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Pathology Section

Advanced Stage Lung Cancer: Persisting Challenges in the Era of Molecular Targeted Therapy-Our Experience

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ABSTRACT

Introduction: Lung cancer is the pioneer among all the cancers and also the leading cause of cancer related mortality worldwide. In India unlike in western countries most patients are diagnosed at advanced stage (Stage III/Stage IV) which in turn adversely affects the patient prognosis and survival. Studying the proportion of the total lung cancer cases which will present in advanced stage and their clinical, pathological and radiological profile will give us an insight into the problem.

Aim: To know the percentage incidence of patients presenting with advanced stage lung cancer (Stage IIIB/Stage IV) and to study the clinical, pathological and radiological profile of these patients along with treatment details and follow-up.

Materials and Methods: This was a descriptive retrospective study spanning four years from January 2013 to December 2016. All patients with a histopathological diagnosis of Stage IIIB and Stage IV lung cancer, treated during this period were included. Clinical features, radiological (X-ray and CT) findings, histopathological findings including immunohistochemistry if done, treatment modality and survival were analysed based on the information collected from the medical records.

Results: Out of 82 cases diagnosed as advanced stage disease, complete clinical data was available for 67 cases which formed the material for the study. Of 67 patients, 47 were male and 20 were female forming a Male: Female ratio of 2.35:1. The mean age of the patients was 61.3 years.

Patients presented with cough (59.7%), chest pain (34.3%) dyspnoea (29.8%), weight loss (17.9%), fever (16.4%), haemoptysis (11.9%). Histologically majority were Adenocarcinoma (ADC) (35.8%) followed by Squamous Cell Carcinoma (SCC) (29.8%) small cell carcinoma (14.92%) and just one case of large cell carcinoma. Forty five cases (64.17%) presented with metastases. The most common site for metastasis was bone followed by brain. Three patients who tested positive for Epidermal Growth Factor Receptor (EGFR) mutation were treated with Erlotinib/Gefitinib. The remaining 64 cases were treated with regimens including combinations of premetrexed, platinum based compounds and etoposide. On follow-up 17 patients died during the course of the treatment.

Conclusion: High proportion of lung cancer patients present at advanced stage. This demand for public awareness programs about the smoking hazards, early symptoms and importance of early treatment.

Keywords: Adenocarcinoma, Smoking, Squamous cell carcinoma

INTRODUCTION

Globally lung cancer is the pioneer not only as the most common cancer but also as the leading cause of cancer related deaths [1]. Worldwide 1.8 million new lung cancer cases are diagnosed each year and 1.6 million deaths are being attributed to the lung cancer [2]. In India also the prevalence of lung cancer is increasing as in western countries [3]. However in India unlike in western countries most patients are diagnosed at an advanced stage (Stage III/Stage IV) which results in compromise in the patient prognosis and survival [4]. Poverty, ignorance of the early symptoms, misdiagnosis in primary healthcare levels and delayed referral to higher centers, lack of awareness about preventive measures all can contribute to the advanced stage presentation in these patients. Studies have shown that 50-70% cases of Non Small Cell Lung Cancers (NSCLCs) and up to 2/3rd of Small Cell Lung Cancers (SCLCs) usually present in advanced stage [5].

Stage at diagnosis is one of the important prognostic factors in lung cancer [4]. Knowing the demographic, clinicopathological profile of these advanced stage lung cancer patients will help us to understand the magnitude of the problem. It also highlights the importance of increasing the awareness of the problem in the society and healthcare professionals along with focus on early diagnosis and preventive measures. Our study aims to know the percentage incidence of patients presenting with advanced stage lung cancer (Stage IIIB/Stage IV) and also to study the clinical, pathological and radiological profile of these patients along with treatment details and follow-up.

MATERIALS AND METHODS

This was a time bound descriptive retrospective study spanning for four years from January 2013 to December 2016, carried out at Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, a referral center in Southern India. All patients with a histopathological diagnosis of lung cancer, staged IIIB and IV, treated during this period were included. Cases for which further clinical details could not be retrieved due to limited records available were excluded. The present study was approved by the Institutional Ethics Committee.

Clinical features, radiological (X-ray and CT) findings, histopathological findings including immunohistochemistry if done, treatment modality and survival were analysed based on the information collected from the medical records.

