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ORIGINAL ARTICLE

A Comprehensive Meta-Analysis of Association between EGFR Mutation Status and Brain Metastases in NSCLC

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Abstract

Non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation have different clinicopathological characteristics compared with EGFR wild type NSCLC. A growing number of studies focused on the relevance between EGFR mutation status and brain metastases (BM) in NSCLC, but it remains controversial. Therefore, this study performed a comprehensive meta-analysis to untangle this issue. Several electronic databases including Pubmed, Embase, Web of science and Cochrane database were thoroughly searched. The odds ratio (OR) with 95% confidence interval (95%CI) was pooled to evaluate the relevance. Meta-regression analysis and subgroup analysis were conducted according to the heterogeneity. A total of 26 studies were identified finally in this meta-analysis. The overall OR was 1.58 (95%CI: 1.36–1.84), which indicated that EGFR mutation had a positive association with BM of NSCLC. The subgroup analysis resulted from eleven studies with lung adenocarcinoma revealed a higher possibility of BM in NSCLC with EGFR mutation compared with EGFR wild ($p < 0.05$). There was no significant difference in the risk of BM between NSCLC EGFR exon 19 mutation and exon 21 point mutation ($p = 0.23$). This meta-analysis suggests that EGFR mutation can be a risk factor for BM in NSCLC.

Keywords Epidermal growth factor receptor · NSCLC · Brain metastases · Meta-analysis

Introduction

Lung cancer remains the leading cause of cancer death and more than one-half of patients were in the advanced stage at their first diagnosis without the chance of curative treatment [1]. Non-small cell lung cancer (NSCLC) is the most common type which accounts for approximately 85% of all lung cancer. Brain is one of common metastatic sites in NSCLC and the incidence of brain metastases (BM) is approximately 20–54% [2–4]. Despite diversified treatments such as radiotherapy, chemotherapy or surgery being widely used, the prognosis of BM is poor. There are little survival benefits and poor median overall survival (OS), usually less than 10 months [5]. Recently, the prognosis of BM in NSCLC with epidermal growth factor receptor (EGFR) mutation has been improved by the contributions of tyrosine kinase inhibitor (TKI). Previous studies showed that the median OS ranged from 11.8–15.9 months in cases who were treated with EGFR-TKI [6, 7]. Even so, the new statistic data from this report showed that the 5-relative survival rate is 18% without obvious increase compared with other cancers and the quite high proportion of distant stage may be responsible for it [1]. Therefore, better management of BM in NSCLC may contribute to increase the survival rate and improve the quality of patients' life.

EGFR signaling pathways in lung cancer have some impacts on tumor growth, which may be linked with complicated process such as up-regulated angiogenesis and tumor cell proliferation [8–10]. Recently, EGFR-TKI has been an important new treatment manner for EGFR-mutated lung adenocarcinoma. At the same time, it has been widely accepted that EGFR-mutated NSCLC have different clinicopathological features

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compared with EGFR wild type NSCLC, so this work intended to analyze the possible different metastatic characteristics between them. Several previous studies had reported that there was no strong relation between the risk of BM and EGFR mutation status in NSCLC [11, 12], but some other studies suggested the relevance between EGFR mutation and the higher risk of BM [4, 13]. Therefore, we conducted this meta-analysis of current available observational studies to clarify the association between EGFR mutation status and BM in NSCLC.

Methods

Literature Search and Selection Criteria

Databases including Pubmed, Embase, Web of science and Cochrane database were searched to screen relevant publications until August 31, 2017. A combination of terms was used as follows: "EGFR" or "epidermal growth factor receptor mutation" or "EGFR mutation", "brain metastasis" or "intracranial metastases" and "lung cancer" or "NSCLC" or "non-small cell lung cancer". We also check the reference lists of included studies to find other relevant studies.

Included studies in this meta-analysis must meet the following criteria: studies on the relationship between EGFR mutation and BM in NSCLC; full text in English were included; the number of BM or without BM in each group would be greater than 3 cases; observational studies were included; odd ratio (OR) and their corresponding 95% confidence interval (95%CI) were provided, if these statistical variables were not available in primary articles, sufficient information should be provided to calculated them; if the same patient population was reported in more than one studies, the most informative studies was selected. Articles didn't meet inclusion criteria would be excluded. In addition, studies such as meeting abstracts, case reports, letters or commentaries were excluded. Two authors (Li Tan and Yinying Wu) identified eligible articles independently with inclusion and exclusion criteria. If disagreements occurred, the discussion will be carried out to resolve it.

