Systematic Review and Meta-Analysis

Medicine

OPEN

A meta-analysis of adjuvant EGFR-TKIs for patients with EGFR mutation of resected non-small cell lung cancer

Ran Cui, MD[a], Chun Wei, MD[a], Xianyi Li, MD[a], Ou Jiang, PhD[a,*]

Abstract

Background: The role of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKIs) in improving the prognostic outcome of non-small cell lung cancer (NSCLC) cases harboring EGFR mutation following radical surgery is still controversial. This work focused on comparing EGFR-TKIs and adjuvant chemotherapy (ACT) or placebo in treating NSCLC cases, specifically on those with EGFR-mutant, being in the stage of IB-IIIA and possibly gained benefits from the above treatment after radical resection.

Methods: The Cochrane Library, MEDLINE, and Embase databases were searched to identify eligible clinical trials; two authors were responsible for screening the results. The primary outcomes were evaluated by disease-free survival (DFS) and overall survival (OS) based on hazard ratios (HRs) and a relevant 95% confidence interval (CI).

Results: The literature search yielded twelve eligible studies, including four retrospective cohort studies and eight randomized controlled trials (RCTs) that enrolled 1694 cases and were of acceptable quality. In patients receiving adjuvant EGFR-TKIs compared with ACT or placebo treatment, HR regarding DFS was 0.47 (95% CI: 0.40, 0.55), whereas the OS rate was 0.74 (95% CI: 0.58, 0.95). For patients who received adjuvant EGFR-TKIs in combination with conventional chemotherapy compared to chemotherapy, the efficiency was significantly enhanced, with the HR for DFS being 0.29 (95% CI: 0.15, 0.58) and that for OS being 0.51 (95% CI: 0.25, 1.04), separately.

Conclusion: For NSCLC cases who had EGFR mutations and surgery, adjuvant EGFR-TKI combined with chemotherapy achieved superior effect over chemotherapy or placebo with reference to DFS and may prolong the OS up to some extent.

Abbreviations: ACT = adjuvant chemotherapy, CI = confidence interval, DFS = disease-free survival, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = non-small cell lung cancer, OS = overall survival, RCTs = randomized controlled trials, TKIs = tyrosine kinase inhibitors.

Keywords: adjuvant therapy, chemotherapy, EGFR tyrosine kinase inhibitor, meta-analysis, non-small-cell lung cancer

1. Introduction

Lung cancer is one of the most common cancers in the world, with the highest mortality rate (18.0%). NSCLC (non-small cell lung cancer) accounts for 80% of all lung cancers. 5-year survival after radical resection for NSCLC patients in stages IB-IIIA remains 26% to 62%.[1] Postoperative adjuvant therapy is therefore essential. From 2003 to 2008, several large randomized controlled trials (RCT) were conducted to determine whether adjuvant chemotherapy (ACT) after radical surgery effectively improves long-term survival in this patient population.[2,3] The studies also showed that in stage IB-IIIA NSCLC cases undergoing radical surgery, cisplatin-based chemotherapy could only increase 5-year survival by 5% (40–45%).[4]

Adjuvant therapy after radical surgery has become a rational approach to lowering the risk of recurrence and improving overall survival (OS) outcomes. According to some studies, adjuvant epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKIs) can significantly improve the survival of NSCLC patients with EGFR mutations after radical resection compared to standard chemotherapy.[5–9] In the studies CTONG1104 and EVIDENCE, disease-free survival (DFS) was improved when Adjuvant EGFR-TKIs were compared with standard of care chemotherapy in patients with NSCLC and EGFR mutation, with hazard ratio (HR) = 0.60, 95% CI: 0.42, 0.87; Phet = 0.0054)

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The study was approved by the Human Research Ethics Committees of the Affiliated Hospital of Southwest Medical University (China) in accordance with the Declaration of Helsinki. Written informed consent was obtained from all individual patients included in the study.

[a] Department of Oncology, The Affiliated Hospital of Southwest Medical University, Luzhou, China.

** Correspondence: Ou Jiang, Department of Oncology, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan 646000, China (e-mail: jiangou628@163.com).*

How to cite this article: Cui R, Wei C, Li X, Jiang O. A meta-analysis of adjuvant EGFR-TKIs for patients with EGFR mutation of resected non-small cell lung cancer. Medicine 2022;101:47(e31894).

Received: 10 June 2022 / Received in final form: 27 October 2022 / Accepted: 27 October 2022

http://dx.doi.org/10.1097/MD.0000000000031894

and HR = 0.36 [95% CI: 0.24, 0.55]; Phet < 0.0001),[7,10]respectively. Furthermore, the recently updated ADAURA study found that, regardless of disease stage, patients who received osimertinib after radical surgery had a better DFS than those who received adjuvant chemotherapy (HR = 0.16, 95% confidence interval: 0.10, 0.26).[11] While those studies did not show a significant difference in OS due to DFS advantage. Simultaneously, some studies yielded negative results.[12,13] The IMPACT study found no statistically significant differences in DFS or OS, with HR = 0.92 (95% CI: 0.67, 1.28) and HR = 1.03 (95% CI: 0.65, 1.65), respectively, in patients with completely resected pathologic stage II-III non-small-cell lung cancer harboring EGFR mutations receiving gefifitinib.[13]Therefore, the use of EGFR-TKI after surgery is still debatable.