STATISTICAL ANALYSIS

The data was analysed by proportions, tables and graphs using Statistical Software Process Improvement (SSPI) version 20.0. Various histological features were analysed and compared using chi-square value (χ^2) and Fischer's exact test, wherever appropriate. A p-value of <0.05 was considered to be significant.

RESULTS

Age and Sex Distribution

Of the 67 patients 47 were male and 20 were female with a male:

female ratio of 2.35:1. Age of the patients ranged from 40 years to 89 years with the mean age of the patients being 61.3 years. The details of the age distribution of the patients are shown in [Table/Fig-1].

Age groups	Number of cases
40-49 years	10
50-59 years	14
60-69 years	30
70-79 years	12
80-89 years	1

[Table/Fig-1]: Distribution of advanced stage lung cancer cases among the different age groups.

Risk Factors

History of smoking was present in only 18 (26.86%) cases. About 4 cases (40%) of the small cell carcinoma patients had history of smoking. Only three patients (4.47%) had a positive family history of lung cancers. Chronic Obstructive Pulmonary Disease (COPD) was present in 5 (7.4%) cases. Three patients (4.4%) had pulmonary tuberculosis and 11 (16.4%) patients had coexisting diabetes and hypertension. One patient had past history of carcinoma of buccal mucosa. On statistical analysis past history (p=0.025) of tuberculosis/ diabetes/hypertension/COPD or any combinations of these were found to be significantly associated with lung cancer.

Clinical Presentation

The time delay between the development of symptoms and patient presentation to the clinician varied among the patients as shown in the [Table/Fig-2]. Most of the patients (28 cases: 41.8%) presented within a month of development of the symptoms. Nine (13.4%) patients presented later than 3 months of development of the disease.

Time delay between symptoms and patient presentation	Number of cases
Below 1 month	28 (41.8%)
1-2 months	10 (14.9%)
1-3 months	20 (29.8%)
Above 3 months	9 (13.4%)

[Table/Fig-2]: Showing the time delay between the development of symptoms and patient presentation.

Patients presented with various symptoms which included cough (40 cases: 59.7%), chest pain (23 cases: 34.32%), dyspnoea (20 cases: 29.8%), weight loss (12 cases: 17.9%), fever (11 cases: 16.4%), haemoptysis (8 cases: 11.9%). All these symptoms were strongly associated with advanced stage lung cancer (p-value=0.001).

The most common physical sign elicited was reduced breath sounds on the affected side and bronchial breath sounds on auscultation (57.3%).

Radiological Findings

Of 67 cases 46 (68.65%) patients had got an X-ray done. Fifty four percent (36 cases) of the patients got a CT scan done. On radiological evaluation mass lesion was identified in 35 cases, pleural effusion was seen in 16 cases and collapse/consolidation were seen in 12 cases. On CT scan 9 cases showed single/multiple lymph node enlargement. The details of the radiologic findings are shown in [Table/Fig-3]. On statistical analysis CT scan detection (p=0.001) was more significant.

Histopathological Types of Tumours

Out of 67 cases the majority was ADC (24 cases: 35.8%) followed by SCC (20 cases: 29.8%), small cell carcinoma (10 cases: 14.92%) and just one case of large cell carcinoma [Table/Fig-4]. The distribution of the various clinical symptoms in different histological subtypes is given in [Table/Fig-5].

X-ray/CT	SCC	ADC	Small cell	Non small cell	Large cell	Total
Mass	17	12	3	2	1	35
Collapse/ consolidation	4	6	2	-	-	12
Pleural effusion	3	7	1	5	-	16
Laterality						
Right	8	6	3	3	1	21
Left	6	10	4	3	-	23
Both	-	-	-	2	-	2

[Table/Fig-3]: Showing radiological features and laterality in different histopathological types of lung cancer.
SCC: Squamous cell carcinoma; ADC: Adenocarcinoma; SCLC: Small cell lung carinoma; LCLC: Large cell lung carcinima; NOS: No special type on histology

Histological type	N (/67)	percentage
Adenocarcinoma	24	35.8%
Squamous cell carcinoma	20	29.8%
Large cell carcinoma	1	1.4%
Small cell carcinoma	10	14.92%
Non small cell carcinomas (No special type)	12	17.91%

[Table/Fig-4]: Showing percentage distribution of various histological types.

