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KLİNİK ÇALIŞMA
RESEARCH ARTICLE

Regional distribution of genetic mutation in lung cancer in Turkey (REDIGMA)

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ABSTRACT

Regional distribution of genetic mutation in lung cancer in Turkey (REDIGMA)

Introduction: *The results of standard chemotherapy in lung cancer are not very satisfactory, so it is important to identify genetic mutations that provide targeted therapies. Recent reports have suggested influences of racial difference on the frequency of mutation in lung cancer. We aimed to determine the frequency and regional distribution of genetic mutations of non-small cell lung cancer (NSCLC) in Turkey.*

Materials and Methods: *Regional distribution of genetic mutations in lung cancer in Turkey (REDIGMA) study was carried out as a prospective, cross-sectional, observational study in a large number of centers in which lung cancer patients were followed and could perform genetic mutation analysis on patients' biopsy materials.*

Results: *The 703 patients (77.7% male, mean age 63.3 ± 12.5 years) who were diagnosed as NSCLC from 25 different centers were included in the study. Tumor samples from patients were reported as 87.1% adenocarcinoma, 6.4% squamous cell carcinoma and 6.5% other. Mutation tests were found to be positive in 18.9% of these patients. The mutations were 69.9% EGFR, 26.3% ALK, 1.6% ROS and 2.2% PDL. Mutations were higher in women and non-smokers (p< 0.000, p< 0.001). Again, the frequency of mutations in adenocarcinoma was higher in metastatic disease. There was no difference between the patient's age, area of residence, comorbidity and clinical stage and mutation frequency.*

Conclusion: *Our study revealed that the EGFR mutation rate in Turkey with NSCLC was similar to East European, African–American and Caucasian patients, and was lower than in East Asia.*

Key words: *ALK; EGFR; carsinoma, non-small cell lung cancer; Turkey; regional distribution*

ÖZ

Türkiye'de akciğer kanserinde genetik mutasyonların bölgesel dağılımı (REDIGMA)

Giriş: *Akciğer kanserinde standart kemoterapinin sonuçları çok tatmin edici değildir, bu nedenle hedefe yönelik tedavileri sağlayan genetik mutasyonları belirlemek önemlidir. Son raporlar, ırksal farklılığın ve bölgesel değişikliğin akciğer kanserinde mutasyon sıklığı üzerindeki etkilerini göstermiştir. Çalışmamızda küçük hücreli dışı akciğer kanseri (KHDAK)'nde genetik mutasyonların Türkiye'deki sıklığını ve bölgesel dağılımını belirlemeyi amaçladık.*

Materyal ve Metod: *Türkiye'de akciğer kanserinde genetik mutasyonların bölgesel dağılımı (REDIGMA) çalışması, akciğer kanseri hastalarının takip edildiği ve hastaların biyopsisinde genetik mutasyon analizi yapılabilecek çok sayıda merkezde prospektif, kesitsel ve gözlemsel bir çalışma olarak gerçekleştirildi.*

Bulgular: *Çalışmaya 25 farklı merkezden KHDAK tanısı konan 703 hasta (%77.7 erkek, ortalama yaş 63.3 ± 12.5 yıl) alındı. Hastalardan alınan tümör örnekleri %87.1 adenokarsinom, %6.4 skuamöz hücreli karsinom ve %6.5 diğer olarak bildirildi. Mutasyon testleri bu hastaların %18.9'unda pozitif bulundu. Mutasyonlar %69.9 EGFR, %26.3 ALK, %1.6 ROS ve %2.2 PDL idi. Mutasyonlar kadınlarda ve sigara içmeyenlerde istatistiksel olarak daha yüksek tespit edildi (p< 0.000, p< 0.001). Yine, adenokarsinomdaki mutasyonların sıklığı metastatik hastalıkta daha yüksekti. Hastanın yaşı, ikamet alanı, komorbiditesi, klinik evresi ve mutasyon sıklığı arasında farklılık saptanmamıştır.*

Sonuç: *Çalışmamızın sonucunda Türkiye geneli mutasyon pozitifliği literatür ile karşılaştırıldığında Türkiye'de KHDAK'lı hastalarda EGFR mutasyon oranının Doğu Avrupa, Afrikalı-Amerikalı ve Kafkasyalı hastalara benzer ve Doğu Asya'dan daha düşük olduğu ortaya koyulmuştur.*

