J Oncol Sci 5 (2019) 65–69

Contents lists available at ScienceDirect

J Oncol Sci

journal homepage: www.journalofoncology.org

Original Article

The relationship between EGFR mutation and metastasis pattern in lung adenocarcinoma

Ismail Beypinar [a,*], Hacer Demir [a], Murat Araz [b], Mukremin Uysal [a]

[a] Afyonkarahisar Health Sciences University School of Medicine, Department of Internal Medicine and Medical Oncology, Turkey
[b] Necmettin Erbakan University School of Medicine, Department of Internal Medicine and Medical Oncology, Turkey

ARTICLE INFO

Article history:
Received 19 June 2019
Received in revised form
17 July 2019
Accepted 6 August 2019
Available online 9 August 2019

Keywords:
Non-small cell lung cancer
Adenocarcinoma
EGFR mutation
Metastasis pattern

ABSTRACT

Aim: The metastatic pattern of non-small cell lung cancer (NSCLC) has been described in several studies. Frequent metastatic sites are lung, liver, bone, surrenal, and brain. Hypotheses were speculated to explain the tendency of specific sites. Over-expression of EGFR alters the biology and tumoral behavior. The mutations of EGFR mainly occur in exon 19, and 21and could lead the way through the tumor growth and metastasis. We try to elucidate the relationship between EGFR mutation and metastatic pattern.
Material and Method: In this retrospective nested case-control study, one hundred and five patients diagnosed with lung adenocarcinoma included who had EGFR mutation status and imaging studies at the time of diagnosis.
Results: The metastatic pattern was not different between EGFR mutant and wild type patients. There was no statistical difference in terms of survival between EGFR mutant and wild type patients ($p = 0.25$). The OS according to the organ metastasis between EGFR mutant and wild type group was not significant except liver. The EGFR mutant patients with liver metastasis had better survival compared with wild type patients ($p = 0.04$). Also, the multiplicity and solidarity of the metastatic tumors were compared in metastatic organs. There was no significant difference between groups. The subsequent EGFR mutation type was not related to the metastatic pattern.
Conclusion: The incidence of the metastatic sites was not different between EGFR mutant and wild type patients in our study. In contrast to the literature, liver metastasis found to be related to improved OS.

1. Introduction

Several studies have been described as the metastatic pattern of non-small cell lung cancer (NSCLC). The most frequent metastatic sites are lung, liver, bone, surrenal, and brain. Hypotheses were speculated to explain the tendency of specific sites.[1,2] In the first theory, Paget tried to explain the metastatic spread with hospitable environmental factors.[3] The secondary theory suggested for vascular and lymphatic flow pattern by Ewing.[4] Multiple properties acquired by tumors for metastatic spread, numbers, and sites. These features might reflect tumor development.[5]

New discovered factors for the development metastasis are driver mutations which determine the tumoral behavior. The epidermal growth factor receptor (EGFR) regulates the signal transducing through the nucleus, which is responsible for DNA synthesis and cell proliferation. Over-expression of EGFR alters the biology and tumoral behavior. EGFR mutations mainly occur in exon 19 and 21. The mutations of EGFR could lead the way through the tumor growth, and metastasis.[6] Also, after the discovery of the tyrosine kinase inhibitors (TKIs) the mutations related to treatment response and survival.[7–9] The EGFR mutant tumors reported having increased progression-free survival and overall survival when compared with EGFR wild type and KRAS mutant tumors.[8,10,11] The amplification in human epidermal growth factor receptor-2 (HER-2) in EGFR/ERB pathway alters the tumor biology in breast cancer.[12] Some studies showed that EGFR mutant lung cancer might have more frequent brain metastases.[13–17]

This study tries to compare the effect of EGFR mutation on the metastatic sites of the lung adenocarcinoma.

* Corresponding author. Afyonkarahisar Health Sciences University School of Medicine, Department of Internal Medicine and Medical Oncology, Afyonkarahisar, Turkey.
E-mail address: ibeypinar@yahoo.com (I. Beypinar).
Peer review under responsibility of Turkish Society of Medical Oncology.

https://doi.org/10.1016/j.jons.2019.08.002

2. Material and Methods

2.1. Patient selection

In this retrospective nested case-control study, 1085 lung cancer patient records between 2013 and 2019 were retrospectively analyzed. Nine hundred and eighty patients excluded due to non-adenomatous histology, lost follow-up and lack of EGFR testing. One hundred and five patients included in this study who had EGFR mutation status and imaging studies at the time of diagnosis. The patients who harbored ROS-1, ALK were excluded (Fig. 1). The EGFR testing was heterogenous among the study population. Although some patients had RAS, C-KIT and other mutations; this data was ignored lack of next generation sequencing for whole study population. The age, gender, smoking period, and stages of the patients were recorded.