Data Extraction and Quality Assessment

Given all studies are retrospective observational studies, we adapted the Newcastle-Ottawa Quality Assessment Scale (NOS) to assess the quality of included studies [14]. Relevant information was extracted from final identified studies: the first author's name, publication year, region, patient's number, study periods, histology, disease stage, median follow-up time (Table 1). Two independent authors (Li Tan and Yinying Wu) examined retrieved data from included studies and disagreements were resolved by the supervisor (Juan Ren) to reach a consensus. We attempted to contact authors for data that were not shown in primary articles. Dr. Han and Dr. Hsu provided the specific BM number of patients with EGFR exon 19/21 mutation.

Statistical Analysis

We pooled OR corresponding 95%CI to assess the association between EGFR mutation status and BM in NSCLC. The heterogeneity amid studies was tested by I^2 statistic; If test results showed I^2 value >50%, we considered high heterogeneity within studies and the random effect model was applied; If not (I^2 value ≤50%), the fixed effect model was used [37]. Additionally, if there is considerable heterogeneity, meta-regression analysis with restricted maximum likelihood (REML) method and subgroup analysis will be conducted. Funnel plot and Egger's test were used to estimate publication bias. To evaluate the stability of the results, we conducted sensitivity analysis to test it. These statistic data was performed using STATA version 12.0. A $p < 0.05$ was considered statistically significant differences.

Results

Search Results

A total of 2178 records were searched: 408 from Pubmed, 963 from Embase, 0 from Cochrane and 807 from Web of science. We obtained sixty relevant articles in English were selected through reviewing titles and abstract. Finally, 26 studies were identified in this meta-analysis after reading the full text [4, 11–13, 15–36, 38, 39]. The selection procedure was showed in Fig. 1.

Study Characteristics

The characteristics of twenty-six studies are showed in Table 1. These studies were conducted in different regions: 17 studies from Asia, 5 studies from Europe and 4 studies from North America, all of them are observational studies. Overall, 4007 cases with EGFR mutation and 10,022 cases with EGFR wild are collected. There were eleven studies only included patients with a diagnosis of lung adenocarcinoma. Five articles provided multiple analysis OR with 95%CI to adjust for confounders. The quality of studies was evaluated with NOS ranged from 4 to 8 (Table 1).

Correlation between EGFR Mutation and the Frequency of BM in NSCLC

The results of the association are showed in Fig. 2. The 26 included studies evaluating the relationship were analyzed by a random-effect model (OR = 1.58, 95%CI:1.36–1.84, $p < 0.05$, $I^2 = 52\%$), which indicated NSCLC patients with EGFR