Because recent studies have reached conflicting conclusions.[5–13] We conducted this meta-analysis to compare adjuvant EGFR-TKI with conventional chemotherapy in NSCLC cases undergoing radical surgery, with the goal of determining the best treatment for patients with stage IB-IIIA EGFR mutations.

2. Methods

2.1. Strategy for literature search

This study systemically searched Embase, PubMed, Cochrane, and Web of Science databases for identifying related studies that compared EGFR-TKI with chemotherapy among NSCLC cases harboring EGFR mutation and received radical surgery from inception to March 10, 2022. The keywords included non-small cell lung cancer, EGFR, TKI, postoperative, and chemotherapy. The search terms included ("Non-small cell lung cancer" or "lung tumor" or "lung cancer") and ("EGFR-TKI" or "EGFR-tyrosine kinase inhibitor" or "erlotinib" or "gefitinib" or "afatinib" or "icotinib" "neratinib" or "vandetanib" or "dacomitinib" or "osimertinib" or "canertinib" and ("Adjuvant" or "auxiliary" or "accessory" OR "adjunct" or "intercalated" or "alternative").

2.2. Study selection

Study inclusion criteria were shown below:

1. Studies, including adult cases with the diagnosis of NSCLC (pathological stage IB-IIIA) who could receive ACT;
2. Those evaluating the effect of EGFR-TKIs-ACT compared with placebo or chemotherapy, or TKIs-ACT compared with chemotherapy;
3. Those that reported one or more related clinical outcomes like overall survival (OS) and DFS and had available long-time follow-up data; and
4. Those with adequate raw data to calculate HRs and *P*-values. All the enrolled articles were published in English, and the publication type was not restricted.

Studies conforming to the following criteria were excluded:

1. Single-arm articles that reported outcomes of EGFR-TKI-ACT;
2. Articles that had inadequate data to carry out statistical analysis;
3. Duplicate studies;
4. No available full texts in the original studies.

2.3. Outcomes and data extraction

Basic information from all the enrolled articles was collected by two researchers (CW and XYL). Any disagreements between them regarding study screening and data collection were settled down through mutual negotiation or by the opinion of a third researcher (RC). Furthermore, we recorded the available data like first author, publication year, case numbers and baseline features, clinical stage, tumor histology, interventions, EGFR status, outcomes, study design and phase, OS, and DFS for comparing the benefits of EGFR-TKI-ACT and traditional chemotherapy for NSCLC cases receiving radical surgery. Those original and acquired data were imported into the standard tables.

2.4. Quality assessment

The bias risk approach (Cochrane Handbook for Systematic Reviews of Interventions) was implemented by two reviewers for the independent assessment of study quality.[14] This meta-analysis also assessed the generation of sequences, concealment of allocation, missing data, blinding, selective reporting, as well as additional biased sources. Any disagreement was settled down through mutual negotiation or the opinion of a third investigator.

This work utilized the Newcastle–Ottawa Scale (NOS) in non-RCTs, including three categories, selection, outcome, and comparability. Our enrolled RCTs quality was evaluated following Cochrane Collaboration's approach to evaluating bias risk (5.3.0) by the methodological items below, generation of random sequences, concealment of allocation, outcome assessment blinding, participant and personnel blinding, selective reporting, insufficient outcome data, as well as additional possible bias sources. The items were categorized into low, high, or unclear risk, and together they determined the general quality. Figures 1 and 2 display the risk-of-bias graph and summary. Table 1 display the Newcastle–Ottawa scale for quality assessment of non-randomized cohort studies. The opinion of a third researcher settled down disagreements.

2.5. Statistical analysis

This meta-analysis was carried out by integrating survival data from articles conducted by Parmar and Tierney.[15,16] Log (HR) and standard error data of enrolled RCTs were collected to analyze the time-to-event data.

The I^2 test was applied to analyze heterogeneity, where $I^2 < 50\%$ and $P > .1$ indicated no heterogeneity, and the fixed-effects model was applied, whereas $I^2 > 50\%$ stood for significant heterogeneity, and the random-effects model should thereby be utilized. $P < .05$ denotes statistical significance. Review Manager Software, version 5.3 (Cochrane Collaboration, Oxford, UK), was employed for statistical analysis.

DFS was considered the primary endpoint, and it characterized the duration between randomization and disease recurrence or death. OS was regarded as the secondary endpoint.

3. Results

Figure 3 represents the study screening flowchart. Among those 4135 studies obtained from the literature review, just 12 articles were qualified for our meta-analysis. Of which eight were RCTs, and four were RCSs. Table 2 displays enrolled study features.

This work enrolled 1694 cases for meta-analysis altogether; among them, 926 received adjuvant EGFR-TKI, whereas 768 received placebo. In four studies (5, 25, 23, 18), not all patients have EGFR mutation, but these studies analyzed the data from cases harboring EGFR-mutation, in which the analyzed got positive results. All the patients included in the other eight studies had EGFR mutations.

