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Gefitinib Plus Chemotherapy Versus Cetuximab Plus Chemotherapy in Patients with Advanced Non-small Cell Lung Cancer: *A Network Meta-Analysis*

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Abstract: Recent randomized control trials have revealed the efficacy and safety of gefitinib plus chemotherapy and cetuximab plus chemotherapy on the treatment of advanced non-small cell lung cancer, but little is known about the differences between them lacking of direct evidences. Randomized control trials were selected by formal search of electronic databases (PubMed, Embase, and Cochrane Library) and trials registers on the Internet. This systematic review and meta-analysis is reported in accordance with the Preferred Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews. 14 trails were identified finally, with 8 studies about gefitinib plus chemotherapy vs chemotherapy alone and 6 studies about cetuximab plus chemotherapy plus vs chemotherapy alone. For overall survival and progression-free survival, the relative HRs of gefitinib plus chemotherapy vs cetuximab plus chemotherapy were 0.96 (0.81-1.13, p=0.583) and 0.69 (0.45-1.05, p=0.080) on first-line treatment and 1.60 (1.01-2.54, p=0.044) and 0.83 (0.61-1.15, p=0.267) on second-line treatment. For objective response rate and one-year survival rate on first-line treatment, the relative RRs of gefitinib plus chemotherapy vs cetuximab plus chemotherapy were 0.89 (0.69-1.15, p=0.395) and 0.84 (0.72-0.98, p=0.026). For adverse events, the risk of relative RR of leukopenia all grades was 0.73 (0.58-0.91, p=0.006), while other events didn't exhibit significant differences. Subgroup analysis found that comparing to cetuximab plus chemotherapy, gefitinib plus chemotherapy appeared a better improvement in one-year survival rate of USA advanced NSCLC population [RR=0.83 (0.70-0.99, p=0.042)]. It concluded that, on the treatment of advanced NSCLC patients, the efficacy and safety of gefitinib plus chemotherapy are superior to cetuximab plus chemotherapy on first-line treatment, while the latter may be a better choice as well when it occurs to second-line treatment.

Keywords: Non-small Cell Lung Cancer, Gefitinib, Cetuximab, Chemotherapy, Network Meta-Analysis

1. Introduction

As one of the most threatening diseases to mankind, non-small cell lung cancer is a leading cause of cancer death worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 83% cases, and most patients with NSCLC that has been diagnosed are in the late stage, with an average survival rate of 10 to 12 months [1]. It is predicted that new NSCLC cases of American are 234030 in 2018, and 154050 of them will die of it [2]. The epidermal growth factor receptor (EGFR) is a kind of protein tyrosine kinase receptor which consists of an extracellular ligand binding domain structure, across a membrane structure domain and a domain with tyrosine kinase activity of cytoplasm structure. And it is closely related to the occurrence of cancer. It has been confirmed that EGFR mutation plays an essential role in development of lung cancer, mediating the proliferation and infiltration [3, 4]. The proportion of EGFR over-expression

in advanced non-small cell lung cancer and primary non-small cell lung cancer is 88% and 40%-80% respectively [5]. And according to the latest statistics, the occurrence rate of EGFR-mutant non-small cell lung cancer in Asian people is 30-40%, while 7-8% in North American [6]. Consequently, the EGFR-targeted medicines such as small molecule tyrosinase inhibitors-gefitinib and EGFR molecular targeted drug-cetuximab have been approved and applied in clinical treatment, and it appears a promising curative effect. As the original second- and third-line medicine, gefitinib is widely used in clinical treatment and the effective rate of second-line treatment is up to 10% [7]. And it is eutherapeutic, no matter monotherapy or combining chemotherapy or molecular targeting treatment [8, 9].

Cetuximab has better prospects for treating advanced NSCLC, which may benefit patients with overall survival and progression-free survival [10]. Recently, many studies have shown that Gefitinib plus chemotherapy or Cetuximab plus chemotherapy are both superior to chemotherapy alone for advanced NSCLC patients. However, there is no conclusion concerning the difference between Gefitinib plus chemotherapy and Cetuximab plus chemotherapy for advanced NSCLC.

Physicians also want to explore whether there are differences between them to provide scientific decisions for treatment. However, there is no direct comparison to reach a decisive conclusion so far. As a kind of special network meta-analysis, indirect comparison meta-analysis has been applied widely when direct evidences not enough, with excellent validity [11-13]. Therefore, we performed this systematic review and indirect comparison of meta-analysis to compare the differences between Gefitinib plus chemotherapy and Cetuximab plus chemotherapy in treating advanced NSCLC without head-to-head studies published, expecting to provide assistance for clinical purposes [14].