Anahtar kelimeler: *ALK; EGFR; küçük hücreli dışı akciğer kanseri; Türkiye; bölgesel dağılım*

INTRODUCTION

Currently, lung cancers are among the most common cancers leading to death (1). According to data from Cancer Department of Public Health Institute of Turkey, the lung cancer rates in Turkey is the first in men and the fifth in women (2). According to Globocan 2012 data published by International Cancer Agency (IARC), among in the first five types of cancer in men are the first in our country and in the world, lung cancers (3). Approximately 80% of all these lung cancers are non-small cell lung cancers (NSCLC) and many of these patients present with metastasis (2). However, the results of standard chemotherapy in advanced lung cancers are not satisfactory. The identification of genetic mutations that provide targeted treatment for new treatment seeking is a promising condition and is becoming increasingly important. Positive results have been obtained for treatment of 'anaplastic lymphoma kinase' ALK and 'epidermal growth factor receptor' EGFR mutations, especially in NSCLC (4). In the NCCN Guidelines Version 4.2019 for NSCLC; in the histologic subtype of adenocarcinoma, large cell and NSCLC not otherwise specified (NOS); molecular testing (ALK; EGFR; ROS 1; BRAF) and PD-L-1 testing is recommended. For squamous cell carcinoma; molecular testing EGFR and ALK is recommended for never smokers or mixed histology, ROS1 and BRAF in mixed histology

and PD-L-1 testing is recommended in routine (5). While genetic predisposition may be the direct cause of lung cancer, the environmental factors and tobacco use is also largely responsible for the individual (6).

Considering the studies conducted, it is noteworthy that gene mutations in lung cancer differ according to various regions. High rates of EGFR mutation have been reported, especially in Japan and Thailand (7,8). Gene mutation was found to be positive in 51% of patients with Asian origin and this rate was found to be high even in male smokers (7). In the patients followed up in our clinic, the rarity of gene mutations is the question of the extent to which targeted therapies can be used in our country. Turkey is a country that has seven geographic regions with ethnic differences with different genetic pools. The frequency, risk factors and regional differences of these mutations in our country are not known today.

The aim of this study was to evaluate the distribution of genetic mutations to regions and factors affecting having a genetic mutation in NSCLC patients in our country. We believe that these data will make a significant contribution to the local cancer information system and provide evidence-based predictions for the treatment decisions related to NSCLC patients and will contribute positively to the prognosis and survival of our patients.

MATERIALS and METHODS

Study Design and Study Population

REDIGMA is a multicentric prospective, cross-sectional, descriptive study. The study participants included NSCLC patients who underwent the genetic mutation analysis from medical centers that met the participation criteria and volunteered to participate in the study, located in different parts of Turkey. The sequencing and polymerase chain reaction process were used for EGFR test. FISH, PCR and immunohistochemical methods were used to determine the ALK test. Demographic characteristics, disease variables, family history, occupational and environmental exposures, and smoking status data were recorded by centers participating in the study using a standard questionnaire and hospital records filled in during clinical interviews for each patient. The data combined in a common database and discussed for statistical analysis. The data obtained from this study and demographic information was examined, the frequency and distribution of genetic mutations were evaluated.

Statistical Analysis

Data analysis was performed using SPSS software (version 23.0, SPSS Inc., Chicago, IL, USA). The Chi-square test was used to compare categorical variables. The Kolmogorov-Smirnov test was used to test for normal distribution of variables. The parametric student's t-test was used for comparing mean or median values of normally distributed data, and the nonparametric Mann-Whitney U test was used to compare data that were not normally distributed. The independent risk factors for genetic mutation were investigated by univariate and multivariate logistic regression. To define the relationship between the other values of Turkey in the region is made binary logistic regression. Multivariate logistic regression analysis was used as a stepwise descending method from predictive factors with a significance < 0.05 in the univariate analysis.

The regional distribution of the obtained data is shown schematically with the help of geostatic methods, region density map of positive gen mutations in Turkey.

Informed consent was obtained from the patients included and this study was approved by the Ethics Committee of Karadeniz Technical University.