Table 1 Characteristics of included studies

First author	Year	Country	Study time	Histology	Stage	No. of patients EGFR±	Media follow time (months)	NOS
Lee et al.	2009 [15]	Korea	1995–2005	AC	IA-IIIA	49/68	40.3	7
Doebele et al.	2012 [16]	USA	2008.6–2011.5	non-squamous	IV	39/80	NA	6
Enomoto et al.	2013 [17]	Japan	2009.4–2011.10	AC	IV	35/60	NA	7
Akamatsu et al.	2014 [18]	Japan	2002.9–2009.12	AC	III	13/31	37.7*	8
Fujimoto et al.	2014 [19]	Japan	2007.1–2012.4	AC	IV	98/148	21.5/28.6	8
Stanic et al.	2014 [11]	Slovenia	2009.12–2012.1	AC	I-IV	137/492	53*	6
Shin et al.	2014 [20]	Korea	2005.10–2011.12	AC	NA	138/176	28.6*	7
Hendriks et al.	2014 [12]	Netherlands	2008.10–2012.8, 2004.11–2012.1	NSCLC	NA	62/62	NA	8
Iuchi et al.	2015 [21]	Japan	2006.1–2013.1	NSCLC	I-IV	331/796	NA	7
Li et al.	2015 [22]	China	2010.4–2013.9	AC	I-IV	51/49	NA	6
Schuette et al.	2015 [23]	Germany	2009.11–2012.10	NSCLC	IV	396/3011	NA	6
Tanaka et al.	2015 [24]	Japan	2006–2013	AC	III	29/75	35	7
Yagishita et al.	2015 [25]	Japan	2001.1–2010.12	non-squamous	III	29/155	29	7
Baek et al.	2018 [13]	Korea	2010.1–2013.8	NSCLC	IV	73/186	41.4*	6
Chen et al.	2016 [26]	China	2010.11–2014.3	NSCLC	IIIB-IV	308/247	33.5	7
Han et al.	2016 [4]	China	2007–2014	AC	I-IV	108/126	16.2*	8
Hsu et al.	2016 [27]	Canada	2010.3–2012.3	non-squamous	IV	121/422	34.9	7
Li et al.	2016 [28]	USA	2004–2008	NSCLC	IV	17/27	84	4
Li et al.	2017 [29]	China	2010.8–2015.5	AC	NA	456/607	NA	6
Luo et al.	2017 [30]	China	2006.3–2012.11	AC	I-IV	239/135	NA	6
Renaud et al.	2016 [31]	France	2007.1–2012.12	NSCLC	NA	103/473	39	5
Mizuno et al.	2016 [32]	Japan	2001.1–2013.12	NSCLC	I-III	185/155	38.1	5
Bhatt et al.	2017 [33]	USA/India	2007–2014	NSCLC	I-IV	452/1070	NA	5
Ge et al.	2017 [34]	China	2008.1–2016.10	NSCLC	NA	37/63	NA	8
Russo et al.	2017 [35]	Italy	2013.1–2015.11	non-squamous	IIIB-IV	36/101	NA	7
Wang et al.	2017 [36]	China	2005.1–2013.6	non-squamous	IIIB-IV	465/1207	NA	7

NA not available; * partial patients

AC adenocarcinoma, *NSCLC* non small cell lung cancer

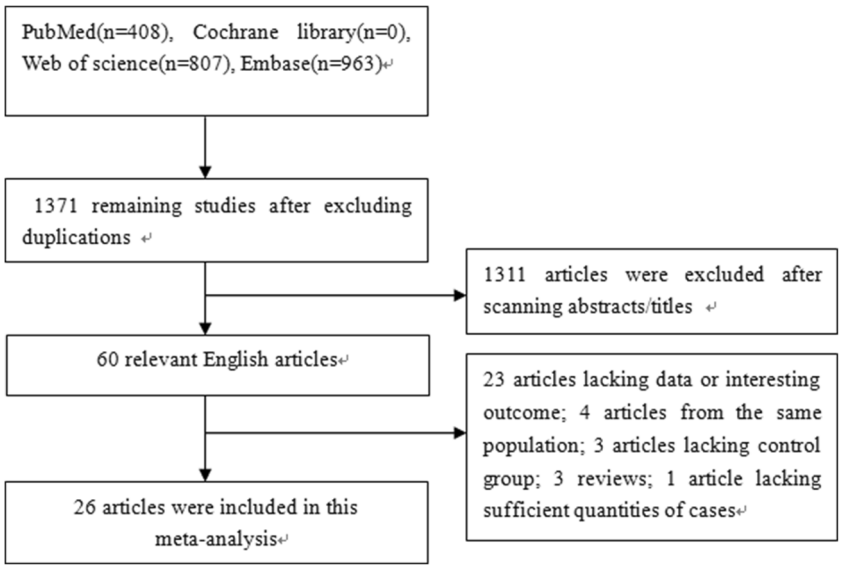

Fig. 1 The flow chart for retrieving eligible articles

mutation are more likely to develop BM. Due to the value of $I^2 > 50\%$, heterogeneity sources need to be explored. Meta-regression analysis with REML method showed different histology among studies may influence combined effect size ($p < 0.05$). Subgroup analysis of adenocarcinoma group were performed and the result with moderate heterogeneity ($I^2 = 25.9\%$) revealed a higher possibility of BM for NSCLC with EGFR mutation compared with EGFR wild ($p < 0.05$). Furthermore, combined effect size using multivariate logistic regression analysis were calculated with negligible heterogeneity (OR = 2.39, 95%CI: 1.87–3.07, $I^2 = 0\%$), also provided the evidence that EGFR mutation might augment the risk of BM in NSCLC.

