Risk Factors of Brain Metastasis in Patients with EGFR-Mutated Advanced Non-Small Cell Lung Cancer

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Wen Ouyang
Wuhan University Zhongnan Hospital

Jing Yu
Wuhan University Zhongnan Hospital

Yan Zhou
Wuhan University Zhongnan Hospital

Jing Hu
Wuhan University Zhongnan Hospital

Zhao Huang
Wuhan University Zhongnan Hospital

Junhong Zhang
Wuhan University Zhongnan Hospital

Conghua Xie
Wuhan University Zhongnan Hospital Department of Chemotherapy and Radiation Therapy

chxie_65@whu.edu.cn Corresponding Author
ORCID: https://orcid.org/0000-0003-2836-6373

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Abstract
Purpose NSCLC patients with EGFR mutation was associated with higher incidence of developing brain metastasis (BM). BM is associated with high mortality. Reducing risk of BM becomes increasingly significant for achieving prolonged survival. The aim of the study was to explore the possible risk factors of developing BM during EGFR-TKIs treatment, and to identify the potential candidates for prophylactic cranial irradiation (PCI) or the first-line osimertinib treatment.

Methods A total of 157 consecutive EGFR-mutated advanced NSCLC patients without BM at initial diagnosis in our institute between 2014 and 2018 were included. Comparisons of OS were performed based on BM status. The cumulative incidence of secondary BM was calculated by the Kaplan-Meier method, and the independent risk factors of secondary BM were investigated by multivariate analysis.

Results Patients with secondary BM had worse survival (mOS: 28.6 months) than patients not-developing BM (mOS: 44.8 months). Moreover, the multivariate analysis indicated that age ≤ 49 years (P=0.035), number of extracranial metastases (P=0.013), and malignant pleural effusion (P =0.002) were independent risk factors of secondary BM. Furthermore, the 1-year actuarial risk of developing secondary BM in patients with no risk factor (n =101), 1 risk factor (n =46), and 2 risk factors (n =10) were 7.01%, 14.61%, and 43.75%, respectively (P<0.001).

Conclusions Patients developing secondary BM during EGFR-TKIs treatment have worse outcomes. Our results suggested that EGFR-mutated advanced NSCLC patients with ≥ 1 risk factors were candidates for PCI or the first-line osimertinib treatment.

Introduction
Lung cancer is the leading cause of cancer death all over the world [1]. 80–85% of patients are diagnosed as non-small cell lung cancer (NSCLC) [2]. Despite the presence of the blood-brain barrier (BBB), brain is still a frequent site of NSCLC metastasis. 10% of NSCLC patients present brain metastasis (BM) at their initial diagnosis, and 40–50% of patients develop secondary BM during the course of the disease [3]. The median survival in patients who experience BM without treatment is less than 1 month, and the median survival after whole brain radiation therapy (WBRT) was only 3–6 months [4]. BM is associated with high morbidity, poor prognosis, neurocognitive and life quality
deficits [5]. Therefore, reducing risk of BM becomes increasingly significant for achieving prolonged survival.

Epidermal growth factor receptor (EGFR) mutations are observed in approximately 10-15% of the Caucasian population [6] and more than 50% of the Asian population [7] with non-squamous NSCLC. It was reported that NSCLC patients with EGFR mutation was associated with higher incidence of developing BM [8-10]. In addition, EGFR-tyrosine kinase inhibitors (TKIs) largely improved the survival of EGFR-mutated advanced NSCLC patients [11-13], whereas patients with longer survival exposed to higher risk of BM [8]. Although EGFR-TKIs was reported to pass through BBB and reduce BM in EGFR-mutated NSCLC patients [14,15], there remain some patients developing secondary BM during the course of EGFR-TKIs therapy. Lee et al found that 26% of the patients developed central nervous system (CNS) failure and 13% experienced isolated CNS failure among 166 patients with a clinical benefit to first-generation EGFR-TKIs (gefitinib or erlotinib) treatment [16]. Moreover, EGFR-mutated NSCLC patients with BM had a worse median OS of 25.1 months than the patients without BM (30.2 months) [17]. These results suggested that it was necessary for EGFR-mutated advanced NSCLC patients to reduce risk of developing BM.

