INTRODUCTION

Non–small–cell lung cancer (NSCLC) accounts for approximately 80%–85% of all lung cancer cases, and 30%–54% of NSCLC patients will develop brain metastases (BM) after treatment1–5; half of the patients with locally advanced NSCLC (LA–NSCLC) may develop BM in the course of the disease.6–8 BM are the most common and severe complication of NSCLC because effective treatment is lacking. Patients with brain metastases, whose median survival time is <1 year, usually have a low quality of life and poor prognosis.9–11

Advances in multimodal therapeutic regimens have moderated the locoregional relapse of LA–NSCLC and improved overall survival (OS).6,12,13 Systemic chemotherapy has led to improvements in the control of extracranial diseases and therefore in survival,14,15 but its role in the management of brain metastases is limited because of the poor diffusion rate for drug molecules across the blood–brain barrier (BBB).14,16 Whole brain radiotherapy (WBRT) is widely used for the treatment of BM in NSCLC. Some studies have shown that radiosurgery or surgical resection combined with WBRT can effectively control brain metastases in LA–NSCLC.17 However, in 2016, the ISRCTN3826061 study found that compared to the control group, BM patients exhibited little clinically significant benefit from WBRT.18

1Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong University, Jinan, China
2Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong Academy of Medical Sciences, Jinan, China
3Department of Hematology, Qilu Hospital, Shandong University, Jinan, China

Correspondence
Hui Zhu, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong Academy of Medical Sciences, Jinan, China.
Email: drzhuh@126.com

Funding information
This work was supported by the Key Research and Development Program of Shandong Province under Grant 2016GSF201148 (to Hui Zhu) and the National Key Research & Development (R&D) Plan under Grant 2016YFC0105708 (to Hui Zhu).

Abstract
Brain metastases (BM) are severe incidents in patients with non–small–cell lung cancer (NSCLC). The controversial value of prophylactic cranial irradiation (PCI) in NSCLC in terms of survival benefit prompted us to explore the possible risk factors for BM in NSCLC and identify the potential population most likely to benefit from PCI. Risk factors for brain metastases in NSCLC are reviewed in this article. Identifying patients with a higher risk of BM could possibly increase the benefit of PCI while reducing the discomfort and risks caused by unnecessary invasive procedures in the NSCLC patient population. Future studies might focus on finding a solid basis for the prediction of the occurrence of brain metastases and for the therapeutic decision on the use of PCI.

KEYWORDS
brain metastases, gene mutation, non–small–cell lung cancer, prophylactic cranial irradiation
Prophylactic cranial irradiation (PCI) is the most effective method for preventing the morbidity associated with BM in NSCLC patients. Previous studies have shown that PCI was able to reduce the occurrence rate of BM by approximately 50%.19,21-22 However, many studies have shown that PCI might have no beneficial effect on OS.24 In the RTOG-0214 study, PCI failed to improve OS (P = 0.86; 1-year OS 75.6% vs 76.9% for PCI vs observation, respectively).23 In 2012, the ASTRO 3014 study reported that although PCI could significantly reduce the incidence of BM, PCI had no effect on OS or might even be associated with a significant reduction in OS.24 These facts suggest that PCI may not be appropriate for all the patients with NSCLC. It is necessary to identify potential patients who may benefit from it. The evaluation of the risk factors for brain metastases to find the patients with NSCLC who may develop BM and benefit from PCI is meaningful. Although studies have focused on this problem,25,26 a systematic summary is still necessary because of the rapid development of treatments for NSCLC, such as targeted therapy and immunotherapy. This review discusses several publications on the risk factors for BM and describes the risk factors for developing brain metastases in NSCLC patients.

2 | PATHOLOGY

Non–small‐cell lung cancer can be further classified into squamous cell carcinoma, adenocarcinoma, and large cell carcinoma types, and many researchers in recent years have reported that patients with adenocarcinoma or non‐squamous cell carcinoma are more likely to develop BM.2,5,25,27-30 For operable NSCLC, the incidence of brain metastases in patients with adenocarcinoma was 2.86 times higher than that in non‐adenocarcinoma patients (95% CI: 1.58‐5.16, P = 0.001).31 Adenocarcinoma was also reported to be one of the predictive factors for BM (RR: 3.39; 95% CI: 1.78‐6.46 and P = 0.0002) in a group of stage I‐III NSCLC patients.27 There were also some studies comparing non‐squamous cell carcinoma with squamous cell carcinoma, which found that non‐squamous cell carcinoma was an independent risk factor for BM (P = 0.000; HR = 3.73; 95% CI: 2.25‐6.16).25 Therefore, non‐squamous cell carcinoma, especially adenocarcinoma, may be an independent risk factor for the metastasis of NSCLC.

