/14	CR,PR,SD,PD,RR,DCR	YES
LiLiu 2019	35/35	55/55	16/15	CR,PR,SD,PD,RR,DCR,PFS,medium OS,1-year survival rates	YES
Xiaolei Wang 2015	33/30	59/62	21/16	CR,PR,SD,PD,RR,DCR,Medium PFS,medium OS, 1-year survival rates,PFS	YES
MiaoZhang 2018	28/28	69/67	12/13	CR,PR,SD,PD,RR,DCR,overall survival,1-year survival rates	YES
Yong Cai 2013	43/92	NO	NO	CR,PR,SD,PD,RR,DCR,Medium PFS,Medium OS,1-year survival rates	YES
H. Zhuang 2012	23/31	NO	NO	ORR,Median follow-up, Median LPFS of brain, Median PFS	NO
Siow Ming Lee 2014	40/40	61/62	25/19	median neurological PFS , the 2-month PFS rate , medium OS,6-month OS rates	YES
Hongqing Zhuang 2013	23/31	60/63	13/18	CR,PR,SD,PD,RR,DCR,,median PFS, median OS,survival rates at 6 months, at 1 year , at 2 year, local progression more than 1 year after treatment.	YES

Data are expressed as the experimental group/control group unless indicated otherwise. NP, number of patients; MA, median age; CR, complete response; PR, partial response; SD, stable disease; PD,

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progressive disease; RR, response rate; DCR, disease control rate; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; AEs, adverse events; NO/YES mentioned in the manuscript.

3.1.2 Quality Assessment of Selected Studies

Eligible studies were evaluated based on the Cochrane Handbook for Systematic Reviews recommendations. Fifteen of the studies were RCTs; only four stated suitable methods of random sequence generation, and two trials employed an unsuitable method of randomization. None of the studies reported allocation concealment. One trial reported that blinding was double blind, but neither described the method of blinding. There were no significant differences in baseline data between the trials (Table 1). The results of the bias risk assessment are shown in Figure 2 and 3, respectively. Three non-RCT studies were assessed by NOS, and the scores were five stars, as shown in Table 2. A funnel plot was used to analyze the publication bias (Figure 4).

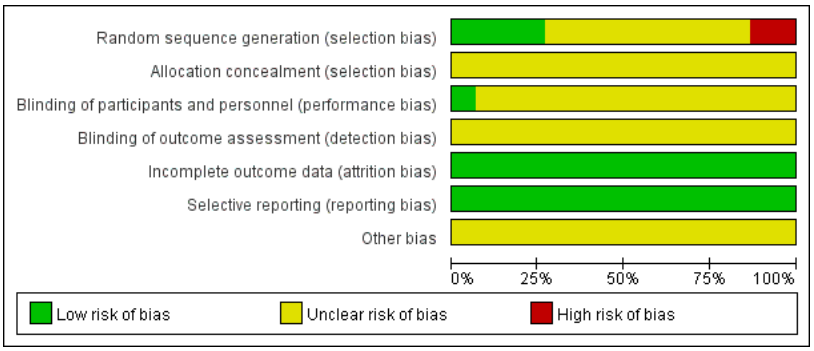

Figure 2: Risk of bias graph. The reviewer's judgment for each area of bias was expressed as a percentage of the included studies. The quality of the enrolled studies was assessed against the Cochrane criteria.

