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

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ABSTRACT

Objectives: We performed this meta-analysis to compare adjuvant EGFR-TKIs with a placebo or adjuvant chemotherapy among patients with resected non-small cell lung cancer (NSCLC).

Materials and Methods: A literature search was performed using relevant keywords. All randomized controlled trials (RCTs) that compared the survival benefits of adjuvant EGFR-TKIs with those of placebo or adjuvant chemotherapy for resected NSCLC were eligible for inclusion.

Results: The literature search yielded five eligible RCTs including three RCTs that compared adjuvant EGFR-TKIs with a placebo, and two RCTs that compared adjuvant EGFR-TKIs with chemotherapy. For unselected intent-to-treat patients who received adjuvant EGFR-TKIs versus a placebo, the hazard ratio (HR) of disease-free survival (DFS) was 0.88 (95% confidence interval (CI): 0.59–1.32; P = 0.54). For patients with an EGFR mutation, the DFS after adjuvant EGFR-TKIs was superior to that after a placebo, with a HR of 0.59 (95% CI: 0.40–0.88; P = 0.009). For patients with an EGFR mutation, the DFS after EGFR-TKIs was greater than that after chemotherapy, with a HR of 0.42 (95% CI: 0.19–0.93; P = 0.03). For patients with wild-type EGFR, the DFS of adjuvant EGFR-TKIs was similar to the placebo, with a RR of 1.00 (95% CI: 0.62–1.60; P = 0.99). Treatment with EGFR-TKIs resulted in more adverse events compared with the placebo, with a risk ratio (RR) of 2.72, (95% CI: 2.23–3.33; P < 0.00001), but fewer adverse events compared with chemotherapy, with an RR of 0.26 (95% CI: 0.18–0.38; P < 0.00001).

Conclusions: For patients with resected NSCLC harboring EGFR mutations, treatment with an adjuvant EGFR-TKI was superior to that of a placebo or chemotherapy in terms of DFS. Treatment with adjuvant EGFR-TKIs were not effective among patients with wild type EGFR NSCLC.

1. Background

The most effective treatment for lung cancer is complete surgical resection, with anatomical resection as the preferred surgical procedure. According to the IASLC staging database for lung cancer, the average 5-year survival rate is approximately 56–65% for patients with pathological stage IIa–IIb lung cancer and 24–41% for those with stage IIIa–IIIb [1]. Adjuvant chemotherapy improves the survival of stage II–III lung cancer patients after surgery, corresponding to a 5-year absolute benefit of 5.4% [2]. Although targeted therapy has been the standard first-line therapy for advanced lung cancer harboring driver gene mutations, the recommended standard-of-care adjuvant treatment for stage IIa–IIIb resected non-small cell lung cancer (NSCLC), irrespective of epidermal growth factor receptor (EGFR) mutation status, is cisplatin-based chemotherapy [3,4]. Several randomized controlled trials (RCT) comparing adjuvant EGFR–tyrosine kinase inhibitors (TKIs) with a placebo have shown conflicting results regarding whether adjuvant EGFR-TKI treatment prolongs the survival of patients with resected NSCLC, and in clinical practice, it is still controversial whether EGFR-TKI treatment improves survival compared with adjuvant chemotherapy or a placebo. To define the role of adjuvant EGFR-TKIs in the management of patients with resected NSCLC, we conducted this meta-analysis of patients with resected NSCLC treated with adjuvant EGFR-TKIs versus a placebo or adjuvant chemotherapy.

2. Material and methods

All RCTs that compared the survival benefits of adjuvant EGFR-TKIs with chemotherapy or a placebo for patients with resected NSCLC were eligible for inclusion. The PubMed (United States National Library of

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Medicine, Bethesda, MD, USA) and Scopus (Elsevier) databases (https://www.scopus.com/home.uri) and EMBASE (https://www.embase.com/) were searched for studies published between January 1, 2010 and June 30, 2019 using the terms "lung cancer," "adjuvant therapy," and "Erlotinib, Gefitinib, Osimertinib, Icotinib, Dacomitinib" and randomized control trial or randomized trial search filters. These searches were supplemented by searching conference proceedings, review articles, and reference lists of trial publications. Only published trial was included in this meta-analysis.

