Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 3
Open Access

An anatomical pathology and immunohistochemistry analysis of lung cancer patients at the Military Hospital of Oran (Algeria).

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Received: 02-05-2024 **Published: 10-09-2024**

Cite this paper as: Chama Zouaouia, Medles Meriem, Bouchouicha Sara, Derras Hadria, Meddah Dalila, Meroufel Hadjer and Kheloufi Siham. (2024) An anatomical pathology and immunohistochemistry analysis of lung cancer patients at the Military Hospital of Oran (Algeria).. *Frontiers in Health Informatics*, *Vol.13, No.3*, 11417-11447

ABSTRACT

Introduction: Lung cancer represents a significant health problem in the Algerian population, with a progressively increasing incidence. The risks associated with this pathology are linked to several factors such as age, sex, heredity, diet, lifestyle, and smoking.

Objective: Our work is based on a descriptive retrospective epidemiological study aimed at conducting an anatomical pathology and immunohistochemistry study of lung cancer types and their distribution according to various criteria such as sex, age, histological type, specimen type, and risk factors.

Materials and Methods: This study was conducted at the Regional Military University Hospital of Oran (HMRUO), focusing on 115 patient records with lung cancer. A standardized approach is necessary to assess the percentages of patients affected by lung cancer from January 1, 2019, to December 30, 2020.

Results: The results demonstrated a male predominance in lung cancer, with a higher percentage in men (84%). In contrast, the incidence in females is only 16%, with these women living in an environment of passive smoking. This cancer includes several histological types: non-small cell carcinomas are adenocarcinoma (ADC) 61%, squamous cell carcinoma (SCC) 11%, non-small cell carcinoma not otherwise specified (NSCLC NOS) 12%, and small cell carcinoma (SCC) 11%, utilizing specific panels for diagnosis through immunohistochemical techniques.

Conclusion: Lung cancer is formidable, especially in the male population, linked to risk factors such as tobacco and asbestos, diagnosed using panels like TTF1, P40, P63, CK5/6, CK7, synaptophysin, and chromogranin.

Keywords: Lung cancer, Regional Military University Hospital (HMRUO), TTF1, anatomical pathology, immunohistochemistry.

INTRODUCTION

The rates of incidence and mortality differ significantly around the world. In low- to medium-income countries, lung cancer accounts for approximately 50% of all new cases(WHO, 2019;

de Groot PM et *al*., 2018)

In 2020, lung cancer was the second most frequently diagnosed cancer and the leading cause of cancer-related deaths, accounting for 11.4% of all diagnosed cancers and 18% of total cancer deaths. Among men, lung cancer is the primary cause of cancer morbidity (14.3%) and mortality (21.5%). For women, it ranks third in incidence (8.4%) and second in mortality (13.7%)(Sung H, et *al*., 2020)

The primary risk factor continues to be tobacco smoking. Additional risk factors include older age, race, male gender, occupational exposures (particularly to radon), existing health conditions (such as chronic obstructive pulmonary disease and tuberculosis), and genetic predispositions linked to specific chromosomal alterations, notably on chromosomes 15q24-15q25.1, 5p15.33, 6p21.33, and 13q31.36.(Malhotra J et *al*., 2016; Spyratos D,et *al*., 2013)

Lung cancer is a heterogeneous condition characterized by diverse trends and significant socio-economic consequences. Recognizing the epidemiological characteristics within a specific region can enhance survival outcomes by tailoring screening programs and treatment strategies(Gaga Met *al*.,2013). Lung cancer remains the most commonly diagnosed cancer among men in North-West Africa or the Maghreb region, including Algeria, Morocco, Tunisia, and Libya, posing a real public health problem (World Health Organization, 2020). In Algeria, cancer has emerged as a national priority, culminating in the establishment of a National Cancer Plan for 2015–2019 (Algeria's cancer plan 2015-2019). In 2014, the crude and age-standardized cancer incidence rates were 14.9 and 22.7 per 100,000 inhabitants, respectively(M. Hamdi et *al* ., 2015). These rates were modeled using data from Setif and various Cancer Registries published in "Cancer in Africa," as well as "Cancer Incidence in Five Continents" for the period of 2000–2014, alongside Globocan data from 2012((M. Hamdi et *al*., 2015).While lung cancer incidence and mortality rates are gradually rising in the Arab League countries, they remain relatively low compared to those in Europe and the USA(E.I. Salim, et *al*., 2011). Lung cancer is the leading cause of cancer-related deaths across all age groups, accounting for over 4,300 fatalities, which represents 13.2% of all cancer cases(World Health Organization International, 2020).This rise coincides with an increase in tobacco consumption: in Algeria, by December 31, 2018, the prevalence of daily smoking was 28.1% among males and 0.3% among females, resulting in an overall rate of 14.3% for both sexes (WHO, 2019). In comparison, the overall prevalence was only 7.7% in 1978(M. Hamdi et *al*., 2015; F. Skander, D. Larbaoui; M. Hamdi et *al* ., 2014). Globally, 80% to 85% of lung cancer cases are linked to tobacco smoking (M. Hamdi et *al*., 2014).Despite significant therapeutic advances, the relative survival rate remains low due to the lack of early cancer screening, with most diagnoses occurring at an advanced stage.As of now, Algeria lacks reliable and accurate epidemiological data on lung cancer diagnoses made by oncologists, pulmonologists, and pathologists across the entire country. The objectives of this study are to conduct an anatomical pathology examination of lung cancer, perform an immunohistochemical analysis of lung cancer, and determine the frequency of lung cancer in western Algeria at the Military Regional University Hospital of Oran (HMRUO).

