



The impact of epidermal growth factor receptor mutations on the prognosis of resected non-small cell lung cancer: a meta-analysis of literatures

Qihua He^{1,2#}, Peiling Xin^{3#}, Mingzhe Zhang⁴, Si Jiang⁵, Jianrong Zhang⁶, Shengyi Zhong⁷, Yang Liu^{1,2}, Minzhang Guo^{1,2}, Xuwei Chen^{1,2}, Xiaojun Xia^{1,2}, Zhenkui Pan⁸, Chenye Guo⁸, Xiuyu Cai⁹, Wenhua Liang^{1,2}, Jianxing He^{1,2}

¹Department of Thoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510000, China; ²Guangzhou Institute of Respiratory Disease & China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, Guangzhou 510120, China; ³Department of Radiation Oncology, ⁴Department of Cardiology, First Hospital of Quanzhou Affiliated to Fujian Medical University, Quanzhou 362000, China; ⁵Department of Ultrasound, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510000, China; ⁶George Warren Brown School, Washington University in St. Louis, St. Louis, USA; ⁷Department of Cardiothoracic Surgery, Xianning Central Hospital, Xianning 437000, China; ⁸Department of Oncology, Qingdao Municipal Hospital, Qingdao 266000, China; ⁹Department of General Medicine, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510000, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: W Liang, J He; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Q He, P Xin; (V) Data analysis and interpretation: M Zhang, S Jiang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Wenhua Liang; Jianxing He. Department of Thoracic Surgery and Oncology, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510000, China; Guangzhou Institute of Respiratory Disease & China State Key Laboratory of Respiratory Disease, No. 151, Yanjiang Rd, Guangzhou 510120, China. Email: liangwh@gird.cn; drjianxing.he@gmail.com.

Background: Epidermal growth factor receptor (EGFR) mutation represents a good response to EGFR-tyrosine kinase inhibitor and an advantageous prognostic factor in advanced-stage non-small cell lung cancer (NSCLC). However, the predictive value of EGFR mutation for prognosis in NSCLC patients after complete surgery, which more reflective of natural process, remains controversial. We sought to examine the predictive value of EGFR mutation in NSCLC. Several studies with small sample sizes have been reported but small studies bring bias especially in a postoperative setting. Therefore, we sought to pool all current evidence to show the true effects.

Methods: Electronic databases were used to search the relevant articles. Disease-free survival (DFS), which will be less effected by subsequent treatments after recurrence, was the primary endpoint. The DFS between EGFR mutated and wild-type patients were compared focus on stage I patients who are rarely received adjuvant therapy. Besides, the DFS of patients with 19 exon deletion (19del) and 21 exon L858R mutation (L858R) were compared. A random effects model was used.

Results: A total of 19 relevant studies which involved 4,872 cases were enrolled and 2,086 patients were EGFR-mutated. The majority of studies used PCR-based methods to detect EGFR mutations. Through meta-analysis, we observed the DFS of EGFR-mutated patients were similar to wild type patients in overall population (HR 0.93, 95% CI: 0.74 to 1.17). Similar results were observed in stage I subgroup (HR 0.82, 95% CI: 0.50 to 1.33). DFS of 19 del patients were potentially inferior to L858R patients but the difference was not significant (HR 1.38, 95% CI: 0.76 to 2.52).

Conclusions: There was no significant difference in postoperative DFS between EGFR-mutant patients and wild-type with resected NSCLC. In addition, there is still insufficient evidence to support different postoperative treatment strategies (especially for stage I) for both mutated and wild-type patients. However, 19 del may be a negative factor, which may require more strict management. Thus, we strongly encourage

reporting specific prognostic impacts of different mutation types.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor mutation (EGFR mutation); disease-free survival (DFS); meta-analysis

Submitted Jun 14, 2018. Accepted for publication Mar 20, 2019.

doi: 10.21037/tlcr.2019.03.14

View this article at: <http://dx.doi.org/10.21037/tlcr.2019.03.14>

Introduction

Primary lung cancer has become the leading cause of cancer-related death in both male and female populations in most part of the world (1). Non-small cell lung cancer (NSCLC) which predominantly consists of adenocarcinoma, squamous cell carcinoma and large cell carcinoma, accounts for 80–85% of all lung cancer cases (2). Complete surgical resection is the gold standard treatment of early-stage NSCLC. However, even patients with completely resected stage IA NSCLC have a 5-year mortality rate of approximately 30% (3). A meta-analysis which was composed of 52 randomized clinical trials and included 9,387 cancer patients concluded that adjuvant chemotherapy only reduced 13% of the risk mortality in the first year and suggested a considerable number of patients do not benefit from adjuvant chemotherapy (4). It is important to identify high-risk patients for poor outcome with adjuvant chemotherapy and find other adjuvant therapies that can improve survival in this population. Previous studies regarding the prognostic factor of lung cancer focus on the clinical features and gene expression (5–7). In recent years, the discovery of oncogenic driver mutations have led to the emergence of a new therapeutic strategy in lung cancer. Furthermore, different oncogenic driver mutations have exhibited a tendency to correlate with different biological behaviors which suggests that some clinical findings need to be reconsidered. Epidermal growth factor receptor (EGFR) is a crucial mutation that the frequency of which ranges from 15% to 44% in East Asian patients with adenosquamous lung carcinoma.

EGFR, a 170-kDa receptor tyrosine kinase (TK), plays a critical role in promoting cell division, migration, angiogenesis and inhibits apoptosis (8). The exon 19 deletion and exon 21 L858R mutations are the most common EGFR mutations which account for 85–90% of all EGFR mutation cases (9,10). EGFR mutation is associated with advantageous clinical outcomes in patients with advanced NSCLC, predominantly as a result of its favorable response to EGFR-tyrosine kinase inhibitors (11,12). In

addition to their important role in the planning of treatment strategies for advanced or recurrent NSCLC, EGFR mutations have intrinsic impact on the prognosis (13). However, its impact on the prognosis of resectable NSCLC after complete surgery remains controversial. To elucidate the prognostic value of EGFR mutation status, we attempted to conduct a meta-analysis of all available evidence to assess the correlation between EGFR mutations and prognosis in surgically resected lung cancer.

Methods

Literature search

Relevant studies were retrieved by searching PubMed, Embase and the Central Registry of Controlled Trials of the Cochrane Library, using the following terms: “EGFR mutation” AND “disease-free survival” AND Resected OR resectable OR Prognosis. The last research time was May 6, 2017. Language was restricted to Chinese and English. In addition, a manual search through reference lists of relevant reviews and included studies were conducted. The search was carried out independently by two authors.