3. Quality assessment

Two investigators used the risk of bias tool (Cochrane Handbook for Systematic Reviews of Interventions) to independently assess the quality of the trials [5]. Sequence generation, allocation concealment, blinding, incomplete data, selective reporting, and other sources of bias were assessed. Disagreements between the two investigators were resolved by discussion with a third investigator.

4. Statistical analysis

The meta-analysis was performed by combining the reported survival outcomes of individual studies according to Parmar and Tierney [6,7]. For time-to-event data, we extracted the log-transformed hazard ratio [log(HR)] and standard error values from trial reports. For dichotomous outcomes (e.g., adverse events), if it was not possible to use the HR, we extracted the number of events and participants in each treatment arm to estimate the risk ratio (RR).

Heterogeneity was conducted using I^2 tests, and no heterogeneity was regarded if P > 0.1 and I^2 < 50% using a fixed-effects statistical model, while I^2 > 50% was suggestive of substantiously heterogeneity, so a random effects model was used. A value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed using Review Manager software, version 5.3 (Cochrane Collaboration, Oxford, UK).

The primary endpoint was disease-free survival, which was defined as time from randomization to documented disease relapse or death. The secondary endpoints were overall survival (OS), safety and tolerability.

5. Results

5.1. Description of the studies

5.1.1. Results of the search

The flow of study selection was shown in Fig. 1. Of the 5632 records identified by our literature search, only six studies were RCTs that met the selection criteria for the meta-analysis. The characteristics of included studies are shown in Table 1.

5.1.2. Excluded studies

The study by Feng [8] was a small RCT comparing adjuvant chemotherapy plus icotinib with chemotherapy alone for patients with EGFR-mutant NSCLC. The patients in both group had been followed up for only 2 years. At the data cutoff, 6 patients (33.3% in 18) in the chemotherapy group and 2 (9.5% in 21) patients in the chemotherapy plus icotinib group had recurrence or metastasis. Because of the short follow-up time, the number of events was not sufficient, and the HR could not be calculated. At the study cutoff, the majority patients (n = 31;79%) are still at risk. This study was considered to have a very high bias and was excluded. The other five studies were included in the meta-analysis.

5.1.3. Risk of bias in the included studies

The study by Li et al. was not a double-blinded trial and had a moderate risk of bias (performance bias and detective bias) [9]. The other four included trials were well designed and were at a low risk of bias (Fig. 2).

5.1.4. Included studies

Five RCTs met our inclusion criteria. The Radiant [10] and Br.19 [11] trials compared adjuvant EGFR-TKIs with a placebo after adjuvant chemotherapy. Approximately 50% of the patients enrolled in the Radiant trial received adjuvant chemotherapy. Among the patients with mutated EGFR in the Radiant trial, 45.1% of the patients in the erlotinib group and 55.9% of the patients in the placebo group received adjuvant chemotherapy. The trial by Li et al. [9] compared adjuvant chemotherapy followed by EGFR-TKIs with adjuvant chemotherapy alone, which were considered similar treatments as those in the Radiant trial; thus, the two trials were pooled for analysis. The CTONG 1104 [12] and EVAN [13] trials compared adjuvant EGFR-TKIs with chemotherapy. The Br.19 and Radiant studies compared patients with resected stage IB to IIIA NSCLC with those with wild-type or mutated EGFR. The study by Li et al. included only patients with resected stage IIIA (N2) NSCLC harboring mutated EGFR. The characteristics of the eligible studies are summarized in Table 1.

5.1.5. The DFS after adjuvant EGFR-TKIs versus placebo

Three RCTs compared adjuvant EGFR-TKIs with a placebo or no TKI. The Br.19 and Radiant trials compared adjuvant EGFR-TKIs with a placebo. The trial by Li et al. compared adjuvant chemotherapy followed by gefitinib with adjuvant chemotherapy alone. The primary endpoint was disease-free survival (DFS) in the intent-to-treat population in these RCTs, defined as the time from random assignment to relapse or until death in the absence of relapse.