MATERIAL AND METHODS

This is a descriptive retrospective epidemiological study (anatomical pathology and immunohistochemical) involving 115 patients diagnosed with lung cancer at the anatomy pathology department of the Military Regional University Hospital of Oran (HMRUO).

The records were collected over a one-year period, from January 1, 2019, to December 30, 2020.

Case Study

Lung cancer was histologically confirmed and diagnosed between January 2019 and December 2020. The patients' ages ranged from 25 to 107 years. We identified 115 eligible cases during this period in the clinical setting.

Inclusion Data

- We had 115 cases of lung cancer:
    - Patients diagnosed with non-small cell carcinoma.
    - Patients diagnosed with small cell carcinoma.
    - Patients with histological lesions

Epidemiological Data

In our study, we utilized patient records for data collection, which allowed us to gather the following parameters:

- Sex
- Age
- Histological type
- Smoking status
- Used panels
- Metastasis
- Statistical Analysis
- The data were processed using SPSS software, version 22.

Panels Used

- **Non-Small Cell Carcinoma (NSCLC):**
    - ADC (TTF1+/P40-)
    - CE (TTF1-/P40+)
    - CNPC-NOS (TTF1-+/P40-+)
- **Small Cell Carcinoma (SCLC):**
    - Ki +++ 60%
    - CD56
    - SYN
    - CHROMO
    - TTF1+
- **Immunohistochemical Technique**
- Immunohistochemistry is a technique that combines immunology and histochemistry, allowing for the localization and identification of proteins.

RESULT

1. **Statistical Survey**

The results obtained, presented in the tables below, following the statistical analysis related to lung cancers, while considering the parameters: age, sex, histological types, panels used,

smoking status, and metastases.
Annual Distribution of Patients with Lung Cancer Found in the HMRUO Region2019-2020
Our results, shown in the table below for 2019 and 2020, represent 52% and 46% of lung cancers, respectively (Table .1).

Table.1: Annual Distribution of Patients with Lung Cancer Found in the HMRUO Region 2019-2020

Year	2019	2020	Total
Numberofpatients	60	55	115
Percentage	52%	48%	100%

2. Distribution of patients with lung cancer by sex

Lung cancer affects both sexes, but with a male predominance, accounting for 84% of cases. Among females, the incidence is only 16%, with these women living in a passive smoking environment (Figure 1)

