

Analysis of Imaging, Pathology and Demographic Data of Lung Cancer Patients Diagnosed in a Tertiary Medical Center in the South-West Region of Romania

OVIDIU CÎMPEANU¹, ILONA MIHAELA LILIAN^{2,3},
DANIEL-NICOLAE PIRICI^{2,3}, MIHAI OLTEANU⁴, COSTIN-TEODOR STREBA⁴

¹Doctoral School, University of Medicine and Pharmacy of Craiova, Romania

²Department of Histology, University of Medicine and Pharmacy of Craiova, Romania

³Research Centre for Microscopic Morphology and Immunology,
University of Medicine and Pharmacy of Craiova, Romania

⁴Department of Pulmonology, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT: Introduction: Lung cancer is the most common type of primary tumor in both males and females, accounting for significant mortality worldwide. Clear evidence regarding comorbidities and aggravating factors exist, with multiple pathways being cited in recent literature. Patients and methods: Our aim was to review relevant sources and demonstrate through an original statistical study that tumor type, location, comorbidities, as well as demographic factors, may play a limited role in the evolution of lung adenocarcinoma. After obtaining ethical clearance, we enrolled consenting lung cancer patients in an observational cross-sectional study, collecting relevant demographic and medical information. Patients were recruited from a single tertiary medical center in Craiova, Romania, between January 2021 and January 2025. We used the Anova and the chi-square tests, considering p values below 0.05 as statistically significant. Results: We enrolled 189 patients (143 males, 75.6% of the entire lot), from urban and rural settings (49.7% from urban areas). The mean age was 64.94±10.47 years, with minimal variance when accounting for gender or provenance (Anova test, p>0.05). Most tumors were located in the upper portions of the lungs, with 111 cases, 53.44%. We found that 55.24% of males had tumors of the right lung, while only 39.13% of females had this location. Men had higher COPD rates (79 cases, 55.24%) and only two females (4.34%), p<0.05. However, we found statistically significant more women smokers than men (82.6% women vs. 41.25% of men). Conclusion: We hereby demonstrated that lung cancer remains a significant medical burden for the medical system, with prevalence in both sexes, irrespective of provenance. Most cases were diagnosed between 40 and 65 years, smoking and toxic exposure being predominant.

KEYWORDS: Lung cancer, inflammation, immunohistochemistry.

Introduction

Lung cancer (LC) is a major cause of death worldwide and a major public health problem.

Lung cancer continues to be the most common cause of cancer death, accounting for 1.8 million deaths (18%) in 2020, according to the International Agency for Research on Cancer's (IARC) and GLOBOCAN 2020 estimates of cancer incidence and mortality.

Lung cancer is classified into two types according to the cell of origin: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).

Adenocarcinoma (cancer that originates from glandular cells), squamous cell carcinoma (SCC), and neuroendocrine malignancies such as small cell carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC), and carcinoid are the most prevalent forms of lung cancer, according to the WHO classification [1].

In the past, the lung cancer epidemic appears to have affected mainly the developed nations.

Recent data reveal that the incidence of lung cancer is drastically increasing with almost half of new cases, 49.9%, identified in undeveloped countries [1].

Lung cancer often spreads to the liver, adrenal glands, bones, and brain as distant metastases [2].

Lung cancer has a dismal prognosis; in most countries, the overall 5-year survival rate is still around 30% [3,4].

Prior to the 1990s, the most prevalent histologic subtype was squamous cell lung carcinoma, especially in men.

Since that time, the incidence of adenocarcinoma has risen to surpass that of squamous cell carcinomas in the United States, Canada, numerous European countries, and Japan [1].

Risk reduction is crucial to lowering the burden of lung cancer because early identification and clinical therapy have had limited success.

Decreasing tobacco exposure could be the most efficient method to lower the incidence and burden of lung tumors from its underlying cause, which is why stricter laws and regulations on the manufacture, sale, and consumption ought to be established and implemented globally.

This is because 80-90% of cancers of the lungs are linked to tobacco exposure.

Quitting smoking should be strongly encouraged and carried out more successfully [5].

Several other factors, including nutrition, sleep patterns and physical activity, may potentially raise the risk of lung cancer [6].

Furthermore, based on individual heterogeneity, these diverse risk factors may have varying contributions to the risk of lung cancer [7].

For example, only a small percentage of smokers will get lung cancer in their lifetime, even though tobacco smoke is responsible for 80-90% of the disease's causes.

These people may be at varying risk for lung cancer due to non-tobacco risk factors [7].

However, over a long period of time, most of these risks probably add up to lung carcinogenesis.

Strategies should be put in place to target each stage of these processes, regardless of the etiology, in order to successfully lower the risk of lung cancer and enhance its prognosis [8].

Lung cancer and smoking

A history of smoking is linked to a higher likelihood of centrally situated squamous cell and small cell malignancies, particularly in men.

Women and people without a history of smoking are prone to develop adenocarcinoma, which develops peripherally and tests positive for tar.

Table gene mutations such ROS1, BRAF, anaplastic lymphoma kinase (ALK), and epidermal growth factor receptor (EGFR).

Recent years have seen the replacement or augmentation of chemotherapy in eligible individuals who have receptor tyrosine kinase small molecule inhibitors targeting these types of mutations, in addition to immunotherapies including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors and programmed cell death protein 1 (PD-1) [9].

Lung cancer is most frequently caused by smoking. Smoking is thought to be the cause of 90% of cases of lung cancer [3].

Male smokers are at the biggest risk.

Contact with other carcinogens, such as asbestos, further increases the risk.

Because of the intricate interactions between smoking, environmental variables, and genetics, there is no association between the number of packs smoked annually and lung cancer.

Passive smoking raises the likelihood of lung cancer by 20% to 30% [10].

The consumption of filter and lower-tar cigarettes correlates with an increased risk of peripherally positioned lung cancers, such as adenocarcinoma and large cell cancer.

