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EGFR inhibitors as adjuvant therapy for resected non-small cell lung cancer harboring EGFR mutations

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ABSTRACT

Objectives: Cisplatin-based chemotherapy as an adjuvant therapy for resected non-small cell lung cancer (NSCLC) has reached its plateau, and it is limited by a high risk of recurrence and significant toxicities. The clinical value of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in resected NSCLC harboring EGFR mutations remains controversial. In this study, we performed a meta-analysis to evaluate the role of EGFR inhibitors as an adjuvant therapy for targeted patients.

Materials and methods: Studies were identified via electronic search. The pooled odds ratio (OR) for disease-free survival (DFS) and overall survival (OS) were calculated for the meta-analysis.

Results: There were 11 trials (1,152 resected NSCLC patients with EGFR sensitive mutations) in this meta-analysis. The results showed that adjuvant treatment with EGFR-TKIs can prolong both the OS and DFS when compared to treatment without TKIs as an adjuvant therapy (OS: OR, 0.63; 95% CI, 0.46 to 0.87, P = 0.004; heterogeneity I^2 = 61%, P = 0.008; DFS: OR, 0.56; 95% CI, 0.43 to 0.72, P < 0.00001; heterogeneity I^2 = 37%, P = 0.10). The results of the predefined subgroup analyses in this meta-analysis suggested a greater DFS with the mono EGFR-TKIs compared with chemotherapy, whereas the OS benefit failed to show a similar difference between the two arms (p = 0.30). We also found that treatment with EGFR-TKIs plus chemotherapy was associated with a significantly longer DFS and OS compared to mono chemotherapy in patients with completely resected EGFR-mutant NSCLC (DFS: OR, 0.48; 95% CI, 0.34-0.68; P < 0.0001; heterogeneity I^2 = 47%, P = 0.07; OS: OR, 0.50; 95% CI, 0.31-0.78; P = 0.003; heterogeneity I^2 = 57%, P = 0.05). Additionally, less severe adverse events (SAEs) were observed in the TKIs group (OR, 0.22; 95% CI, 0.14 to 0.37, P < 0.00001; heterogeneity I^2 = 22%, P = 0.28).

Conclusion: The addition of EGFR-TKIs to adjuvant chemotherapy can prolong the OS and PFS for resected NSCLC. Adjuvant EGFR-TKIs may be a potential treatment option compared to adjuvant chemotherapy in completely resected patients with EGFR mutation-positive NSCLC.

Statement of significance: The clinical value of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in resected non-small cell lung cancer (NSCLC) harboring EGFR mutations remains controversial. This study demonstrates that EGFR-TKIs as an adjuvant therapy could prolong the DFS and potentially prolong the OS in postoperative patients. Therefore, this therapy paves the way for EGFR-TKIs to be an adjuvant treatment for NSCLC.

Abbreviations: EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; OS, overall survival; DFS, disease free survival; AC, adjuvant chemotherapy

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1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide. The most common type is non-small cell lung cancer (NSCLC), which makes up an impressive 85% of the population for all lung cancer cases [1]. Among the newly diagnosed patients, approximately 30% of them are lucky enough to present locally with the disease [2], and surgery is the primary and preferred treatment for them. However, the long-term survival rate of NSCLC patients who received aggressive surgical management is still poor with high recurrence rate [3], so the adjuvant therapy after surgery is crucial.

Based on the results from large randomized trials and meta-analyses, cisplatin-based chemotherapy as an adjuvant therapy is strongly recommended for stage II-IIIA NSCLC after complete resection [2,4,5], which brings a survival improvement of 5% at 5 years (from 40% to 45%) [6]. However, this improvement clearly cannot meet clinical needs. Furthermore, the significant toxicity of adjuvant chemotherapy often reduces patients' compliance rates as well as their quality of life (45%–73.8%) [7].

With the advent of the genetic age, targeted molecular therapy aimed at the mutation of lung cancer driver genes has gradually become a mainstay of precision treatment in advanced NSCLC. Epidermal growth factor receptor (EGFR), the most frequent biomarker for which an available targeted therapy exists, plays a key role in the targeted molecular therapy of lung cancer. EGFR tyrosine kinase inhibitors (TKIs) have been accepted as the standard first-line treatment for metastatic NSCLC patients with EGFR mutations [8,9], and EGFR-TKIs such as osimertinib can also be used as a first line or second line in the setting of pretreated EGFR T790 M mutated patients. However, there is limited evidence to support the use of EGFR tyrosine kinase inhibitors as an adjuvant therapy for those resected patients harboring EGFR mutations. In the past five years, several trials that compared the efficacy and toxicity of EGFR tyrosine kinase inhibitors (TKIs) with that of chemotherapy or placebo among the resected patients harboring EGFR mutations were reported. Some of the trials indicated that EGFR TKIs are superior to chemotherapy as an initial treatment for patients with the EGFR mutation following surgical resection [10–14], while other trials showed no difference [15,16]. Prior to this current study, we found only one meta-analysis of the adjuvant treatment of resected NSCLC, which was published five years ago, but its study subjects were all patients (rather than patients harboring EGFR mutations) [17], and there were no large clinical trials such as the Adjuvant and Evan trials at that time. Considering the limited number of cases and the controversial results, we decided to carry out this research to explore the clinical significance of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as an adjuvant therapy for EGFR-mutated NSCLC patients after surgery.

In this meta-analysis, we included 11 trials that had completed accrual from 2005 to 2018. We expected that a systematic review of all the available randomized evidence and a combination of the results of these trials in a meta-analysis might provide sufficient statistical power for a better treatment plan for completely resected patients with EGFR mutation-positive NSCLC.