The DFS of unselected intent-to-treat patients treated with adjuvant EGFR-TKIs for patients was not superior to those treated with the placebo, with an HR of 0.88 (95% CI: 0.59–1.32; P = 0.54, Random effect, I^2 = 76%) (Fig. 3A). For patients with an EGFR mutation, the DFS after adjuvant EGFR-TKI was superior to that after placebo treatment, with an HR of 0.59 (95% CI: 0.40–0.88; P = 0.009, Fixed effect, I^2 = 45%) (Fig. 3B). If we included Feng's [8] trial, the DFS after adjuvant EGFR-TKI was also better than that after placebo for patients with an EGFR mutation, with a HR of 0.56 (95% CI: 0.39–0.82; P = 0.003 Fixed effect, I^2 = 38%) (Fig. 3C). Whether we excluded Feng's trial, it didn't impact the results. For patients with wild-type EGFR, the DFS of adjuvant EGFR-TKIs was not superior to the placebo, with a RR of 1.00 (95% CI: 0.62–1.60; P = 0.99, Random effect, I^2 = 76%) (Fig. 3D).

5.1.6. The OS after adjuvant EGFR-TKI versus placebo

The Br. 19 trial, Radiant trial and Li's trial all reported overall survival data. The median follow up time was 4.7 years(range, 0.1–6.3 years) for Br.19 trial, 3.9 years for Radiant trial, and 2.5 years(range, 0.3–4.39), respectively. For unselected intent-to treat patients, The OS after adjuvant EGFR-TKI was similar as placebo, with a HR of 1.09 (95% CI: 0.80–1.49; P = 0.59, Random effect, I^2 = 52%) (Fig. 4A). For EGFR mutant patients, the OS after adjuvant EGFR-TKI was also similar as placebo, with a HR of 0.97 (95% CI: 0.36–2.61; P = 0.95, Random effect, I^2 = 59%) (Fig. 4B).

5.1.7. The DFS after adjuvant EGFR-TKI versus adjuvant chemotherapy

Two RCTs compared adjuvant EGFR-TKIs with adjuvant chemotherapy. In the CTONG1104 trial, adjuvant gefitinib was compared with adjuvant vinorelbine plus cisplatin in patients with completely resected stage II–IIIA (N1–N2) EGFR-mutant NSCLC. In the EVAN trial, adjuvant erlotinib was compared with adjuvant vinorelbine plus cisplatin in patients with completely resected stage IIIA (N2) NSCLC harboring mutated EGFR. The DFS after adjuvant EGFR-TKIs was better than that after adjuvant chemotherapy, with a HR of 0.42 (95% CI: 0.19–0.93; P = 0.03, Random effect, I^2 = 76%) (Fig. 4C).

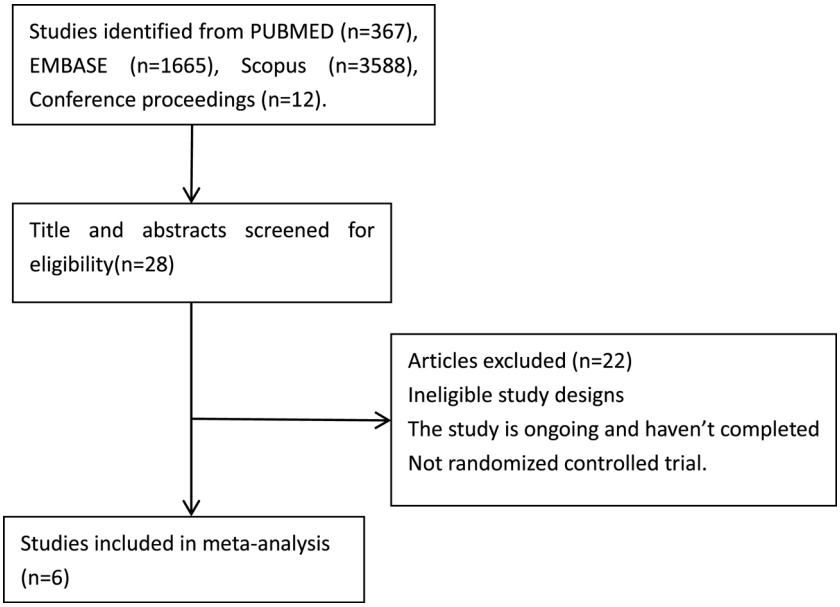

Fig. 1. Flow chart of study selection.

5.1.8. The OS after adjuvant EGFR-TKI versus adjuvant chemotherapy

The EVAN trial reported the OS after adjuvant EGFR-TKI was superior to adjuvant chemotherapy, although the median overall survival was not reached in either group. In the CTONG1104 trial, the overall survival data are immature and not presented. So, we can't synthesize the OS.