2. Methods

2.1. Search Strategy and Study Selection

This systematic review and meta-analysis is reported in accordance with the Preferred Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (number CRD42018091579). Literature was retrieved by formal search of electronic databases (PubMed, Embase, and Cochrane Library) and trials registers on the Internet without date limitation, and by hand searching of reference lists of related articles. To achieve the maximum sensitivity of the search strategy, we used appropriated free text and thesaurus terms including “Non-small cell lung carcinoma”, “Gefitinib”, “Cetuximab” and “Chemotherapy”. These computer searches were limited to English language articles and the retrieval strategy of Pubmed as follow: (((((Carcinoma, Non Small Cell Lung [Title/Abstract] OR Carcinomas, Non-Small-Cell Lung [Title/Abstract] OR Lung Carcinoma, Non-Small-Cell [Title/Abstract] OR Lung Carcinomas, Non-Small-Cell [Title/Abstract] OR Non-Small-Cell Lung Carcinomas [Title/Abstract] OR Nonsmall Cell Lung Cancer [Title/Abstract] OR Non-Small-Cell Lung Carcinoma [Title/Abstract] OR Non-Small Cell Lung Carcinoma [Title/Abstract] OR Carcinoma, Non-Small Cell Lung [Title/Abstract] OR Non-Small Cell Lung Cancer [Title/Abstract])) OR "Carcinoma, Non-Small-Cell Lung" [Mesh])) AND (((((Monoclonal Antibodies or “cetuximab” [Substance Name] or “monoclonal antibody” OR “monoclonal antibodies” OR mab OR mcab OR moab OR cetuximab OR erbitux OR c225 OR c-225)) OR "Antibodies, Monoclonal" [Mesh])) OR (gefitinib OR ZD1839 OR Iressa))) AND (((((((randomized [Title/Abstract]) OR drug therapy [Title/Abstract]) OR randomly [Title/Abstract]) OR trial [Title/Abstract])) OR "Controlled Clinical Trial" [Publication Type]) OR "Randomized Controlled Trial" [Publication Type]) Filters: Humans.

Inclusion criteria: (1) Gefitinib plus chemotherapy versus chemotherapy alone; (2) Cetuximab plus chemotherapy versus chemotherapy alone; (3) Patients with advanced non-small cell lung cancer; (5) Overall survival (OS) and/or Progression-free survival (PFS) was reported; (4) Randomized control trial. Exclusion criteria: (1) Review and meta-analysis; (2) Observational studies and letters; (3) Animal studies and basic research; (4) Radiotherapy; (5) About other antibodies (e.g. Bevacizumab and Tocilizumab) and other -tinibs (e.g. Sorafenib and erlotinib); (6) Monotherapy or single chemotherapy.

2.2. Data Abstraction and Quality Assessment

Two authors (H S and Z L) independently extracted the original data. Disagreement was resolved by discussion. If the two authors could not reach a consensus, the result was reviewed by the third author (BB Z). The extracted data were consisted of the follow items: the first author’s name, publication year, population (Ethnicity), methods, matching criteria, sex, total number of cases and controls, and age (years).

The quality assessment of the included trials was undertaken independently by two review authors, following *Cochrane Hanbook* [15] for assessing risk of bias. Seven main quality criteria were examined: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective outcome reporting (reporting bias); (7) other bias.

2.3. Statistical Analysis

We measured the treatment effect on dichotomous outcomes (e.g. Objective response rate and adverse events) and on time-to-event outcomes (e.g. overall survival and progression-free survival) by risk ratio (RR) with 95% confidence interval (CI) and hazard ratio (HR) with 95% CI,

respectively. Review manager 5.3 and Stata 14.0 software were used to perform the meta-analysis in the present study. Adjusted indirect comparison meta-analysis was used to explore the difference between Gefitinib plus chemotherapy and Cetuximab plus chemotherapy in patients with advanced NSCLC due to insufficient direct data. [16, 17] Sensitivity analysis was performed by subgroup analysis. The potential publication bias was investigated using Egger's test with limited to small size studies. Egger's test ($P<0.05$) was also considered to be representative of statistically significant publication bias. Heterogeneity among studies was assessed by I^2 statistic. $I^2 > 50\%$ indicated evidence of heterogeneity. If heterogeneity existed among the studies, the random effects model was used to estimate the pooled effect size. Otherwise, the fixed effects model was adopted.

3. Results

3.1. Trial Flow, Characteristic and Quality Assessment of Including Studies

A total of 1990 studies were retrieved. After duplicates were removed, 1697 studies were evaluated. Further screening titles and abstracts, Finally, only 14 papers (8 papers about Gefitinib plus chemotherapy and 6 papers about Cetuximab plus chemotherapy) were included with excluding no-related researches. [18-31] Figure 1 details literature search and study selection results. The main features of eligible studies are summarized in Table 1. Most of researches are from the USA and China, the size is range from 70 to 1125, and chemotherapy regimens include gemcitabine, cisplatin, Paclitaxel, carboplatin, Platinum, pemetrexed, docetaxel, and vinorelbine. Results of quality assessment were shown in Figures 2, 3.