2.2. Statistical analysis

The association between pre-treatment EGFR mutation status, metastatic sites, and other clinical categorical parameters were evaluated with Pearson's chi-square test. The numerical data of age and cumulative smoking time of the patients were compared between EGFR groups with the Mann-Whitney U test. A p-value <0.05 was determined to be statistically significant.

2.3. Ethics

The study was approved by the ethics committee at Afyonkarahisar Health Sciences University Faculty of Medicine and carried out by the Declaration of Helsinki principles and all applicable regulations.

3. Results

Out of 105 patients, 27 patients were EGFR mutant, while 78 patients were EGFR wild type. The median age of the two groups was 64 years. The genders of the patients due to EGFR mutations were not significantly different between groups. Also, smoking status was not different between groups. The metastatic pattern at the time of diagnosis was not different between groups (Table 1) (Graph 1). Also, the multiplicity and solidarity of the metastatic tumors were compared in metastatic organs. There was no significant difference between groups. The subsequent EGFR mutation type was not related to the metastatic pattern (Table 2).

Sixty-six percent of the EGFR mutant patient received anti-EGFR tyrosine kinase inhibitors (TKIs). Most of the patients who harbor EGFR mutation treated with TKIs on the second-line (77.8%). The patients who had not received TKIs mostly harbored untreatable EGFR mutations. Two patients had concurrent ALK rearrangement and received anti-ALK TKIs before anti-EGFR treatment. Only one patient had treated with immunotherapy in the whole study population who harbored EGFR mutation.

There was no statistical difference in terms of survival between EGFR mutant and wild type patients ($p = 0.25$) (Fig. 2). The median OS was 14 and 13 months, respectively.

The similarity between groups in terms of OS remained even when the untargeted EGFR mutations excluded ($p = 0.17$). The patients who harbored targetable (exon 19 and 21) significantly had an improved OS when compared with insignificant EGFR mutations (exon 17,20,23). ($p = 0.02$).

The OS according to the organ metastasis between EGFR mutant

Table 1
The demographic and metastatic pattern of the groups according to the EGFR mutation.

	EGFR mutant (n:27)	EGFR WT (n:78)	P value
Age (Years)	64*	64*	0.64
Gender (Male/Female)	18/9	62/16	0.17
Smoking Status (Yes/No)	14/12	56/12	0.07
Lung	13/27 (48%)	28/78 (35%)	0.26
Liver	4/27 (14%)	9/78 (11%)	0.65
Bone	11/27 (40%)	33/78 (42%)	0.88
Brain	5/27 (18%)	14/78 (17%)	0.94
Adrenal	5/27 (18%)	13/78 (16%)	0.82
Lymph node	25/27 (92%)	75/78 (96%)	0.45
Pleura	7/27 (25%)	17/78 (21%)	0.66

*: Median values, WT: Wild Type.