However, there are different views. Some studies found no correlation between pathology and BM.32-34 As the study by Ceresoli reported, there was no statistically significant pathological effect when squamous cell carcinoma was compared with non‐squamous cell carcinoma.32 The possible explanation may be the variability caused by the method of brain metastases assessment. Jens et al reported in their study that brain autopsies were performed on 87 patients with adenocarcinoma, and 38 patients (44%) were BM‐positive.35 However, the frequency of BM in patients with adenocarcinoma who were clinically diagnosed was 24%‐35.7%.36-38

3 | GENDER

The predictive value of gender for BM may still remain controversial. The results of several studies showed that the effects of gender on BM were limited, especially in LA‐NSCLC.27,29 Earlier studies presented a meta‐analysis on risk factors for BM and found that gender could not be used as a marker to predict the development of BM.26 However, in patients with completely resected early‐stage NSCLC, being female may have predictive value for the incidence of BM.30 This conclusion was also confirmed in another study.40 Gender may have predictive value in early‐stage NSCLC, but this may not be suitable for LA‐NSCLC.

4 | T AND N STATUSES AND TUMOR STAGES

Some articles reported that the T and N statuses were both predictive factors. Bajard et al analyzed 305 patients with stage I‐III NSCLC and found that T4 (RR: 3.75; 95% CI: 1.72‐8.21; P = 0.0009) and N2‐3 (RR: 2.61; 95% CI: 1.32‐5.15; P = 0.0057) were risk factors for BM. A study of 264 patients with stage I‐IV NSCLC found that the incidence of BM increased with rising T and N stages (P = 0.05).41 More studies focused on the influence of N status on BM in NSCLC. Compared with the risk of BM in the absence of lymphatic involvement, the risk of brain metastases was significantly higher when the hilar (RR = 4.26 and P = 0.013) or homolateral mediastinal lymph nodes (RR = 5.49 and P = 0.001) were metastatic.36 In the study by Ding et al,30 an increased risk of developing BM was associated with a number of metastatic lymph nodes >5 (P = 0.000), LNR ≥30% (P = 0.000), number of metastatic mediastinal lymph nodes ≥3 (P = 0.001), number of metastatic mediastinal lymph node stations between 2 and 4 (P = 0.000), and ratio of metastatic mediastinal lymph node stations >50% (P = 0.000). Regarding the relationship between tumor size or stage and BM, Robnett et al analyzed 150 patients with stage II‐III NSCLC and found that IIIIB patients had an increased risk for BM (RR: 2.8; 95% CI: 1.3‐6.1). However, the relationship between tumor size or stage and BM was not found by Keith et al (stage IB‐IIIB) or Horinouchi et al (unresectable stage III). Another study did not find this relationship either.25 Most of the articles that we found showed that tumor stage has not previously been regarded as a predictive factor for brain metastases in resected NSCLC patients.27,43,44 Therefore, we concluded that lymph node metastases are
an independent risk factor, especially when the mediastinal lymph nodes were multiple metastatic.

However, several studies failed to prove the T and N statuses were predictive factors. The reasons underlying this difference need to be further explored. The possible reasons for this difference were due to only LA-NSCLC being included in these studies and the variability in biology and pathology between unresectable and resectable NSCLC.

5 | AGE

Many studies have reported that younger age is a risk factor for BM in NSCLC. They analyzed the predictive value of age and found that a patient aged younger than 60-70 years of age was associated with a risk of brain metastases. In studies by Ceresoli et al, an age <60 years was a risk factor for brain metastases (RR = 2.5; 95% CI: 1.33-4.76; P = 0.004). Dimitropoulos et al reported that the incidence rate of BM was reduced with increasing age (OR = 0.91; 95% CI: 0.87-0.96; P < 0.001).

It was unclear why young patients have a higher BM risk. Several studies have shown that BM is associated with the angiogenic microenvironment, and the cerebrovascular microenvironment factors of young patients may be better than those of older patients. Whether there were differences in the expression of biomarkers, such as vascular endothelial growth factor, Ki-67, and caspase-3, between younger and older patients also needs further exploration. In addition, young people may have better performance statuses, which are associated with longer survival.

6 | PERFORMANCE STATUS

The initial performance status following protocol entry was a predictor for brain metastases. Compared with patients in the group whose Karnofsky performance status was 50%-60%, patients in the best performance groups (Karnofsky performance status >60%) developed metastases at a higher rate after protocol entry. In addition, the patients who responded to the treatment better may develop brain metastases during the therapy. However, neither difference was significant. In addition, in the study by Bajard, they did not find performance status to be a significant predictive factor.

Patients in the best performance status groups have a somewhat higher risk for the development of brain metastases. Since the performance status has been shown to be a major prognostic factor for survival, differences in brain metastatic frequency may also be at least partially interpreted as the risk of such complications being changed at different times during disease progression.