Inclusion criteria and Exclusion criteria

The following criteria was used to select publications: (I) studies assessed the correlation between disease-free survival (DFS) and EGFR status in resectable NSCLC after complete surgery; (II) all patients had never been treated with EGFR-TKI; (III) the available tumor tissue samples instead of circulating free DNA in serum were used to analyze the EGFR mutations; (IV) studies needs to be in English or Chinese in spite of publication time. Studies that fail to meet all above criteria were excluded from analyses.

Data collection

The primary outcome of our study was progression-free

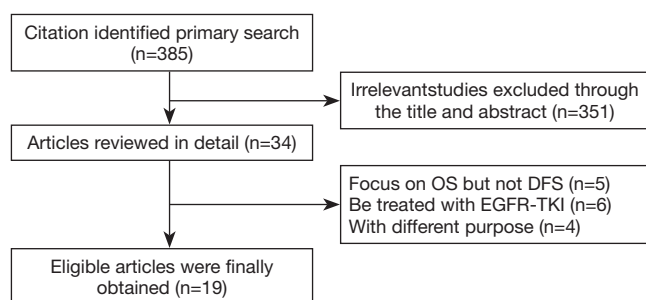


Figure 1 Profile summarizing the trial flow.

survival (PFS). Publication characteristics details such as first author's name, publication year, tumor type, sample size, EGFR status, stage, evaluation method of EGFR mutation status was extracted by two independent investigators. Any disagreement was discussed amongst investigators to reach consensus. Only univariate analysis results were used when both univariate and multivariate analysis results were supplied in a study as the most of included studies were univariate analysis. We used the data directly when the included studies provided precise HR (95% CI). In the case of the studies only provided Kaplan-Meier survival curves, Engage Digitizer version 2.11 software was used to extract relevant numerical value from survival curves and calculate the HR (95% CI) (14,15).

Statistical analysis

The heterogeneity of the individual HR was calculated using Cochran's Q-statistic test and I^2 test. $I^2 < 25\%$ was considered as no heterogeneity, $I^2 = 25\text{--}50\%$ and $I^2 > 50\%$ were considered as moderate heterogeneity and strong heterogeneity respectively (16,17). P value less than 0.05 was considered to be statistical significance. In order to avoid any potential heterogeneity, a random-effects model was used in this meta-analysis. When available, subgroup and sensitivity analysis were stratified for predisposed factors. To assess the strength of the findings, sensitivity analyses were conducted by excluding one study at a time. Egger's test was used to investigate publication bias. All statistical analyses were performed using STATA 11.0 software.

Results

Eligible studies

We identified 385 potentially relevant records through

the search strategy. And 351 studies were excluded after checking the title and abstract, for it was very clear that their research contents didn't meet our inclusion criteria. Then the full texts of 34 articles were carefully screened, and a total of 19 studies (18-36) were eligible for the final analysis. *Figure 1* summarized the flow chart.

Our meta-analysis was composed of 19 studies to include a total of 4,872 cancer patients with no history of EGFR-TKI as adjuvant or neoadjuvant therapy. The period of included studies ranged from 2007 to 2016. The DFS between EGFR mutated and wild-type patients were compared in 18 studies (18-35); 7 of them reported specific data on stage I patients. DFS of patients with 19 exon deletion (19del) and 21 exon L858R mutation (L858R) were compared in 4 studies. *Table 1* summarized the characteristics of all involved studies.

Meta-analysis

According to all literatures with available data, 18 studies consisting of 4,353 patients reported the results on the DFS between EGFR mutated and wild-type patients. As shown in *Figure 2*, the DFS of EGFR-mutated patients were similar to wild type patients in overall population (HR 0.93, 95% CI: 0.74 to 1.17; heterogeneity, $P=0.000$, $I^2=66.8\%$). We conducted subgroup analysis based on information provided by 7 studies (18,21-23,26,33,34). We found that EGFR status had no significant effect on DFS in stage I patients, with the HR of 0.82 (95% CI: 0.50 to 1.33), and obvious heterogeneity existed among them ($I^2=45.4\%$, $P=0.089$; *Figure 3*). There was also no significant difference between patients with EGFR mutation and patients with wild type on DFS in stage II-III patients (HR 0.73, 95% CI: 0.43 to 1.24; heterogeneity, $P=0.002$, $I^2=79.7\%$; *Figure 4*). To avoid the selection bias of the EGFR status, we performed retrospective test subgroup and retrospective review subgroup. And no significant difference was observed in retrospective test subgroup (HR 0.86, 95% CI: 0.65 to 1.15; $P=0.316$; heterogeneity, $P=0.005$, $I^2=59\%$; *Figure 5*) and retrospective review subgroup (HR 1.09, 95% CI: 0.81 to 1.48; heterogeneity, $P=0.002$, $I^2=79.7\%$; *Figure 6*). Additionally, we pooled the results of 19del patients and L858R patients. Four studies composed of 1,471 patients reported this data (19,21,22,36). However, no differences between 19del and L858R groups were observed (HR 1.38, 95% CI: 0.76 to 2.52; heterogeneity: $P=0.062$, $I^2=59.1\%$; *Figure 7*). Additional subgroup analysis was performed since significant heterogeneity was observed

Table 1 Characteristic of the included studies

First author	Year	Tumor type	No. of patients	Mt	Region	Stage	Evaluation
Dong	2013	Adenocarcinoma	301	158	China	Ia–IIIa	Real-time quantitative PCR + DNA sequencing technology
Isaka	2016	Adenocarcinoma	202	100	USA	I–III	Cycleave polymerase chain reaction or loop-hybrid mobility shift assays
Zhi	2016	Adenosquamous	106	29	China	Ia–IIIa	–
Nishii	2017	Adenosquamous	388	185	Japan	I	–
Liu	2014	Adenosquamous	131	58	China	Ia–IIIa	Nested PCR amplification
Izar	2013	NSCLC	317	62	USA	I	Direct sequencing and SNaPshot
Lin	2014	Adenosquamous	163	97	Taiwan	I	PCR
Ragusa	2014	NSCLC	230	22	Italy	Ia–IIIa	DNA Sequencing
Kobayashi	2008	Adenosquamous	127	64	Japan	Ia	PCR
Lim	2007	Adenosquamous	27	15	Taiwan	Ia–IIIa	PCR
Nose	2009	Adenosquamous	393	147	Japan	Ia–IIIa	PCR
Sun	2013	NSCLC	150	43	China	IIIa	PCR
Lee	2009	Adenosquamous	117	53	Korea	Ia–IIIa	Nested PCR amplification
Hayasaka	2017	Adenosquamous	519	519	–	Ia–IIIa	–
Koh	2010	NSCLC	130	–	Korea	I–III	PCR
Tsao	2011	NSCLC	436	393	Canada	Ib–II	PCR
Maki	2013	Adenosquamous	28	7	Japan	Ia	Mutant non-enriched PCR
Ohba	2014	Adenosquamous	242	122	Japan	I	PCR
Kim	2013	NSCLC	865	354	Korea	I–III	Nested PCR

NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction.

in the overall analysis. After stratification by tumor type, no significant difference was observed in adenocarcinoma studies (HR 0.92, 95% CI: 0.77 to 1.11; heterogeneity, $P=0.328$, $I^2=12.2\%$; *Figure 8*) and NSCLC studies (HR 0.90, 95% CI: 0.53 to 1.52; heterogeneity, $P=0.000$, $I^2=82.4\%$; *Figure 9*). *Table 2* summarized the results of all subgroups.

Publication bias

The funnel plot and Egger's test were performed for the overall comparison. No obvious visual asymmetry was observed in funnel plots (*Figure 10*) for DFS, and the P values of the Egger's test were greater than 0.05.

Discussion

Due to the predictive value to EGFR-TKI, EGFR mutation

plays a crucial role in precision medicine. Except for its contribution to predict the response to EGFR-TKI, EGFR mutations are anticipated to have inherent prognostic implication. A prior research indicated that EGFR may be a positive prognostic factor for survival in patients with advanced NSCLC (35). In addition, the effect of EGFR mutations on the prognosis of resected NSCLC has been reported by previous studies, but the results were disputed. A meta-analysis is required to integrate all available results to provide further insight on this controversial issue. Combined with the available data provided by the included studies, our results supported the assumption that EGFR mutations have no prognostic value in complete resected NSCLC, but significant heterogeneity was observed.

A previous study has suggested that the status of EGFR mutations was associated with sensitivity to chemotherapy (37), however, it is difficult to determine the

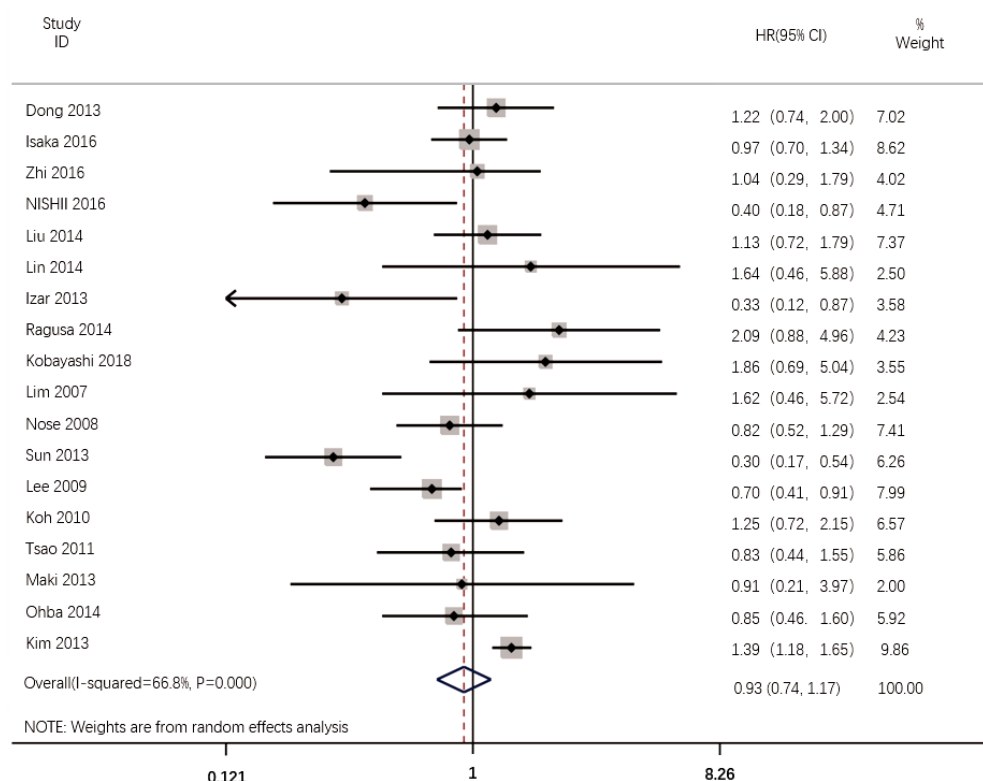


Figure 2 Forest plot of the pooled HRs for DFS by overall population. DFS, disease-free survival; HR, hazard ratio.

prognostic value of EGFR mutations when patients have received adjuvant treatment. Thus, we carried out subgroup analyses in patients with stage I NSCLC who rarely receive adjuvant therapy. Interestingly, our results show that there is no significant difference in DFS between the EGFR-mutated patients and those with wild type in stage I subgroup (HR 0.82, 95% CI: 0.5 to 1.33), which is consistent with the overall result. This result implies that EGFR mutation may not be an independent prognostic factor for DFS.

Our study found no significant difference in DFS between patients with mutant-type EGFR and those with wild-type which is consistent with a previous meta-analysis (38). It suggested that EGFR mutations may merely play a detrimental role in advanced stage and may not have much impact on early stages of NSCLC. However, the population of this study is mixed with significant heterogeneity ($P < 0.01$, $I^2 = 66.8\%$). After carrying out a subgroup analysis by tumor type, we suspect that it was the tumor type that resulted in the heterogeneity.

Several studies have shown that patients with advanced NSCLC harboring Ex19 mutations have better OS than those with Ex21 mutations treated with EGFR-TKI (39-41). Moreover, a prior study showed advanced NSCLC patients

harboring Ex19 mutations have shown better responses to chemotherapy than those with Ex21 deletions (42). Conversely, a recently published study from Tetsuya Isaka (43) reported that Ex21 adenocarcinomas were low grade with a lepidic growth pattern, whereas wild-type tumors were high grade and contained solid and papillary components with vascular invasion; Ex19 tumors were intermediate grade (44). This finding is consistent with the findings of Yang *et al.* (44) which showed that Ex21 adenocarcinomas had a higher ratio of ground-glass opacity than Ex19 tumors (43). In the present study, patients with 19del potentially had inferior DFS to those with L858R but the result did not reach statistical significance (HR 1.38, 95% CI: 0.76 to 2.52). As stated above, we surmise that the result may be confused by chemotherapy which is a subsequent treatment after surgery for patients with stage II-III disease.

