


Research Article

The Efficacy and Safety of Afatinib in Non-Small Cell Lung Cancer Patients with Brain Metastasis: A Meta-Analysis

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Aim. The aim of this study is to evaluate the efficacy and safety of afatinib in the treatment of non-small cell lung cancer (NSCLC) patients with brain metastasis based on meta-analysis. **Methods.** Related literatures were searched in the following databases: EMbase, PubMed, China Knowledge Network (CNKI), Wanfang, Weipu, Google Scholar, the China Biomedical Literature Service System, and other databases. Clinical trials and observational studies that met the requirements were selected for meta-analysis using Revman 5.3. The hazard ratio (HR) was used as an indicator of the impact of afatinib. **Results.** A total of 142 related literatures were acquired, but after screening, five literatures were selected for data extraction. The following indices were compared: the progression-free survival (PFS), overall survival (OS), and common adverse reactions (ARs) of grade 3 and above. A total of 448 patients with brain metastases were included and were divided into two groups: the control group (no afatinib treatment, with chemotherapy alone and the first-generation EGFR-TKIs) and the afatinib group. The results showed that afatinib could improve PFS (HR: 0.58, 95% CI: 0.39–0.85, $P < 0.05$) and ORR (OR = 2.86, 95% CI: 1.45–2.57, $P < 0.05$), but had no benefit on OS (HR: 1.13, 95% CI: 0.15–8.75, $P > 0.05$) and DCR (OR = 2.87, 95% CI: 0.97–8.48, $P > 0.05$). For the safety of afatinib, the incidence of grade-3-and-above ARs was low (HR: 0.01, 95% CI: 0.00–0.02, $P < 0.05$). **Conclusion.** Afatinib improves the survival of NSCLC patients with brain metastases and shows satisfactory safety.

1. Introduction

The incidence of advanced non-small cell lung cancer (NSCLC) with brain metastases is 20–40% and increases to 44–63% in EGFR-positive patients [1, 2]. The traditional treatment for NSCLC patients with brain metastasis is whole-brain radiotherapy (WBRT). However, after receiving WBRT, cognitive dysfunction will lead to a decrease in the quality of life. With the application of a tyrosine kinase inhibitor (TKI), the survival of NSCLC patients with brain metastasis has been significantly prolonged, with a median overall survival (OS) of about 14.8 months [3–5].

The epidermal growth factor receptor (EGFR) signaling pathway plays an important role in carcinoma [6]. In recent years, the use of EGFR-TKIs as a targeted therapy for NSCLC patients with brain metastases has been widely

practiced. Afatinib, as a second-generation EGFR-TKI, is a powerful and irreversible dual inhibitor of EGFR and HER2 tyrosine kinases, with a longer inhibition time and elevated efficacy [7–10]. The NCCN guidelines have listed EGFR-TKIs as the first-line treatment for advanced NSCLC with EGFR mutations [7, 11]. However, afatinib has not been recommended as the first-line agent for NSCLC patients with brain metastases. EGFR-TKIs have a small molecular weight, good fat solubility, and a great ability to penetrate the blood-brain barrier (BBB). It has been shown that afatinib can easily penetrate the blood brain barrier to control the brain metastasis of EGFR-mutant NSCLC [9]. However, there is a lack of multicenter clinical evidence currently. Therefore, a meta-analysis was performed in this study by including different studies on the treatment of NSCLC patients with brain metastasis with afatinib, and the

results will provide a reference for promoting the clinical application of afatinib.

2. Materials and Methods

2.1. Inclusion and Exclusion Criteria. PROSPERO registration number for this meta-analysis is 373151. According to the PICOS principle, the inclusion criteria were as follows: (1) Aged at least 18 years, advanced recurrent or metastatic NSCLC (confirmed by histology or cytology) with EGFR mutation, the brain metastasis was confirmed by CT or MRI. (2) Intervention measures included at least two groups: control and afatinib (single afatinib or afatinib combined with other treatments), (3) with the following data: primary outcome indicators including progression-free survival (PFS), overall survival (OS), and hazard ratio (HR), and secondary outcome indicators including treatment-related deaths and AEs (Grade 3 or 4, according to the National Cancer Institute's common toxicity standards). (4) Research types: RCT, non-RCT, observational studies (cohort studies, case-control studies, and cross-sectional studies); the language should be either Chinese or English. Animal experiments, mechanistic studies, repeated publications, case reports, and reviews were excluded.