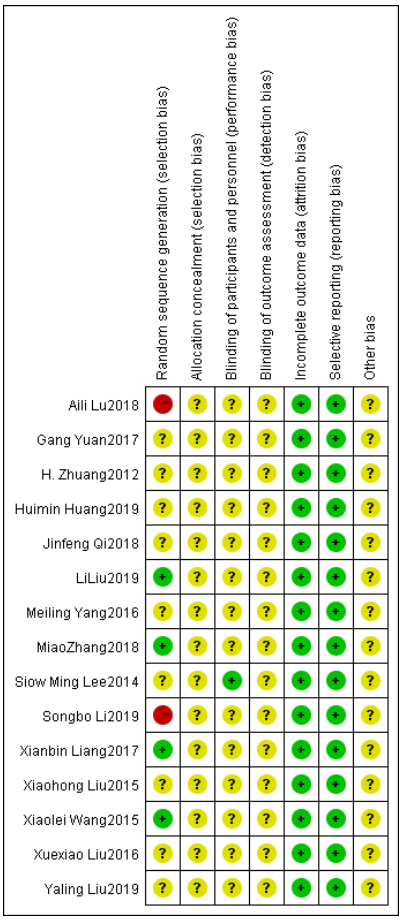

Figure 3: Risk of bias summary. The authors' judgments of bias in each of the areas included in the study are summarized.

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Table 2: The score of the NOS

First author/Total number of patients	Selection	Comparability	Exposure
MoLi /67	2	1	2
Hongqing Zhuang/ 54	2	1	2
Cai Yong Cai/157	3	1	1

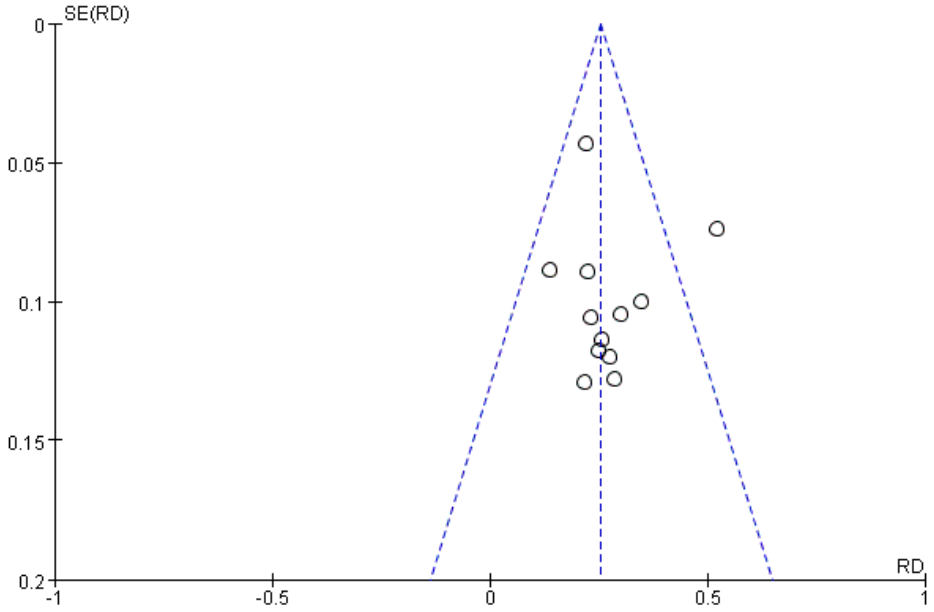

Figure 4: Funnel plot of publication bias.

3.1.3 Effects of the Intervention

Overall Response Rate Seventeen studies were included in this analysis, comprising a total of 1,663 patients. According to heterogeneity testing (I2 = 57%; P = 0.002), a random-effects model was used for the analysis. During treatment, the overall response rate in the experimental group was higher than that in the control group (RR = 1.55; 95% CI [1.35, 1.77]; P < 0.00001) (Figure 5).