3.1. Effects of adjuvant TKIs versus placebo or chemotherapy on DFS and OS

In eight RCTs and four RCSs, DFS was analyzed. As a result, EGFR-TKI-ACT improved patient DFS (HR, 0.47; 95% CI: 0.40, 0.55) (Fig. 4). There was obvious heterogeneity among enrolled articles by using the random-effects model

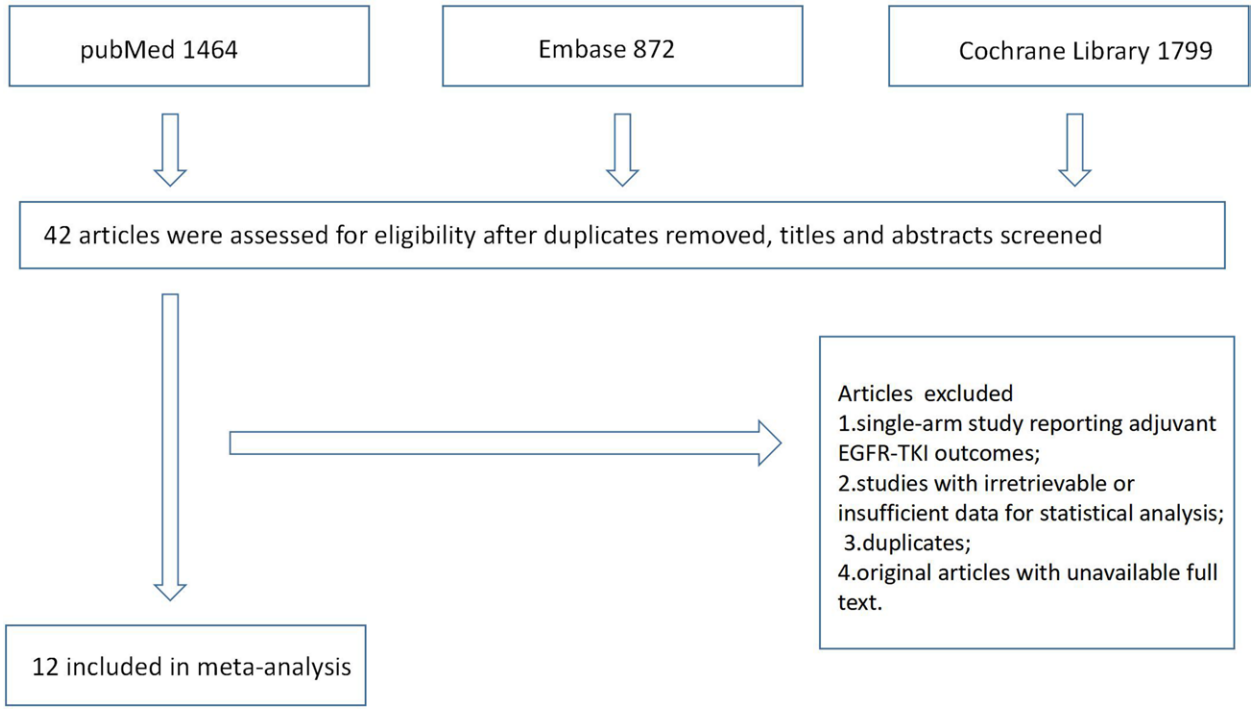

Figure 1. Study screening flowchart. EGFR = epidermal growth factor receptor, TKIs = tyrosine kinase inhibitors.

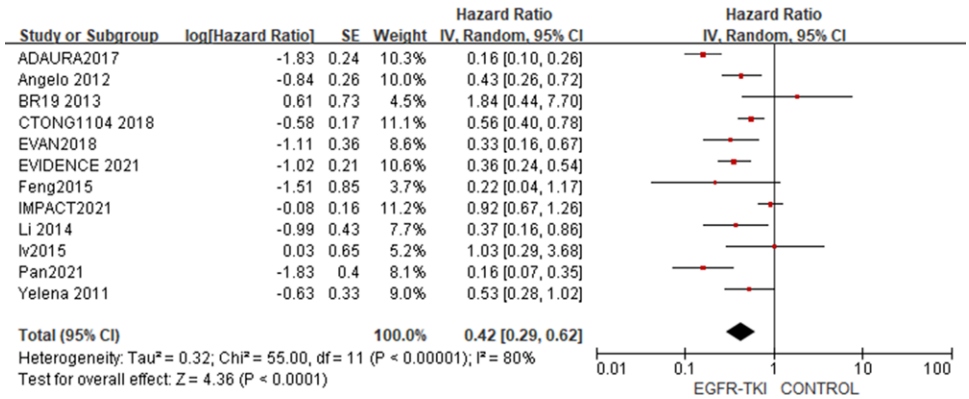

Figure 2. Forest plots showing HR regarding DFS for adjuvant EGFR-TKI compared with placebo among NSCLC cases receiving radical surgery. CI = confidence interval, DFS = disease-free survival, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = non-small-cell lung cancer, SE = standard error, TKI = tyrosine kinase inhibitor.