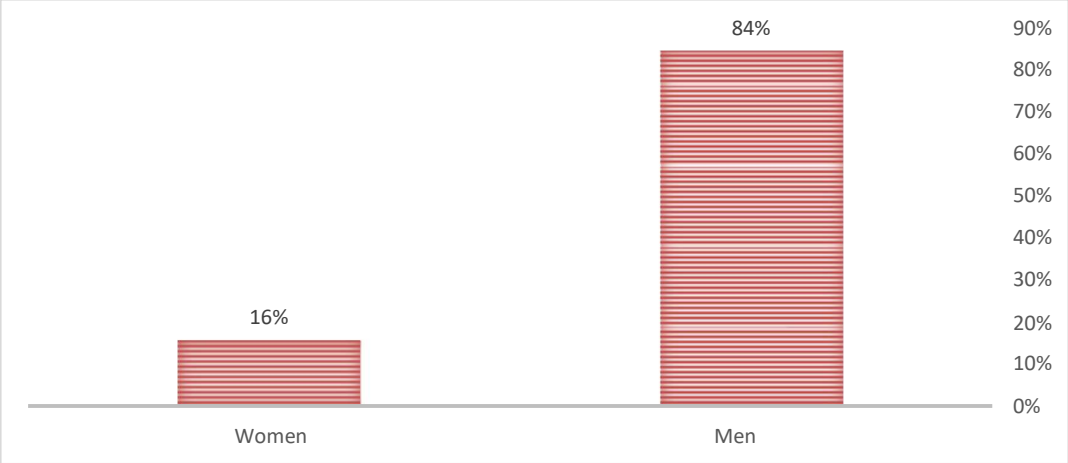


Figure 1: Distribution of patients with lung cancer by sex

3. Distribution of patients by age group

In our study, patients ranged from 20 to 90 years old, with an average age of 63.282 ± standard deviation of 36.5542. We found that the age groups most affected by lung cancer are [61-70] and [71-80] years, representing successive rates of 30% (35 cases) and 25% (29

cases) (Figure 2).

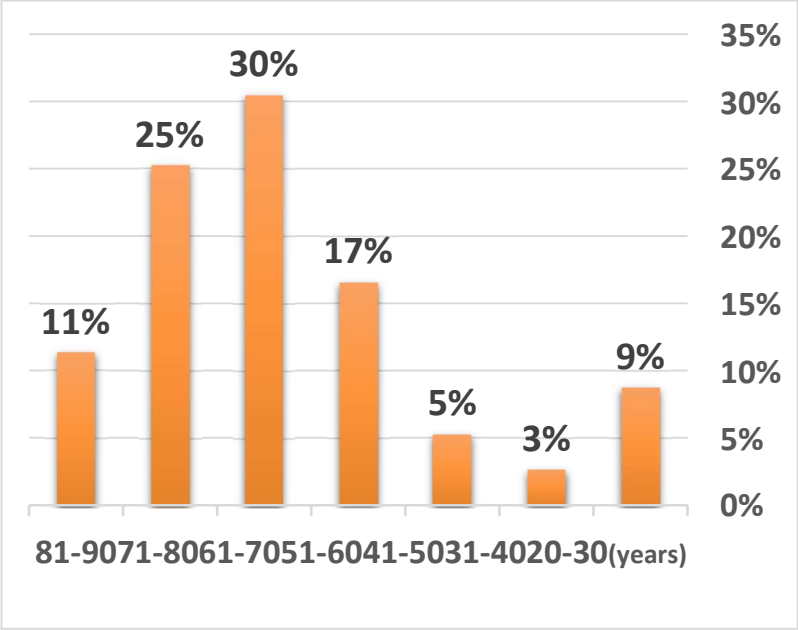


Figure2: Distribution of patients by age group

4. Distribution of patients by risk factors

According to our study illustrating the distribution of patients by risk factors, we noted that smokers represent 40% (46 cases), while one patient is attributed to occupational exposure toasbestos, accounting for 1%. Non-smokers represent 59% (68 cases) (Table 5.4).

5. Distribution of Smoking and Non-Smoking Patients by Sex

Our study illustrates the distribution of smoking and non-smoking patients by sex. It was noted that men are more affected by this risk, representing 40% (Figure 3).

Risk factors	Tobacco	Asbestos	Non-smoking patients	total
Number of patients	46	1	68	115
percentage	**40%**	**1%**	**59%**	**100%**

Figure 3: Distribution of smoking and non-smoking patients by sex

6. Distribution of Patients by Tobacco Use

According to the data results, we found that non-smoking patients are more affected by lung cancer, with a total of 69 cases (Table 5.6).

Table 2: Distribution of patients by tobacco use.

Age Group(Years)	Smoking Patients	Non-smoking Patients	Totalof patients	Percentage
20-30	0	10	10	0%
31-40	1	2	3	33%
41-50	0	6	6	0%
51-60	7	12	19	37%
61-70	18	17	35	51%
71-80	16	13	29	55%
81-90	4	9	13	31%
total	46	69	115	40%