How to reduce risk of developing BM for EGFR-mutated advanced NSCLC patients. Firstly, prophylactic cranial irradiation (PCI) is a technique that delivers radiation therapy (RT) to the whole brain to prevent BM occurrence. It was reported to significantly reduce risk of BM and improve overall survival (OS) in patients with limited-stage small cell lung cancer (SCLC) [18]. In addition, osimertinib is an oral, irreversible third-generation EGFR-TKIs with higher penetration in CNS [19-21]. FLAURA study showed the frequency of events of CNS progression was lower in the osimertinib group than in the standard EGFR-TKIs group [21]. However, the results of RTOG-0214 on the effects of PCI in localized NSCLC indicated that PCI reduced BM incidence, whereas failed to improve overall OS [22] and led to decline in immediate and delayed recall [23]. But the 10-years update of RTOG-0214 indicated that patients treated non-operatively have an improved OS (P = 0.026, HR = 1.42, 95% CI: 1.04-1.94) and DFS (P = 0.014) by subgroup analyses, suggesting that PCI might not benefit all patients. For osimertinib, only patients with BM were required to have regular brain scans in FLAURA study, some
cases of asymptomatic progression may not have been detected [13]. Moreover, considering the cost of osimertinib, the first-line osimertinib treatment for EGFR-mutated advanced NSCLC patients still not widely available in most developing countries. These findings prompted us to identify population subsets with higher risk of BM. These patients are candidates for PCI or the first-line osimertinib treatment. Previous studies identified several risk factors of BM in NSCLC, including younger age [24-26], non-squamous cell carcinoma [24], high serum CEA level [27], and disease stages [25,28]. However, they are still controversial and not specific for EGFR-mutated advanced NSCLC patients developing BM during the course of EGFR-TKIs therapy. Consequently, we established a retrospective single-institutional database including consecutive patients with EGFR-mutated advanced NSCLC between January 2014 and June 2018, to evaluate the impact of BM status on OS, to explore the possible risk factors for developing secondary BM during the course of first-generation EGFR-TKIs therapy, and to identify the potential candidates for PCI or the first-line osimertinib treatment. Patients And Methods

Patients

Between January 2014 and June 2018, a total of 157 consecutive EGFR-mutated advanced NSCLC patients without BM at initial diagnosis were studied at the Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University. Our inclusion criteria are: (1) NSCLC was confirmed by cytology (17 pts), or histology (209 pts) (World Health Organization, WHO); (2) EGFR mutations were confirmed by real-time quantitative PCR (ARMS, 188 pts) or Next Generation Sequencing (NGS, 38 pts), using histological or cytological specimens from primary or metastatic lesions; (3) The disease was clinically diagnosed as stage IIIB (10 pts)-IV (216 pts) (American Joint Committee on Cancer, the 7th Edition); (4) Patients had negative results of enhanced magnetic resonance imaging (MRI, 149 pts) or computed tomography (CT, 8 pts) scan of brain before initial treatment; (5) The patients were treatment naive for EGFR-TKI treatment. All patients received comprehensive assessments within 1 month before treatment, including physical and pathological examination, EGFR mutation test, and TNM stage evaluation. The clinical and treatment
characteristics of these included patients grouped by BM status are shown in Table 1

**Treatment and Follow up**
Among the 157 patients without BM at initial diagnosis, 24 patients received chemotherapy as their first-line therapy, and the other 133 patients received EGFR-TKIs treatment initially. EGFR-TKIs (gefitinib, erlotinib, or icotinib) were continuously administered until progression of disease (PD) or intolerable side effects. Treatment beyond PD was allowed upon the judgement of continuously clinical benefit by the oncologists.

Follow-up examinations were performed every 2 months, including thoracic and abdominal CT scan, brain MRI scan. Progression-free survival (PFS) was defined as the time from EGFR-TKIs treatment to PD (including local, regional, or distant progression) or death from any cause. OS was defined as the time from EGFR-TKIs treatment to death from any cause. Brain-metastasis-free survival (BMFS) was defined as the time from EGFR-TKIs treatment to BM occurrence. Treatment responses were evaluated by the response evaluation criteria in solid tumors as complete response (CR), partial response (PR), stable (SD), and progression (PD).

