Original Article

Impact of EGFR mutation status on tumor response and progression free survival after first-line chemotherapy in patients with advanced non-small-cell lung cancer: a meta-analysis

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Objectives: Non-small-cell lung cancer (NSCLC) patients harboring sensitive epidermal growth factor receptor (EGFR) mutations derive greater benefits from EGFR-tyrosine kinase inhibitors (EGFR-TKIs) than those with wild type tumors. However, whether EGFR mutation status is associated with the efficacy of cytotoxic chemotherapy or prognosis in advanced NSCLC patients remained controversial. Thus, we sought to conduct a meta-analysis to answer this question.

Methods: Electronic databases were searched for eligible literatures. The primary outcomes were objective response rate (ORR) and 6-month progression-free survival (PFS) rate. The pooled odds ratio (OR) was calculated using random-effects model. Subgroup analyses stratified by study types, EGFR mutation detection methods, chemotherapy regimens, and patient origins were proposed.

Results: A total of 14 studies involving 1,772 advanced NSCLC patients with known EGFR mutation status who had received first-line chemotherapy were included. Patients with positive EGFR mutation had numerically higher ORR than wild type patients (36.2% *vs*. 30.1%) without significant differences (OR 1.24, 95% CI, 0.90 to 1.70; P=0.19). However, patients with EGFR mutants had significantly superior 6-month PFS rate than wild-type patients (58.6% *vs*. 47.2%; OR 1.88, 95% CI, 1.33 to 2.65; P=0.0003). Results of the subgroup analyses were concordant with the overall ones.

Conclusions: This comprehensive analysis revealed that advanced NSCLC patients with sensitivity EGFR mutation had higher 6-month PFS rate and potentially greater ORR compared with wild-type patients after first-line chemotherapy. It suggested that EGFR mutation status should be considered a significant factor for patient stratification in evaluating the efficacy of antitumor agents in addition to EGFR-TKIs.

Keywords: Non-small-cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR) mutation; first-line chemotherapy; meta-analysis

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Introduction

Lung cancer, predominantly non-small-cell lung cancer (NSCLC), is the leading cause of cancer-related mortality worldwide (1). The majority of patients are diagnosed at advanced stages in which there are few treatment options (2). Despite the limited efficacy, platinum-based doublet chemotherapy remains the standard first-line treatment for advanced NSCLC in recent years (3,4). Advances in genetic testing allowed the discovery of existence and clinical significance of driver oncogenes which could be selected as a therapeutic target, such as activated epidermal growth factor receptor (EGFR) mutations (5). It has been

extensively proved that NSCLC patients who harbor sensitive EGFR mutations (exon 19 deletion or L858R mutation in exon 21) derive greater benefits from EGFR-tyrosine kinase inhibitors (EGFR-TKIs), such as erlotinib and gefitinib, than those with wild type tumors (6,7). The predictive value of EGFR mutation status for EGFR-TKIs efficacy has been substantially confirmed.

In contrast, people used to believe there is no correlation between EGFR mutation status and cytotoxic chemotherapy. Data from some previous studies suggested that Asians represented higher response rate than Caucasians in receiving chemotherapy (8). From the present point of view, the most prominent intrinsic genetic variance between these two races is the proportion of patients with EGFR mutations. Considering the huge differences in tumor biology between EGFR mutation-positive and -negative NSCLC, it is interesting to investigate whether EGFR mutation status also influence chemotherapy efficacy. Several recent studies revealed that advanced NSCLC patients with positive EGFR mutation had favorable response to first-line cytotoxic chemotherapy compared with wild type patients (9,10), while another study showed contrary results (11). In addition, another clinical research reported that there was no obvious association between EGFR mutation status and first-line chemotherapy response in NSCLC (12). Therefore, whether EGFR mutation status is associated with responsiveness to front-line chemotherapy in advanced NSCLC is still not clear. A comprehensive analysis of the various outcomes is warranted. Thus, we sought to perform a meta-analysis incorporating all available evidences to evaluate the clinical outcome according to the EGFR mutation status in patients with advanced NSCLC treated with front-line conventional chemotherapy.

Methods

Literature search

All relevant articles were retrieved by searching PubMed, Embase and the Central Registry of Controlled Trials of the Cochrane Library using a combination of the terms "EGFR", "epidermal growth factor receptor", "mutation", "lung", "non-small-cell lung cancer", "NSCLC" and "chemotherapy". An additional search through Google Scholar and a manual search through reference lists of relevant reviews and included studies were additionally performed. Two authors (ZY and KS) carried out the search independently. No restriction by language or year was set in the search.

