



Original Article

The relationship between EGFR mutation and metastasis pattern in lung adenocarcinoma

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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 21 and 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.

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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.

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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.

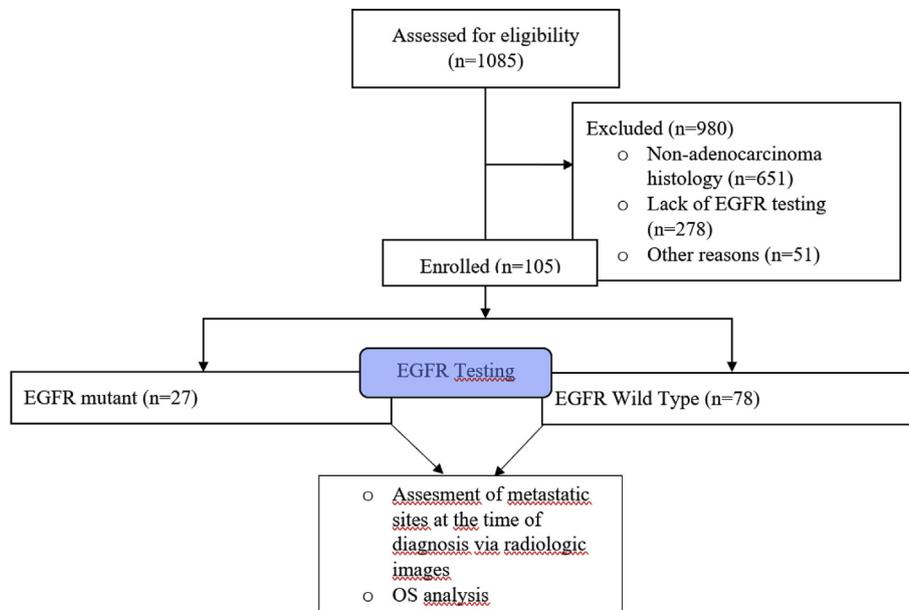
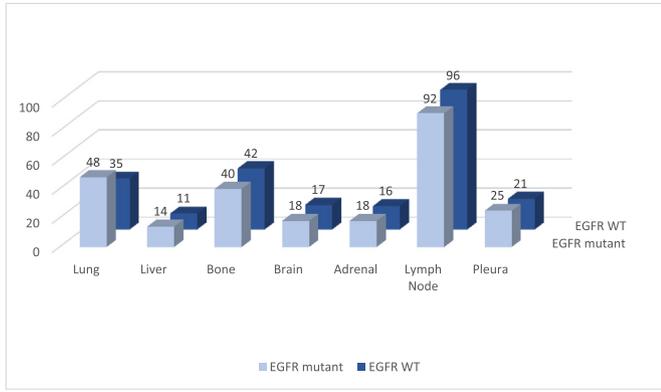


Fig. 1. Study flow diagram.



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, miliary 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