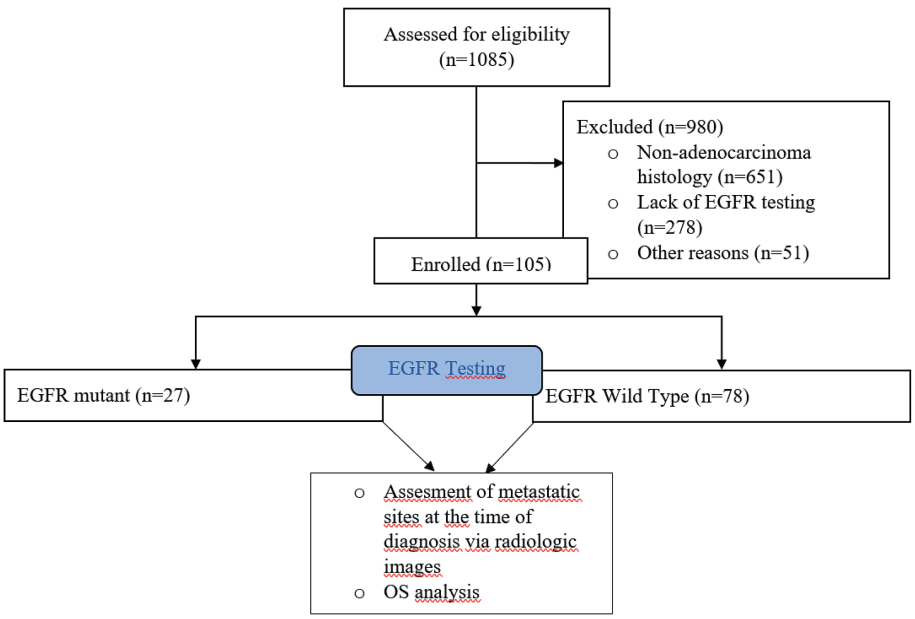
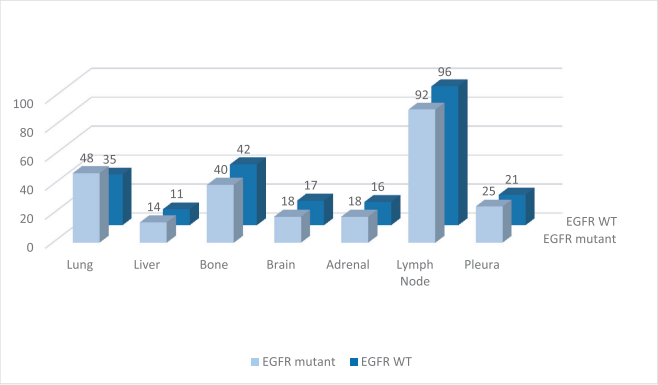


Fig. 1. Study flow diagram.



Graph 1. The percentage of metastatic organs due to EGFR mutation status.

Table 2
The metastatic locations of the tumors due to the type of EGFR mutations.

EGFR mutation	Exon 19	Exon 21	Insignificant	P value
Lung	2/5	4/8	4/5	0.40
Liver	1/5	2/8	1/5	0.96
Bone	3/5	4/8	1/5	0.40
Brain	2/5	0/8	1/5	0.16
Adrenal	1/5	1/8	1/5	0.91
Lymph node	5/5	6/8	5/5	0.24
Pleura	3/5	2/8	0/5	0.10

and wild type group was not significant except liver. The EGFR mutant patients with liver metastasis had better survival compared with wild type patients ($p = 0.04$) (Fig. 3). The median OS in EGFR mutant and wild type patients was 14 and 2 months, respectively.

4. Discussion

Our study showed no difference between the metastatic pattern of the lung adenocarcinoma according to the EGFR mutation. Also, the type of EGFR mutation has not related to the spread of the primary tumor. Although some studies reported an elevation in the incidence of the lung and brain metastases in EGFR mutant population when compared with EGFR wild type group, our study failed to show a relationship between these groups.[18] The difference of metastasis characteristics of the lung adenocarcinoma was described by case reports which showed the miliary spread of the tumor which had exon 19 deletions in EGFR gene.[19] Sekin et al. showed the EGFR mutations in exon 19 might have a relationship in smaller and multiple brain metastases.[20] Some other studies recurrently reported small, military metastasis of EGFR mutated tumors in lung cancer.[18,20,21] The solidarity of the metastases was also compared across groups in our study, but no significant difference was observed. The racial and genetic differences between these study populations may alter the study results. Although the smoking status was not different between groups, Kirsten rat sarcoma viral oncogene homolog (K-RAS) mutation status was unknown. It is known that the tumors are harboring K-RAS mutation significantly aggressive.[8,10,11,22] The study, which compared the bone and brain metastasis between EGFR and K-RAS mutant patients, showed no difference.[22] In a different study, the metastatic pattern of the EGFR, K-RAS, anaplastic lymphoma kinase (ALK) and triple negative patients was not different across groups.[12] Most reported results from the Asian population, which may differ in Caucasian ethnicity. In all these studies, the targetable driver EGFR mutations were evaluated. It is still unclear the insignificant EGFR mutations affecting the metastatic patterns of the lung adenocarcinoma.