RESULTS

A total of 25 medical centers from different geographical region of Turkey, volunteered to join this study, and 703 patients diagnosed with NSCLC were included in the study from 01.10.2016 to 01.10.2018 [546 (77.7%) male; 157 (22.3%) female and mean age 63.3 ± 12.5]. The most common histological type was adenocarcinoma. Tumor subtypes included 87.1% adenocarcinoma, 6.4% squamous cell carcinoma, 4.6% unclassified NSCLC, others mixed tumors (Figure 1). When the tumor location and size were examined, the tumor was most often localized on the right side and at the upper side, and the mean tumor size was 4.5 (min 0.7-max

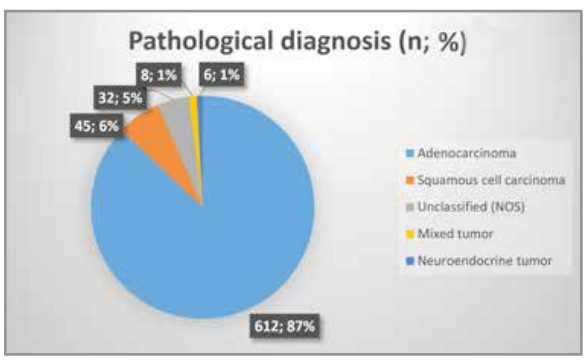

Figure 1. Patient distribution according to pathological diagnosis. NOS: Not otherwise specified.

Table 1. Patient characteristics

Male/female		546/157
Age (median, interquartile range)		63.3 ± 12.5
Smoking status (%)	Never smoked	16.5
	Exsmoker	52.9
	Active smoker	26.5
	Passive smoker	4.1
ECOG performance status (%)	0	37
	1	37
	2	19
	3	6
	4	1
Comorbidity (n)	Absent	352
	Present	351
Cancer in the family	Absent	490
	Present	212

18.5) cm. The general characteristics of patients are summarized in Table 1.

From the patients 25.8% of was diagnosed with a bronchoscopic mucosal biopsy, 6.9% transbronchial needle aspiration, 12.4% endobronchial ultrasonographic biopsy, and 31.3% computed tomography-guided transthoracic biopsy. In addition, 4.3% mediastinoscopy, 5.4% thoracoscopy and 6% thoracotomy were used. 4.3% of the patients were diagnosed with pleural fluid or pleural biopsy, while 3.6% were detected by biopsies from other organ metastases. In our study, no patient was diagnosed with liquid biopsy.

Gen mutation was positive in 18.9% of all patients. Of these, 69.9% were EGFR, 26.3% ALK, 1.6% ROS and 2.2% PDL. However, ROS and PDL mutation could not be studied in all centers.

The proportion of patients who had never used tobacco products was 16.5%. The smoking rate was according to the gender difference of 94.3% in men and 45.9% in women ($p< 0.001$). There was a statistically significant difference between the regions in terms of tobacco use, the condition of the patient's home and the presence of chronic disease ($p< 0.005$). In the Marmara region, the exsmoker was the majority, whereas in the Mediterranean region there were more active smokers. The frequency of having no tobacco was highest in the Aegean region. While the stove house was in the majority in the Eastern Anatolia region, the central heating system was in the Marmara region. In the presence of additional chronic disease, the least frequency was in the Aegean region.

There was no difference between the regions in terms of the presence of cancer in the family. While the rate of cancer in the family was 30%, this positivity was not found to be an independent risk factor on genetic mutation ($p= 0.581$). It was found that most of the patients with a family history of cancer had cancer in their siblings. The most common type of cancer was lung cancer.

In terms of occupational exposure, there was the most common chemical gas / dust exposure in the Marmara region, while the Black Sea and Aegean region had the most frequent exposure to asbestos. Eastern Anatolia and Central Anatolia were the regions with the highest environmental exposure. The number of patients with occupational exposure is shown in Figure 2. In our study, no statistical significance was found between occupational and environmental exposure and genetic mutation in lung cancer.

