Research Article

Clinicopathological and immunohistochemistry profile of 100 cases of lung cancer in a tertiary care occupational centre in north India

Isha[1], Vipra Malik[2],Onkar Kaur[3],Anand Verma[4], Jaskran Singh[5] , Akshay Budhraja[6]

[1]Consultant Histopathologist ,Dr Lal Path Labs , NRL, Rohini, New Delhi,India
[2]Consultant,Junior Pathologist ,Core Diagnostics, Gurugram,Haryana,India
[3]Assistant Professor NFSG CMO Pathology Deptt ,ESI PGIMSR Model Hospital Basaidarapur,New Delhi,India
[4]Associate professor Specialist Pathology Deptt,ESI PGIMSR Model Hospital Basaidarapur,New Delhi,India
[5]Senior Data Product Manager, New Delhi,India
[6] Consultant , Department of Respiratory and Sleep Medicine, Aakash Healthcare Superspeciality Hospital, New Delhi,India

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Abstract

Background: According to estimates, the global cancer burden increased to 18.1 million new cases and 9.6 million deaths in 2018..Lung cancer is the most common cancer-related cause of death in both men and women. In most Western and Asian countries, adenocarcinoma has now surpassed squamous cell carcinoma. In India, however, the clinical and pathological picture of lung cancer varies greatly.**Aim**: The goal of this study is to look at the clinicopathological and immunohistochemical profiles of 100 patients of lung cancer in a North Indian tertiary care occupational centre.**Material and methods:**This is a retrospective study of lung carcinoma patients who were diagnosed with biopsy-proven lung cancer in the previous four years (between May 2016 and May 2020). Patients were diagnosed using the WHO classification of lung malignancies 2015as nonsmall cell lung carcinoma (SCC), adenocarcinoma, nonsmall cell lungcarcinoma not otherwise defined [NSCLCNOS]), small cell lung carcinoma, and others based on morphology in H&E stained sections. In all cases, immunohistochemistry (IHC) was used to help the sub-classification. In some cases, IHC was used to detect EGFR and ALK rearrangements.**Result:**The average age of the patients in our study was 61.04 years old (12 percent were under 50 years old and 6% were under/equal to 45 years old). Smokers made up 54 percent of all lung cancer patients. COPD was seen in 43.8 percent of lung cancer patients, and it was often linked to smoking. 4.5 percent of the patients had a history of ATT ingestion, while 36.6 percent of the patients had no relevant medical history. Cough (26%) was the most common symptom, followed by chest pain (23%), and shortness of breath (28%) in almost equal percentages and were most frequently occurring together.Squamous cell carcinoma (38 percent), adenocarcinoma (27 percent), non-small cell carcinoma-not otherwise specified(NOS) (5 percent), adenosquamous carcinoma (3 percent), and small cell carcinoma (17 percent) were the subtypes with the highest percentages histologically, with immunohistochemical confirmation.**Conclusion:**Along with age, radon exposure, environmental pollution, occupational exposures, gender, race, pre-existing lung disease, and genetic factors, cigarette smoking is the leading cause of lung cancer and lung cancer in the occupational category.

Keywords: lung cancer, clinicopathological, occupational, smoking, histologically, immunohistochemical confirmation

Introduction

According to estimates, the global cancer burden increased to 18.1 million new cases and 9.6 million deaths in 2018. Lung cancer, female breast cancer, and colorectal cancer account for one-third of all cancer cases and deaths globally. Lung and female breast cancer diagnoses are expected to total 2.1 million in 2018, accounting for 11.6 percent of the total cancer incidence burden.Lung cancer is the most frequent cancer in men (14.5 percent of all cases in men versus 8.4 percent in women) and the main cause of cancer death in men (22.0 percent , i.e. about one in 5 of all cancer deaths).Breast cancer is the leading cause of cancer death in women (15.0%), followed by lung cancer (13.8%).In developing countries, lung cancer deaths lag behind those due to breast cancer in females[1,2]Lung cancer is the leading cause of cancer-related fatalities in both men and women, accounting for 1.8 million deaths (18.4% of all deaths). India has some of the lowest lung cancer incidence and fatality rates in the world. Head and neck, stomach, and esophageal cancers are the most prevalent malignancies in men, whereas cervical and breast cancers are the most common cancers in women. In India, a total of 67,795 new lung cancer cases (5.9% of all malignancies) were reported in 2018, with 48698 (8.5%) occurring in men[3,4].According to the Indian Council of Medical Research cancer registry, 57,795 new cases of lung cancer were diagnosed in 2012, with 67,000 new cases expected in 2013.Lung cancer claimed the lives of 63,475 people in India, accounting for 8.1 percent of all cancer-related deaths. Smoking (both active and passive), the environment, a range of occupational agents, and genetics are all risk factors for lung cancer. Cigarette smoking habits are strongly linked to lung cancer incidence and mortality. Lung cancer incidence and death climb in future decades as smoking rates rise, often first in males and subsequently