Inclusion and exclusion criteria

Eligible studies should meet the following criteria: (I) studies which investigate or report a subset of patients with first-line chemotherapy without combination of EGFR inhibitors (e.g., TKIs or monoclonal antibodies) or other agents potentially targeting the EGFR pathway (e.g., multitargeted antiangiogenic TKIs) in patients with local advanced or metastatic (IIIB or IV) NSCLC; (II) prior neoadjuvant or adjuvant chemotherapy in patients with recurrence after surgery was permitted if it had elapsed from last administration to relapse at least 6 months; (III) EGFR mutation analysis was performed on available tumor tissue samples instead of circulating free DNA in serum in first-line chemotherapy treatment cohort; (IV) at least one primary outcomes was available. Studies failed to meet the inclusion criteria will be excluded.

Outcomes measures, data extraction and quality assessment

Primary outcomes for this meta-analysis were objective response rate (ORR), namely partial response (PR) plus complete response (CR), and 6-month progression-free survival (PFS) rate. The data collection and assessment of methodological quality followed the QUORUM and the Cochrane Collaboration guidelines (http://www.cochrane.de). The data on study type, treatment regimens, major clinical features, ORR and 6-month PFS rate were extracted by two investigators (FW and PH) independently. Figures were electronically digitized and Kaplan-Meier curves were downloaded by appropriate software (Engauge Digitizer, ver 2.12, Mark Mitchell, 2002, free software down loaded from http://sourceforge.net). Two reviewers (SW and DQ) used a JADAD score to evaluate the quality of randomized controlled trials (RCTs) and a modified Newcastle-Ottawa scale to assess the quality of non-RCT studies (13). Discrepancies were discussed by all investigators to reach consensus.

Statistical analysis

In consideration of any potential heterogeneity, we conducted this meta-analysis with a random-effect model in order to avoid any potential heterogeneity. The results were reported as pooled odds radios (ORs) with the corresponding 95% confidence interval (CI). Subgroup and sensitivity analysis were stratified for literature type, EGFR mutation analysis method, therapeutic regimen, patient

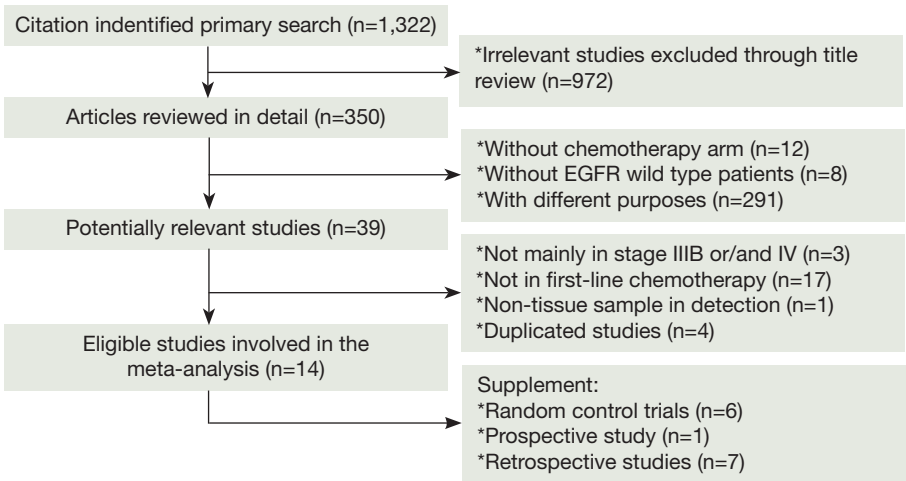

Figure 1 Profile summarizing the trial flow.

origins. An OR greater than one reflected a better ORR or 6-month PFS rate in the EGFR mutant arm. Statistical heterogeneity across studies was assessed with a forest plot and the inconsistency statistic (I^2). Statistical significance was considered at P<0.05. All calculations were performed using REVIEW MANAGER (version 5.0 for Windows; the Cochrane Collaboration, Oxford, UK).

Publication bias

An extensive search strategy was made to minimize the potential for publication bias. Graphical funnel plots were generated to visually assess a publication bias (14). The statistical methods to detect funnel plot asymmetry were the rank correlation test of Begg and Mazumdar and the regression asymmetry test of Egger (14,15).