**Statistics**
All statistical analyses were conducted using Statistical Package for Social Scientists (SPSS/Windows, Version 22.0, SPSS Inc., Chicago, USA). Descriptive statistics were used for categorical variables (frequency and percentage) and continuous variables (median and range). The cumulative incidence of BM and survival were calculated by the Kaplan-Meier method with 95% confidence intervals (CIs). Univariable and multivariable Cox regression analyses were performed to explore the risk factors of secondary BM. The multivariable Cox regression analysis simultaneously included factors that had shown associations ($P < 0.100$) in the univariable Cox regression analyses, and variables based on their clinical significance according to previously literature reports. The optimal cut-off values of continuous valuables were calculated by X-tile software [29]. All tests were two-sided and $P < 0.05$ were considered statistically significant.

**Results**
**Patient characteristics**
A total of 229 consecutive patients with EGFR-mutated advanced NSCLC were prospectively studied.
Three patients were excluded due to short EGFR-TKI treatment (< 1 month). And 69 patients were excluded due to synchronous BM. Among the 157 eligible patients, 30 patients (19.1%) developed secondary BM during EGFR-TKIs treatment and 127 patients (80.9%) didn't. The clinical and treatment characteristics of these patients grouped by BM status are shown in Table 1. The median age of the patients without BM and patients developing BM was 60 and 54 years, respectively. Patients who would develop secondary BM were more likely to have a more favorable prognosis (KPS score ≥ 80; 90.5% patients without BM vs. 100% patients developing BM). There was no difference between the two groups with respect to gender, histology, BMI, smoking status, tumor markers level, clinical stages, and extracranial metastases.

The incidence of secondary BM and survival

The median duration of follow-up was 24.1 months (95% CI: 19.6–28.6 months). Thirty patients (19.1%) developed secondary BM during EGFR-TKIs treatment. Among them, patients with symptomatic and asymptomatic BM were 18 (60%) and 12 (40%) respectively. Fourteen patients (46.7%) received WBRT, and 8 patients (26.7%) received stereotactic radiosurgery (SRS) plus continuous EGFR-TKIs treatment, 2 patients (6.7%) received continuous EGFR-TKIs plus supportive care, and 6 patients (20%) switched to chemotherapy. In addition, 9 patients (9/30, 30%) receiving chemotherapy as the first-line treatment developed secondary BM during EGFR-TKIs therapy later. The 1-, 2- and 3-year risks of BM were 11.6%, 22.6% and 29.4% respectively (Fig. 1).

The median OS of these 157 patients was 37.5 months (95% CI: 27.6–47.4 months). The 1-, 2- and 3-year OS rates were 86.9%, 69.8% and 55.9% respectively (Fig. 1). For PFS, 105 patients (66.9%) progressed during follow-up time. Median PFS was 13.6 months (95% CI: 11.2–15.9 months). The 1-, 2- and 3-year PFS rates were 57.8%, 29.4% and 21.3% respectively (Fig. 1). Our median OS and PFS were longer than those of the clinical trials for patients with EGFR-mutated advanced NSCLC [30]. It was largely attributed to the intervention of radiotherapy during EGFR-TKIs treatment.

The overall response rates were partial for 76.4%, stable for 23.0%, and progressive for 0.6% of EGFR-TKIs treatment at the first follow-up examination.

Overall survival of patients grouped by BM status
To evaluate the impact of BM status on OS, these 157 patients were grouped by developing BM and without BM during EGFR-TKIs treatment. Compared with patients without BM, patients developing secondary BM during the course of EGFR-TKIs treatment were at higher risk on OS (HR = 1.86, 95%CI:1.07–3.26). Our findings confirmed that patients developing secondary BM during EGFR-TKIs treatment had poorer outcomes (median OS: 28.6 months) than patients without BM (median OS: 44.8 months, Fig. 2).

Risk factors of developing secondary BM
Several clinical and pathological factors were associated with secondary BM in both univariate and multivariate analyses (Table 2). In univariate analyses, BM was associated with age, the first-line treatment regimens, types of EGFR mutations, numbers of extracranial metastases, and malignant pleural effusion. Other factors such as gender, KPS scores, smoking status, tumor marker levels before treatment, clinical stages, types of EGFR-TKIs, and metastatic locations were not associated with secondary BM.