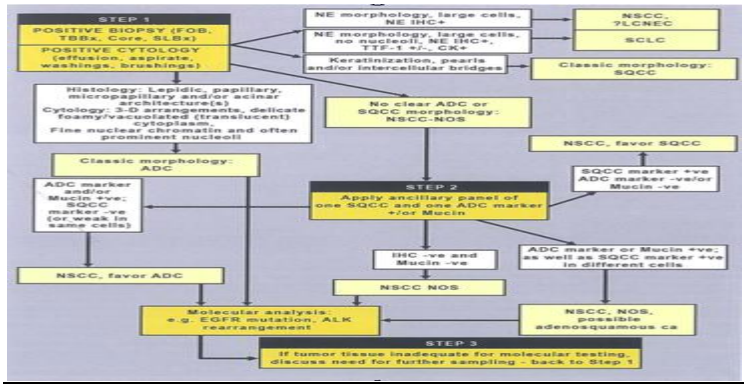
**Correspondence*
Dr.Isha
Consultant Histopathologist ,Dr Lal Path Labs , NRL, Rohini, New Delhi, India

E-mail: singhisha8916@gmail.com

in women, before declining following the implementation of comprehensive tobacco control programmes[5,6].Squamous cell lung cancer was the most prevalent histology overall and among smokers, according to a research in northern India. Cigarette smoking is claimed to be prevalent in men at rates ranging from 28 to 57 percent, with bidi smoking (hand-rolled tobacco) being the most popular tobacco product (92 percent).In recent years, there has been a lot of interest in the histological characterization and genomic categorization of lung cancer due to the availability of various new targeted therapy approaches.In most Western and some Asian countries, the form of lung cancer is also evolving, with adenocarcinoma becoming more common and eventually equaling or surpassing squamous cell carcinoma[7,8].The clinical and pathological profile of lung cancer in India, on the other hand, appears to be quite variable. The goal of this research is to look at the clinicopathological and immunohistochemical profiles of 100 lung cancer cases in a tertiary care occupational centre in North India.

Material and methods

This study looked at patients with biopsy-proven lung cancer who were diagnosed in a tertiary care occupational centre in North India over the course of four years (between May 2016 and May 2020).
The following parameters were recorded in an excel sheet: name, registration number, age, gender, smoking history, past history, symptoms and signs, details of imaging findings [X-ray, computed tomoFigy(CT), bronchoscopy, or endobronchial ultrasound (EBUS)], other diagnostic investigations (BAL analysis, sputum analysis, pleural fluid analysis, periphera analysis, etc.)Patients were classified on the basis of morphology in H & E stained sections using the WHO classification of lung tumours 2015as non-small cell lung carcinoma (SCC,adenocarcinoma,non-small cell lungcarcinoma - not otherwise specified [NSCLC-NOS]), small cell lung carcinoma and others.The sub-classification was aided with immunohistochemistry (IHC) in all the cases. EGFR and ALK rearrangements were also determined by IHC in some of the cases.



Statistical analysis: An excel spreadsheet was used to keep track of the information. The near normality of quantitative variables was evaluated. SPSS (Statistical Package for the Social Sciences) for Windows was used for statistical analysis (version 24.0). Continuous parameters were described using mean standard deviation for categorical variables and frequency (%) for categorical variables. The Student T test was used to compare differences between two groups.The data for non-parametric variables are provided as medians (min-max).In this case, the nonparametric Mann–Whitney test was used for statistical comparisons. Categorical variables were compared between two or more groups using the Chi-square test. For all analyses, a two-tailed p-value of <0.05 was considered statistically significant.