2. Methods

2.1. Search strategy and selection criteria

We searched for studies evaluating EGFR-TKIs as an adjuvant therapy after operation for EGFR mutant NSCLC. Studies were identified by searching the PubMed, ISI Web of Science, ScienceDirect, SpringerLink, The Cochrane library, AACR, and the Ovid databases as far back as they extend. The search terms were as follows: erlotinib, gefitinib, target therapy, EGFR, chemotherapy, lung cancer, clinical study, and clinical trial. This search was supplemented by manual searches (e.g., reference lists of trial publications, review articles). We excluded the studies that examined EGFR-TKIs as a first-line therapy for advanced lung cancer, or included immunotherapy in the adjuvant therapy. Among the reports that pertained to overlapping patient cohorts, we retained only the largest study to avoid duplication of data. Only those articles published in English were included.

2.2. Data processing

Data extraction was performed independently by two reviewers. The study data was extracted as accurately as possible. Investigators of the eligible studies were contacted and asked to supply additional data when key information relevant to the meta-analysis was missing. Occasionally, we evaluated the primary data from its survival curves if contact with the authors was not possible. The characteristics and outcomes of the included trials as well as the data extracted from the trials were entered into RevMan version 5.1 (Cochrane Collaboration, Oxford, United Kingdom). Some of the studies analyzed the effects of EGFR inhibitors added to conventional systematic therapy (EGFR-TKIs + chemotherapy) compared with those without EGFR inhibitors (only conventional systematic therapy), while others employed EGFR-TKIs instead of chemotherapy (EGFR-TKIs VS chemotherapy). Therefore, in this meta-analysis, we enrolled all studies to evaluate the effects of patients who received EGFR-TKIs compared with those who had not received EGFR-TKIs. In a subgroup analysis, some studies were employed to compare EGFR-TKIs plus chemotherapy with chemotherapy, and others were employed to compare mono EGFR-TKIs with chemotherapy.

2.3. End points

The primary end points were DFS and OS, and the secondary outcome was the presence of a severe adverse events (SAEs). To minimize the potential for within-study selective reporting bias, some studies where the primary outcome measure of overall survival was not reported were included if all other inclusion criteria were met. The authors of these studies were contacted and asked to supply data for the primary outcome measure if collected.

3. Results

3.1. Study selection and characteristics analysis

The detailed study selection procedure is presented in Fig. 1, in the form of a flow diagram. The initial search retrieved 2058 potentially eligible articles from all databases and a manual cross-reference of articles. A total of 1802 studies were immediately excluded. The reasons for exclusion included duplicate articles, case reports, reviews, non-English articles and nonhuman studies; in some cases, articles were excluded directly in the primary screening. An additional 229 articles were eliminated because they did not report the adjuvant therapy for locally advanced lung cancer, they employed EGFR-TKIs as a first-line therapy for advanced lung cancer, or they included immunotherapy in the adjuvant therapy, among other reasons. The full text of the remaining 27 studies was retrieved and examined on the basis of relevance, according to the predefined criteria. Six of these studies were excluded because they were not completed, seven studies were excluded due to single-arm design. Others were excluded for various reasons, such as the same author publishing two reports on an overlapping population (n = 1), no results being published (n = 1), or 2 trials being completed in the same institute (n = 1). Only a portion of the patients in the BR19 trial were enrolled into the meta-analysis to compare the OS and DFS because some of those patients did not harbor EGFR mutations in the study. Finally, a total of 11 studies (all in English) that assigned 1152 patients were enrolled for data extraction. All patients enrolled in this study harbored EGFR-sensitive mutations. The principal characteristics of the studies evaluated in this meta-analysis