(Phet < 0.00001, I^2 = 80%). Also, our analysis showed that the OS (HR,0.74; 95% CI: 0.58, 0.95) (Fig. 5) after adjuvant EGFR-TKIs was better than chemotherapy, in which five RCTs (7, 8, 10, 11,23) and four RCSs (5, 20, 26, 28) were included. While there was obvious heterogeneity among those involved articles (Phet < 0.00001, I^2 = 80%), the significant heterogeneity mainly comes from the study ADAURA2017 according to the sensitivity analyses. No significant publication bias was found.

3.2. Effects of adjuvant TKIs versus chemotherapy on DFS and OS

Four RCTs (7, 8, 10, and 23) and one RCS (20) were included in this analysis to assess DFS and OS. Adjuvant TKIs significantly improved DFS (HR,0.43; 95% CI: 0.26, 0.72) (Fig. 6) among EGFR-mutation cases. Significant heterogeneity was noted (Phet < 0.00001, I^2 = 85%). At the same time, there is no

Table 1

Newcastle–Ottawa quality assessment scale.

Study	Selection				Comparability	Exposure		
	1	2	3	4		1	2	3
Angelo 2012	b	a	a	b	ab	a	a	a
Yelena 2011	b	a	a	a	ab	a	a	b
Iv2015	b	a	a	b	a	a	a	a
Pan2021	b	a	a	a	ab	a	a	b

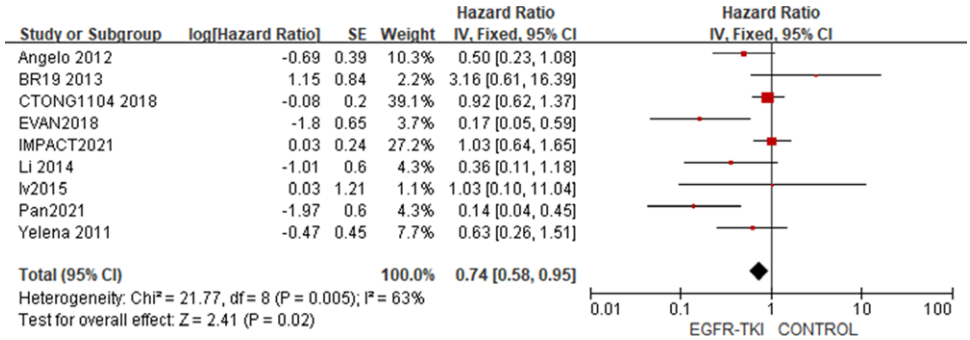

Figure 3. Forest plots showing HR regarding OS for adjuvant EGFR-TKI compared with placebo among NSCLC cases receiving radical surgery. CI = confidence interval, EGFR = epidermal growth factor receptor, HR = hazard ratio, OS = overall survival, NSCLC = non-small-cell lung cancer, SE = standard error, TKI = tyrosine kinase inhibitor.

Table 2

Major features of qualified studies enrolled in this meta-analysis.

Study	Intervention	Size	EGFR mutation (%)	TKI vs Control arm number	Stage			Median follow up (mo)	Design	Primary endpoint
					IB	II	III			
CTONG1104 2018[7]	gefitinib	222	100%	111	0	74	148	36.5	RCT	DFS/OS
	chemotherapy			111						
EVIDENCE 2021[10]	icotinib	322	100%	161	88	14	181	25	RCT	DFS
	chemotherapy			161						
IMPACT2021[23]	gefitinib	232	100%	116	74	9	144	70	RCT	DFS/OS
	chemotherapy			116						
EVAN2018[8]	erlotinib	102	100%	51	0	0	102	33	RCT	DFS/OS
	chemotherapy			51						
ADAURA2017[11]	osimertinib + chemotherapy	682	100%	203	216	231	235	22	RCT	DFS
	placebo + chemotherapy			207						
	osimertinib		100%	135						
	Placebo			136						
Iv2015[5]	erlotinib\gefitinib\icotinib	257	138 (53.6%)	30	126	48	83	31	RCS	DFS/OS
	Placebo			30						
Angelo 2012[26]	erlotinib or gefitinib	1118	284 (25.4%)	84	718	166	167	27	RCS	DFS/OS
	placebo			202						
BR19 2013[27]	gefitinib	503	15 (4%)	7	260	175	67	56.4	RCT	DFS/OS
	placebo			8						
Yelena 2011[28]	erlotinib or gefitinib + chemotherapy	167	100%	56	117	25	25	20	RCS	DFS/OS
	placebo + chemotherapy			111						
Li 2014[25]	gefitinib + chemotherapy	60	100%	30	0	0	60	30.6	RCT	DFS/OS
	placebo + chemotherapy			30						
Feng2015[29]	icotinib + chemotherapy	39	100%	21	17	10	12	46.4	RCT	DFS
	chemotherapy			18						
Pan 2021[20]	icotinib	43	100%	22	0	43	0	35.5	RCS	DFS/OS
	chemotherapy			21						

DFS = disease-free survival, OS = overall survival, RCTs = randomized controlled trials.

