Efficacy of EGFR-TKIs Targeted Therapy as Adjuvant Systemic Treatment for Non-small Cell Lung Cancer: A Systematic Review and Meta-analysis

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Abstract

1) *Introduction:* Surgery followed by chemotherapy is a standard treatment for early-stage non-small cell lung cancer (NSCLC). Recent study investigated epidermal growth factor receptor, tyrosine kinase inhibitors (EGFR-TKIs) as the novel targeted therapy for these patients. The previous meta-analysis has reported disease-free survival (DFS) benefit of adjuvant EGFR-TKIs. However, time to recurrence or death have not been explored completely. 2) *Objective:* The objectives were to evaluate DFS, overall survival (OS), and time to recurrence or death of adjuvant EGFR-TKIs. 3) *Methodology:* The randomized controlled trials (RCTs) comparing EGFR-TKIs vs. chemotherapy or placebo in resected early-stage NSCLC patients were identified from PubMed, Scopus, Cochrane Central Register of Controlled Trials. The probabilities along with times of DFS and OS were extracted from Kaplan-Meier curves using WebPlotDigitizer, and then simulated to individual patient data. A mixed-effect survival model was applied to estimate hazard ratio (HR), median DFS, and median OS. 4) *Result and Discussion:* A total of eleven RCTs comprising 3,365 patients were included. There was significant improvement on DFS of EGFR-TKIs compared with chemotherapy or placebo (HR = 0.50, 95% confidence interval (CI): 0.32, 0.77; median DFS: 70.61 vs. 36.55 months, respectively). However, there was not significant improvement in terms of OS (HR = 0.85, 95% CI: 0.66, 1.05; median OS: 91.66 vs. 87.90 months, respectively). *5) Conclusion:* This meta-analysis results supported the advantage of adjuvant EGFR-TKIs for DFS improvement, but OS benefit was not significantly different compared with chemotherapy or placebo.

Keywords**:** *Non-Small Cell Lung Cancer, Adjuvant Therapy, EGFR-Tkis, Targeted Therapy, Meta-Analysis*

1. Introduction

Lung cancer is the most commonly diagnosed malignancy worldwide, with an anticipated 2.2 million new cases in 2020 (Sung et al., 2021). It is the leading cause of mortality from cancer with approximately 1.8 million deaths, or 18% of all malignancy deaths globally (Sung et al., 2021). Among lung cancer cases, stage I – IIIA of non-small cell lung cancer (NSCLC) are categorized as early-stage disease that accounts for 50% of all NSCLC diagnoses (Ganti, Klein, Cotarla, Seal, & Chou, 2021). Surgery followed by adjuvant chemotherapy is the cornerstone of treatment for this stage. However, adjuvant chemotherapy improves an absolute 5-year overall survival (OS) only by 5% when compared with surgery alone (Arriagada et al., 2010; Pignon et al., 2008).

Epidermal growth factor receptor (EGFR) is a frequent sensitive oncogenic driving mutation in NSCLC (Sharma, Bell, Settleman, & Haber, 2007). Recent research has looked towards using EGFR tyrosine kinase inhibitors (EGFR-TKIs) as an adjuvant therapy for NSCLC. According to the recent results from Complete Tumor Resection With or Without Adjuvant Chemotherapy (ADAURA) study (Wu et al., 2020), third-generation EGFR-TKI (osimertinib) added to adjuvant chemotherapy significantly increased median disease-free survival (DFS) for patients with EGFR mutation early-stage NSCLC compared with chemotherapy alone (HR = 0.17, p-value < 0.001).

To date, there have been several systematic reviews and meta-analyses (SRMAs) conducted on adjuvant EGFR-TKIs for early-stage NSCLC. The largest and most recent one comprising 9 RCTs was published in 2022 (Zhao, Zhen, Zhao, Zhao, & Cao, 2022). The result of this SRMA indicated that adjuvant EGFR-TKIs enhanced DFS compared with chemotherapy alone or placebo but had no significant effect on OS. However, the efficacy of treatment reported from recent SRMA is limited to relative treatment effects such as HR of DFS and OS, whereas time to disease recurrence or death has not yet been explored in recent study. These time to event data were useful information for treatment planning. This SRMA was therefore conducted to determine the efficacy of adjuvant EGFR-TKIs for early-stage NSCLC in terms of HR of DFS, HR of OS, and median time to disease recurrence or death compared with adjuvant chemotherapy alone or placebo.

