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Research Article

Decoding Lung Cancer Mutations: A 5-year Investigation in Ordu Province

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Abstract

Aim: Lung cancer is the leading cause of cancer-related mortality worldwide and is most often diagnosed at an advanced stage. The increasing prominence of targeted therapy approaches in recent years has made the identification of genetic variations within tumors clinically significant. This study aimed to determine the prevalence of key mutations such as EGFR, ALK, KRAS, and PDL-1 in lung cancer cases over a five-year period, along with their distribution across histological subtypes and their association with demographic characteristics, specifically within the province of Ordu.

Material and Method: This retrospective, cross-sectional study included a total of 202 patients who were diagnosed with Non-small cell lung cancer (NSCLC) and presented to the Medical Oncology Clinic of Ordu State Hospital between January 2019 and December 2023. Demographic data such as age and sex, histological subtypes, and genetic mutation analyses and other clinical parametres were evaluated. Mutation analysis focused on actionable biomarkers including EGFR, ALK, KRAS, and PDL-1, and their relationships with demographic characteristics were assessed.

Results: The median age was 67 years (91.1% male). The most frequently observed histological subtype was squamous cell carcinoma (49.5%). In female patients, adenocarcinoma was the predominant (83.3%). The most commonly detected genetic alteration was PDL-1 (10.4%). EGFR mutations were significantly more frequent in older patients, whereas ALK mutations occurred in significantly younger patients.

Conclusion: This study represents the first large-scale lung cancer mutation screening conducted specifically in the Ordu province. Our findings indicate regional differences, with PD-L1 being the most common alteration and squamous cell carcinoma the predominant subtype, in contrast to national data where EGFR mutations and adenocarcinoma are more frequent. These discrepancies indicate that regional characteristics and the genetic profile of the patient population should be taken into consideration during treatment planning.

Keywords: Lung cancer, Ordu province, genetic analysis, mutation

INTRODUCTION

Lung cancer is most often diagnosed at an advanced stage, making its treatment more challenging. In these stages, where the possibility of surgical intervention is generally lost, the response to chemotherapy may be limited. Therefore, the identification of genetic mutations and the development of targeted therapeutic approaches have become increasingly important (1).

According to the most recent national cancer statistics updated in 2020, lung cancer is the most common cancer type among men in Türkiye, accounting for 51.9%, while it ranks fourth among women with a rate of 10.2% (2). Globally, according to the latest GLOBOCAN data from 2022, lung cancer is the leading cancer type among men and ranks second among women, following breast cancer (3). According to national data, adenocarcinoma is the most frequently observed histological subtype of lung cancer (39%), followed by squamous cell carcinoma (29.6%) (2). In recent years, the emergence of novel treatment modalities in lung cancer has offered hope by contributing to improved survival outcomes. Particularly, the identification of genetic mutations and the development of targeted therapies have increased awareness and transformed treatment strategies. Several scientific studies conducted in Türkiye have also reported the distribution and clinical relevance of mutation analyses in lung cancer (4).

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In the latest version of the National Comprehensive Cancer Network (NCCN) Guidelines updated in June 2025, for patients with advanced or metastatic non-small cell lung cancer (NSCLC), if the histological subtype is adenocarcinoma, large cell carcinoma, or not otherwise specified (NOS), testing for Epidermal growth factor receptor (EGFR), anaplastic lymphoma receptor tyrosine kinase (ALK), kirsten rat sarcoma virus (KRAS), proto-oncogene tyrosine-protein kinase (ROS1), BRAF, neurotrophic tyrosine receptor kinase (NTRK 1/2/3), MET exon 14 skipping, RET, ERBB2 (HER2), neuregulin 1 (NRG1), HER2 (via immunohistochemistry- IHC), and programmed death ligand 1 (PD-L1) is recommended.

Similarly, for patients with advanced or metastatic squamous cell carcinoma, the guidelines recommend testing for EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping, RET, ERBB2 (HER2), NRG1, HER2 (IHC), and PD-L1 (1). The prevalence of mutations varies across different geographic regions. In a study including early-stage (stage IA–IIIB) lung cancer cases from Asia, Latin America, the Middle East, and Africa, the overall EGFR mutation rate was reported as 51%, with a higher prevalence observed particularly among non-smoking women with early-stage disease (5). EGFR mutation rates are generally highest in Asia, reaching up to 49% (6), whereas the prevalence is approximately 17% in the Middle East and North Africa, and the lowest rates have been reported in Europe (14%) (7). It is noteworthy that most of these studies were conducted in patient populations with advanced-stage disease.