In contrast, nonfiltered cigarette use is associated with a higher occurrence of centrally located lung cancers, including squamous cell lung cancer and small cell lung cancer [11], which may contribute to the observed decline in SCLC incidence [12].

Significant efforts at both international and national levels have been implemented in tobacco control, encompassing smoking bans, health warnings, advertising restrictions, and tobacco taxation.

Although there have been many positive developments, there is still much space for improvement because the rate of reduction in smoking prevalence has varied by nation, gender, and age category [13].

Patients and methods

We prospectively analyzed relevant medical and epidemiological data from a cohort of confirmed lung cancer patients who were admitted at the Clinical "Victor Babeş" Infectious Disease and Pulmonology Hospital over a period of four years (January 2021-January 2025).

Ethical clearance was obtained from the Ethical Boards of the University of Medicine and Pharmacy of Craiova (approval 73/07.09.2020), and all patients agreed in writing to the use of their anonymized medical information for statistical purposes.

The study was conducted in accordance with all national and international regulations, as well as all GDPR requirements at the time of patient inclusion.

We did not collect, stored or processed any personal data or any identifiable information regarding participants.

All persons above 18 years of age, irrespective of gender or comorbidities were included.

We collected age at inclusion, gender, broad demographics (rural/urban setting), main cancer diagnosis and tumor location and histological type (according to pathology results), any known comorbidities, smoking habits and environmental exposure to toxins.

Data was collected from the anonymized medical records as well as direct patient interviews upon hospital admission.

Data was stored in an Excel spreadsheet (Microsoft Excel 365, Microsoft corp., USA) and statistical analysis was performed using the included Analysis pack.

We used the Anova test for comparing the means of continuous variables such as age, the chi-square test for proportions.

We considered *p* values below 0.05 as statistically significant.

Results

We enrolled 189 persons, of which the majority were males (n=43, 75.6%).

The lot was almost symmetrically distributed according to background, with 49.7% from urban areas (n=94), versus 50.3% (n=95) with a rural residence.

No significant differences were recorded in terms of distribution according to background (47.55% males and 56.52% females with urban residence, 56.52% males and 43.48% females with rural residence, chi square test *p*=0.289).

However, significantly more females came from urban than from rural areas.

A synthesis of these results can be seen in Table 1.

Table 1. Distribution of age and gender in the studied population.

	Male		Female		Total	%
	N	%	N	%		
Urban	68	47.55	26	56.52	94	49.7%
Rural	75	52.45	20	43.48	95	50.3%
Total	143	75.6%	46	24.4%	189	

The mean age of the study group was 64.94±10.47 years (mean± standard deviation, SD), with minimal variance depending on gender (65.15±9.36 years for males vs 64.3±13.44 years for females) and background (65.45±10.09 years for urban vs 64.44±10.85 years for rural settings).

We did not find statistically significant differences between categories (Anova test, *p*=0.96) (Figure 1).

Average and SD values are presented in Table 2, and a histogram representation of the distributions among all groups can be seen in Figure 2.

We could observe a statistically higher density of cases distributed between the ages of 60 and 75 years (*p*<0.05), with only one rural female patient below 22 years and the rest above 35 years of age.

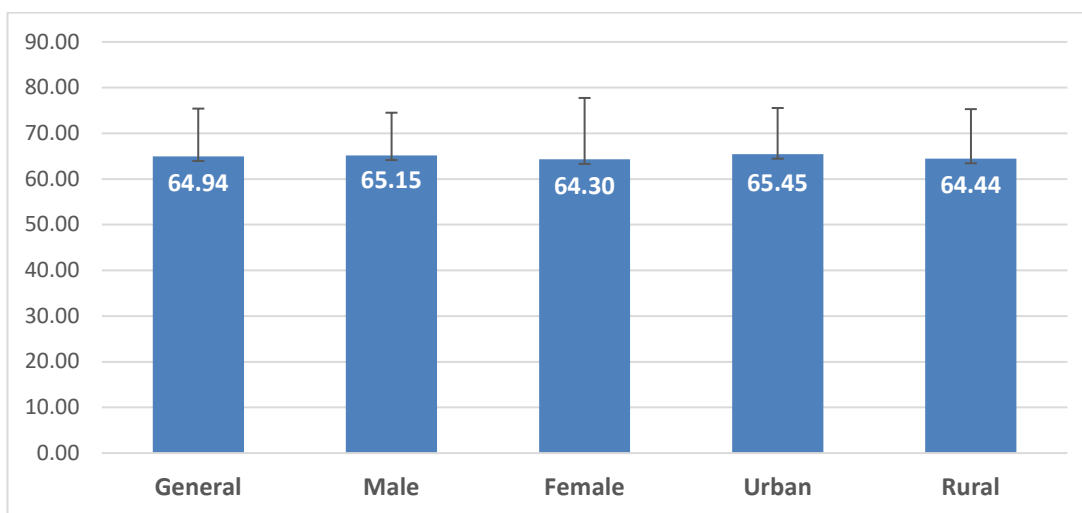


Figure 1. Distribution of mean ages (±SD) in each sub-lot, as well as the general group.

Table 2. Distribution of mean ages.