Results

Eligible studies

We identified 1,322 records according to the search strategy and finally included 14 studies (six RCTs, one prospective study and seven retrospective studies) involving 1,772 advanced NSCLC patients who had been tested for EGFR mutations in first-line chemotherapy treatment cohort (9-12,16-25). *Figure 1* summarized the flow chart. Among these studies, chemotherapy regimens were platinum-based doublets at standard dose, namely cisplatin/carboplatin plus one of the third generation agents (including gemcitabine, paclitaxel, docetaxel, vinorelbine, and pemetrexed), or some non-platinum based regimens. Regimens were not specific in five retrospective studies (10,21-24) so that they were excluded in subgroup analysis stratified for therapeutic regimen. Detecting approaches for EGFR mutation included direct sequencing, nested polymerase chain reaction (PCR), amplification refractory mutation system (ARMS), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP); real time-quantitative PCR (RT-qPCR), denaturing high-performance liquid chromatography (DHPLC), which were also a sub-grouping factor. We considered time to progression (TTP) as PFS in studies by Eberhard (11) and Lee (21). *Table 1* summarized the characteristics of all involved studies.

Objective response rate and six-month PFS rate

According to all literature with available data, patients with positive EGFR mutation had higher pooled ORR than wild type patients (35.8% *vs.* 30.1%), but there was no significant difference between the two groups (OR 1.24, 95% CI, 0.90 to 1.70; P=0.19; heterogeneity: Chi^2 =17.47, P=0.13, I^2 =31%; *Figure 2A*). Subgroup analyses stratified by study type (RCT *vs.* non-RCT), EGFR mutation detecting method (direct sequencing *vs.* non-sequencing methods), therapeutic regimen (gemcitabine-based *vs.* non-gemcitabine-based regimens and cisplatin-based *vs.* carboplatin-based regimens) and patient origin (Asians *vs.* non-Asians) consistently revealed no significant difference between the mutant group and wild type group (*Table 2*). EGFR mutants had higher 6-month PFS rate than wild type patients (62.1%

Table 1 Characteristics of included studies

Lead author [year]	Country	Study category (phase)	Therapeutic regimen [cases in total]	Age, median [range] [y]	Female (%)	Non-smoker (%)	Adenocarcinoma (%)	Evaluable cases for EGFR mutation	EGFR mutation analysis method	EGFR exons identified as mutant	EGFR mutation status	ORR (%)	Six-month PFS rate (%)
David A. Eberhard [2005]	USA	RCT (III)	Paclitaxel 200 mg/m^2 BSA, d1, q3w + carboplatin (AUC =6), d1, q3w ×6 cycles [540]	NA	100 (18.5)	20 (3.7)	105 (19.4)	113	Nested PCR	18, 19, 20, 21	Positive	3/14 (21.4)	10/14 (71.43)
											Negative	27/99 (27.3)	78/99 (78.79)
Tony S. Mok [2009]	Asia	RCT (III)	Paclitaxel 200 mg/m^2 BSA, d1, q3w + carboplatin (AUC =5-6) d1, q3w ×6 cycles [608]	57.0 [25-84]	481 (79.1)	569 (93.6)	591 (97.2)	214	DxS ARMS	18, 19, 20, 21	Positive	61/129 (47.3)	64/129 (49.61)
											Negative	20/85 (23.5)	35/85 (41.18)
Shirin Khambata-Ford [2010]	USA	RCT (III)	Paclitaxel 225 mg/m^2 BSA or docetaxel 75 mg/m^2 BSA, d1, q3w + carboplatin (AUC =6) d1, q3w ×6 cycles [338]	65.0 [34-85]	134 (39.6)	25 (7.4)	NA	87	Direct sequencing	18, 19, 20, 21	Positive	1/9 (11.1)	7/9 (77.78)
											Negative	17/78 (21.8)	25/78 (32.05)
Ji-Youn Han [2012]	Asia	RCT (III)	Gemcitabine 1,250 mg/m^2 on d1 and 8+ cisplatin 80 mg/m^2 on d1 q3w × ≤9 cycles [150]	56.5 [19-74]	134 (89.3)	150 (100.0)	NA	43	Direct sequencing	19, 20, 21	Positive	6/16 (37.5)	9/16 (56.25)
											Negative	14/27 (51.9)	15/27 (55.56)
Cesare Gridelli [2012]	International	RCT (III)	Gemcitabine 1,200 mg/m^2 BSA, d1, 8, q3w + cisplatin 80 mg/m^2 BSA, d1, q3w × ≤6 cycles [380]	62.0 [34-81]	128 (33.7)	79 (20.8)	212 (55.8)	137	PCR-RFLP	19, 21	Positive	5/20 (25.0)	14/20 (70.00)
											Negative	NA/117 (NA)	45/117 (38.46)
Yi-Long Wu [2013]	Asia	RCT (III)	Gemcitabine 1,250 mg/m^2 BSA, d1, 8, q4w + carboplatin (AUC =5) or cisplatin 75 mg/m^2 BSA, d1, q4w + placebo d15-28, q4w ×6 cycles [225]	57.3 [37-88]	85 (38.0)	107 (48.0)	168 (75.0)	115	RT-qPCR	18, 19, 21	Positive	7/48 (14.6)	27/48 (56.25)
											Negative	13/67 (19.4)	26/67 (38.81)
Yuko Kawano [2013]	Japan	Prospective (II)	Pemetrexed 500 mg/m^2 BSA, d1, q3w + cisplatin 75 mg/m^2, d1, q3w × ≤4 cycles [50]	60.0 [28-74]	14 (28.0)	14 (28.0)	41 (82.0)	33	RT-qPCR	19, 21	Positive	6/9 (66.7)	3/9 (33.33)
											Negative	11/24 (45.8)	5/24 (20.83)
Kyung-Hun Lee [2006]	Korea	Retrospective	Platinum-based regimen [75]	NA	NA	NA	NA	75	Direct sequencing	18, 19, 21	Positive	6/14 (42.9)	11/14 (78.57)
											Negative	21/61 (34.4)	31/61 (50.82)
Katsuyuki Hotta [2007]	Japan	Retrospective	Platinum-based regimen [35] or non-platinum-based regimen [19]	NA	NA	NA	NA	54	Direct sequencing	19, 21	Positive	3/14 (21.4)	7/14 (45.80)
											Negative	6/40 (15.0)	9/40 (21.90)