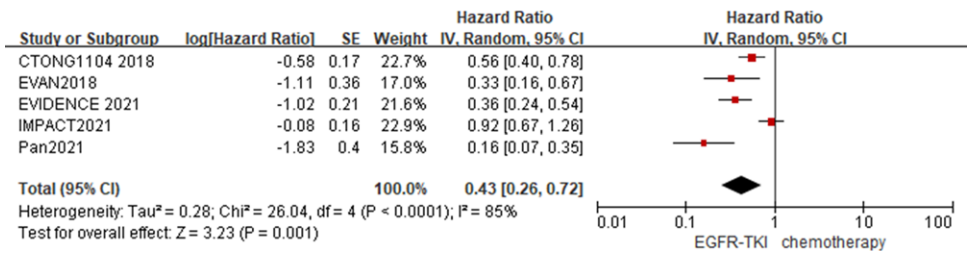

Figure 4. Forest plots showing HR regarding DFS for adjuvant EGFR-TKI compared with chemotherapy among NSCLC cases receiving radical surgery. CI = confidence interval, DFS = disease-free survival, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = non-small-cell lung cancer, SE = standard error, TKI = tyrosine kinase inhibitor.

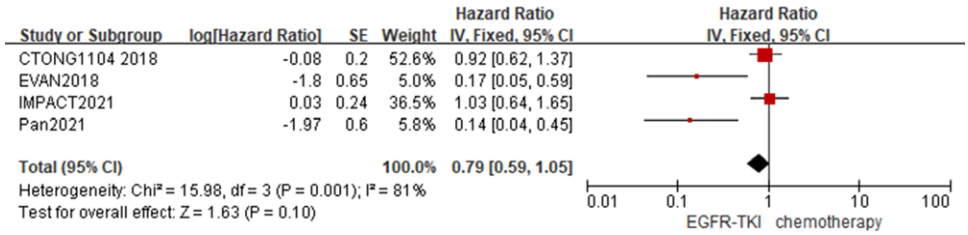

Figure 5. Forest plots showing HR regarding OS for adjuvant EGFR-TKI compared with chemotherapy among NSCLC receiving radical surgery. CI = confidence interval, EGFR = epidermal growth factor receptor, HR = hazard ratio, OS = overall survival, NSCLC = non-small-cell lung cancer, SE = standard error, TKI = tyrosine kinase inhibitor.

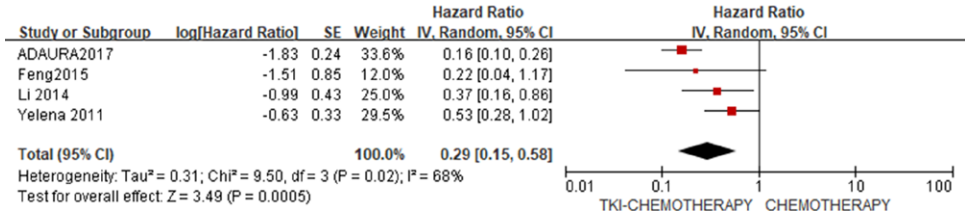

Figure 6. Forest plots showing HR regarding DFS for adjuvant EGFR-TKI in combination with chemotherapy compared with chemotherapy among NSCLC cases receiving radical surgery. CI = confidence interval, DFS = disease-free survival, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = non-small-cell lung cancer, SE = standard error, TKI = tyrosine kinase inhibitor.

significant beneficial effect of TKI treatment on OS (HR,0.79; 95% CI: 0.59, 1.05) (Fig. 7) compared with chemotherapy in the patients with NSCLC. The heterogeneity mostly comes from study Pan2021 with no significant publication bias.

3.3. Effects of adjuvant TKIs plus chemotherapy versus chemotherapy alone on DFS and OS

The analysis included three RCTs (11, 25, 29) and one RCS (26), showing that TKIs plus chemotherapy were superior to those of chemotherapy in both DFS (HR, 0.29; 95% CI: 0.15, 0.58) (Fig. 8) as well as OS (HR, 0.51; 95% CI: 0.25, 1.04) (Fig. 9). Upon sensitivity analysis, the combined results were not significantly affected by any study, despite the apparent heterogeneity (Phet = 0.001, I^2 = 79%) regarding DFS. And no significant publication bias was found.

3.4. Ongoing clinical trials

According to Table 3, seven ongoing RCTs enrolling 1819 cases were conducted using the intervention model, including

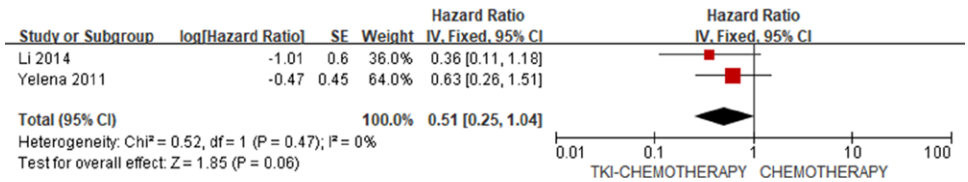

Figure 7. Forest plots showing HR regarding OS for adjuvant EGFR-TKI in combination with chemotherapy compared with chemotherapy among NSCLC cases receiving radical surgery. CI = confidence interval, EGFR = epidermal growth factor receptor, HR = hazard ratio, OS = overall survival, NSCLC = non-small-cell lung cancer, SE = standard error, TKI = tyrosine kinase inhibitor.

