Original Article

Clinicopathologic Spectrum of Lung Malignancies and Detection of EGFR Mutations in Non-Small Cell Lung Cancers from a Tertiary Care Centre

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Abstract

Background: Lung cancer is the most common cause of cancer-related deaths. Lung cancers are increasingly being studied for molecular targets that are amenable to treatment. EGFR mutation is one such target, and we have attempted to determine the histological types and EGFR mutations in lung cancer patients. Aim of the study: To study the patient demographics, clinicopathological profile, histological subtypes, and the EGFR mutations in lung cancers.

Materials and Methods: The patient details were collected from all biopsy-proven cases of lung cancers. The histopathological types of lung cancers were noted. The EGFR mutation assay was done by polymerase chain reaction (PCR) and pyrosequencing, and findings were noted.

Results: Our study comprised 93 cases, with 64 male and 29 female patients, and the M:F ratio was 2.2:1. NSCLC were 97%, and small cell lung cancers were 3%. Among the NSCLC, adenocarcinomas were more common than squamous cell carcinomas. EGFR mutations were observed in 21.5% of cases. Most (95%) EGFR mutations were seen in adenocarcinomas, and 5% were seen in squamous cell carcinoma. Exon 19 was more commonly affected (60% of cases).

Conclusion: Lung cancers are twice as common in males as in females. Among NSCLC, adenocarcinomas are more common, and one-fifth of adenocarcinomas are positive for EGFR mutations, with exon 19 mutation being the most common. EGFR mutation testing is encouraged in all lung cancer patients in view of available treatment options.

Keywords:

Lung cancers, EGFR mutation, Adenocarcinoma lung, Exons 19, 20 and 21, Squamous cell carcinoma lung

Introduction

Lung cancer is the most common cause of cancer-related deaths globally and contributed to about 2.2 million new cases and 1.8 million deaths in 2020 [1]. The highest lung cancer rate has been reported among males in Turkey and females in Hungary [2]. In India, lung cancer accounted for 8% of the new cases in 2018 [3]. The prognosis of lung cancer is generally poor, especially in developing countries, and has a mean 5-year survival rate of just 15 percent [4]. In recent times, there have been many advances in diagnostic modalities, including various molecular markers and the introduction of customized treatment strategies. Variation is seen in the statistics for lung cancer-related deaths across different countries due to various factors such as non-availability of

good infrastructure in rural areas, socioeconomic status, limited access to healthcare facilities, late presentation, and delayed diagnosis. Diagnosing lung cancers is a challenge to pathologists, especially when the biopsy tissue is small and has to be used for routine histopathology, special stains, immunohistochemistry markers, and molecular studies. Pleural fluid cell blocks from effusions also can be used for diagnosis. Advances in lung cancer are increasing at a rapid pace, and the present day has come a long way from histological classification to molecular classification. At present, with the availability of molecularly targeted therapeutic agents, the median survival—which was earlier a dismal 12 to 14 months—has now improved to two to three years [5].

As ours is a tertiary care centre, we receive lung carcinoma patients and their tissue biopsies. Errors in the EGFR gene are a biomarker for lung cancers and are also related to the treatment. The presence or absence of a particular exon mutation dictates the further management of patients. Hence, in this study, we have attempted to determine the EGFR mutations in cases of lung cancers.

Aim of the Study: To study the demographic and clinicopathological profile of lung cancer, the distribution of various histological subtypes, and to determine the EGFR mutations in lung cancers.

Materials and Methods

This was a prospective study in the Department of Pathology at ESIC Medical College and Hospital over a period of three years, from March 2021 to March 2024. There were no ethical issues involved in the study, and Institute Ethics Committee approval was taken. Written informed consent was taken from all the participants in the study.

Inclusion criteria: Primary malignancies of lung parenchyma were included. Secondary tumors, i.e., metastatic deposits in lung, were excluded.

Exclusion criteria: All benign tumors and tumor-like conditions of lung were excluded. Malignancies of pleural origin were excluded. Sarcomatous tumors were excluded. Secondary tumors, i.e., metastatic deposits in lung, were excluded. Lung biopsies with inadequate material were excluded.

All the cases of primary lung malignancies reported from the Department of Pathology during the study period were analyzed for the patient demographics of age, gender, smoking habits, laterality of lung tumors, the clinical presentation, histopathological type of lung cancer, and presence or absence of epidermal growth factor receptor (EGFR) mutation status.

A total of 93 lung biopsies were received in the histopathology section and were fixed in an adequate amount of 10% neutral buffered formalin. The tissue was processed routinely, and sections were cut at 5-micron thickness, were stained by Hematoxylin and Eosin stains, and were examined under light microscope for the pathological diagnosis.