Table 1 (*continued*)

Table 1 (*continued*)

Lead author [year]	Country	Study category (phase)	Therapeutic regimen [cases in total]	Age, median [range] [y]	Female (%)	Non-smoker (%)	Adenocarcinoma (%)	Evaluable cases for EGFR mutation	EGFR mutation analysis method	EGFR exons identified as mutant	EGFR mutation status	ORR (%)	Six-month PFS rate (%)
Meina Wu [2009]	China	Retrospective	Platinum-based regimen [132] or non-platinum-based regimen [13]	61.0 [21-78]	66 (45.5)	NA	106 (73.1)	145	DHPLC	19, 21	Positive	19/55 (34.5)	NA
											Negative	30/90 (33.3)	NA
Aristea Kalikaki [2010]	Greece	Retrospective	Platinum-based regimen [79]	NA	30 (23.4)	39 (30.5)	96 (75.0)	79	Direct sequencing	18, 19, 20, 21	Positive	5/8 (62.5)	NA
											Negative	17/71 (23.9)	NA
			Non-platinum-based regimen [49]					49			Positive	0/1 (-)	NA
											Negative	9/48 (18.8)	NA
Jin Hyun Park [2012]	Korea	Retrospective	Gemcitabine + cisplatin/carboplatin [131]	59.0 [26-82]	120 (55.3)	144 (66.4)	174 (80.2)	131	RT-qPCR	18, 19, 20, 21	Positive	26/85 (30.6)	23/85 (27.06)
											Negative	16/46 (34.8)	13/46 (28.26)
			Paclitaxel + cisplatin/carboplatin [86]					86			Positive	20/52 (38.5)	25/52 (48.08)
											Negative	12/34 (35.3)	15/34 (44.12)
M. Takeda [2012]	Japan	Retrospective	Platinum-based regimen [200]	63.0 [29-81]	73 (36.5)	65 (32.5)	178 (89.0)	182	ARMS/the PCR-Invader method	NA	Positive	14/31 (45.2)	16/31 (51.61)
											Negative	59/151 (39.1)	57/151 (37.75)
Xiao-Peng Dong [2013]	China	Retrospective	Gemcitabine + cisplatin [81]	57.0	17 (42.5)	57	24 (60.0)	81	Direct sequencing	18, 19, 20, 21	Positive	13/40 (32.5)	36/40 (90.00)
				61.0	19 (46.3)	61	21 (51.2)				Negative	13/41 (31.7)	35/41 (85.37)
			Docetaxel + cisplatin [77]	62.0	19 (43.2)	62	24 (54.5)	77			Positive	16/44 (36.4)	42/44 (95.45)
				58.0	15 (45.5)	58	19 (57.6)				Negative	12/33 (36.4)	28/33 (84.85)
			Vinorelbine + cisplatin [71]	60.0	16 (44.3)	60	22 (61.1)	71			Positive	13/36 (36.1)	35/36 (97.22)
				63.0	16 (45.7)	63	20 (57.1)				Negative	13/35 (37.1)	26/35 (74.29)

RCT, random control trial; AUC, area under the concentration time curve; BSA, body-surface area; ADK, adenocarcinoma; EGFR, epidermal growth factor receptor; ORR, objective response rate; TTP, time to progression; PFS, progression-free survival; PCR, polymerase chain reaction; ARMS, amplification refractory mutation system; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; RT-qPCR, real time-quantitative PCR; DHPLC, denaturing high-performance liquid chromatography; NA, not available.