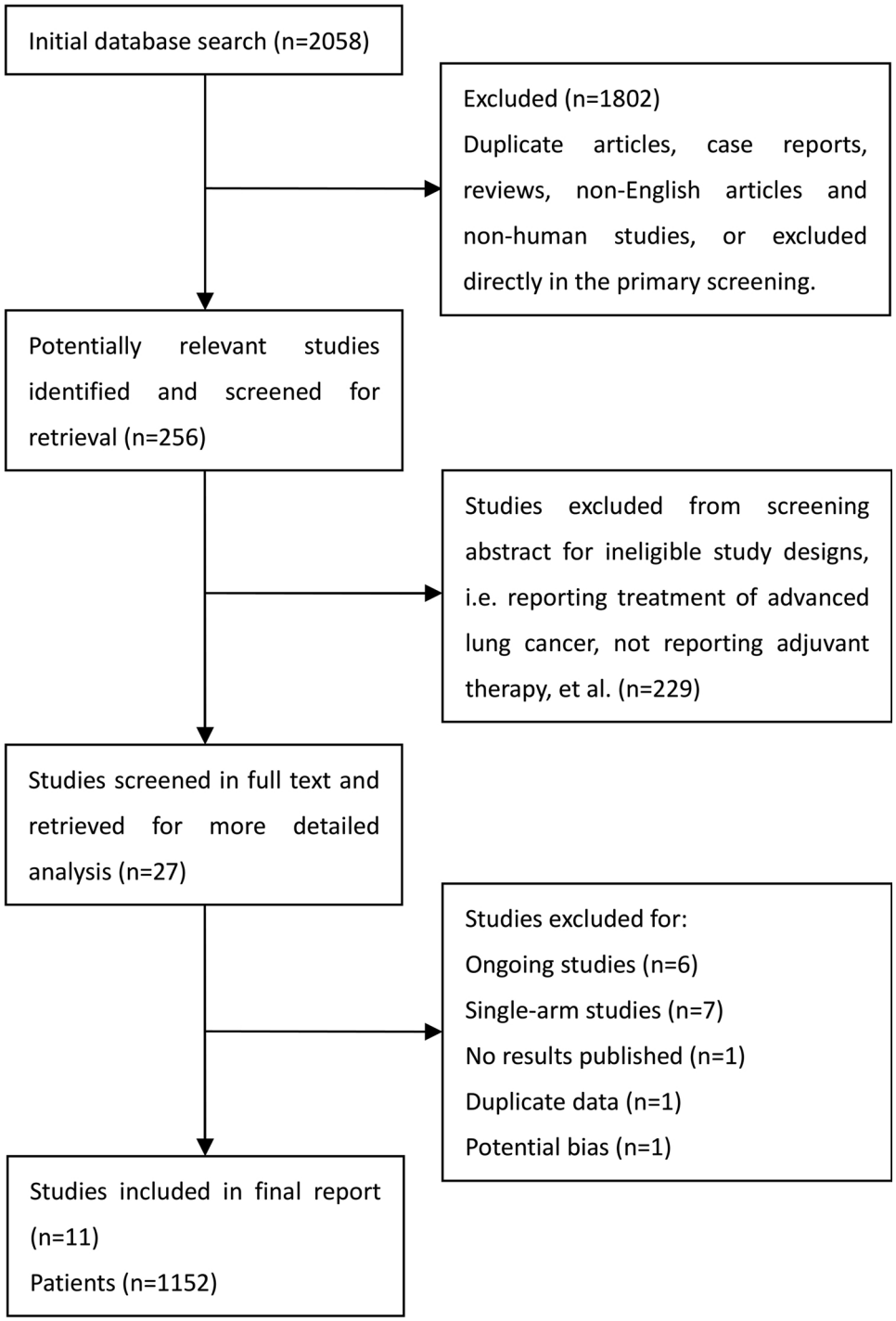


Fig. 1. PRISMA flow chart of the search result of the meta-analysis.

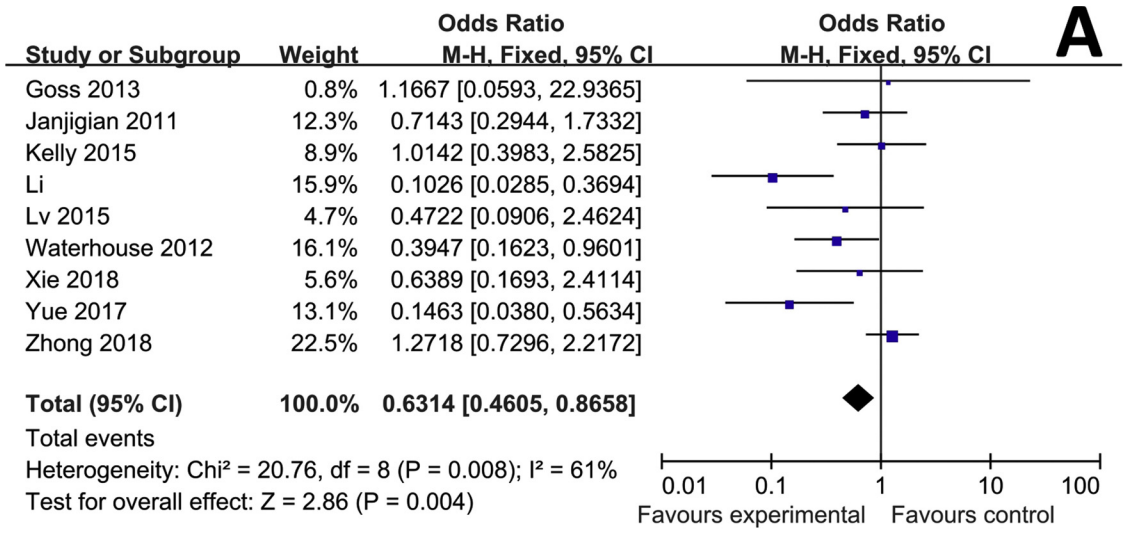
are shown in Table 1.