7. Distribution of patients by histological types.

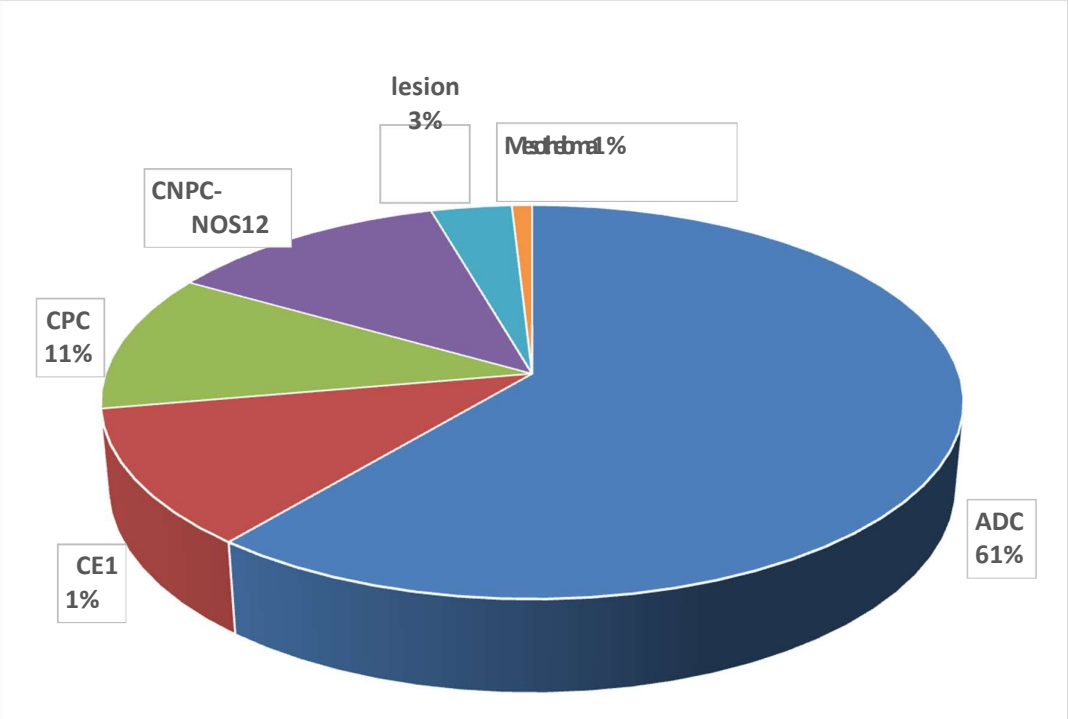
In our study, the histological forms represent 95%, or 110 cases, distributed as follows:

- Adenocarcinomas rank first with 70 patients (61%).
- Squamous cell carcinomas rank second with 13 patients (11%).
- Small cell carcinomas rank third with 13 patients (11%).
- Non-small cell carcinomas - NOS rank fourth with 14 patients (12%).
- Lesions rank fifth with 4 patients (3%).
- Other types of carcinoma, such as mesothelioma, which is a rare malignant tumor, rank sixth with 1 patient (1%).

Thus, our results are consistent with the arrangement of histological types (Table 4).

Figure 4: Distribution of patients by histological types.

8. Distribution of histological types by sex



Our study shows that adenocarcinoma in men is the predominant histological type, accounting for 50%, followed by squamous cell carcinoma at 11% in men and absent in women, and small cell carcinoma (CPC) at 11% in men and absent in women. Next is non-small cell carcinoma (CNPC) with 8% in men and 4% in women, and mesothelioma in the last position with 1% in men. Thus, the low incidence in women is related to passive smoking.

Table 3: Distribution of histological types by sex

Histological type	**ADC**	**CE**	**CPC**	**CNPC-NOS**	**Lésion**	**Mesothelioma**	**Total**
Men	58	13	13	9	3	1	97
Women	**12**	**0**	**0**	**5**	**1**	**0**	**18**
Percentage Men	50%	11%	11%	8%	3%	1%	84%
Percentage Women	**10%**	**0%**	**0%**	**4%**	**1%**	**0%**	**16%**

9. Distribution of Cancer Types by Panels Used

Our study shows the following data results:

- Use of panels including TTF1, CK5/6, CK7 only for ADC.

- Use of panels including TTF1 and P40 for ADC.
- Use of TTF1/P63 in the following histological types:
    - ADC with a percentage of 29%.
    - CPC with a percentage of 23%.
    - CE with a percentage of 23%.
    - CNPC-NOS with a percentage of 25%.

We noted the use of TTF1/P63, with 0% concerning mesothelioma.

- Specific use of calretinin and CK5/6 on mesothelioma (Table 4 / Figures 5.6.7.8).

Table 4: Distribution of Cancer Types by Panels Used.

