Original Research Article

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Study of clinical presentations of lung cancer in tertiary level hospital

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ABSTRACT

Background: Lung cancer is the most common cancer diagnosed worldwide. It is also the leading contributor to cancer-related mortality, resulting in around 1.38 million cancer deaths per year worldwide. The aim and objective of the study was to study the clinical presentations including paraneoplastic manifestations and metastatic effects of lung cancer and to identify reasons for delay in diagnosis of lung cancer.

Methods: Hospital based observational study was conducted on 100 consecutive cases.

Results: Mean age of the cases with lung cancer was 56.36 years and 30% of the cases. Male predominance was seen with 63% males to 37% females. Tobacco smoking was present in 59% cases while exposure to second hand smoke and biomass fuel was seen in 11% and 9% patients. Most common presenting symptoms were cough (22.21%), chest pain (16.13%), fever (14.37%), dyspnea (11%) and hemoptysis (5.22%). Most common type of lung tumor was Adenocarcinoma (53%) followed by Small cell carcinoma (22%) and Squamous cell carcinoma (19%). Mutation analysis by molecular testing where possible in 76.66% NSCLC cases and showed with RAS (26.19%), EGFR (23.8%), ALK1 (11.9%) and ROS (4.7%) mutation. Stage I and II of lung cancer was seen in 17% cases while stage III and IV was seen in 39% and 44% cases respectively.

Conclusions: Present study shown tobacco smoking as the most common risk factor in the causation of lung cancer (59%) followed by passive smoking (11%) and biomass fuel exposure (9%). Mortality in the present study was 72% in 2 years of follow up and Median survival in the study was 11 months. We recommend high index of suspicion in the high-risk groups as smokers and those with chronic respiratory diseases to avoid delay in diagnosis.

Keywords: Clinical presentations, Lung, cancer

INTRODUCTION

Lung Cancer is one the leading cause of cancer related deaths and causes tremendous suffering and economic losses worldwide.^{1,2} The incidence of lung Cancer in developing countries is rising at alarming rates.³ In India, lung cancer was initially thought to be extremely rare, but now 1 million of the current 5 million deaths in world, and 2.41 million in developing countries are from India.^{4,5} In Indian patients with lung cancer, active

tobacco smoking was found in 87% of males and 85% of females.

Exposure to second hand tobacco is seen in 3%.⁶ The major risk factor for developing lung cancer is smoking of tobacco and hence this disease is often viewed solely as a smoker's disease. Two major types of lung cancer are Non small cell lung cancer (NSCLC) and Small cell lung cancer (SCLC). Adenocarcinoma, Squamous cell

carcinoma and large cell carcinoma are subtypes of non small cell carcinoma lung.⁷

In Indians, however, SCLC is predominant over NSCLC.^{8,9} Other factors responsible for lung Cancer include genetic predisposition, radon gas, asbestos, pesticides and air pollution. The main symptoms of lung cancer in Indian series include cough with expectoration (40.0-94.3%), chest pain (16.0-66.7%), weight loss (11.4-90.0%), breathlessness (24.0-59.0%), weakness (4.0-90.0%), hemoptysis (8.0-69.2%), fever (19.6-68.6%), anorexia (20.5-90.0%), hoarseness of voice (9.0-33.0%), nausea and vomiting (6.0-25.0%), puffiness of face (2.9-19.8%), and dysphagia (2.9-20.8%).¹⁰ A vast majority of lung cancer patients have delayed presentation due to lack of awareness and lack of affordable health care facilities in the vast parts of rural and semi-urban India. Further the facilities for imaging and diagnostic work up such as bronchoscopy are available at selected centers which are located in cities and are expensive for rural poor patients. The initial presentation of lung cancer is variable and may be due to local disease, pressure effects on vital structures located inside the chest or due to distant metastasis or paraneoplastic syndromes.⁶

Lung cancer has been a major medical and public health problem with tobacco smoking being recognized as the primary causative agent in majority of cases. There are tremendous efforts being made by most government agencies to prevent tobacco smoking and reduce various aero-digestive cancers, but millions of people still continue to smoke tobacco and large numbers of new smokers are added each year.¹¹ The relatives and close friends are exposed to environmental tobacco smoke, which is known to be carcinogenic. For a smoker it would take 30 years of abstinence to reduce risk of lung cancer to the level of never-smokers.¹² Thus century-long efforts will be required to abolish the effect of tobacco smoking on lung cancer incidence and mortality from our society. In view of the above, present study was aimed to study the clinical presentations including paraneoplastic manifestations and metastatic effects of Lung Cancer in Department of General Medicine, INM, INHS, ASVINI, Colaba, Mumbai (Affiliated to Maharashtra University of Health Sciences, Nashik).