Results

The total number of lung biopsies received over the four-year study period, from 2016 to 2020, was 490, with 100 cases identified as lung cancer. Males made up 81 percent of the cases, while females made up 19 percent. [1st Table] The average age of the patients in our study was 61.04 years old (12 percent were under 50 years old and 6% were under/equal to 45 years old). [Section 2] Smokers made up 54 percent of all lung cancer patients. [Figure 3] COPD was seen in 43.8 percent of lung cancer patients, and it was often linked to smoking. 4.5 percent of the patients had a history of ATT ingestion, while 36.6 percent of the patients had no relevant medical history. [4th Table]Cough (26%) was the most common symptom, followed by chest pain (23%) and shortness of breath (28%) in approximately equal proportions. [Table No. 5] Squamous cell carcinoma (38 percent; fig.2 A-F), adenocarcinoma (27 percent; fig.1 A-E), non-small cell carcinoma-not otherwise specified(NOS) (5 percent; fig.4A), adenosquamous carcinoma (3 percent), and small cell carcinoma (17 percent; fig.3 A-C); other subtypes constituted 10%. (1 percent). [Figure 6]P40 and P63 were found to be positive in 86.5 percent and 84 percent of squamous cell carcinoma cases, respectively; TTF-1 and Napsin A were found to be positive in 84 percent and 86.9% of adenocarcinoma cases, respectively; both markers were found to be positive in different tumour cells in 3% of cases, indicating adenosquamous carcinoma. Because 5% of the tumours tested negative for both markers, they were classified as NSCLC-NOS. EGFR and ALK were tested in 48.2 percent of adenocarcinoma cases, with EGFR positive in 69.2 percent of the cases and ALK positive in 23.07 percent.

Table 1:Gender

Gender	Non-LC		LC		Total	
	N	%	N	%	N	%
Males	312	80.0	81	81.0	393	80.2
Females	78	20.0	19	19.0	97	19.8
Total	390		100		490	100.0

Yates corrected chi-square = 0.05013; p-value = 0.933 (not significant)

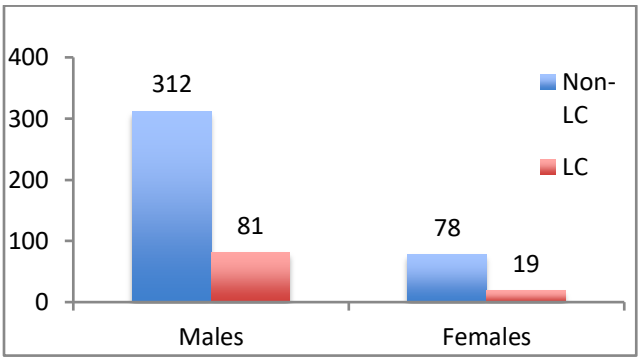


Fig 1: **Gender distribution**

Table 2:Age

Age of Respondents	N	Mean	SD	SE	Min	Max
Non-LC	390	59.22	8.251	1.033	38	78
LC	100	61.04	9.151	0.915	40	82
Total	490	59.60	8.455	0.936	38	82
Independent t test = 0.334; p-value = 0.882 (not significant)						

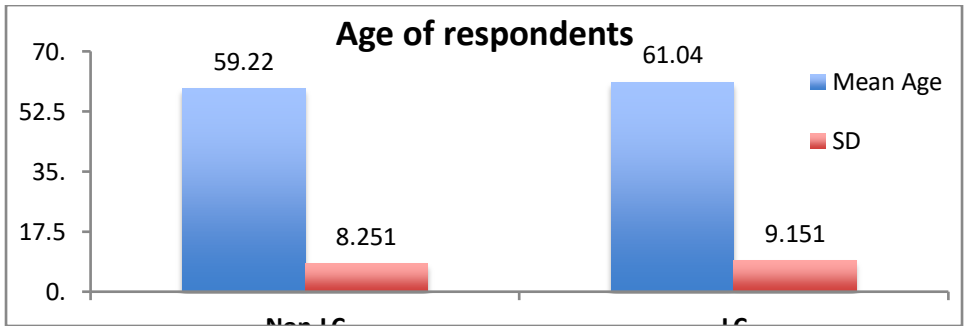


Fig 2: Age of respondents

Table 3. History of Smoking

History of Smoking	Non-LC		LC		Total	
	N	%	N	%	N	%
Yes	95	24.4	54	54.0	149	30.4
No	245	62.8	10	10.0	255	52.0
Didn't say	50	12.8	36	36.0	86	17.6
Total	390		100		490	

Chi-square = 90.03; p-value = 0.001* (Significant)