2.2. Search Strategy. The following databases were searched: CNKI, Wanfang, PUBMED, EMBASE, CBM, OVID, Cochrane library, ClinicalTrials, and OpenGrey. The latest date was May 31, 2021. The search terms were "Afatinib" or "Gilotrif," "non-small cell lung cancer" or "lung cancer," "brain metastases" or "CNS." For each acquired paper, we also reviewed its references. Our analysis was in accordance with the "Cochrane Intervention System Evaluation Manual" and the PRISMA statement.

2.3. Literature Screening. The inclusion criteria for literature were as follows: (1) A study that included patients with NSCLC and brain metastases; (2) There are clear result data verifying the safety and/or efficacy of afatinib; (3) If multiple articles were published based on the same original data, only the latest and most complete articles were used.

2.4. Data Extraction. Two investigators independently conducted the search process and evaluated the included articles, and any inconsistencies were discussed until a consensus was reached. For each article, we collected the first author, publication year, number of registrations, number of patients, treatment plan, and demographic factors (such as age and histological type). Besides, a treatment for patients who had not received systemic treatment (e.g., chemotherapy) before was defined as the first-line treatment, and a treatment for patients who had received platinum-based chemotherapy was defined as the second-line treatment.

2.5. Statistical Analysis. The Revman 5.3.0 software was used for efficacy meta-analysis focusing on PFS, OS, and hazard

ratio (HR). First, the heterogeneity was evaluated, if there was significant heterogeneity ($I^2 > 50\%$, $P < 0.1$), we analyzed the reasons (such as clinical heterogeneity), then subgroup analysis was conducted to eliminate the heterogeneity. If the heterogeneity was not due to clinical heterogeneity but statistical heterogeneity, the random effects model was used for pooled analysis. If there was no heterogeneity ($I^2 \leq 50\%$, $P \geq 0.1$), the fixed effects model was used for pooled analysis. If the sample size was sufficient, a funnel plot analysis was performed to observe whether there was a publication bias.

3. Results

3.1. Search Results. We acquired 142 articles from all available databases. After reviewing the title and abstract, fifty-six articles were included. After reading the full text and checking the indices, nine articles were included, and finally five articles were screened for meta-analysis [9, 12–15]. The flowchart is shown in Figure 1.

3.2. Basic Characteristics of Included Studies. For the nine included studies, they are all cohort studies. All cases included were confirmed NSCLC patients with brain metastases, and afatinib was used in the treatment. The possible factors related to the risk of brain metastasis were recorded, including age, histological characteristics, the dose of afatinib (40 mg), the early-stage treatment for brain metastasis (such as WBRT), and drugs used in the control group (such as platinum, gemcitabine, erlotinib, pemetrexed, etc.). To evaluate the efficacy and safety of afatinib, the median PFS, OS, and HR of each group were extracted (Table 1).

3.3. Afatinib Prolongs the PFS of NSCLC Patients with Brain Metastasis. In the included five studies, the total HR of afatinib as the first-line treatment is 0.58 (95% CI: 0.39–0.85), and the inverted funnel figure shows no publication bias (Figure 2). This result proves that afatinib can prolong the PFS of NSCLC patients with brain metastasis.

3.4. Afatinib Has No Effects on OS. In the three included studies, the heterogeneity of OS was extremely low ($I^2 = 0\%$), and its overall HR was 1.13 (95% CI: 0.15–8.75). There is no significant difference in OS between afatinib and control therapies (gemfibrozil, erlotinib, or chemotherapy) (Figure 3).

3.5. Afatinib Provides Better Objective Response Rate (ORR) and Disease Control Rate (DCR). In the three included studies, the results of the ORR were heterogeneous ($I^2 > 50\%$), and the odds ratio (OR) is 2.86 (95% CI: 1.45–2.57). In comparison with chemotherapy, afatinib can provide a better ORR (Figures 4 and 5). Meanwhile, the heterogeneity of the disease response rate (DCR) is extremely low ($I^2 = 0\%$), and the odds ratio (OR) is 2.87 (95% CI: 0.97–8.48).