EGFR mutation assay was done by polymerase chain reaction (PCR) and pyrosequencing using Cobas 4800 to detect a mutation in DNA isolated from formalin-fixed, paraffin-embedded tumors. DNA was isolated using the Cobas DNA sample preparation kit. PCR amplification and detection of target DNA was done using complementary primer pairs and oligonucleotide probes labeled with fluorescent dyes. A mutant control and negative control were included in each run to confirm the validity of the run. PCR products were sequenced by pyrosequencing and then analyzed for mutations in exons 18, 19, 20, and 21 using pyrosequencing software.

The PCR assay was designed to detect G719X substitution mutation in exon 18, deletion mutations in exon 19, T790M and S768I

substitution mutations in exon 20, insertion mutations in exon 20, and L858R and L861Q substitution mutations in exon 21.

Limit of detection: Cobas EGFR test can detect mutations in EGFR exons 18, 19, 20, and 21 with at least 5% mutation level using the standard input of 50 ng per reaction well. A negative result cannot entirely exclude the presence of EGFR mutation in the specimen.

Results

This was a prospective cross-sectional study. During the study period, a total of 96 lung biopsies were received from patients with an age range from 29 years to 85 years, with the median age being 62 years. Of the 96 patients, three cases were of metastatic tumor deposits to the lungs and were excluded from the EGFR mutation study. The male-to-female ratio was 2.2:1. In the present study, a history of smoking was present in 84% of males, and none of the women had a history of smoking. There was no history of exposure to any known carcinogens in the remaining 16% of cases.

Discussion

Lung cancers are increasing globally and also in India. Lung cancers are broadly divided into Non-small cell lung cancer (NSCLC), and Small cell lung cancer. The NSCLC mostly comprises adenocarcinomas and squamous cell carcinomas and, particularly in advanced stages, has a very poor prognosis. The conventional systemic chemotherapy given to these patients offers an increase of less than one year for overall survival (OS). Also, the available chemotherapy is usually associated with high toxicity [6]. Whenever there are mutations in epidermal growth factor receptor (EGFR), it gives rise to enhanced downstream signaling that leads to cell proliferation, differentiation, and growth. Tyrosine kinase inhibitors (TKIs) that block EGFR-derived signal transduction have demonstrated good efficacy in many patients with EGFR mutations [7]. According to the National Comprehensive Cancer Network guidelines, TKIs are currently recommended as first-line treatment for advanced EGFR-mutant NSCLC [8]. In the present study, we have attempted to determine the histopathologic types and the type of EGFR mutations in our patient population.

Age and gender-wise distribution (Table 1): In the present study, there were a total of 93 cases with a male to female ratio of 2.2:1, and the patient age ranged from 29 years to 85 years, with median age being 62 years. Ramani VK et al. [8], in a study on clinicopathologic profile of lung cancers, observed a male to female ratio of 2.95:1 with median patient age of 61 years. They observed most of the cases, i.e., more than 60%, in the 51–70 year age group. In our study too, the 51 to 70 year age group contributed to 51% of cases. Dash et al. [9], in a similar study from Odisha, observed mean age of lung cancers to be 58.8 years. Dattatreya et al. [5] studied 446 lung cancer cases. They observed the gender distribution to be 2:1, i.e., males were affected twice as commonly as females, reflecting the rising trend of lung cancer in women. They have attributed it to increased smoking habits in urban women. The median age of diagnosis in their study was 60 years, with 49.1% of patients in the forty to sixty years age group.

Noronha et al. [10] studied 489 lung cancer patients treated over a period of a year and reported a median age of 56 years with a male to female ratio of 3.5:1. Babu G et al. [11] conducted a retrospective study on metastatic lung cancer patients at Kidwai Institute and observed 55.6% of patients in the age group of 41–60 years. However, in the present study we have not focused on metastatic tumors to the lungs.

Risk factors: In our study, history of smoking was present in 84% of males, and none of the women had a history of smoking. The

remaining 16% of cases did not have a history of exposure to any known carcinogens. Smoking tobacco, either as cigarettes and/or beedis, is the main risk factor for causation of lung cancer in Indian men. However, smoking as an etiological agent is not so common among Indian women due to socio-cultural aspects, indicating the probability of other risk factors in women besides smoking [10]. The data on epidemiology of lung cancer in India indicates the effect of industrialization and smoking trends on cancer in the community. Like other countries, here too, smoking tobacco remains the most important risk factor (80–90%). However, a smaller proportion (10–20%) is due to occupational exposure to various other cancer-causing factors or agents.

In the study by Dattatreya et al. [5], 69% of patients were either current or past smokers. Dash et al. [9] from India observed history of smoking in 57.5% of male patients, and none of the female patients had any history of smoking. Kumar BS [12], in their study from Kolkata at a tertiary medical care center, reported a high incidence of smoking of 81.2%. Babu et al. [11], in a similar study on 304 patients, observed that 63.5% were smokers.

