# Correlation between EGFR mutation status and the incidence of brain metastases in patients with non-small cell lung cancer

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**Background:** Lung cancer is the leading cause of cancer-related death worldwide. Numerous studies have been performed to investigate the correlation between epidermal growth factor receptor (EGFR) mutation status and the incidence of brain metastases (BMs) in patients with non-small cell lung cancer (NSCLC), however, the outcomes were inconsistent. Thus, we performed this study to establish the role of EGFR mutation status in BMs.

**Methods:** Electronic databases PubMed, Embase, Cochrane Library, CBM, WanFang, CNKI were searched to identify relevant trials. The primary endpoint was the incidence of BMs in EGFR mutations or wild type NSCLC and the secondary endpoint was overall survival calculated from the BMs emerging (BMOS).

**Results:** Twenty-two studies incorporating 8,152 participants were eligible. EGFR mutations group possessed a significantly higher risk of BMs (OR =1.99; 95% CI, 1.59–2.48; P=0.000) than EGFR wild type group. In the stratified analysis, compared with EGFR wild type group, EGFR mutations group had a significant higher incidence (OR =2.01; 95% CI, 1.56–2.59; P=0.000) of subsequent BMs while only a trend of increasing the incidence of initial BMs (OR =1.38; 95% CI, 0.98–1.94; P=0.066). Moreover, exon 19 deletion had a trend of increasing the incidence of BMs than exon 21 mutation (OR =1.44; 95% CI, 0.77–2.68; P=0.252). Compared with EGFR wild type group, EGFR mutations group possessed a prolonged overall BMOS (HR =0.68; 95% CI, 0.47–0.98; P=0.038) and a longer BMOS in initial BMs (HR =0.50; 95% CI, 0.31–0.80; P=0.004) but no significant difference in NSCLC with subsequent BMs (HR =0.95; 95% CI, 0.42–2.15; P=0.901).

**Conclusions:** Patients with EGFR mutations were more susceptible to develop into BMs than those with EGFR wild type, especially during the course of disease.

**Keywords:** Brain metastases (BMs); non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); meta-analysis

## Introduction

Brain metastases (BMs) are life-threatening complications of non-small cell lung cancer (NSCLC)，accounting for approximately 20–40% of patients (1,2), and are associated with a poor prognosis. The median overall survival (OS) after BMs is only 3 to 7 months despite whole-brain radiation therapy (3-5). Moreover, the development of BMs was concealed under most circumstance which inspired us to seek out a predictive factor of BMs to remind oncologists to screen the BM lesions earlier. Additionally, prophylactic cranial irradiation (PCI), a routine practice for stage I–III small cell lung cancer system treatment (6), may also be used for NSCLC patients. Previous studies have revealed that PCI curtailed the development of BMs in NSCLC patients (7), but it was not routinely delivered due to a lack of improving survival. Therefore, it is critical to identify the high-risk population of BMs.

Recently, several clinical factors, such as younger age, non-squamous cell carcinoma, larger tumor size, lymph node involvement and higher serum tumor markers level (NSE >18 ng/mL, CA125 ≥35 U/mL and CEA ≥23 ng/mL), were observed to be associated with actuarial risk of developing into BMs in NSCLC (8-10). However, risk factors of BMs in molecular level remain to be identified.

Noticeably, epidermal growth factor receptor (EGFR) mutations occur in approximately 20% of lung adenocarcinomas in Western countries (11) and 40–60% in East Asia (12-14). Additionally, the EGFR was routinely detected in clinical practice and widely used as a target for the TKIs in managing patients with BMs. D. Luo *et al.* (15) showed a similar EGFR mutation frequency (52.9% *vs.* 46.7%, P=0.644) and a high concordance rate of 93.3% between BMs and the primary NSCLC tumors. Meanwhile, some studies revealed that patients with EGFR mutations were confronted with a higher risk of BMs than those with EGFR wild-type (16-18), whereas others (19,20) argued no distinct occurrence of BMs between them. On that account, we conducted a meta-analysis aiming to evaluate correlation between the EGFR status and incidence of BMs or overall survival calculated from the BMs emerging (BMOS).

## Methods

This study was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (21) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) (22).