2. Objectives

1) To estimate HR of DFS and OS of adjuvant EGFR-TKIs compared with chemotherapy alone or placebo among early-stage NSCLC patients

2) To estimate median time to disease recurrence or death in terms of median DFS and OS of adjuvant EGFR-TKIs compared with chemotherapy alone or placebo among early-stage NSCLC patients

3. Materials and Methods

The study design was a SRMA of adjuvant EGFR-TKIs targeted therapy for early-stage NSCLC patients which was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Databases and search strategies

The relevant studies were identified from MEDLINE via PubMed, Scopus, Cochrane Central Register of Controlled Trials, and conference proceedings from major medical oncology meetings through to 30th June, 2022. The search terms and search strategies were constructed based on patients (early-stage NSCLC), interventions (adjuvant therapy, EGFR-TKIs, gefitinib, erlotinib, icotinib, afatinib, dacomitinib, osimertinib), outcomes of interest (DFS, OS), and study design (randomized controlled trial (RCT)).

Selection of studies

All phase II or III RCTs were included. RCTs were eligible if they met the following criteria: studies in patients diagnosed with early-stage (stage I – IIIA) NSCLC with complete surgical resection, compared adjuvant EGFR-TKIs targeted therapy with chemotherapy alone or placebo, and reported at least one outcome of interest including DFS, or OS. If they were published in non-English, which were untranslatable languages, or had insufficient data for pooling after three contact attempts with authors every two weeks, they would be excluded.

Identified studies were independently selected by 2 reviewers (Sa-nguansai. S. and Pornsuriyasak. P.) using the information from the title and abstract based on the eligible criteria. Full articles were subsequently reviewed after title and abstract screening.

Data extraction

Summary data was extracted independently by 2 reviewers (Sa-nguansai. S. and Pornsuriyasak. P.) using the data extraction form (DEF). The DEF consisted of 6 parts including general information (e.g., the author, year of publication), study characteristics (e.g., phase of study, region), general characteristics of participants (e.g., age, gender, ECOG (Eastern Cooperative Oncology Group) performance status, staging, EGFR status), information about study factors (e.g., medication name, treatment duration), summary of outcomes, and data for pooling.

The data for pooling were extracted into time-to-event outcomes. The probabilities and times of DFS, OS at each time point were extracted from the Kaplan-Meier curve using WebPlotDigitizer program version 4.5 (Drevon, Fursa, & Malcolm, 2017), then these data were used to simulate individual patient time-to-event data (Wei, & Royston, 2017).

Risk of bias assessment

The quality of studies was independently assessed by 2 reviewers (Sa-nguansai. S. and Pornsuriyasak. P.) using Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019). Disagreement was solved by discussion with the reviewer team. This tool consisted of 5 domains of risk of bias; randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The study was judged to be overall "Low", "Some concerns", and "High" risk of bias if all five domains were ranked as low risk, at least one domain was ranked as some concern without high risk, and at least one domain was ranked as high risk, respectively.

Statistical analysis

For individual patient time-to-event outcomes of DFS and OS, a multi-level mixed-effect parametric survival model (Crowther, 2019; StataCorp., 2021) was applied to estimate HRs of DFS, HRs of OS, and median time to events of each treatment. Appropriate survival distributions (e.g., Weibull, exponential, log-logistic, log-normal, generalized gamma) were selected by using a model with the smallest Akaike's Information Criterion (AIC).

HRs and 95% confidence interval (CI) derived from a mixed-effect parametric survival model were used to pool across studies. A fixed-effect model with inverse variance method was used when there was no heterogeneity (p-value of Cochrane's Q test > 0.1 and I^2 < 25%). Otherwise, a random-effects model with the method of DerSimonian and Laird would be applied instead. All analyses were performed using STATA software package, version 17.0 (Stata Corp, College Station, Texas, USA). A two-sided p-value of less than 0.05 was considered statistically significant.