Age (years)	Whole group	Males	Females	Urban	Rural
Mean (SD)	64.94 (10.47)	65.15 (9.36)	64.30 (13.44)	65.45 (10.09)	64.44 (10.85)

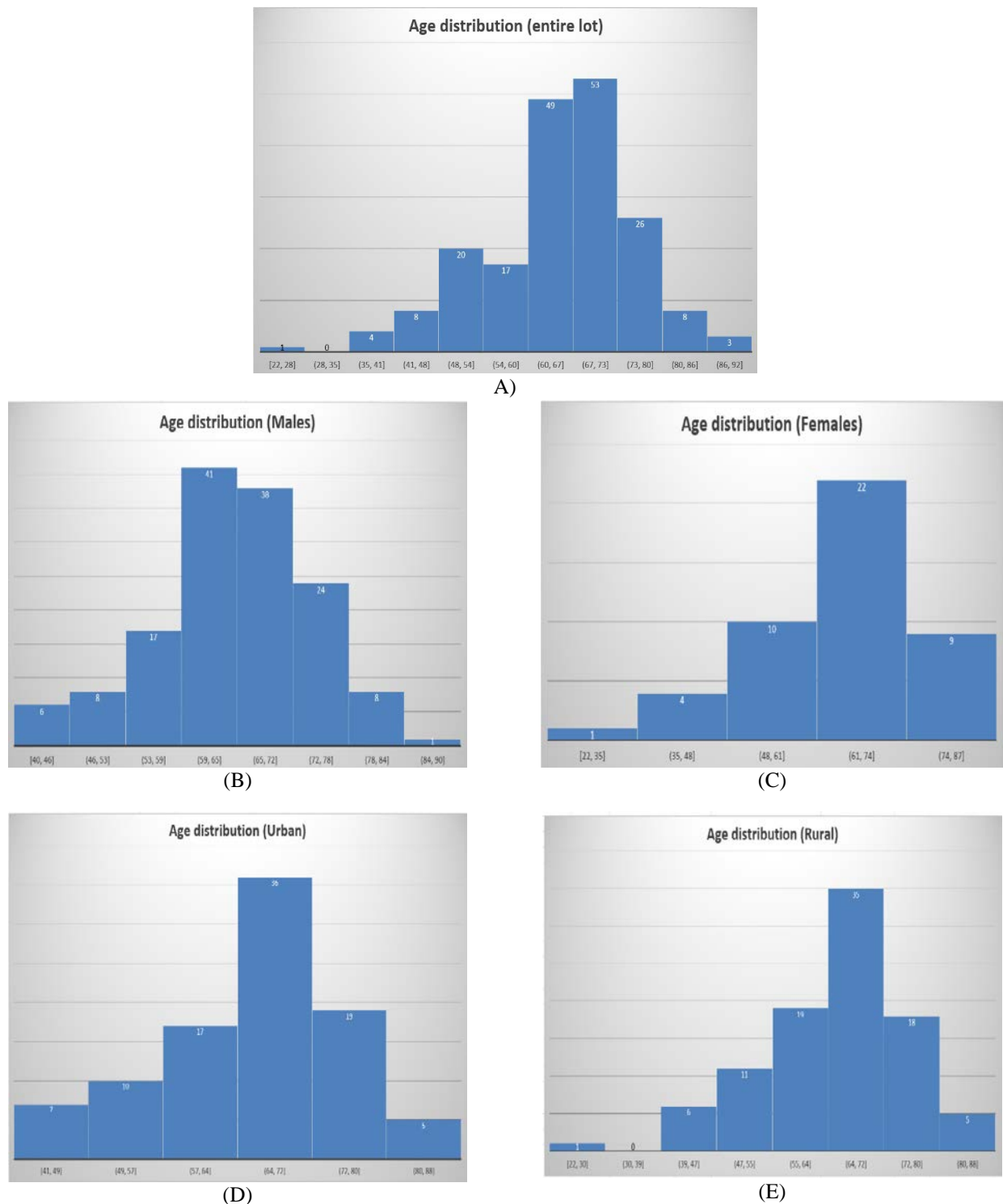


Figure 1. Histogram distribution of ages in the patient lot (A) and each subgroup (B-males, C-Females, D-Urban environment and E-Rural environment). We could observe that the largest part of the population was between 60-75 years of age at the time of diagnosis.

We found that the majority of tumors were located in the upper lobes (111 cases, 53.44%), with a predominance on the right lung (93 cases, 49.2% vs 65 cases, 34.39%).

Another 31 patients had multiple locations (16.4%).

No significant differences were noted when we analyzed the distribution within each sub-lot ($p > 0.05$).

We found that 55.24% of males had tumors of the right lung, while only 39.13% of females had this location. Results can be seen in Table 3.

Table 3. Distribution of the tumor locations according to imaging.

	Total	%	Male	Female	Urban	Rural
Upper right lobe	53	28.04	47	6	27	26
Lower right lobe	29	15.34	23	6	12	17
Median Lobe	11	5.82	9	2	6	5
Upper left lobe	48	25.40	32	16	27	21
Lower left lobe	17	8.99	11	6	10	7
Multiple locations	31	16.40	21	10	12	19
Total	189	100	143	46	94	95

Most cases were adenocarcinomas (83, 43.92%), of whom 72 males (86%); the second most common histopathological type was squamous carcinoma (52 cases, 27.51%), of whom 32 males (61.53%).

This predominance was statistically relevant ($p < 0.05$); however, when analyzing the

distribution according to demographical background, we found an almost equal distribution between urban and rural.

We found 27 cases (14.81%) of small cell carcinoma and 26 other types of malignant lung tumors (13.76%).

Results can be found in Table 4.

Table 4. Distribution of histopathological type, in the whole group and each sub-group.

Histopathology type	Total	%	Male	Female	Urban	Rural
Adenocarcinoma	83	43.92	72	11	41	42
Small cell carcinoma	28	14.81	22	6	12	16
Squamous carcinoma	52	27.51	32	20	30	22
Other types of lung cancer	26	13.76	17	9	11	15
Total	189	100	143	46	94	95

In terms of comorbidities, most subjects reported chronic obstructive pulmonary disease (COPD)-81 patients, 42.86%.

We found significant more COPD cases in men (79 cases, 55.24% of males) compared to women (only two cases, 4.34%), the difference being statistically significant ($p < 0.05$).

This result was particularly interesting, since smoking was more prevalent in women, which could have led to a higher COPD incidence in this category of cancer patients.

This shows that inflammation in COPD, as well as subsequent carcinogenesis, may have

other causes and influences the evolution of the disease in multiple ways.

Cardiovascular complications ranked second (75 cases, 39.68% of which the majority had hypertension-51 cases, 26.98% of the entire lot).

Also, 17 cancer patients also had known diabetes (17 cases, 8.99%).