7 | THE LEVELS OF TUMOR MARKERS

While most tumor markers are currently used in lung cancer examination, they may contribute to the clinical and histologic diagnosis of the disease, prognosis prediction, and therapeutic evaluation.

7.1 | Neuron-specific enolase (NSE)

As a key glycolytic enzyme, NSE is mainly expressed in neuroendocrine tumors but rarely expressed in NSCLC, except for in patients with neuroendocrine differentiation, which accounts for approximately 10% of NSCLC patients.

Recent studies of patients with locally advanced NSCLC have shown that NSE is an independent risk factor for BM. A multicenter retrospective study showed a high serum NSE level was an independent determinant of poor survival in patients with NSCLC with BM. NSE was identified as a significant predictive factor based on the stage I-III NSCLC-resected patients in the study by Zhang. In Ji’s study, increased NSE and CA125 levels are both independent risk factors for BM. The association between elevated NSE levels and BM might reflect tumor heterogeneity, but the exact mechanism is unclear. No other reports referred to the relationship between CA125 levels and BM. Further clinical trials and functional studies are needed to validate these findings.

These results suggest that NSE plays a significant role in brain metastases, not only for locally advanced NSCLC but also for all stages of NSCLC.

7.2 | Carcinoembryonic antigen (CEA)

Serum CEA levels are positively associated with advanced disease and tumor recurrence in resected NSCLC. Despite this well-known association, there are few studies on the relationship between serum levels of CEA and brain metastases in advanced NSCLC.

Arrieta et al demonstrated a significant relationship between high CEA serum levels and BM development in adenocarcinoma compared with other histological types. In a prospective manner, they studied 293 patients with NSCLC in the IIIB-IV clinical stage and found that CEA concentrations ≥40 ng/mL (RR 11.4; 95% CI, 1.7-74; P < 0.01) were an independent risk factor. This result is consistent with the study by Ma. That study revealed that CEA concentrations ≥23 ng/mL (P = 0.001) were a predictive factor for
developing BM after analyzing 134 patients with EGFR-mutated advanced lung adenocarcinoma.59

The results above suggest that elevated serum CEA levels in NSCLC patients are an independent predictive factor for brain metastases.

8 | ONCOGENE

Recently, targeted therapy that is based on the mutation state of molecular biomarkers has been developed for the treatment of non–small-cell lung cancer.60 In fact, approximately 60%-80% of the patients whose tumor samples contain somatic mutations in the kinase domain of the epidermal growth factor receptor (EGFR) gene respond to EGFR tyrosine kinase inhibitors (TKIs).61 Mutated KRAS, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (HER-2), and serine-threonine kinase BRAF are also involved in the development and progression of NSCLC.62,63

Although the molecular status of EGFR in primary NSCLC has been extensively studied, the data on the molecular status of BM from NSCLC are limited.64-69 Studies of molecular pathways that mediate brain metastases have shown that oncogenes play an important role and that the molecular statuses of these genes need to be further investigated because they can be part of the patient risk stratification.70

8.1 | EGFR mutations

It has been reported that the epidermal growth factor receptor (EGFR) mutation status could have an influence on the central nervous system (CNS) progression of NSCLC.9,39,60,69,71,72 The study by Li et al analyzed 110 patients with NSCLC whose EGFR status was detected in the primary tumors and brain metastases. The EGFR mutation rates in patients with and without brain metastases were 64% and 31%, respectively, suggesting that brain metastases were more common in patients with EGFR mutations.73 However, this study had small sample sizes, which may have limitations. In 2016, a retrospective study including 1522 consecutive NSCLC patients reported that patients with EGFR mutations at the time of diagnosis have a nearly twofold higher risk of brain metastases.74 The results above suggest that the EGFR mutation status could have an influence on the CNS progression of NSCLC. The mechanisms for this phenomenon may be due to Met activation and epithelial-mesenchymal transition (EMT).74-76 Some patients with EGFR mutations may undergo EMT, which may result in increased motility and invasiveness in their cancer cells.76

Heon et al found that the CNS progression of TKI-treated NSCLC was dependent on the EGFR genotype. Compared with tumors with L858R mutations, tumors with exon 19 deletions showed a higher morbidity of CNS involvement (3% vs 21%, respectively).77 The patient’s ethnic origin is also a determinant because the frequency of EGFR mutations is much higher in Asian patients (40%).78 Two studies found EGFR mutations in 44%-63% of brain metastases in East Asian patients.66,71 This is similar to the prevalence reported in primary tumors of East Asian people, which varies from 30% to 50%.78,79 However, in the Caucasian population, only three studies reported the prevalence of EGFR mutations in BM, and they found that the rate was between 0% and 2%,64,65,80 which is far lower than the prevalence in primary tumors (10%).81,82 In fact, the prevalence of EGFR mutations in NSCLC in non-Asian patients is quite low in published studies.80

This difference maybe caused by patient variability because it is reported that EGFR mutations in NSCLC are significantly associated with the female gender and nonsmoking status.77,83 Another hypothesis is that tumor heterogeneity at the molecular level may be responsible for the difference.