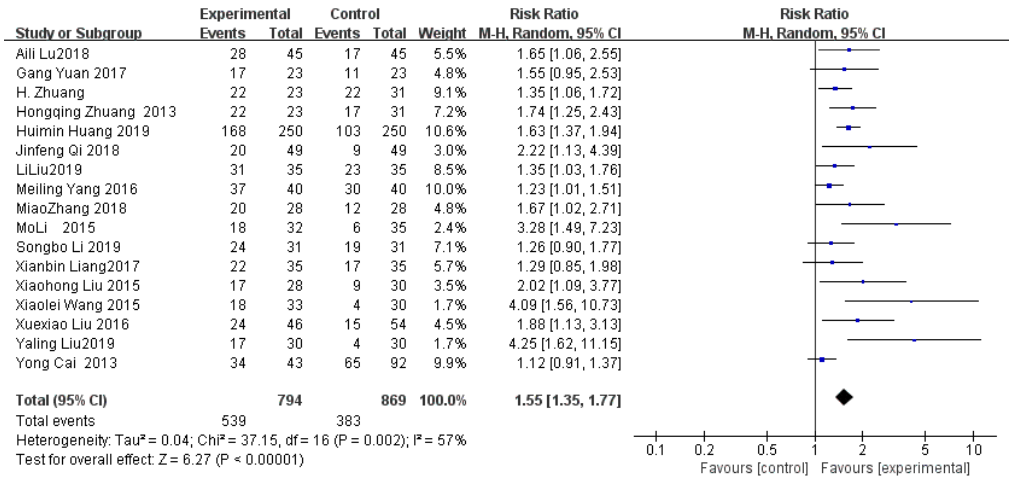

Figure 5: Forest plot of overall response rate in WBRT plus erlotinib compared with WBRT.

Disease Control Rate Sixteen studies reported the disease control rate of 1,609 patients. The heterogeneity test showed that a random-effects model could be used (I2 = 86%; p <0.00001). Compared with WBRT alone, WBRT combined with erlotinib showed a significant improvement in DCR (RR = 1.23, 95% CI [1.12, 1.36]; P < 0.0001) (Figure 6).

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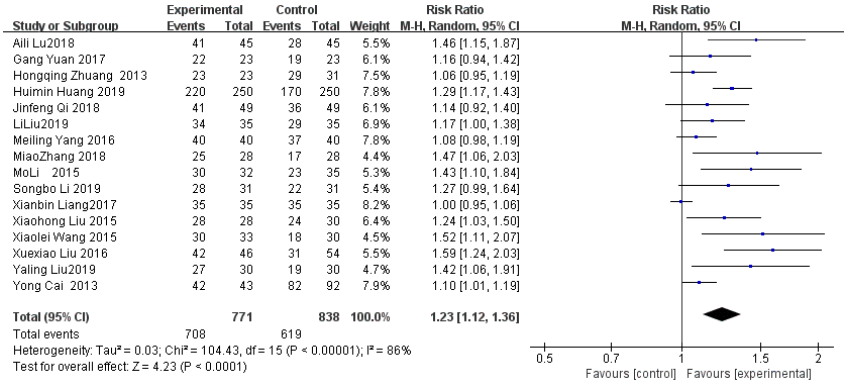

Figure 6: Forest plot of disease control rate in WBRT plus erlotinib compared with WBRT.

1-Year Survival Rate Twelve studies reported the 1-year survival rate of 1,352 patients. Based on the results of the heterogeneity test (I2 = 39%; P = 0.08), a fixed-effect model was used. In the meta-analysis, WBRT in combination with erlotinib significantly extended the 1-year survival rate compared with WBRT alone (RR = 1.78, 95% CI [1.57, 2.01]; P < 0.00001) (Figure 7).

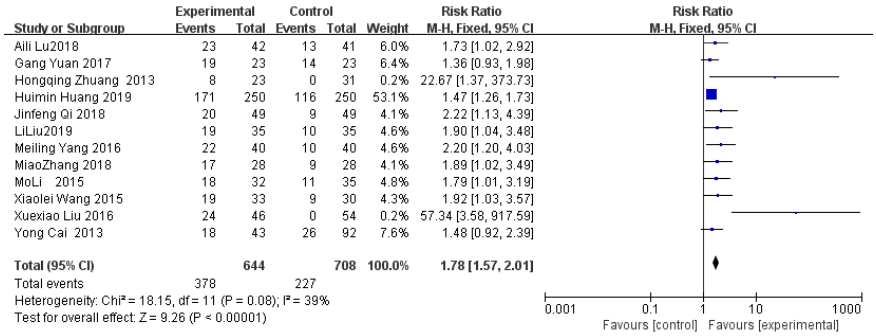

Figure 7: Forest plot of 1-year survival rate in whole-brain radiotherapy (WBRT) plus erlotinib compared with WBRT.