In our study, we found no difference in terms of OS between EGFR mutant and wild type patients. Although some studies

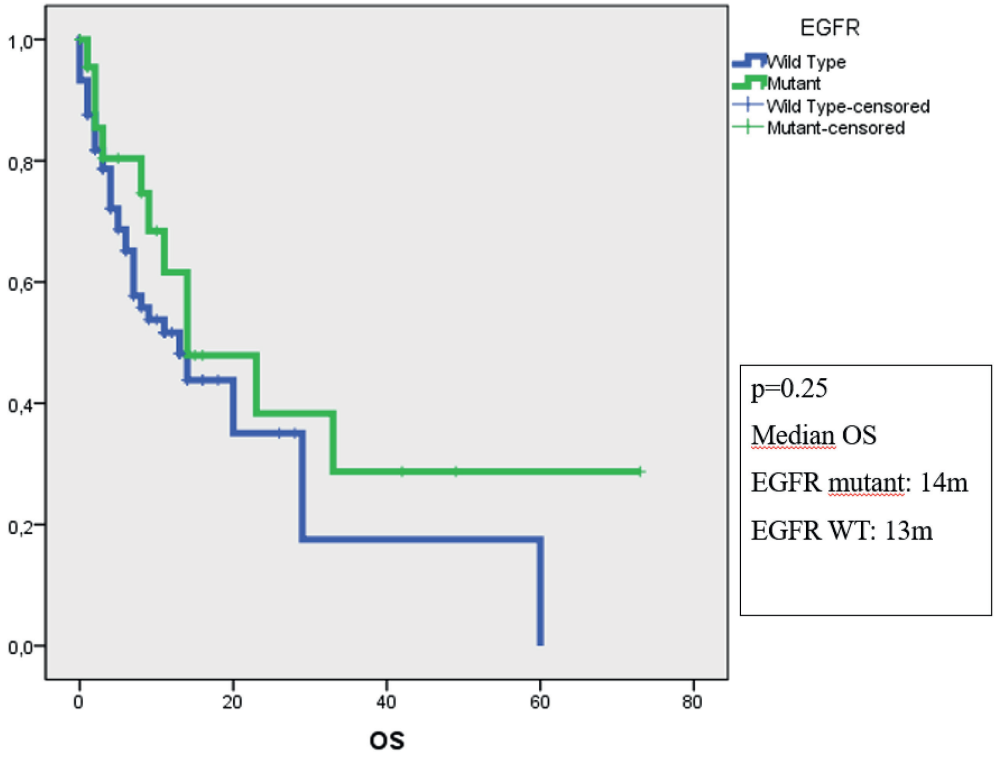


Fig. 2. The OS of the patients according to the EGFR mutations.

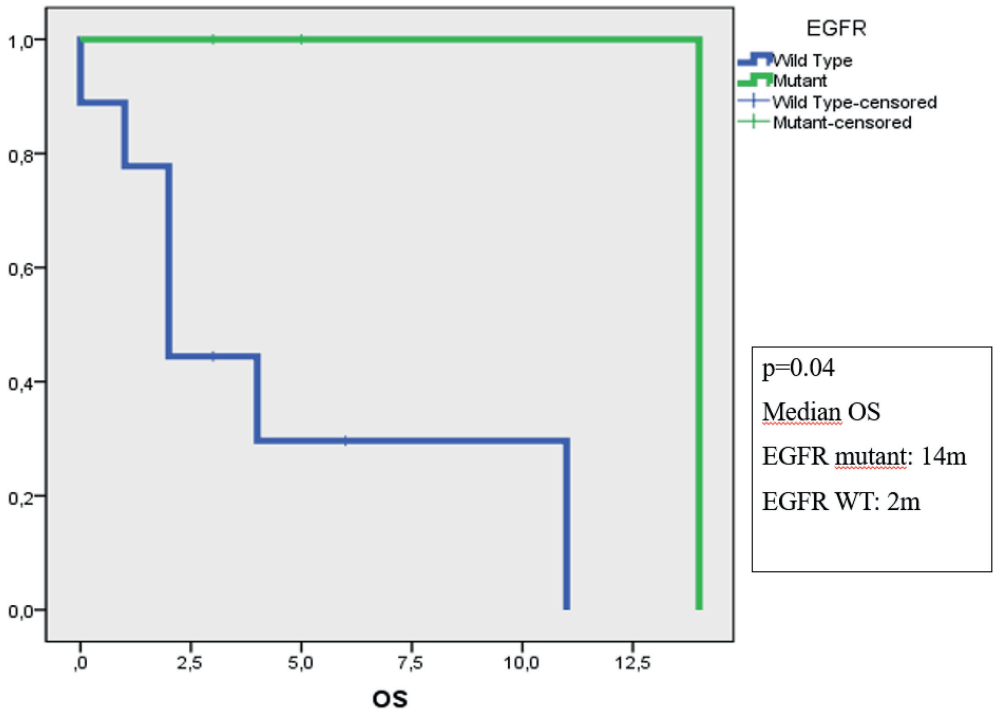


Fig. 3. The OS of the patients with liver metastasis according to the EGFR mutation status.