METHODS

The present prospective, observational, clinical study was conducted in the Department of General Medicine, INM, INHS, ASVINI, Colaba, Mumbai (Affiliated to Maharashtra University of Health Sciences, Nashik). A total of 100 diagnosed cases of primary Lung carcinoma aged more than 18 years coming to our hospital were included in the study during September 2017 to September 2019 (2 years) were included in the study. All patients below 18 years of age, patients having cancer that is metastatic to lung and patients not willing to give written consent were excluded from the study. Patients with suspected lung cancer underwent screening tests. Once space occupying lesion is seen on chest CT scan, patients underwent invasive procedure for tissue diagnosis with bronchoscopy guided biopsy, brush cytology, needle aspiration etc or CT guided biopsy, needle aspiration or USG guided pleural fluid aspiration for cytology. Once diagnosis got final, patient included in the study.

Informed consent of all patients was taken. The patients of primary lung cancer diagnosed and evaluated in our hospital were included. A detailed medical history of the patients regarding their clinical symptoms, past medical or surgical history, occupational history was taken. The smoking history included the current status, the mode of smoking, and any other mode of tobacco intake. ECOG (Eastern Co-operative Oncology Group)/ World Health Organisation (WHO) performance status was also evaluated. A detailed history taking and clinical examination of the patient was carried out. Freshly diagnosed lung cancer patients were included and retrospectively history was taken about every symptom with duration of complaints that may be related to primary lung cancer or its paraneoplastic manifestation. Through clinical examination were carried out and searched for any clinical sign related to lung cancer.

Statistical analysis

The quantitative data was represented as mean \pm SD. Categorical and nominal data was expressed in percentage. The significance threshold of p-value was set at <0.05. All analysis was carried out by using SPSS software version 21.

RESULTS

Mean age of the cases with lung cancer was 56.36 ± 7.16 years and 30% of the cases were over 60 years of age and 67% of cases were over 50 years of age. Male predominance was seen in present study with 63% males to 37% females of lung cancer. On routine examination, the mean systolic blood pressure was 126.87 ± 11.23 mmHg, diastolic blood pressure 83.23 ± 7.89 mmHg, pulse rate 71.48 ± 8.67 , respiratory rate 17.13 ± 4.26 , SpO2 96.49 ± 1.73 , body weight 63.6 ± 9.98 kg and body mass index was 19.45 ± 4.17 kg/m2.

Most common associated co-morbidity was type 2 diabetes (21.77%) and hypertension (16.93%) followed by COPD (11.29%) and Old tuberculosis (8.06%). History of smoking (ie. cigarette or beedi) was given by 59% cases while that of second-hand smoking by 11% cases. History of biomass fuel exposure given by 9% and tobacco chewing by 13% of cases. No known risk factor was seen in 6% of the subjects. Total of 9% of study population gave history of cancer in their 1st degree relatives. Amongst them 4% were having lung cancer cases in their families. Major (91%) study population doesn't have family history of any cancer (Table 1).

Table 1: Distribution of patients as per co-morbidity.

Co-morbidity		Ν	%
Diabetes mellitus		27	21.770
Hypertension		21	16.930
COPD		14	11.29
Tuberculosis		10	8.06
Other	Stroke	09	7.25
	Seizure	06	4.83
	Dyslipidaemia	5	4.03
	Coronary artery disease	4	3.22
	Chronic liver disease	2	1.61
	Gout	2	1.61
	Schizophrenia	1	0.806
No comorbidity		23	18.54

Table 2: Distribution of patients as er complaints.

Symptoms		Ν	%
Cough	<3 weeks	8	5.22
	3-8 weeks	9	5.88
	> 8 weeks	17	11.11
Dyspnoea	< 1 month	8	5.22
	≥ 1 month	9	5.88
Chest Pain		25	16.33
Hemoptysis		8	5.22
Wheeze		3	1.96
Fever		22	14.37
Head ache		10	6.53
Back ache and/or bone pain		9	5.88
Anorexia		8	5.22
Weight Loss		7	4.57
Easy Fatigability		7	4.57
Hoarseness of voice		2	1.31
Seizure		1	0.65
Total		153	100

Table 3: Distribution of patients as per type ofneoplastic syndrome.