The factors showing associations ($P < 0.100$) in the univariable Cox regression analyses, as well as other factors that were reported to be associated with BM in previous studies [27,31] were further examined by multivariable Cox regression analysis. Results of multivariate analysis indicated that age $\leq$ 49 years ($P = 0.035$), numbers of extracranial metastases ($P = 0.013$), and documented malignant pleural effusion ($P = 0.002$) were independent high-risk factors of developing secondary BM. Whereas the first-line treatment regimens and types of EGFR mutations were not associated with secondary BM in multivariate Cox regression analysis. Furthermore, the 1-year actuarial risk of developing secondary BM in patients with no risk factor ($n = 101$), 1 risk factor ($n = 46$), and 2 risk factors ($n = 10$) were 7.01%, 14.61%, and 43.75%, respectively ($P < 0.001$, Fig. 3). Obviously, patients with more risk factors had a higher risk of developing secondary BM. Our studies suggested that the patients with $\geq$ 1 risk factors were more likely to benefit from PCI or were candidates for the first-line osimertinib treatment.

Discussion
During the past two decades, the advances of EGFR-TKIs revolutionarily improved the prognosis of
EGFR-mutated advanced NSCLC patients. The WJTOG3405 trial reported that the median OS of
patients with EGFR-mutated advanced NSCLC was up to 30.2 months [32], which is non-inferior to the
outcomes of patients with stage III disease. Our results of 157 EGFR-mutated advanced NSCLC
patients without BM at initial diagnosis showed a median OS of 37.5 months and a median PFS of 13.6
months (Fig.1). Although EGFR-TKIs was reported to be more effective than chemotherapy for BM in
EGFR-mutated NSCLC patients [14,15], patients with longer survival exposed to higher risk of BM [8],
and patients with EGFR mutation was associated with higher incidence of developing BM [8–10]. In
our study, 30 patients (30/157, 19.1%) developed secondary BM during first-generation EGFR-TKIs
treatment, and 1-, 2- and 3-year risks of developing BM were 11.6%, 22.6% and 29.4% respectively
(Fig.1). Therefore, the first-generation EGFR-TKIs therapy resulted in decreased risk of non-BM but
had limited impact on BM.

It was well known that BM is a common reason leading to treatment failure associated with poor
prognosis [33]. In our study, compared with patients without BM, patients developing secondary BM
during the course of EGFR-TKIs treatment were at higher risk on OS (HR = 1.86, 95%CI:1.07–3.26).
Our findings confirmed that patients with secondary BM had worse outcomes (Fig.2) on the condition
that there was no difference on clinical and treatment characteristics between the two groups
grouped by BM status (Table 1). Therefore, reducing risk of BM in EGFR-mutated advanced NSCLC
patients becomes increasingly significant for achieving prolonged survival.

The use of PCI or first-line osimertinib treatment could reduce risk of developing secondary BM for
EGFR-mutated advanced NSCLC patients. However, existing evidences suggest that PCI might just
suitable for patients with a high risk of developing BM, and the high cost of osimertinib leaded to the
first-line osimertinib treatment limited in most developing countries. Therefore, it is important to
identify population subsets with higher risk of BM as candidates for PCI or the first-line osimertinib
treatment. But there is a lack of data for EGFR-mutated advanced NSCLC in literature.

In the present study, multivariate analysis indicated that age ≤ 49 years was correlated with higher
risk of secondary BM (Table. 2). Despite the difference of age cut-off, our results were consistent with
previous studies [25,34]. The underlying mechanism is still to be investigated. It was partly
interpreted that young people may have better performance status, which are associated with longer survival. Moreover, 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 [35]. Further investigations are required to identify the specific reasons that younger patients are more likely to develop BM.

The numbers of extracranial metastases and malignant pleural effusion were also independent risk factors of secondary BM (Table. 2). The underlying mechanism was also unclear. It may be interpreted that both pleural effusion and BM is associated with the angiogenic microenvironment [35]. In addition, the numbers of extracranial metastases are reflection of tumor burden, which was positive correlated with the development of BM.

Furthermore, our results confirmed that the predictive value of gender and KPS score for secondary BM may remain controversial [36]. Previous studies reported that elevated CEA [27,31,36], NSE [24], and CA125 [24] were independent risk factors of BM. However, there is no correlation between tumor markers levels before treatment (including CEA, NSE, and CA125) and the secondary BM in our study. And the first-line treatment regimen was also not associated with secondary BM in our multivariate Cox analysis. Koo et al [37] reported that EGFR-TKIs were effective for EGFR-mutated NSCLC, regardless of treatment timing, which is consistent with our results. In addition, EGFR exon 19 or 21 mutations are now well recognized as different prognostic markers for NSCLC. A recent retrospective study [31] showed that point mutations in exon 21 were independent risk factors of BM. However, our results failed to show a statistical difference in the association between types of EGFR mutations and secondary BM.