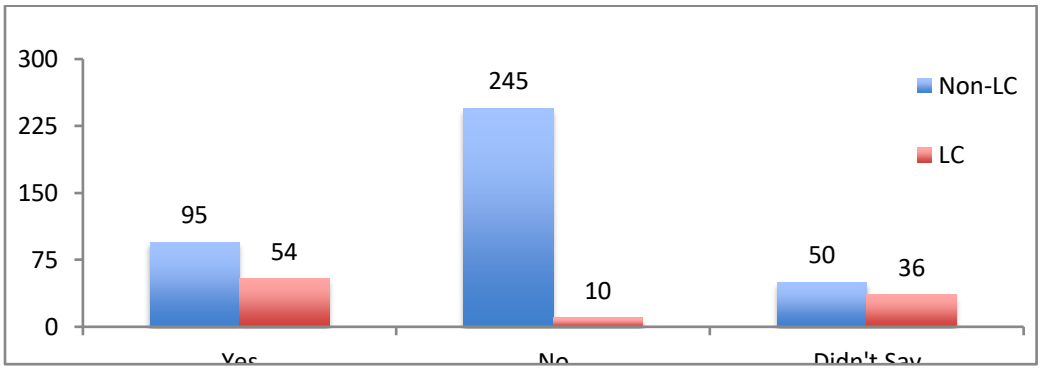


Fig 3: Smoking history

Table 4:Medical History

Medical History	Non-LC		LC		Total	
	N	%	N	%	N	%
COPD	35	8.8	49	43.8	84	15.2
ATT intake/ATT history	20	5.0	5	4.5	25	4.5
CAD	12	3.0	3	2.7	15	2.7
HTN	15	3.8	4	3.6	19	3.4
DM	17	4.3	7	6.2	24	4.4
History of Carcinoma	9	2.3	3	2.7	13	2.4
No Relevant Medical History	290	72.9	41	36.6	331	60.1
Chi-square = 12.46; p-value = 0.003* (Significant)						

Table 5. Symptom/Signs of Lung Cancer Patients

Symptoms/Signs	Lung Cancer Patients	
	N	%
Anorexia/Weakness	7	6.8
Weight Loss	5	4.9
Breathlessness/Shortness of Breath	28	27.2
Voice change/hoarseness	2	1.9

Blood in Sputum	7	6.8
Chest pain	23	22.3
Abdominal pain	2	1.9
Cough	26	25.2
Fever	3	2.9

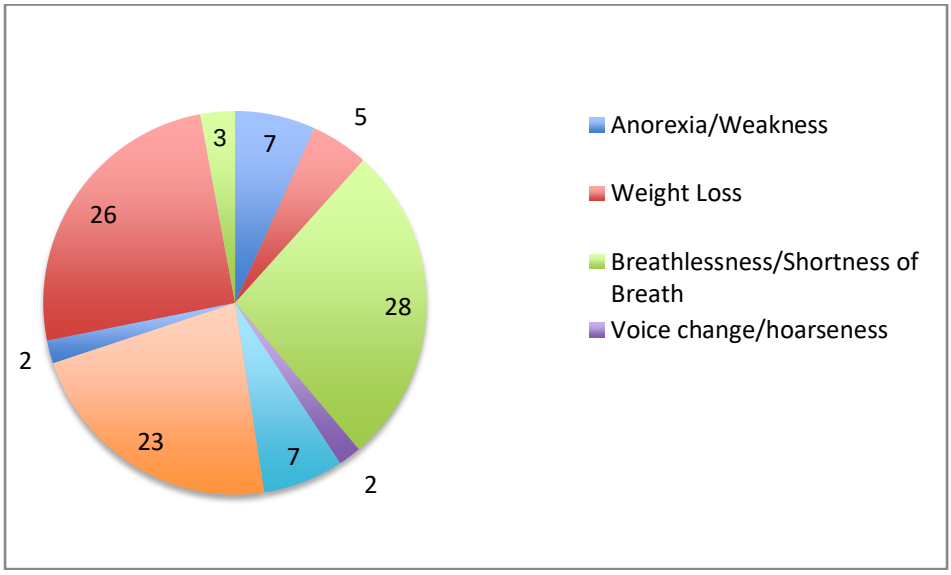


Fig 4: Symptoms/Signs

Table 6:Histopathological Diagnosis

Histo-pathological Diagnosis	Lung Cancer Patients	
	N	%
Squamous cell carcinoma	38	38.0
Adenocarcinoma	27	27.0
Non-small cell carcinoma, NOS	5	5.0
Adenosquamous carcinoma	3	3.0
Small cell carcinoma	17	17.0
Poorly differentiated carcinoma	7	7.0
Mesothelioma	2	2.0
Pleomorphic carcinoma	1	1.0