### Search strategy

Electronic databases PubMed, Embase, Cochrane Library, CBM, WanFang, CNKI were thoroughly searched to identify relevant trials up to October 2016 without language restriction and were conducted with the following keywords: "brain metastases", "cerebral metastases", "neoplasm metastasis", "central nervous system", "encephalon", "epidermal growth factor receptor", "receptor, epidermal growth factor", "EGFR", "EGFR mutation", "lung neoplasms", "lung cancer", "lung carcinoma", "Pulmonary Neoplasm", "Pulmonary Cancers", and "non-small cell lung cancer". Articles and general reviews of this topic were carefully examined and excluded. Furthermore, we manually reviewed the references of the included studies to screen additional articles.

### Selection criteria

Trials meeting the following criteria were included in this study: (I) NSCLC with known mutation status (EGFR mutation or EGFR wild-type); (II) the incidence of BMs could be acquired from EGFR mutation and EGFR wild-type group respectively; (III) BMs were assessed by imaging methods or medical records; (IV) the study design was case control study or cohort study.

Letters, comments, and expert opinions, reviews without original data, and case reports were excluded in this meta-analysis.

### Quality assessment

The methodological quality of this meta-analysis was the Newcastle Ottawa Quality Assessment Scale (NOS) (23) and two investigators independently assessed the quality of each study. Any discrepancy was resolved by a third reviewer. This scale with a maximum score nine is composed of eight items and mainly containing patient selection, study comparability and outcome/exposure. Included studies were categorized into high-quality (≥6 score) and low-quality studies (<6 score).

### Definition

The BMOS was calculated from the date of occurrence of BMs till the date of the last follow-up or death. Initial BMs were defined as intracranial metastasis appearing at initial diagnosis of NSCLC and subsequent BMs as brain lesions occurring during or after treatment.
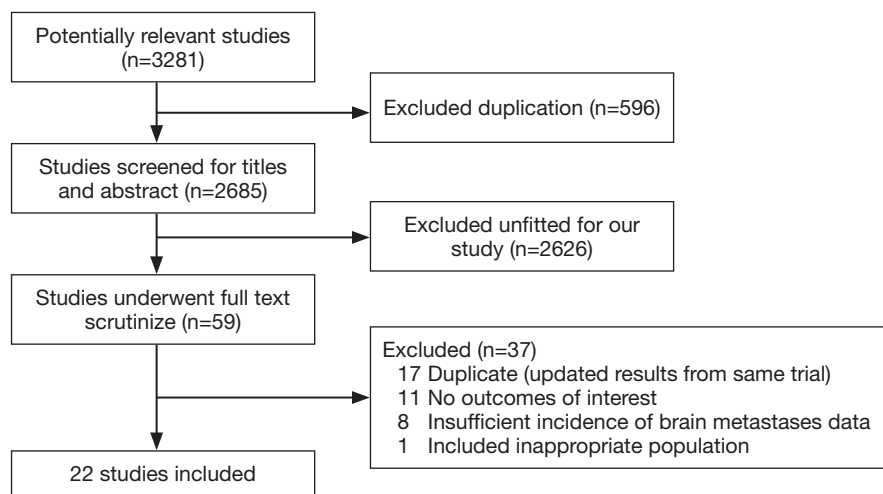
**Figure 1** Flow diagram of included studies.

### Data extraction

Two reviewers extracted data from each trial independently and disagreements were addressed by consensus. The following information was abstracted from each included studies: first author's name, published date, study type, country, EGFR status, gender, smoking history, histology, Eastern Cooperative Oncology Group (ECOG) performance status, clinical stage, outcomes incorporating the incidence of BMs and BMOS.

### Methods of statistics

All data analyses were performed through the Stata/SE 12.0 in this study. The primary endpoints were the incidence of BMs and the secondary endpoints BMOS. Chi-square and I-square tests were used to test the heterogeneity of involved trials. If P>0.1 and $I^2$<50%, the studies were defined as low heterogeneity and fixed effect model was applied, otherwise as high heterogeneity and random effect model was adopted. We also conducted subgroup analyses by study design types (cohort study and case control study), timing of BMs (initial and subsequent) and EGFR mutation types (exon 19 vs. 21). Furthermore, classified analyses were performed on stage IV population and patients with adenocarcinoma, respectively.