Furthermore, the 1-year actuarial risk of developing secondary BM in patients with no risk factor (n = 101), 1 risk factor (n = 46), and 2 risk factors (n = 10) were 7.01%, 14.61%, and 43.75%, respectively ($P < 0.001$, Fig. 3). Obviously, patients with more risk factors had a higher risk of developing secondary BM. Our studies suggested that the patients with $\geq$ 1 risk factors were more likely to benefit from PCI or were candidates for the first-line osimertinib treatment. Certainly, there are several limitations in our study, this was a retrospective study in a single institution, which inevitably
resulted in a selection bias. More finely devised prospective and random study is needed to confirm our results, and the mechanisms of the correlation between these risk factors and secondary BM is to be further explored.

At last, the findings of this study were as follows. First, our studies confirmed EGFR-mutated advanced NSCLC patients with secondary BM had worse outcomes. Second, the multivariate Cox analysis indicated that younger age (≤ 49 years), more extracranial metastases, and malignant pleural effusion were independent risk factors of secondary BM. Third, the patients with more risk factors are more likely to benefit from PCI or the first-line osimertinib treatment.

List Of Abbreviations
BM, brain metastasis; PCI, prophylactic cranial irradiation; BBB, blood-brain barrier; CI, confidence interval; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; CNS, central nervous system; NGS, Next Generation Sequencing; NSE, neuron-specific enolase; DFS, disease free survival; OS, overall survival; PD, progression of disease; PFS, progression-free survival; BMFS, Brain-metastasis-free survival; CR, complete response; PR, partial response; SD, stable; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Declarations
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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions
Conception and design of the work: Wen Ouyang, Jing Yu and Conghua Xie. Acquisition, analysis and interpretation of data: Wen Ouyang, Yan Zhou, Jing Hu, Jing Hu and Yu Xu. Drafting and revising of the article: Wen Ouyang, Junhong Zhang and Conghua Xie. Final approval of the manuscript and
agreement to be accountable for all aspects of the work: All authors.

Ethics approval and consent to participate
This retrospective study was approved by the Ethics Committee of Zhongnan hospital of Wuhan University. Ethics Committee approved oral informed consent, as the data were reviewed and analyzed anonymously. Informed consent was obtained orally from the included patients by telephone.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

References
1. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol. 2006;24:4539-44. https://doi.org/10.1200/JCO.2005.04.4859.
2. Saad AG, Yeap BY, Thunnissen FB, et al. Immunohistochemical markers associated with brain metastases in patients with nonsmall cell lung carcinoma. Cancer. 2008;113:2129-38. https://doi.org/10.1002/cncr.23826.
3. Lin NU, Wefel JS, Lee EQ, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group. Lancet Oncol.2013;14:e407-16. https://doi.org/10.1016/S1470-2045(13)70308-5
4. Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. J Clin Oncol. 2005;23:6207-19. https://doi.org/10.1200/JCO.2005.03.145
5. Kepka L, Cieslak E, Bujko K, et al. Results of the whole-brain radiotherapy for patients with brain metastases from lung cancer: the RTOG RPA intra-classes
analysis. Acta Oncol. 2005;44:389-98. https://doi.org/10.1080/02841860510029699

6. Barlesi F, Mazieres J, Merlio JP, et al. Biomarkers France contributors. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). Lancet. 2016;387:1415-26. https://doi.org/10.1016/S0140-6736(16)00004-0.

7. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947-57. https://doi.org/10.1056/NEJMoa0810699.

8. Han G, Bi J, Tan W, et al. A retrospective analysis in patients with EGFR-mutant lung adenocarcinoma: is EGFR mutation associated with a higher incidence of brain metastasis?. Oncotarget. 2016;7:56998-7010. https://doi.org/10.18632/oncotarget.10933.

9. Bhatt VR, D'Souza SP, Smith LM, Cushman-Vokoun AM, Noronha V, Verma V, et al. Epidermal Growth Factor Receptor Mutational Status and Brain Metastases in Non-Small-Cell Lung Cancer. J Glob Oncol. 2016;3:208-17. https://doi.org/10.1200/JGO.2016.003392.