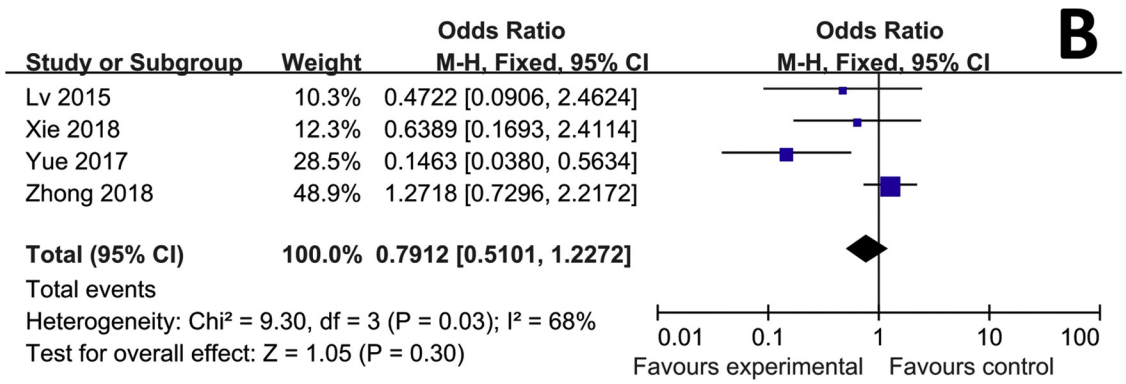
3.2. Overall survival

A meta-analysis of nine studies, which included a total of 980 patients, showed that the effects of EGFR-TKIs (TKIs only/TKIs plus chemotherapy) versus no TKIs (placebo/chemotherapy) on the overall survival (OR, 0.63; 95% CI, 0.46 to 0.87, P = 0.004; heterogeneity I^2 = 61%, P = 0.008; Fig. 2A) was comparable. The result was also significant when retrospective studies were excluded from the analysis (Fig. 3A). For the comparison of EGFR-TKI monotherapy with mono chemotherapy, four trials (471 patients) were included in the analysis, and results indicated that EGFR-TKIs did not promote a better overall survival compared to chemotherapy (OR, 0.79; 95% CI, 0.51 to 1.23, P = 0.30; heterogeneity I^2 = 68%, P = 0.03; Fig. 2B). Additionally, five trials (509 patients) were included in the analysis of overall survival between EGFR-TKIs plus chemotherapy versus mono chemotherapy. It is demonstrated that EGFR-TKIs plus concurrent chemotherapy performed better than chemotherapy alone for overall survival (OR, 0.50; 95% CI, 0.31 to 0.78, P = 0.003; heterogeneity I^2 = 57%, P = 0.05; Fig. 2C). Moreover, all of the heterogeneity levels were within acceptable ranges.

Table 1
Characteristics of the eligible studies.

Trial	Phase	Period	Patients Number	Mutation Type	Pathologic Stage	Experimental Events	Control Events	Outcome
Goss 2013	III	Sept.2002-Apr.2005	15	Exon19 deletion and Exon21 Leu858Arg	IB-IIIA	TKIs(Gefitinib)	Placebo	No statistic DFS or OS benefit
Janjigian 2011	Retrospective	May.2002-Aug.2008	167	Exon19 n = 93(56%) Exon21 n = 74(44%)	I-III	TKIs(Erlotinib/Gefitinib) + Chemotherapy	Chemotherapy	DFS benefit but no OS benefit
Kelly 2015	III	Nov.2007-Jul.2010	161	Exon19 n = 89(55.3%) Exon21 n = 72(44.7%)	IB-IIIA	TKIs (Erlotinib) + Chemotherapy	Placebo	DFS benefit; OS data immature
Li 2014	II	Aug.2008-Sept.2011	60	Exon19 n = 20(33.3%) Exon21n = 40(66.7%)	IIIA-N2	TKIs (Gefitinib) + Chemotherapy	Chemotherapy	DFS benefit but no OS benefit
Lv 2015	Retrospective	Sept.2004-May.2013	138	Exon18 n = 4(2.9%) Exon19 n = 58(42%) Exon21 n = 70(50.7) Complex Mutation n = 6 (4%)	I-IIIA	TKIs(Erlotinib/Gefitinib/Icotinib)	Chemotherapy	DFS benefit but no OS benefit
Waterhouse 2012	II	Tus.2008-Jan.2012	106	Mutation type not mentioned	IB-IIIA	TKIs + Chemotherapy (docetaxel, bevacizumab, and erlotinib)	Chemotherapy	No statistic DFS or OS benefit
Xie 2018	Retrospective	Jan.2013-Mar.2017	104	Exon19 n = 58(55.8%) Exon21 n = 46(44.2%)	II-IIIA	TKIs (Gefitinib)	Chemotherapy	DFS benefit but no OS benefit
Yue 2017	II	Sept.2012-May.2015	102	Exon19 n = 58(56.8%) Exon21 n = 43(42.2%) Complex Mutation n = 1 (1%)	IIIA	TKIs (Gefitinib)	Chemotherapy (vinorelbine plus cisplatin)	DFS benefit; OS data immature
Zhong 2018	II	Sept.2011-Apr.2014	222	Exon19 n = 58(52%) Exon21 n = 53(48%)	II-IIIA	TKIs (Gefitinib)	Chemotherapy (Vinorelbine plus cisplatin)	DFS benefit; OS data immature
Feng 2015	II	Feb.2011-Dec.2012	39	Exon18 n = 1(3%) Exon19 n = 16(41%) Exon21 n = 22(56%)	IB-IIIA	TKIs (Icotinib) + Chemotherapy	Chemotherapy	No statistic DES or OS benefit
Tsuboi 2005	III	Oct.2002-Mar.2003	38	Mutation type not mentioned	I-IIIA	TKIs (Gefitinib)	Placebo	No survival data





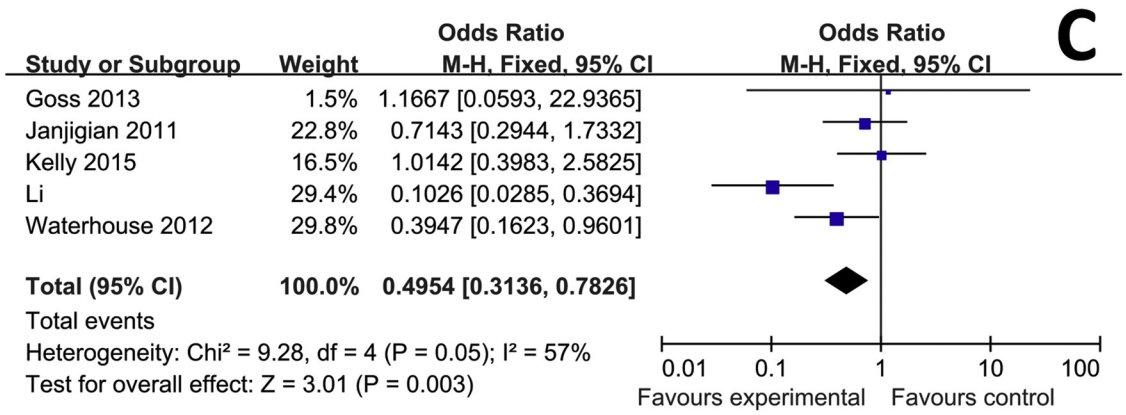


Fig. 2. Forest plots of overall survival when comparing TKIs VS no TKIs (A), TKIs VS chemo (B) and TKIs + chemo VS chemo (C). Solid diamond indicates the pooled OR of OS, square indicates odds ratio value of each study.