4. Results and Discussion

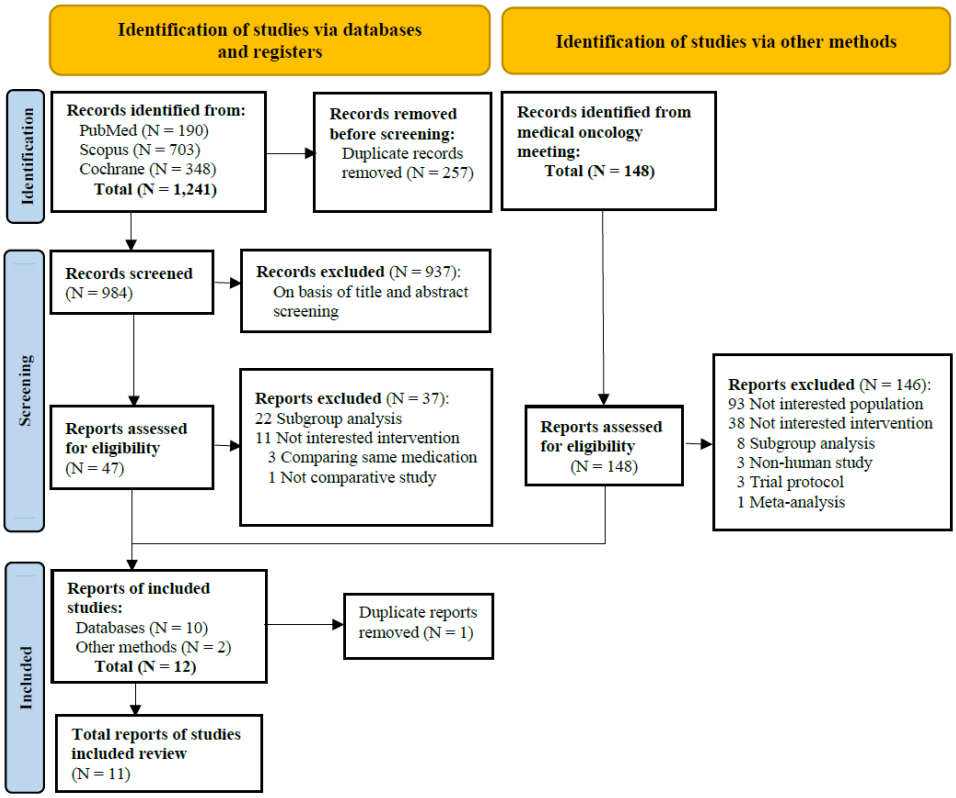

Figure 1 PRISMA Flow diagram

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Table 1 Study characteristics and details of intervention of the included studies

Author, year	Region	Intervention (n)	Control (n)	Staging	EGFR status	Median age (year)	Female (%)	ECOG 0 – 1 (%)
Goss et al. 2013	North America	Gefitinib for 24 months (n = 251)	Cisplatin/ Vinorelbine (n = 252)	IB - IIIA	Not specified	66.5	46.1	97.0
Li et al. 2014	China	Gefitinib for 6 months (n = 30)	Pemetrexed/ Carboplatin (n = 30)	IIIA (N2)	Mutation	57.1	41.7	100.0
Feng et al. 2015	China	Icotinib for 4 – 8 months (n = 21)	Platinum-based CMT (n = 18)	IB (high risk) - IIIA	Mutation	55.0	30.8	100.0
Kelly et al. 2015	Inter national	Erlotinib for 24 months (n = 623)	Platinum-based CMT (n = 350)	IB - IIIA (microscopic N2 only)	Expression	62.0	40.9	98.7
Yue et al. 2018	China	Erlotinib for 24 months (n = 51)	Cisplatin/ Vinorelbine (n = 51)	IIIA	Mutation	58.0	63.7	98.1
Wu et al. 2020	Inter national	Osimertinib for 36 months (n = 339)	Platinum-based CMT (n = 343)	IB - IIIA	Mutation	63.0	70.0	100.0
He et al. 2021	China	Icotinib for 24 months (n = 161)	Platinum-based CMT (n = 161)	II - IIIA	Mutation	59.0	53.4	98.9
Yue et al. 2021	China	Erlotinib for 24 months (n = 51)	Cisplatin/ Vinorelbine (n = 51)	IIIA	Mutation	58.0	63.7	98.1
Zhong et al. 2021	China	Gefitinib for 24 months (n = 111)	Cisplatin/ Vinorelbine (n = 111)	II - IIIA (N1 - N2)	Mutation	59.0	58.6	96.4
Li et al. 2022	China	Icotinib for 12 months (n = 63)	All placebo (n = 65)	IB	Mutation	56.5	58.6	100.0
Tada et al. 2022	Japan	Gefitinib for 24 months (n = 116)	Cisplatin/ Vinorelbine (n = 116)	II - III	Mutation	64.0	61.6	100.0