5.1.9. Adverse events

The meta-analysis showed that treatment with adjuvant EGFR-TKIs was associated with more adverse events compared with the placebo but fewer adverse events compared with adjuvant chemotherapy. The adjuvant EGFR-TKIs caused more grade 3–4 adverse events than did the placebo, with an RR of 2.72 (95% CI: 2.23–3.33; $P < 0.00001$) (Fig. 5A). Compared with adjuvant chemotherapy, patients treated with adjuvant EGFR-TKIs experienced fewer grade 3–4 adverse events, with a RR of 0.26 (95% CI: 0.18–0.38; $P < 0.00001$) (Fig. 5B).

6. Discussion

6.1. Summary of the main results

The meta-analysis showed that among unselected NSCLC patients, treatment with EGFR-TKIs did not improve the DFS compared with the placebo. Among patients with EGFR-mutant NSCLC, adjuvant EGFR-TKIs improved the DFS compared with the placebo and adjuvant chemotherapy. Adjuvant EGFR-TKIs were not effective among patients with wild type EGFR NSCLC. The OS after adjuvant EGFR-TKIs were similar to placebo. Patients treated with adjuvant EGFR-TKIs experienced more grade 3–4 adverse events than did those treated with a placebo but fewer grade 3–4 adverse events than did those treated with adjuvant chemotherapy.

EGFR-TKIs have been the recommended initial therapies for patients with metastatic EGFR-mutant NSCLC, based on the prolonged progression-free survival, overall response rate, disease control rate, and improved quality of life compared with chemotherapy in several phase III trials [14–16]. For patients with resected stage II and III NSCLC, cisplatin-based adjuvant chemotherapy is currently the standard of care, regardless of the EGFR mutation status, but the treatment effect is not satisfactory. Postoperative radiotherapy increased the 5-year survival rate in patients with N2 disease by 5–7% [17]. However, the results from retrospective studies and a single-arm phase II SELECT study indicated that patients with EGFR-mutant stage IB–IIIA resected NSCLC might benefit from adjuvant EGFR TKIs [18]. Patients (n = 100) with resected stage IA to IIIA (7th edition of the American Joint Committee on Cancer Staging System) NSCLC harboring EGFR mutations were treated with erlotinib (150 mg/day for 2 years) after standard adjuvant chemotherapy, with or without radiotherapy. The median follow-up was 5.2 years, and the 2-year DFS rate was 88% (96% stage I, 78% stage II, and 91% stage III). The median DFS and overall survival (OS) have not been reached; the 5-year DFS and OS rates were 56% (95% CI, 45–66%) and 86% (95% CI: 77–92%). Another retrospective study reported a trend toward an improvement in the disease-free survival among individuals with resected stage I–III lung adenocarcinomas harboring EGFR mutations compared with a historical comparator [19]. These two studies present a low rate of recurrence and an encouraging overall survival of adjuvant TKTs. A limitation of these studies was that they were non-randomized controlled trials.

EGFR-TKIs have no effect for patients with wild type EGFR. Similar to the Isel trial, which showed that EGFR-TKIs did not improve survival in unselected patients with advanced NSCLC compared with the placebo [20], treatment with adjuvant EGFR-TKIs did not prolong survival for unselected patients with resected lung cancer. The Br.19 and Radiant trials were two large RCTs that compared adjuvant EGFR-TKIs with a placebo in unselected and resected NSCLC patients. The Br.19 trial was a negative trial. It recruited unselected patients, of which only 15 had EGFR mutations. Most of these patients were EGFR wild type. The BR.19 study was therefore underpowered because it was terminated prematurely. The patients were planned to be treated for 2 years, but they received treatment for an average of only 5 months, which is considered suboptimal [11]. The Radiant trial also enrolled unselected patients. Among the 973 enrolled patients, 161 were in the EGFR mutation subgroup, in which erlotinib prolonged the DFS of the patients.

The CTONG1104 and EVAN trials compared adjuvant EGFR-TKIs with adjuvant chemotherapy for patients with resected and EGFR-mutant NSCLC. EGFR-TKIs improved the DFS and lowered the rate of adverse events compared with chemotherapy. The TKIs may have inhibited the growth of sensitive mutant tumor cells rather than by eradicating potential micrometastases. For patients with EGFR-mutant and resected lung cancer, whether the optimal treatment was adjuvant EGFR-TKIs alone or EGFR-TKIs combined with chemotherapy still needs to be determined by further clinical trials.