3.3. Disease-free survival

Eleven studies (1,152 patients) were included in the analysis of disease-free survival for the comparison between the group of EGFR-TKIs (TKIs only/TKIs plus chemotherapy) versus no TKIs (placebo /chemotherapy), where the former clearly exhibited superiority (OR, 0.56; 95% CI, 0.43 to 0.72, P < 0.00001; Fig. 4A). Meanwhile, there was a moderate level of heterogeneity between the sample estimates for DFS expressed as OR (I^2 = 37%, P = 0.10; Fig. 4A). The result was also significant when retrospective studies were excluded from the analysis (Fig. 3B). In the subgroup analysis, we explored the value of mono EGFR-TKIs compared to chemotherapy only, and EGFR-TKIs exhibited their superiority again, with the OR expressing 0.67 (95% CI, 0.45 to 0.98; Fig. 4B), and there was no evidence of important statistical heterogeneity, with an I^2 value of 0% (P = 0.56). EGFR-TKIs plus concurrent chemotherapy also performed better than chemotherapy alone for disease free survival as OR (OR, 0.48; 95% CI, 0.34-0.68; P < 0.0001; heterogeneity I^2 = 47%, P = 0.07). Eight trials (724 patients) were included.

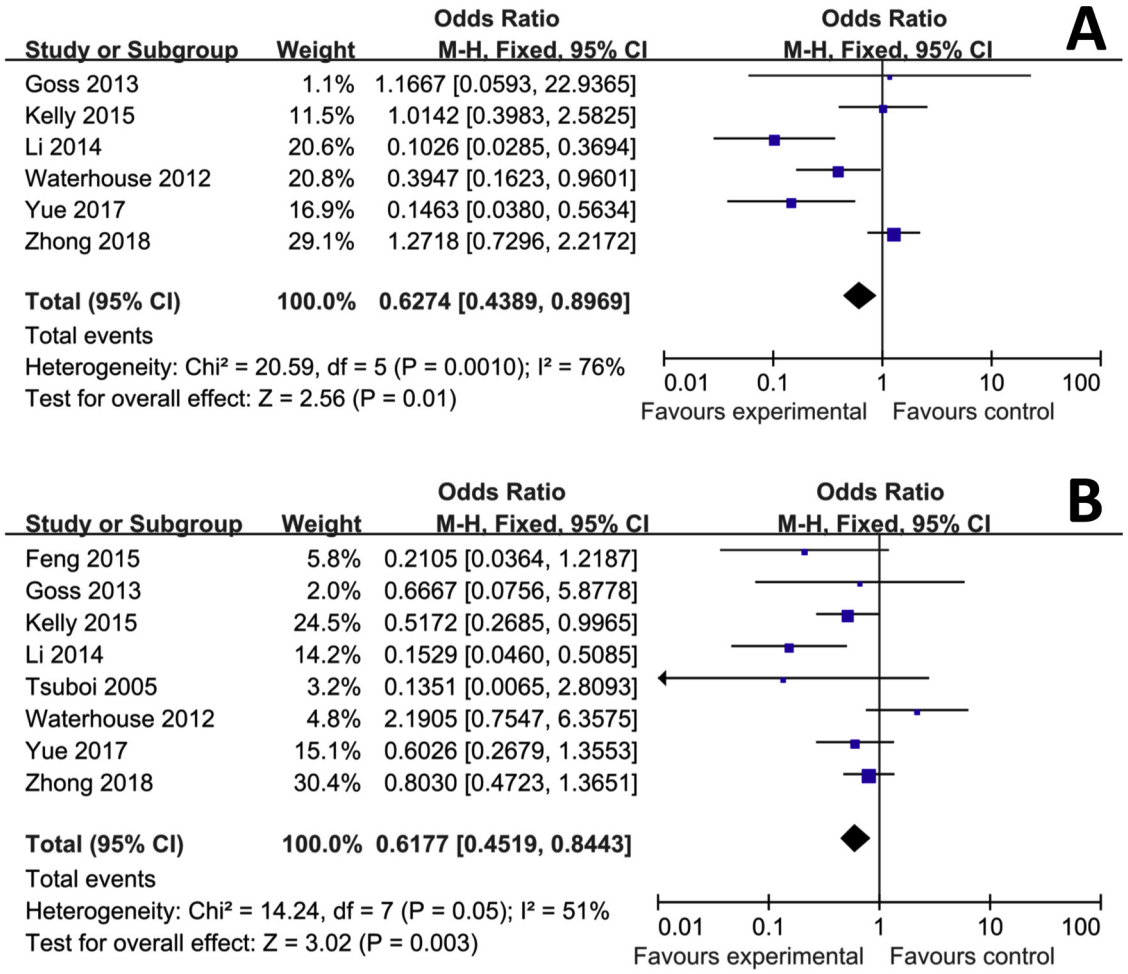


Fig. 3. Forest plot of overall survival (A) and disease-free survival (B) when retrospective studies were excluded from the analysis. Solid diamond indicates the pooled OR of OS, square indicates odds ratio value of each study.

3.4. Severe adverse events

The results indicated that EGFR-TKI monotherapy caused less SAEs than chemotherapy (OR, 0.22; 95% CI, 0.14 to 0.37, P < 0.00001; heterogeneity I^2 = 22%, P = 0.28), and the most common adverse event (i.e., skin rash) had no influence on the results (P = 0.15). We also explored whether chemotherapy plus TKIs could cause more severe adverse events, and it was found that EGFR-TKIs did not increase toxicity (P = 0.57) when patients used it with chemotherapy at the same time.