n, number of patients; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; CMT, chemotherapy; N, regional lymph node metastasis status

4.1 Results

A total of eleven RCTs (Feng et al., 2015; Goss et al., 2013; He et al., 2021; Kelly et al., 2015; Li et al., 2014; Li et al., 2022; Tada et al., 2022; Wu et al., 2020; Yue et al., 2018; Yue et al., 2021; Zhong et al., 2021) were included in this meta-analysis. One study (Li et al., 2022) was identified from a major medical oncology meeting, while the others were identified via databases and registers. The selection process was illustrated in Figure 1 and the individual study characteristics were presented in Table 1.

All included studies were published between 2013 to 2022 and comprised 3,365 patients with resected early-stage NSCLC. The majority of included studies were conducted in the Asia-Pacific region (7 studies from China, and 1 study from Japan). The included staging ranged from stage IB to stage IIIA disease. According to EGFR status, most of them were EGFR mutation positive (9 studies, 81.8%). The median age

of patients was 59.0 years (range from 55.0 to 66.5). The mean percentage of females was 53.6%. Almost all of them (98.8%) had ECOG performance status of 0 – 1.

For the type of intervention received in all eligible studies, all were EGFR-TKIs targeted therapy. Gefitinib, erlotinib, icotinib, and osimertinib were prescribed as interventions of interest, with the corresponding numbers of included studies being 4, 3, 3, and 1, respectively. The median duration of treatment was 24.0 months (range from 6.0 to 36.0). The majority of studies used chemotherapy as a standard treatment, except one study (Li et al., 2022) which used placebo as a control or comparator. Among chemotherapy treatment, cisplatin/vinorelbine was the most common regimen which was found in 5 out of 10 studies.