Progression-Free Survival Four studies reported progression-free survival (PFS) at 12 months, involving 288 patients. The heterogeneity test showed that a fixed-effects model could be applied (I2 = 24%; p = 0.27). The meta-analysis indicated that WBRT plus erlotinib significantly prolonged PFS compared with WBRT alone (RR = 1.87, 95% CI [1.48, 2.52]; P < 0.0001) (Figure 8).

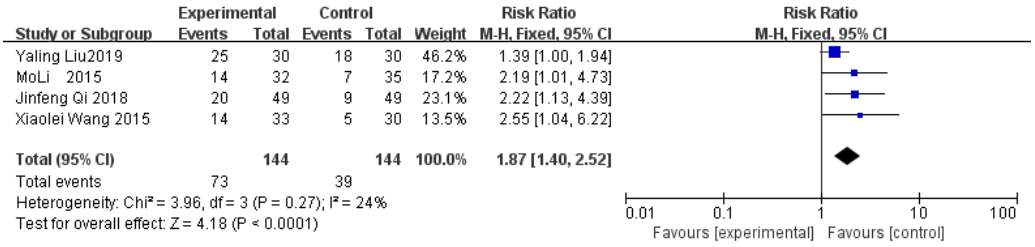

Figure 8: Forest plot of PFS in WBRT plus erlotinib compared with WBRT.

Median Survival Time SPSS 21 analysis showed a significant difference in median survival time between the two groups in the nine studies (P < 0.05) (Table 3). Compared to WBRT alone, WBRT combined with erlotinib had a longer median survival time.

Table 3: Median survival time in trials included in the meta-analysis.

Intervention/ months	Xuexiao Liu 2016	Gang Yuan 2017	MoLi 2015	Meiling Yang 2016	LiLiu 2019	Xiaolei Wang 2015	Yong Cai 2013	Siow Ming Lee 2014	Hongqing Zhuang 2013
WBRT + erlotinib	9	15.8±2.4	13. 0	9.13±1.09	9.26±2.56	12.9	11.2	3.4	10.7
WBRT	6	9.1±1.0	7. 5	6.34±1.34	6.25±2.33	5.4	7.7	2.9	8.9

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Medium PFS SPSS 21 analysis showed a statistically significant difference in median PFS between the two groups in the six related studies ($P < 0.05$) (Table 4). The median PFS with WBRT plus erlotinib was longer than that with WBRT alone.

Table 4: Medium PFS in trials included in the meta-analysis.

Intervention/months	Yaling Liu 2019	MoLi 2015	Xiaolei Wang 2015	Yong Cai 2013	H.Zhuang 2012	Hongqing Zhuang 2013
WBRT+erlotinib	6	10. 0	8.2	6.9	7.3	6.8
WBRT	8	5. 5	4.7	3.4	5.6	5.2

Adverse Events Adverse events were analyzed in 15 studies. The results of the meta-analysis of AEs are shown in Table 5. The incidence of rash was higher in the WBRT combined with erlotinib group than in the WBRT group (RR = 2.72, 95% CI: 1.20–6.15; P = 0.02), according to the results of heterogeneity test (P = 0 .0001, I2 = 71.0%), random effects model was used. The incidence of diarrhea in the WBRT combined with erlotinib group was higher than that in the WBRT group (RR = 2.14, 95% CI: 1.00–4.57; P = 0.05). Due to the heterogeneity test results (P = 0.002, I2 = 65.0%), the random effect model was selected.