10. Fan Y, Xu X, Xie C. EGFR-TKI therapy for patients with brain metastases from non-small-cell lung cancer: a pooled analysis of published data. Onco Targets Ther. 2014;7:2075-84. https://doi.org/10.2147/OTT.S67586.

11. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362:2380-8. https://doi.org/10.1056/NEJMoa0909530.

12. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017;376:629-40. https://doi.org/10.1056/NEJMoa1612674.
13. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378:113-25.
https://doi.org/10.1056/NEJMoa1713137.

14. Wu YL, Zhou C, Cheng Y, et al. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG-0803). Ann Oncol. 2013;24:993-9.
https://doi.org/10.1093/annonc/mds529.

15. Weber B, Winterdahl M, Memon A, et al. Erlotinib accumulation in brain metastases from non-small cell lung cancer: visualization by positron emission tomography in a patient harboring a mutation in the epidermal growth factor receptor. J Thorac Oncol. 2011;6:1287-9. https://doi.org/10.1097/JTO.0b013e318219ab87.

16. Lee YJ, Choi HJ, Kim SK, et al. Frequent central nervous system failure after clinical benefit with epidermal growth factor receptor tyrosine kinase inhibitors in Korean patients with non small-cell lung cancer. Cancer. 2010;116:1336-43.
https://doi.org/10.1002/cncr.24877.

17. Sperduto PW, Yang TJ, Beal K, et al. The Effect of Gene Alterations and Tyrosine Kinase Inhibition on Survival and Cause of Death in Patients With Adenocarcinoma of the Lung and Brain Metastases. Int J Radiat Oncol Biol Phys. 2016;96:406-13.
https://doi.org/10.1016/j.ijrobp.2016.06.006.

18. Komaki R, Scott CB, Byhardt R, et al. Failure patterns by prognostic group determined by recursive partitioning analysis (RPA) of 1547 patients on four radiation therapy oncology group (RTOG) studies in inoperable nonsmall-cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys. 1998;42:263-7.
https://doi.org/10.1016/S0360-3016(98)00213-2.

19. Cross DA, Ashton SE, Ghiorghi S, et al. AZD9291, an irreversible EGFR TKI,
overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014;4:1046-61. https://doi.org/10.1158/2159-8290.cd-14-0337.

20. Ballard P, Yates JW, Yang Z, et al. Preclinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant NSCLC Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity. Clin Cancer Res. 2016;22:5130-40. https://doi.org/10.1158/1078-0432.ccr-16-0399.

21. Vansteenkiste J, Reungwetwattana T, Nakagawa K, et al. CNS response to osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFR-TKI sensitising mutation (EGFRm)-positive advanced non-small cell lung cancer (NSCLC): Data from the FLAURA study. Ann Oncol. 2017;28. https://doi.org/10.1093/annonc/mdx729.007.

22. 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;29:272-8. https://doi.org/10.1200/JCO.2010.29.1609.

23. Sun A, Bae K, Gore EM, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. J Clin Oncol. 2011;29:279-86. https://doi.org/10.1200/JCO.2010.29.6053

24. 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;89:330-7. https://doi.org/10.1016/j.ijrobp.2014.02.025

25. Ceresoli GL, Reni M, Chiesa G, et al. Brain metastases in locally advanced nonsmall cell lung carcinoma after multimodality treatment: risk factors analysis. Cancer. 2002;95:605-12. https://doi.org/10.1002/cncr.10687.
26. 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;23:2955-61. https://doi.org/10.1200/JCO.2005.08.026.

27. Arrieta O, Saavedra-Perez D, Kuri R, et al. Brain metastasis development and poor survival associated with carcinoembryonic antigen (CEA) level in advanced non-small cell lung cancer: a prospective analysis. BMC Cancer. 2009;9:119. https://doi.org/10.1186/1471-2407-9-119

28. Robnett TJ, Machtay M, Stevenson JP, et al. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. J Clin Oncol. 2001;19:1344-9. https://doi.org/10.1200/JCO.2001.19.5.1344.

29. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res. 2004;10:7252-9. https://doi.org/10.1158/1078-0432.CCR-04-0713.