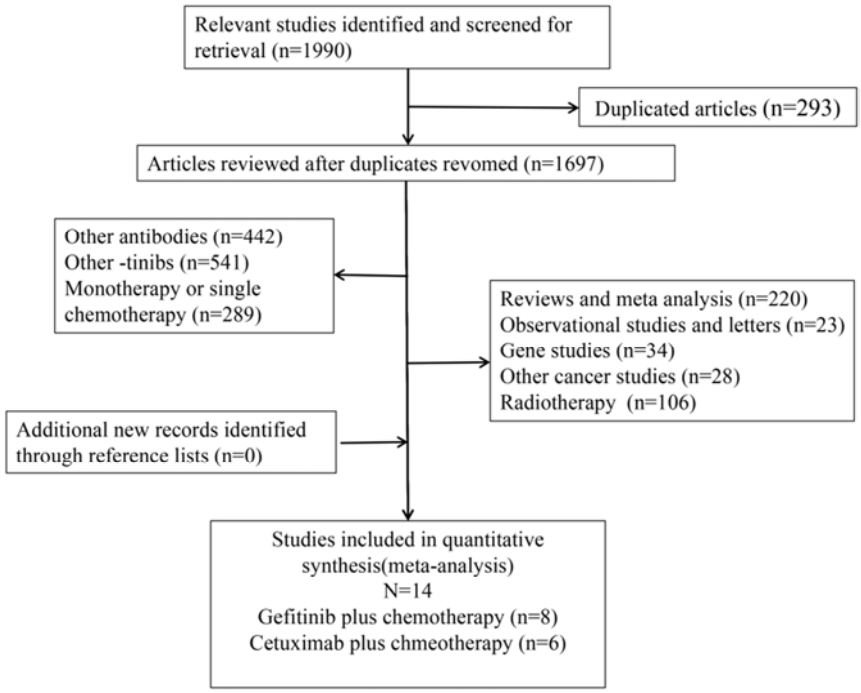

Figure 1. *Flow diagram for literature selection.*

Table 1. *Characteristics of include studies.*

Author	Country, year	Intervention	Treatment	Size (n)	Chemotherapy Regimens
Giaccone et al	USA, 2004	Ge plus CT	First-line	1093	Gemcitabine, cisplatin
Herbst et al	USA, 2004	Ge plus CT	First-line	1037	Paclitaxel, carboplatin
Soria et al	France, 2015	Ge plus CT	Second-line	265	Pemetrexed, cisplatin,
Takeda et al	Japan, 2010	Ge plus CT	First-line	604	Platinum doublet
Yu et al	China, 2014	Ge plus CT	First-line	117	Pemetrexed, cisplatin, carboplatin
Mok et al	China, 2017	Ge plus CT	First-line	265	Pemetrexed, cisplatin
Han et al	China, 2017	Ge plus CT	First-line	121	Pemetrexed, carboplatin
Choi et al	Korea, 2015	Ge plus CT	First-line	90	Paclitaxel, carboplatin
Butts et al	USA, 2007	Ce plus CT	First-line	131	Gemcitabine, cisplatin, carboplatin
Kim et al	USA, 2013	Ce plus CT	Second-line	605	Platinum, pemetrexed, docetaxel
Lynch et al	USA, 2010	Ce plus CT	First-line	676	Paclitaxel, carboplatin, docetaxel
Herbst et al	USA, 2017	Ce plus CT	First-line	753	Carboplatin, paclitaxel
Rosell et al	Spain, 2007	Ce plus CT	First-line	86	Cisplatin, vinorelbine
Pirker et al	Brazil, 2009	Ce plus CT	First-line	1125	Cisplatin, vinorelbine

NR, not reported directly
Ge plus CT, gefitinib plus chemotherapy
Ce plus CT, cetuximab plus chemotherapy

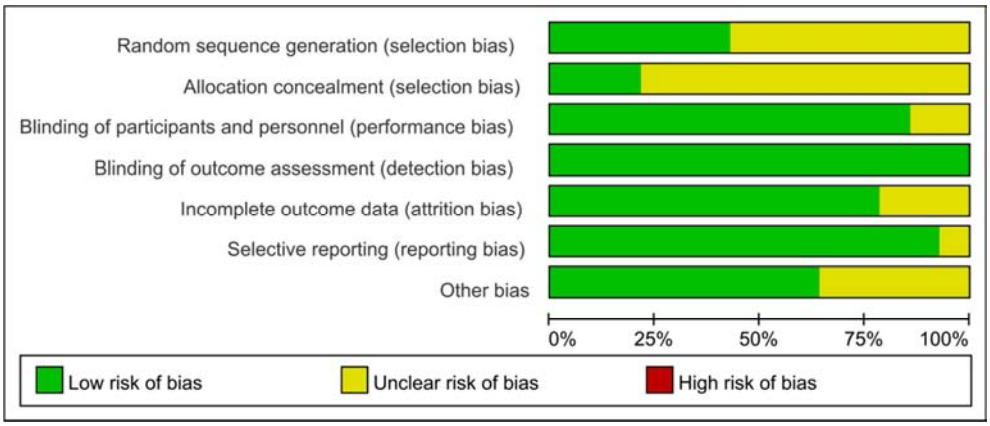

Figure 2. *Risk of bias summary: review authors' judgments about each risk of bias item for each included study.*