Ongoing and future RCTs will help define the clinical benefit of

Table 1
Baseline characteristics of included studies. *NA, not assessable.

Trials	Intervention	No.	AgeMedian	Stage (No.)	Adjuvant chemotherapy		Primary endpoint	EGFR mutation positive patients	Median follow up(year)	Median TKI treatment duration (month)
					Yes	No				
RADIANT [10]	erlotinib	N = 623	62	IB to IIIA	315(50.6%)	308(49.4%)	DFS	N = 102	3.9	11.9
	Placebo	N = 350	62	IB to IIIA	200(57.1%)	150(42.9%)	DFS	N = 59		
Br.19 [11]	gefitinib	N = 251	66	IB to IIIA	43(17%)	208(83%)	OS and DFS	N = 7	4.7 (range, 0.1–6.3)	4.8
	placebo	N = 252	67	IB to IIIA	44(17%)	208(83%)	OS and DFS	N = 8		
Li [9]	chemotherapy-gefitinib	N = 30	59.5	IIIA N2	30	0	DFS	N = 30	2.5 (range, 0.3–4.39)	6
	chemotherapy	N = 30	54.6	IIIA N2	30	0	DFS	N = 30		
Feng [8]	Chemotherapy-Icotinib	N = 21	57	IB to IIIA	21	0	DFS	21	2	NA*(Range, 4–8)
	chemotherapy	N = 20	55	IB to IIIA	18	2	DFS	20		
CTONG1104 [12]	gefitinib	N = 111	58	II–IIIA (N1–N2)	0	0	DFS	N = 111	3.04(IQR 1.98–3.73)	21.9
	Vinorelbine plus cisplatin	N = 111	60	II–IIIA (N1–N2)	111	0	DFS	N = 111		
EVAN [13]	erlotinib	N = 51	59	IIIA	0	0	2 year DFS	N = 51	2.75(IQR1.48-3.59)	23.9(IQR20.7–24
	Vinorelbine plus cisplatin	N = 51	57	IIIA	51	0	2 year DFS	N = 51		

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

adjuvant EGFR TKIs in this setting.

Ongoing trials

The ALCHEMIST trial is a RCT assessing whether adjuvant therapy with erlotinib will improve the OS compared with patients with completely resected stage IB (≥ 4 cm) to IIIA EGFR-mutant NSCLC following complete resection and standard postoperative therapy. The WJOG6410 L trial is a RCT in western Japan comparing vinorelbine plus cisplatin with gefitinib in patients with resected NSCLC with activating EGFR mutations.

Osimertinib is a third-generation EGFR-TKI that potently and selectively inhibits both EGFR-TKI-sensitizing and EGFR-resistance mutations [21,22]. In a phase III trial of patients with EGFR-mutant advanced NSCLC, first-line osimertinib treatment compared with gefitinib or erlotinib resulted in clinically and significantly improved progression-free survival (median, 18.9 versus 10.2 months; HR: 0.46; 95% CI: 0.37–0.57; $P < 0.001$). Osimertinib is superior to standard EGFR-TKIs as the first-line treatment of EGFR-mutant advanced NSCLC [23]. The ADAURA trial was a phase III double-blind randomized study of osimertinib versus placebo for EGFR-mutant early-stage NSCLC after complete surgical resection. Standard postoperative adjuvant chemotherapy was allowed. This study is ongoing and will further confirm whether adjuvant osimertinib improves the DFS and OS for EGFR-mutant early-stage NSCLC after complete surgical resection [24].

Although the most important treatment goal for early stage cancer was to cure, the primary endpoint of majority of these studies included