Türkiye is considered one of the high-risk countries in terms of genetic disorders. The main contributing factors include the high prevalence of consanguineous marriages, regional isolation, geographic variation in genetic diversity, and historically limited access to screening and diagnostic services (8). Consequently, the prevalence of genetic mutations in lung cancer may be higher in certain regions of Türkiye (4).

Our study was conducted in Ordu, a province located in the northern part of the country, within the Black Sea region—one of Türkiye's seven geographical regions. Due to the mountainous geography of the Black Sea region, certain rural areas have preserved relatively isolated and close-knit populations, which may have contributed to the conservation of specific genetic variants across generations. The rate of consanguineous marriage in this region is close to the national average (approximately 20%). Given its unique population structure and geographic characteristics, the Black Sea region should not be overlooked in terms of genetic disease risk and warrants detailed genetic investigation.

Therefore, in our study, we aimed to investigate—for the first time in the literature—the prevalence of lung cancer-related genetic mutations specifically in the Black Sea region, along with the potential factors influencing these rates.

MATERIAL AND METHOD

Study Design and Patient Selection

This retrospective cross-sectional study was performed at the Medical Oncology Clinic of Ordu State Hospital. The clinical, pathological, and molecular data of patients diagnosed with lung cancer between January 2019 and December 2023 were intended to be explored. Ethical approval was obtained from the Ordu University Noninterventional Scientific Researches Ethics Committee (Date: 22.12.2023, Decision no: 26/330). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Inclusion criteria: Patients who were eighteen years and above diagnosed with lung cancer within the defined period. Patients whose information could be accessed through the system or medical records were included in the study.

Exclusion criteria: Patients who were less than 18 years old and patients with inconclusive lung cancer diagnoses. Patients whose information could not be accessed through the system or medical records were excluded from the study.

Data Collection and Evaluated Parameters

Medical records of all patients who presented to the outpatient clinic within the specified dates and met the inclusion criteria were reviewed. Of the total 235 patients, 33 were diagnosed with small cell lung cancer and were excluded from the study since mutation analyses were not performed for this subtype. Demographic data, year of diagnosis, histological subtype of lung cancer, disease stage at diagnosis, localization of the primary tumor, diagnostic method, whether genetic mutation analysis was performed, type of mutation (if present), presence of metastasis, and sites of metastasis were recorded from patient files and the hospital's electronic medical record system.

Data Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.0. Descriptive characteristics of lung cancer patients were presented as frequencies (n) and percentages (%). Age was summarized using mean, standard deviation, median, minimum, and maximum values. The normality of the age distribution was assessed based on skewness and kurtosis values. A reference range of ±1.96 was accepted as indicative of normal distribution.

To compare the clinical and diagnostic characteristics of lung cancer patients by histological subtype and gender, the Chi-Square (χ^2) test was used. One-Way Analysis of Variance (ANOVA) was applied to compare patients' ages across different clinical and diagnostic groups. In cases where a statistically significant difference in age was

found among groups, post-hoc tests were performed to determine which groups differed, and group differences were indicated using letter coding.

In all analyses, p-values <0.05 and <0.01 were considered statistically significant.

RESULTS

When molecular testing were evaluated, it was found that no genetic testing had been performed in 57.4% of the cases, while 21.8% were mutation negative. Among the molecular testing, PD-L1 expression was the most frequently observed (10.4%), followed by EGFR (4.0%) and KRAS (3.0%). When comparing adenocarcinoma and squamous cell carcinoma subtypes, a broader spectrum of molecular testing was observed in patients with adenocarcinoma. Specifically, EGFR mutation (7.6%), PD-L1 expression (17.4%), and KRAS (6.5%) mutation were identified in adenocarcinoma cases, whereas these molecular tests were less frequently detected in squamous cell carcinoma. However, the overall distribution of molecular tests between subtypes was not statistically significant (p>0.05).

