Original Article

# Non small cell Carcinoma- Lung: Distribution and spectrum of mutations among patients in Eastern India

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**ABSTRACT**

**Background**: Lung cancer is one of the most common malignancies in the world. About 80–85% of lung cancers are non-small cell lung cancer (NSCLC). The development of therapeutic agents targeting products of epidermal growth factor receptor (EGFR) gene mutation and anaplastic lymphoma kinase (ALK) rearrangements has significantly improved survival in patients with NSCLC. Thus, the patients eligible for the treatment should be selected through appropriate molecular tests. **Objective**: The main objective was to study the distribution of NSCLC and its genetic mutations, in the patients of Eastern India. **Methodology**: A prospective study was carried out among 228 patients, in a tertiary care hospital of Eastern India during a period of 2 years from January 2016 to January 2018. We have included all the patients who were screened and found to have lug carcinoma. The detailed clinical history of the patients was recorded. We have used techniques such as radiology, histopathology, immunohistochemistry (IHC) and molecular study by FISH technique. **Results**: Out of 138 cases of NSCLC on histopathology 78 cases (56.7%) were reported as squamous cell carcinoma, 46 cases (33.3%) as adenocarcinoma and 14 cases (10.1%) as NSCLC. IHC was used for categorization of NSCLC cases which showed adenocarcinoma in 4 patients and squamous cell carcinoma in 10 patients. EGFR exon 19 deletion mutation was the predominant mutation in adenocarcinoma. **Conclusion**: Molecular study for genetic analysis has improved the scope for targeted therapy in Nonsmall cell carcinoma patients, thereby reducing mortality and morbidity in cases of lung carcinoma.

***Key words:*** *Non-small cell lung cancer, Adenocarcinoma, EGFR mutation, ALK mutation, smoking.*

Lung cancer is the most common cause of cancer deaths with approximately 1.4 million deaths worldwide annually [1]. Owing to the absence of clinical symptoms and effective screening programs, most of the patients have advanced stages or metastatic disease at the time of presentation [1]. Deaths in the USA attributable to lung cancer, are more than the next three most common cancers combined [2]. WHO classifies non-small-cell lung cancer (NSCLC) as adeno carcinoma, squamous cell carcinoma and the subtypes of large-cell carcinoma–adeno squamous, sarcomatoid carcinoma [2,3].

In the past, an increased rate of lung carcinoma among the male population was seen, predominantly in the smokers [3]. It is well known that smoke exposure can lead to well-characterized series of morphological changes of the bronchial epithelium progressing from basal cell hyperplasia to metaplasia, severe dysplasia to carcinoma in situ and, finally, frank carcinoma [3]. This series of changes is primarily associated with the squamous sub-type of NSCLC. At present, NSCLC accounts for more than 85% of lung cancers in western countries, with 20–30% of NSCLC occurring in non smokers [4]. This finding

has coincided with the discovery that a proportion of lung cancers occurring in non or light smokers, are driven by oncogenic mutations which, when selectively inhibited, can lead to dramatic tumor regression and prolonged survival [5].

Hence, targeted therapies for genes such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and KRAS have become the hotspot of attention and study in lung cancer treatment for the last 10 years. In the past, these two molecular alterations have been viewed as mutually exclusive, but recent cases of lung cancer with concurrent EGFR mutation and ALK rearrangement have been identified [5,6]. Clinical guidelines have now incorporated molecular testing and the use of drugs targeting those genes [6]. The aim was to study the distribution of the various histological subtypes of NSCLC, spectrum of mutations, and its use for targeted therapy and better prognosis.

## METHODS

This prospective study was conducted from January 2016 to January 2018 in a tertiary care hospital, Kolkata, West Bengal, India. After getting the ethical committee approval and informed consent from the patienst we have included all the cases diagnosed as lung carcinoma, on histopathology. Cases, who were diagnosed as nonmalignant on histopathology, were excluded from the study. All the 228 patients reported to the chest OPD with various pulmonary complaints in a tertiary care hospital of eastern India, within our study period. Their detailed clinical history (including smoking history) and radiological findings were noted.

Chest X-ray and contrast enhanced cytotopography (CECT) of lung followed by CT guided Trucut biopsy of lung lesions were performed. Patients were selected for CT guided Trucut biopsy on the basis of their radiological findings such as solid homogenous or cavitary mass/ consolidation in one or both of the lung fields.Prior to the biopsy, complete hematological profile of the patient including coagulation profile (PT/INR) was obtained. Immunohistochemistry (IHC) was done for those cases where categorization of the carcinoma was not possible on histopathological examination alone. Molecular study by Fluorescent in situ Hybridization (FISH) technique using the paraffin blocks was carried out in all the cases of lung carcinoma (detected on histopathology), to detect ALK and EGFR mutations. Other superadded features like pleural effusion, pleural thickening, the shift of the trachea and mediastinal lymphadenopathy, were the important findings on radiology.

A correlation study was done based on the observations from radiological, histopathological and molecular study findings of patients reported as Lung carcinoma on biopsy. The data were calculated manually and the results were noted.