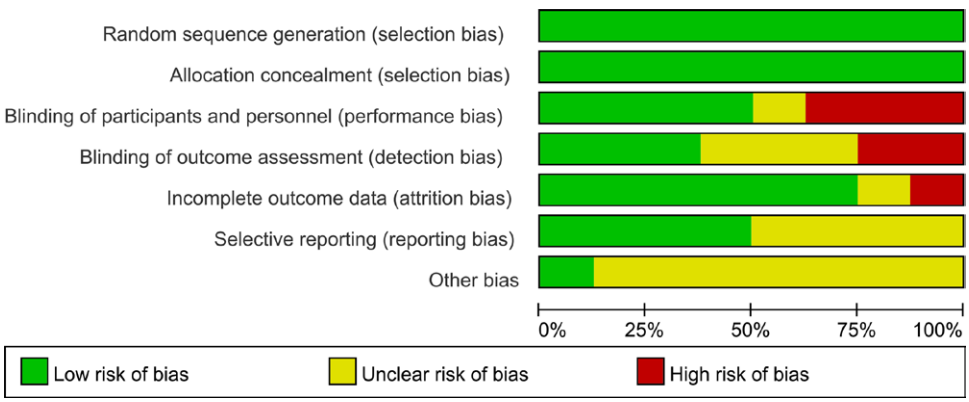

Figure 8. Risk of bias graph.

2 (NCT02264210, NCT05120349) that collected early cases; the others involved the treatment of patients at different stages.

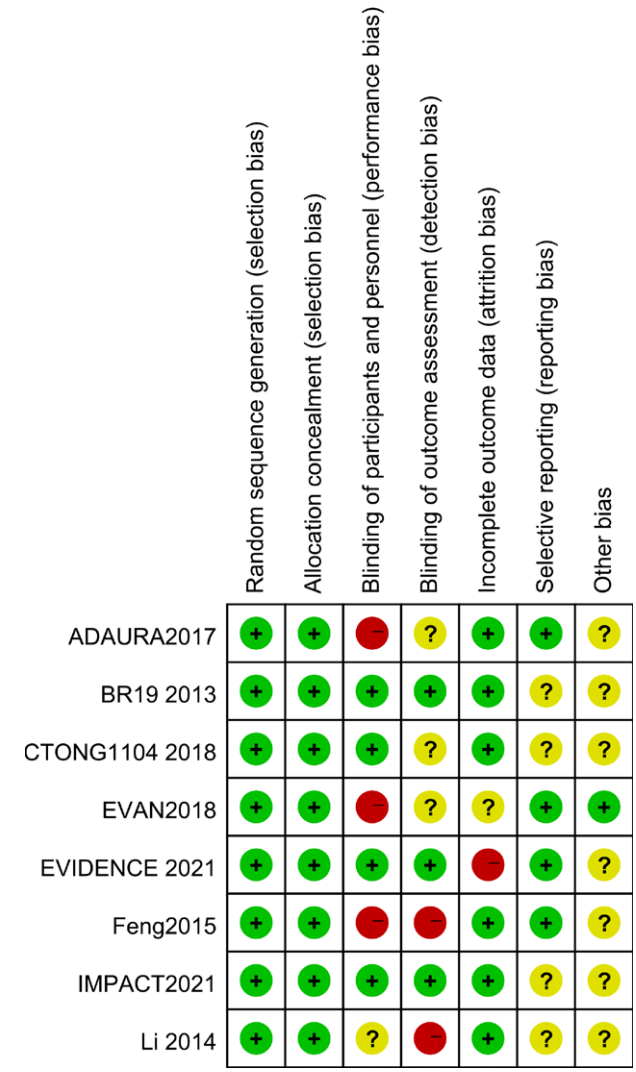

Figure 9. Risk of bias summary.

4. Discussion

The continuous innovation and research progress of EGFR-TKIs in recent years has provided clinical researchers with novel therapies and application ideas. Although TKIs have increased efficacy in EGFR mutation advanced NSCLC compared with chemotherapy,[17] whether TKI should be used in NSCLC cases receiving radical surgery remains controversial. According to our findings, adjuvant EGFR-TKIs enhanced DFS among cases with EGFR mutation after radical resection compared with chemotherapy, whereas OS was not significant. The adjuvant EGFR-TKIs plus chemotherapy demonstrated a significant beneficial effect on DFS and OS. The meta-analyze may support these results, showing that TKIs plus chemotherapy, the first-line therapy, significantly increase ORR while improving OS and DFS for advanced NSCLC cases with EGFR mutation.[18]

EGFR-TKIs have been recommended as first-line therapies for patients with EGFR-mutant NSCLC, and patients tend to benefit from adjuvant EGFR-TKI treatment in terms of DFS and OS. The ability of adjuvant EGFR-TKI treatment, however, remains unsatisfactory. According to some studies[7,8,23] EGFR-TKI DFS is superior to chemotherapy in EGFR mutation NSCLC patients. However, TKI cannot effectively prolong patients' survival when compared to chemotherapy.[7,8,23] The recent IMPACT study found that gefitinib as postoperative adjuvant therapy for patients did not improve DFS or OS.[10] The reason why TKI can only prolong DFS but not show DFS advantage translate to a significant OS difference in those studies (even in IMPACT both DFS and OS were not positive) may be that previous studies' follow-up time (The median follow-up time for most experiments was no more than 40 months) were shorter than IMPACT (70 months), and the performance of TKI's DFS was more superior in the early stage, while the DFS of TKI gradually decreased to the same level as the placebo.