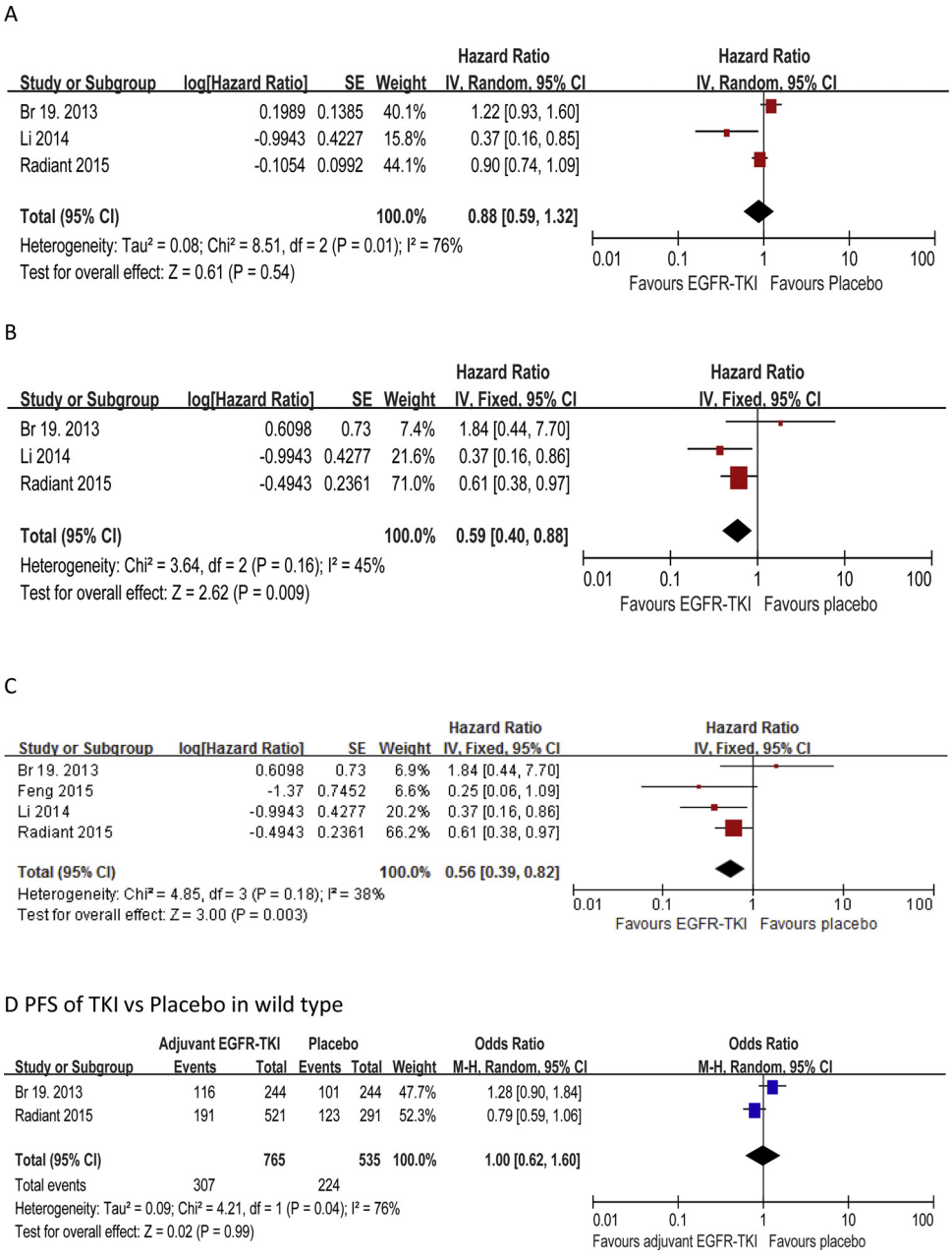

Fig. 3. Forest plot of hazard ratio of disease-free survival for adjuvant TKI VS placebo in resected patients with NSCLC. A. The hazard ratio of disease-free survival for adjuvant TKI VS placebo in resected unselected ITT patients with NSCLC. B. The hazard ratio of disease-free survival for adjuvant TKI VS placebo in resected patients with EGFR mutant NSCLC. C. The hazard ratio of disease-free survival for adjuvant TKI VS placebo in resected patients with EGFR mutant NSCLC including Feng's trial. D. The hazard ratio of disease-free survival for adjuvant TKI VS placebo in resected patients with EGFR wild type NSCLC.