Clinical features (Table 2): In our study, the most common clinical complaints were of cough, seen in 55.9% of cases. Kumar BS et al. [12], in a similar study, observed cough as the presenting complaint in 68.4% of their patients.

Table 1: Age and gender-wise distribution

Age (in years)	M	%	F	%	Total	%
20–30	–		1		1	1.08%
31–40	3		3		6	6.45%
41–50	16		10		26	27.96%
51–60	18		8		26	27.96%
61–70	16		5		21	22.58%
71–80	9		2		11	11.83%
81–90	2		–		2	2.15%
Total	64		29		93	100%

The 41 to 60-year age group was most commonly affected by lung cancers.

Table 2: Clinical features at presentation

Presentation	No. of cases	Percent (%)
Cough	52	55.91%
Vague symptoms of fatigue, weight loss, loss of appetite	49	52.68%
Chest pain	31	33.33%
Blood-tinged sputum	18	19.35%
Wheezing/Hoarseness	9	9.67%
Mass detected incidentally	8	8.60%
Pleural effusion	7	7.52%
Bone pain due to metastasis	6	6.45%

Laterality: In our study, the right lung (54% of cases) was affected slightly more commonly than the left. Dattatreya et al. [5] observed the right lung to be more commonly involved than the left, and so was seen by Kumar BS et al. [12] (65.79%) and Mohan et al. [13] (52.3%) in their studies. Prognosis of various solid tumors is associated with the location of the tumors, including lung cancers. Lung cancers are usually said to be 'central versus peripheral tumors.' Central tumor means it is located within <2 cm of the bronchial tree or near the mediastinal or pericardial pleura. The exact location has a bearing on the lymph nodal metastasis and treatment, as reviewed by Xie X et al. [14].

Histopathological type of lung cancer (Table 3): In the present study, we observed NSCLC in 97%, and small cell lung cancers

(SCLC) in 3%. Among the NSCLC, 62.2% were adenocarcinomas and 37.8% were squamous cell carcinomas. In general, NSCLC are more common than small cell lung cancer, and the latter are presumed to constitute 14% of all lung cancers [15].

In the past forty years, there has been a shift in the pathologic distribution of NSCLC. In the study by Dattatreya et al [5], NSCLC constituted the major histological type and contributed to 81.1% of cases, and adenocarcinoma was the most common type, seen in 66% of patients, followed by squamous cell carcinoma in 11.6% of patients. In the study by Noronha et al [10], conducted at Tata Memorial Hospital (n = 489 patients), they observed that 92% had NSCLC histology, with adenocarcinoma constituting 43.8%, and squamous cell carcinoma made up 26.2% of cases. In other studies, like that of Babu et al [11], there was an almost equal distribution of adenocarcinoma and squamous cell carcinoma. Kumar BS et al [12], from Kolkata (n = 266 patients), observed squamous cell carcinoma histology to be the more common type in their study.

Molecular/EGFR Mutation data (Table 4): In our study, we observed 20 of 93 cases, i.e., 21.5% of cases, were positive for EGFR mutations, of which there were 17 (85%) males and 3 (15%) females.

Table 3: Histopathological diagnosis (n = 93)

Diagnosis	No. of cases	Percent (%)
Invasive Nonmucinous Adenocarcinoma		
– Acinar pattern	24	25.81
– Papillary pattern	5	5.38
– Micropapillary pattern	2	2.15
– Lepidic pattern	11	11.83
– Solid pattern	9	9.68
– Focal enteric differentiation	1	1.08
– Spindle and pleomorphic differentiation	1	1.08
Mucinous adenocarcinoma	2	2.15
Adenosquamous cell carcinoma	1	1.08
Squamous cell carcinoma	34	36.56
Small cell carcinoma	3	3.23
Total	**93**	**100%**

Non-small cell lung cancers accounted for 97%, and small cell lung cancers for 3%. Among the NSCLC, 62.2% were adenocarcinomas and 37.8% were squamous cell carcinomas.

Table 4: Type of mutations (n = 20)

Mutation detected	No. of cases (%)	Histopathology	No. of cases
Exon 19	12 (60%)	Adenocarcinoma nonmucinous	10
		Adenocarcinoma mucinous	1
		Squamous cell carcinoma	1
Exon 20	4 (20%)	Adenocarcinoma nonmucinous	4
Exon 21	4 (20%)	Adenocarcinoma nonmucinous	4
Total	**20**		**20**

EGFR mutations were observed in 20 of 93 cases, i.e., in 21.5% of cases. Most (95%) EGFR mutations were seen in adenocarcinomas, and 5% were seen in squamous cell carcinoma. Exon 19 was more commonly affected (60% of cases). None of the cases showed exon 18 mutation.