We found no Table differences between genders, in respect to cardiovascular comorbidities.

Atelectasis, either partial or of the entire lung, was found in 12 cases (6.35%) and was more predominant in men (10 cases).

Table 5. Comorbidities in the whole group and each sub-group.

	Total	%	Male	Female	Urban	Rural
Hypertension	51	26.98	37	14	20	31
COPD	81	42.86	79	2	43	38
Atelectasis	12	6.35	10	2	7	5
Cardiac insufficiency	24	12.70	14	10	10	14
Diabetes	17	8.99	14	3	8	9

We found 66 cases with metastases (34.92%), with equal proportional distribution among men and women (34.26% of men vs 36.95% in women).

In our lot, most metastases were from adenocarcinomas (28 cases, 33.73% of this type), followed by squamous carcinomas

(16 cases, 30.77% of this type) and small cell carcinomas (12 cases, 42.85% of all small cell carcinomas).

We could thus observe that small cell carcinomas were the most aggressive cancers, even if lower overall in numbers ($p < 0.05$).

Results can be seen in Table 6.

Table 6. Distribution of either metastases or other malignancies according to each histopathological type, gender and provenance.

	Total	Male	Female	Urban	Rural	Adeno-carcinoma	Small cell carcinoma	Squamous carcinoma	Other types of lung cancer
Methastasis	66 (34.92%)	49	17	33	33	28 (33.73%)	12 (42.85)	16 (30.77%)	10 (38.46%)
Other malignancy	7 (3.7%)	4	3	2	5	4 (14.29%)	3 (5.77%)	0 (0%)	0 (0%)

Smoking habits among study participants revealed that the majority (97 patients, 51.32%) were non-smokers; surprisingly, most females were smokers (38 cases, 82.6% of all included women) and only 59 of the 143 men smoked (41.25%).

Smokers came from an urban environment in 53 cases, 56.38%, with insignificant differences

in regard to the rural environment ($p > 0.05$) (Table 7 and Figure 3).

Analyzing the pack-year consumption, most were smoking 21-30 pack-year equivalent (31 cases, 16.4% of the entire lot and 33.69% of all smokers) (Figure 4).

Table 7. Distribution of pack-year values in the studied lot, as well as each sub-group considered for the analysis.

Smoking	Overall	%	Males	Females	Urban	Rural
Non-smoking	97	51.32	59	38	43	54
Smoking	92	48.68	84	8	53	39
10-20PY	12	6.35	10	2	8	4
21-30PY	31	16.40	30	1	14	17
31-40PY	24	12.70	21	3	17	7
41-50PY	12	6.35	11	1	6	6
Above 50PY	13	6.88	12	1	8	5

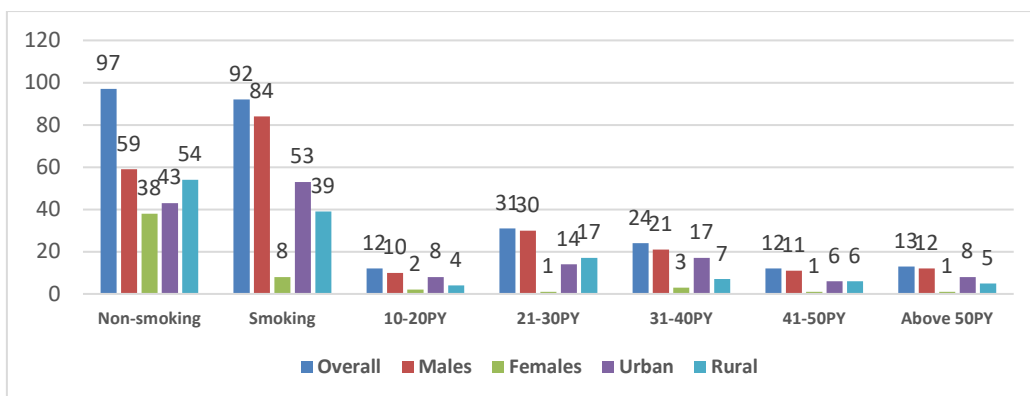


Figure 3. Distribution of smoking habits among all sub-lots, as well as the overall values of the studied groups.

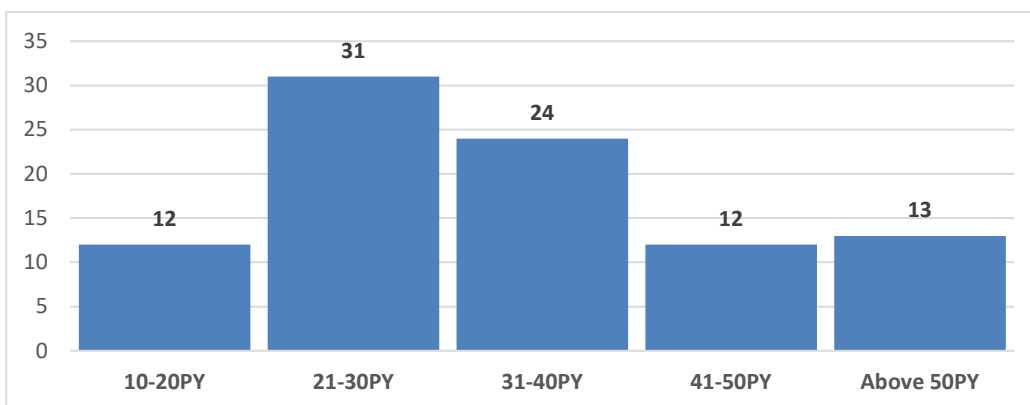


Figure 4. Histogram distribution of pack-year values in the whole lot.

When accounting for toxic exposure, only 15.87% of the lot (30 patients) reported either professional or environmentally respiratory pollution.

Association with smoking was not a factor, 15 being non-smokers (50%).

Most exposure was in males (27 cases vs only 3 females) and most came from urban areas (22 cases vs 8 from rural areas).

Results can be seen in Table 8.