Patients with ALK mutations had a notably lower mean age (39 years), indicating that this mutation is more prominent in younger individuals (p<0.05). In female patients, EGFR (16.7%) and ALK (11.1%) mutations were observed more frequently compared to male patients (2.7% and 0.0%, respectively) (p<0.01).

The majority of patients were male (91.1%, n=184), with a mean age of 66.17±9.06 years, ranging from 38 to 90 years, and a median age of 67. Regarding lung cancer subtypes, the most common histological type was squamous cell carcinoma (49.5%), followed by adenocarcinoma (45.5%) (Figure 1). At the time of diagnosis, 47.5% of patients were in stage IV, indicating that most cases were diagnosed at an advanced stage. Stage III patients accounted for 30.7%, while stage I and II patients represented 11.9% and 9.9%, respectively.

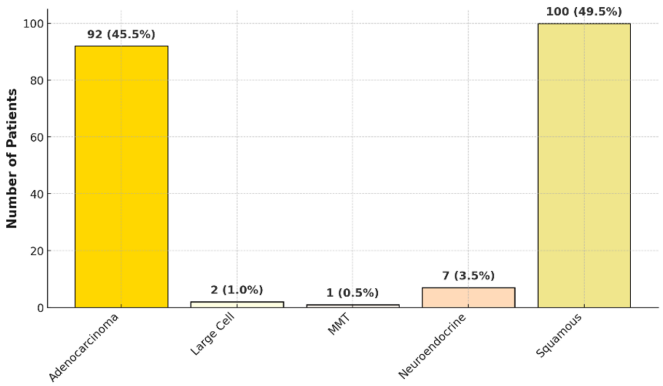

Figure 1. Distribution of lung cancer subtypes

In terms of metastasis, 53% of patients had no detectable metastases. Among those with metastatic disease, the bone was the most common site (16.3%), followed by brain (10.9%), contralateral lung (6.9%), and liver (4.5%) (Table 1).

Table 1. Demographic, clinical, and diagnostic characteristics of NSCLC patients (n=202)

Variables	Number	%
Gender		
Female	18	8.9
Male	184	91.1
Lung cancer subtype		
Adenocarcinoma	92	45.5
Large cell lung cancer	2	1.0
MMT	1	0.5
Neuroendocrine tumor	7	3.5
Squamous cell carcinoma	100	49.5
Stage		
Stage 1	24	11.9
Stage 2	20	9.9
Stage 3	62	30.7
Stage 4	96	47.5
Metastases		
Bone	33	16.3
Brain	22	10.9
Cervical lymph node	1	0.5
Kidney	2	1.0
Liver	9	4.5
Opposite lung	14	6.9
Pleura	6	3.0
Surrenal	8	4.0
None	107	53.0
Molecular testing		
Not examined	116	57.4
Negative	44	21.8
KRAS	6	3.0
PD-L1	21	10.4
EGFR	8	4.0
ALK	2	1.0
ROS1	1	0.5
HER2	1	0.5
PIK3CA	1	0.5
RET	1	0.5
BRAF	1	0.5
Age		
Mean±SD; Median (Min–Max)	66.17±9.06 67 (38-90)	

Regarding treatment, 53.5% of the patients received radiotherapy, 3.0% received targeted therapy, and 11.9% received immunotherapy. The most common sites of primary tumor localization were the right upper lobe (33.2%) and the left upper lobe (26.2%). In terms of diagnostic methods, image-guided transthoracic lung biopsy (40.6%) and bronchoscopic biopsy (37.1%) were the most frequently utilized techniques. When examining the distribution by year of diagnosis, the highest number of cases were diagnosed in 2023 (27.2%).

When demographic, clinical, and diagnostic characteristics were analyzed by gender (Table 2), adenocarcinoma was the most common histological subtype in female patients (83.3%), while the corresponding rate in male

patients was 41.8% (p=0.013). Conversely, squamous cell carcinoma was more prevalent in males (53.3%), whereas this subtype was observed in only 11.1% of female patients. These findings suggest that different histopathological patterns predominate between males and females (p<0.05).