Subsequently, we conducted a sensitivity analysis to further evaluate the influence of individual studies on the final conclusion. Incidence of BMs was dichotomous variables and analyzed by pooling odds ratio (OR). We extracted the hazard ratio (HR) and its 95% confidence

intervals (CIs) of BMOS from survival curves using the methods described by Tierney et al. (24). Publication bias was assessed via funnel plot and was statistically analyzed using Egger and Begg's test.

## Results

### Selection of trials

Firstly, 3,281 relevant papers were identified after thoroughly searching the databases. Then, 596 duplicates were excluded. Furthermore, 2,626 papers unfitted design were excluded after reviewing the titles and abstracts. Moreover, full text of 59 papers were intensively scrutinized and 37 were excluded for following reasons: 17 studies for duplication, 11 studies for lacking of outcomes of interest, 8 studies for full-text unavailable, and 1 study for unfitted design. Eventually, 22 studies (16-19,25-42) fulfilling all of the inclusion criteria were eligible for this meta-analysis. A flow chart presented the search results and exclusion reasons (*Figure 1*).

### Study description and quality assessment

Primary characteristics of these included studies were presented in *Table 1*. Of all studies, 18 were cohort studies and other 4 case control studies. Additionally, eight of the 22 studies described treatment strategies (*Table 2*). Among 8,152 patients, 2,664 harbored EGFR mutations.

The NOS was used to perform quality assessment on all 22 studies and 14 (17,18,25-28,30,32-36,38,42) were evaluated as

**Table 1** Features of the studies included in the meta-analysis

| Study | Year | Country | NOS | BMs diagnosis | Stage | EGFR status | | Gender | | Smoking history | | Histology | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | EGFR + | EGFR − | Male | Female | Never | Former/current | Adenocarcinoma | Others |
| Guan J. (16) | 2016 | China | 4 | PET CT/MRI | I–IV | 159 | 242 | 280 | 121 | 195 | 206 | 308 | 93 |
| Hsu F. (17) | 2016 | Canada | 7 | CT/MRI | IV | 121 | 422 | 216 | 327 | NM | NM | NM | NM |
| Baek MY. (18) | 2016 | Korea | 7 | MRI | IV | 73 | 186 | 167 | 92 | 106 | 153 | 180 | 79 |
| Li B. (19) | 2015 | China | 5 | MRI | I–IV | 51 | 49 | NM | NM | NM | NM | NM | NM |
| Enomoto Y. (25) | 2013 | Japan | 6 | MRI | IV | 35 | 60 | 57 | 38 | 34 | 61 | 95 | 0 |
| Hendriks LE. (26) | 2014 | Netherlands | 9 | Medical records | NM | 62 | 62 | 52 | 72 | 34 | 90 | 109 | 15 |
| Lee YJ (27) | 2009 | Korea | 8 | Brain imaging | IA–IIIA | 49 | 68 | 45 | 72 | 83 | 34 | 117 | 0 |
| Fujimoto D. (28) | 2014 | Japan | 6 | MRI | IV | 98 | 148 | 142 | 104 | 113 | 133 | 246 | 0 |
| Iuchi T. (29) | 2015 | Japan | 4 | MRI | IA–IV | 331 | 796 | 735 | 392 | 368 | 723 | 895 | 232 |
| Stanic K. (30) | 2014 | Slovenia | 8 | CT/MRI | I–IV | 137 | 492 | 326 | 303 | 147 | 453 | 629 | 0 |
| Shin DY. (31) | 2014 | Korea | 5 | MRI | NM | 138 | 176 | 151 | 163 | NM | NM | 314 | 0 |
| Liu Y. (32) | 2015 | China | 7 | CT/MRI | IV | 22 | 24 | NM | NM | NM | NM | NM | NM |
| Xing Z. (33) | 2015 | China | 7 | NM | IIA–IV | 68 | 56 | 78 | 46 | 53 | 71 | 65 | 59 |
| Zhao Y. (34) | 2013 | China | 7 | CT/MRI | I–IV | 87 | 104 | 108 | 83 | 99 | 92 | NM | NM |
| Ge M. (35) | 2016 | China | 9 | MRI | NM | 23 | 67 | 57 | 33 | 39 | 51 | 54 | 36 |
| Han G. (36) | 2016 | China | 8 | MRI | I–IV | 108 | 126 | 125 | 109 | 131 | 103 | 234 | 0 |
| Bhatt VR. (37) | 2016 | India/America | 4 | CT/MRI | I–IV | 452 | 1070 | 987 | 532 | 894 | 624 | 1318 | 204 |
| Doebele RC. (38) | 2012 | America | 6 | CT/MRI | IV | 39 | 80 | 48 | 71 | 47 | 72 | 115 | 4 |
| Tomasini P. (39) | 2016 | France | 4 | Medical records | IV | 16 | 79 | 63 | 32 | 28 | 66 | 81 | 14 |
| Russo A. (40) | 2017 | Italy | 5 | Medical records | IIIB–IV | 36 | 101 | 81 | 56 | 26 | 106 | 100 | 37 |
| Li H. (41) | 2017 | China | 5 | CT/MRI | NM | 456 | 607 | 580 | 483 | 578 | 485 | 1063 | 0 |
| Renaud S. (42) | 2016 | France | 8 | CT/MRI | NM | 103 | 473 | 347 | 229 | 134 | 442 | 576 | 0 |