When we look at the distribution of cancer according to regions, the presence of stage 4A/4B and metastasis was highest in Eastern Anatolia. The mutation positivity in the Black Sea region is at least; In the Mediterranean region, it is the most common. However, there was no statistical difference between the regions in terms of gene mutation positivity. The most common mutation in all regions was EGFR and the second was ALK.

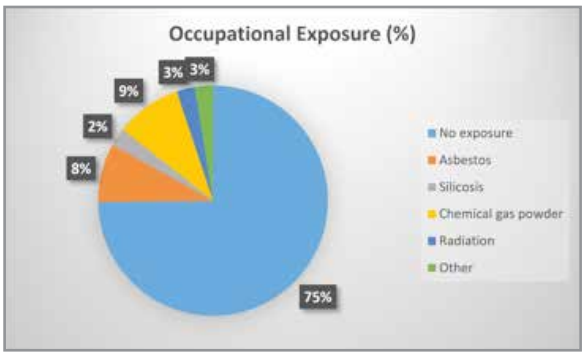

Figure 2. Number of patients with occupational exposure.

The independent risk factors for genetic mutation were investigated by univariate and multivariate logistic regression. According to the Univariate analysis results, the risk of women getting positive as a result of genetic mutation was 4.557 times higher than males ($p< 0.001$). And the rate of genetic mutation in non-smokers was significantly higher ($p< 0.001$). In conclusion, non-smokers and female gender variables were found to be effective factors in gene mutation positivity.

In all patients, the patients with positive gene mutation were 18.9% and the negative ones were 81.1%. Of the mutations, 69.9% EGFR, 26.3% ALK, 1.6% ROS and 2.2% PDL were detected. Similar to the literature, gene mutation frequency was higher in adenocarcinoma, non-smokers, female sex and metastatic disease ($p< 0.000$, $p< 0.001$, $p< 0.001$).

There was no difference in the mutation rate between the patient's age, place of residence, comorbidity and clinical stage. When we look at the distribution of mutations, it was mostly in the Mediterranean region but there was no statistically significant difference between the regions.

DISCUSSION

In lung cancer, which is the most common cancer among all cancers, cancer cell type, tumor stage, molecular characteristics, and patient performance status are determined for the selection of therapy regimen. Systemic treatments are usually applied in metastatic disease. However, since the beginning of 2000s, molecular pathways that are thought to be effective in carcinogenesis in NSCLC and many other cancers have begun to be understood. New agents are being developed in cancer cells against specific targets in these molecular pathways. Lung cancer is a solid tumor that has been successful in recent years in terms of targeted therapies. Therefore, molecular tests are becoming more important. Molecular tests are not only involved in determining the treatment process, but also in understanding the mechanisms of treatment resistance and in understanding the pathogenesis of cancer (9). All developments described here are more effective for non-squamous NSCL patients. However, recent data suggest that squamous cell carcinomas, such as adenocarcinomas, are also molecularly heterogeneous tumors (10). These mutations predict a better prognosis with EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib and afatinib (11). At the same time, reorganization of ALK is clinically important. Because this mutation predicts susceptibility to ALK tyrosine kinase inhibitors such as crizotinib and ceritinib (11,12).

In addition, after a targeted treatment, NSCLC is a new area of research in immunotherapy. Successful results are promising in patients with PD-L1 immunostaining. The combination of immunotherapy and targeted therapies is currently an active clinical research area. Recently, different treatment options have been developed, such as combination with other immunotherapy agents, combination with targeted agents, combination with chemotherapeutic agents, or combination with radiotherapy (13).

Molecular tests can be performed at the time of initial diagnosis or progression. Genetic techniques may be used to obtain gene mutation from diagnostic material. Liquid biopsy is a peripheral blood sample of cancer patients. Many materials such as circulating tumor cells, circulating tumor DNA, exosomes, micro RNA or platelets can be obtained from this sampling. With this process, it is easier to take a repeat biopsy in progression (9). In our study, there was no possibility to use of liquid biopsy. The most common diagnostic tools were bronchoscopic methods and CT-guided biopsy.

There are many studies supporting the family history of lung cancer in the literature (14). In our study, 30% of patients with cancer cases were found but there was no relationship between the family history of cancer and the positivity of genetic mutation.