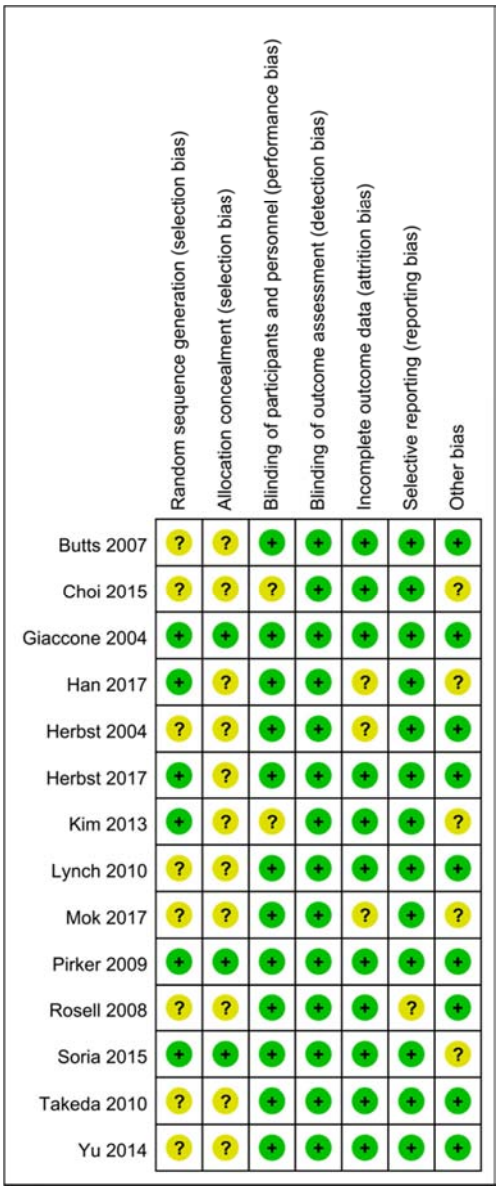

Figure 3. *Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.*

3.2. Meta-Analysis

As shown in Figures 4, 5, the pooled hazard ratios for overall survival (OS) were 0.85 (0.73-0.98, p=0.03) and 0.89 (0.83-0.96, p=0.004) in gefitinib plus chemotherapy vs chemotherapy alone group and cetuximab plus chemotherapy vs chemotherapy alone group for first-line and 1.62 (1.05-2.49, p=0.03) and 1.01 (0.86-1.18, p=0.90) for second-line, respectively. Indirect comparison meta-analysis showed there was significant difference for second-line [HR= 1.60 (1.01-2.54), p=0.044], but not for first-line [HR= 0.96 (0.81-1.13), p=0.583].

In addition, the pooled estimates of objective response rate (ORR) were 1.18 (0.95-1.46, p=0.14) and 1.32 (1.14-1.52, p=0.0002) in gefitinib plus chemotherapy vs chemotherapy alone group and cetuximab plus chemotherapy vs chemotherapy alone group, and indirect comparison meta-analysis exhibited there didn't exist significant difference [HR= 0.89 (0.69-1.15), p=0.395]. While, we discovered that the pooled hazard ratios for progression-free survival (PFS) were 0.63 (0.42-0.94, p=0.02) and 0.91 (0.83-1.00, p=0.04) in gefitinib plus chemotherapy vs chemotherapy alone group and cetuximab plus chemotherapy vs chemotherapy alone group for first-line and 0.86 (0.65-1.13, p=0.28) and 1.03 (0.88-1.21, p=0.71) for second-line, and indirect comparison meta-analysis exhibited there no evidence of difference between gefitinib plus chemotherapy group and cetuximab plus chemotherapy both of first-line and second-line.

For one-year survival rate of first-line advanced NSCLC patients, gefitinib plus chemotherapy group could benefit more than cetuximab plus chemotherapy group [HR=0.84 (0.72-0.98), p=0.026], USA NSCLC patients particularly [HR=0.83 (0.70-0.99), p=0.042]. What's more, in the risk of adverse events, gefitinib plus chemotherapy could reduce the risk of all grades of leukopenia [HR=0.73 (0.58-0.91), p=0.006] over cetuximab plus chemotherapy, but there was no statistical difference among other events. All of the comparison results were shown in Tables 2, 3.