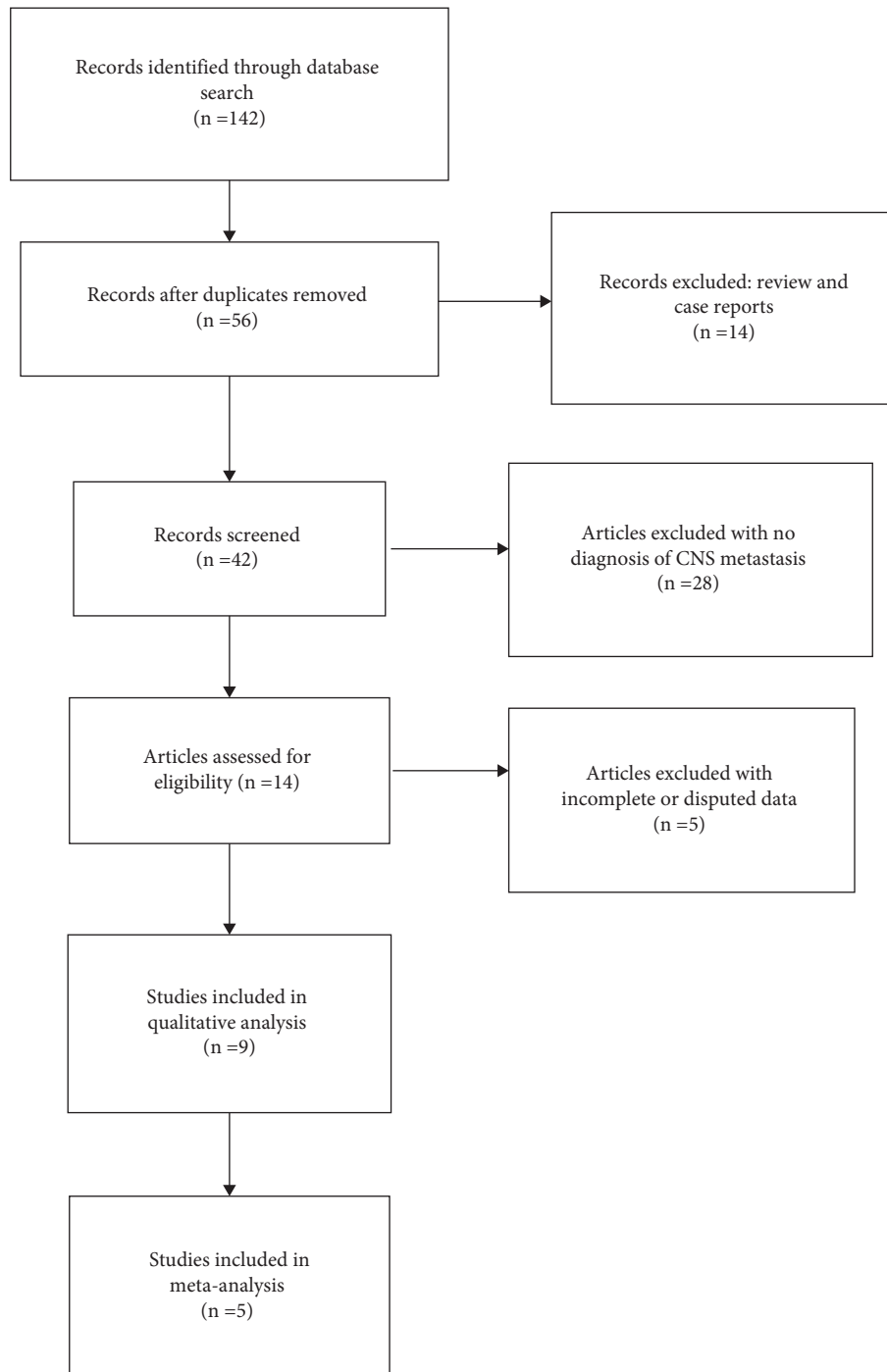


FIGURE 1: Flow diagram of the study selection process.

3.6. *Adverse Reactions (ARs) of Afatinib in the Treatment of NSCLC with Brain Metastases.* The common ARs were investigated [19, 20]. Overall, the incidence of ARs is high. The overall OR of ARs is 1.56 (95% CI: 1.44–1.70). Diarrhea, stomatitis, and paronychia were among the most common ones. The overall OR of Grade ≥ 3 ARs is 2.04 (95% CI: 1.47–2.82). Diarrhea was among the most common one (Figure 6).

4. Discussion

The incidence and mortality of lung cancer are still remarkably high currently [17]. About 10% of patients have brain metastasis at the time of diagnosis, and about 40% may develop brain metastasis during treatment [16]. At present, the commonly used local treatments for this cohort are: WBRT, stereotactic radiotherapy (SRT), and surgical

TABLE 1: Main characteristics of each study included.