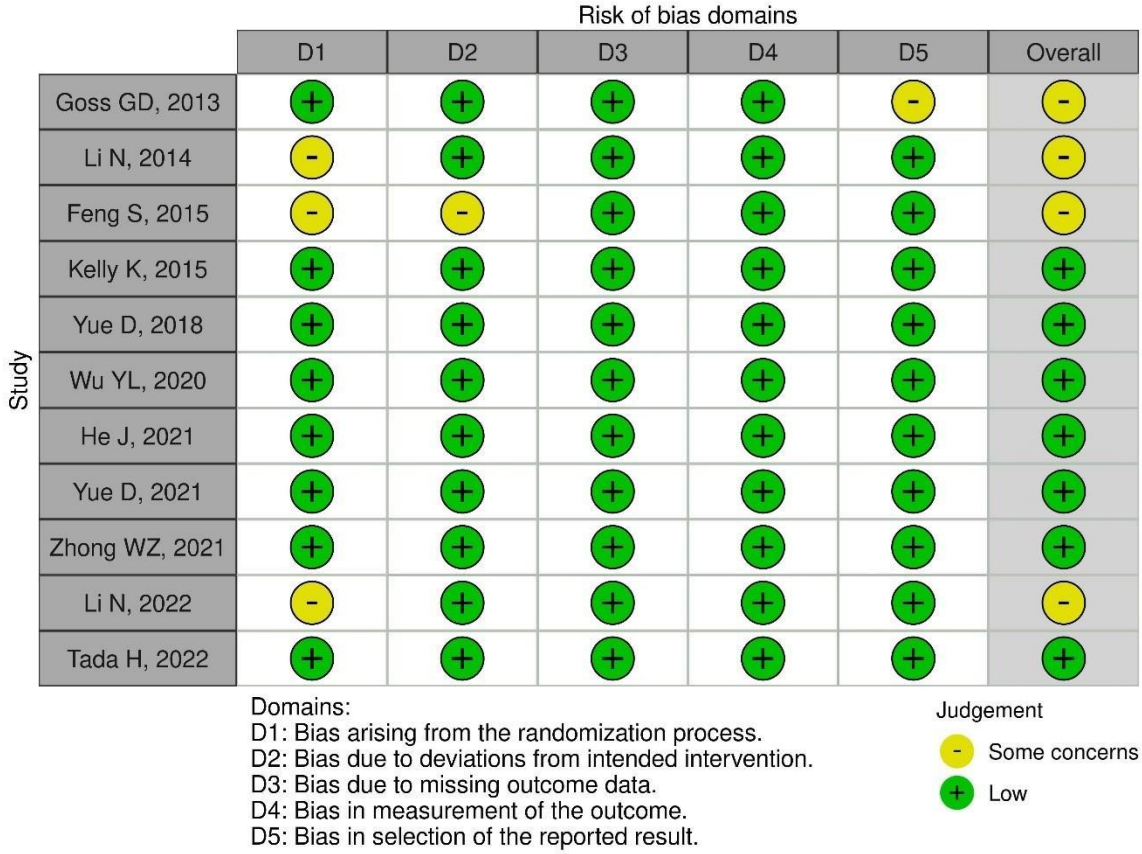

Figure 2 Risk of bias assessment according to RoB 2 algorithm

The result of overall the risk of bias assessment was presented in Figure 2. The overall risk of bias was "Low" at 63.6%. Four studies (Feng et al., 2015; Goss et al., 2013; Li et al., 2014; Li et al., 2022) showed "Some concerns" about the risk of bias, while the remaining studies had "Low" risk of bias.

DFS outcome

Ten RCTs (Feng et al., 2015; Goss et al., 2013; He et al., 2021; Kelly et al., 2015; Li et al., 2014; Li et al., 2022; Tada et al., 2022; Wu et al., 2020; Yue et al., 2018; Zhong et al., 2021) comprising of 3,263 patients assessed DFS outcomes along with Kaplan-Meier curves. A mixed-effect parametric proportional hazard model with Weibull survival distribution was applied to estimate relative the treatment effects (HRs of DFS) between EGFR-TKIs and chemotherapy alone or placebo of each study. The result of the meta-analysis of ten studies was demonstrated in Figure 3. Pooled HR of DFS using random-effect model was 0.50

(95% CI: 0.32, 0.77; p-value < 0.01) with evidence of heterogeneity (I^2 = 92.09%; Q test: chi^2 = 113.81, degrees of freedom = 9, p-value < 0.01). This result suggested that early-stage NSCLC patients receiving adjuvant EGFR-TKIs were significantly (50%) less likely to experience disease recurrence compared with those receiving chemotherapy alone or placebo.

In terms of time to disease recurrence, a mixed-effect parametric accelerated failure time model with log-normal survival distribution was applied to estimate median DFS of EGFR-TKIs and chemotherapy alone or placebo. The result of the predicted median DFS curve was shown in Figure 4A. The predicted median DFS of EGFR-TKIs was significantly longer than chemotherapy alone or placebo (median DFS: 70.61 vs. 36.55 months, respectively).