Paraneoplastic Syndrome	N	%
Hematological manifestations	20	20.0
CNS manifestations (encephalopathy,		
cerebellar ataxia, opsoclonus, transverse	8	8.0
myelitis, peripheral neuropathy, etc)		
Hypercalcemia of malignancy	6	6.0
SIADH	6	6.0
Dermatomyositis/ polymyositis	2	2.0
Horner syndrome	2	2.0
Cushing's syndrome	1	2.0

Most common presenting symptoms observed in cases of lung cancer was cough (22.21%), chest pain (16.13%), fever (14.37%) and dyspnoea (11%). Also, patients of

lung cancer presented with predominant respiratory symptoms. Patients with lung cancer diagnosed in this study group were having predominant respiratory symptoms (cough, dyspnoea, wheeze, hemoptysis, chest pain) in 39% cases, general symptoms and symptoms of other system (focal weakness, fever, anorexia, hoarseness of voice, weight loss, etc) were observed in 55% cases whereas 6% cases were asymptomatic and were diagnosed incidentally during non-related evaluation for and routine health check-up (Table 2).

Table 4: Distribution of cases as per CT chestfindings.

CT chest finding	Ν	%
Lung mass with bilateral lung / distant metastasis ie. liver, bone, brain, adrenal, skin etc	27	27
Lung mass + pleural effusion	17	17.0
Lung mass with spread to other unilateral lobe	17	17
Lung mass only	14	14.0
Consolidation with lung mass	7	7
Solitary pulmonary nodule	5	5
Lung mass + pleural effusion + mediastinal LN	4	4.0
Collapse of lobe/lung	3	3.0
Cavitary lung lesion	3	3
Lung mass + mediastinal LN	2	2.0
Lung mass + pneumothorax	1	1

Significant number of cases were cachexic (6%) and underweight (3%) while 5% were overweight by BMI. (Cases with Cushing's syndrome as a paraneoplastic manifestation included in overweight category). Majority of the cases were presented with normal Blood pressure (90-95%), pulse rate (86%) and respiratory rate (83%). Systolic and diastolic hypertension was observed in 8% and 5% cases each while tachycardia was seen in 17% cases.

On general examination, lymphadenopathy (axillary and cervical group of lymph nodes) and clubbing was observed in 16% and 19% cases while pallor and cachexia (BMI- <16 kg/m2) was seen in 12% cases and 6% cases each respectively. Findings of SVC obstruction were seen in 5% cases. Cyanosis was not seen in a single case. On respiratory system examination, majority of the patients showed findings suggestive of pleural effusion (28%) and obstructive airway disease (11%). Findings suggestive of consolidation were seen in 8% and that of collapse of lobe seen in 4% of study population. On gastrointestinal system examination, hepatomegaly and splenomegaly was observed in 8% and 7% of study population. On CNS examination, 3% cases observed with paraplegia and 2% cases with hemiplegia and ataxia each. On CVS examination, 1% cases were found to have findings of pericarditis.

Diagnosis	No.	Males (%)	Smokers (%)	Positive X-ray finding (%)	Para-neoplastic syndrome (%)
Adenocarcinoma	53	25 (47.2)	32 (60.4)	29 (50.87)	23 (43.39)
Squamous cell carcinoma	19	17 (89.5)	18 (94.7)	9 (47.36)	10 (52.6)
Large cell carcinoma	6	3 (50.0)	4 (66.7)	6 (100.0)	3 (50.0)
Small cell carcinoma	22	18 (81.8)	19 (86.4)	13 (59.09)	9 (40.9)

Table 5: Association of study variables with type of lung carcinoma.

Hematological manifestations like anemia, leukopenia and thrombocytopenia were seen in 20% cases while CNS pathologies (like cerebellar ataxia, transverse myelitis, peripheral neuropathy, seizure, lambert eatons myasthenic syndrome etc.) being the next common manifestation, seen in 8% cases. Other common paraneoplastic syndromes were SIADH and hypercalcemia of malignancy seen in 6% and 4% cases respectively. Dermatomyositis/ polymyositis and Horner's syndrome was seen in 2% cases each. Cushing's syndrome was seen in a single study subject. On chest xray, pleural effusion was seen in 28% cases while mass lesion and consolidation were observed in 9% and 8% cases respectively. 4% were detected to have collapse (Table 3).

Most common type of lung malignancy was adenocarcinoma (53%) followed by small cell carcinoma (22%) and squamous cell carcinoma (19%). Stage I and II of lung cancer was seen in 17% cases while stage III and IV was seen in 39% and 44% cases respectively. Molecular study of 42 adenocarcinoma cases showed EGFR (epithelial growth factor receptor) mutation in 23.8%, RAS mutation in 26.19%, ALK1 in 11.9% and ROS in 4.7% cases. Mutation was not detected in 33.33% cases underwent molecular study. Only 42 of 53 cases underwent molecular study due to multiple reasons like inadequacy of sample, financial constrains etc. As per ECOG grade, most of the cases (90%) were in either ECOG grade 1 or 2 i.e. restriction in strenuous activity or more than 50% ability for routine work (Table 4, 5).