Our study gives further evidence to support previous assumptions that EGFR mutations had no impact on the prognosis of resected NSCLC. However, there are several limitations. First, this is a retrospective analysis, prospective analysis is needed to further illustrate these issues. Second, since follow-up time of each study was not the same,

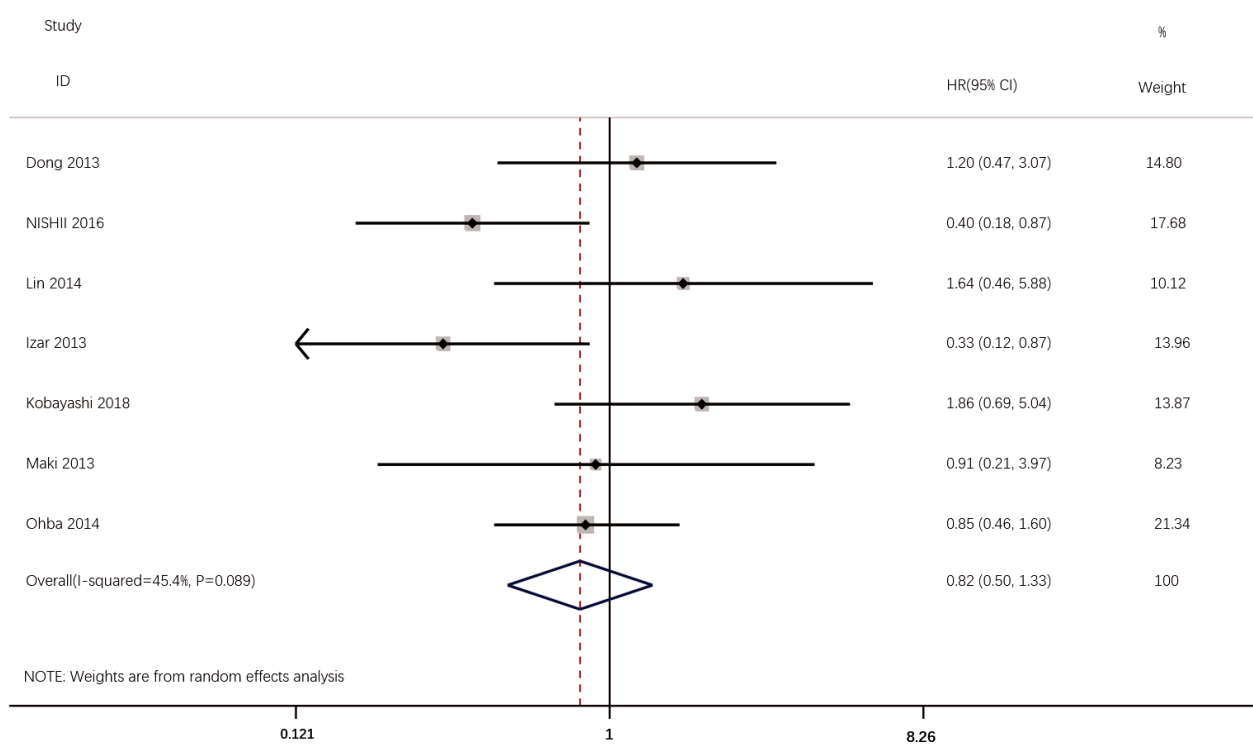


Figure 3 Forest plot of the pooled HRs for DFS by stage I subgroup. DFS, disease-free survival; HR, hazard ratio.

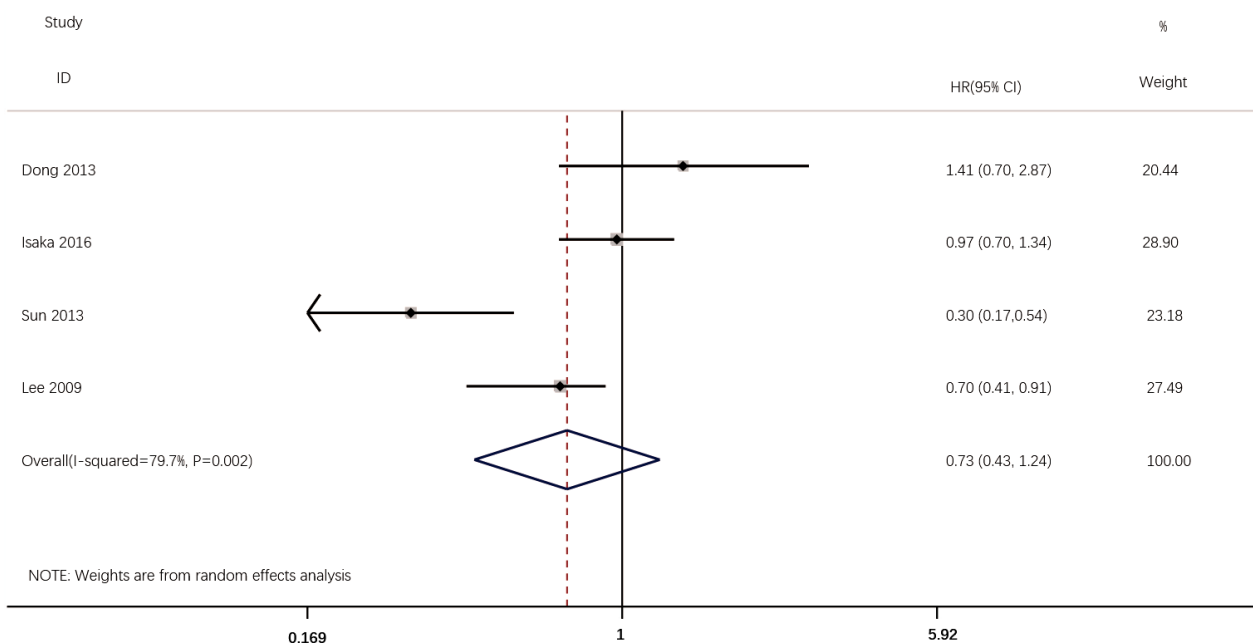


Figure 4 Forest plot of the pooled HRs for DFS by stage II-III subgroup. DFS, disease-free survival; HR, hazard ratio.