Table 5: Reported adverse events from the 15 included studies were analyzed

Adverse event	Number of studies	Number of patients	Test of association				Test of heterogeneity	
			RR	95% CI	Z	P	I2 %	P
Headache	6	232/297	1.01	0.81-1.26	0.07	0.95	0.0%	0.41
Dizziness	2	66/123	1.56	0.69-3.54	1.07	0.28	58%	0.12
Fatigue	4	114/124	1.03	0.83-1.28	0.74	0.46	30%	0.23
Rash	12	418/393	2.72	1.20-6.15	2.40	0.02	71%	0.0001
Diarrhea	11	387/454	2.14	1.00-4.57	1.96	0.05	65%	0.002
Astriction	2	81/89	0.64	0.10-4.06	0.47	0.64	51%	0.15
Nausea / Vomiting	8	299/367	1.02	0.83-1.25	0.18	0.86	26%	0.23
Leukopenia	10	358/425	0.84	0.62-1.13	1.18	0.24	32%	0.15
Thrombocytopenia	3	101/120	0.79	0.48-1.30	0.92	0.36	27%	0.25
Hair loss	5	182/192	0.81	0.55-1.19	1.09	0.28	0.0%	0.86
Damage to liver and kidney function	6	200/216	0.89	0.55-1.46	0.45	0.65	0.0%	0.73
Total	4	356/356	0.61	0.32-1.18	1.47	0.14	82%	0.0008

RR= risk ratio; CI= confifidence interval.

3.2 Network Pharmacology

3.2.1 Retrieving results of erlotinib targets and non-small cell lung cancer with Brain metastases

Fifteen targets of erlotinib were obtained by searching DrugBank. Using "Brain metastases from non-small cell lung cancer" as the key word, 2,912 disease targets were found from Genecards database. Intersection of the targets of erlotinib and NSCLC with brain metastases was carried out to obtain a Venn diagram, with 13 common targets, as shown in Figure 9A. Common elements in erlotinib and brain metastases from NSCLC include EGFR, CYP3A4, CYP3A5, CYP1A2, CYP1A1, CYP2D6, CYP2C8, CYP1B1, ABCG2, ABCB1, UGT1A1, NR1I2, and ALB.

3.2.2 Construction and analysis of protein-protein interaction network

The common targets of drugs and diseases were submitted to String 11.0 to construct a protein-protein interaction (PPI) network, as shown in Figure 9B.

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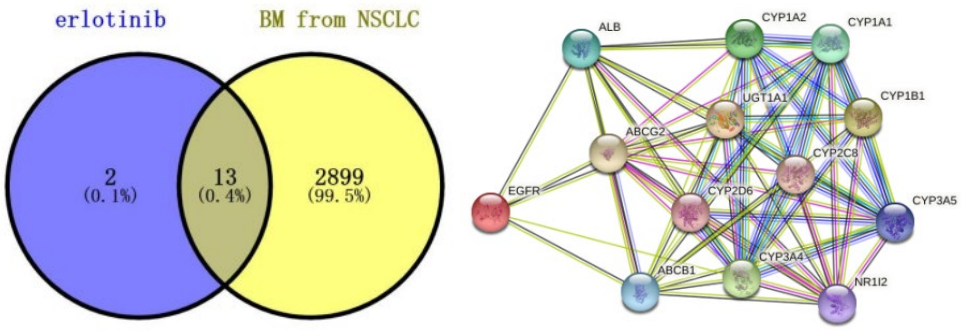
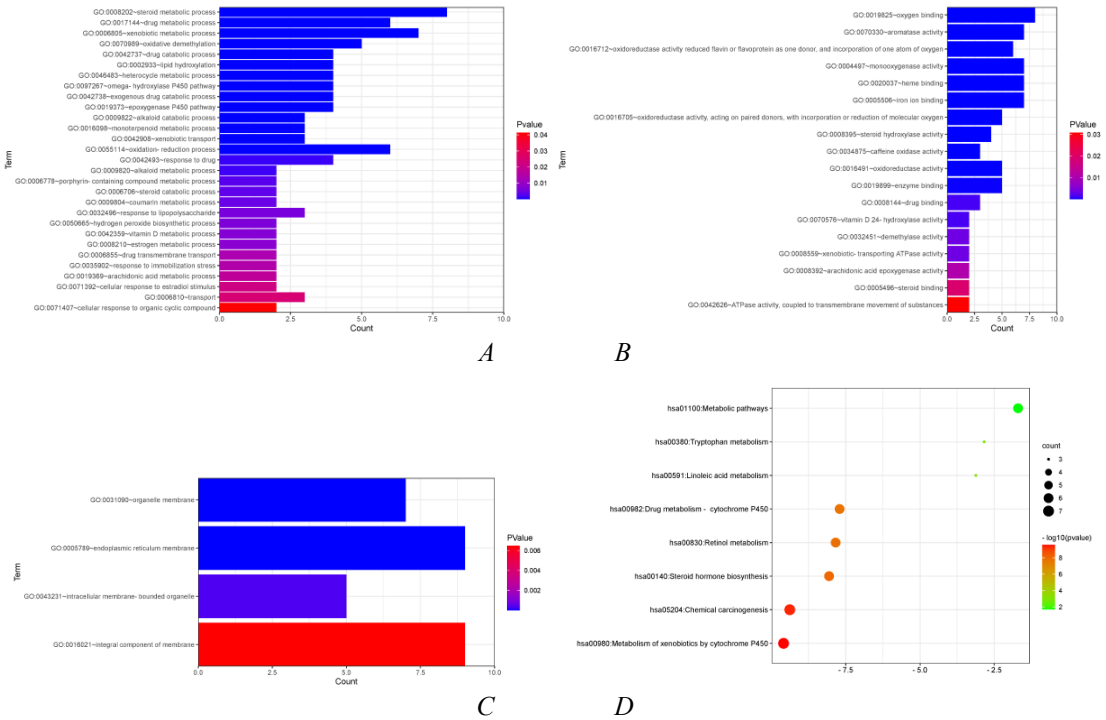


