EJMO

DOI: 10.14744/ejmo.2020.13543
EJMO 2020;4(3):215–218

Research Article

The Relationship Between Primary Tumor Localization and Driver Mutation in Lung Cancer

Cengiz Karacin,[1] Tulay Eren,[2] Goksen Inanc Imamoglu,[2] Sema Turker,[2] Fevzi Coskun Sokmen,[1] Mustafa Altinbas[2]

[1]Deparmant of Medical Oncology, Dr Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, Turkey
[2]Deparmant of Medical Oncology, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey

Abstract

Objectives: Driver mutations are detected in 30–35% of metastatic patients with non-small cell lung cancer (NSCLC), and mutation discordance may occur between biopsies. Therefore, false-negative results for a driver mutation are reported in some patients who may need re-biopsy. We aim to identify a clinicopathological feature (especially tumor localization), other than smoking and sex, that predicts driver mutation in metastatic non-squamous NSCLC.

Methods: A total of 75 patients with driver mutation reports were included in the study. The age, gender, smoking status, pathology, primary tumor location, and mutation of each patient were evaluated. The relationship between the clinicopathological features and driver mutations was analyzed.

Results: The median age of the patients was 66 (range: 36–85); 55 (73%) of the patients were male. A driver mutation was detected in 23 (30.7%) patients. EGFR, ALK, and ROS1 rates were 22.7%, 6.7%, and 1.3%, respectively. Driver mutations were mostly found found in females and non-smokers (the p-values were 0.029 and <0.001, respectively). Driver mutation rates were similar in the right and left lungs (p=0.504).

Conclusion: There was no relationship between primary tumor localization and driver mutations. Driver mutations were more common in females and in non-smoking patients.

Keywords: ALK, Driver mutation, EGFR, lung cancer, primary tumor localization

Cite This Article: *Karacin C, Eren T, Inanc Imamoglu G, Turker S, Sokmen FC, Altinbas M. The Relationship Between Primary Tumor Localization and Driver Mutation in Lung Cancer. EJMO 2020;4(3):215–218.*

Lung cancer is the leading cause of cancer-related deaths, and causes approximately 1.7 million deaths worldwide annually.[1] In cases of metastatic NSCLC (especially in the histological subtype of adenocarcinoma), EGFR, ALK, and ROS-1 are the molecular genetic tests to be analyzed to detect driver mutations.[2] These genetic deviations provide specific molecular targets for treatment.[2] An increased response rate to standard cytotoxic chemotherapy and longer progression-free survival has been obtained using EGFR and ALK inhibitors.[3–5]

Driver mutations are detected in 30–35% of metastatic non-squamous NSCLC patients.[6] Recent studies have shown that driver mutations occur more frequently in non-smoking young women.[6, 7] Driver mutations are identified from tissue or liquid biopsy. Approximately 30% of tissue biopsies are insufficient for analysis.[8] In addition, tumor mutation discordance may occur between biopsies due to tumor heterogeneity or differing molecular testing techniques. For these reasons, false-negative results for driver mutation analysis occur in some patients, and these pa-

Address for correspondence: Cengiz Karacin, MD. Abdurrahman Yurtaslan Onkoloji Egitim ve Arastirma Hastanesi, Tibbi Onkoloji Bolumu, Ankara, Turkey
Phone: +90 553 475 56 01 **E-mail:** cengizkaracin@yahoo.com
Submitted Date: November 24, 2019 **Accepted Date:** January 06, 2020 **Available Online Date:** July 16, 2020

tients cannot receive targeted treatment.[8] These patients may need re-biopsy. Some clinical features—such as non-smoking and female sex—may help determine whether a patient should be biopsied again.[6]

In some cancers, there is a relationship between cancer characteristics and tumor localization. For example, Nosheen et al.[9] showed that breast cancer has a lower incidence in the right breast but is more aggressive in these cases. In addition, some differences have been identified in colon cancer. Right-sided colon cancers exhibit primarily mucinous histology, involve RAS/RAF mutations, and are more likely to have MSI-H. However, left colon cancers are diagnosed with obstructive symptoms and are predominantly chromosomally unstable.[10] Furthermore, in a study by Roychoudhuri et al.,[11] left testicular cancer, left ovarian cancer, and right lung cancer showed significantly better overall survival than cases of contralateral disease. This study aims to determine a clinicopathological feature (especially tumor localization) other than smoking and sex that predicts the presence of driver mutations in metastatic NSCLC.

Methods

The data of 275 patients who presented between 2010 and 2018 were analyzed retrospectively analyzed. Patients with small-cell or squamous cell carcinoma, patients under the age of 18 , and patients without mutation analysis were excluded from the study. One hundred and eighty-six patients with small-cell or squamous cell lung cancer and non-metastatic patients were eliminated. A total of 75 patients with driver mutation reports were included in the study. The age, sex, smoking status, metastasis site, pathology, primary tumor location, and mutations of each patient were evaluated.