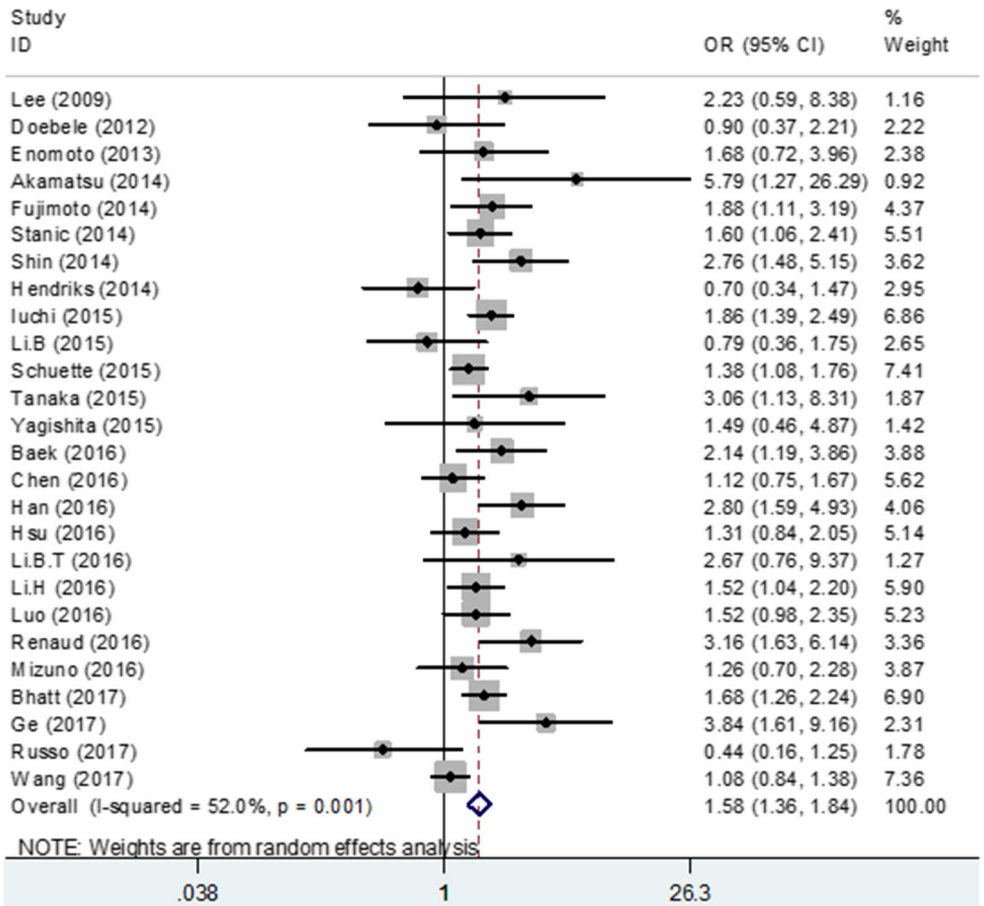

Fig. 2 Forest plots of studies evaluating the association between EGFR mutation status and BM in NSCLC

Difference between EGFR19/21 Exon Mutation and BM in NSCLC

We can finally get the frequency of BM between EGFR exon 19 mutation and exon 21 mutation from nine studies (Fig. 3). The pooled results of 9 studies showed the difference was not statistically significant (OR = 1.15, 95%CI: 0.91–1.46, p = 0.23). It indicated that there is no significant difference in the risk of BM in NSCLC between EGFR mutation types (19/21 exon mutation).

Other Relevant Studies

The comparative result of EGFR-TKI treatment or not were reported from two studies, one study [27] using Fine-Gray model indicated EGFR-TKI treatment was not significant factors (HR = 1.48, 95%CI: 0.84–2.63), the other [36] using COX model suggested EGFR-TKI treatment was significant factors for BM (HR = 1.57, 95%: 1.35–1.85). We conducted subgroup analysis of NSCLC patients without TKI treatment before suffered BM, including three studies enrolled stage III patients who were performed chemoradiotherapy and three studies enrolled NSCLC patients after radical surgery. The pooled OR was 2.12 (95%CI: 1.48–3.03) with moderate heterogeneity (I^2 = 27.9%), which showed the susceptibility of BM for NSCLC with EGFR mutation after controlling EGFR-TKI.