Another interesting point is that EGFR has been shown to be unstable during tumor progression. Italiano et al found that discordant EGFR expression can reach 33.3% in a cohort of 30 matched primary tumors and metastases.84

In conclusion, EGFR mutations play an important role in the metastasis of NSCLC and may support risk stratification, especially in East Asian patients, but the status of these mutations needs to be further investigated.

8.2 | ALK mutations

The overall incidence rate of BM in patients with anaplastic lymphoma kinase (ALK)-positive NSCLC is high.85-87 Some studies have shown that patients with ALK overexpression mutations have stable or asymptomatic BM at the initial diagnosis or with progression. In the study of 21 patients with NSCLC with mutated ALK by Deepa Rangachari,88 23.8% (5/21) of patients had BM at the initial diagnosis or with progression. In the study of 30 matched primary tumors and metastases.84

In conclusion, EGFR mutations play an important role in the metastasis of NSCLC and may support risk stratification, especially in East Asian patients, but the status of these mutations needs to be further investigated.

8.3 | KRAS mutations

In contrast to EGFR, there are relatively few reports concerning the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) status in the brain metastases of lung cancer patients.64,68,69,89

In the study by Villalva, KRAS mutational status did not facilitate the metastasis of NSCLC.60 This finding is consistent with several studies that showed that KRAS mutations were related to the suppression of progression.90,91 The
overall mutation rate of KRAS in primary tumors was not significantly different from that of matched metastases in a meta-analysis by Wang; the odds ratio was 1.224 (95% CI: 0.808-1.856, \(P = 0.340\)). That study did not find significant differences in overall KRAS mutation rates between primary and metastatic NSCLC either.

### 8.4 PD-1/PD-L1 and TMB

Immune evasion has been seen as an important feature of the tumor. The expression of PD-1/PD-L1 and tumor mutational burden (TMB) is the main predictive factors of the state of the tumor. The number of studies about the relationships between the expression of PD-1/PD-L1 or TMB and brain metastases is relatively small.

Some studies supported the conclusion that TMB is associated with BM. TMB was significantly higher in NSCLC with BM than in NSCLC with other types of metastases. The current evidence shows that TMB is different in NSCLC with BM compared to other types of NSCLC. Further study is required to identify the relationship between TMB and BM.

To our knowledge, there are few reports studying the relationship between the expression of PD-1/PD-L1 and BM. Several studies reported higher PD-L1 expression in primary tumor compared with matched brain metastases (52% vs 32%, respectively). Few studies have reported that the expression of PD-1/PD-L1 is a predictive factor of BM.

### 9 CONCLUSIONS

Patients with locally advanced NSCLC are at high risk for CNS relapse. Previous review articles reported that non-squamous cell carcinoma type, elevated serum CEA level, and lymph node metastases (especially multiple metastases in the mediastinal lymph nodes) are independent risk factors for brain metastases (Table S1). We collected more articles, summarized the latest studies and found that adenocarcinoma type, younger age (<60 years), and elevated serumNSE levels also need to be considered (Table S1).

With the development of targeted therapy and gene testing, the predictive value of oncogenes should be better assessed. EGFR mutations have been reported to be an independent risk factor for brain metastases. Although there was not sufficient evidence, ALK mutation and high TMB were also believed to be associated with high BM incidence (Table S1).

According to several nomograms for predicting brain metastases that were published in recent years, patients with an increased number of risk factors had a much higher risk of BM. Non-squamous cell carcinoma type, especially adenocarcinoma; lymph node metastases; and high levels of serum tumor markers largely predict the occurrence of brain metastases. However, these nomograms did not cover the effects of oncogenes, which may play an increasingly valuable role in the future.

Detection of a higher risk of BM could possibly identify patients who would receive a greater benefit from PCI and thus reduce the discomfort and risks associated with unnecessary invasive procedures. Therefore, the stratification of patients with newly diagnosed NSCLC using risk factors for brain metastases could have important meaning. There have been published nomograms that attempt to build models that include the risk factors for brain metastases to provide risk estimates, but a more solid basis for therapeutic decisions needs to be created in the future.

### CONFLICT OF INTEREST

None declared.