Statistical Analysis

For statistical analysis, the SPSS (Statistics Program for Social Scientists) 20 program was used. All data were expressed as medians and interquartile ranges or as numbers (%) in the text and in tables. Cross-group comparisons were made by the Mann–Whitney U test for continuous variables, and Pearson's χ^2 or Fisher's exact tests were used for categorical variables. A p-value <0.05 indicated statistical significance.

Results

A total of 75 patients who were analyzed for driver mutations were included in the study. The median age was 66 (range: 36–85); and of the patients 55 (73%) were male. A driver mutation was detected in 23 (30.7%) patients (Table 1).

Table 1. Demographic and Clinicopathological Features of the Patients

	n=75
Age, median (range) - yr	66 (36-85)
Male sex - no. (%)	55 (73)
Smoking status - no. (%)	
Never smoked	19 (26)
Former smoked	13 (17)
Current smoker	43 (57)
Histological subtype - no. (%)	
Adenocarcinoma	63 (84)
NOS or Mixt	12 (16)
Primary tumor localization - no. (%)	
Right	48 (64)
Left	27 (36)
Site of metastases - no. (%)	
Bone	21 (28)
Brain	14 (18.7)
Lung	14 (18.7)
Liver	18 (24)
Suprarenal	8 (10.6)
Driver mutation - no. (%)	
EGFR	17 (22.7)
ALK	5 (6.7)
ROS1	1 (1.3)
Negative	52 (69.3)
First-line treatment - no. (%)	
Cisplatin + pemetrexed	46 (61.3)
Carboplatin + paclitaxel	6 (8)
Erlotinib	17 (22.7)
Crizotinib	6 (8)
The median time of follow-up, (range) - month	5 (0-77)

NOS: Not otherwise specified; EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; ROS1: a receptor tyrosine kinase encoded by the gene ROS1.

A comparison of the clinicopathological features of the patients according to their driver mutation status is shown in Table 2. Driver mutations were more common in female and non-smoking patients (the p values were 0.029 and <0.001, respectively). There was no significant difference between the groups in terms of age, histological subtype, or primary tumor localization.

Discussion

Our study is the first to investigate the relationship between driver mutations and primary tumor localization in advanced lung cancer. Driver mutations were more common in non-smokers and women. However, no relationship was found between driver mutations and primary tumor localization in our study.

Table 2. Comparison of Clinicopathological Features of Patients According To Driver Mutation Status

	Driver Mutation		p
	Yes n=23	No n=52	
Age, Median (range) - yr	65 (36-80)	66 (48-85)	0.265
Male sex - no. (%)	13 (56.5)	42 (80.8)	0.029
Never smoked - no. (%)	12 (52.2)	7 (13.5)	<0.001
Histological subtype - no. (%)			0.091
Adenocarcinoma	22 (95.7)	41 (78.8)	
NOS or Mixt	1 (4.3)	11 (21.2)	
Primary tumor localization - no. (%)			0.504
Right	16 (69.6)	32 (61.5)	
Left	7 (30.4)	20 (38.5)	

NOS: Not otherwise specified.

Recent studies have investigated the relationship between primary tumor localization and mutation and prognosis in colon cancer. There are significant embryological differences between the right and left colon.[12] In addition, the arterial, venous, and lymphatic systems of the right and left colons are different.[12] The BRAF mutation is more common in right colon cancer.[13] Right colon tumors have a worse prognosis than left colon tumors.[14] This relationship between mutation and prognosis and primary tumor localization in colon cancer has been lassociated with embryological and anatomical differences.[14]

There are three lobes in the right lung, while on the left there are only two lobes.[15] Although there are partial differences in the venous and lymphatic systems of the left and right lungs, there is no significant difference between their embryological origins.[16] The absence of a relationship between tumor localization and mutation in our study may be related to the lack of differences between the left and right lungs in terms of embryological origin.

Sex and smoking are prognostic factors in lung cancer.[17, 18] In addition, sex and smoking are closely associated with driver mutations in lung cancer.[6, 7] The EGFR mutation and the ALK rearrangement are most common in women and non-smokers.[6, 7] In our study, driver mutations were more common in women and non-smokers, which is in accordance with the literature.

Driver mutations in lung cancer are more common in adenocarcinoma subgroup than squamous cell cancer.[19] In our study, no correlation was found between histological subgroups and driver mutation. It was thought that the relation between driver mutation and histological subgroups could not be shown because the majority of patients had adenocarcinoma in this study.

EGFR is the most common driver mutation in lung cancer. EGFR mutation is more common in the Far Eastern countries than in Western Europe.[20] Up to 50% EGFR mutation rate in Asian countries is around 15% in Western Europe.[20] In our study, EGFR mutation was detected at a rate close to what is seen in European countries (22.7%). In NSCLC, ALK and ROS-1 rearrangement are found at 5% and 1%, respectively.[21] Similar to the literature, ALK and ROS-1 rearrangement were 6.7% and 1.3%, respectively in our study.