NOS, Newcastle Ottawa Quality Assessment Scale; BMs, brain metastases; NM, no mention; EGFR, epidermal growth factor receptor; EGFR +, EGFR mutations; EGFR −, EGFR wild type; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography.

**Table 2** Treatment strategies of the studies included in the meta-analysis

| Study | Treatment strategies | EGFR mutations | EGFR wild type |
|---|---|---|---|
| Hsu F. (17) | Chemotherapy (yes/no) | 59/62 | 208/214 |
| | TKIs (yes/no) | 105/16 | 117/305 |
| Baek MY. (18) | Patients with BMs: TKIs (yes/no) | 26/1 | NM |
| Hendriks LE. (26) | First line treatment (none/chemotherapy/TKIs) | 3/18/41 | 11/46/5 |
| | TKIs during the course of disease | 58 | 15 |
| Lee YJ. (27) | All accepted curative-intent operation | | |
| | TKIs used after relapsed (yes/no) | 11/15 | 21/26 |
| Fujimoto D. (28) | First line chemotherapy (TKIs/platinum combination/single-agent/no chemotherapy) | 52/41/3/2 | 5/88/32/23 |
| | Line of TKIs (first line/second or beyond) | 52/44 | – |
| Iuchi T. (29) | Treatment of BMs (surgical removal/cytotoxic chemotherapy/TKIs) | 16/9/65 | 35/45/12 |
| | Radiation (SRS/LBRT/WBRT) | 20/1/18 | 64/7/42 |
| Han G. (36) | Treatment after BMs | | |
| | Radiotherapy (yes/no) | 27/21 | 17/11 |
| | Chemotherapy (yes/no) | 19/29 | 19/9 |
| | TKIs (yes/no) | 21/27 | 2/26 |
| Renaud S. (42) | All accepted curative-intent operation | | |
| | Neo-adjuvant treatment (yes/no) | 17/10 | 107/151 |
| | Adjuvant treatment (chemotherapy/radiotherapy/radio-chemotherapy/no) | 15/1/0/11 | 74/4/20/160 |

Only 8 of the 22 studies provided treatment strategies. EGFR, epidermal growth factor receptor; TKIs, tyrosine Kinase inhibitors; BMs, brain metastases; NM, no mention; SRS, stereotactic radiosurgery; LBRT, local brain radiation therapy; WBRT, whole-brain radiation therapy.