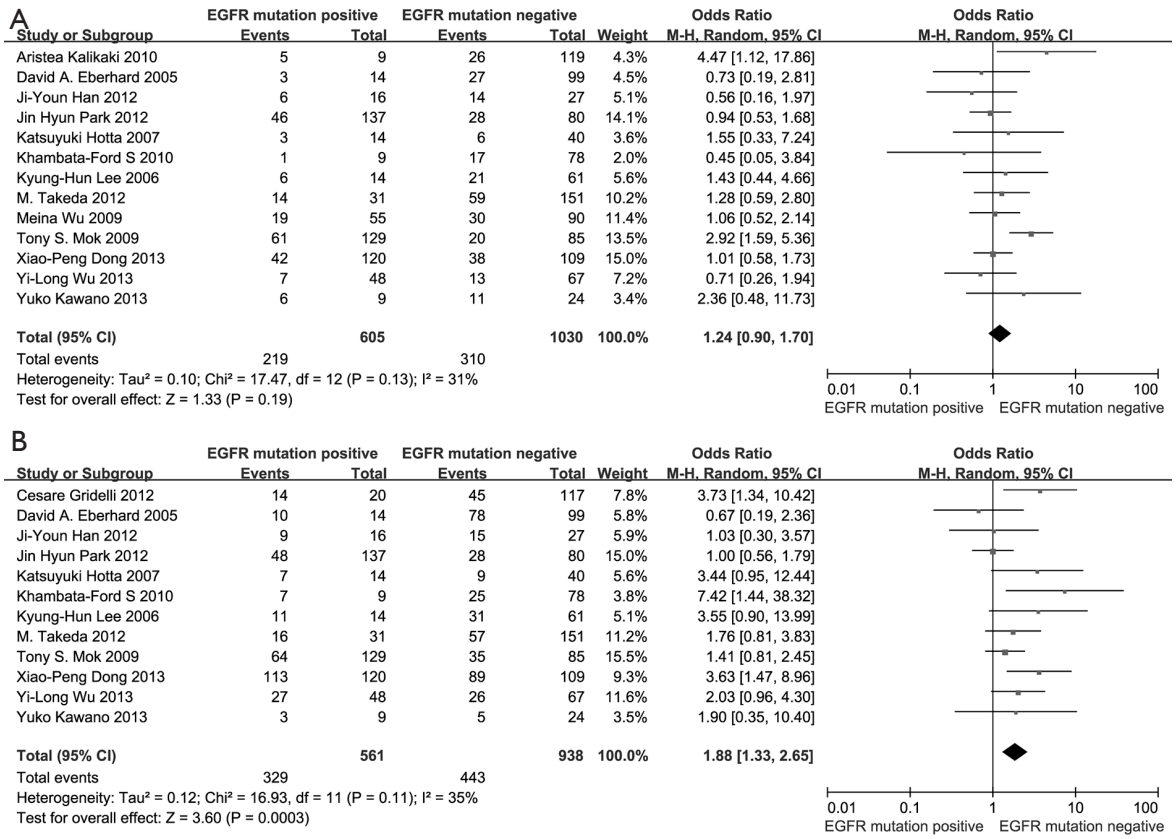

Figure 2 (A) Meta-analysis on objective response rate among advanced NSCLC patients receiving first-line chemotherapy according to EGFR mutation status; (B) meta-analysis on 6-month PFS rate among patients receiving first-line chemotherapy according to EGFR mutation status. NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; PFS, progression-free survival; CI, confidence interval; I^2, inconsistency statistic.

vs. 45.1%) with significance (OR 1.88, 95% CI, 1.33-2.65; P=0.0003; heterogeneity: Chi^2 =16.93, P=0.11, I^2 =35%; *Figure 2B*). Subgroup analyses also revealed similar tendency of significantly superior 6-month PFS of EGFR mutants, regardless of study types, methods of EGFR mutation detection, chemotherapy regimens and patient origins (*Table 3*). Additionally, we pooled the results of DCR although only five studies reported this data. No differences between EGFR mutation positive and negative groups were observed (OR 1.33, 95% CI, 0.93-1.91; P=0.11; heterogeneity: Chi^2 =2.23, P=0.69, I^2 =0%; *Figure 3*).