First author	Year	Study design	Included studies	Treatment status	Number of BM	Age (years)/population	Pre-treatment	Dose (mg)	Quality score
Schuler [9]	2016	Coh	Lux-lung 3 adenocarcinoma	First-line	42	62/Asian	WBRT	40	6
		Coh	Lux-lung 6 adenocarcinoma	First-line	49	54/Asian	WBRT	40	6
Li [6]	2018	Coh	Adenocarcinoma	First-line	28	60/Asian	NA	40	6
Su [16]	2018	Coh	NA	First-line	306	60/Asian	NA	40	6
Tan [15]	2019	Coh	Adenocarcinoma	First-line	42	62/Asian	WBRT	30	6
Wang [13]	2019	Coh	Adenocarcinoma	First-line	24	58/Asia	SRTWBRT	40	6
Chen [14]	2019	Coh	Stage III B or IV adenocarcinoma	First-line	134	65/Asian	Radiotherapy of brain metastases	40	6
Lin [17]	2019	Coh	Adenocarcinoma	First-line	125	60/Asian	NA	40	6
Wei [18]	2019	Coh	Advanced lung adenocarcinoma	First-line	74	60/Asian	NA	40	6
Jung [12]	2020	Coh	Adenocarcinoma	First-line	157	60/Asian	SRTWBRT	40	6

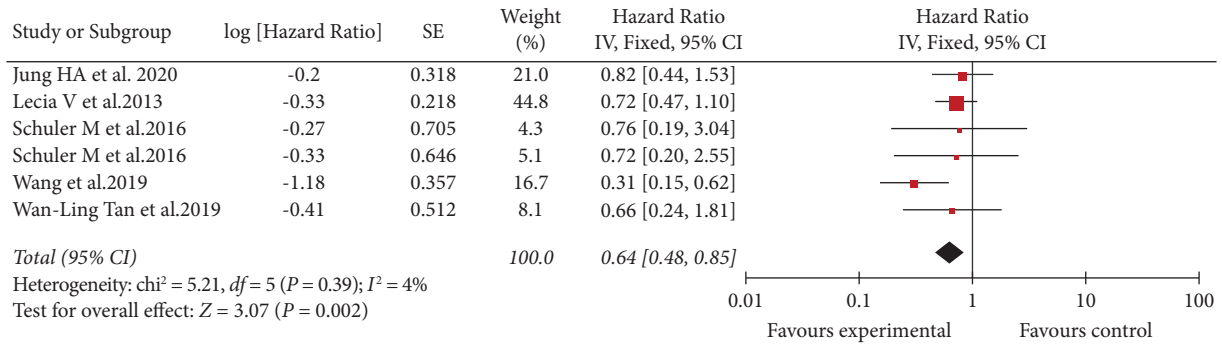


FIGURE 2: Meta-analysis of PFS of afatinib in brain metastases.

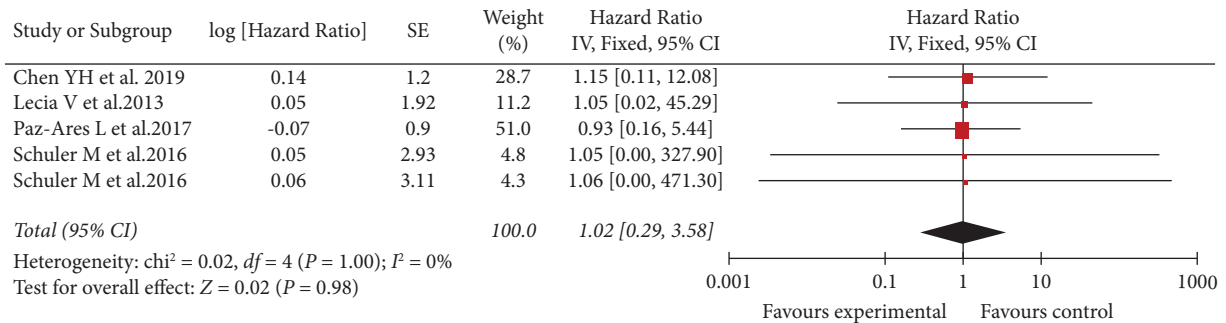


FIGURE 3: Meta-analysis of OS of afatinib in brain metastases.