### ORCID

Hui Zhu http://orcid.org/0000-0001-9422-3886

### REFERENCES

1. The Diagnosis and Treatment of Lung Cancer (Update). National Institute for Health and Clinical Excellence: Guidance. Cardiff (UK). 2011.

2. Pugh TJ, Gaspar LE. Prophylactic cranial irradiation for patients with lung cancer. *Clin Lung Cancer*. 2007;8(6):365-368.

3. Park HS, Decker RH, Wilson LD, Yu JB. Prophylactic cranial irradiation for patients with locally advanced non-small-cell lung cancer at high risk for brain metastases. *Clin Lung Cancer*. 2015;16(4):292-297.

4. Stuschke M, Eberhardt W, Pottgen C, et al. Prophylactic cranial irradiation in locally advanced non-small-cell lung cancer after multimodality treatment: long-term follow-up and investigations of late neuropsychologic effects. *J Clin Oncol*. 1999;17(9):2700-2709.

5. Carolan H, Sun AY, Bezjak A, et al. Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer justify prophylactic cranial irradiation or early detection? *Lung Cancer*. 2005;49(1):109-115.

6. Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol*. 1995;13(8):1880-1892.

7. Yavuz AA, Topkan E, Onal C, Yavuz MN. Prophylactic cranial irradiation in locally advanced non-small cell lung cancer: outcome of recursive partitioning analysis group 1 patients. *J Exp Clin Cancer Res*. 2008;27:80.

8. Mamon HJ, Yeap BY, Janne PA, et al. High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J Clin Oncol*. 2005;23(7):1530-1537.
9. Burel-Vandenbos F, Ambrosetti D, Coutts M, Pedetour F. EGFR mutation status in brain metastases of non-small cell lung carcinoma. *J Neuro Oncol*. 2013;111(1):1-10.

10. Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain. *Cancer*. 2007;109(8):1668-1675.

11. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997;37(4):745-751.

12. Eberhardt W, Wilke H, Stamatis G, et al. Preoperative chemoradiotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: mature results of a phase II trial. *J Clin Oncol*. 1998;16(2):622-634.

13. Choi NC, Carey RW, Daly W, et al. Potential impact on survival of improved tumor downstaging and resection rate by preoperative twice-daily radiation and concurrent chemotherapy in stage IIIA non-small-cell lung cancer. *J Clin Oncol*. 1997;15(2):712-722.

14. Cox JD, Scott CB, Byhardt RW, et al. Addition of chemotherapy to radiotherapy alters failure patterns by cell type within non-small-cell carcinoma of lung (NSCCL): analysis of radiation therapy oncology group (RTOG) trials. *Int J Radiat Oncol Biol Phys*. 1999;43(3):505-509.

15. Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst*. 1995;87(3):198-205.

16. Cortes J, Rodriguez J, Aramendia JM, et al. Front-line paclitaxel/cisplatin-based chemotherapy in brain metastases from non-small-cell lung cancer. *Oncology*. 2003;64(1):28-35.

17. Zabel A, Debus J. Treatment of brain metastases from non-small-cell lung cancer (NSCLC): radiotherapy. *Lung Cancer*. 2004;45(Suppl 2):S247-S252.

18. Mulvenna P, Nankivel M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet*. 2016;388(10055):2004-2014.

19. Xie SS, Li M, Zhou CC, Song XL, Wang CH. Prophylactic cranial irradiation may impose a detrimental effect on overall survival of patients with non-small cell lung cancer: a systematic review and meta-analysis. *PLoS ONE*. 2014;9(7):e103431.

20. Cox JD, Stanley K, Petrovich Z, Paig C, Yesner R. Cranial irradiation in cancer of the lung of all cell types. *JAMA*. 1981;245(5):469-472.

21. Pottgen C, Eberhardt W, Grannass A, et al. Prophylactic cranial irradiation in operable stage IIIA non-small-cell lung cancer treated with neoadjuvant chemoradiotherapy: results from a German multicenter randomized trial. *J Clin Oncol*. 2007;25(31):4987-4992.

22. De Ruyscher D, Dingesmans AC, Praag J, et al. Prophylactic cranial irradiation versus observation in radically treated stage III non-small-cell lung cancer: a randomized phase III NVALT-11/DLCRG-02 study. *J Clin Oncol*. 2018;36:2366-2377.

23. Gore EM, Bae K, Wong SJ, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. *J Clin Oncol*. 2011;29(3):272-278.

24. Corradetti MN, Xanthopolous E, Cheng S, et al. An analysis of survival after prophylactic cranial irradiation for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2012;84(3):S599-S600.

25. Ji Z, Bi N, Wang J, et al. Risk factors for brain metastases in locally advanced non-small cell lung cancer with definitive chest radiation. *Int J Radiat Oncol Biol Phys*. 2014;89(2):330-337.