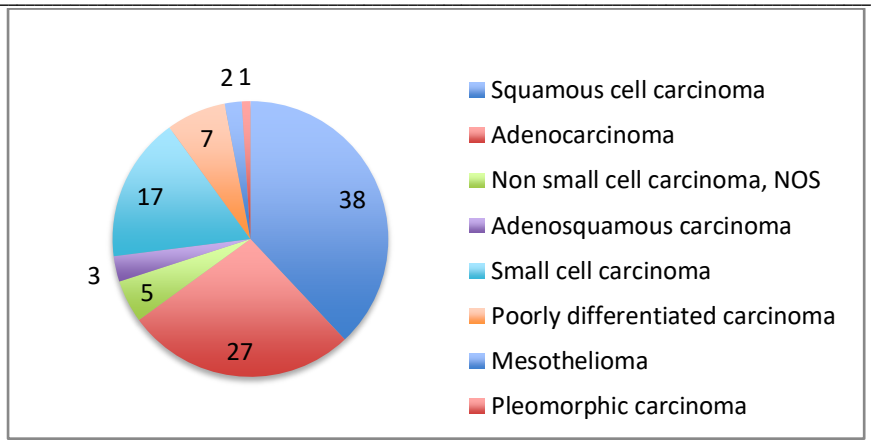


Fig 5 : Histo-pathological Diagnosis

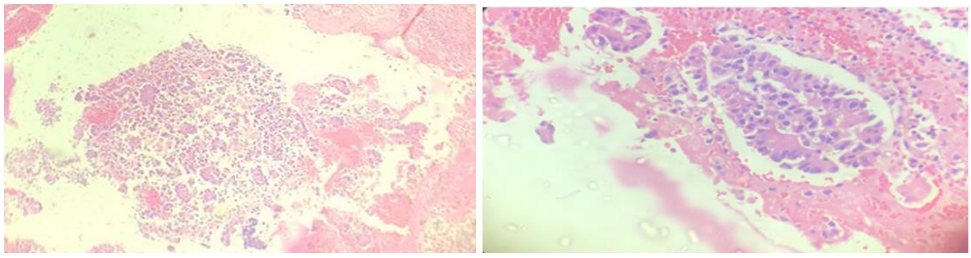


Fig 1A: Adenocarcinoma, H&E stain, 4X

Fig 1B: Adenocarcinoma, H&E stain, 10X

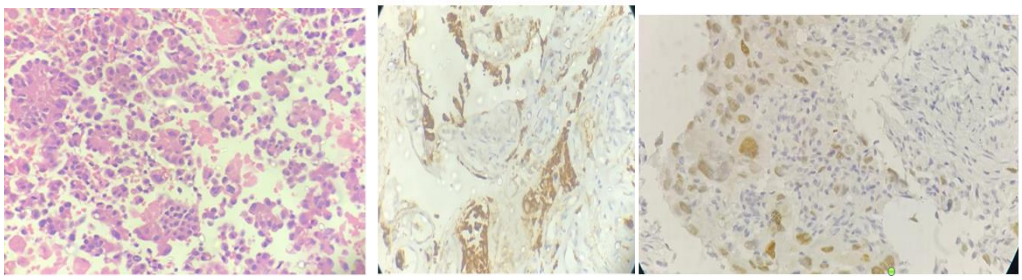


Fig 1C: Adenocarcinoma, H&E stain, 10X

Fig 1D: IHC showing Napsin A positivity (cytoplasmic) in adenocarcinoma , 10X

Fig 1E: IHC showing TTF-1 positivity (nuclear) in adenocarcinoma , 10X

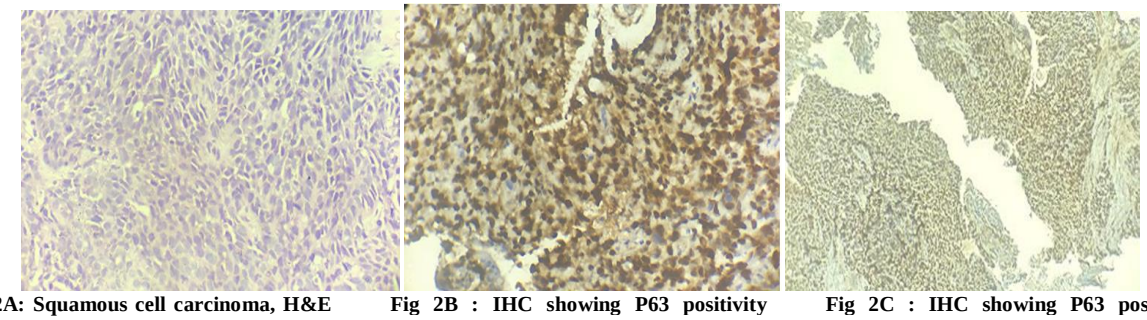


Fig 2A: Squamous cell carcinoma, H&E stain, 40X

Fig 2B : IHC showing P63 positivity (nuclear) in squamous cell carcinoma, 40X