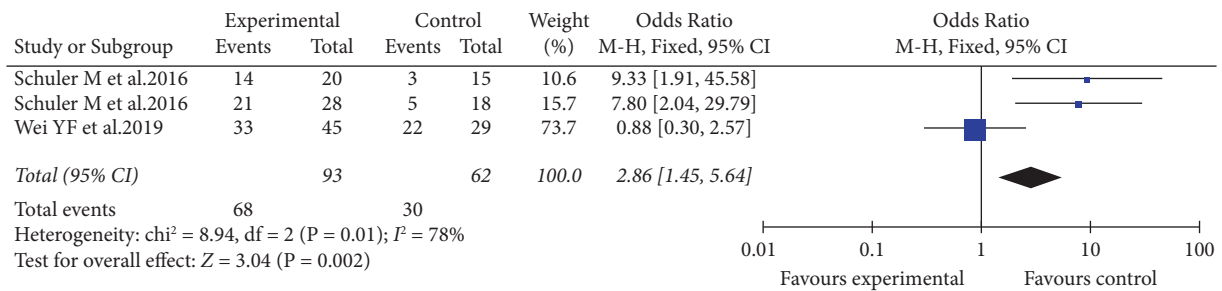


FIGURE 4: Meta-analysis of ORR of afatinib in brain metastases.

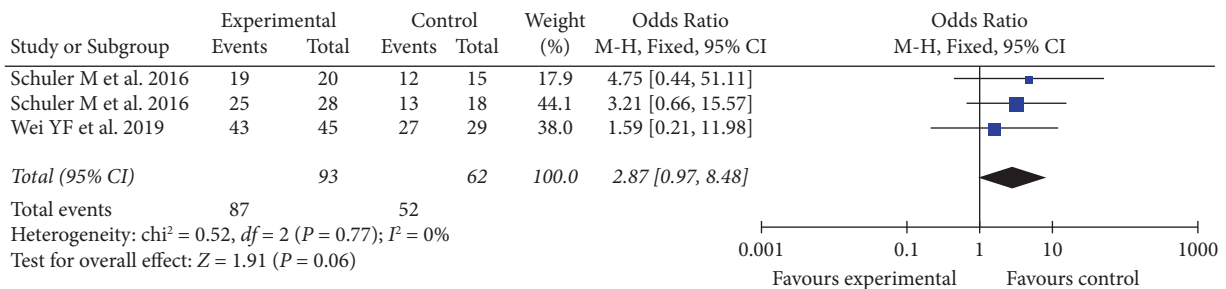


FIGURE 5: Meta-analysis of DCR of afatinib in brain metastases.

resection. The local treatments play an important role in combination with systemic therapies (such as chemotherapy, immunotherapy, and EGFR TKI combined therapy). Afatinib is an oral ErbB-family blocker [8]. Compared with the first-generation EGFR TKI, afatinib binds to EGFR irreversibly and suppresses the carcinogenic signaling

pathway. Afatinib can control tumor progression and improve the prognosis of EGFR mutant NSCLC patients with brain metastasis [9]. By reviewing real-world data, this study used first-line chemotherapy or the first-generation EGFR-TKIs as the control group and observed the efficacy and safety of the afatinib group as the first-line therapy. In the afatinib