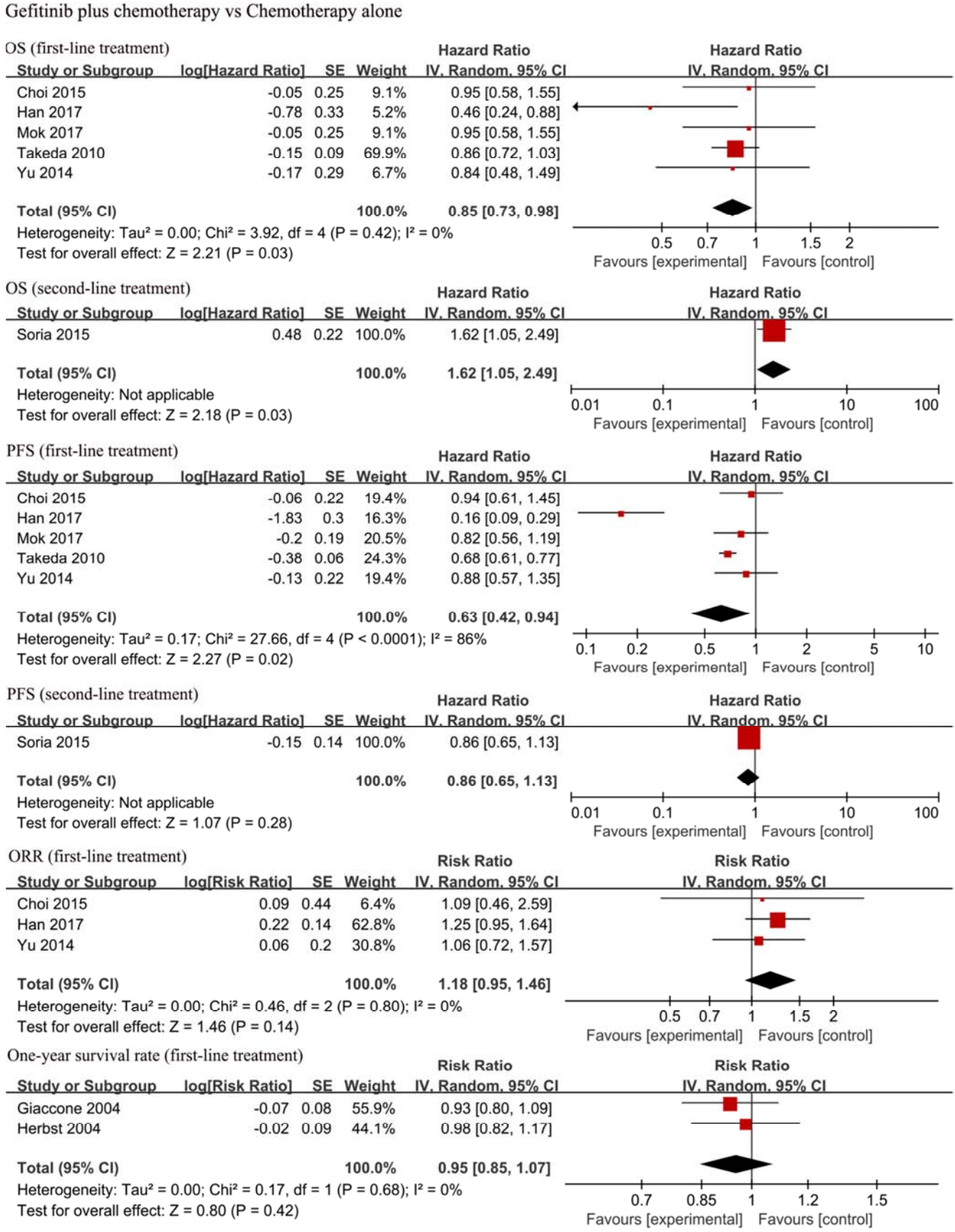

Figure 4. *Forrest plots for overall survival, progression-free survival, objective response rate and one-year survival rate comparing gefitinib plus chemotherapy to chemotherapy alone.*