Table 8. Regular toxic exposure corroborated with smoking habits, both in the whole group and each demographic sub-group.

	Overall	%	Males	Females	Urban	Rural
Toxic exposure	30	15.87	27	3	22	8
Of which non-smoking	15	50.00	13	2	10	5
Of which 10-20PY	3	10.00	3	0	2	1
Of which 21-30PY	3	10.00	3	0	2	1
Of which 31-40PY	2	6.67	2	0	2	0
Of which 41-50PY	5	16.67	4	1	4	1
Of which Above 50PY	2	6.67	2	0	2	0

Discussion

In our study, we demonstrated that lung cancer has various associated factors that may ultimately determine its evolution.

Co-existing pathology, exposure to respiratory pollutants and, especially, smoking habits, influence cancer incidence and predict medical outcomes.

We demonstrated several patterns in location, histological type and risk of metastasis, with possible links to the aforementioned conditions associated with malignancies.

One interesting observation is the higher female proportion among females that actively smoke, inversely correlated with the COPD prevalence in this subplot.

This shows that multiple inflammatory pathways are involved in the evolution of lung obstructive diseases and subsequent carcinogenesis.

Lung cancer and vaping

To address nicotine cravings, the tobacco industry began promoting e-cigarettes in the early 21st century. Because vaping involved inhaling an aerosolized liquid rather than burning tobacco, the idea was that e-cigarettes were "safer" than traditional cigarettes. The industry generally agreed that vape aerosol is "safer" than tobacco smoke since it contains fewer harmful and/or cancer-causing chemicals, even though it effectively delivers nicotine into the lungs [14,15].

Some recent studies have shown that the risk of lung cancer was four times higher for people who mixed vaping and cigarette smoking than for those who only smoked, and that vaping and

cigarette smoking were eight times more common in cases of lung cancer than in the control patients. These results held true for all main cell types of lung cancer and for both men and women. According to this findings, smoking cigarettes and vaping together increases the risk of lung cancer development more quickly than smoking alone [16].

According to estimates, there were around 70 million e-cigarette users worldwide in 2020 [17].

Other risk factors

SCLC has been linked to a variety of environmental and workplace exposures, as well as hormonal variables. In many communities, household radon exposure is the second leading cause of cancer of the lungs after cigarette smoking [18].

Metal exposure, including arsenic, chromium, nickel, and polycyclic aromatic hydrocarbons, has been linked to lung cancer.

Lung disorders, especially idiopathic pulmonary fibrosis, raise the possibility of lung cancer independent of the habit of smoking [19].

Asbestos, diesel engine emissions, different combinations of polycyclic aromatic hydrocarbons, arsenic, crystalline silica, and certain heavy metals are some of the main causes of lung cancer, which has been revealed to be up to 15% in men and 5% in women due to exposure at work [20,21].

A direct correlation between the amount of radon found in homes and the risk of lung cancer was found in a meta-analysis of 13 studies; the authors calculated that radon exposure may be accountable for as much as 2% of lung cancer deaths in Europe [22].

IARC classifies air pollution and fine particles as group 1 carcinogens [23,24].

According to WHO estimates, lung cancer accounted for about 6% of premature deaths in 2016 caused by outdoor air pollution [24]; correlations between the risk of lung cancer and mortality have been shown in both smokers and nonsmokers (HR<2) [25-28], and the risk of lung cancer linked to air pollution is likely impacted by underlying hereditary susceptibility [26,27].

A variety of viruses have been linked to the emergence of cancer. Hepatitis B and C, Epstein-bar virus (EBV), and Human papillomavirus (HPV) are a few of these.

Among these, HPV has been linked to head and neck malignancies and may have an impact on lung cancer [29].

Prolonged inhalation of cooking fumes from frying or burning wood has been associated with a higher incidence of lung cancer in nonsmokers in underdeveloped nations [30].

This issue is particularly noticeable in poorer nations where women handle the majority of cooking responsibilities and may spend hours every day in front of open flames. Some of the disproportionately high incidences of lung cancer in this population are believed to be caused by this exposure [30].

Underlying pulmonary disease is a significant risk factor for the occurrence of lung cancer in nonsmokers. Many factors, including pre-existing conditions, chemotherapy, and radiation therapy, can contribute to lung illness [31].

Obesity is a substantial risk factor for LC, influencing several aspects of the disease. It affects disease biology by promoting tumor formation and progression via pathways such as chronic inflammation, hormonal abnormalities, and metabolic dysregulation. Obesity also influences treatment outcomes, potentially affecting the efficacy and tolerability of medicines such as chemotherapy, immunotherapy, and radiotherapy.

Furthermore, obesity worsens patient outcomes, frequently resulting in poorer prognoses, greater treatment-related problems, and a higher chance of comorbidities. Understanding and managing these complex effects is critical for improving the treatment and outcomes of LC in obese populations [32].

Socioeconomic status

Socioeconomic status (SES) influences health and disease through a variety of interconnected pathways involving assets,

physical and psychological and social stressors, health-related behaviors, and risk factors. SES is highly connected with various lung cancer risk variables, particularly tobacco smoking behavior. Uptake may be higher among people with low SES, and attempts to stop are less probably to be successful [33].

After managing smoking, a pooled study of 17,021 cases and 20,885 controls revealed that low SES based on the International Socio-Economic Index correlated with an 84% higher likelihood of lung cancer among males and a 54% increased risk among women [34].

In our study, even though we did not directly account for income or other socioeconomic indicators, we found an equal distribution of rural and urban patients, showing that provenance may not play a direct role in exposure to risk factors for lung carcinogenesis.