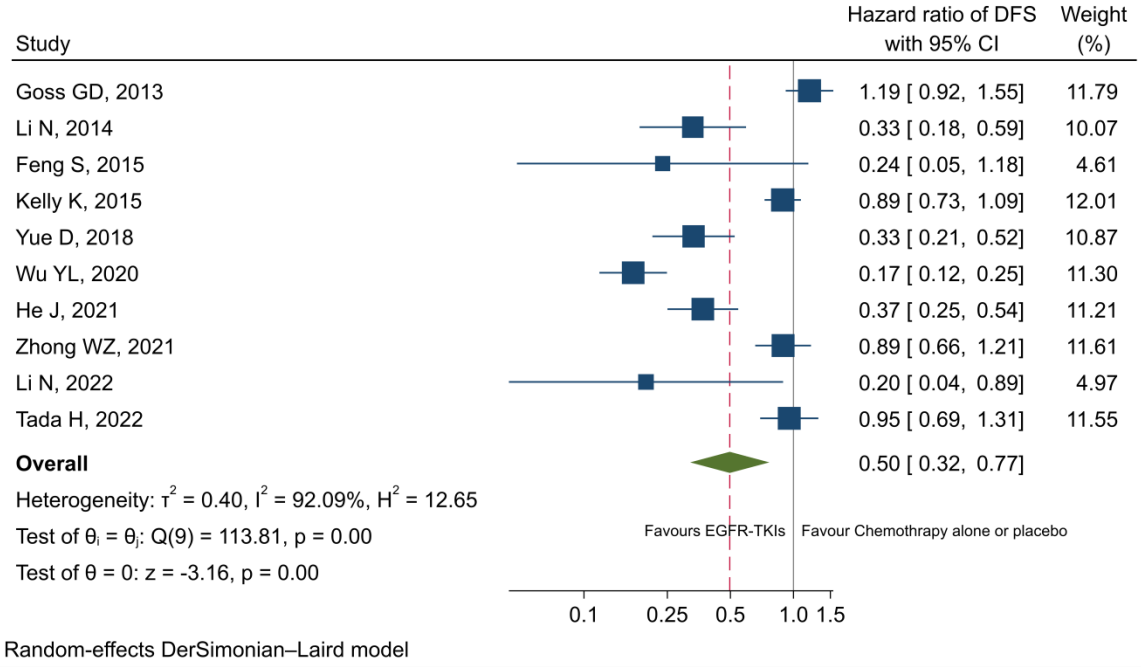

Figure 3 Forest plot for a meta-analysis of EGFR-TKIs vs. chemotherapy alone or placebo on DFS outcome