Type of panel used	ADK	CE	CNPC-NOS	CPC	Mesothelioma	Total
TTF1/CK5/6/CK7	32	0	0	0	0	**32**
TTF1/p40	22	0	0	0	0	**22**
TTF1/p63	**16**	**13**	**14**	**13**	**0**	**56**
TTF1/CKHPM	0	0	0	0	0	**0**
Calretininand CK5/6	0	0	0	0	1	**1**
Total	**70**	**13**	**14**	**13**	**0**	**110**

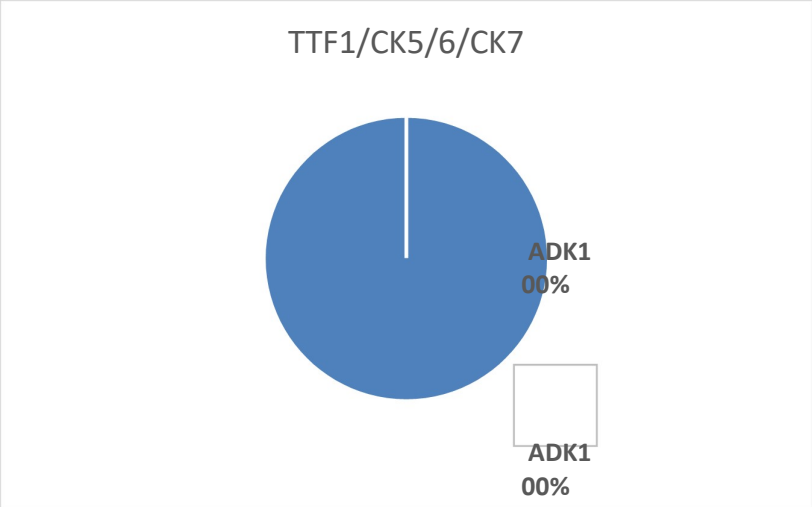
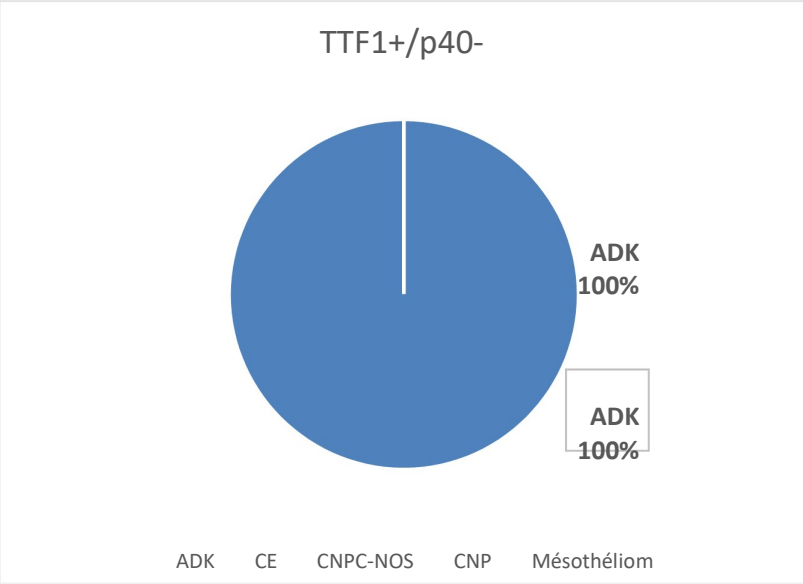


Figure 5: Distribution of ADC (Adenocarcinoma) of cancer according to TTF1, CK5/6, CK7.