Molecular abnormalities

A greater comprehension of pathogenesis and the impact of genetic factors in the formation of lung cancer allows for the detection of morphological and molecular abnormalities that are specific not only of invasive cancer, but also of preinvasive lesions in the lungs of former and present smokers. Morphological abnormalities such as hyperplasia, metaplasia, dysplasia, and carcinoma in situ (CIS) can precede or follow invasive malignancy. Bronchial epithelial hyperplasia and squamous metaplasia are widely regarded as reactive changes generated by prolonged inflammation and mechanical damage. Hyperplasia and metaplasia are thought to be transient alterations that may spontaneously resolve following smoking cessation. Dysplasia and carcinoma in situ are premalignant alterations that commonly precede squamous cell carcinoma of the lung [35-37].

Several molecular anomalies have been found in lung cancer patients in recent years, especially in those with adenocarcinoma histology and NSCLC. EGFR, HER2, KRAS, BRAF, MET exon 14, ALK, NTRK, RET, and ROS1 gene rearrangements/fusions are among the many of these anomalies that are currently being treated [38].

The appearance of immune checkpoint inhibitors (ICI) has resulted in significant advances in the management of NSCLC over the previous decade. ICIs target PD-1, PD-L1, and CTLA-4, preventing tumor cells from escaping the immune system. Patients with tumor cells that express PD-L1 at $\geq 50\%$ benefit the most from ICIs. Thus, PD-L1 expression in tumor cells appears to be a promising biomarker for

therapy response. Thus, immunohistochemistry (IHC) should be used to assess the tumor proportion score, which represents PD-L1 expression on cancer cells and is characterized as the proportion of immunoreactive cancer cells measured toward the total number of tumor cells, prior to ICI therapy in lung cancer patients [39].

Epigenetic mechanisms perform an important role in the control of gene expression and are triggered by an environmental exposure, such as repeated exposure to the harmful substances found in tobacco smoke [40-42].

Advances and challenges in the treatment of lung cancer-perspectives

The following advantages make nanocarrier-based drug delivery a cutting-edge approach to treating lung cancer. To improve the therapeutic effects on cancer of the lungs, these include higher safety through site-specific administration of anticancer medications, improved bioavailability of pharmaceuticals in the body, and the ability to release drugs in a continuous and controlled manner during targeted drug delivery [43].

A prospective therapeutic strategy to investigate in the field of lung cancer therapy is the nanomedicine delivery system, which offers an alternative to the traditional chemotherapy medication with several side effects [44].

Checkpoint inhibitors are one example of a safe and successful immunotherapy technique that may offer an alternative to current NSCLC treatment options [45,46].

It may be preferable in some circumstances to combine immunotherapy with other medicines or treatment approaches [47-49].

With positive outcomes in treating tumors, photothermal therapy was regarded as a promising less invasive treatment approach [50].

In order to treat malignancies, photothermal therapy can use a photothermal agent in conjunction with local laser irradiation to transform light energy into local heat energy [51].

In the treatment of tumors, the combination of photothermal therapy and nanotechnology has a synergistic impact, suggesting intriguing potential [52].

For NSCLC, molecular targeted therapy has emerged as a key therapeutic approach [53].

Numerous receptor tyrosine kinases, including anaplastic lymphoma kinase (ALK), hepatocyte growth factor receptor (c-Met), and epidermal growth factor receptor (EGFR), are essential targets for molecular targeted therapy

because they are involved in cell development and survival [54,55].

Conclusions

In conclusion, our review and statistical study show that lung show that primary lung cancer remains a major health problem in all clinical settings, with high mortality rates, also being the most common cancer in both males and females.

Co-morbidities play a defining role in its management, with preexisting inflammatory obstructive diseases severely affecting prognosis; smoking and toxic exposure remain the main aggravating factors, irrespective of tumor type and morphology.

Conflict of interest

None to declare.

References

1. Barta JA, Powell CA, Wisnivesky JP. Global Epidemiology of Lung Cancer. *Ann Glob Health*, 2019, 85(1):8.
2. Gheonea IA, Popp CG, Ivan ET, Gheonea DI. Unusual triple combination of prostate, lung and skin cancer. *Rom J Morphol Embryol*, 2017, 58(2):567-574.
3. Zeng H, Chen W, Zheng R, Zhang S, Ji JS, Zou X, Xia C, Sun K, Yang Z, Li H, Wang N, Han R, Liu S, Li H, Mu H, He Y, Xu Y, Fu Z, Zhou Y, Jiang J, Yang Y, Chen J, Wei K, Fan D, Wang J, Fu F, Zhao D, Song G, Chen J, Jiang C, Zhou X, Gu X, Jin F, Li Q, Li Y, Wu T, Yan C, Dong J, Hua Z, Baade P, Bray F, Jemal A, Yu XQ, He J. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. *Lancet Glob Health*, 2018, 6(5):e555-e567.
4. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, Bonaventure A, Valkov M, Johnson CJ, Esteve J, Ogunbiyi OJ, Azevedo ESG, Chen WQ, Eser S, Engholm G, Stiller CA, Monnereau A, Woods RR, Visser O, Lim GH, Aitken J, Weir HK, Coleman MP, Group CW. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*, 2018, 391(10125):1023-1075.
5. Stone E, Vachani A. Tobacco Control and Tobacco Cessation in Lung Cancer-Too Little, Too Late? *Semin Respir Crit Care Med*, 2016, 37(5):649-658.
6. Nigro E, Perrotta F, Scialo F, D'Agnano V, Mallardo M, Bianco A, Daniele A. Food, Nutrition, Physical Activity and Microbiota: Which Impact on Lung Cancer? *Int J Environ Res Public Health*, 2021, 18(5):2399.
7. Schabath MB, Cote ML. Cancer Progress and Priorities: Lung Cancer. *Cancer Epidemiol Biomarkers Prev*, 2019, 28(10):1563-1579.