Sensitivity Analysis and Publication Bias

We performed the sensitivity analysis to evaluate the stability of the results by sequentially excluding individual study, and the exhibition indicated that the results of this meta-analysis was relatively stable (Fig. 4). Egger's test ($p > 0.05$) showed that there was no significant publication bias of studies included this meta-analysis. The shapes of the funnel plot are symmetric visually (Fig. 5) and no proof of publication bias was obtained.

Discussions

BM is the most common complication of NSCLC and always is a focus in the entire management of them. Previous studies analyzed the link between some clinicopathological characteristics and BM from different perspectives. Some investigators have already shown that younger age, larger tumor size, lymph node involvement were the risk factors of BM for early stage NSCLC [38]. A systemic review supported the relationship between squamous cell carcinoma and the low risk of BM, however, some clinicopathological features such as age, gender, adenocarcinoma have no association with BM [39]. In view of the limited predicated value of clinicopathological characteristics and huge heterogeneity, it has become an overwhelming trend to search predictors from the viewpoint of molecular biology.

Expression of E-cadherin, microRNA or high-level CXCR4 expression were reported as the important predictors for BM in NSCLC [40–42], however, these researches at molecule level are comparatively limited in the number of studies. EGFR is one of significant ErbB receptor tyrosine kinase family members, and the activation of EGFR will generate multiple signal transduction pathways which regulated biochemical changes of cells [43]. NSCLC with EGFR mutation have

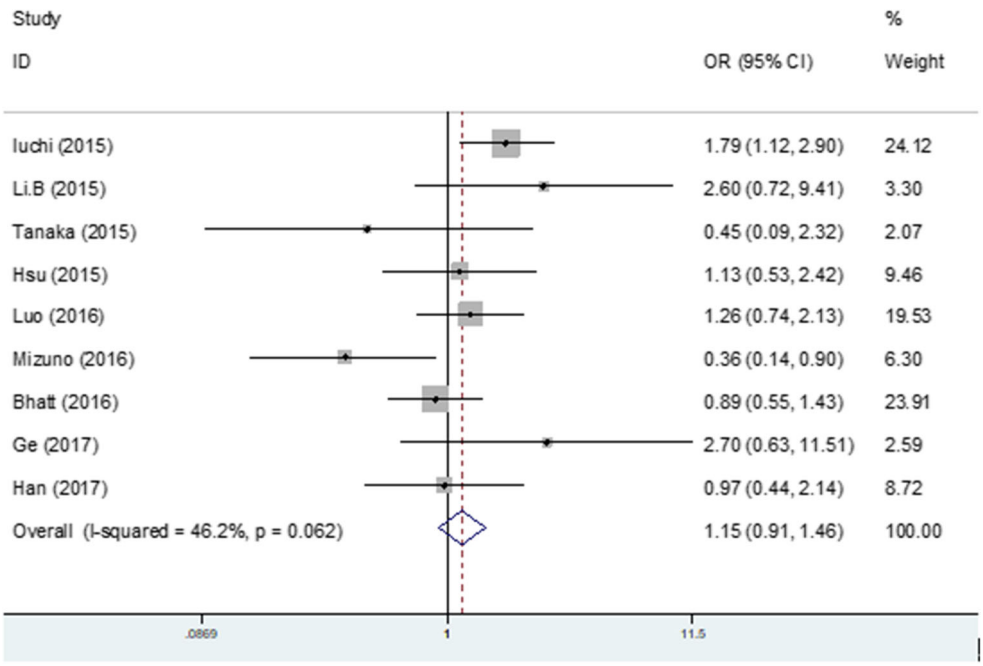

Fig. 3 Forest plots of studies evaluating the risk of BM between NSCLC with EGFR exon 19 mutation and exon 21 mutation