Assessment of heterogeneity and publication bias

As described above, the statistical heterogeneity was moderate. Any potential clinical heterogeneity was examined and subsequently excluded by subgroup analyses. In addition, sensitivity analysis by leaving any study out did not alter the general results. There was no publication bias for both outcome measures, with asymmetrical appearance on funnel plot analysis (*Figure 4*) and all P values greater than 0.05 in Begg's test and Egger's test.

Discussion

The association of EGFR mutation status with the responsiveness or prognosis in patients with advanced NSCLC after first-line chemotherapy was controversial based on previous small-size reports. A meta-analysis that could incorporate all available results, including subgroup data from RCTs as well, is a good way to address our concerns. In the current study, we found that 6-month PFS rate was significantly higher in EGFR mutants than in wild type patients after first-line chemotherapy, while the ORR and DCR appeared to be higher but the difference did not reach significance. These results admit of two

Table 2 Subgroup analysis on objective response rate among advanced NSCLC patients receiving first-line chemotherapy according to EGFR mutation status

Categories of included studies	Number of included studies	Objective response rate (event/total)		Test of heterogeneity			Test of effect size	
		EGFR mutation positive	EGFR mutation negative	Chi^2	P value	I^2 (%)	OR (95% CI)	P value
Total	13	219/605	310/1,030	17.47	0.13	31	1.24 (0.90-1.70)	0.19
Literature type								
Random control trial	5	78/216	91/356	11.36	0.02	65	0.97 (0.41-2.29)	0.94
Non-random control trial	8	141/389	219/674	5.56	0.59	0	1.17 (0.88-1.56)	0.28
EGFR mutation analysis method								
Direct sequencing method	6	63/182	122/434	6.20	0.29	19	1.17 (0.70-1.96)	0.56
Non-direct sequencing methods[1]	7	156/423	188/596	10.95	0.09	45	1.27 (0.83-1.95)	0.28
Therapeutic regimen								
Gemcitabine based regimens	4	52/189	56/181	0.67	0.88	0	0.80 (0.50-1.28)	0.36
Non-gemcitabine based regimens	6	120/293	112/388	9.11	0.10	45	1.36 (0.78-2.38)	0.28
Therapeutic regimen								
Cisplatin based regimens	3	54/145	63/160	1.93	0.38	0	1.00 (0.62, 1.61)	0.99
Carboplatin based regimens	3	65/152	64/262	5.49	0.06	64	1.27 (0.38, 4.32)	0.70
Patient origin								
Asia	10	210/573	240/734	12.72	0.18	29	1.22 (0.89-1.68)	0.21
Non-Asia area	3	9/32	70/296	4.75	0.09	58	1.27 (0.31-5.20)	0.74

[1]Non-direct sequencing methods included Nested PCR, ARMS, PCR-RFLP, RT-qPCR, and DHPLC. NSCLC, non-small-cell lung cancer; PCR, polymerase chain reaction; ARMS, amplification refractory mutation system; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; RT-qPCR, real time-quantitative PCR; DHPLC, denaturing high-performance liquid chromatography; EGFR, epidermal growth factor receptor; I^2, inconsistency statistic; OR, odds radio; CI, confidence interval.

Table 3 Subgroup analysis on six-month PFS rate among advanced NSCLC patients receiving first-line chemotherapy according to EGFR mutation status

Categories of included studies	Number of included studies	Six-month PFS rate (event/total)		Test of heterogeneity			Test of association	
		EGFR mutation positive	EGFR mutation negative	Chi^2	P value	I^2 (%)	OR (95% CI)	P value
Total	12	329/561	443/938	16.93	0.11	35	1.88 (1.33-2.65)	0.0003
Literature type								
Random control trial	6	131/236	224/473	8.74	0.12	43	1.80 (1.06-3.05)	0.0300
Non-random control trial	6	198/325	219/465	8.18	0.15	39	2.01 (1.20-3.36)	0.0080
EGFR mutation analysis method								
Direct sequencing method	5	147/173	169/315	4.27	0.37	6	3.04 (1.73-5.37)	0.0001
Non-direct sequencing methods[1]	7	182/388	274/623	7.37	0.29	19	1.50 (1.07-2.11)	0.0200
Therapeutic regimen								
Gemcitabine[2] based regimens	5	109/209	134/298	5.16	0.27	23	1.63 (0.99-2.68)	0.0500
Non-gemcitabine[3] based regimens	6	186/293	212/388	10.66	0.06	53	1.88 (0.97-3.62)	0.0600
Therapeutic regimen								
Cisplatin based regimens	4	178/286	167/330	3.26	0.35	8	2.61 (1.44, 4.71)	0.0020
Carboplatin based regimens	3	81/152	138/262	5.27	0.07	62	1.65 (0.59, 4.65)	0.3400
Distribution area of patients								
Asia	9	298/518	295/644	9.46	0.31	15	1.71 (1.25-2.33)	0.0008
Non-Asia area	3	31/43	148/294	6.48	0.04	69	2.53 (0.66-9.63)	0.1700

