Original research article

Observational study at tertiary care hospital regarding clinical profile of lung cancer and its paraneoplastic manifestations

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 Abstract
Lung cancer is a common cause of mortality in Indian population amongst cancer causes. Risk factor identification and past medical comorbidities are predisposing factors for occurrence of carcinoma. Identification of other symptoms associated with endogenous hormone release could have positive outcome by early diagnosis of lung cancer.
Method: This prospective observational study was conducted in 18-80 year patients of armed forces hospital who met the inclusion criteria. Clinical presentation, all risk factors were identified, paraneoplastic manifestations noted and managed.
Results: Mean age was 61.5 years, 48 males and 12 females with associated risk factor of smoking intake identified. Cough (58%) and chest pain (18%) were main presenting symptoms. Cachexia, hypercalcemia, SIADH and superior mesenteric artery thrombosis were paraneoplastic manifestations noted.
Conclusion: Delayed diagnosis due to nonspecific symptoms are responsible for worrisome outcome of lung cancer. Vigilant diagnosis of paraneoplastic manifestations can help in early diagnosis of primary carcinoma and better outcome.
Keywords: Lung carcinoma, Cachexia, hypercalcemia, Thrombosis

Introduction
Lung cancer is a malignant tumour of air passages and parenchyma with high mortality. Nonsmall cell carcinoma is the most common type with further subtypes such as squamous cell, adenocarcinoma or large cell carcinoma. Adenocarcinoma arise from small bronchioles or alveolar epithelial cells in the periphery of lung with characteristic glandular microscopic structures and is the most common type with occurrence in nonsmokers and females [1].
Risk factors for lung cancer includes active smoking in around 85% of new cases [2]. Prevalence of smoking is high around 20% of patients at risk of cancer [3]. Environmental factors such as wood, dust, radon and asbestos exposure for prolonged duration has a positive correlation for carcinoma lung [4]. Family history have a positive correlation for lung cancer with one first degree relative as a diagnosed case which shows genetic factors as a risk factor. Genetic markers include micro RNA, cytokines blocked micronucleus assay, p53 mutation and retinoblastoma gene mutation [5].
The common lung diseases such as pneumonia, chronic bronchitis, COPD, emphysema, tuberculosis can be predisposing risk factor by damaging parenchymal cells followed by mutations [6]. Presence of these comorbidities have also elevated the risk in nonsmokers [7]. Incidence of lung cancer increases by age with higher mortality in elderly as surgical treatment becomes a limiting factor. Major concern for carcinoma lung is late stage diagnosis with worst survival rates following other two types such as pancreatic and liver carcinoma [8].

Material and Methods
This prospective observational study was conducted in the tertiary health care centre of Armed Forces Chandimandir, panchkula. All male and female between 18-80 year of age. All study subjects meeting inclusion and exclusion criteria were taken over 1 year period. The inclusion criteria included all patients attending OPD or IPD irrespective of their age and sex presenting with risk factors and clinical features of lung cancer willing to comply with study and ability to provide written informed consent prior to procedure. The diagnosis was biopsy proven cases of lung cancer. The patients with comorbidities like hypertension, diabetes mellitus, hypothyroidism, chronic obstructive lung disease, interstitial lung disease were noted and included. The exclusion criteria were patient not willing for participation,

critically ill patient on ventilator support on admission who were unable to provide consent. Oral and written information about the study in english and hindi were provided and written informed consent was obtained from each subject prior to participation in the study. It was made clear that study participants can withdraw from study at any time and confidentiality was maintained at all times during and after study.