Symptoms	SCC	ADC	LCLC	SCLC	NOS	Total	Percentage
Cough	12	17	-	9	2	40	59.7%
Dyspnoea	4	11	-	5	-	20	29.8%
Chest pain	5	11	1	1	5	23	34.3%
Haemoptysis	4	1	-	3	-	8	11.9%
Weight loss	5	3	-	4	-	12	17.9%
Fever	3	5	-	2	1	11	16.4%

[Table/Fig-5]: Showing the clinical symptoms of patients in various histological subtypes.
SCC: Squamous cell carcinoma; ADC: Adenocarcinoma; SCLC: Small cell lung carcinoma; LCLC: Large cell lung carcinoma; NOS: No special type on histology

Distant Metastasis

Out of the 67 cases 45 (64.17%) cases presented with distant metastases at the time of diagnosis. The most common site for distant metastasis was bone (16 cases) followed by brain (13 cases), adrenals (9 cases) and liver 7 cases. Adenocarcinoma was the most common to metastasise (14 cases) followed by SCC (10 cases) and small cell carcinoma (5 cases). Out of 16 cases which had pleural effusion malignant tumour cells on cytology were seen in 9 cases [Table/Fig-6].

Site	SCC	ADC	Small cell	NOS	Total
Brain	5	4	1	3	13
Bone	4	7	1	4	16
Liver	2	3	-	2	7
Adrenal	3	2	3	1	9
Pleural effusion	3	4	-	2	9

[Table/Fig-6]: Various sites of metastasis in different histological types of lung cancer at presentation.

Cytology Details

Of 67 cases cytological evaluation was done in 25 cases. Two cases were reported negative on cytology. In the remaining 23 cases, Trans Bronchial Needle Aspiration (TBNA) was positive in 12 cases, broncho alveolar lavage was positive in 13 cases and bronchial brushings showed tumour positivity in ten cases. Cytology was not done in the remaining 42 cases. Histological confirmation was done in all the cases.

Treatment and Follow-up

Out of 67 cases eight cases were evaluated for EGFR mutations. In that 3 cases had EGFR mutation and treated with Erlotinib/Gefitinib. The remaining 64 cases were treated with regimens including combinations of premetrexed, platinum based compounds and etoposide. Patients were followed up from 6 months to 4 years. Seventeen patients died during the course of the treatment. Twelve patients were lost to follow-up. The remaining patients are on palliative maintenance therapy.

DISCUSSION

Lung cancer is the most common cancer and also the deadliest of all as it presents in advanced stage. Over the world 13% of newly diagnosed cancers and 19% of cancer related deaths are attributed to lung cancer. In India also lung cancer accounts for 6.9% of total cancer cases and 9.3% of all cancer related deaths [6]. In spite of advancement in diagnostic modalities and molecular treatments the 5-year survival rate of lung cancer is minimal with approximately 15% in developed countries and only 5% in developing countries [7].

In present study advanced stage lung cancer accounted for 54.3% of the total lung cancers. Study done by Murali AN et al., also show majority of lung cancer patients are diagnosed in the advanced stage in India [8]. Ignorance of the clinical symptoms by the patient, low index of clinical suspicion, empirical therapy in primary healthcare centers, financial constraints for diagnostic facilities, treating a common disease like COPD or tuberculosis first to see the response are some of the factors responsible for the delay in the diagnosis [9].

As in most other studies conducted on lung cancer in India [10-12]. present study also shows that males are affected more than females with the M:F ratio of 2.35:1 and this is generally attributable to the increased incidence of smoking, outdoor air pollution exposure in men. Worldwide about 85% of lung cancers in men and 47% in women are because of tobacco smoking [13]. In contrast history of smoking was present in only 26.86% of the patients in present study. This contradicts the statement that lung cancer is exclusively a smoker's disease [5]. The WHO (World Health Organisation) estimated that 25% of the lung cancer worldwide occurs in never smokers [14]. These are more common in females and more often associated with EGFR mutations and mostly adenocarcinomas [14]. In present study ADC (38.8%) was the most common tumour in females.

