Lung cancer is the leading cause of cancer-related deaths, and causes approximately 1.7 million deaths worldwide annually. 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. These genetic deviations provide specific molecular targets for treatment. An increased response rate to standard cytotoxic chemotherapy and longer progression-free survival has been obtained using EGFR and ALK inhibitors.

Driver mutations are detected in 30–35% of metastatic non-squamous NSCLC patients. Recent studies have shown that driver mutations occur more frequently in non-smoking young women. Driver mutations are identified from tissue or liquid biopsy. Approximately 30% of tissue biopsies are insufficient for analysis. 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-
tients cannot receive targeted treatment. 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.

In some cancers, there is a relationship between cancer characteristics and tumor localization. For example, Nosheen et al. 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. Furthermore, in a study by Roychoudhuri et al., 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.
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 associated 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 Committee, 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.

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

| Driver Mutation | Yes n=23 | No n=52 | p       |
|-----------------|---------|---------|---------|
| 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.
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