After explained informed consent, complete history taking and clinical examination of patient done. The socio-demographic history, family history, smoking history (type and number smoked, duration of smoking, exposure to ETS or biomass fuel) and past history were recorded. The patients had radiological evaluation with chest X-ray posterior anterior view and contrast enhanced computed tomography scan of the thorax and upper abdomen. The diagnosis was established by various procedures including CT-guided transthoracic fine needle aspiration/ biopsy for peripheral tumours, fiberoptic bronchoscopic wash, brush or biopsy and transbronchial needle aspiration for central tumours or closed pleural or thoracoscopic guided biopsy for patients presenting with pleural effusions. Ultrasound of the whole abdomen and whole body Positron Emission Tomography CT done for all patients as part of metastatic work up. Sputum smear examination for acid fast bacilli (AFB), CBNAAT and cytological evaluation for malignant cells were sent for patients wherever indicated. Blood sampling for complete haemogram and biochemical tests like liver function tests, renal function tests, Serum electrolytes and lactate Dehydrogenase done. For patients with pleural effusion, pleural fluid sent for cell counts, biochemistry, cytology and adenosinedeaminase (ADA) levels. Paraneoplastic association like Hypercalcemia, Hypoglycemia, Syndrome of Inappropriate ADH Secretion, Cushing syndrome, Acromegaly, Pulmonary carcinoid, Myasthenia Gravis syndrome, Lambert Eaten syndrome, Subacute Cerebellar degeneration, Subacute Sensory neuropathy, Venous Thromboembolism, Hypertrophic Pulmonary Osteoarthropathy, Nephrotic syndrome were noted and included.

Results

A total of 60 subjects meeting the inclusion and exclusion criteria are included in the final analysis with a mean age of 61.5 years, with 80% males and 20% females (Figure1). Risk factor assessment showed majority to have direct or indirect smoking. Haemodynamic monitoring were done and patients were managed according to presentation (Figure 2,3). Majority patients had cough and anorexia as presenting symptoms. Chest pain due to involvement of pleura or underlying cardiac condition was seen in 18% (Table 1). The histological diagnosis in our study group was adenocarcinoma 45%, squamous cell carcinoma 35%, carcinoid 1.6%, small cell carcinoma 18.3% for the complete cohort (Figure 4). On PET scan for visceral metastasis, 5% had liver metastasis, 10% had adrenal mets, 11.6% brain metastasis, 10%pleural metastasis, 38.33% had lymph node metastasis (Figure 5). Right lower lobe (13) involvement followed by left lower lobe (12) involvement was seen in maximum patients. Associated anaemia was found in 23% patients. Lymphadenopathy was observable in 38% (Figure 6). Cachexia was major paraneoplastic manifestation in 28%, 5% had hypercalcemia, 1.6% had cushing syndrome, 1.6% SIADH, 1.6% superior mesenteric artery thrombosis cutaneous lesions in 3.3% (Figure 7).

Discussion

Clinical identification of lung cancer patients among high risk population can be an edge for early intervention and better prognosis of patients. Paraneoplastic manifestations are to be identified through detailed examination and investigation so as timely management is possible. The current study is aimed at determining the clinical features, histologic types, metastatic lesions and paraneoplastic manifestation in lung cancer at a Tertiary care centre.

Geographic prevalence varies according to pattern of smoking and high trends seen in Delhi, Chennai and bangalore in both sexes [9]. In 2021, around 1.8 million cases were reported [10]. There are reported age adjusted rate around 28.3 in males and 28.7 per lac in females [11]. The mean age presentation in our study was around 65 years with majority male (80%) presentation.

Over the last decade, median survival of 11months have increased to an overall 5 year survival of 17.8% [12]. Mild cough have been the main nonspecific symptom which could be easily missed at an early stage. The low 5-year survival rate (16%) is mainly due to late diagnosis with metastasized disease at time of diagnosis and aggressive behaviour of the tumour [13].

Cachexia syndrome due to release of tumour necrosis factor is a paraneoplastic manifestation with unfavourable prognosis and affects majority of patients with advanced cancer. TNF alpha known as cachectin is most common cytokine in cachexia through NF-KB pathway induced anorexia and skeletal muscle wasting. IL-1 and interferon gamma promotes muscle wasting in synergism with TNF alpha. It was major paraneoplastic manifestation in our study. There is decrease in insulin like growth factor and development of insulin resistance involved in anabolism [14].

Consistent with previous studies, hypercalcemia occurred most commonly in the NSCLC squamous subtype, compared to the SCLC explained by ectopic parathyroid hormone-related protein (PTHrP) production by the NSCLC squamous tumour [15].