Table 6 shows significant association was observed between squamous cell carcinoma with male gender and history of smoking. Positive x-ray findings were seen in all the 6 cases of large cell carcinoma (pleural effusion in 4 and consolidation in 2 cases). No strong association was observed between type of lung carcinoma and paraneoplastic syndrome, though maximum cases (23) were seen with adenocarcinoma.

DISCUSSION

Lung malignancy accounts for maximum deaths than any other type of cancer. Several epidemiological observations completed across varied demographic cohorts in India confirm the significant burden of lung cancer cases in India, contributing significantly towards the cancer morbidity and mortality. As per the GLOBOCAN 2018 report, the expected incidence of lung cancer in India was 67,795 in all ages and both sexes; the crude incidence rate per 1 lakh was 5.9, the agestandardized rate per 1 lakh (world) was 6.9, and the cumulative risk was 0.65. With respect to incidence rates, lung cancer tiered fourth overall among the various types of cancer.

In the present study, mean age of the cases with lung cancer was 56.36 years and 30% of the cases were over 60 years of age. Most common associated co-morbidity was type 2 diabetes (21.77%) and hypertension (16.93%) followed by COPD (11.29%) and tuberculosis (8.06%). Association between these comorbidities and lung cancer is not really explainable as diabetes mellitus and hypertension are prevalent diseases in general population as well for respective age and gender. Mean age reported by various authors is similar to present study as the disease is usually found in the senior lots of population because of prolonged exposure to risk factors. Among both women and men, the incidence of lung cancer is low in people aged <40 years and increases up to age 75–80 years in most population. Dubey et al13 reported the mean age of lung cancer was 58.6 years.

Male predominance was seen in present study with 63% males to 37% females which is in accordance with the GLOBOCAN 2018 report, males predominate with a male:female ratio of 4.5:1 has been reported. This is also seen in other Indian studies conducted by Jindal and Behera6, all have reported male predominance in their studies.

Tobacco smoking is the major cause of all major histological types of lung cancer. History of smoking was given by 59% cases while second hand smoke and biomass fuel exposure was seen in 11% and 9% patients. Dubey et al also found that besides the tobacco smoke there was no significant exposure to any other carcinogenic substance except in female patients who were exposed to Chulha smoke and environmental tobacco smoke at home.¹³ Majority of the patients were 'Bidi' smokers in their study. Smoking as the most important risk factor for lung cancer in study, is also reported by Rawat et al.¹⁴

Present study revealed that lung cancer shares the common symptomatology as other respiratory diseases. In the present study most, common presenting symptoms observed in cases of lung cancer was cough (22.21%), chest pain (16.13%), fever (14.37%) and dyspnoea (11%)

followed by Hemoptysis (5.22%). Our findings our similar to study of Jindal et al6 in terms of complaints, they also reported unexplained cough of several weeks is the commonest symptoms along with fever, weight loss, chest pain, and shortness of breath.

Total of 9% of study population gave family history of cancer. Amongst them 4% were having lung cancer cases in their families. 11.29% of the patients of the present study had COPD as a co-morbidity. 21.77% patients were having diabetes as a comorbidity. Incidence of lung cancer in a subject with diabetes might be different than in non-diabetes. Amongst the lung cancer patients in our study 8.06% had suffered from pulmonary tuberculosis. In our study a significant number of patients had a history of TB. On general examination, lymphadenopathy and clubbing was observed in 16% and 19% cases while pallor and cachexia were seen in 12% cases and 6% cases each respectively. In our study we have observed 16% patients with lymphadenopathy, which is statistically significant number.

On respiratory system examination, majority of the patients showed findings suggestive of pleural effusion (28%) (i.e. fullness of intercostal spaces, absent breath sounds, stony dull note on percussion, etc) and obstructive airway disease (11%) (unilateral or bilateral wheeze with or without prolonged expiratory phase of respiration). Findings suggestive of consolidation (i.e. impaired note on percussion, inspiratory crackles, etc) were seen in 8% and that of collapse of lobe (shift of trachea/ mediastinum, rib crowding with or without crackles on auscultation) seen in 4% of study population. Hyde et al and Chute et al have found in their studies that the findings suggestive of malignant pleural effusion, consolidation, obstructive airway disease are common in patients with lung cancer.^{15,16}

On gastrointestinal system examination, hepatomegaly and splenomegaly was observed in 8% and 7% of study population. On CNS examination, 3% cases observed with paraplegia and 2% cases with hemiplegia and ataxia each. Amongst these paraplegic cases 2 had spinal metastasis with pathological fracture leading to compressive myelopathy 1 case detected to have transverse myelitis. Hemiplegia was related to metastasis to the brain.