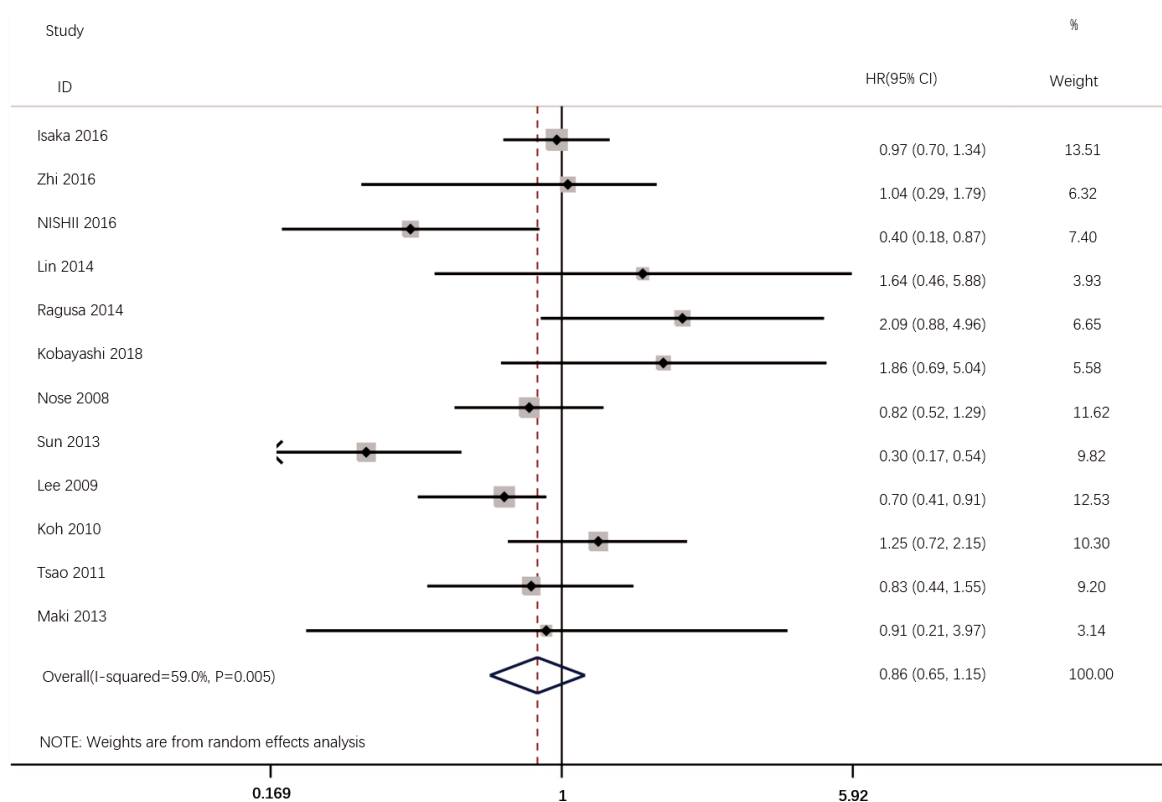


Figure 5 Forest plot of the pooled HRs for DFS by retrospective test EGFR status subgroup. DFS, disease-free survival; HR, hazard ratio; EGFR, epidermal growth factor receptor.

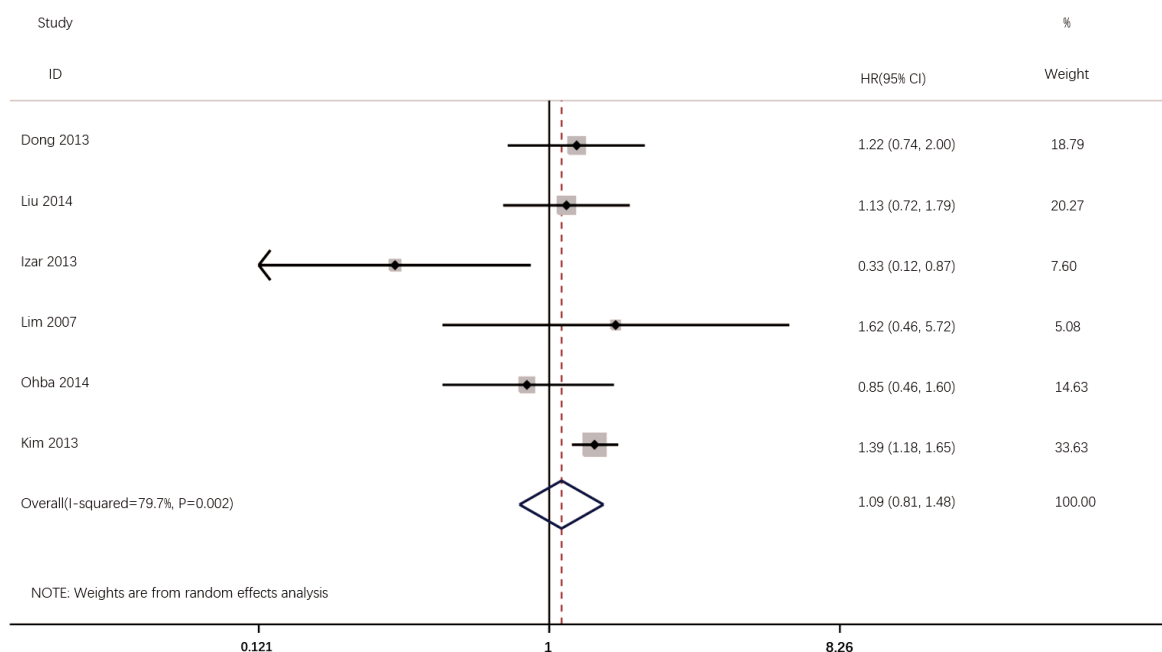


Figure 6 Forest plot of the pooled HRs for DFS by retrospective review EGFR status subgroup. DFS, disease-free survival; HR, hazard ratio; EGFR, epidermal growth factor receptor.