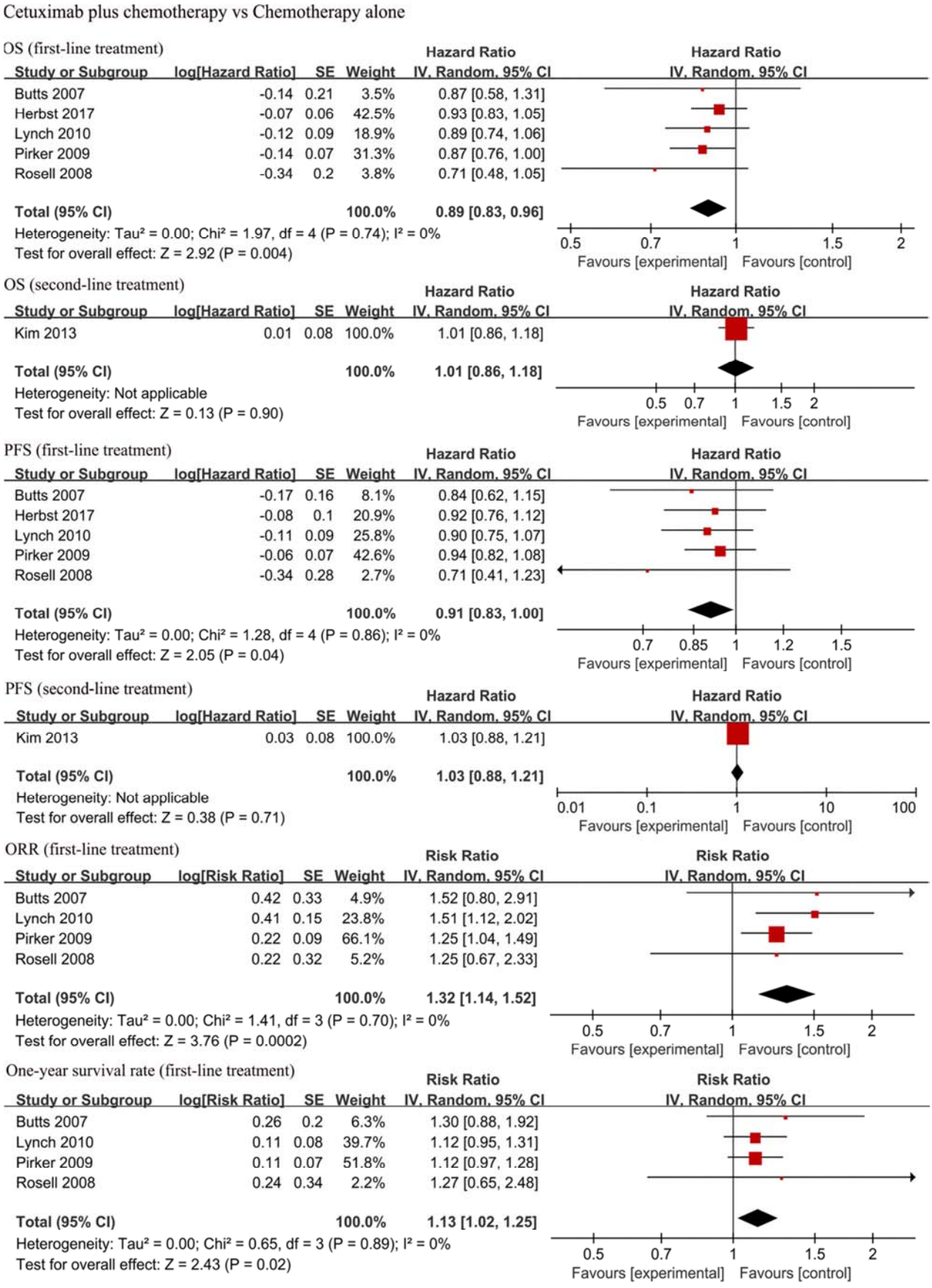

Figure 5. *Forrest plots for overall survival, progression-free survival, objective response rate and one-year survival rate comparing cetuximab plus chemotherapy to chemotherapy alone.*

Table 2. *Results summary for survival indexes.*

Outcome/Subgroup	No. Of studies	Statistical method	Effect size (relative value)	P value
OS				
First-line treatment	5 vs 5	Hazard Ratio (Random, 95%CI)	0.96 (0.81-1.13)	0.583
Second-line treatment	1 vs 1	Hazard Ratio (Random, 95%CI)	1.60 (1.01-2.54)	0.044
PFS				
First-line treatment	5 vs 5	Hazard Ratio (Random, 95%CI)	0.69 (0.45-1.05)	0.080
Second-line treatment	1 vs 1	Hazard Ratio (Random, 95%CI)	0.83 (0.61-1.15)	0.267
ORR				
First-line treatment	3 vs 4	Risk Ratio (Random, 95%CI)	0.89 (0.69-1.15)	0.395
One-year survival rate				
First-line treatment	2 vs 4	Risk Ratio (Random, 95%CI)	0.84 (0.72-0.98)	0.026
USA patients				
One-year survival rate (First-line treatment)	2 vs 2	Risk Ratio (Random, 95%CI)	0.83 (0.70-0.99)	0.042
Chemotherapy Regimens (First-line treatment)				
cisplatin				
PFS	1 vs 2	Hazard Ratio (Random, 95%CI)	0.88 (0.59-1.32)	0.538
carboplatin				
OS	2 vs 2	Hazard Ratio (Random, 95%CI)	0.74 (0.36-1.53)	0.414
PFS	2 vs 2	Hazard Ratio (Random, 95%CI)	0.43 (0.08-2.43)	0.339
ORR	2 vs 1	Risk Ratio (Random, 95%CI)	0.81 (0.55-1.21)	0.307
One-year survival rate	1 vs 1	Risk Ratio (Random, 95%CI)	0.88 (0.69-1.11)	0.275
Cisplatin+carboplatin				
OS	1 vs 1	Hazard Ratio (Random, 95%CI)	0.97 (0.48-1.94)	0.921
PFS	1 vs 1	Hazard Ratio (Random, 95%CI)	1.05 (0.62-1.78)	0.863
ORR	1 vs 1	Risk Ratio (Random, 95%CI)	0.70 (0.33-1.48)	0.349
Paclitaxel				
OS	1 vs 2	Hazard Ratio (Random, 95%CI)	1.03 (0.63-1.70)	0.900
PFS	1 vs 2	Hazard Ratio (Random, 95%CI)	1.03 (0.65-1.62)	0.888
ORR	1 vs 1	Risk Ratio (Random, 95%CI)	0.88 (0.69-1.11)	0.274
One-year survival rate	1 vs 1	Risk Ratio (Random, 95%CI)	0.72 (0.29-1.80)	0.484