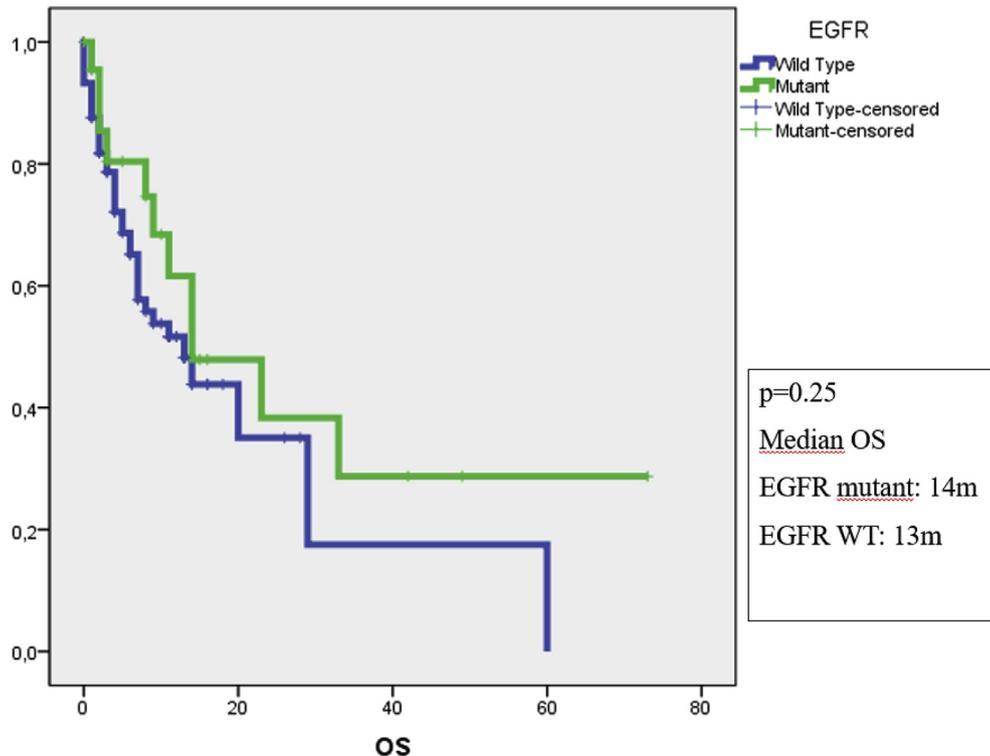


Fig. 2. The OS of the patients according to the EGFR mutations.

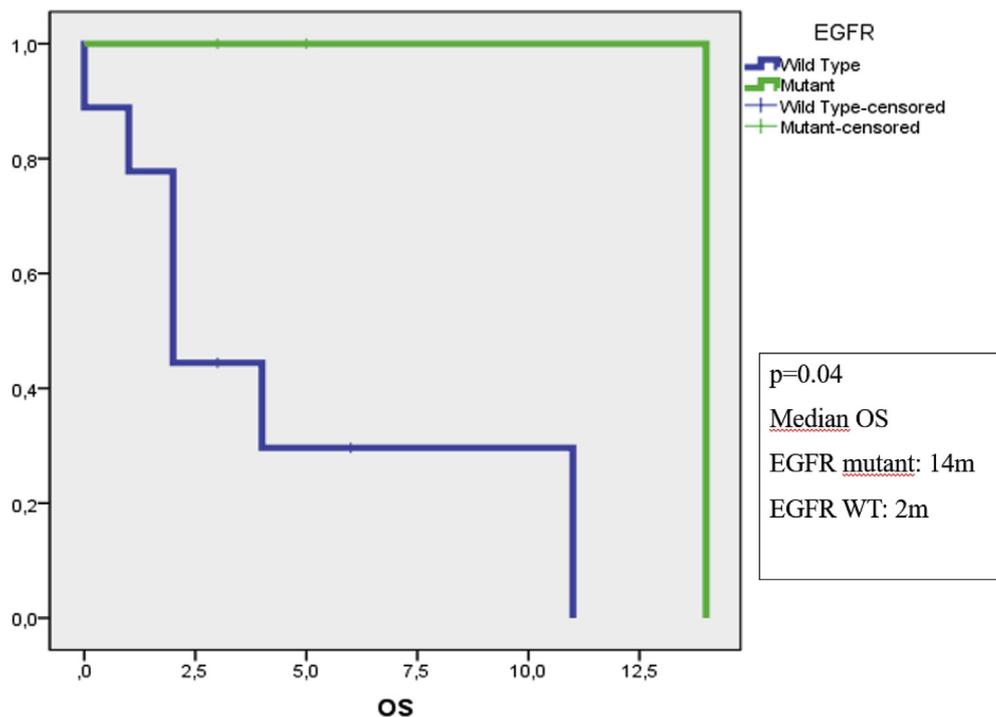


Fig. 3. The OS of the patients with liver metastasis according to the EGFR mutation status.

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 unavailable 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.

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