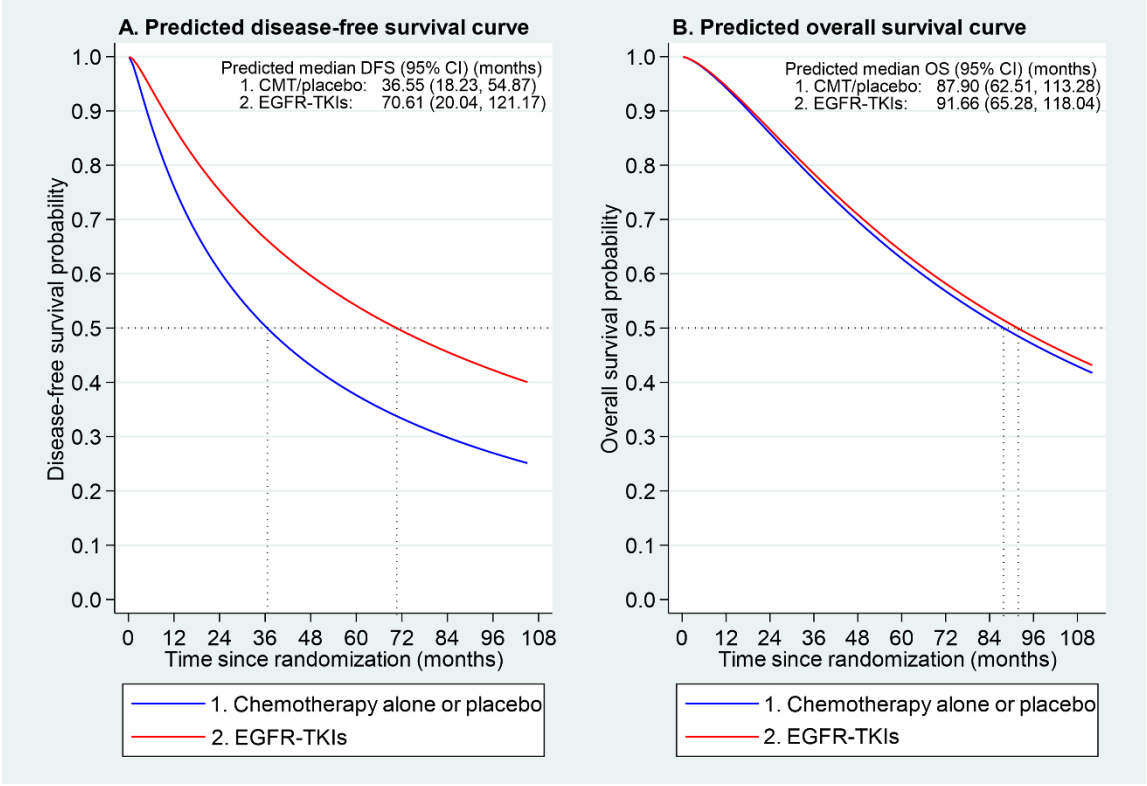

Figure 4 Survival curves between EGFR-TKIs vs. chemotherapy alone or placebo on DFS outcome (A) and OS outcome (B) from multi-level mixed-effect parametric survival analysis

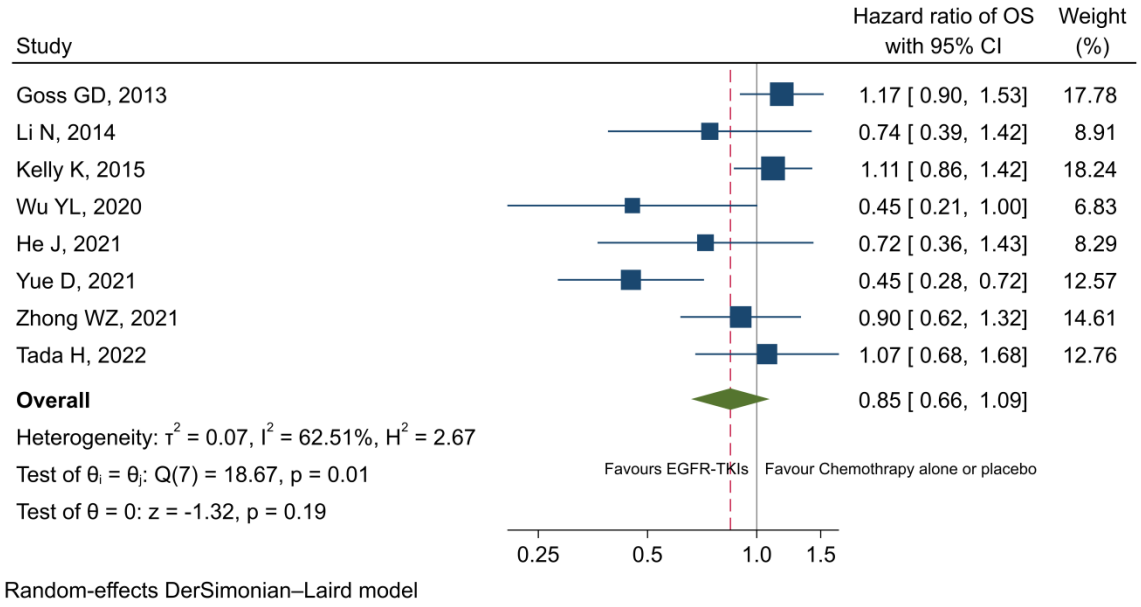

Figure 5 Forest plot for a meta-analysis of EGFR-TKIs vs. chemotherapy alone or placebo on OS outcome

OS outcome

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OS outcomes along with Kaplan-Meier curves were reported in eight RCTs (Goss et al., 2013; He et al., 2021; Kelly et al., 2015; Li et al., 2014; Tada et al., 2022; Wu et al., 2020; Yue et al., 2021; Zhong et al., 2021) included 2,884 early-stage NSCLC patients. A mixed-effect parametric proportional hazard model with Weibull survival distribution was applied to estimate HRs of OS between EGFR-TKIs and chemotherapy alone or placebo of each study. The forest plot of the meta-analysis was shown in Figure 5. Pooled HR of OS using random-effect model was 0.85 (95% CI: 0.66, 1.09; p-value = 0.19) with evidence of heterogeneity (I^2 = 62.51%; Q test: chi^2 = 18.67, degrees of freedom = 7, p-value = 0.01). Pooled HR of OS suggested that there was 15% less risk of death in EGFR-TKIs compared with chemotherapy alone or placebo, but this result was not statistically significant.