Figure 6: Distribution of ADC (Adenocarcinoma) according to TTF1 and P40



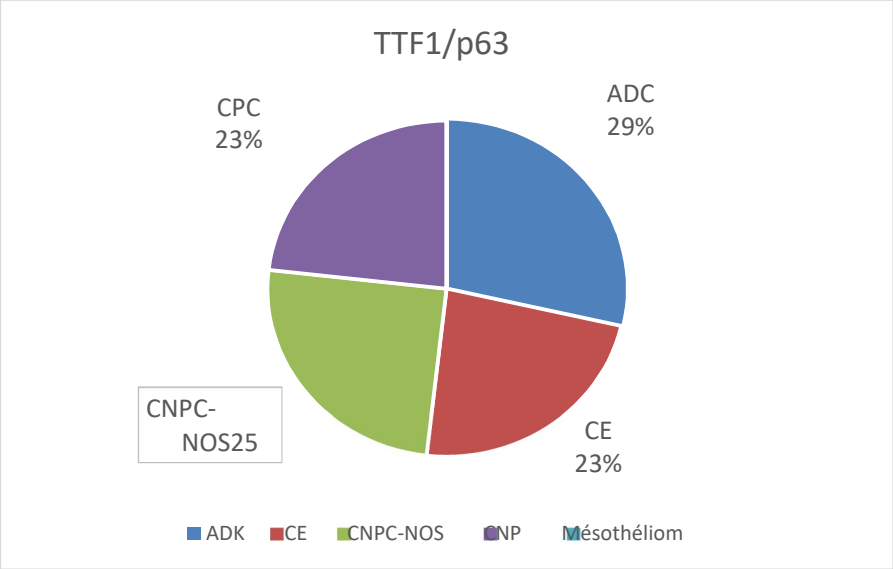


Figure 7: Distribution of histological types according to TTF1/P63

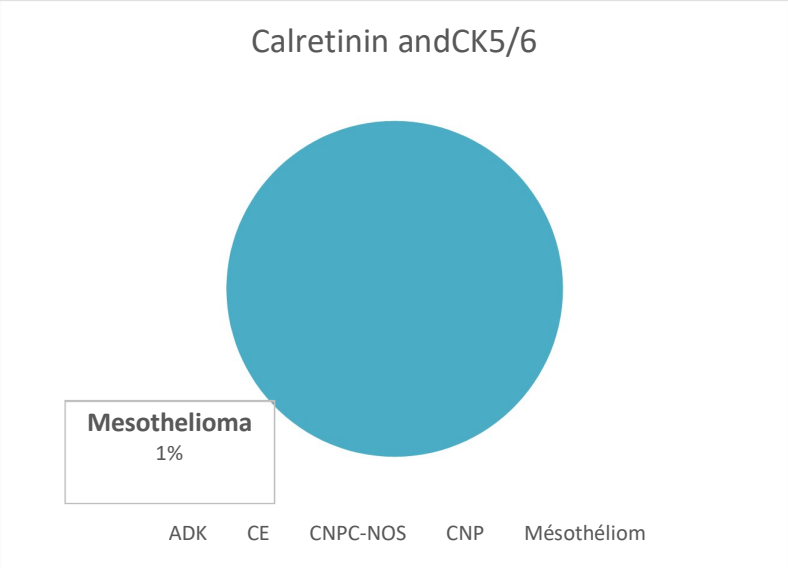


Figure 8: Distribution of mesothelioma according to calretinin and CK5/6.

10. Frequency of Panels Used

In our study, we used the following panels (courtesy of Dr. BOUAKLINE):

- TTF1/P63 with a percentage of 50%.
- TTF1/CK5/6/CK7 with a percentage of 29%.
- TTF1/P40 with a percentage of 20%.
- Calretinin and CK5/6 with a percentage of 1%.

Thus, the most commonly used panel is TTF1/P63 (Figure 9).

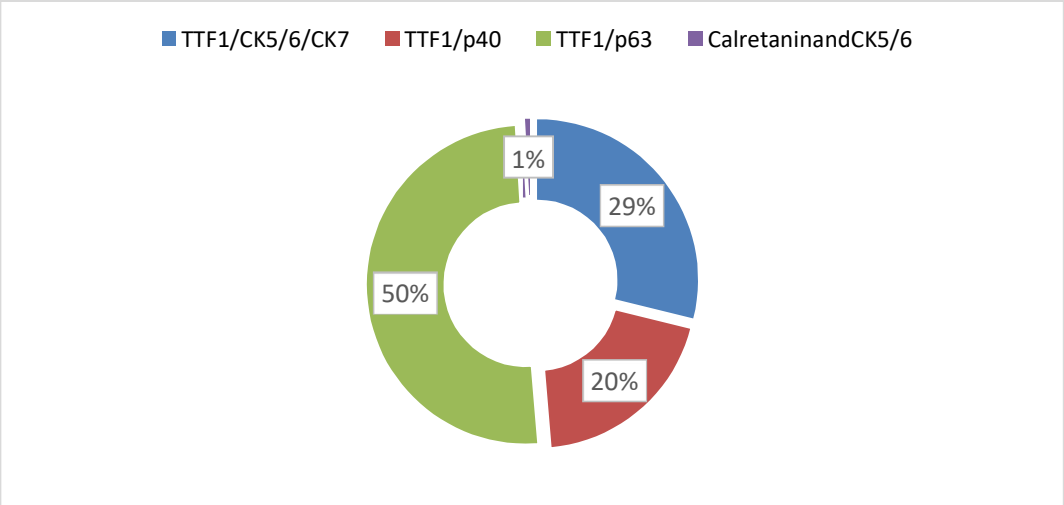


Figure 9: Frequency of Panels Used.