3.5. Publication bias analyses

Funnel plots that evaluated the publication bias between TKIs and no TKIs were constructed based on the data for disease-free survival and overall survival, as shown in Fig. 5; these plots are visually symmetric. For the comparison of EGFR-TKIs or EGFR-TKIs plus chemotherapy with mono chemotherapy, the number of studies was too small for investigation due to publication bias. Since not all of the included patients had EGFR mutations in several of the studies, only a subset of patients in these studies were enrolled in this meta-analysis, which may increase the publication bias of the study. Bias assessments are shown in Fig. 6.

4. Discussion

According to the previous clinical trials and meta-analysis, cisplatin-based chemotherapy as the previous standard adjuvant treatment do improve the overall survival time for NSCLC patients after radical operation [5]. However, its benefit has reached a plateau, and a high risk of recurrence and adverse events also limits its application. Meanwhile, EGFR tyrosine kinase inhibitors (TKIs) directed at sensitizing mutations in the epidermal growth factor receptor (EGFR) gene is becoming the critical pillar in NSCLC with EGFR sensitive mutation. However, whether it can be employed as an adjuvant therapy for those resected NSCLC patients whose tumors harbor EGFR mutations is still controversial. Consequently, our research came into being to investigate these factors.

This meta-analysis based on patients' data provided by eleven randomized trials in 1,152 resected NSCLC patients with EGFR-sensitive mutations showed that adjuvant treatment with EGFR-TKIs do prolong both the OS and DFS when compared to treatment without TKIs. The results of the predefined subgroup analyses in this meta-analysis also suggest a greater disease-free survival benefit with mono EGFR-TKIs compared with mono chemotherapy among patients with completely resected EGFR-mutant NSCLC. For the overall survival, our data did not show significant differences because the OS data for large studies such as ADJUVANT and EVAN is not yet mature. From the current statistical analysis of EVAN, the OS in patients with EGFR-TKIs has already shown a clear benefit trend. Comparing targeted treatments plus chemotherapy with mono chemotherapy, the former obviously had longer disease-free survival as well as overall survival. In this meta-analysis, we included three retrospective studies because of the limited number of patients. Therefore, we reanalyzed this step without the above studies, and we obtained the same result. Overall, in patients with EGFR-

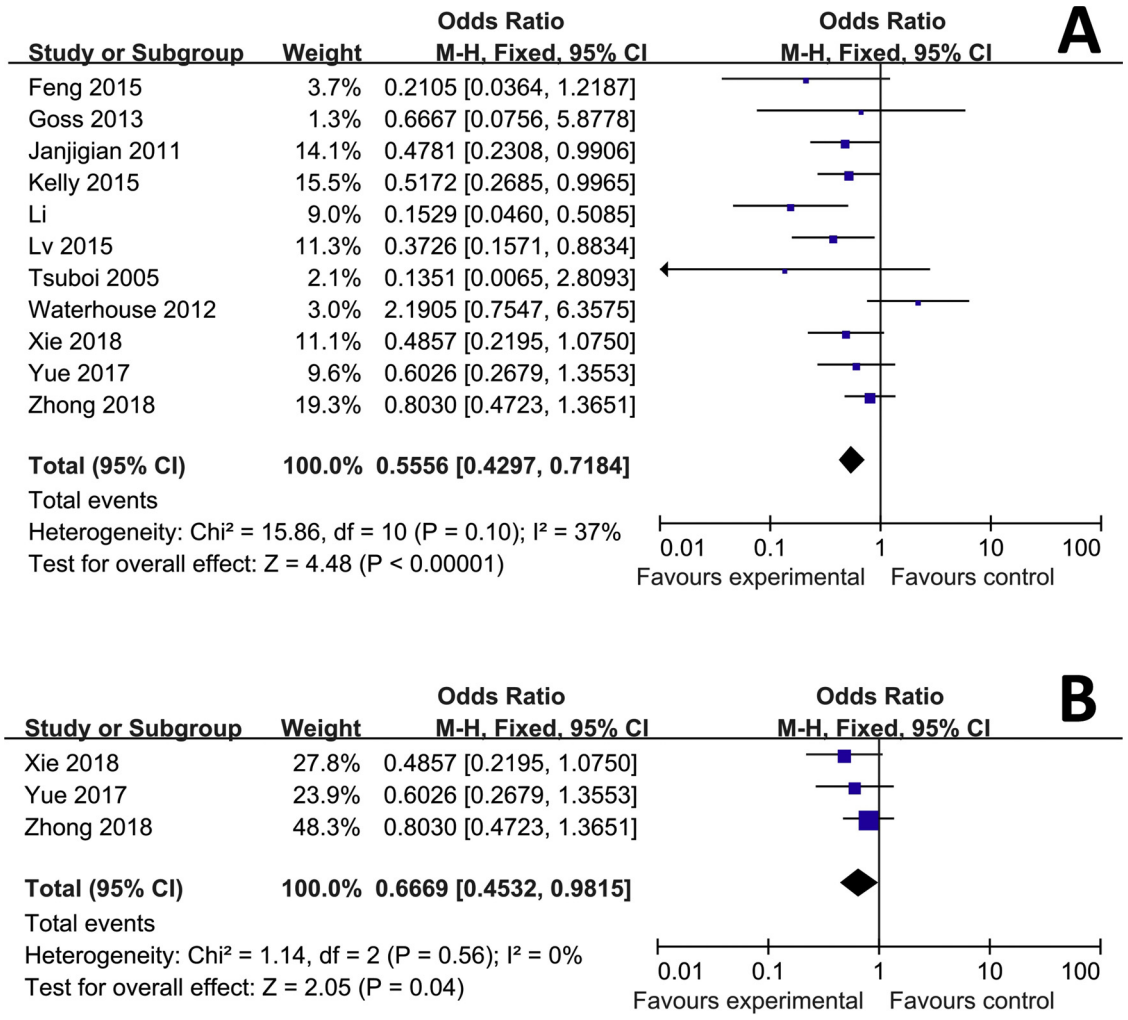


Fig. 4. Forest plot of disease-free survival when comparing TKIs VS no TKIs (A), TKIs VS chemo (B). Solid diamond indicates the pooled OR of OS, square indicates odds ratio value of each study.

mutant lung cancers, the small molecule EGFR-tyrosine kinase inhibitors (TKIs), with or without chemotherapy, achieved superior response rates and disease-free survival compared with the platinum doublet chemotherapy or placebo, and there was no clear difference in overall survival.