high-quality and 8 (16,19,29,31,37,39-41) as low-quality.
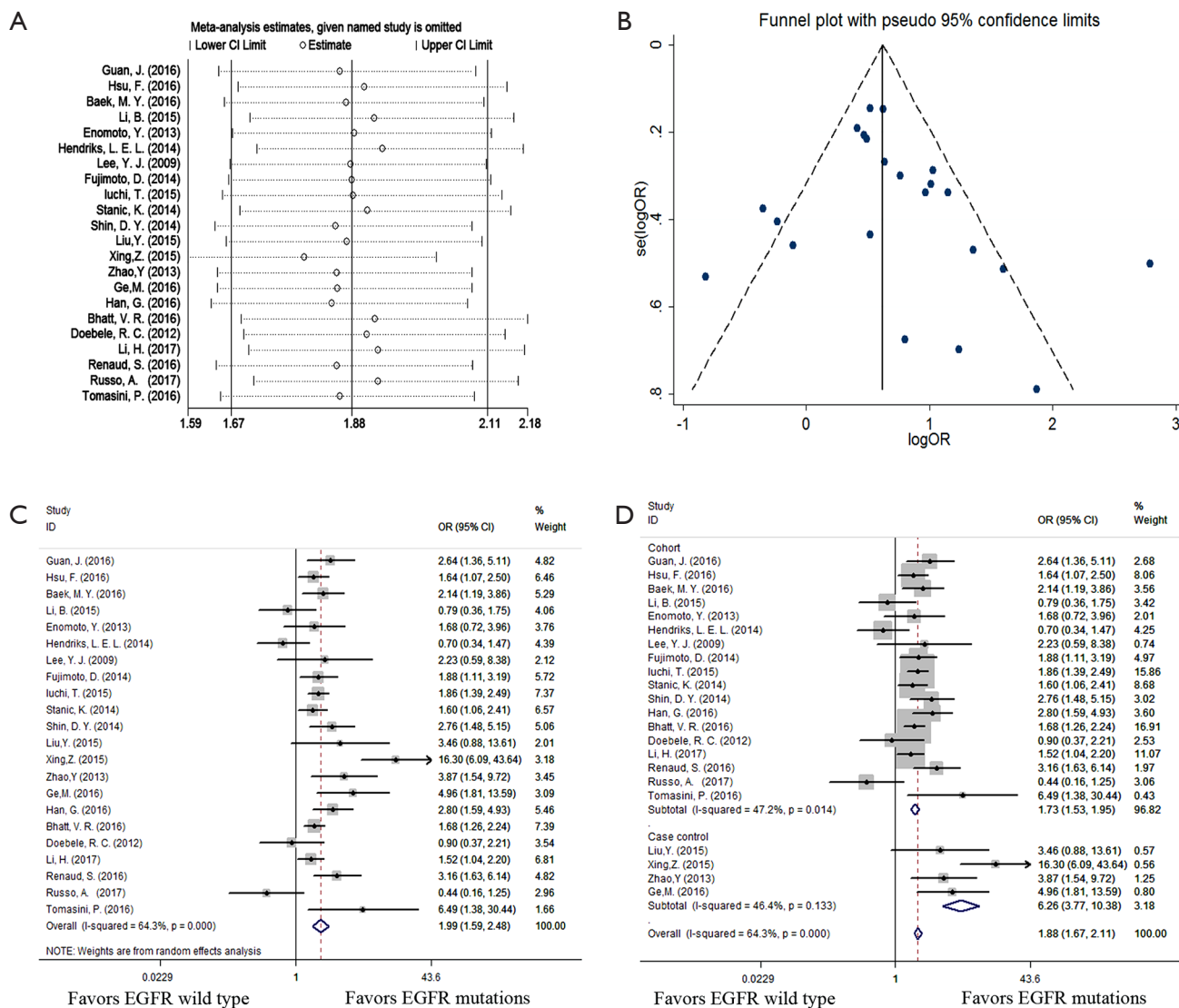
### Sensitivity analysis

Sensitivity analyses were performed after sequentially removing each eligible study. The pooled OR of BMs were not significant influenced by any single study (*Figure 2A*), indicating that our results (incidence of BMs) were statistically robust and stable.

### Publication bias

The funnel plot, Begg's test and Egger's test were used to assess publication bias of the incidence of BMs. The shape of the funnel plots appeared to be generally symmetric (*Figure 2B*). Both the Begg's test (P=0.114) and Egger's test (P=0.253) indicated no publication bias.

### Incidence of BMs

All of 22 eligible trials (16-19,25-42) reported incidence of BMs. A random effect model was employed to analyze these studies due to high heterogeneity (P=0.000, $I^2$ =64.3%). Compared with the EGFR wild type group, EGFR mutations group possessed a significantly higher incidence of BMs (OR =1.99; 95% CI, 1.59–2.48; P=0.000) (*Figure 2C*). Considering the high heterogeneity, analyses stratified by study design (*Figure 2D*) suggested that association was significant between EGFR mutations and the incidence of BMs in cohort (16-19,25-31,36-42) (OR =1.73; 95%CI, 1.53–1.95; P=0.000) or case control studies (32-35) (OR =6.26; 95% CI, 3.77–10.38; P=0.000). Additionally, the heterogeneity of the involved studies diminished when restricted to adenocarcinoma (25,27,28,30,31,36,41,42) (P=0.369, $I^2$=7.9%) or stage IV (17,18,25,28,32,38,39)

**Figure 2** (A) Sensitivity analysis of the association of EGFR mutations and incidence of BMs; (B) funnel plot of incidence of BMs; (C) comparison of BMs between EGFR mutations group and EGFR wild type group; (D) subgroup analyses on incidence of BMs by study design. BMs, brain metastases; EGFR, epidermal growth factor receptor.