8. Liu Y, Li Y, Bai YP, Fan XX. Association Between Physical Activity and Lower Risk of Lung Cancer: A Meta-Analysis of Cohort Studies. *Front Oncol*, 2019, 9:5.
9. Denisenko TV, Budkevich IN, Zhivotovsky B. Cell death-based treatment of lung adenocarcinoma. *Cell Death Dis*, 2018, 9(2):117.
10. Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest*, 2003, 123(1 Suppl):21S-49S.
11. Brooks DR, Austin JH, Heelan RT, Ginsberg MS, Shin V, Olson SH, Muscat JE, Stellman SD. Influence of type of cigarette on peripheral versus central lung cancer. *Cancer Epidemiol Biomarkers Prev*, 2005, 14(3):576-581.
12. Ettinger DS, Aisner J. Changing face of small-cell lung cancer: real and artifact. *J Clin Oncol*, 2006, 24(28):4526-4527.
13. Flor LS, Reitsma MB, Gupta V, Ng M, Gakidou E. The effects of tobacco control policies on global smoking prevalence. *Nat Med*, 2021, 27(2):239-243.
14. Collins L, Glasser AM, Abudayyeh H, Pearson JL, Villanti AC. E-Cigarette Marketing and Communication: How E-Cigarette Companies Market E-Cigarettes and the Public Engages with E-cigarette Information. *Nicotine Tob Res*, 2019, 21(1):14-24.
15. Sapru S, Vardhan M, Li Q, Guo Y, Li X, Saxena D. E-cigarettes use in the United States: reasons for use, perceptions, and effects on health. *BMC Public Health*, 2020, 20(1):1518.
16. Bittoni MA, Carbone DP, Harris RE. Vaping, Smoking and Lung Cancer Risk. *J Oncol Res Ther*, 2024, 9(3):10229.
17. Jerzynski T, Stimson GV, Shapiro H, Krol G. Estimation of the global number of e-cigarette users in 2020. *Harm Reduct J*, 2021, 18(1):109.
18. Rodriguez-Martinez A, Torres-Duran M, Barros-Dios JM, Ruano-Ravina A. Residential radon and small cell lung cancer. A systematic review. *Cancer Lett*, 2018, 426:57-62.
19. Burns DM. Primary prevention, smoking, and smoking cessation: implications for future trends in lung cancer prevention. *Cancer*, 2000, 89(11 Suppl):2506-2509.
20. Driscoll T, Nelson DI, Steenland K, Leigh J, Concha-Barrientos M, Fingerhut M, Pruss-Ustun A. The global burden of disease due to occupational carcinogens. *Am J Ind Med*, 2005, 48(6):419-431.
21. Field RW, Withers BL. Occupational and environmental causes of lung cancer. *Clin Chest Med*, 2012, 33(4):681-703.
22. Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, Deo H, Falk R, Forastiere F, Hakama M, Heid I, Kreienbrock L, Kreuzer M, Lagarde F, Makelainen I, Muirhead C, Oberaigner W, Pershagen G, Ruano-Ravina A, Ruosteenoja E, Rosario AS, Tirmarche M, Tomasek L, Whitley E, Wichmann HE, Doll R. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ*, 2005, 330(7485):223.
23. Humans IWGotEoCRt. Household use of solid fuels and high-temperature frying. *IARC Monogr Eval Carcinog Risks Hum*, 2010, 95:1-430.
24. Humans IWGotEoCRt. Outdoor Air Pollution. *IARC Monogr Eval Carcinog Risks Hum*, 2016, 109:9-444.
25. Turner MC, Krewski D, Pope CA, 3rd, Chen Y, Gapstur SM, Thun MJ. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. *Am J Respir Crit Care Med*, 2011, 184(12):1374-1381.
26. Turner MC, Cohen A, Jerrett M, Gapstur SM, Diver WR, Pope CA, 3rd, Krewski D, Beckerman BS, Samet JM. Interactions between cigarette smoking and fine particulate matter in the Risk of Lung Cancer Mortality in Cancer Prevention Study II. *Am J Epidemiol*, 2014, 180(12):1145-1149.
27. Huang Y, Zhu M, Ji M, Fan J, Xie J, Wei X, Jiang X, Xu J, Chen L, Yin R, Wang Y, Dai J, Jin G, Xu L, Hu Z, Ma H, Shen H. Air Pollution, Genetic Factors, and the Risk of Lung Cancer: A Prospective Study in the UK Biobank. *Am J Respir Crit Care Med*, 2021, 204(7):817-825.
28. Myers R, Brauer M, Dummer T, Atkar-Khattra S, Yee J, Melosky B, Ho C, McGuire AL, Sun S, Grant K, Lee A, Lee M, Yuchi W, Tammemagi M, Lam S. High-Ambient Air Pollution Exposure Among Never Smokers Versus Ever Smokers With Lung Cancer. *J Thorac Oncol*, 2021, 16(11):1850-1858.
29. Gorlova OY, Weng SF, Zhang Y, Amos CI, Spitz MR. Aggregation of cancer among relatives of never-smoking lung cancer patients. *Int J Cancer*, 2007, 121(1):111-118.
30. Taylor R, Najafi F, Dobson A. Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. *Int J Epidemiol*, 2007, 36(5):1048-1059.
31. Alberg AJ, Brock MV, Samet JM. Epidemiology of lung cancer: looking to the future. *J Clin Oncol*, 2005, 23(14):3175-3185.
32. Georgakopoulou VE, Lempesis IG, Trakas N, Sklapani P, He Y, Spandidos DA. Lung cancer and obesity: A contentious relationship (Review). *Oncol Rep*, 2024, 52(5):158.
33. Hiscock R, Bauld L, Amos A, Fidler JA, Munafo M. Socioeconomic status and smoking: a review. *Ann N Y Acad Sci*, 2012, 1248:107-123.
34. Hovanec J, Siemiatycki J, Conway DI, Olsson A, Stucker I, Guida F, Jockel KH, Pohlabein H, Ahrens W, Bruske I, Wichmann HE, Gustavsson P, Consonni D, Merletti F, Richiardi L, Simonato L, Fortes C, Parent ME, McLaughlin J, Demers P, Landi MT, Caporaso N, Tardon A, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabianova E, Field J, Dumitru RS, Bencko V, Foretova L, Janout V, Kromhout H, Vermeulen R, Boffetta P, Straif K, Schuz J, Kendzia B, Pesch B, Bruning T, Behrens T. Lung cancer and socioeconomic status in a pooled analysis of case-control studies. *PLoS One*, 2018, 13(2):e0192999.
35. Wistuba II, Behrens C, Milchgrub S, Bryant D, Hung J, Minna JD, Gazdar AF. Sequential molecular abnormalities are involved in the multistage development of squamous cell lung carcinoma. *Oncogene*, 1999, 18(3):643-650.
36. Hirsch FR, Franklin WA, Gazdar AF, Bunn PA, Jr. Early detection of lung cancer: clinical perspectives of recent advances in biology and radiology. *Clin Cancer Res*, 2001, 7(1):5-22.