Fig 2C : IHC showing P63 positivity (nuclear) in squamous cell carcinoma, 10X

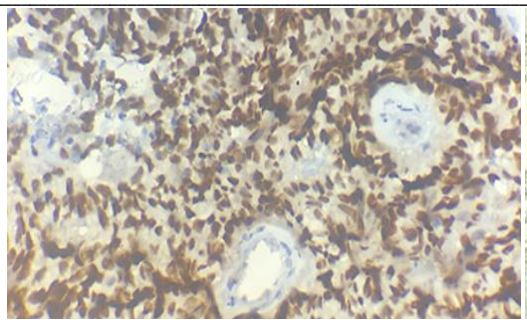


Fig 2D: IHC showing P40 positivity (nuclear) in squamous cell carcinoma, 40X

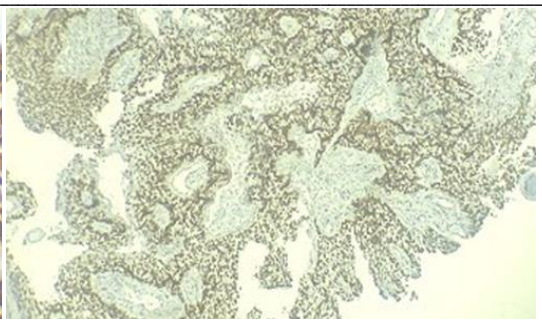


Fig 2E: IHC showing P40 positivity (nuclear) in squamous cell carcinoma, 10X

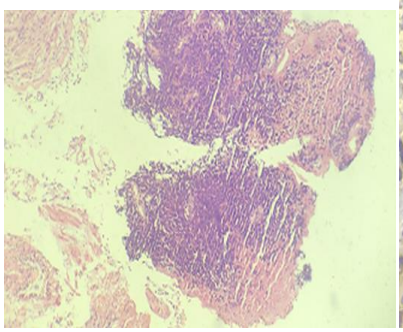


Fig 3A: Small cell carcinoma, H&E stain,10X

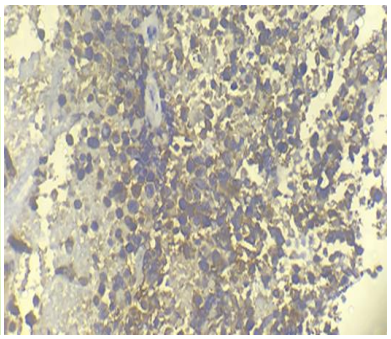


Fig 3B : IHC showing Synaptophysin positivity(cytoplasmic) in small cell carcinoma,40X

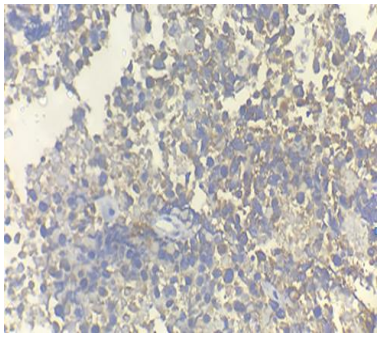


Fig 3C : IHC showing Chromogranin positivity (cytoplasmic) in small cell carcinoma,40X