Chemotherapy remains the guideline-recommended adjuvant treatment, despite having limited benefits for patients. EGFR-TKIs may inhibit sensitive mutant cancer cell growth, while chemotherapy may eliminate tumor cells and prevent micrometastasis.[22,23] Noronha et al recently discovered that TKI combined with chemotherapy can significantly improve DFS and OS in resected NSCLCs.[24,25] Furthermore, the percentage of patients receiving EGFR-TKI combined with chemotherapy who were alive and disease-free at 24 months was 89% (95% CI: 95, 99), while the placebo arm had only 58% (95% CI: 80, 89) in the ADAURA[11] study. A subgroup analysis was also performed in this study for patients after resection who received TKI combined with chemotherapy versus those who received

Table 3

Patient features among ongoing research.

Study (ClinicalTrials.gov)	Study type	Estimated enrollment	Allocation	Intervention mode	Stage	Actual study start date	Estimated primary completion date
NCT02193282	Interventional	450	Randomized	Parallel assignment	IB-IIIA	2014/7/17	2026/10/10
NCT02264210	Interventional	128	Randomized	Parallel assignment	IB	2014/10/15	2025/12/1
NCT02448797	Interventional	320	Randomized	Parallel assignment	II-IIIA	2015/5/19	2023/12/1
NCT04351555	Interventional	328	Randomized	Parallel assignment	II - IIIB N2	2020/4/17	2029/3/29
NCT05132985	Interventional	45	Randomized	Parallel assignment	II-IIIB N2	2021/11/24	2028/1/1
NCT04455594	Interventional	168	Randomized	Parallel assignment	IIIA-N2	2020/7/2	2025/10/1
NCT05120349	Interventional	380	Randomized	Parallel assignment	IA2-IA3	2021/11/15	2032/11/2

chemotherapy alone, and DFS improved significantly, but OS did not. However, due to a lack of studies and patients, and in the study Yelena et al hold, not all of the cases they collected received chemotherapy. According to the published ADAURA results, the osimertinib group had an OS rate of 98% in 2 years, while the placebo arm had an OS rate of 85%. Therefore, TKI combined with chemotherapy may be a promising treatment for advanced NSCLC patients with EGFR mutations after radical resection.

DFS showed great heterogeneity mainly due to the different regimens, individual features, prior treatments, as well as inadequate case numbers. There were no uniform doses of EGFR-TKI or chemotherapy in the enrolled articles. Additionally, most studies did not analyze subtypes of EGFR-mutation. Moreover, the different ratios of patients of clinical tumor stages made it impossible to evaluate the risk and efficacy accurately. After sensitivity analysis, those adjusted results strengthened the study atypism as well as the risk of integrated results.

The present study has certain limitations. Firstly, four retrospective studies were comprised in this analysis which may improve the heterogeneity. Secondly, EGFR-TKIs achieve diverse median durations among diverse studies; thus, possibly leading to a certain selection bias. Moreover, due to the different sample sizes, publication bias exists. Although this analysis shows that the adjuvant EGFR-TKIs combined chemotherapy group improved DFS among cases having EGFR mutation following radical surgery, there are still numerous unanswered questions. Which stage of the patient can gain the most benefits from EGFR-TKI-ACT, and what is the preferred EGFR-TKI-ACT duration? The research included in this study failed to answer this question effectively, and well-designed experiments are needed to explore it.

5. Conclusion

In NSCLC patients with EGFR mutations who underwent radical surgery, adjuvant EGFR-TKI combined with chemotherapy showed superior effect over chemotherapy or placebo with reference to DFS and may prolong the OS up to some extent.

Author contributions

RC and OJ design the study. RC and CW analyzed the data. XYL prepared the methodology. CW and XYL carried out the formal analysis; provide the software. RC and OJ wrote the original draft. RC and XYL were responsible for language revisions. RC reviewed the edited the final manuscript.
Conceptualization: Ran Cui, Ou Jiang.
Data curation: Ran Cui, Chun Wei.
Formal analysis: Chun Wei, Xianyi Li.
Investigation: Ran Cui.
Methodology: Xianyi Li.
Software: Chun Wei, Xianyi Li.
Writing – original draft: Ran Cui, Ou Jiang.
Writing – review & editing: Ran Cui, Xianyi Li.

References

[1] Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7:719–27.

[2] Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. Observation in resected non-small-cell lung cancer. N Engl J Med. 2005;352:2589–97.