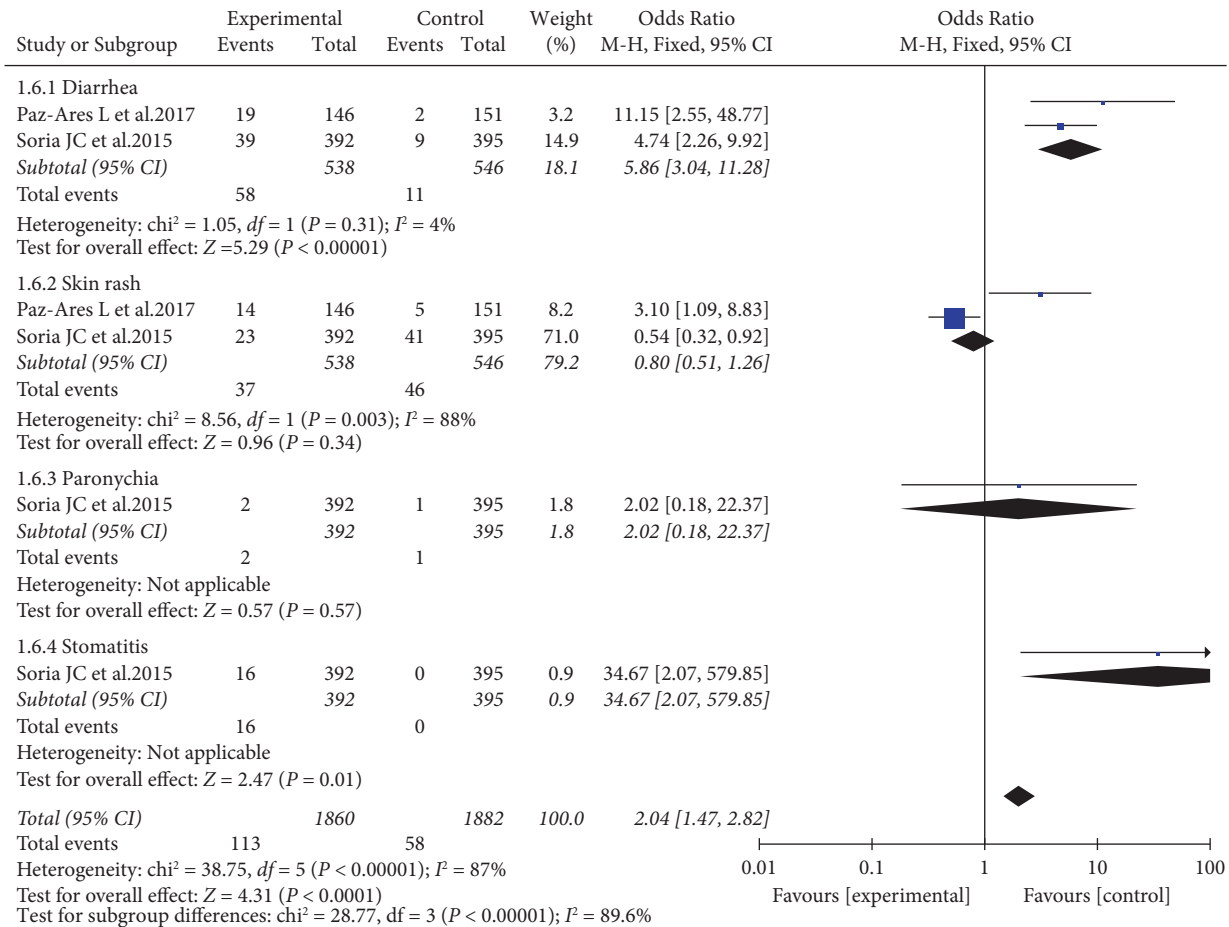


FIGURE 6: Meta-analysis of overall AR of afatinib in brain metastases.

group, the HR of PFS is 0.58 (95% CI: 0.39–0.85), with a reduced risk of progression. The OR of the ORR is 2.86 (95% CI 1.45–2.57) and the OR of the DCR is 2.87 (95% CI 0.97–8.48) in comparison with controls, suggesting that afatinib can provide a better treatment response. This is consistent with the conclusion of the LUX-Lung3/6 trials [9]. In these trials, especially among the brain metastasis cohort, the PFS of the afatinib group was significantly better than the chemotherapy group. In the LUX-Lung 3 trial, the PFS of the afatinib group was 11.1 months, and that of the cisplatin-pemetrexed was 5.4 months. In the LUX-Lung 6 trial, the PFS periods of afatinib and cisplatin-gemcitabine groups were 8.2 months and 4.7 months, respectively. However, we found no benefits of afatinib on OS (HR 1.13, 95% CI: 0.15–8.75). In the LUX-Lung3/6 trials, a negative result of OS was also reported in the total population, but an OS benefit was observed in the EGFR19del subgroup. So far, although afatinib can control the progression of brain metastasis, it does not bring OS benefit versus chemotherapy or the first-generation EGFR-TKIs. In the treatment efficacy assessment, afatinib had a better ORR and DCR versus chemotherapy and the first-generation EGFR-TKI. Overall, this is also consistent with the conclusion of the LUX-Lung3/6 trials. It should be noted that we did not stratify the oral dose of afatinib in our selected

studies because a meta-analysis reported no difference between the efficacy of the 30-mg group and the 40-mg groups [21].

The common AEs of afatinib include skin rash, diarrhea, loss of appetite, stomatitis, vomiting, fatigue, and paronychia. Compared with the first-generation EGFR-TKIs, afatinib has a higher incidence of stomatitis, diarrhea, and paronychia among all grades of AEs, and the incidence of rashes is similar. Among grades 3 and above AEs, afatinib is associated with a higher incidence of diarrhea, while the incidences of rash, stomatitis, and paronychia are similar.