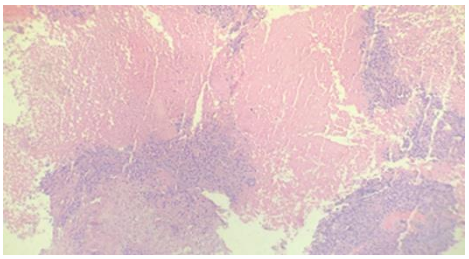


Fig 4: Non-small cell carcinoma,NOS, H&E stain,10X

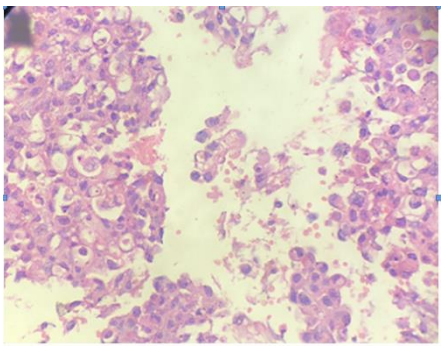


Fig 5A: Mesothelioma, H&E stain, 40x

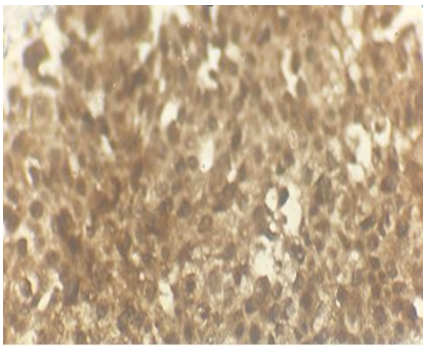


Fig 5B : IHC showing Calretinin positivity (cytoplasmic and nuclear) in mesothelioma,40X