26. Sun DS, Hu LK, Cai Y, et al. A systematic review of risk factors for brain metastases and value of prophylactic cranial irradiation in non-small cell lung cancer. *Asian Pac J Cancer Prev*. 2014;15(3):1233-1239.

27. Bajard A, Westeel V, Dubiez A, et al. Multivariate analysis of factors predictive of brain metastases in localised non-small cell lung carcinoma. *Lung Cancer*. 2004;45(3):317-323.

28. Gaspar LE, Chansky K, Albain KS, et al. Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol*. 2005;23(13):2955-2961.

29. Robnett TJ, Machtay M, Stevenson JP, Algazy KM, Hahn SM. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. *J Clin Oncol*. 2001;19(5):1344-1349.

30. Ding X, Dai H, Hui Z, et al. Risk factors of brain metastases in completely resected pathological stage IIIA-N2 non-small cell lung cancer. *Radiat Oncol*. 2012;7:119.

31. Zhang F, Zheng W, Ying L, et al. A nomogram to predict brain metastases of resected non-small cell lung cancer patients. *Ann Surg Oncol*. 2016;23(9):3033-3039.

32. Ceresoli GL, Reni M, Chiesa G, et al. Brain metastases in locally advanced non-small cell lung carcinoma after multimodality treatment: risk factors analysis. *Cancer*. 2002;95(3):605-612.

33. Dimitropoulos C, Hillas G, Nikolakopoulou S, et al. Prophylactic cranial irradiation in non-small cell lung cancer patients: who might be the candidates? *Cancer Manag Res*. 2011;3:287-294.

34. Keith B, Vincent M, Stitt L, et al. Subsets more likely to benefit from surgery or prophylactic cranial irradiation after chemoradiation for localized non-small cell lung cancer. *Am J Clin Oncol*. 2002;25(6):583-587.

35. Sorensen JB, Hansen HH, Hansen M, Dombournowsky P. Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. *J Clin Oncol*. 1988;6(9):1474-1480.

36. Jacobs RH, Awan A, Bitran JD, et al. Prophylactic cranial irradiation in adenocarcinoma of the lung. A possible role. *Cancer*. 1987;59(12):2016-2019.

37. Tang SG, Lin FJ, Leung WM. Impact of prophylactic cranial irradiation in adenocarcinoma of the lung. *J Formos Med Assoc*. 1993;92(5):413-419.

38. Komaki R, Meyers CA, Shin DM, et al. Evaluation of cognitive function in patients with limited small cell lung cancer prior to and shortly following prophylactic cranial irradiation. *Int J Radiat Oncol Biol Phys*. 1995;33(1):179-182.

39. Arrieta O, Saavedra-Perez D, Kuri R, et al. Brain metastasis development and poor survival associated with carcinoembryonic
AN et al.

40. Jacot W, Quantin X, Boher JM, et al. Brain metastases at the time of presentation of non-small cell lung cancer: a multicentric AERIO analysis of prognostic factors. Br J Cancer. 2001;84(7):903-909.

41. Mujoomdar A, Austin JH, Malhotra R, et al. Clinical predictors of metastatic disease to the brain from non-small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases. Radiology. 2007;242(3):882-888.

42. Horinouchi H, Sekine I, Sumi M, et al. Brain metastases after definitive concurrent chemoradiotherapy in patients with stage III lung adenocarcinoma: carcinoembryonic antigen as a potential predictive factor. Cancer Sci. 2012;103(4):756-759.

43. Won YW, Joo J, Yun T, et al. A nomogram to predict brain metastases as the first relapse in curatively resected non-small cell lung cancer patients. Lung Cancer. 2015;88(2):201-207.

44. Wang SY, Ye X, Ou W, Lin YB, Zhang BB, Yang H. Risk of cerebral metastases for postoperative locally advanced non-small-cell lung cancer. Lung Cancer. 2009;64(2):238-243.

45. Hubbs JL, Boyd JA, Hollis D, Chino JP, Saynak M, Kelsey CR. Factors associated with the development of brain metastases: analysis of 975 patients with early stage nonsmall cell lung cancer. Cancer. 2010;116(11):2682-2687.

46. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer. 2002;94(10):2698-2705.

47. Fidler IJ, Yano S, Zhang RD, Fujimaki T, Bucana CD. The seed and soil hypothesis: vascularisation and brain metastases. Lancet Oncol. 2002;3(1):53-57.

48. Saad AG, Yeap BY, Thunnissen FB, et al. Immunohistochemical markers associated with brain metastases in patients with nonsmall cell lung carcinoma. Cancer. 2008;113(8):2129-2138.

49. Barak V, Holdenrieder S, Nisman B, Stieber P. Relevance of circulating biomarkers for the therapy monitoring and follow-up investigations in patients with non-small cell lung cancer. Cancer Biomarkers. 2010;6(3-4):191-196.