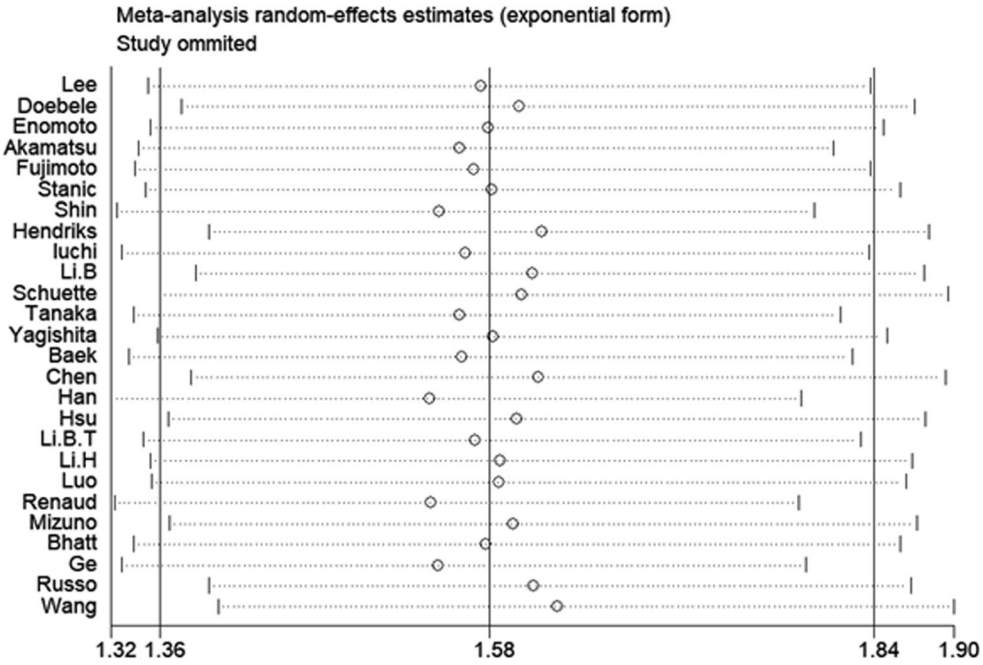

Fig. 4 Sensitivity analysis

individual clinicopathological characteristics compared with EGFR wild, but it's still unclear whether it more likely to develop BM. Our present meta-analysis included 26 observational studies is the first study to report the association.

This analysis showed that EGFR mutation can be a risk factor for BM in NSCLC, but higher statistical heterogeneity ($I^2 = 52\%$) was presented. Meta-regression analysis showed heterogeneity derived from histology ($p < 0.05$). As we all known, EGFR mutation is mainly found in cases with lung adenocarcinoma. A meta-analysis reported EGFR mutation rate in lung squamous cell carcinomas were 3.3% in Western (11/334) and 4.6% in Asian (22/474) [44]. So the source of heterogeneity within studies might be relevant to EGFR mutation status with lung squamous cell carcinomas. In addition, it is worth mentioning that this correlation between EGFR and BM also was demonstrated by using multivariate analysis.

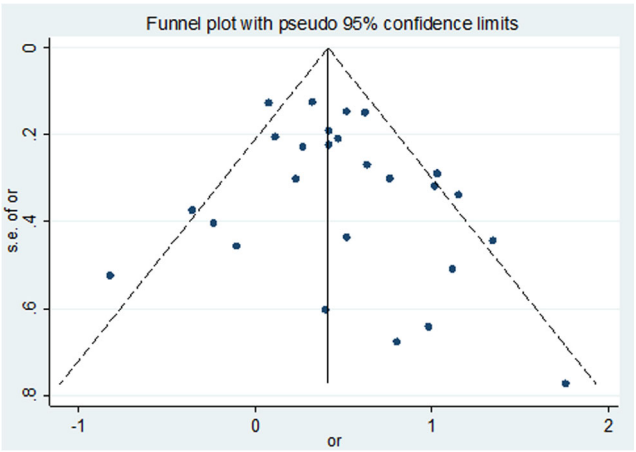

Fig. 5 Publication bias test of all included studies (the funnel plot)

Most of them controlled confounders of age, sex, smoking, T stage or N stage, providing more convictive evidence.