For time to death assessment, a mixed-effect parametric accelerated failure time model with log-logistic survival distribution was applied to estimate median OS of EGFR-TKIs and chemotherapy alone or placebo. The predicted median OS curve was demonstrated in Figure 4B. However, the predicted median OS of EGFR-TKIs was not significantly longer than chemotherapy alone or placebo (median OS: 91.66 vs. 87.90 months, respectively).

4.2 Discussion

This SRMA was performed to evaluate the efficacy of adjuvant EGFR-TKIs targeted therapy for early-stage NSCLC patients. The results found that there was significant improvement on DFS in EGFR-TKIs compared with chemotherapy alone or placebo (HR of recurrence = 0.50, 95% CI: 0.32, 0.77; median DFS: 70.61 vs. 36.55 months, respectively). However, it was not statistically significant in terms of OS (HR of death = 0.85, 95% CI: 0.66, 1.05; median OS: 91.66 vs. 87.90 months, respectively).

According to current international guideline proposed by American Society of Clinical Oncology (ASCO) (Pisters, Kris, Gaspar, & Ismaila, 2022), adjuvant osimertinib, third-generation EGFR-TKI, is recommended for patients with EGFR mutation stage II – IIIA NSCLC. This recommendation is based on a recent RCT (Wu et al., 2020) which has reported DFS improvement for early-stage NSCLC patients with EGFR mutation compared with chemotherapy alone (HR = 0.17, p-value < 0.001). This RCT (Wu et al., 2020) was also included in this SRMA and the similar result of pooled outcome was found from this review. Although studies of first-generation EGFR-TKIs, such as gefitinib, erlotinib, and icotinib were included in this SRMA, the result in terms of DFS was still robust. A prior SRMA (Zhao et al., 2022) found that adjuvant EGFR-TKI improved DFS compared with chemotherapy or placebo (HR = 0.46, 95% CI: 0.29, 0.72) but had no significant improvement on OS (HR = 0.87, 95% CI: 0.69, 1.11). In comparison with the previous one, this SRMA provided the similar tendency of DFS and OS outcome. However, median time to disease recurrence or death (median DFS and median OS) were the additional outcomes reported in this review. According to the method of survival model section, AIC was applied. These information criteria were a standard measurement for selecting the most appropriate survival distribution model. A smaller AIC indicated a better-fitting survival distribution model. Thus, HR of DFS, median DFS, HR of OS, and median OS derived from this method were accurate and reliable.

The strength of this study was that the probabilities along with times of DFS and OS were extracted from Kaplan-Meier curves, and then simulated to individual patient data. This analytic method was more flexible in applying a mixed-effect survival model (Crowther, 2019; StataCorp., 2021). Thus, not only HR of DFS or OS outcome were obtained from this analysis, but median DFS or OS were also reported. These outcomes provided more solid and more applicable results in terms of specific median time to disease recurrence or death. They were valuable information for patient counseling to illustrate the benefit of adjuvant EGFR-TKIs treatment. However, there were also limitations on this study. Firstly, the heterogeneity of pooled outcomes was high. Therefore, sources of heterogeneity from specific subgroups (i.e., EGFR mutation status, treatment duration) should be explored in the further study. Secondly, there were other types of adjuvant treatment for early-stage NSCLC patients, such as immune checkpoint inhibitors that were not included in this review. The network meta-analysis including all types of adjuvant treatment for early-stage NSCLC patients should be comprehensively conducted to select the best appropriate treatment for these patients.

5. Conclusion

This meta-analysis results could support the advantage of EGFR-TKIs targeted therapy compared with chemotherapy alone or placebo on adjuvant treatment of NSCLC following surgical resection. Adjuvant EGFR-TKIs significantly prolonged DFS in patients with resected early-stage NSCLC. However, the benefit in terms of OS was not significantly different compared with standard chemotherapy alone or placebo. Further research is needed to demonstrate the efficacy of adjuvant EGFR-TKIs, particularly focusing on subgroup analysis for more potential benefit of this treatment in specific populations.

6. Acknowledgements

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