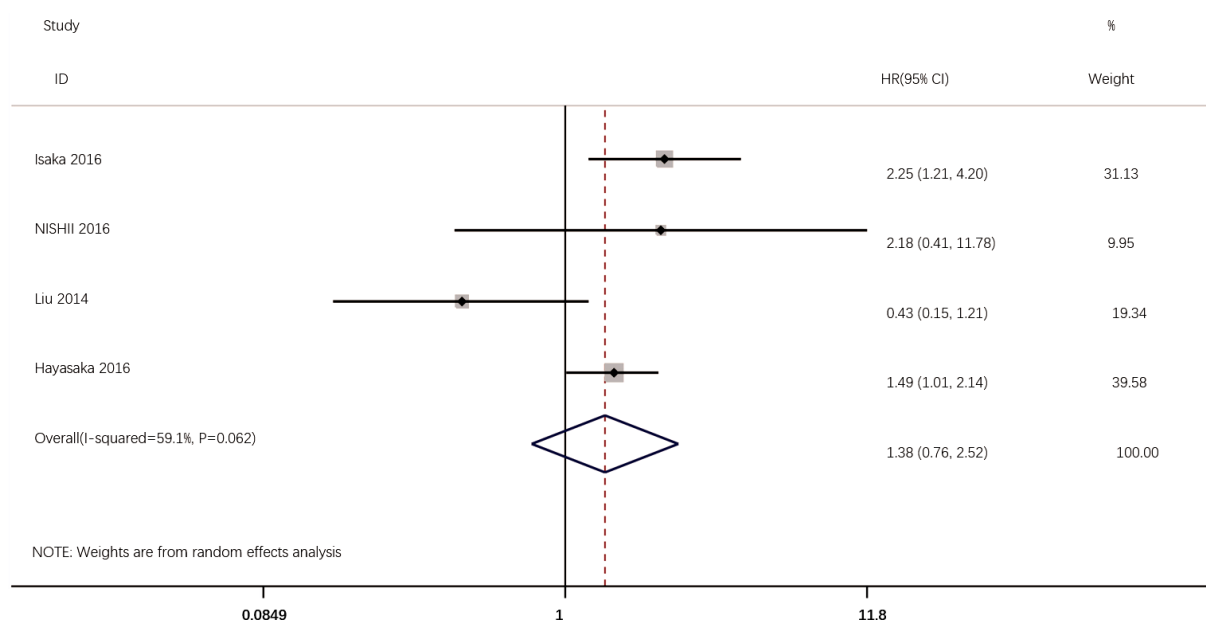


Figure 7 Forest plot of the pooled HRs for DFS by 19del or L858R subgroup. DFS, disease-free survival; HR, hazard ratio.

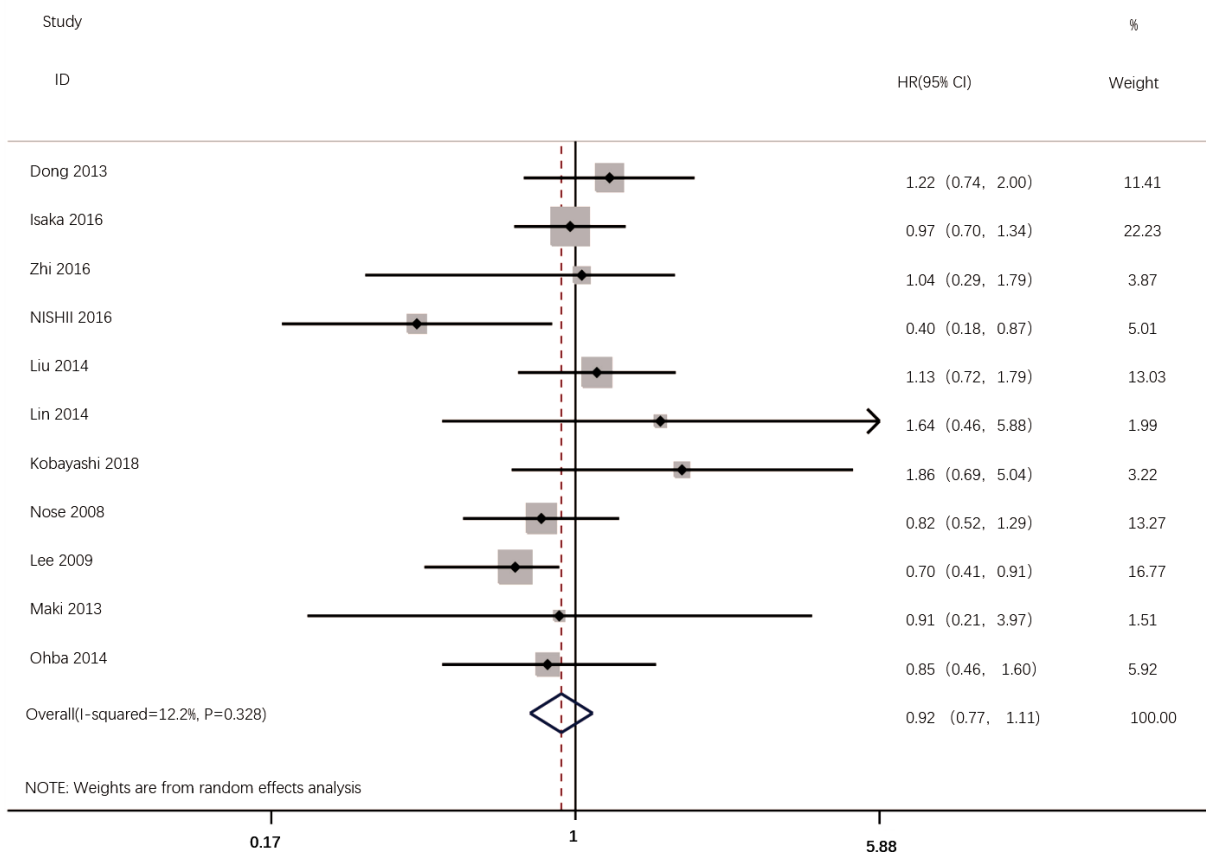


Figure 8 Forest plot of the pooled HRs for DFS by adenocarcinoma subgroup. DFS, disease-free survival; HR, hazard ratio.