[3] Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: A pooled analysis by the lace collaborative group. J Clin Oncol. 2008;26:3552–9.

[4] Group NM-aC. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet. 2010;375:1267–77.

[5] Lv C, An C, Feng Q, et al. A retrospective study of stage I to IIIa lung adenocarcinoma after resection: What is the optimal adjuvant modality for patients with an EGFR mutation? Clin Lung Cancer. 2015;16:e173–81.

[6] Xie H, Wang H, Xu L, et al. Gefitinib versus adjuvant chemotherapy in patients with stage II-IIIa non-small-cell lung cancer harboring positive EGFR mutations: a single-center retrospective study. Clin Lung Cancer. 2018;19:484–92.

[7] Zhong W-Z, Wang Q, Mao W-M, et al. ADJUVANT investigators. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIa (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol. 2018;19:139–48.

[8] Yue D, Xu S, Wang Q, et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIa EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. Lancet Respir Med. 2018;6:863–73.

[9] Tsuboi M, Kato H, Nagai K, et al. Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small cell lung cancer. Anticancer Drugs. 2005;16:1123–8.

[10] He J, Su C, Liang W, et al. Icotinib versus chemotherapy as adjuvant treatment for stage II-IIIa EGFR-mutant non-small-cell lung cancer (evidence): a randomised, open-label, phase 3 trial. Lancet Respir Med. 2021;9:1021–9.

[11] Wu YL, John T, Grohe C, et al. Postoperative chemotherapy use and outcomes from ADAURA: osimertinib as adjuvant therapy for resected EGFR-mutated NSCLC. J Thorac Oncol. 2022;17:423–33.

[12] Kelly K, Altorki NK, Eberhardt WE, et al. Adjuvant erlotinib versus placebo in patients with stage Ib-IIIa non-small-cell lung cancer (radiant): a randomized, double-blind, phase III trial. J Clin Oncol. 2015;33:4007–14.

[13] Tada H, Mitsudomi T, Misumi T, et al. Randomized phase iii study of gefitinib versus cisplatin plus vinorelbine for patients with resected stage II-IIIa non-small-cell lung cancer with EGFR mutation (impact). J Clin Oncol. 2022;40:231–41.

[14] Higgins JP, Altman DG, Gøtzsche PC, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343.

[15] Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998;17:2815–34.

[16] Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:1–16.

[17] Shi Q, Guan M, Wang Y, et al. Survival analysis of patients with advanced non-small cell lung cancer receiving tyrosine kinase inhibitor (TKI) treatment: a multi-center retrospective study. Thor Cancer. 2018;9:278–83.

[18] Wu Q, Luo W, Li W, Wang T, Huang L, Xu F. First-generation EGFR-TKI plus chemotherapy versus EGFR-TKI alone as first-line treatment in advanced NSCLC with EGFR activating mutation: a systematic review and meta-analysis of randomized controlled trials. Front Oncol. 2021;11:883.

[19] Wu Y-L, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med. 2020;383:1711–23.

[20] Pan S, Wang S, Li W, Chai Y. Icotinib versus cisplatin plus docetaxel as adjuvant chemotherapy in patients with stage II (n1+) non-small cell lung cancer harboring positive EGFR mutations: a single-center retrospective study. OncoTargets Ther. 2021;14:1083–91.

[21] Hosomi Y, Morita S, Sugawara S, et al. Gefitinib alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated epidermal growth factor receptor: Nej009 study. J Clin Oncol. 2020;38:115–23.

[22] Peng S, Wang R, Zhang X, et al. EGFR-TKI resistance promotes immune escape in lung cancer via increased PD-L1 expression. Mol Cancer. 2019;18:165.

[23] Eguchi T, Kodera Y, Nakanishi H, et al. The effect of chemotherapy against micrometastases and isolated tumor cells in lymph nodes: an in vivo study. In Vivo. 2008;22:707–12.

[24] Noronha V, Patil VM, Joshi A, et al. Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in EGFR-mutated lung cancer. J Clin Oncol. 2020;38:124–36.

[25] Li N, Ou W, Ye X, et al. Pemetrexed-carboplatin adjuvant chemotherapy with or without gefitinib in resected stage IIIa-N2 non-small cell lung cancer harbouring EGFR mutations: a randomized, phase II study. Ann Surg Oncol. 2014;21:2091–6.

[26] D'Angelo SP, Janjigian YY, Ahye N, et al. Distinct clinical course of EGFR-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. J Thorac Oncol. 2012;7:1815–22.
[27] Goss GD, O'Callaghan C, Lorimer I, et al. Gefitinib versus placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study. J Clin Oncol. 2013;31: 3320–6.
[28] Janjigian YY, Park BJ, Zakowski MF, et al. Impact on disease-free survival of adjuvant erlotinib or gefitinib in patients with resected lung adenocarcinomas that harbor EGFR mutations. J Thorac Oncol. 2011;6:569–75.
[29] Feng S, Wang Y, Cai K, et al. Randomized adjuvant chemotherapy of EGFR-mutated non-small cell lung cancer patients with or without Icotinib consolidation therapy. PLoS One. 2015;10:e0140794.