(P=0.381, $I^2$=6.1%) (*Figure 3A*). Patients with EGFR mutations were more susceptible to BMs than wild type cases either in adenocarcinoma patients (OR =1.93; 95% CI, 1.59–2.35; P=0.000) or in advanced (stage IV) NSCLC patients (OR =1.83; 95% CI, 1.43–2.36; P=0.000).

Then several subgroup analyses were conducted to estimate other risks of increasing BMs in NSCLC patients. As respects of timing of BMs (17-19,26,29,30,36,39), compared with EGFR wild type group, EGFR mutations group had a significant higher incidence (OR =2.01; 95% CI, 1.56–2.59; P=0.000) of subsequent BMs (*Figure 3B*)

while only a trend of increasing the incidence of initial BMs (OR =1.38; 95% CI, 0.98–1.94; P=0.066) (*Figure 3C*). With regard to EGFR mutation type (19,35,36), patients harboring exon 19 mutation suffered a potential higher risk of BMs than those harboring exon 21 mutation (OR =1.44; 95% CI, 0.77–2.68; P=0.252) (*Figure 3D*).

### BMOS

Seven eligible trials (17,18,26,29,30,36,40) compared BMOS between EGFR mutations and wild type group.

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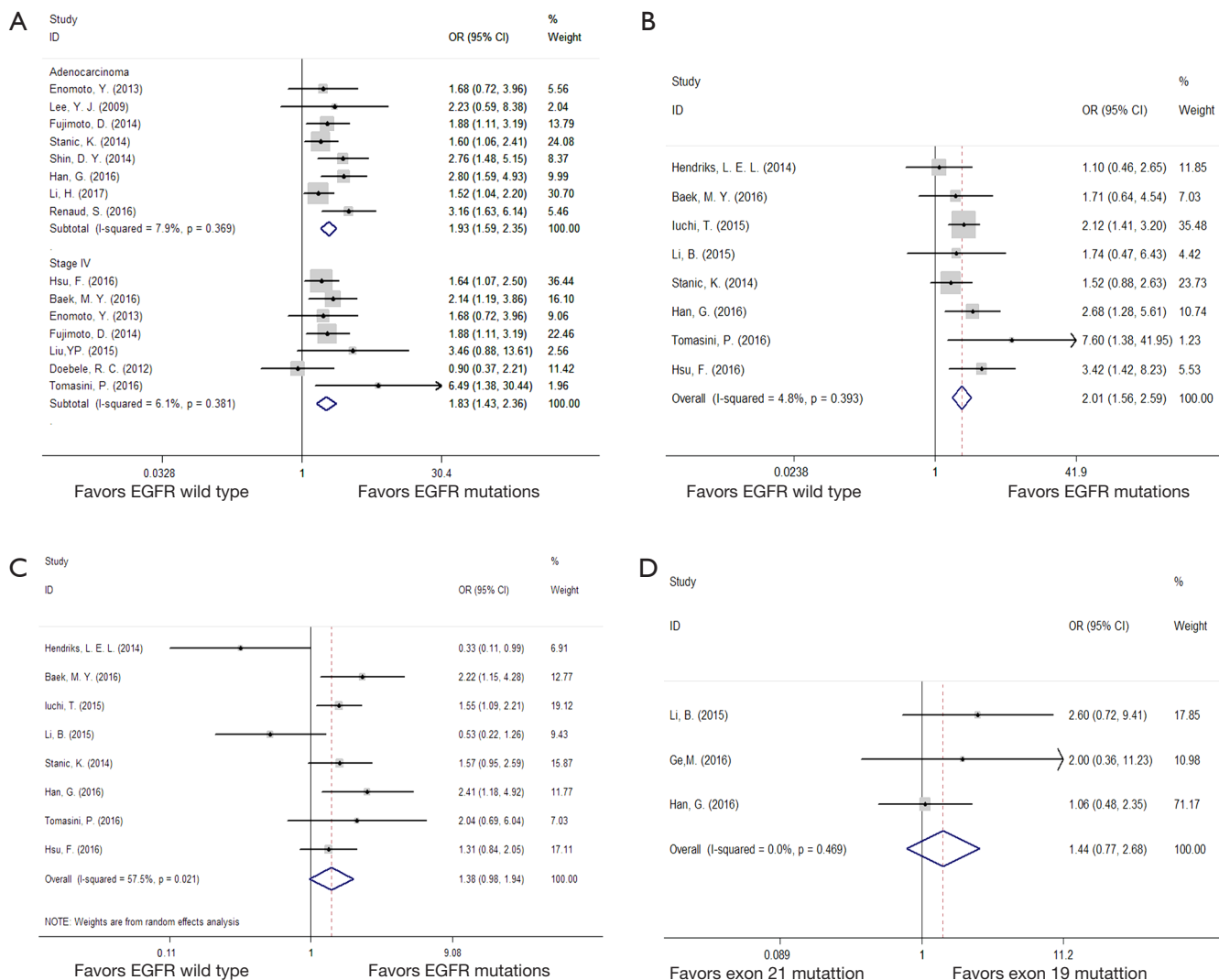