30. Roeper J, Griesinger F. Epidermal growth factor receptor tyrosine kinase inhibitors in advanced nonsmall cell lung cancer: what is the preferred first-line therapy?. Curr Opin Oncol. 2019;31:1-7. https://doi.org/10.1097/CCO.0000000000000495.

31. Ma X, Zhu H, Guo H, et al. Risk factors of brain metastasis during the course of EGFR-TKIs therapy for patients with EGFR-mutated advanced lung adenocarcinoma. Oncotarget. 2016;7:81906-17. https://doi.org/10.18632/oncotarget.11918.

32. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010;11:121-8. https://doi.org/10.1016/S1470-2045(09)70364-X.

33. Arrieta O, Villarreal-Garza C, Zamora J, et al. Long-term survival in patients with non-
small cell lung cancer and synchronous brain metastasis treated with whole-brain radiotherapy and thoracic chemoradiation. Radiat Oncol. 2011;6:166. https://doi.org/10.1186/1748-717X-6-166.

34. 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;3:287-94. https://doi.org/10.2147/CMR.S22717.

35. Cedrés S, Nuñez 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;12:172-9. https://doi.org/10.1016/j.cllc.2011.03.019.

36. An N, Jing W, Wang H, et al. Risk factors for brain metastases in patients with non-small-cell lung cancer. Cancer Med. 2018;7:6357-64. https://doi.org/10.1002/cam4.1865.

37. Koo DH, Kim KP, Choi CM, et al. EGFR-TKI is effective regardless of treatment timing in pulmonary adenocarcinoma with EGFR mutation. Cancer Chemother Pharmacol. 2015;75:197-206. https://doi.org/10.1007/s00280-014-2631-5.

Tables

Table 1. Baseline and treatment characteristics of patients grouped by BM status
| Characteristic                                      | Patients without BM (n=127) | Patients developing BM (n=30) |
|----------------------------------------------------|-----------------------------|-----------------------------|
|                                                    | NO.  | %     | NO.  | %     |
| Age, years                                         |      |       |      |       |
| ≤ 49                                               | 24   | 18.9  | 12   | 40.0  |
| > 49                                               | 103  | 81.1  | 18   | 60.0  |
| Median(Range)                                      | 60(28-93) |     | 54(33-75) |     |
| Gender                                             |      |       |      |       |
| Male                                                | 63   | 49.6  | 14   | 46.7  |
| Female                                              | 64   | 50.4  | 16   | 53.3  |
| KPS score                                           |      |       |      |       |
| ≥80                                                 | 115  | 90.5  | 30   | 100   |
| <80                                                 | 12   | 9.5   | 0    | 0     |
| Histology                                          |      |       |      |       |
| Adenocarcinoma                                     | 122  | 96.1  | 28   | 93.3  |
| Non-adenocarcinoma                                 | 5    | 3.9   | 2    | 6.7   |
| BMI Mean(95%CI)                                    | 21.9 (14.9-28.8) |     | 22.7 (16.3-29.2) |     |
| Smoking status                                      |      |       |      |       |
| Yes                                                 | 42   | 33.1  | 8    | 26.7  |
| No                                                  | 85   | 66.9  | 22   | 73.3  |
| CEA (ng/ml) Median(Range)                          | 23.5 (0.5-8048) |     | 30.5 (1.5-1819) |     |
| CA125 (ng/ml) Median(Range)                        | 52.9 (4.76-3369) |     | 69.4 (11.3-954.5) |     |
| NSE(ng/ml) Median(Range)                           | 15.0 (4.4-133.1) |     | 15.2(7.6-55.2) |     |
| First-line treatment regimen                        |      |       |      |       |
| EGFR-TKI treatment                                  | 112  | 88.2  | 21   | 70    |
| Chemotherapy                                        | 15   | 11.8  | 9    | 30    |
| Type of EGFR mutations                              |      |       |      |       |
| Exon 21 point                                       | 49   | 38.6  | 14   | 46.7  |
| Exon 19 deletion                                    | 67   | 52.8  | 11   | 36.7  |
| Other                                               | 11   | 8.6   | 5    | 16.7  |
| NO. of extracranial metastases                     |      |       |      |       |
| 0                                                   | 8    | 6.3   | 2    | 6.7   |
| 1                                                   | 65   | 51.2  | 14   | 46.7  |
| 2                                                   | 42   | 33.1  | 10   | 33.3  |
| 3 or more                                           | 12   | 9.4   | 4    | 13.3  |
| Clinical stages                                     |      |       |      |       |
| Stage IIIB                                          | 8    | 6.3   | 2    | 6.7   |
| Stage IV                                           | 119  | 93.7  | 28   | 93.3  |
| Location of extracranial metastatic sites          |      |       |      |       |
| Pleural effusion                                    | 8    | 6.3   | 6    | 20.0  |
| Liver                                               | 17   | 13.4  | 4    | 13.3  |
| Adrenal                                             | 17   | 13.4  | 1    | 3.3   |
| Bone                                                | 73   | 57.5  | 18   | 60    |
| Lung                                                | 75   | 59.1  | 17   | 56.6  |
| Other                                               | 12   | 9.4   | 2    | 6.7   |
| Types of EGFR-TKIs                                  |      |       |      |       |
| Gefitinib                                           | 80   | 63.0  | 19   | 63.3  |
| Erlotinib                                           | 31   | 24.4  | 7    | 23.3  |
| Icotinib                                            | 16   | 12.6  | 4    | 13.4  |
| Local therapy for BM                                |      |       |      |       |
| None                                                | NA   |       | 8    | 26.7  |
| WBRT                                                | NA   |       | 14   | 46.7  |
| SRS                                                 | NA   |       | 8    | 26.6  |