37. Gazdar AF, Brambilla E. Preneoplasia of lung cancer. *Cancer Biomark*, 2010, 9(1-6):385-396.
38. La Savia A, Meyer ML, Hirsch FR, Kerr KM, Landi L, Tsao MS, Cappuzzo F. Rediscovering immunohistochemistry in lung cancer. *Crit Rev Oncol Hematol*, 2024, 200:104401.
39. Gompelmann D, Sarova P, Mosleh B, Papaportfyriou A, Oberndorfer F, Idzko M, Hoda MA. PD-L1 assessment in lung cancer biopsies-pitfalls and limitations. *Int J Biol Markers*, 2024, 39(1):3-8.
40. McDermott U, Downing JR, Stratton MR. Genomics and the continuum of cancer care. *N Engl J Med*, 2011, 364(4):340-350.
41. Pass HI, Beer DG, Joseph S, Massion P. Biomarkers and molecular testing for early detection, diagnosis, and therapeutic prediction of lung cancer. *Thorac Surg Clin*, 2013, 23(2):211-224.
42. McBride CM, Koehly LM. Imagining roles for epigenetics in health promotion research. *J Behav Med*, 2017, 40(2):229-238.
43. Kim SJ, Puranik N, Yadav D, Jin JO, Lee PCW. Lipid Nanocarrier-Based Drug Delivery Systems: Therapeutic Advances in the Treatment of Lung Cancer. *Int J Nanomedicine*, 2023, 18:2659-2676.
44. Alshammari MK, Almomen EY, Alshahrani KF, Altwalah SF, Kamal M, Al-Twallah MF, Alsanad SH, Al-Batti MH, Al-Rasheed FJ, Alsalamah AY, Alhazza MB, Alasmari FA, Abida, Imran M. Nano-Enabled Strategies for the Treatment of Lung Cancer: Potential Bottlenecks and Future Perspectives. *Biomedicines*, 2023, 11(2):473.
45. Tang S, Qin C, Hu H, Liu T, He Y, Guo H, Yan H, Zhang J, Tang S, Zhou H. Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer: Progress, Challenges, and Prospects. *Cells*, 2022, 11(3):320.
46. Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, Ladwa R, O'Byrne K, Kulasinghe A. Immune Checkpoint Inhibitors in Cancer Therapy. *Curr Oncol*, 2022, 29(5):3044-3060.
47. Passaro A, Attili I, de Marinis F. Neoadjuvant Chemotherapy Plus Immunotherapy in Early-Stage Resectable Non-Small-Cell Lung Cancer. *J Clin Oncol*, 2022, 40(25):2871-2877.
48. Krzyzanowska N, Krawczyk P, Wojas-Krawczyk K, Kucharczyk T, Milanowski J. Immunotherapy in Non-Small-Cell Lung Cancer Patients with Driver Alterations: A New Strategy? *Cells*, 2022, 11(20):3280.
49. Banna GL, Hassan MA, Signori A, Giunta EF, Maniam A, Anpalakhan S, Acharige S, Ghose A, Addeo A. Neoadjuvant Chemo-Immunotherapy for Early-Stage Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. *JAMA Netw Open*, 2024, 7(4):e246837.
50. Saleem HM, Ramaiah P, Gupta J, Jalil AT, Kadhim NA, Alsaikhan F, Ramirez-Coronel AA, Tayyib NA, Guo Q. Nanotechnology-empowered lung cancer therapy: From EMT role in cancer metastasis to application of nanoengineered structures for modulating growth and metastasis. *Environ Res*, 2023, 232:115942.
51. Li Q, Parchur AK, Zhou A. In vitro biomechanical properties, fluorescence imaging, surface-enhanced Raman spectroscopy, and photothermal therapy evaluation of luminescent functionalized CaMoO₄:Eu@Au hybrid nanorods on human lung adenocarcinoma epithelial cells. *Sci Technol Adv Mater*, 2016, 17(1):346-360.
52. Han HS, Choi KY. Advances in Nanomaterial-Mediated Photothermal Cancer Therapies: Toward Clinical Applications. *Biomedicines*, 2021, 9(3):305.
53. Li S, de Camargo Correia GS, Wang J, Manochakian R, Zhao Y, Lou Y. Emerging Targeted Therapies in Advanced Non-Small-Cell Lung Cancer. *Cancers (Basel)*, 2023, 15(11):2899.
54. Schrank Z, Chhabra G, Lin L, Iderzorig T, Osude C, Khan N, Kuckovic A, Singh S, Miller RJ, Puri N. Current Molecular-Targeted Therapies in NSCLC and Their Mechanism of Resistance. *Cancers (Basel)*, 2018, 10(7):224.
55. Pottier C, Fresnais M, Gilon M, Jerusalem G, Longuespee R, Sounni NE. Tyrosine Kinase Inhibitors in Cancer: Breakthrough and Challenges of Targeted Therapy. *Cancers (Basel)*, 2020, 12(3):731.

**Corresponding Author: Ilona Mihaela Liliac, Department of Histology,
University of Medicine and Pharmacy of Craiova, Romania,
Research Centre for Microscopic Morphology and Immunology,
University of Medicine and Pharmacy of Craiova, Romania, e-mail: ilona.mihaela.liliac@gmail.com**