A *B*

Figure 9: A.Erlotinib-brain metastases from NSCLC of Venn diagram of target. B.Erlotinib-brain metastases from NSCLC of target PPI network

3.2.3 GO and KEGG Pathway Analysis

Common targets were imported into the DAVID database for GO enrichment and KEGG enrichment analysis, and the process or pathway of $P < 0.05$ was screened and visualized using the online mapping platform Weishengxin. In GO analysis, biological process(BP) resulted in the drug metabolic process, xenobiotic metabolic process, steroid metabolic process, oxidative demethylation, oxidation-reduction process, etc., 29 items, as shown in Figure 10A. 18 molecular function(MF) entries were obtained, including oxygen binding, aromatase activity, monooxygenase activity, heme binding, iron ion binding, etc. as shown in Figure 10B. Cellular component(CCs) obtains organelle membranes, endoplasmic reticulum membranes, and integral components of membranes. There were 4 intracellular membrane-bound organelle entries in total, as shown in Figure 10C. The molecular signaling pathways of the core targets in erlotinib against brain metastases from NSCLC were closely associated with the metabolism of xenobiotics by cytochrome P450, drug metabolism-cytochrome P450, chemical carcinogenesis, steroid hormone biosynthesis, retinol metabolism, linoleic acid metabolism, tryptophan metabolism, and metabolic pathways (Figure 10D).



A *B*

C *D*

Figure 10: GO and KEGG pathway analysis (A: GO-BP analysis; B: GO-MF analysis; C: GO-CC analysis; D: KEGG analysis)

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3.2.4 Construction of Erlotinib-Target-Pathway-Brain Metastases from NSCLC Network

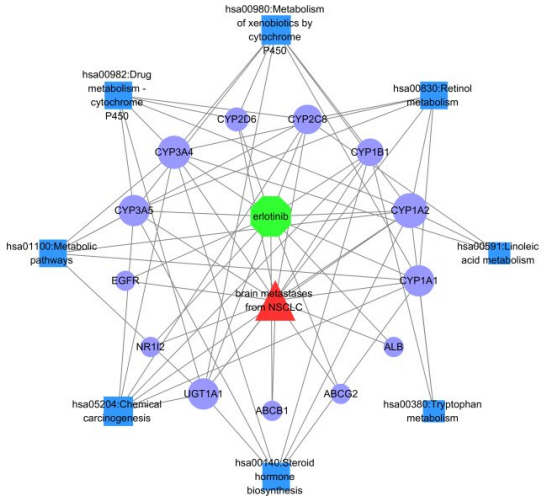

Figure 11: Erlotinib-target-pathway-brain metastases from NSCLC network.