**Figure 3** Subgroup analyses of incidence of BMs: (A) subgroup analysis on the incidence of BMs (EGFR mutations versus wild type) in patients with adenocarcinoma and stage IV respectively; (B) subgroup analysis on the incidence of subsequent and (C) initial BMs (EGFR mutations versus wild type); (D) subgroup analysis on the BMs incidence of exon 19 mutation versus exon 21 mutation. BMs, brain metastases; EGFR, epidermal growth factor receptor.

A random effect model was performed owing to high heterogeneity (P=0.001, $I^2$ =72.4%). Compared with EGFR wild type group, EGFR mutations group displayed a prolonged overall BMOS (HR =0.68; 95% CI, 0.47–0.98; P=0.038) (*Figure 4A*). Further subgroup analysis (18,30) on BMOS showed that, compared with EGFR wild type group, EGFR mutations group with initial BMs (*Figure 4B*) gained a longer BMOS (HR =0.50; 95% CI, 0.31–0.80; P=0.004) while those with subsequent BMs (*Figure 4C*) had an equal BMOS (HR =0.95; 95% CI, 0.42–2.15; P=0.901).

## Discussion

To our best knowledge, this meta-analysis of 22 studies incorporating 8,152 participants was the first study to evaluate the risk of BMs in various EGFR status. The results revealed that EGFR mutations were closely associated with a significant higher incidence of BMs (P=0.000). Furthermore, stratified analysis of BMs showed that, compared with EGFR wild type, EGFR mutations group had a significant higher incidence of subsequent BMs and a trend of increasing the incidence of initial
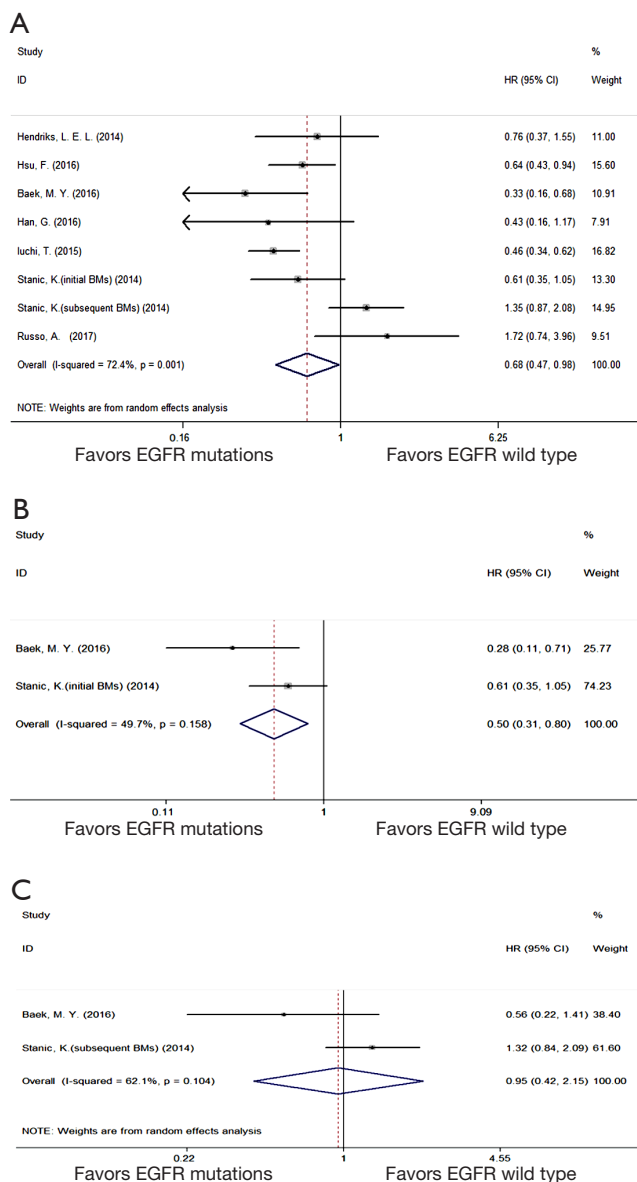
**Figure 4** (A) Comparison of BMOS between EGFR mutations group and EGFR wild type group: BMOS in overall BMs (initial BMs + subsequent BMs); (B) BMOS in initial BMs; (C) BMOS in subsequent BMs. BMs, brain metastases; EGFR, epidermal growth factor receptor; BMOS, overall survival calculated from BMs emerging.