Para-neoplastic syndromes are a group of clinical disorders that are associated with malignant diseases and are not directly related to the physical effects of the primary or metastatic malignancy. A wide range of para-neoplastic syndromes were seen in present study cases. Haematological manifestations like anemia, leucopenia and thrombocytopenia was seen in 20% cases while Neurologic syndromes being the next common manifestations related to CNS were encephalopathy, peripheral neuropathy, transverse myelitis, cerebellar ataxia and Opsoclonus were observed in the study

population. Other common para-neoplastic syndromes were SIADH and hypercalcemia, seen in 6% cases each. Cancer-related or cancer treatment–related anemia occurs frequently seen in patients with lung cancer with one comprehensive review reporting incidences of anemia (haemoglobin [Hb] <12 g/dL) and severe anemia (Hb <8 g/dL) as high as 100% and 55%, respectively, The severity of anemia in these patients is dependent on disease stage, as well as the duration, type, and intensity of chemotherapy, various studies across the India have reported high incidence of Anemia in their studies. Kosmidis et al and Kasuga et al have studied anemia profile in a patient with lung cancer. Incidence of anemia in a lung cancer is high as 100% ranging from 20-100%.^{17,18}

Paraneoplastic neurological syndromes (PNSs) are neurological disorders caused by the remote effects of cancer and are not caused by the tumour itself, its metastasis, infection, ischemia or metabolic disruption. Dasgupta et al reported neurological manifestations in 5 to 10% of cases of lung cancer which is in accordance to the present study.¹⁹

Present study observed SIADH in 6% of the cases, which is in accordance to List et al.²⁰ They reported SIADH in 7% of the cases of lung cancer.

The most common radiographic findings of bronchogenic carcinoma are pulmonary masses, pleural effusion, hilar enlargements and multiple pulmonary nodules. In the present study, on chest x-ray, pleural effusion was seen in 28% cases while mass lesion and consolidation was observed in 9% and 8% cases respectively. 4% cases were detected to have collapse of the lobe.

CT scan is able to detect even very small nodule in the lung, LDCT is special screening test for lung cancer and CT fast is used for the patients who are not able to hold their breath. In our study, lung mass with bilateral lung or distant metastasis i.e. liver, bone, brain, adrenal, skin etc was observed in 27%, lung mass with pleural effusion in 17%, lung mass with other unilateral lobe involvement in 17% and only lung mass was seen in 14% cases.

In the present study, most common type of lung cancer was adenocarcinoma (53%) followed by small cell carcinoma (22%) and squamous cell carcinoma (19%). ADC accounts for 50% of all lung cancer and its incidence has increased greatly in the last years.

Stage I and II of lung cancer was seen in 17% cases while stage III and IV was seen in 39% and 44% cases respectively. Dubey et al13 observed of 44 patients of NSCLC 29 (65.8%) were having advanced disease with TNM stage IIIB and IV at the time of diagnosis. Molecular analysis for mutation done in adenocarcinoma cases has observed RAS mutation in 26.19%, EGFR mutation in 23.8%, ALK mutation in 11.9% and ROS 1 mutation in 4.7% in our study. Squamous cell carcinomas were seen to be significantly associated with males and history of smoking in the present study. Adenocarcinomas were more common in females. We did not observe significant associations between histological form of cancers and para-neoplastic syndrome. The pattern of lung cancer has been changing in the West Lung cancer is being increasingly diagnosed in women and adenocarcinoma has over taken SCC as the most common histological cell type.

CONCLUSION

This study has shown tobacco smoking as the most common risk factor in the causation of lung cancer (59%) followed by passive smoking (11%) and biomass fuel exposure (9%). In our study 83% patients presented in advanced stages 3 and 4 of the disease. Majority of the cases presented late due to non-specific symptoms leading to delay in presentation and lack of access to health care facility causing delay in the diagnosis. Our patients received specific targeted therapy (21%) along with standard chemotherapy (80%) and palliative therapy (17%). Mortality in our series was 72% in 02 years of follow up and Median survival in our series was 11 months (1 month- 49 months). We recommend lung cancer should always be suspected in Smokers who present with cough of more than 3 weeks duration with or without weight loss, hemoptysis, chest pain and those with non-resolving pneumonia and rapidly recurring or massive pleural effusions. There must be high index of suspicion in the high-risk groups as smokers and those with chronic respiratory diseases to avoid delay in diagnosis.

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