Cytoscape 3.8.0 was used to construct erlotinib-target-pathway-brain metastases from NSCLC network, as shown in Figure 11, 23 nodes and 70 edges of drug-target- pathway-disease network. The greater the connectivity degree of a node, the more nodes in the network that are directly related to the node and the more important the node. The pathways were hsa00980, metabolism of xenobiotics by cytochrome P450; hsa00982, drug metabolism-cytochrome P450; hsa01100, metabolic pathways; hsa05204, chemical carcinogenesis; hsa00140, steroid hormone biosynthesis; hsa00830, retinol metabolism; hsa00591, linoleic acid metabolism; and hsa00380, tryptophan metabolism.

CytoHubba, the embedded tool in Cytoscape, was used to analyze the network topology parameters of erlotinib in the treatment of NSCLC with brain metastases, as shown in Figure 12. According to the degree value of network topology parameters, the core targets of drug therapeutic effect were determined to be ABCB1, ABCG2, CYP3A4, and CYP3A5.

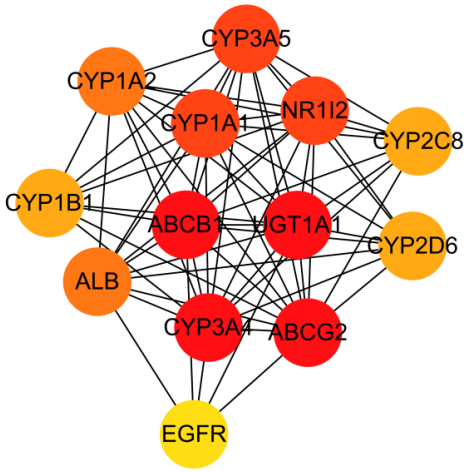

Figure 12: The core targets of erlotinib in the treatment of NSCLC with brain metastases (Take degree as the standard).

4. Discussion

In this meta-analysis, we compared the efficacy and safety of WBRT combined with erlotinib and WBRT alone for the treatment of brain metastases from NSCLC. We found that WBRT plus erlotinib is an effective and safe treatment for brain metastases from NSCLC compared to WBRT alone. Additionally, we demonstrated that compared to WBRT alone, WBRT plus erlotinib can significantly improve the overall response rate and disease control rate and prolong the 1-year survival rate, progression-free survival, median survival time, and median PFS. With regard to the occurrence of adverse events, WBRT plus erlotinib was not life-threatening but increased the risk of rash and diarrhea

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problems in the treatment of patients with brain metastases from NSCLC.

Approximately 40% of patients with NSCLC develop brain metastases and have a poor outcome (median survival < 5 months)[9-11]. Currently, the main treatment methods for NSCLC patients with brain metastases include surgery, whole brain radiotherapy (WBRT), stereotactic radiotherapy (SRS), and chemotherapy[12]. The standard treatment for brain metastases is WBRT[13], which controls local disease but carries a high risk of central nervous system and systemic progression[14]. However, an enhanced understanding of the pathology of brain metastases from NSCLC and the development of molecularly targeted drugs offers hope for improving the prevention and treatment of brain metastases from NSCLC[15].

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as erlotinib were approved by the US Food and Drug Administration in 2004 for the treatment of locally advanced or metastatic NSCLC[16]. Although WBRT kills tumor cells, radiation also destroys the blood-brain barrier. Endothelial cells, the main components of the blood-brain barrier, can be damaged by radiation through a variety of mechanisms, leading to increased blood-brain barrier permeability. Erlotinib, an inhibitor of the epidermal growth factor receptor (EGFR) pathway, is currently approved as a first-line therapy for advanced NSCLC patients with EGFR mutations, as well as second -or third-line maintenance therapy after chemotherapy[17-20].Preclinical data have shown that erlotinib enhances the inhibitory effect of ionizing radiation on lung cancer and provides adequate radiosensitization and therapeutic effects in the brain across the blood-brain barrier[21-25]. Theoretically, both treatments could enhance each other, and WBRT could increase the permeability of the blood-brain barrier, leading to a significant increase in the erlotinib concentration in the brain. Consequently, WBRT and erlotinib complement and reinforce each other and have a synergistic effect on brain metastases from lung adenocarcinoma.