Table 2: Univariate and multivariate analyses for the factors associated with risks for secondary BM
| Factors | Univariate analysis Incidence of BM (%) |
|---------|---------------------------------------|
|         | HR    | 95% CI      | P     |
| Gender: female VS male | 1.139 | 0.556-2.337 | 0.772 |
| Age, years | 0.963 | 0.931-0.995 | 0.023 |
| > 49 VS ≤ 49 | 0.341 | 0.160-0.720 | 0.005 |
| KPS score: <80 VS ≥80 | 0.045 | 0.000-4.173 | 0.371 |
| BMI | 1.035 | 0.922-1.161 | 0.562 |
| Smoking: yes VS no | 0.798 | 0.353-1.801 | 0.586 |
| Tumor markers level before treatment | | | |
| CEA (ng/ml) | 1.000 | 0.999-1.000 | 0.685 |
| CA125 (ng/ml) | 1.000 | 0.998-1.001 | 0.498 |
| NSE (ng/ml) | 1.014 | 0.985-1.043 | 0.351 |
| First-line treatment regimen | | | |
| Chemotherapy VS EGFR-TKI | 2.296 | 1.050-5.018 | 0.037 |
| Type of EGFR mutations | | | |
| 19-del VS L858R | 0.579 | 0.263-1.277 | 0.176 |
| Other VS L858R | 1.968 | 0.703-5.508 | 1.968 |
| Clinical stapes:IIIB VS.IV | 0.501 | 0.152-1.653 | 0.257 |
| Type of EGFR-TKIs | | | |
| Erlotinib VS Gefitinib | 0.422 | 0.118-1.503 | 0.518 |
| Icotinib VS Gefitinib | 0.460 | 0.109-1.946 | 0.292 |
| NO. of extracranial metastasis | | | |
| 0-2 VS 3 or more | 0.523 | 0.181-1.514 | 0.232 |
| Location of extracranial metastasis | | | |
| Pleural effusion | 3.245 | 1.300-8.098 | 0.012 |
| Liver | 1.066 | 0.371-3.062 | 0.906 |
| Adrenal | 0.242 | 0.033-1.779 | 0.163 |
| Bone | 1.161 | 0.558-2.413 | 0.690 |
| Lung | 1.543 | 0.685-3.475 | 0.295 |
| Other | 1.332 | 0.317-5.605 | 0.696 |

Figures
Kaplan-Meier plot of OS, PFS, and BMFS in EGFR-mutated advanced NSCLC patients without BM at initial diagnosis. OS, overall survival; PFS, progression-free survival; BMFS, brain-metastasis-free survival; NSCLC, non-small cell lung cancer; BM, brain-metastases; CI, confidence interval.
Figure 2

Kaplan-Meier plot of OS in patients with EGFR-mutated advanced NSCLC grouped on BM status. OS, overall survival; NSCLC, non-small cell lung cancer; BM, brain-metastases; CI, confidence interval.
Figure 3

Comparison of the actuarial risk of developing secondary BM among patients with different numbers of risk factors.