BMs. The mechanisms behind it may be as follows: EGFR activated MET through mitogen activated protein kinases (MAPK) to promote BMs in NSCLC (43); moreover, EGFR activated the STAT3 via elevating expression of interleukin-6 (IL-6) in lung cancer which results in the up-regulation of incidence of BMs (44,45). Whereas, the

inconsistent conclusions between the initial and subsequent BMs were possibly due to the intervention of EGFR-TKIs. Being highly effective agents for patients harboring EGFR mutations (46), TKIs were more widely used in those cases to prolong OS, which accordingly resulted in more chances of developing BMs in those patients during the course of disease. Additionally, compared with EGFR wild type patients, EGFR mutations had a significantly shorter median Brain-metastasis-free survival (P=0.018) (19), which might also partly account for the higher incidence of BMs of EGFR mutations patients during a given period.

On account of the different clinical characteristics and pathogenesis between exon 19 deletion and 21 point mutations (47-49), we further performed a subgroup analysis to compare the discrepant outcomes between the two kinds of mutations. The results showed that participants with exon 19 deletion displayed a potential trend to promote BMs compared with exon 21 mutation. The mechanisms underlying it might be that patients with EGFR mutations accepted TKIs inhibiting the phosphorylation of EGFR, Akt, and Erk to a greater degree in exon 19 deletion cells than in exon 21 mutation cells (48). Moreover, subgroup analysis on incidence of BMs of patients with lung adenocarcinoma or of patients with stage IV lowered the heterogeneity notably, indicating that both histology and stage might be impact factors for BMs.

Additionally, compared with patients with EGFR wild type, individuals harboring EGFR mutations who suffered from initial BMs had a longer BMOS, but this benefit did not occur in those who suffered from subsequent BMs. The reasons for this finding might be as followings. Compared with EGFR wild type patients, EGFR mutations individuals with initial BMs possessing a longer BMOS might be partly derived from TKIs which yielded a definitely higher response rate and longer time to central nerves system progression (50,51). Furthermore, EGFR mutations individuals with subsequent BMs probably had undergone EGFR-TKIs therapy and developed acquired resistance to some extent when BMs occurred. Accordingly, they could not benefit from EGFR-TKIs anymore, which partly explained the equal BMOS between the EGFR mutations and EGFR wild type group.

However, our study confronted with some limitations: the potential confounding bias of included retrospective studies; the latent mismatched characters, such as age, histology and tumor size, between the EGFR mutations and wild type group; and the impact of various treatment strategies among eligible studies. Thereby, high-quality

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prospective cohort studies are recommended.

Summarily, patients with EGFR mutations were more susceptible to develop into BMs than those with EGFR wild type, especially during the course of disease. Therefore, careful brain screening and prophylactic interventions possess a potential clinical value for these patients.

## Acknowledgements

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## Footnote

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

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