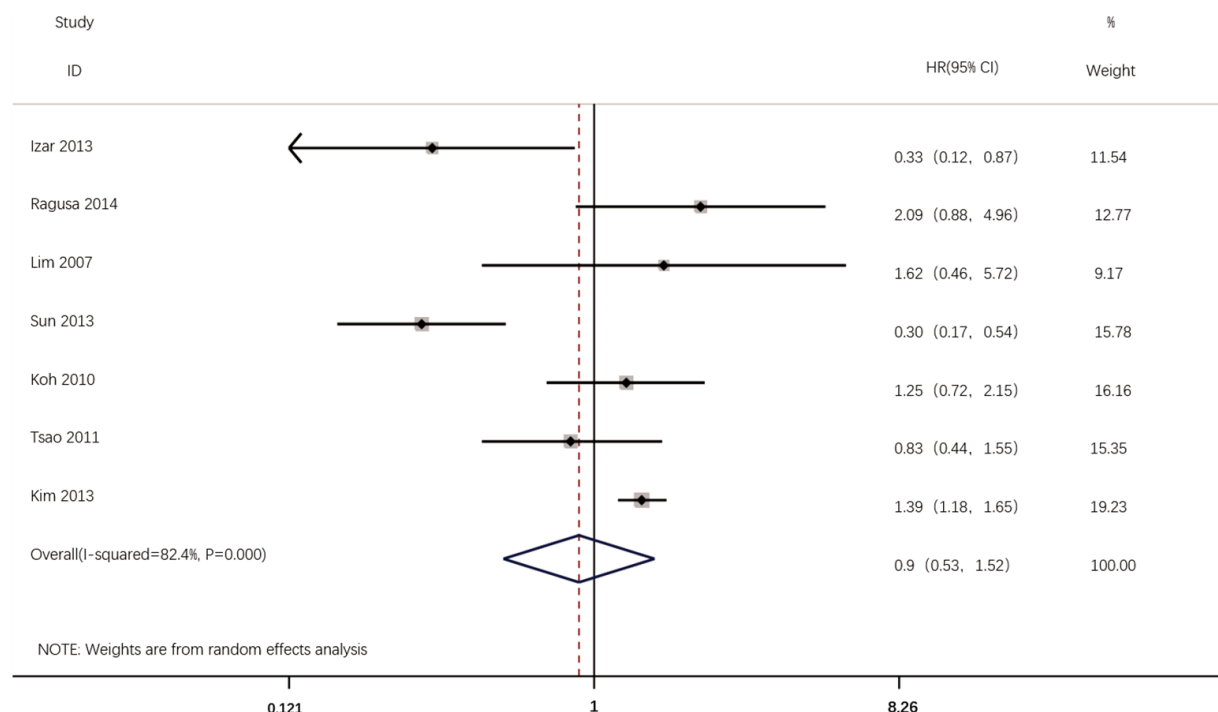


Figure 9 Forest plot of the pooled HRs for DFS by NSCLC subgroup. DFS, disease-free survival; HR, hazard ratio; NSCLC, non-small cell lung cancer.

Table 2 Subgroup analysis on DFS among cancer patients according to EGFR status

Subgroup	HR	95% CI	P
Stage			
I	0.82	0.50 to 1.33	0.423
II–III	0.94	0.56 to 1.57	0.243
EGFR type			
19del or L858R	1.38	0.76 to 2.52	0.288
The selection method of the EGFR status			
Retrospective test	0.86	0.65 to 1.15	0.316
Retrospective review	1.09	0.81 to 1.48	0.567
Race			
Asian	0.94	0.74 to 1.19	0.6
Caucasian	0.85	0.34 to 2.16	0.71
Tumor type			
Adenocarcinoma	0.92	0.77 to 1.11	0.379
NSCLC	0.90	0.53 to 1.52	0.694

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; HR, hazard ratio.

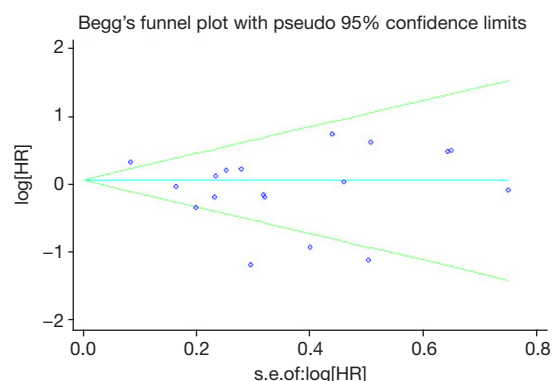


Figure 10 Funnel plot for publication bias. The two oblique lines indicate the pseudo 95% CI.

significant heterogeneity was observed. In addition, we can't avoid the influence of the adjuvant chemotherapy or postoperative radiotherapy based on the original reports. Further studies are necessary.

Conclusions

In summary, our results demonstrated that EGFR mutations

showed no prognostic value in primary resected NSCLC. When deciding treatment strategy for postoperative (especially stage I) patients, there is no evidence support difference between mutated and wild-type patients. However, 19 del might be a negative factor through indirect reason, which may require more strict management. We strongly encourage reporting the specific prognostic impacts of different mutation types.

Acknowledgements

We want to give sincere thanks to all authors and patients of our included studies. We cannot complete this work without your work and participation.

Funding: This study was funded by the grant 2016YFC0905403 and 2016YFC0905403 from the National Key R&D Program of China.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87-108.
2. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9-29.
3. Mountain CF. Revisions in the International system for staging lung cancer. *Chest* 1997;111:1710-7.
4. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Non-small cell Lung Cancer Collaborative Group. *BMJ* 1995;311:899-909.
5. Kuo SW, Chen JS, Huang PM, et al. Prognostic significance of histologic differentiation, carcinoembryonic antigen value, and lymphovascular invasion in stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2014;148:1200-7.e3.
6. Sun Z, Aubry MC, Deschamps C, et al. Histologic grade is an independent prognostic factor for survival in non-small cell lung cancer: an analysis of 5018 hospital- and 712 population-based cases. *J Thorac Cardiovasc Surg* 2006;131:1014-20.
7. Kratz JR, He J, Van Den Eeden SK, et al. A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies. *Lancet* 2012;379:823-32.
8. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 2005;97:339-46.
9. Gazdar AF, Shigematsu H, Herz J, et al. Mutations and addiction to EGFR: the Achilles 'heel' of lung cancers? *Trends Mol Med* 2004;10:481-6.
10. Pao W, Miller VA. Epidermal growth factor receptor mutations, small molecule kinase inhibitors, and non-small-cell lung cancer: current knowledge and future directions. *J Clin Oncol* 2005;23:2556-68.
11. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129-39.
12. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497-500.
13. Ou SH, Zell JA, Ziogas A, et al. Prognostic factors for survival of stage I nonsmall cell lung cancer patients: a population-based analysis of 19,702 stage I patients in the California Cancer Registry from 1989 to 2003. *Cancer* 2007;110:1532-41.
14. Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;17:2815-34.
15. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to event data in meta-analysis. *Trials* 2007;8:article16.
16. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
17. Geller N, Freedman L, Lee YJ, et al. Conference on meta-analysis in the design and monitoring of clinical trials. *Stat Med* 1999;18:753-54.
18. Dong Y, Li Y, Peng H, et al. Predictive role of EGFR mutation status on postoperative prognosis in patients with resected lung adenocarcinomas. *Zhongguo Fei Ai Za Zhi* 2013;16:177-83.
19. Isaka T, Nakayama H, Yokose T, et al. Epidermal Growth Factor Receptor Mutations and Prognosis in Pathologic N1-N2 Pulmonary Adenocarcinoma. *Ann Thorac Surg* 2016;102:1821-8.
20. Zhi Q, Wang Y, Wang X, et al. Predictive and prognostic value of preoperative serum tumor markers in resectable adenosquamous lung carcinoma. *Oncotarget* 2016;7:64798-809.
21. Nishii T, Yokose T, Miyagi Y, et al. Prognostic value of EGFR mutations in surgically resected pathological stage I lung adenocarcinoma. *Asia Pac J Clin Oncol* 2017;13:e204-11.
22. Liu WS, Zhao LJ, Pang QS, et al. Prognostic value of epidermal growth factor receptor mutations in resected lung