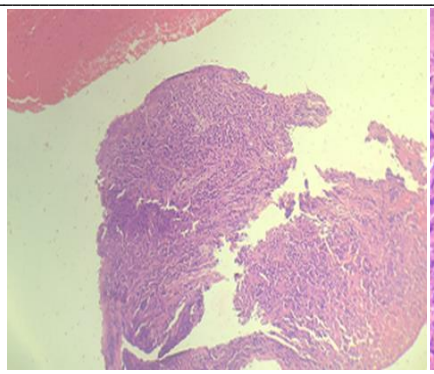


Fig 6A: Poorly differentiated carcinoma,H&E stain,4X

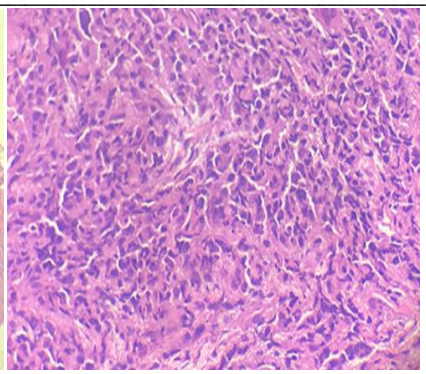


Fig 6B: Poorly differentiated carcinoma,H&E stain,40X

Discussion

Both smokers and nonsmokers are at an increased risk of lung cancer as they get older. Lung cancer is extremely uncommon in adults under the age of 40, particularly among nonsmokers. Women outweigh men when it comes to lung cancer patients who have never smoked. This does not imply that women who have never smoked are more likely than men to develop lung cancer. Women are more than twice as likely as males to have never smoked when they are 60 years old or older, and this female advantage grows with age [9,10].Wakelee and colleagues discovered that lung cancer incidence rates were marginally higher in women than males among never smokers aged 40 to 79 years, though not considerably. Women are more likely than men to be diagnosed with lung cancer when screened with spiral CT, according to Henschke and colleagues. Incidence has a less obvious link with sex than mortality. Regardless of smoking status, prospective cohort studies have consistently indicated that males die from lung cancer at a higher rate than women[11,12].Among a study of North American insulators, Markowitz and colleagues discovered that asbestos exposure and asbestosis are linked to an elevated risk of lung cancer in smokers, with synergistic effects. Smoking, food, and inhaled carcinogen exposures at the workplace and in the general environment are all linked to socioeconomic status and lung cancer risk. All of these elements have an adverse profile when one's socioeconomic standing is low. The most well-known risk factor for lung cancer is cigarette smoking[13,14]. Secondhand smoking exposure also increases the risk of lung cancer in a dose-dependent manner.Never-smokers account for 10 to 20% of lung cancer cases, with women having a substantially greater prevalence than men. Environmental and occupational exposures, as well as genetic vulnerability, are thought to have a role in lung cancer in never-smokers. Lung cancer is caused by factors other than active smoking in about 10% to 15% of cases, resulting in 16,000 to 24,000 fatalities each year, making it one of the most common causes of cancer mortality in never smokers[15,16].The risk of lung cancer has been linked to a history of lung disorders such as tuberculosis, asthma, emphysema, and chronic obstructive pulmonary disease (COPD). Although epidemiological studies show that 20–30 percent of smokers get COPD and 10–15 percent develop lung cancer, COPD is by far the most common comorbidity among lung cancer patients, with prevalence ranging from 30 to 70 percent. According to one study, the frequency of COPD was six times higher among newly diagnosed lung cancer cases than among matched smokers without cancer. There is very little evidence on the risk of COPD and lung cancer among non-smokers[17,18]. People with tuberculosis have a 50 percent increased risk of lung cancer, according to studies. However, just a few research have looked at the disparities in smoking status. Among one study of lung cancer risk in smokers and never smokers with tuberculosis, it was discovered that female never smokers with tuberculosis had an eightfold increased lung cancer risk, but female smokers had no such risk[19,20].A study found that 16.7% of lung cancer cases had a history of tuberculosis. In a study conducted in an Indian tertiary cancer centre, 4.5 percent of lung cancer patients had a history of tuberculosis..Asthma has also been studied as a possible lung cancer risk factor in numerous research. In these investigations, never smokers with asthma had a higher risk of lung cancer. Several studies have suggested that patients with idiopathic pulmonary fibrosis or other fibrotic illnesses had a higher risk of lung cancer than nonsmokers, although these risk variables have not been well established in never smokers[21,22].Three out of every 100 lung cancer patients had previously treated cancers: pyriform sinus (after CTRT), breast (following chemotherapy), and stomach (following surgery) (post surgery and chemotherapy) Cough (26%) was reported in roughly equal percentages with chest discomfort (23%) and shortness of breath (28%) in our study, and they were most frequently seen combined. The most common signs of lung cancer are cough with or without blood, chest pain, dyspnoea, weight loss, anorexia, weakness, bone pain, and other non-specific symptoms [23,24]. Chest pain (46.7 percent), cough (35.2 percent), shortness of breath (24.8 percent), hemoptysis (21.9 percent), fever (17.1%), swelling of the face/neck (11.4 percent), and loss of appetite (4.8 percent) were the most common symptoms in a study by PK Sharma and R Bansal. Other symptoms included backache, hoarseness of voice, dysphagia, weakness, giddiness, and weight loss[25,26]. Cough, dyspnea, chest discomfort, and hemoptysis were the most common symptoms in another study conducted in Northeast India, with cough alone accounting for 35.8% of the total symptoms, followed by a combination of the aforementioned symptoms. Weight loss (77 percent) and fever (34 percent) were the most prevalent symptoms in a study of patients with primary bronchogenic carcinoma in mid-west Rajasthan, with cough (68 percent), dyspnoea (59 percent), chest discomfort (22 percent), hemoptysis (20 percent), and dysphagia following closely behind (6 percent)[27,28].IHC is critical in lung cancer for histological typing, routine diagnosis, and the discovery of prognostic variables in order to guarantee proper and specific treatment and to identify tumours with a higher risk of recurrence and catastrophic outcomes. IHCstains aid in the differentiation between primary tumours and pulmonary metastases when the volume of tumour is limited or the form is uncertain. TTF-1, Napsin A, and cytokeratin-7 are all positive in adenocarcinoma tumour cells. P-63, p 40, cytokeratin-5/6, and NTRK-1 and NTRK-2 are all seen in squamous cell carcinomas. TTF-1, Napsin A, p-63, and p-40 markers were employed for all NSCLC (squamous or adenocarcinoma) on morphological diagnosis[29].Travis et al. studied the expression of nine immunohistochemical markers on 588 lung carcinomas, of which 200 cases were adenocarcinoma and 225 were squamous cell carcinoma. The sensitivity of TTF-1 was found to be 62% and the specificity was found to be 92%. p-63 is considered as the single best marker to separate squamous cell carcinoma and adenocarcinoma, with a sensitivity of 84% and a specificity of 85%.This made it possible to assign NSCLCs to clinically relevant high or low EGFR expression groups in a very

repeatable manner. ALK gene rearrangements are seen in 2–5% of all non-small cell lung cancers and are more common in lifelong non-smokers with adenocarcinoma, although the prevalence of ALK rearrangements in long-term ex-smokers (who stopped smoking >10 years before to diagnosis) is less well understood. Given the outstanding response to targeted inhibitors, accurate and timely identification of ALK-rearranged cancers is critical. Fluorescence in situ hybridization (FISH) can reveal ALK gene rearrangement, while immunohistochemistry can detect aberrant ALK protein expression (IHC).

Conclusion

Along with age, radon exposure, environmental pollution, occupational exposures, gender, race, pre-existing lung disease, and genetic factors, cigarette smoking is the leading cause of lung cancer. The study's findings support/confirm lung cancer in the occupational category. The type of agent and the duration of exposure in the occupational group could be investigated further in order to reduce the incidence in this group.

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