There is a strong association between non-tobacco users and EGFR mutation positivity (15). In a study investigating this relationship, individuals who were younger than 15 years of age or less smokers were compared and significantly higher EGFR mutation rates were found (16). A meta-analysis investigating the relationship between smoking history and EGFR mutation reported a 4.8-fold increase in EGFR mutation compared to smokers in non-smokers (17). However, in Taiwan and Bangladesh, the frequency of mutations was higher in smokers (18,19). In our study higher rates of EGFR mutation were found in the non-smoker group than the smokers ($p< 0.001$). When analyzed by multivariate analysis,

only sex and non-smoking were obtained as an independent risk factor for the genetic mutation ($p< 0.001$). The risk of females is 4.011 times higher than males. These findings are parallel with the literature data (19).

The most comprehensive meta-analysis study on the ethnic distribution of genetic mutations has been shown by MutMapII; when analyzed according to geographic regions, Asia-Pacific group has the highest EGFR mutation frequency with 47% (20). Among the Asian countries, Taiwan has the highest mutation rate with a 57% positive rate (19). Overall, the rate of female patients with gene mutation was higher in all studies. In our study, the rate of gene mutation in women was high in accordance with the literature. On the other hand, among the studies all over the world, that the rate of gene mutation in males is higher in Bangladesh (18). As a result of MutMapII study, the frequency of mutations in Asian-Pacific descent was found to be 47% and 15% in people of European origin. In other studies in the literature, Vietnam (64.2%) had the highest rate, while India had the lowest incidence (22.2%). In a study from the Philippines, the EGFR mutation rate was reported to be 42% (21,22). In a study conducted in Greece, the rate of mutation in men was 11.96 and in women was 27.09% (23).

On the other hand, in Argentina the incidence of EGFR mutations was 19%, and 67% in Peru (24). An investigation among African- Americans found a lower incidence (11%) of EGFR mutation (25). Similarly, a study conducted in the United Kingdom, its incidence was revealed as 11% (26). In North America, the last few reports on EGFR testing generally show a higher prevalence (about 25%), but most contain heterogeneous groups of breeds and smoking habits (27).

The PIONEER study, one of the large-scale studies on this subject, has shown that approximately half (51.4%) of the patients with NSCLC from seven regions in Asia harbor the EGFR mutation. Although EGFR mutations were more common in women, Asians and non-smokers, EGFR mutations were not limited to patients with these clinical features. At the same time, more than 50% of patients with EGFR mutation in the PIONEER trial were not smokers (21). Therefore, these findings support the EGFR mutation test in all patients with NSCLC, especially in tumors containing adenocarcinoma component.

Turkey is composed of a combination of a mixed society where people of various ethnic backgrounds. In previous studies, Unal et al. found the genetic mutation rate in the Mediterranean region was 37.5% (28). In our study, the frequency of mutation in the Mediterranean region was higher, although it was not statistically significant. The genetic mutation rate was found to be 16.7% in a large-scale study analyzing data retrospectively from various regions of Turkey (29). Like this study, we found the genetic mutation was 18.9% compared to all patients.

When we look at the literature, our study is one of the large-scale distribution of mutations in NSCLC study conducted in Turkey. When studies examining genetic mutations in Turkey increased, a comprehensive review can be made. So; we believe that our work will make a great contribution to the national cancer information system of our country.

LIMITATIONS

Although our study is wide-ranging, it has some limitations. First, our pathological samples were analyzed by different molecular platforms in different centers in relative technical differences related to equipment or manpower. In addition, although the number of patients was different from Turkey's seven geographical regions is not reached an equal number of patients from each region.

CONCLUSION

Our study revealed that EGFR mutation rate in Turkish patients with NSCLC is similar to that of East European, African-American and Caucasian patients and lower than East Asia. Gene mutation frequency was higher in adenocarcinoma, female gender and in metastatic disease. There was no difference in mutation rate with regard to patient's age, the region of residence, comorbidity and clinical stage.

CONFLICT of INTEREST

No conflict of interest declared by the authors.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: NÖ, TÖ

Analysis/Interpretation: NÖ, EAÖ, AEÖ, TÖ, YB

Data Acquisition: All of authors.

Writting: NÖ, TÖ, YB

Critical Revision: NÖ, TÖ, YB

Final Approval: All of authors.

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