Table 2. Distribution of clinical and diagnostic characteristics of lung cancer patients by gender

Variables	Female (n=18)		Male (n=184)		p
	Number	%	Number	%	
Lung cancer subtype					
Adenocarcinoma	15	83.3	77	41.8	**0.013***
Large cell lung cancer	0	0.0	2	1.1	
MMT	0	0.0	1	0.5	
Neuroendocrine tumor	1	5.6	6	3.3	
Squamous cell carcinoma	2	11.1	98	53.3	
Stage					
Stage 1	4	22.2	20	10.9	0.450
Stage 2	1	5.6	19	10.3	
Stage 3	4	22.2	58	31.5	
Stage 4	9	50.0	87	47.3	
Metastases					
Bone	2	11.1	31	16.8	**0.014***
Brain	1	5.6	21	11.4	
Cervical lymph node	1	5.6	0	0.0	
Kidney	0	0.0	2	1.1	
Liver	3	16.7	6	3.3	
Opposite lung	1	5.6	13	7.1	
Pleura	1	5.6	5	2.7	
Surrenal	0	0.0	8	4.3	
None	9	50.0	98	53.3	
Molecular testing					
Not examined	8	44.4	108	58.7	**0.000****
Negative	2	11.1	42	22.8	
KRAS	0	0.0	6	3.3	
PD-L1	3	16.7	18	9.8	
EGFR	3	16.7	5	2.7	
ALK	2	11.1	0	0.0	
ROS1	0	0.0	1	0.5	
HER2	0	0.0	1	0.5	
PIK3CA	0	0.0	1	0.5	
RET	0	0.0	1	0.5	
BRAF	0	0.0	1	0.5	

*p<0.05; **p<0.01, Test statistic: Chi-Square Test

A statistically significant difference was observed between genders regarding metastatic spread (p<0.05). Notably, liver metastasis was detected in 16.7% of female patients compared to 3.3% of male patients (p<0.05). However, no statistically significant differences were found between genders for other variables including disease stage, radiotherapy, targeted therapy, immunotherapy, primary tumor localization, and diagnostic method (p>0.05). The distribution of disease stages was similar between male and female patients, with a high proportion of advanced-stage diagnoses in both groups.

When comparing tumor subtypes, the majority of cases were diagnosed at stage IV, though no statistically significant difference was found between subtypes (p>0.05). Metastatic patterns varied according to tumor subtype. Liver metastasis was most frequently observed in neuroendocrine tumors (28.6%), while adrenal and bone metastases were more common in squamous cell carcinoma and adenocarcinoma cases. However, these differences did not reach statistical significance (p>0.05).

Regarding primary tumor localization, the right upper lobe was the most frequently involved site in both adenocarcinoma (33.7%) and squamous cell carcinoma (31.0%) cases. However, no statistically significant difference was observed in tumor localization between subtypes (p>0.05). When diagnostic methods were

evaluated, image-guided needle biopsy was the most commonly used technique, with the highest usage rate observed in patients with squamous cell carcinoma (33.0%). Differences among diagnostic methods were not statistically significant (p>0.05). Comparison of clinical and diagnostic characteristics according to age revealed that patients with brain metastases were diagnosed at a younger mean age (61.8 years), whereas those with liver metastases were diagnosed at an older mean age (71.8 years) (p<0.05).

DISCUSSION

Lung cancer is a malignancy in which early-stage diagnosis allows for significant survival benefits through surgical intervention, whereas in advanced stages, the opportunity for surgery is generally lost, necessitating systemic therapies. Similar to global trends, lung cancer is frequently diagnosed at advanced stages in Türkiye (9). In our study, the majority of patients were diagnosed at stage III (30.7%) and stage IV (47.5%).

In NSCLC, clinical improvements have been observed not only with platinum-based chemotherapy but also through the discovery of genetic molecular tests and the development of mutation-targeted therapies. Several studies have demonstrated that the clinical benefit derived from targeted therapies exceeds that of conventional chemotherapy (10). Furthermore, molecular test-negative NSCLC patients respond better to conventional chemotherapy compared to tyrosine kinase inhibitors (TKIs) directed against EGFR mutations. This underscores the importance of considering molecular results status in treatment selection and adopting a multidisciplinary approach (11).

In Türkiye, it is recommended that molecular testing for EGFR, ALK, and ROS1 genes be performed at the time of diagnosis in all patients with advanced or metastatic (stage IIIB and IV) non-squamous NSCLC. For early-stage patients who have not undergone prior molecular testing, molecular analyses should be conducted upon recurrence or progression, preferably using new biopsy specimens when possible (12).