Safety and tolerability in our study also favored EGFR-TKIs compared with chemotherapy. For the group of EGFR-TKIs, the most frequent adverse events were rash, liver dysfunction and diarrhea [18], and the most common adverse events associated with adjuvant chemotherapy treatment were hematologic toxic effects and appetite loss [19]. In the subgroup analysis comparing mono EGFR-TKIs versus chemotherapy only, we have found a significant reduction of SAEs (grade 3 or worse) in the former group, and this difference was not influenced by the most common side effects (i.e., skin rash). In the subgroup analysis, EGFR-TKIs have been shown to have no increase in toxicity even when combined with chemotherapy. All of the results clearly support the idea that EGFR-TKIs have fewer side effects and can be an appealing treatment option for patients with resected NSCLC harboring EGFR mutations.

In the 11 studies we included, as far as we know, the ADJUVANT study was the first prospective phase III trial to show that adjuvant EGFR-TKIs (gefitinib in this trial) lead to significantly better disease-free survival compared with that for cisplatin-based chemotherapy in patients with resected NSCLC whose tumors harbor EGFR mutations and to date, its overall survival data is still not mature [12]. In another placebo-controlled trial, the BR19 study, adjuvant TKIs (gefitinib) failed to show any beneficial effect on DFS (HR, 1.84) or OS (HR, 3.16) for patients with EGFR-mutated tumors [15]. It is possible that because the number of patients with EGFR mutation-positive tumors was small in this study (only 15 in 503, 7 on gefitinib and 8 on placebo), the small sample size was not enough for a sufficiently effective analysis to yield a convincing conclusion. The recently published SELECT study, a single-arm, open-label phase II clinical trial, has proven that adjuvant TKIs after surgery and standard adjuvant treatment of patients with early-stage EGFR-mutant NSCLC resulted in a higher 2-year DFS rate than historical [20], and its OS data is still tracking. Another EVAN study is also underway, and notably, its current data has already shown a trend of OS benefit in the patient group treated with TKIs. We are looking forward to seeing the ultimate result of the ADJUVANT study and other ongoing trials, such as ALCHEMIST (NCT02193282) and ADAURA (NCT02511106). ADAURA is a double-blind, randomized, phase III study to explore the safety and efficiency of osimertinib in an adjuvant setting, which may have a higher clinical reference value. We believe those ongoing and future randomized trials can provide more information to further identify if EGFR tyrosine kinase inhibitors do provide an overall survival benefit in the adjuvant setting. For neoadjuvant therapy in patients with operable NSCLC, current data from the ongoing CTONG1103 study indicate that EGFR-TKIs are significantly more effective and well tolerated; also the PFS is significantly prolonged. In addition, one problem worth noting is that the effect of postoperative radiotherapy or other treatments after disease recurrence during targeted therapy was not included in the 11 studies, which may