[1]Non-direct sequencing methods included Nested PCR, ARMS, PCR-RFLP, RT-qPCR, and DHPLC; [2]We defined gemcitabine + platinum-based regimen as gemcitabine + cisplatin/carboplatin; [3]We defined non-gemcitabine + platinum-based regimen as taxane/paclitaxel/docetaxel + cisplatin/carboplatin or vinorelbine/pemetrexed + cisplatin. NSCLC, non-small-cell lung cancer; PCR, polymerase chain reaction; ARMS, amplification refractory mutation system; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; RT-qPCR, real time-quantitative PCR; DHPLC, denaturing high-performance liquid chromatography; EGFR, epidermal growth factor receptor; PFS, progression-free survival; I^2, inconsistency statistic; OR, odds radio; CI, confidence interval.

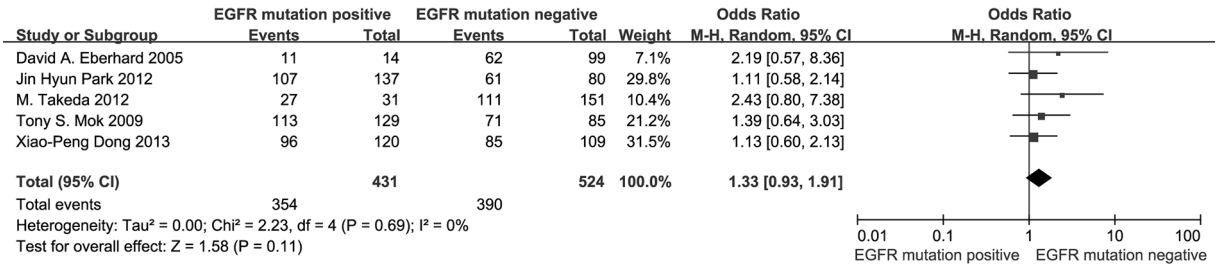

Figure 3 Meta-analysis on disease control rate among advanced NSCLC patients receiving first-line chemotherapy according to EGFR mutation status. NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; CI, confidence interval; I^2, inconsistency statistic.

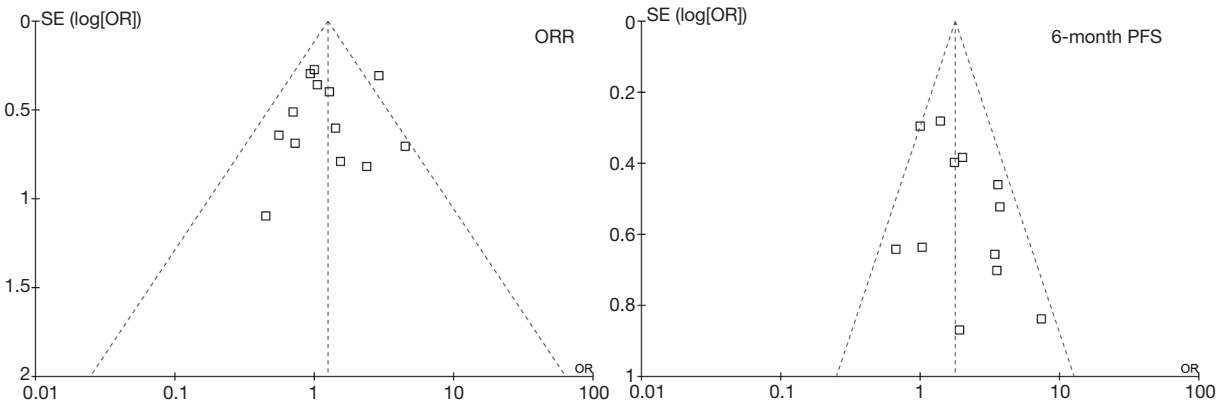

Figure 4 Funnel plots of ORR and 6-month PFS. OR, odds radio; ORR, objective response rate; PFS, progression-free survival.

interpretations.