in this meta-analysis were DFS. Our analysis shown that the OS after adjuvant EGFR-TKIs was similar to placebo. These maybe have several reasons. First, both the Radiant trial and Br.19 trial included unselected patients, only 15 (2.9%) patients in Br.19 trial and 161 (16.5%) patients in Radiant trial with EGFR mutation, of which there are some imbalances between subgroup. Second, the primary endpoint of Radiant trial and Li's trial were DFS. For the OS, like the adjuvant chemotherapy for lung cancer [2,25], We need larger sample size and extended follow up to detect small but significant difference. There are totally 263 patients with EGFR mutation in these three trials, which are underpower to detect small OS difference. Third, the duration of TKTs are awaited to be optimal. The median duration of TKI was 11, 6, 4.8 months for the Radiant, Li and Br.19 trial, respectively. The median duration of TKI was 23 months for Select trial. Although the median PFS of EGFR-TKIs is about 10–12 months in advanced NSCLC, continuation of EGFR-TKI in patients with gradual progression can improve survival [26]. In Select trial, the majority of patients with recurrence were retreated with erlotinib (n = 26; 65%) for a median duration of 13 months. In CTONG1104, the median EGFR-TKI treatment duration is 21.9 months. The Kaplan-Meier curves of DFS in each treatment group separated at month 12 and converged again at month 36, indicating that patients treated with gefitinib could maintain benefit for 12 months after TKI termination at 24 months. The long duration of TKI was the reason of the low rate recurrence and promising OS. The CTONG1104 and EVAN trial were well designed trial, which shown improved DFS of adjuvant TKIs compared with adjuvant chemotherapy. The EVAN trial reported that the OS of adjuvant TKI has improved compared with that adjuvant chemotherapy. We also expect the complete follow-up and mature OS data for these two trials in the near future. Last, which stage of patients benefit most from adjuvant TKI? The DFS HR value from three positive

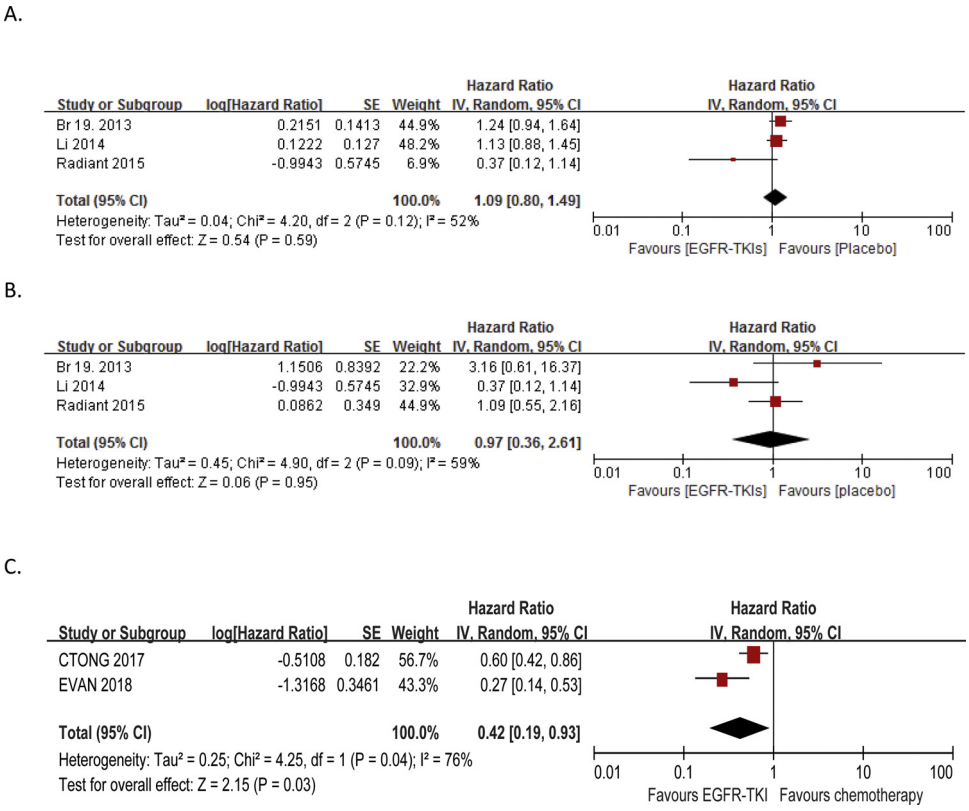

Fig. 4. A. Forest plot of the OS of adjuvant TKIs vs placebo for ITT unselected patients. B. The OS of adjuvant TKIs vs placebo for EGFR mutant patients. C. The DFS after adjuvant EGFR-TKIs was better than that after adjuvant chemotherapy for patients with EGFR mutation.

trial was 0.60, 0.268, 0.37 for the CTONG1104, EVAN and Li' trial respectively. The EVAN trial and Li's trial included only stage IIIA, and CTONG1104 trial included stage II-IIIA (N1-N2) patients. It seems that the higher stage of patient might benifite more from adjuvant TKI.