EGFR detection was performed in most advanced and metastatic NSCLC in clinical practice. Whether the use of EGFR-TKI influenced the incidence of BM is still controversial. Heon et al. suggested that a lower risk of BM for advanced NSCLC cases who selected EGFR-TKI as first-line treatment compared with other published studies [45]. Among the included studies, one study [27] using Fine-Gray model indicated that EGFR-TKI treatment was not a significant factor, but the other [36] using COX model supported that it's a significant factor. Different statistical methods and target population induce different conclusions. It's a reminder that our subgroup analysis from six studies without EGFR-TKI treatment before suffered BM indicated the higher possibility of BM for EGFR-mutated NSCLC, both for early stage NSCLC after radical surgery and local advanced stage NSCLC after definitive chemo- radiotherapy. This result also reflected the higher risk of BM for EGFR-mutated NSCLC without treated with EGFR-TKI, which may be attributed to primary biological susceptibility.

This meta-analysis indicated the correlation between EGFR mutation status and BM, in addition, we also interested in which subtypes of EGFR mutation more likely to develop BM. Sekine et al. [46] reported that NSCLC patients with the exon 19 deletion have unique way of BM, presenting multiple small metastases sites compared with EGFR-wild type patients, whereas there was no significant difference in the exon 21 point mutation patients compared with the same EGFR wild group. In this study [39], authors considered that just lung adenocarcinoma with exon 19 deletions had the higher possibility of BM, while other EGFR mutation subtypes did

not. However, no significant difference in the risk of BM was observed between EGFR mutation in the exon 21 point and in the exon 19 from this meta result. Because they are retrospective studies with limited value, more prospective studies with a large cohort need to be conducted.

The exact mechanism of the higher probability of BM is still unclear. One studies came up with the activation of EGFR-MET associated signaling through MAP kinase is important for invasion and BM of NSCLC [47], and another believed that MET expression and phosphorylation was correlated with a higher likelihood of the development of BM [48]. Fang's experimental in a brain-trophic clone of human MDA-MB-231 breast carcinoma cells indicated that EGFR would affect cell migration and invasion to the brain [49]. Recently, some researchers started looking at signal transducers and activators of transcription 3 (STAT3) to favor possible hypotheses. Some reported the activation of the STAT3-mir-21 pathway play a regulated role in lung-to-BM [50]; mutant EGFR could mediate STAT3 activation by means of IL-6 regulation leading to tumorigenesis through complicated pathway in lung adenocarcinoma [51]. Further studies with signal pathways and molecular mechanisms are needed to reveal exact association between EGFR and BM of NSCLC.

The complication of BM will become a main cause of death, so it's necessary to perform close follow-up and interventions for groups with higher BM risk. Prophylactic cranial irradiation (PCI) has been proven to reduce the rate of BM in small cell lung cancer and is widely used in its comprehensive treatment. For NSCLC, some randomized trials shown a decrease of the cumulative incidence of BM but no overall survival benefit [52, 53]. Previous researches didn't distinguish high-risk from low-risk patients, limiting the value of PCI. A research suggested patients such as younger age, large tumor size and without other metastases may be suiTable for PCI [54]. Based on this meta-analysis result, combinations of clinical features, epidemiological factors and molecular markers with high-risk might get benefits from PCI in NSCLC.

There are several weaknesses in this study. First, the languages of all include articles is English so as to some relevant studies in other languages were omitted, which might lead to publication bias and the limitation of applicable populations. Second, the use of different EGFR detection technologies also might affect consistency within studies. Third, selection bias and recall bias from retrospective studies couldn't be avoided. Fourth, it's almost impossible to completely match baseline characteristics such as age, sex, disease stage, pathologic types or treatments, so this meta-analysis take the ways of multivariate analysis and subgroup analysis to control or reduce confounding factors in some extent. Fifth, this meta-analysis just provided evidence of association between EGFR mutation and BM in NSCLC patients, but that doesn't mean a causal relationship between them, cautious interpretation of the result is important and more precise prospective studies is desperately needed.

Conclusions

In conclusion, EGFR mutation is correlated with the higher possibility of BM for NSCLC, which might attribute to primary biology characteristic and genotype. There was no significant difference in the risk of BM between EGFR exon 19 mutation and exon 21 point mutation. These may provide implications and a theoretical basis in the management of NSCLC patients.

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Compliance with Ethical Standards

Conflicts of Interest These authors confirm that this article content has no conflicts of interest.

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