50. Ceders S, Nunez I, Longo M, et al. Serum tumor markers CEA, CYFRA21-1, and CA-125 are associated with worse prognosis in advanced non-small-cell lung cancer (NSCLC). Clin Lung Cancer. 2011;12(3):172-179.

51. Kalemkerian GP, Akerley W, Bogner P, et al. Small cell lung cancer. J Natl Compr Canc Netw. 2013;11(1):78-98.

52. Cooper EH, Splinter TA, Brown DA, Mueers MF, Peake MD, Pearson SL. Evaluation of a radioimmunoassay for neuron specific enolase in small cell lung cancer. Br J Cancer. 1985;52(3):333-338.

53. Ettinger DS, Akerley W, Borghaei H, et al. Non-small cell lung cancer. J Natl Compr Canc Netw. 2012;10(10):1236-1271.

54. Fiala O, Pesek M, Finek J, et al. The role of neuron-specific enolase (NSE) and thymidine kinase (TK) levels in prediction of efficacy of EGFR-TKIs in patients with advanced-stage NSCLC [corrected]. Anticancer Res. 2014;34(9):5193-5198.

55. Chen Y, Peng W, Huang Y, et al. Significance of serum neuron-specific enolase before treatment in predicting brain metastases and prognosis of advanced non-small cell lung cancer. Zhonghua Zhong Liu Za Zhi [Chin J Oncol]. 2015;37(7):508-511.

56. Icard P, Regnard JF, Essomba A, Panebianco V, Magdeleinat P, Levasseur P. Preoperative carcinoembryonic antigen level as a prognostic indicator in resected primary lung cancer. Ann Thorac Surg. 1994;58(3):811-814.

57. Hotta K, Segawa Y, Takigawa N, et al. Evaluation of the relationship between serum carcinoembryonic antigen level and treatment outcome in surgically resected clinical-stage I patients with non-small-cell lung cancer. Anticancer Res. 2000;20(3b):2177-2180.

58. Graziano SL, Tatum AH, Newman NB, et al. The prognostic significance of neuroendocrine markers and carcinoembryonic antigen in patients with resected stage I and II non-small cell lung cancer. Can Res. 1994;54(11):2908-2913.

59. Ma X, Zhu H, Guo H, et al. Risk factors of brain metastasis during the course of EGFR-TKI therapy for patients with EGFR-mutated advanced lung adenocarcinoma. Oncotarget. 2016;7(49):81906-81917.

60. Villalva C, Duranton-Tanneur V, Guilloteau K, et al. EGFR, KRAS, BRAF, and HER-2 molecular status in brain metastases from 77 NSCLC patients. Cancer Med. 2013;2(3):296-304.

61. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304(5676):1497-1500.

62. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Science. 2002;417:949-954.

63. Pao W, Girard N. New driver mutations in non-small-cell lung cancer. Lancet Oncol. 2011;12(2):175-180.

64. Cortot AB, Italiano A, Burel-Vandenbos F, Martel-Planche G, Hainaut P. KRAS mutation status in primary non-small cell lung cancer and matched metastases. Cancer. 2010;116(11):2682-2687.

65. Daniele L, Cassoni P, Bacillo E, et al. Epidermal growth factor receptor gene in primary tumor and metastatic sites from non-small cell lung cancer. J Thorac Oncol. 2009;4(6):684-688.

66. Gow CH, Chang YL, Hsu YC, et al. Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. Ann Oncol. 2009;20(4):696-702.

67. Han C, Zou H, Ma J, Zhou Y, Zhao J. Comparison of EGFR and KRAS status between primary non-small cell lung cancer and corresponding metastases: a systematic review and meta-analysis. Zhonghua Zhong Liu Za Zhi [Chin J Oncol]. 2010;13(9):882-891.

68. Monaco SE, Nikiforova MN, Cieply K, Teot LA, Khalbuss WE, Dacic S. A comparison of EGFR and KRAS status in primary lung carcinoma and matched metastases. J Natl Compr Canc Netw. 2010;8(1):94-102.

69. Munfs-Mccray D, Harada S, Adams C, et al. EGFR and KRAS mutations in metastatic lung adenocarcinomas. Hum Pathol. 2011;42(10):1447-1453.

70. Eichler AF, Chung E, Kodack DP, Loeffler JS, Fukumura D, Jain RK. The biology of brain metastases—translation to new therapies. Nat Rev Clin Oncol. 2011;8(6):344-356.

71. Matsumoto S, Takahashi K, Ikawa K, et al. Frequent EGFR mutations in brain metastases of lung adenocarcinoma. Int J Cancer. 2006;119(6):1491-1494.