## RESULTS

Among 228 cases of lung lesions studied, 156 cases were reported as lung carcinoma of which, 138 cases (88.5%) had NSCLC and small cell carcinoma was diagnosed in 18 cases (13.05%) (Table1). Predominant clinical presentation among the patients was cough, chest pain, and breathlessness. Among 228 patients, male patients were predominant (82.5%) with the age ranging from 46 to 74 years in males while 52 to 67 years in females. Patients were from urban and rural areas of different parts of West Bengal.

**Table 1: Distribution of Lung Lesions**

| **Histology (n=228)** | **Cases** |
|---|---|
| Small cell carcinoma | 18 |
| Squamous cell carcinoma | 78 |
| Adenocarcinoma | 46 |
| Non small cell Ca(non differentiated) | 14 |
| Others(SFT, TB, NHL, METS, Pneumocyte hyperplasia, germ cell tumor) | 60 |
| **In conclusive** | **12** |

On histopathological examination alone, 78 cases (56.7%) were reported as squamous cell carcinoma, 46 cases (33.3%) as adenocarcinoma and 14 cases (10.1%) as NSCLC-NOS. IHC was used for categorization of NSCLC-NOS cases which resulted in 4 as adenocarcinoma and 10 as squamous cell carcinoma (Table 2). Male predominance was seen in all cases of NSCLC (3:1 in squamous cell carcinoma and 2.6:1 in adenocarcinoma cases). The age ranged from 63-65 yrs in males and 47-55 yrs in females. Middle-aged females with no smoking habit showed an increased incidence of adenocarcinoma. Out of 156 patients, 140 had a history of smoking for a minimum of 11 years. A molecular study using FISH technique was carried out in 134 cases. Out of 50 cases diagnosed as adenocarcinoma, 12 cases (24.0%) showed EGFR deletion mutation of exon 19 and 4 cases (8.0%)

showed EGFR deletion mutation of exon 21. ALK was negative in all cases. Four cases of morphologically diagnosed squamous cell carcinoma showed EGFR deletion mutation of exon 19. On follow up, the patients were started on targeted therapy and no mortality was reported till date.

**Table 2: Distribution of NSCLC**

| Non-small cell carcinoma (n=138) | Histo-pathology | IHC (TTF1, P40, P63) |
|---|---|---|
| Adenocarcinoma (n=50) | 46 | |
| Squamous cell carcinoma (n=88) | 78 | |
| NSCLC-NOS | 14 | Adenocarcinoma-04 Squamous cell carcinoma- 10 |

## DISCUSSION

The molecular basis of lung cancer is complex and heterogeneous. The molecular changes (genetic, epigenetic, protein expression) and the improvements in understanding of the functional expressiveness of these changes have potential effects on the diagnosis, prognosis, and treatment of lung cancer [7]. EGFR mutations in NSCLC are seen in the intra cellular tyrosine kinase domain. Deletion of exon 19 is most commonly followed by missense mutations, exon 21, a single nucleotide point mutation leading to a single amino acid change from leucine to arginine at codon 858 [5,7].

Ture et al in their study of 132 patients of NSCLC found 30.3% (19) cases of lung carcinoma had EGFR exon 19 mutation. Eighteen of these cases were histologically diagnosed as adenocarinoma [6]. Marino et al found EGFR mutation in 32.7% cases (336/977) of lung carcinoma in a Chinese population [3]. In the present study, we found EGFR mutation in 32% cases (16/50) out of which exon 19 mutation was 24% (12/50) and exon 21 mutation was 8.0% (4/50). Sweis et al, in their retrospective study of 20 cases of NSCLC, found the disease control rates in patients treated with EGFR inhibitors was 46% (6/13) [4]. Wang et al in their study of 300 cases of NSCLC found ALK rearrangement mutation in 4.33% cases of adenocarcinoma (13/300) [8]. In our study, ALK mutation was found to be negative in all cases. Won et al in their study screened 1458 patients, out of which 91 patients were selected for molecular study by direct sequencing FISH method. EGFR and ALK mutations were found to be 42.4% and 6.3% respectively. Concomitant mutations were found in 4.4% (4 cases) [9]. Lee T et al in their study found that 12 out of 6637 patients had concomitant mutations [10]. In our study, none of the cases showed a concomitant mutation. Concomitant genetic alteration of NSCLC is unusual because EGFR, KRAS, and ALK mutations are widely known as mutually exclusive. Most are associated with acquired mutation after targeted therapy and are related to drug resistance [10].

Wang et al in their study found the distribution to be 239 (79.67%) cases of squamous cell carcinoma, adenocarcinoma in 36 cases (12%) and adenosquamous carcinoma 10 cases ( 3.33%). In our study, the distribution of nonsmall cell carcinoma was found to be adenocarcinoma 36.23% (50/138) and squamous cell carcinoma 63.7% (88/100). Ture et al and Wang et al in their study found male population predominant in lung carcinoma, 74.2% (98/132) and 59.33% (178/300) respectively [6,8]. In our study we also found 72.7% of patients of lung carcinoma were males with an average age of 63.2 yrs.

## CONCLUSION

Histomorphological examination and Immunohisto-chemistry are essential for a definite diagnosis of non-small cell lung carcinoma. EGFR mutation, single and concomitant with ALK mutation is the most common genetic alteration seen in patients diagnosed as adeno carcinoma among non-small cell carcinoma cases. Males with smoking history with more than ten years are at risk for developing lung carcinoma.

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