In this study, ABCB1, ABCG2, CYP3A4, and CYP3A5 were selected as the core targets of erlotinib for the treatment of brain metastases from NSCLC using a network pharmacological method. The ATP-binding box (ABC) transporter belongs to the membrane protein family, which uses the energy of ATP hydrolysis to export the extracellular substrate, thereby reducing its effective intracellular concentration. Its overexpression has been associated with multidrug resistance. ABC transporters are expressed in cancer stem cell-like cells, including ABCG2/BCRP and ABCB1/ PGP. Induction of ABC transporter-dependent chemotherapeutic resistance.Therefore, the ATP binding box (ABC) protein family is an important anti-tumor target. Effective anticancer agents are also effective inhibitors of ABC transporters, including HhAntag691, EGFR tyrosine kinase inhibitors, gefitinib, and erlotinib. ABCB1 and ABCG2 are highly expressed in the blood brain barrier (BBB) and some tumors, which can limit the oral effectiveness and brain concentration of many clinically used anticancer drugs, and can also directly confer multidrug resistance on tumor cells, which may well limit the therapeutic effect of these drugs, especially for the treatment of brain metastases.These tyrosine kinase inhibitors (TKIs) have higher selectivity and lower systemic toxicity against tumors than conventional cytotoxic drugs, and are superior to standard cytotoxic therapy in patients with NSCLC with EGFR gene activation mutations[26-28].

Cytochrome P450 (CYP) is central to the exobiotic response system and plays an important role in the metabolism of endogenous molecules. Cytochrome P450 (CYP) proteins are divided into 18 families: the CYP1, CYP2, and CYP3 families mediate the biotransformation of most exotic organisms, whereas other families of CYPs are involved in endogenous metabolism. Approximately 80% of clinical drugs are metabolized by members of the CYP1, CYP2, or CYP3 family, and 50% are completely metabolized by members of the CYP3A subfamily. CYP3A4 and CYP3A5 are expressed at higher levels in many cancer tissues than in nontumor tissues[29]. The plasma concentrations and bioavailability of many drugs are greatly affected by CYP3A4/5, which significantly affects the therapeutic outcomes of patients[30]. Erlotinib is mainly metabolized by CYP subtypes 3A4 and 3A5, and is the substrate drug metabolized by the CYP3A4 enzyme[31-33]. The simultaneous use of a CYP3A4 inducer can reduce erlotinib and increase the formation of metabolites, which may lead to adverse drug reactions in clinical practice.

Limitations This study had some limitations. The overall methodological quality of the included studies was low, which may have reduced the reliability of the statistical analysis. Most experiments did not mention random sequence generation, assignment concealment, blinding of participants and people, or blinding of outcome assessment. Although there were strict inclusion criteria in this meta-analysis, there was still significant clinical heterogeneity, and we hypothesized that the important factor might be the different stages of the disease. There may be a certain degree of publication bias in this area of study, as positive results are more likely to be published, and we only included studies

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published in English and Chinese. Eligible studies published in other languages may be excluded from the meta-analysis, so publication bias cannot be excluded. Due to the limitations of the experimental conditions, the results of network pharmacology were not verified, but can lay a foundation for future research.

5. Conclusion

In this study, a meta-analysis showed that WBRT combined with erlotinib for the treatment of BM from NSCLC is more effective and safe than WBRT alone. Network pharmacology revealed that the core targets of erlotinib in the treatment of BM from NSCLC include ABCB1, ABCG2 and CYP3A4, etc., mainly function the metabolism of xenobiotics by cytochrome P450, chemical carcinogenesis, etc., and its main function is to regulate metabolism and fight cancer. In the future, more high-quality, large-scale clinical trials are needed to confirm the efficacy and safety of WBRT plus erlotinib in patients with NSCLC and BM. In addition, this study lays the foundation for the study of the mechanism of erlotinib in the treatment of BM from NSCLC.

Ethics approval and consent to participate

Not applicable.

Reference to prior publication of study in abstract form

Not applicable.

Availability of data and materials

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

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Declaration of Competing Interest

The authors declare that we have no conflict of interests.

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