- adenocarcinomas. *Med Oncol* 2014;31:771.
23. Izar B, Sequist L, Lee M, et al. The impact of EGFR mutation status on outcomes in patients with resected stage I non-small cell lung cancers. *Ann Thorac Surg* 2013;96:962-8.
 24. Lin MW, Wu CT, Shih JY, et al. Clinicopathologic characteristics and prognostic significance of EGFR and p53 mutations in surgically resected lung adenocarcinomas ≤ 2 cm in maximal dimension. *J Surg Oncol* 2014;110:99-106.
 25. Ragusa M, Vannucci J, Ludovini V, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcome in resected non-small cell lung cancer patients. *Am J Clin Oncol* 2014;37:343-9.
 26. Kobayashi N, Toyooka S, Ichimura K, et al. Non-BAC component but not epidermal growth factor receptor gene mutation is associated with poor outcomes in small adenocarcinoma of the lung. *J Thorac Oncol* 2008;3:704-10.
 27. Lim KH, Huang MJ, Liu HC, et al. Lack of prognostic value of EGFR mutations in primary resected non-small cell lung cancer. *Med Oncol* 2007;24:388-93.
 28. Nose N, Sugio K, Oyama T, et al. Association between estrogen receptor-beta expression and epidermal growth factor receptor mutation in the postoperative prognosis of adenocarcinoma of the lung. *J Clin Oncol* 2009;27:411-7.
 29. Sun HB, Ou W, Li Y, et al. Epidermal growth factor receptor mutation status and adjuvant chemotherapy in resected advanced non-small-cell lung cancer. *Clin Lung Cancer* 2013;14:376-82.
 30. Lee YJ, Park IK, Park MS, et al. Activating mutations within the EGFR kinase domain: a molecular predictor of disease-free survival in resected pulmonary adenocarcinoma. *J Cancer Res Clin Oncol* 2009;135:1647-54.
 31. Koh Y, Jang B, Han SW, et al. Expression of class III beta-tubulin correlates with unfavorable survival outcome in patients with resected non-small cell lung cancer. *J Thorac Oncol* 2010;5:320-5.
 32. Tsao MS, Sakurada A, Ding K, et al. Prognostic and predictive value of epidermal growth factor receptor tyrosine kinase domain mutation status and gene copy number for adjuvant chemotherapy in non-small cell lung cancer. *J Thorac Oncol* 2011;6:139-47.
 33. Maki Y, Soh J, Ichimura K, et al. Impact of GLUT1 and Ki-67 expression on early stage lung adenocarcinoma diagnosed according to a new international multidisciplinary classification. *Oncol Rep* 2013;29:133-40.
 34. Ohba T, Toyokawa G, Kometani T, et al. Mutations of the EGFR and K-ras genes in resected stage I lung adenocarcinoma and their clinical significance. *Surg Today* 2014;44:478-86.
 35. Kim YT, Seong YW, Jung YJ, et al. The presence of mutations in epidermal growth factor receptor gene is not a prognostic factor for long-term outcome after surgical resection of non-small-cell lung cancer. *J Thorac Oncol* 2013;8:171-8.
 36. Hayasaka K, Shiono S, Matsumura Y, et al. Difference of Postoperative Survival Due to the Type of EGFR Gene Mutation in Surgically Resected Lung Adenocarcinomas. *J Thorac Oncol* 2017;12:S320-1.
 37. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-57.
 38. Zhang Z, Wang T, Zhang J, et al. Prognostic value of epidermal growth factor receptor mutations in resected non-small cell lung cancer: a systematic review with meta-analysis. *PLoS One* 2014;9:e106053.
 39. Wang Y, Li RQ, Ai YQ, et al. Exon 19 deletion was associated with better survival outcomes in advanced lung adenocarcinoma with mutant EGFR treated with EGFR-TKIs as second line therapy after first-line chemotherapy: a retrospective analysis of 128 patients. *Clin Transl Oncol* 2015;17:727-36.
 40. Riely GJ, Pao W, Pham D, et al. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. *Clin Cancer Res* 2006;12:839-44.
 41. Jackman DM, Yeap BY, Sequist LV, et al. Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib. *Clin Cancer Res* 2006;12:3908-14.
 42. Fang S, Wang Z, Guo J, et al. Correlation between EGFR mutation status and response to first-line platinum-based chemotherapy in patients with advanced non-small cell lung cancer. *Onco Targets Ther* 2014;7:1185-93.
 43. Isaka T, Yokose T, Ito H, et al. Correlations between the EGFR mutation status and clinicopathological features of clinical stage I lung adenocarcinoma. *Medicine (Baltimore)* 2015;94:e1784.
 44. Yang Y, Yang Y, Zhou X, et al. EGFR L858R mutation is associated with lung adenocarcinoma patients with dominant ground-glass opacity. *Lung Cancer* 2015;87:272-7.

Cite this article as: He Q, Xin P, Zhang M, Jiang S, Zhang J, Zhong S, Liu Y, Guo M, Chen X, Xia X, Pan Z, Guo C, Cai X, Liang W, He J. The impact of epidermal growth factor receptor mutations on the prognosis of resected non-small cell lung cancer: a meta-analysis of literatures. *Transl Lung Cancer Res* 2019;8(2):124-134. doi: 10.21037/tlcr.2019.03.14