72. Shin DY, Lee DH, Kim CH, et al. Epidermal growth factor receptor mutations and brain metastasis in patients with nonadenocarcinoma of the lung. J Cancer Res Ther. 2016;12(1):318-322.

73. Li Z, Lu J, Zhao Y, Guo H. The retrospective analysis of the frequency of EGFR mutations and the efficacy of
gefitinib in NSCLC patients with brain metastasis. J Clin Oncol. 2011;29(15_suppl):e18065.

74. Bhatt VR, D’Souza SP, Smith LM, et al. Epidermal growth factor receptor mutational status and brain metastases in non-small-cell lung cancer. J Glob Oncol. 2017;3(3):208-217.

75. Benedettini E, Sholl LM, Peyton M, et al. Met activation in non–small cell lung cancer is associated with de novo resistance to EGFR inhibitors and the development of brain metastasis. Am J Pathol. 2010;177(1):415-423.

76. Buonato JM, Lazzara MJ. ERK1/2 blockade prevents epithelial-mesenchymal transition in lung cancer cells and promotes their sensitivity to EGFR inhibition. Can Res. 2014;74(1):309-319.

77. Heon S, Yeap BY, Britt GJ, et al. Development of central nervous system metastases in patients with advanced non-small cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. Clin Cancer Res. 2010;16:5873-5882.

78. Wu YL, Zhong WZ, Li LY, et al. Epidermal growth factor receptor mutations and their correlation with gefitinib therapy in patients with non-small cell lung cancer: a meta-analysis based on updated individual patient data from six medical centers in mainland China. J Thorac Oncol. 2007;2(5):430-439.

79. Huang S-F, Liu H-P, Li L-H, et al. High frequency of epidermal growth factor receptor mutations with complex patterns in non–small cell lung cancers related to gefitinib responsiveness in Taiwan. Clin Cancer Res. 2004;10(24):8195-8203.

80. Sun M, Behrens C, Feng L, et al. HER family receptor abnormalities in lung cancer brain metastases and corresponding primary tumors. Clin Cancer Res. 2009;15(15):4829-4837.

81. Gazdar A. Activating and resistance mutations of EGFR in non–small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene. 2009:28(Suppl 1):S24.

82. Marchetti A, Martella C, Felicioni L, et al. EGFR mutations in non–small–cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. J Clin Oncol. 2005;23(4):857-865.

83. Eichler AF, Kahle KT, Wang DL, et al. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. Neuro-oncology. 2010;12(11):1193-1199.

84. Italiano A, Vandenbos FB, Otto J, et al. Comparison of the epidermal growth factor receptor gene and protein in primary non-small-cell-lung cancer and metastatic sites: implications for treatment with EGFR-inhibitors. Ann Oncol. 2006;17(6):981-985.

85. Baik CS, Chamberlain MC, Chow LQ. Targeted therapy for brain metastases in EGFR-mutated and ALK-rearranged non-small-cell lung cancer. J Thorac Oncol. 2015;10(9):1268-1278.

86. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;368(25):2385-2394.

87. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014;370(13):1189-1197.

88. Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non–small-cell lung cancers. Lung Cancer. 2015;88(1):108-111.

89. Kalikaki A, Koutoumpoulos A, Trypaki M, et al. Comparison of EGFR and K-RAS gene status between primary tumours and corresponding metastases in NSCLC. Br J Cancer. 2008;99(6):923-929.

90. Brugger W, Triller N, Blasinska-Morawiec M, et al. Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non–small-cell lung cancer. J Clin Oncol. 2011;29(31):4113-4120.

91. Massarelli E, Varella-Garcia M, Tang X, et al. KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non–small–cell lung cancer. Clin Cancer Res. 2007;13(10):2890-2896.

92. Wang S, Wang Z. Meta-analysis of epidermal growth factor receptor and KRAS gene status between primary and corresponding metastatic tumours of non–small cell lung cancer. Clin Oncol (R Coll Radiol). 2015;27(1):30-39.

93. Jiang T, Du B, Zhou C. MA 06.11 Distinct mutational landscape and evolutionary trajectories of brain metastasis and liver metastasis in lung adenocarcinoma. J Thorac Oncol. 2017;12:S1823-S1824.

94. Berghoff AS, Inan C, Ricken G, et al. 1324ptumor-infiltrating Lymphocytes (TILS) AND PD-L1 expression in non–small cell lung cancer brain metastases (BM) and matched primary tumors (PT). Ann Oncol. 2014;25:iv465-iv466.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** An N, Jing W, Wang H, et al. Risk factors for brain metastases in patients with non–small-cell lung cancer. Cancer Med. 2018;7:6357–6364. [https://doi.org/10.1002/cam4.1865](https://doi.org/10.1002/cam4.1865)