OS, overall survival
PFS, progression-free survival
ORR, objective response rate

Table 3. *Results summary for risk of adverse events.*

Adverse events	Grade	No. Of studies	Effect size (relative value)	P value
Acne				
First-line treatment	All grades	4 vs 4	0.15 (0.02-1.23)	0.077
	≥3 grade	4 vs 4	0.26 (0.04-1.67)	0.156
Asthenia				
First-line treatment	All grades	5 vs 2	0.42 (0.08-2.11)	0.290
	≥3 grade	5 vs 2	0.84 (0.06-12.3)	0.900
Diarrhoea				
First-line treatment	All grades	8 vs 4	1.03 (0.59-1.81)	0.915
	≥3 grade	8 vs 4	1.41 (0.61-3.27)	0.421
Second-line treatment	All grades	1 vs 1	1.10 (0.61-1.99)	0.754
	≥3 grade	1 vs 1	3.03 (0.15-59.4)	0.465
Pruritus				
First-line treatment	All grades	5 vs 1	1.29 (0.41-4.07)	0.667
	≥3 grade	5 vs 1	0.74 (0.03-19.4)	0.856
Vomiting				
First-line treatment	All grades	6 vs 3	1.19 (0.84-1.69)	0.326
	≥3 grade	6 vs 3	1.32 (0.81-2.16)	0.271
Second-line treatment	All grades	1 vs 1	0.89 (0.56-1.41)	0.613
	≥3 grade	1 vs 1	0.89 (0.24-3.31)	0.864
Nausea				
First-line treatment	All grades	8 vs 3	0.92 (0.68-1.24)	0.578
	≥3 grade	8 vs 3	0.92 (0.47-1.80)	0.806

Adverse events	Grade	No. Of studies	Effect size (relative value)	P value
Second-line treatment	All grades	1 vs 1	0.82 (0.62-1.09)	0.174
	≥3 grade	1 vs 1	0.84 (0.15-4.55)	0.838
Anorexia				
First-line treatment	All grades	8 vs 2	0.75 (0.34-1.66)	0.476
	≥3 grade	8 vs 2	0.44 (0.07-2.74)	0.382
Dyspnoea				
First-line treatment	All grades	3 vs 2	0.56 (0.15-2.00)	0.370
	≥3 grade	3 vs 2	0.78 (0.12-5.18)	0.799
Second-line treatment	All grades	1 vs 1	1.48 (0.67-3.30)	0.335
	≥3 grade	1 vs 1	0.74 (0.12-4.70)	0.754
Anaemia				
First-line treatment	All grades	8 vs 3	1.08 (0.70-1.68)	0.720
	≥3 grade	8 vs 3	0.80 (0.53-1.21)	0.286
Second-line treatment	All grades	1 vs 1	1.29 (0.81-2.07)	0.288
	≥3 grade	1 vs 1	1.67 (0.49-5.62)	0.410
Leukopenia				
First-line treatment	All grades	7 vs 2	0.73 (0.58-0.91)	0.006
	≥3 grade	7 vs 2	0.77 (0.47-1.28)	0.319
Neutropenia				
First-line treatment	All grades	7 vs 3	0.90 (0.80-1.00)	0.066
	≥3 grade	7 vs 3	0.90 (0.79-1.01)	0.080
Second-line treatment	All grades	1vs 1	1.17 (0.63-2.18)	0.624
	≥3 grade	1 vs 1	1.21 (0.39-3.76)	0.747

Statistical method, Risk Ratio (Random, 95%CI)

3.3. Sensitive Analysis and Publication Bias

Sensitive analysis was conducted by subgroup analysis about chemotherapy regimens. As shown in Table 2, no matter what chemotherapy regimens, the pooled relative estimates were not significant. Thus, sensitive analysis suggested the results were stable. Egger's test for OS of gefitinib plus chemotherapy vs chemotherapy alone group (p=0.771) and cetuximab plus chemotherapy alone group (p=0.462) showed that there were no publication bias and small study effects. Therefore, the pooled results were reliable.