At present, it is still disputable whether TKIs in combination with radiotherapy are beneficial for controlling brain metastasis. Radiotherapy may provide clinical benefits for brain metastasis caused by NSCLC with rare EGFR mutations [22]. Early treatment such as WBRT and chemotherapy can increase the permeability of the BBB. Therefore, a pretreatment of radiotherapy and chemotherapy before the use of afatinib may assist afatinib in penetrating the BBB [23]. In the LUX-lung 3/6 trial, among patients who had received WBRT, afatinib can significantly improve PFS and OS in elderly patients [24]. However, there are also controversial conclusions [18]. A retrospective study of NSCLC patients with EGFR-sensitive mutation and brain

metastasis found that adding WBRT to EGFR-TKI therapy has no additional survival benefit [25]. Another retrospective study showed that the OS of patients receiving early radiotherapy was similar to that of the delayed radiotherapy group [26]. A meta-analysis also showed that only the EGFR-TKI group (but not the WBRT plus EGFR-TKI group) showed superior intracranial PFS. Therefore, it is still too early to answer this question, and further clinical trials and real-world data are needed.

The limitations of this meta-analysis are as follows. First, the small sample size weakens the reliability of the results. Second, we include several retrospective observational studies, and there might be selection bias in these studies.

In conclusion, this meta-analysis suggests that afatinib improves the survival of NSCLC patients with brain metastases and shows satisfactory safety.

Data Availability

All data are available upon reasonable request to the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

HJ, PL, JH, BL, and PW collected and analyzed the data and drafted the manuscript. XH designed the study and wrote the manuscript. All authors read and approved the manuscript. P L, J H, B L, and P W authors contributed equally to this work.