showed significant survival differences with the treatment of anti-EGFR agents, our study showed no difference between groups.[18,23] The possible explanation the insignificant results were high smoking ratio among EGFR mutant group, the unavailability of ALK and ROS-1 mutation results in most of the patients, and frequent second line anti-EGFR treatment selection. Two of the EGFR mutant patients had concurrent ALK mutations, which might result in resistance to treatment with anti-EGFR TKIs.[24] Also, KRAS mutation status was uncertain between groups. The high smoking ratio in EGFR mutant group might be responsible for concurrent KRAS mutations which were reported to be related with anti-EGFR TKIs resistance.[25]

The current literature reports the liver metastasis-related to poorer outcomes and decreased survival in NSCLC with EGFR mutations.[26,27] Tsu et al. also reported decreased survival in patients with liver metastasis. Despite the other results, we found better survival in metastatic liver patients. The difference from the current literature may be related to study populations features. The high smoking ratio among EGFR mutant group and untreatable EGFR mutations have a role in OS difference in patients with liver metastasis. There are several studies which address the bone and brain metastasis in NSCLC related with worse OS. The two metastatic sites were considered to be independent risk factors. Skeletal-related events such as fractures and spinal cord compression may be related to worse outcomes in this patient group.[28–30] In a study which compared NSCLC EGFR mutant, wild type, and KRAS mutant patients, Hendriks et al. found no difference between metastasis patterns of the groups. Interestingly the OS of the groups were different after bone metastasis occurs. The EGFR mutant patients had a better OS when compared with wild type and KRAS mutant patients.[22] The discovery of the second line anti-EGFR agents such as osimertinib increased the control rates of the brain metastasis.[31] In our study, we found no difference between EGFR wild type and mutant patients in terms of OS who had brain and bone metastasis. The similarity of OS in brain metastasis might be related to the use of first-generation anti-EGFR agents. No patients received osimertinib or two lines of anti-EGFR therapies.

4.1. Study limitations

Our study was a retrospective nested case-control study which made data quality low. Also, the high smoking status in the EGFR mutant group may affect survival. The KRAS, ALK, and ROS-1 mutation status were un available in most of the patients, which were a limiting factor. Although the EGFR tyrosine kinase inhibitors were not evaluated across EGFR mutated patients, second generation anti-EGFR agents were not available in the selected patient population, which did not affect the central nervous system disease control and survival.

5. Conclusion

The incidence of the metastatic sites was not different between EGFR mutant and wild type patients in our study. In contrast to the literature, liver metastasis found to be related to improved OS. Although some studies reported the effect of tumoral behavior with targetable EGFR mutations, further studies needed to evaluate different types of mutations in NSCLC.

Conflicts of interest

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Viadana E. K-L A. Patterns of metastases in adenocarcinomas of man. An autopsy study of 4,728 cases. *J Med*. 1975;6(1):1–14.