When examining the frequency of EGFR mutations, the highest rates are observed in Asian countries, while European countries report the lowest frequencies (13). According to the Molecular Testing Guidelines for NSCLC published in 2021 by the Federation of Pathology Societies, EGFR mutation rates are reported to be between 10% and 15%. In our study, however, the EGFR mutation rate was found to be lower, at 4%. Consistent with the literature, EGFR mutations were more frequently detected in female patients in our cohort as well (14).

KRAS mutations represent one of the most common oncogenic alterations in NSCLC worldwide, with prevalence varying by geographic region, ethnicity, and histological subtype (15). The reported prevalence ranges from 8% to 20% in the United States, 9% to 19% in Europe, 7% to 9% in Latin America, and 1.5% to 4% in Asia (16,17). KRAS mutations occur in approximately 37% of adenocarcinomas but are much less frequent in squamous cell carcinoma (~4.4%). In our study, the KRAS mutation frequency was 3%, aligning more closely with rates reported in Asian populations. Additionally, KRAS positivity was higher in adenocarcinoma cases (6.5%) compared to squamous cell carcinoma (0%) in our cohort.

In recent years, the development of immune checkpoint inhibitors (ICIs) has significantly improved lung cancer prognosis. These inhibitors target the programmed cell death receptor-1/programmed death-ligand 1 (PD-1/PD-L1) pathway, activating anti-tumor immunity and facilitating the elimination of cancer cells (18). Selection of immunotherapeutic agents can be guided by PD-L1 expression status.

In our patient group, PD-L1 expression exhibited the highest frequency at 10.4%. Previous studies report PD-L1 expression prevalence in NSCLC patients ranging from 24% to 60%, even when using a positivity cutoff of 5% (19). To our knowledge, there are no prior studies from Türkiye specifically reporting the frequency of PD-L1 expression.

Adenocarcinoma patients exhibited a broader mutation spectrum, with positivity rates of EGFR (7.6%), KRAS (6.5%) and PD-L1 expression (17.4%) observed in our study. In contrast, mutations and analysis were less frequently detected in squamous cell carcinoma cases. However, no statistically significant difference was found in the overall mutation distribution between these histological subtypes (p>0.05). This finding is consistent with previously published literature (20).

One of unexpected finding of a higher frequency of PD-L1 expression compared to EGFR mutations in our cohort, contrary to most national data, may reflect a true regional variation. Several factors could contribute to this discrepancy. The Black Sea region is known for its relatively high smoking rates, and chronic exposure to tobacco smoke is a well-documented inducer of PD-L1 expression in lung tissues. In addition, environmental factors such as air pollution from biomass burning and industrial activity may also play a role in modulating tumor immune markers. Another possible explanation lies in the genetic and ethnic background of the regional population, which may influence tumor biology and immune checkpoint expression patterns. Further studies investigating these environmental and genetic influences are warranted to clarify the underlying mechanisms behind the observed PD-L1 predominance in this region.

Reviewing the literature, our study represents one of the largest single-center analyses to date. Given the regional differences observed, a prospective multicenter study in the Black Sea region appears both necessary and feasible to further elucidate these findings.

Study Limitations

The main limitation of our study is its single-center design. More comprehensive data reflecting the entire Black Sea region could be obtained through multicenter studies involving multiple institutions across the region. Due to the retrospective nature of the study, not all data were accessible from the system, and patients with incomplete records were excluded from the analysis, which may have led to a selection bias in the study population.

CONCLUSION

This study is the first in the Ordu province to provide such comprehensive information about lung cancer. In this study, it was observed that in correlation with research conducted in Türkiye, the majority of patients were diagnosed at advanced stages. This may be attributed to factors such as the non-specific nature of lung cancer symptoms, the late onset of these symptoms, patients attributing the symptoms to smoking, delayed medical consultations, and the absence of a national lung cancer screening program. Developing and implementing lung cancer screening programs, raising public awareness about the harms of smoking and lung cancer, enforcing measures against tobacco and tobacco products, and intensifying smoking cessation programs are necessary to minimize the occurrence and diagnosis of lung cancer in Türkiye.

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