Various factors like ethnicity, genetic background, and environmental factors like cigarette smoking and tobacco chewing may influence the different activating mutations and their frequencies. The exact mechanisms of these factors in activating mutations are not yet clear [10].

Dattatreya et al [5] reported 24% positivity for EGFR testing in their study. Dash et al [9] reported EGFR mutation-positive results in 7 of their 20 cases of adenocarcinoma lung, i.e., 35% positivity, and in 2 out of 19 cases of squamous cell carcinoma, i.e., 10.5% of cases.

Chougule et al [16] conducted a retrospective study (n = 907 patients) in known cases of lung cancer at Tata Memorial Hospital in Mumbai, between August 2011 and December 2012. They observed that female patients are more likely to have mutations than male patients, and their overall mutation rate was 23.2%. In their study, females had 29.8% and males had 20% mutation rates. The EGFR mutation rate has been reported in the literature for East Asian patients to be around 26–30%, and slightly lower rates have been reported in the Western population, around 10–15%. Our rates of EGFR positivity are similar to this study.

In a meta-analysis, Zhang et al [17] observed that EGFR mutations are more common in adenocarcinomas and have higher rates among Asians (around 38.8% to 64.0%) than among the Caucasian population, where it was observed to be 4.9% to 17.4%.

Doval et al [18], in their retrospective study (n = 500 patients), observed a slightly higher EGFR mutation rate of 33%. Within India itself, regional differences have been observed, such as an incidence of 65% in the Southern Indian population and 33% in the Northern Indian population, as reported by Aggarwal et al [19].

Tsubata et al [20] have concluded in their study that EGFR mutation-positive rates in NSCLC are common in East Asia, and approximately 50% of adenocarcinomas harbor EGFR mutations. Similarly, Konho et al [21] have observed EGFR mutations in approximately 15% of lung adenocarcinoma cases in Europe and the United States, whereas in East Asia, 55% of cases are EGFR positive.

In the present study, we observed mutations in exon 19 in 60% of cases, and in exons 20 and 21 in 20% of cases each. None of the cases were positive for exon 18 mutations. Bhatt et al [22] analyzed (n = 104) cases of histologically proven NSCLC for EGFR mutations. They observed EGFR mutation prevalence to be 39.6%, with exon 19 mutation in 80% of cases, followed by exon 21 mutation in 17% of cases, and exon 18 in 3% of cases. Dattatreya et al [5] found exon 19 deletion in 73% of the cases with EGFR mutation. Li AR et al [23] have also observed that most of the EGFR mutations are in exon 19 (E19 dels) or a leucine to arginine substitution (L858R) in exon 21, which are generally referred to as “common mutations.”

Yoon et al [24] have observed that EGFR-positive advanced adenocarcinoma patients have improved overall survival as compared to EGFR-negative patients, as the former have a better response to Tyrosine kinase inhibitor treatment. In lung adenocarcinoma with EGFR positivity, exon 19 deletions predict a good prognosis, while an exon 21 mutation predicts unfavorable prognosis with higher mortality. Goud KI [25], from Hyderabad, India, studied lung cancer cases (n = 267) and observed EGFR mutation in 20.59% of their cases, with exon 19 mutation being the most common (56%).

Kaler A et al [26] studied 212 samples from lung cancers and observed mutations in 38.67% of cases. Among these, five (5.9%) samples had mutations in exon 18, forty-one (48.8%) samples had mutations in exon 19, twelve (14.28%) samples had mutations in exon 20, and twenty-six (30.95%) samples had mutations in exon 21. There were 11 (13.41%) cases which had uncommon EGFR mutations.

In our study, all three women with NSCLC were never-smokers. Yoon et al [24] observed that EGFR mutations are more common

in females and in nonsmokers.

Xia J et al [27] conducted a retrospective study particularly in patients less than 45 years of age to understand the clinicopathologic characteristics and EGFR mutations in younger lung cancer patients. They concluded that lung cancer in younger patients was associated more with female patients, adenocarcinomas, nonsmokers, and advanced tumor stage.

Mohan Anant et al [28], in their study (n = 257), also observed 25.3% EGFR mutation positivity and further noted that younger, never-smoker, female patients were likely to have a higher prevalence of EGFR mutations.

Limitations: Uncommon mutations of EGFR were not studied. Other molecular markers like ALK and ROS were not studied. Sample size was limited. Correlation with stage of lung carcinoma and treatment aspects were not taken into consideration.

Conclusion

Lung cancers are twice as common in males as in females and usually affect patients around the sixth decade. NSCLCs are more common than small cell carcinomas, and among NSCLCs, adenocarcinomas are more common than squamous cell carcinomas. Almost one-fifth of adenocarcinomas are positive for EGFR mutations, and exon 19 mutation is the most commonly encountered mutation. EGFR mutation testing is encouraged in all lung cancer patients in view of available treatment options.

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