11. Distribution of Patients According to Metastases

According to the data from our survey: among the 115 patient records reviewed, 33 patients

developed metastases to other organs. We found 13% with pleural metastases, 10% with lymph node metastases, 3% with bone metastases, and 2% with brain and spinal metastases (Figure 10).

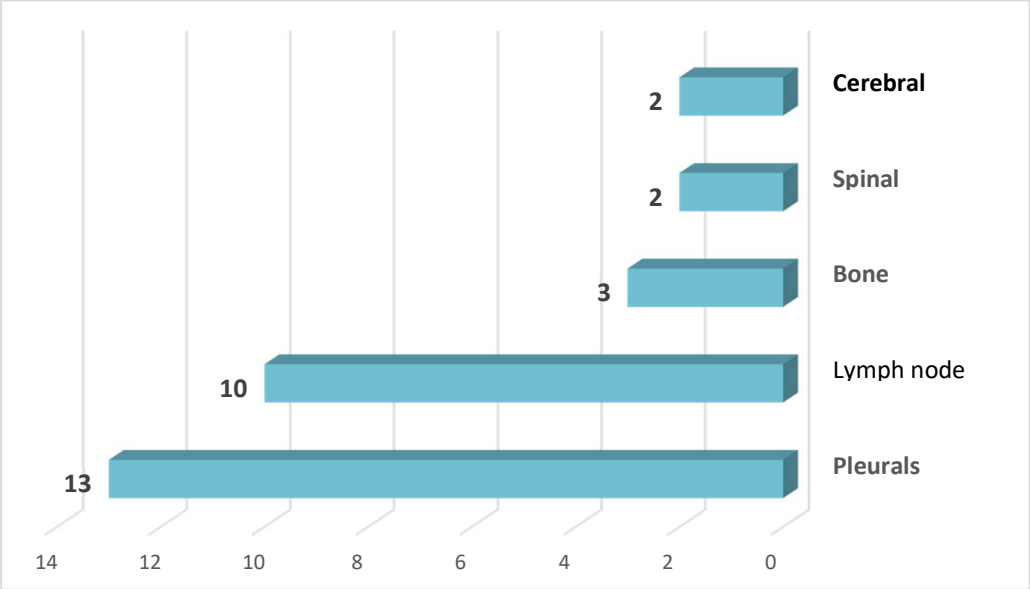


Figure 10: Distribution of patients according to metastases.

Discussion

Annual Distribution of Patients with Lung Cancer

Our results indicate a slight decrease in the incidence of lung cancer in 2019-2020. Approximately one-sixth of countries globally have established cancer registries (Cheng T-YD et *al*.,2016). These registries are crucial for identifying risk factors specific to each geographic area, which can then inform the development of tailored screening programs. Early diagnosis is critical because lung cancer survival rates drop significantly as the disease progresses. Therefore, screening programs are vital for improving survival outcomes (Field JK et *al* ., 2013)

Distribution of patients by age group

We found that the age groups most affected by lung cancer are [61-70] and [71-80] years, representing successive rates of 30% (35 cases) and 25% (29 cases) . Age is a commonly examined factor in research. Some studies have indicated that older age (defined as over 65 or even 70 years) correlates with a poorer prognosis, while other research has failed to support this claim (Carter GC et *al* .,2014). However, the majority of lung cancer diagnoses occur in individuals aged 55 to 74, making it challenging to determine the specific influence of age on survival outcomes(de Groot PM et *al* .,2018).

Distribution of Patients with Lung Cancer by Sex

In recent years, numerous epidemiological studies have noted a decline in lung cancer incidence among men, while an increase has been observed in women (de Groot PM et *al*., .2018). The highest rates among women were found in North America and Northern Europe. (Cheng T-YD et *al* ., 2016). These trends may also be affected by smoking patterns and genetic factors, including the over-expression of the CYP1A1 gene or the X-linked gastrin-releasing peptide receptor, as well as mutations in the glutathione S-transferase M1 enzyme or the p53 tumor suppressor gene (Kligerman S, White C.2011). Despite these factors, the incidence remains higher in men compared to women (www.globocan.iac.fr. (accesed 12 March 2019).), Another study conducted in Romania found similar results, reporting a consistently high incidence in males over the years: 209 cases (80.08%) compared to 317 cases (79.05%).(Bianca

paraschiv et *al* ., 2019)

Distribution of Smokers and Non-Smokers by Sex

According to the work of (Frusch N et al., 2007), the fraction of bronchial cancers attributed to tobacco is estimated at 91% in men and 57% in women. The risk of developing lung cancer in male smokers is 24 times higher than in non-smokers; in women, it is 9 times higher in smokers than in non-smokers. These results are consistent with ours, as we found that this type of cancer is more prevalent in men than in women.