Hereditary factors in carcinogenesis of lung cancer are not yet established. We had only 4.47% of patients with positive family history. Mandal SK et al., also found only 1.1% of patients with positive past history for lung cancer [5].

Developmental risk of lung cancer in patients suffering from COPD, bronchial asthma and emphysema are very well known [15]. Long standing inflammation in these processes has been attributed to the carcinogenesis [16]. We found coexisting COPD in 7.46% of patients. In present study 4.4% (3 cases) of the patients had preexisting tuberculosis. All these patients had SCC. Mandal SK et al., also observed this in his study that SCC was most common histological type in tuberculosis patients [5]. Yu YH et al., in his study observed the 11 times higher risk of lung cancer in tuberculosis patients than in non tuberculosis patients [16].

Histologically ADC followed by SCC formed the predominant histological type in present study. Many previous studies highlighted that SCC is the most common in India [5,10,11]. In contrary to this, recent studies by Noronha V et al., Malik PS et al., reported ADC as the predominant type over SCC in India [17,18]. ADC was mostly seen in the elderly age group (above 60 years). SCLC was found mostly in 7th decade.

Though traditionally smoking has been strongly condemned for causation of SCC and SCLC the rising incidence of adenocarcinoma in smokers in western countries is attributed to smoking of filtered cigarettes [14]. Mohan A et al., in his study found that 84% of ADC patients were either current or previous smokers [3]. In present study also ADC was the common cancer among smokers (33.3%) followed by SCC and SCLC (22.2% each). However in Indian scenario this may be because of the additional factors like air pollution, industrial hazards etc than due to filtered cigarettes which is not very popular in our country. In addition to this, Kirmani N et al., in his study about occupational and environmental carcinogens in lung cancer found out that increased exposure to pesticides along with smoking habit in agricultural workers has increased association with lung cancer than smoking alone [19].

The most common radiological presentation seen in present study was mass followed by combined presentation i.e., collapse-consolidation and pleural effusion; similar to reports published in Indian literature [5,10,20].

More than half of the patients presented with distant metastasis to bone (64.17%) which was followed by brain, adrenal, malignant pleural effusion etc. ADC had maximum metastasis to the bones. Malik PS et al., also reported that bone as the most common site of metastasis for non small cell cancers [18]. Mandal SK et al., differs as he found brain as most common metastatic site in his study [5].

In present study only 12 cases were diagnosed on FNA, 13 cases on bronchoalveolar lavage and 10 cases were detected on bronchial brushings as the preliminary diagnosis. Though various cytological examinations are used as preliminary aid in early diagnosis, diagnostic yield is not up to the mark and combined modalities may be more effective than a single approach. Biopsy with histopathological evaluation is mandatory for definitive histopathological typing in doubtful cytological cases [6].

Though all the patients with diagnosis of non-small cell lung carcinoma were advised for testing EGFR mutations, it was done in only 8 cases. In that 3 cases were positive for EGFR, out of which 2 were females. Of 3 cases 2 were ADC and one was poorly differentiated SCC. These patients received erlotinib. They responded well and on maintenance therapy. Others received premetrexed, platinum, paclitaxel, etoposide based combination chemotherapy.

Even with advancement in thoracic surgery, radiation therapy chemotherapy and molecular therapy the outlook is very poor for these patients. The 5 year survival rate is only 4% for those with distant metastasis [21]. In present study 17 patients (25.37%) succumbed to the disease within a year of the diagnosis.

LIMITATION

It was a retrospective study done based on the information collected by the medical records. So exact reasons because of which there was delay in the diagnosis of lung cancer could not be studied. A prospective study with direct patient interaction would be more appropriate to study the correlation between various causative factors and delay in the cancer diagnosis. In future studies with prospective design occupation can be definitely included.

CONCLUSION

Lung cancer is still a major challenge to our society. High proportion of lung cancer patients present at advanced stage. So this demands for more programs to create awareness among the people regarding the smoking hazards, early symptoms and importance of

early treatment. Community oriented measures should be taken to control air pollution, pesticide exposure, and industrial carcinogens. More research into molecular screening methods for early detection of lung cancer in high risk people may give some solution for this challenge in future days.

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