6.2. Limitations of this analysis

There are still many questions that need to be answered regarding treatment with EGFR-TKIs. For patients with EGFR mutations, which stage of lung cancer benefits most from adjuvant EGFR-TKIs after radical resection? What is the optimal duration of adjuvant EGFR-TKI treatment? Is an adjuvant EGFR-TKI alone or in combination with

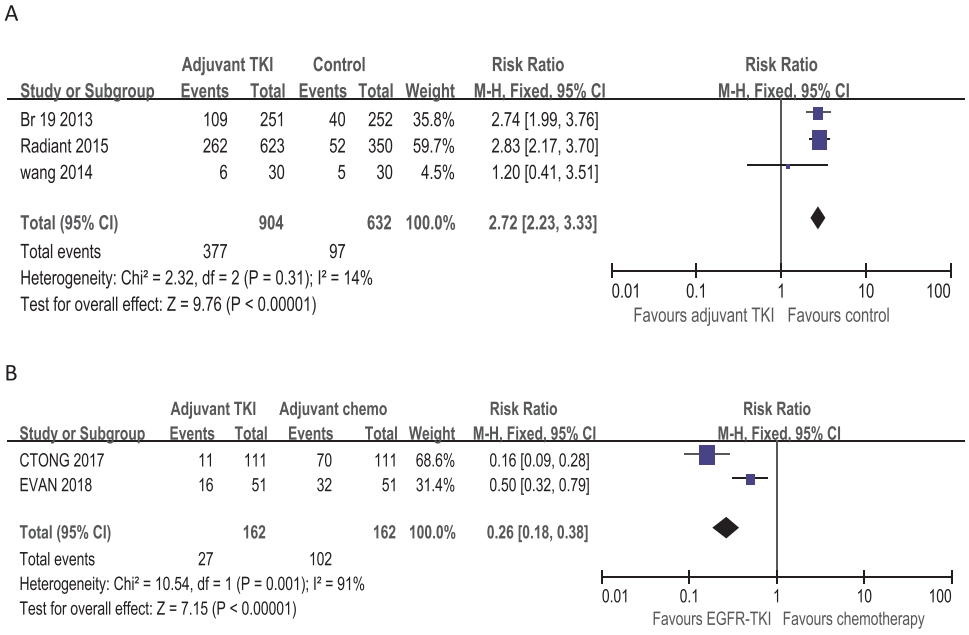

Fig. 5. A. Patients treated with adjuvant TKI experienced more grade 3–4 adverse events than did those treated with placebo. B. Patients treated with adjuvant TKI experienced fewer grade 3–4 adverse events than did those treated with adjuvant chemotherapy.

treatment with chemotherapy the most optimal treatment regimen? Which agent is the best? Could the improvement in the DFS translate into improvement in the OS? The answers to these questions need to be confirmed by additional clinical trials.

The potential bias of this meta-analysis was that we only included published study. Another potential bias was the inhomogeneous study design including patients with wild type EGFR, different stage, different treatment regimen and duration. To reduce the treatment regimen bias, we make two comparison, one is adjuvant EGFR-TKIs versus placebo, the other is adjuvant EGFR-TKIs versus chemotherapy. The quality of included studies was an important issue. We assessed the risk of study bias and excluded one low quality study. Despite these problems, this meta-analysis is very useful to conclude that adjuvant EGFR-TKIs were superior to placebo or adjuvant chemotherapy among paitents with EGFR-mutant NSCLC.

In conclusion, patients with resected EGFR-mutant NSCLC treated with adjuvant EGFR-TKIs had an improved DFS compared with placebo or adjuvant chemotherapy. Adjuvant EGFR-TKIs were not effective among patients with wild type EGFR NSCLC. Treatment with adjuvant EGFR-TKIs resulted in more adverse events than the placebo but fewer adverse events compared with adjuvant chemotherapy. Ongoing studies are therefore needed to further confirm the possible benefits of adjuvant EGFR-TKI therapy in patients with NSCLC.

Declaration of Competing Interest

The authors declare no competing interests.

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