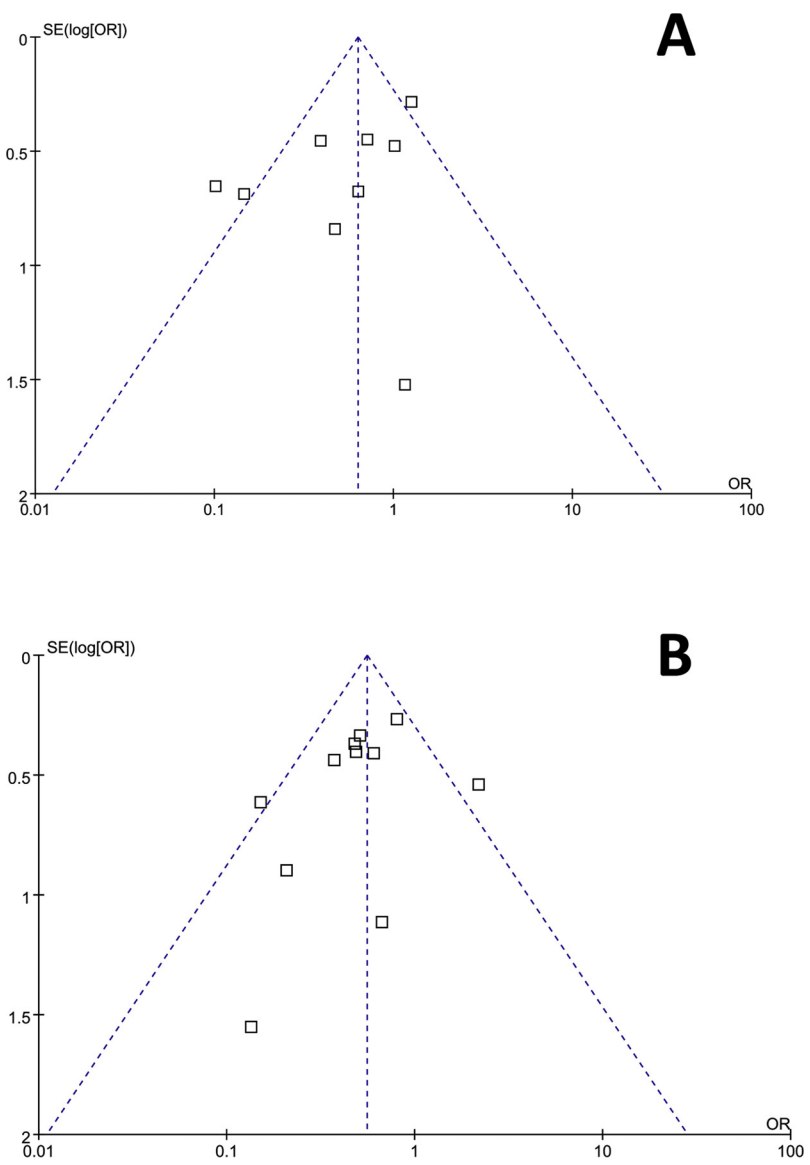


Fig. 5. Funnel plots depicting potential presence of publication bias when analyzing overall survival (A) and disease-free survival (B) as hazard ratios (TKIs VS no TKIs). This triangle indicates the 95% CI.

require further exploration. Targeted therapy combined with immunotherapy also warrants further research. In our research, we focused on comparing the effect of targeted therapy with chemotherapy without taking other therapies into account.

5. Limitations

There are several limitations relevant to this meta-analysis. Firstly, it's unavoidable that the trials considered do not all have the same inclusion and exclusion criteria, design, and a well-described surgery and stage of disease before surgery. Additionally, there was a limited number of phase III studies available to be included in our study, so we included several phase II trials and retrospective studies as well, both of which increased the heterogeneity of this meta-analysis. Secondly, the OS benefit demonstrated in this meta-analysis appears to be mainly driven by two studies (Li et al. and Yue et al.), which enrolled only Stage III patients and represented a small scope of patients. In addition, a major limitation of this systematic review is that the number of studies available for comparison of mono EGFR-TKIs with chemotherapy was limited. This prevented us from drawing a firm conclusion about the effects of tyrosine kinase inhibitors.

6. Conclusion

Adjuvant therapies are required to prevent disease recurrence and improve patient survival after surgery. Our results suggest a benefit in the DFS (and perhaps in the OS) when using adjuvant EGFR-TKIs, with or without the addition of chemotherapy, which indicates that adjuvant EGFR-TKIs could be a potential treatment option compared to adjuvant chemotherapy in completely resected patients with EGFR mutation-positive NSCLC. It may not be curative, but adjuvant EGFR-TKIs do provide clinical benefit for most patients. Moreover, its safety and tolerability also make it an appealing treatment option for patients with resected EGFR-mutant NSCLC.

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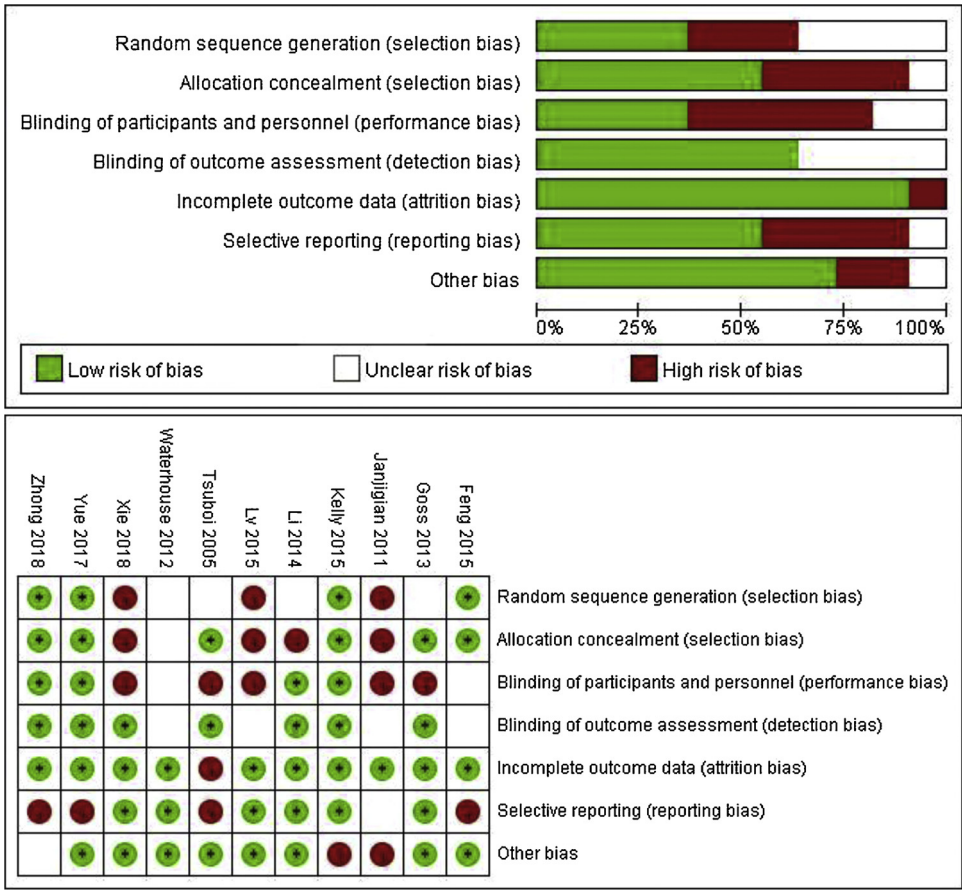

Fig. 6. The assessment of bias of included studies using the Cochrane Risk of Bias Assessment Tool.

Declaration of Competing Interest

There is no conflict of interest among authors to disclose.

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