4. Discussion

This study demonstrate for the first time that gefitinib plus chemotherapy shows a better result than cetuximab plus chemotherapy for advanced NSCLC patients. To our knowledge, this is the first study that systematically reviews and summarizes through an indirect meta-analysis to compare the differences of gefitinib plus chemotherapy and cetuximab plus chemotherapy in patients with NSCLC, account of lacking of direct evaluation.

Contending the Mg -ATP binding site of EGFR- TK and blocking the signal transduction, gefitinib restrains the formation of hemangioma and promotes apoptosis of cancer cells. Kim E S et al. found that the effective rate and survival time after taking gefitinib are superior obviously to monotherapy and optimal support therapy, taking oriental woman with adenocarcinoma of lung who didn't smoke as the research object. [32] As a result, one IressaPan-Asia Study selected 1217 Asian patients with IIIB/IV NSCLC who didn't or less smoke to contrast the difference between paclitaxel plus carboplatin combination therapy and gefitinib monotherapy. The research shows that the curative effect to EGFR-mutant patients using gefitinib is better than chemotherapy (ORR: 71.2% vs 47.3%, P<0.001). [33] Combination of chemotherapy and gefitinib as first-line treatment for patients with advanced lung adenocarcinoma and sensitive EGFR mutations: a randomized controlled trial shows longer overall survival and progression free survival than monotherapy recently. In general, combination of chemotherapy and gefitinib as treatment for advanced non-small cell lung cancer has better curative effect and it has been proven by a systematic review recently. [33]

Cetuximab is an EGFR molecular targeting drug which suppresses dimerization, phosphorylation of tyrosine kinase and signal transduction after binding to EGFR specifically on tumor cells. Apoptosis signal will be passed into nucleus via downstream signal pathway of EGFR which played an important role in inhibiting tumor proliferation and promoting the apoptosis of tumor cells. A case report revealed that Cetuximab combined with Vinorelbine for NSCLC patients resistant to EGFR-TKIs can alleviate dyspnea and make tumor cells disappear completely for 9 months, it indicated that Cetuximab combined with Vinorelbine had good efficacy in treating NSCLC patients with EGFR-TKIs resistance and suggested that Cetuximab played an important role in reversing EGFR-TKIs resistance in patients with EGFR positive mutation. [34] Another clinical study of Cetuximab combined gemcitabine plus carboplatin was performed to treat patients with advanced NSCLC, and it showed longer median overall survival (11.99 months vs 9.26 months) and progression-free survival (5.09 months vs 4.21 months). [18] Furthermore, a multicenter phase III randomized controlled

trial showed that objective response rate (ORR) was effectively improved in advanced NSCLC patients treated by Cetuximab plus paclitaxel/carboplatin compared with chemotherapy alone. [20]

Although both gefitinib plus chemotherapy and cetuximab plus chemotherapy perform well in treating advanced NSCLC, there is no conclusive results about the differences between them. In addition, toxic events appearing in both, such as acne, anorexia and leukopenia, are also unclear in the comparison. This study suggested gefitinib plus chemotherapy performs better than cetuximab plus chemotherapy in the improvement of progression-free survival and one-year survival rate, while there was no difference in overall survival and objective response rate. In terms of toxic events, less odds of anorexia and leukopenia with gefitinib plus chemotherapy was exhibited compared with cetuximab plus chemotherapy, others didn't show significant differences. In conclusion, the efficacy and safety of gefitinib plus chemotherapy are superior to cetuximab plus chemotherapy.

It needs to point out that this study has some limitations. We didn't perform more specific subgroups to explore possible factors further with less studies included, such as age, sex, smoking status, EGFR status, KRAS status and specific chemotherapy and so on. Then, bias risk of most studies was not judged explicitly, potential bias was inevitable.

5. Conclusion

Although this study need explore optimal solution further combining patients' information, the results suggested gefitinib plus chemotherapy is superior to cetuximab plus chemotherapy for patients with first-line advanced NSCLC, while cetuximab plus chemotherapy used for second-line treatment may be much better. In the future, head-to-head studies should be carried out under suitable conditions to verify the results, and distinguish whether there are differences in the effects of particular factors, such as smoking status, EGFR status, KRAS status and specific chemotherapy.

List of Abbreviations

PRISMA: preferred Items for Systematic Reviews and Meta-analysis; NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; EGFR-TK: epidermal growth factor receptor tyrosine kinase; EGFR-TKIs: epidermal growth factor receptor tyrosine kinase inhibitors; HR: hazard ratio; RR: risk ratio; CI: confidence interval; OS: overall survival; PFS: progression-free survival; ORR: objective response rate.

Authors' Contributions

SF J takes charge of accuracy of the data analysis
Study concept and design: H S, Z L
Data extract: H S, Z L, BB Z
Statistical analysis: Z L, BB Z
Quality assessment: H S, Z L

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