The low number of patients was the most important limitation of this study. Another limitation of the study was the analysis of all driver mutations in heterogeneous and limited patient groups.

Conclusion

Non-smokers and women have higher driver mutations in advanced lung cancer. There is no relationship between primary tumor localization and driver mutation.

Disclosures

Ethics Committee Approval: Diskapi Yildirim Beyazit Training and Research Hospital Clinical Trials Ethics Comittee, 61/20, 25 March 2019.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – C.K.; Design – C.K.; Supervision – M.A., F.C.S.; Materials – T.E., G.I.I.; Data collection &/or processing – T.E., G.I.I., S.T.; Analysis and/or interpretation – C.K., T.E.; Literature search – C.K., S.T.; Writing – C.K., S.T.; Critical review – M.A.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Hirsch FR, Scagliotti GV, Mulshine JL, Kwon R, Curran WJ Jr, Wu YL, et al. Lung cancer: current therapies and new targeted treatments. Lancet 2017;389:299–311.
3. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015;16:141–51.
4. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167–77.
5. Kilickap S, Onder S, Dizdar O, Erman M, Uner A. Short-time use of crizotinib as neoadjuvant in ALK-positive non-small cell lung carcinoma can be a chance for resectability. Cancer Che-

mother Pharmacol 2019;83:1195–96.
6. Ha SY, Choi S-J, Cho JH, Choi HJ, Lee J, Jung K, et al. Lung cancer in never-smoker Asian females is driven by oncogenic mutations, most often involving EGFR. Oncotarget 2015;6:5465.
7. Rodig SJ, Mino-Kenudson M, Dacic S, Yeap BY, Shaw A, Barletta JA, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. Clin Cancer Res 2009;15:5216–23.
8. Mlika M, Dziri C, Zorgati MM, Ben Khelil M, Mezni F. Liquid Biopsy as Surrogate to Tissue in Lung Cancer for Molecular Profiling: A Meta-Analysis. Curr Respir Med Rev 2018;14:48–60.
9. Fatima N, Zaman MU, Maqbool A, Khan SH, Riaz N. Lower incidence but more aggressive behavior of right sided breast cancer in Pakistani women: does right deserve more respect? Asian Pac J Cancer Prev 2013;14:43–5.
10. Missiaglia E, Jacobs B, D'Ario G, Di Narzo AF, Soneson C, Budinska E, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol 2014;25:1995–2001.
11. Roychoudhuri R, Putcha V, Møller H. Cancer and laterality: a study of the five major paired organs (UK). Cancer Causes Control 2006;17:655–62.
12. San Roman AK, Shivdasani RA. Boundaries, junctions and transitions in the gastrointestinal tract. Exp Cell Res 2011;317:2711–8.
13. Tie J, Gibbs P, Lipton L, Christie M, Jorissen RN, Burgess AW, et al. Optimizing targeted therapeutic development: analysis of a colorectal cancer patient population with the BRAF(V600E) mutation. Int J Cancer 2011;128:2075–84.
14. Salem ME, Weinberg BA, Xiu J, El-Deiry WS, Hwang JJ, Gatalica Z, et al. Comparative molecular analyses of left-sided colon, right-sided colon, and rectal cancers. Oncotarget 2017;8:86356–68.
15. Kuhnigk J-M, Hahn H, Hindennach M, Dicken V, Krass S, Peitgen H-O, editors. Lung lobe segmentation by anatomy-guided 3D watershed transform. Medical Imaging 2003. International Society for Optics and Photonics, 2003.
16. Berrocal T, Madrid C, Novo S, Gutiérrez J, Arjonilla A, Gómez-León N. Congenital anomalies of the tracheobronchial tree, lung, and mediastinum: embryology, radiology, and pathology. Radiographics 2004;24:e17.
17. Kawaguchi T, Takada M, Kubo A, Matsumura A, Fukai S, Tamura A, et al. Performance status and smoking status are independent favorable prognostic factors for survival in non-small cell lung cancer: a comprehensive analysis of 26,957 patients with NSCLC. J Thorac Oncol 2010;5:620–30.
18. Hsu LH, Chu NM, Liu CC, Tsai SY, You DL, Ko JS, et al. Sex-associated differences in non-small cell lung cancer in the new era: is gender an independent prognostic factor? Lung Cancer 2009;66:262–7.
19. Motoi N, Szoke J, Riely GJ, Seshan VE, Kris MG, Rusch VW, et al. Lung adenocarcinoma: modification of the 2004 WHO mixed subtype to include the major histologic subtype suggests correlations between papillary and micropapillary adenocarcinoma subtypes, EGFR mutations and gene expression analysis. Am J Surg Pathol 2008;32:810–27.
20. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget 2016;7:78985–93.
21. Ye M, Zhang X, Li N, Zhang Y, Jing P, Chang N, et al. ALK and ROS1 as targeted therapy paradigms and clinical implications to overcome crizotinib resistance. Oncotarget 2016;7:12289–304.