References

- [1] L. E. Hendriks, E. F. Smit, B. A. Vosse et al., "EGFR mutated non-small cell lung cancer patients: more prone to development of bone and brain metastases?" *Lung Cancer*, vol. 84, no. 1, pp. 86–91, 2014.
- [2] R. Yamanaka, "Medical management of brain metastases from lung cancer (Review)," *Oncology Reports*, vol. 22, no. 6, pp. 1269–1276, 2009.
- [3] H. Yu, K. O. Lam, M. D. Green et al., "Significance of radiation esophagitis: conditional survival assessment in patients with non-small cell lung cancer," *Journal of the National Cancer Center*, vol. 1, no. 2, pp. 31–38, 2021.
- [4] J. Zeng, W. Ma, R. B. Young, and T. Li, "Targeting HER2 genomic alterations in non-small cell lung cancer," *Journal of the National Cancer Center*, vol. 1, no. 2, pp. 58–73, 2021.
- [5] P. W. Sperduto, N. Kased, D. Roberge et al., "Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases," *Journal of Clinical Oncology*, vol. 30, no. 4, pp. 419–425, 2012.
- [6] C. Y. Hu and Y. He, "Formononetin inhibits non-small cell lung cancer proliferation via regulation of mir-27a-3p through p53 pathway," *Oncologie*, vol. 23, no. 2, pp. 241–250, 2021.
- [7] D. Zhang, H. Liu, Z. Yi et al., "Thymidylate synthase confers pemetrexed resistance of non-small cell lung cancer cells by EGFR/PI3K/AKT pathway," *Biocell*, vol. 45, no. 3, pp. 617–625, 2021.
- [8] J. Zhu, X. Bo, G. Jiang, S. Yao, T. Zhao, and L. Chen, "microR-1294-5p inhibits glycolytic metabolism of non-small cell lung cancer cells via targeting TMPRSS11B," *Biocell*, vol. 45, no. 3, pp. 639–647, 2021.
- [9] M. Schuler, Y. L. Wu, V. Hirsh et al., "First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases," *Journal of Thoracic Oncology*, vol. 11, no. 3, pp. 380–390, 2016.
- [10] S. M. Abdallah and A. Wong, "Brain metastases in non-small-cell lung cancer: are tyrosine kinase inhibitors and checkpoint inhibitors now viable options?" *Current Oncology*, vol. 25, no. 11, pp. 103–114, 2018.
- [11] Nccn, "NCCN clinical practice guidelines in oncology—acute lymphoblastic leukemia," 2021, <http://www.nccn.org>.
- [12] H. A. Jung, S. Y. Woo, S. H. Lee et al., "The different central nervous system efficacy among gefitinib, erlotinib and afatinib in patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer," *Translational Lung Cancer Research*, vol. 9, no. 5, pp. 1749–1758, 2020.
- [13] S. Wang, P. Xing, K. Yang et al., "Efficacy and safety of afatinib in a Chinese population with advanced lung adenocarcinoma with sensitive EGFR mutations," *Thoracic cancer*, vol. 10, no. 6, pp. 1461–1468, 2019.
- [14] Y. H. Chen, Y. F. Chen, C. Y. Chen, J. Y. Shih, and C. J. Yu, "Clinical factors associated with treatment outcomes in EGFR mutant non-small cell lung cancer patients with brain metastases: a case-control observational study," *BMC Cancer*, vol. 19, no. 1, pp. 1006–1010, 2019.
- [15] W.-L. Tan, Q. S. Ng, C. Lim et al., "Influence of afatinib dose on outcomes of advanced EGFR-mutant NSCLC patients with brain metastases," *BMC Cancer*, vol. 18, no. 1, pp. 1198–1207, 2018.
- [16] P. L. Su, Y. L. Wu, W. Y. Chang et al., "Preventing and treating brain metastases with three first-line EGFR-tyrosine kinase inhibitors in patients with EGFR mutation-positive advanced non-small cell lung cancer," *Therapeutic Advances in Medical Oncology*, vol. 10, no. 2, pp. 175883591879758–175883591913540, 2018.
- [17] C. Y. Lin, C. C. Chang, P. L. Su et al., "Brain MRI imaging characteristics predict treatment response and outcome in patients with de novo brain metastasis of EGFR-mutated NSCLC," *Medicine (Baltimore)*, vol. 98, no. 33, pp. 16766–16770, 2019.
- [18] Y. F. Wei, C. K. Lim, M. S. Tsai, M. S. Huang, and K. Y. Chen, "Intracranial responses to afatinib at different doses in patients with EGFR-mutated non-small-cell lung carcinoma and brain metastases," *Clinical Lung Cancer*, vol. 20, no. 3, pp. 274–283, 2019.
- [19] J. C. Soria, E. Felip, M. Cobo et al., "Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial," *The Lancet Oncology*, vol. 16, no. 8, pp. 897–907, 2015.
- [20] L. Paz-Ares, E. H. Tan, K. O'Byrne et al., "Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial," *Annals of Oncology*, vol. 28, no. 2, pp. 270–277, 2017.
- [21] L. Zhang, Y. Luo, J. Chen et al., "Efficacy and safety of afatinib in the treatment of advanced non-small-cell lung cancer with EGFR mutations: a meta-analysis of real-world evidence,"

- Journal of Oncology*, vol. 2021, Article ID 8736288, 16 pages, 2021.
- [22] E. Puchun, Z. Tian, W. Jing, P. Qingsong, and W. Ping, "Brain metastasis in non-small cell lung cancer (NSCLC) patients with uncommon EGFR mutations: a report of seven cases and literature review," *Cancer Biology & Medicine*, vol. 14, no. 4, pp. 418–425, 2017.
- [23] Y. M. Cao, C. I. Tsien, Z. Shen et al., "Use of magnetic resonance imaging to assess blood- brain/blood-glioma barrier opening during con- formal radiotherapy," *Journal of Clinical Oncology*, vol. 23, no. 18, pp. 4127–4136, 2005.
- [24] Y. L. Wu, L. V. Sequist, E. H. Tan et al., "Afatinib as first-line treatment of older patients with EGFR mutation-positive non-small-cell lung cancer: subgroup analyses of the LUX-lung 3, LUX-lung 6, and LUX-lung 7 trials," *Clinical Lung Cancer*, vol. 19, no. 4, pp. 465–479, 2018.
- [25] T. Jiang, C. Su, X. Li et al., "EGFR TKIs plus WBRT demonstrated No survival benefit other than that of TKIs alone in patients with NSCLC and EGFR mutation and brain metastases," *Journal of Thoracic Oncology*, vol. 11, no. 10, pp. 1718–1728, 2016.
- [26] H. Wang, X. Yu, Y. Fan, and Y. Jiang, "Multiple treatment modalities for brain metastasis in patients with EGFR-mutant non-small-cell lung cancer," *OncoTargets and Therapy*, vol. 11, pp. 2149–2155, 2018.