Firstly, EGFR mutation might indeed be a predictor to the efficacy of cytotoxic chemotherapy. Activation of EGFR-dependent pathway plays an important role in the proliferation and aggressive phenotype transition of epithelial cells especially EGFR-mutated tumors (26,27). Moreover, a prior research indicated that a critical level of EGFR signaling was necessary for cisplatin-mediated apoptosis in tumor cells and suggested an inhibitory effect of this pathway on the repair of cisplatin-damaged DNA (28). Therefore, it was reasonable to hypothesize that tumor cells harboring EGFR mutation are more sensitive to cytotoxic chemotherapy. The hypothesis for selective killing of EGFR+ cells was supported by a clinical observation which showed a reduced plasma EGFR mutation frequency after chemotherapy in patients with NSCLC (29). By selectively eliminating or suppressing the 'seeds', tumor growths were persistently restricted, which translated into prolonged PFS as our result indicated. On the other hand, EGFR mutants did have higher pooled response rate although the magnitude of benefit was not as great as that of PFS. We suspected that the magnitude difference was attributed to the intratumoral heterogeneity. A recent study demonstrated that approximately 30% of patients presented intratumoral EGFR mutational heterogeneity through microdissection of the tumor samples (30). Therefore, tumors detected as EGFR mutated not necessarily contain pure EGFR+ cells. In other words, the intratumoral abundace of EGFR+ cells might be small in some patients. Thus, selective killing of EGFR+ cells was probably not associated with significant tumor shrinkage. As a result, patients intrinsically 'responded' to the chemotherapy might fail to meet the criteria for ORR (at least a 30% decrease in the sum of diameters of target lesions) according to Recist 1.1 criteria (31). However, direct evidence to confirm this mechanism requires real-time re-biopsy after treatments, which seems to be an impossible mission considering ethics. Secondly, we can not rule out the possibility that the improved PFS was merely the underlying prognostic effect of EGFR mutation since there was evidence showing that EGFR mutation was likely to be a favorable prognostic factor (32). However, the prognostic value of EGFR

mutation itself in NSCLC was still controversial (33).

Nonetheless, regardless of what the true causes are, this comprehensive analysis confirmed the association between EGFR mutation and PFS. This was highly concordant with an important report this year that among the patients treated with non-targeted therapy, those with a driver mutation detected had a longer median overall survival than those without identified driver mutations (2.4 *vs*. 2.1 years) (34). All these results gave us some important hints. Firstly, we strongly suggested that investigators should consider the proportion of EGFR mutation patients as a stratification factor in designing or reviewing clinical studies regarding chemotherapy regimen or other non-targeted agents. Second, it might partially explain why some clinical trials on chemotherapy in Asia reported higher response rate than those in Europe-American, and similarly, explain the negative results of combination of gefitinib with chemotherapy in patients with EGFR mutation compared with chemotherapy alone in some previous studies (35). In addition, the response to chemotherapy in EGFR wild type patients or projectively driven mutation 'pan-negative' patients was worse than what we acknowledged. Therefore, more efforts should be made to improve the prognosis of this population.

Notably, we only focused on first-line chemotherapy in this analysis in order to minimize the crossover effects. Some previous investigations suggested an inferior response from EGFR-TKIs following treatment of chemotherapy (36). Consistently, the study by Bai *et al*. also showed that the overall incidence of EGFR mutation was lower in plasma DNA after first-line chemotherapy (29). Thus, getting second-line or third-line chemotherapy involved will tangle the discussion.

This is the first study to comprehensively answer the impact of EGFR mutation on chemotherapy, addressing the confusion from inconsistent conclusions of current studies. However, there are several limitations. First, our meta-analysis was based on non-randomized studies and sub-group data extracted from RCTs, which somehow compromised the evidence level. Second, EGFR exons identified as mutant were heterogeneous among included articles but we were unable to assess whether 19 or 21 exon alterations had different impact on chemotherapy. Finally, we failed to investigate different first-line regimens separately with limited data. In addition, we cannot differentiate the respective impact of EGFR mutation on cell-cycle nonspecific antineoplastic agents (platinum) and specific agents (third-generation agents). For clinical practice, after all, it is essential to determine the optimal regimen for EGFR mutant NSCLC patients, especially who have failed front-line EGFR-TKIs or have no access to these agents. Further studies are warranted.

In conclusion, this meta-analysis showed that advanced NSCLC patient with EGFR mutation had significantly higher 6-month PFS rate and potentially higher ORR than wild type patients after first-line chemotherapy. We suggest that EGFR mutation status should be considered a stratification factor not only in studies regarding EGFR-targeted agents but also in those regarding non-EGFR-targeted drugs.

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