2. Hess KR, Varadhachary GR, Taylor SH, et al. Metastatic patterns in adenocarcinoma. *Cancer*. 2006. https://doi.org/10.1002/cncr.21778.
3. Paget S. THE DISTRIBUTION OF SECONDARY GROWTHS IN CANCER OF THE BREAST. *Lancet*. 1889. https://doi.org/10.1016/S0140-6736(00)49915-0.
4. Neoplastic Diseases. A treatise on tumours. By James Ewing, A.M., M.D., Sc.D., professor of pathology at cornell university medical college, N.Y.; pathologist to the memorial hospital. Third edition. Royal 8vo. Pp. 1127, with 546 illustrations. 1928. *Phil. BJS*. 1928;16(61):174–175. https://doi.org/10.1002/bjs.1800166126.
5. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol*. 2011. https://doi.org/10.1038/nrclinonc.2011.44.
6. Fujino S, Enokibori T, Tezuka N, et al. A comparison of epidermal growth factor receptor levels and other prognostic parameters in non-small cell lung cancer. *Eur J Cancer A*. 1996. https://doi.org/10.1016/S0959-8049(96)00243-2.
7. Douillard JY, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. *J Clin Oncol*. 2010. https://doi.org/10.1200/JCO.2009.24.3030.
8. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. *N Engl J Med*. 2004. https://doi.org/10.1056/NEJMoa040938.
9. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non - small-cell lung cancer in Asia (IPASS). *J Clin Oncol*. 2011. https://doi.org/10.1200/JCO.2010.33.4235.
10. Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947–957. https://doi.org/10.1056/NEJMoa0810699.
11. Johnson ML, Sima CS, Chaft J, et al. Association of KRAS and EGFR mutations with survival in patients with advanced lung adenocarcinomas. *Cancer*. 2013. https://doi.org/10.1002/cncr.27730.
12. Lin NU, Winer EP. Brain metastases: the HER2 paradigm. *Clin Cancer Res*. 2007. https://doi.org/10.1158/1078-0432.CCR-06-2478.
13. Eichler AF, Kahle KT, Wang DL, et al. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. *Neuro Oncol*. 2010. https://doi.org/10.1093/neuonc/noq076.
14. 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 nonsmall-cell lung cancer. *Cancer*. 2010. https://doi.org/10.1002/cncr.24877.
15. Matsumoto S, Takahashi K, Iwakawa R, et al. Frequent EGFR mutations in brain metastases of lung adenocarcinoma. *Int J Cancer*. 2006. https://doi.org/10.1002/ijc.21940.
16. Omuro AMP, Kris MG, Miller VA, et al. High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib. *Cancer*. 2005. https://doi.org/10.1002/cncr.21033.
17. Welsh JW, Komaki R, Amini A, et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J Clin Oncol*. 2013. https://doi.org/10.1200/JCO.2011.40.1174.
18. Hsu F, De Caluwe A, Anderson D, Nichol A, Toriumi T, Ho C. Patterns of spread and prognostic implications of lung cancer metastasis in an era of driver mutations. *Curr Oncol*. 2017;24(4):228–233. https://doi.org/10.3747/co.24.3496.
19. Laack E, Simon R, Regier M, et al. Miliary never-smoking adenocarcinoma of the lung: strong association with epidermal growth factor receptor exon 19 deletion. *J Thorac Oncol*. 2011. https://doi.org/10.1097/JTO.0b013e3181fb7cf1.
20. Sekine A, Kato T, Hagiwara E, et al. Metastatic brain tumors from non-small cell lung cancer with EGFR mutations: distinguishing influence of exon 19 deletion on radiographic features. *Lung Cancer*. 2012. https://doi.org/10.1016/j.lungcan.2011.12.017.
21. Poonia S, Berge EM, Aisner DL, Damek D, Doebele RC. EGFR exon 19 deletion mutations and systemic/central nervous system miliary metastasis: clinical correlations and response to therapy. *Clin Lung Cancer*. 2014;15(5):387–389. https://doi.org/10.1016/j.cllc.2014.04.005.
22. Hendriks LEL, Smit EF, Vosse BAH, et al. EGFR mutated non-small cell lung cancer patients: more prone to development of bone and brain metastases? *Lung Cancer*. 2014. https://doi.org/10.1016/j.lungcan.2014.01.006.
23. Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009. https://doi.org/10.1056/NEJMoa0810699.
24. Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. *Clin Cancer Res*. 2008. https://doi.org/10.1158/1078-0432.CCR-08-0168.
25. Ulivi P, Chiadini E, Dazzi C, et al. Nonsquamous, non-small-cell lung cancer patients who carry a double mutation of EGFR, EML4-ALK or KRAS: frequency, clinical-pathological characteristics, and response to therapy. *Clin Lung Cancer*. 2016. https://doi.org/10.1016/j.cllc.2015.11.004.
26. Mordant P, Arame A, De Dominicis F, et al. Which metastasis management allows long-term survival of synchronous solitary M1b non-small cell lung cancer? *Eur J Cardiothorac Surg*. 2012. https://doi.org/10.1093/ejcts/ezr042.
27. Wu KL, Tsai MJ, Yang CJ, et al. Liver metastasis predicts poorer prognosis in stage IV lung adenocarcinoma patients receiving first-line gefitinib. *Lung Cancer*. 2015. https://doi.org/10.1016/j.lungcan.2015.02.012.
28. Kuchuk M, Kuchuk I, Sabri E, Hutton B, Clemons M, Wheatley-Price P. The incidence and clinical impact of bone metastases in non-small cell lung cancer. *Lung Cancer*. 2015. https://doi.org/10.1016/j.lungcan.2015.04.007.
29. Tsuya A, Kurata T, Tamura K, Fukuoka M. Skeletal metastases in non-small cell lung cancer: a retrospective study. *Lung Cancer*. 2007. https://doi.org/10.1016/j.lungcan.2007.03.013.
30. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev*. 2001. https://doi.org/10.1053/ctrv.2000.0210.
31. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol*. August 2018. https://doi.org/10.1200/JCO.2018.78.3118. JCO2018783118.