Distribution of Histological Types by Sex

The most common type is adenocarcinoma at 54%, followed by squamous cell carcinoma at 23.3%. The reasons for these sex-related differences are not yet clear. These results are similar to our study, where adenocarcinoma is the predominant histological type in men at 50%, followed by squamous cell carcinoma at 11% in men but absent in women. Additionally, CPC is found at 11% in men but absent in women, while CNPC is at 8% in men and 4% in women. Mesothelioma is last with 1%. Women show a higher risk for adenocarcinoma at 10%, which is weakly linked to smoking.

Distribution patients by Risque factor:

Our study on the distribution of patients by risk factors revealed that smokers constitute 40% (46 cases) of the population, while only one patient, or 1%, was linked to occupational asbestos exposure. In contrast, non-smokers make up 59% (68 cases) of the cohort.

Smoking has been acknowledged as a risk factor for lung cancer since the 1960s, with approximately 80% of lung cancer cases attributed to tobacco use (Malhotra J et *al*.,2016). Both the length of time spent smoking and the number of cigarettes smoked daily serve as independent risk factors. Given the significant prevalence of smoking among lung cancer patients, a proactive and ongoing effort to encourage cessation can lead to meaningful improvements. For instance, in the USA, the age-adjusted incidence of lung cancer has decreased due to shifts in risk behaviors following increased awareness about tobacco smoking as a primary risk factor. (de Groot PM et *al* ., 2018)

Distribution of Patients by Histological Types

In 2015, the World Health Organization (WHO) released its most recent histopathological classification, which is based on immunohistochemistry, genetic testing, and differentiation levels. Non-small cell lung cancer (NSCLC) has been noted to have the highest prevalence(Travis D et *al*.,2015). Recent research indicates a rising incidence of adenocarcinoma, with a corresponding decline in squamous carcinoma(Dela Cruz CS et *al*., 2011; Paraschiv B et *al*., 2017)

Previous work by Travis (2004) shows that primary malignant lung tumors are divided into two main families: non-small cell bronchopulmonary carcinomas (NSCLC), representing about 80-85% of lung carcinomas, and small cell bronchial carcinomas (SCLC), representing 15%. These results are identical to our study, which also identifies two main families of bronchial cancer (NSCLC and SCLC). Additionally, studies have indicated a greater incidence of adenocarcinoma among male patients(de Groot PM et *al*., 2018)

Distribution of Patients by Metastases

In our study, we found that among the 115 patient records reviewed, 33 patients developed metastases to other organs: 13% with pleural metastases, 10% with lymph node metastases, 3% with bone metastases, and 2% with brain and spinal metastases. (Bàillon et *al*., 2011; Debiais, 2015) found brain and bone metastatic sites.

The prognosis is shaped by multiple factors, including the characteristics of the patients (clinical condition, comorbidities, age) and the attributes of the tumors (TNM stage, histopathology, immunohistochemistry) (Ciuhu AN et *al*., 2017). Notably, the TNM classification holds significant importance, as the survival rate drops substantially from approximately 59 months at stage I to merely 4 months at stage IV.(Midthun DE, 2018).)

Conclusion:

Lung cancer is one of the leading causes of mortality for both men and women, primarily due to tobacco smoke containing genotoxic substances, which account for 85% of this type of cancer. Our anatomical pathology and immunohistochemistry study involving 115 patients with lung cancer reveals that non-small cell lung cancer constitutes 83% of cases, while small cell lung cancer accounts for 11%, and other malignant tumors represent 5%, with a male predominance of 84%. Adenocarcinoma is the most prevalent type, and smoking significantly outweighs non-smoking in terms of incidence. Males are the most affected gender, particularly in the age groups of [61-70] and [71-80], which are linked to higher activity levels and increased exposure to risk factors. Additionally, the most commonly used tumor markers in this study are TTF1 and P63. Lung cancer continues to pose a significant global challenge due to its aggressive nature and steadily rising incidence rates. Effective primary prevention strategies, particularly tobacco control, are crucial for enhancing prognosis. Gaining insight into the changing epidemiological characteristics of lung cancer is vital for developing targeted screening programs for high-risk populations. The establishment of these screening initiatives and national registries is essential for improving survival rates.

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