Tumour cells are known to have procoagulant properties by activation of clotting cascade along platelet,

neutrophil, thrombin and fibrin stimulation. Thromboembolism present in majority of patients as painful edema of superior and inferior extremities as observed by trousseau *et al* [16]. Arterial thrombosis have a rare incidence of 0.25% presenting mostly as acute myocardial infarction or ischaemic stroke in cancer patients [17]. Other arterial thrombosis have rare reported incidence of 0.2% more with prostate cancer followed by lung cancer. One patient presented to us with abdominal pain diagnosed as superior mesenteric artery thrombosis which was managed with low molecular weight heparin. Major peripheral arterial embolism have been reported following lung tumour resection [18] but our patient had no primary diagnosis of cancer lung. Similar rare presentation of case of bowel ischaemia requiring resection have been reported by Togo *et al* with primary cancer found to be lung cancer [19]. Later on in course of disease she developed middle cerebral artery thrombosis stroke leading to hemiplegia after one month of hospitalisation.

According to NLST criteria, one out of ten smoker (11.6% of men and 9.6% of women) and one out of four smokers (24.6% of men and 22.4% of women) according to NELSON criteria are currently at high risk of lung cancer in the Europe. Majority patients in our study were found to have associated smoking as underlying risk factor. The National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer–specific mortality and a 6.7% reduction in all-cause mortality can be achieved by using low-dose helical computed tomography in high-risk individuals [20]. Screening of high risk population can help in early stage diagnosis and reducing mortality. Thorough clinical evaluation of high risk individuals could be helpful in early diagnosis and reducing morbidity in patients. Clinical suspicion for paraneoplastic manifestations due to endogenous hormonal changes could be helpful in early diagnosis of associated stage of carcinoma and appropriate timely management.

Conclusion

Implementation of screening programmes in high risk population can help in diagnosis of early stage lung carcinoma in asymptomatic patients. Risk factor identification and population awareness could be helpful in lifestyle modification and prevention of carcinoma. Extensive clinical workup of paraneoplastic manifestations can help to diagnose primary carcinoma at early stage and its appropriate management can help reduce morbidity in patients of lung carcinoma.
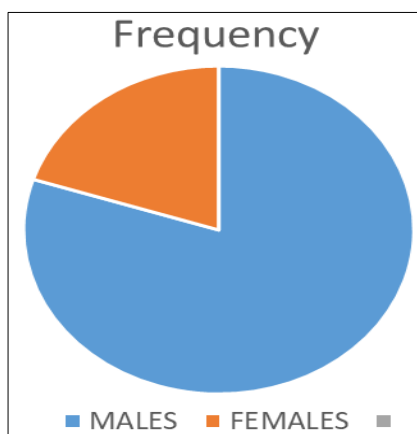

Fig 1: Sex distribution of carcinoma lung

Table 1: Clinical presentation of patients

CLINICAL FEATURES	FREQUENCY n-(60)
Cough	58%
Sputum	28%
Chest pain	18%
Hemoptysis	13%
Dyspnoea	25%
Hoarseness of voice	11%
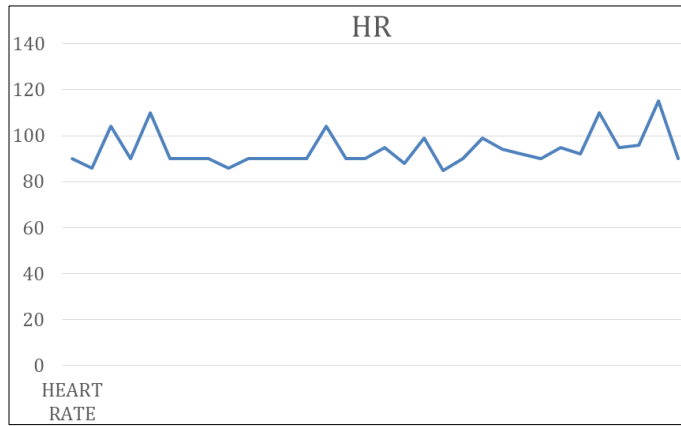
Fig 2

Fig 3

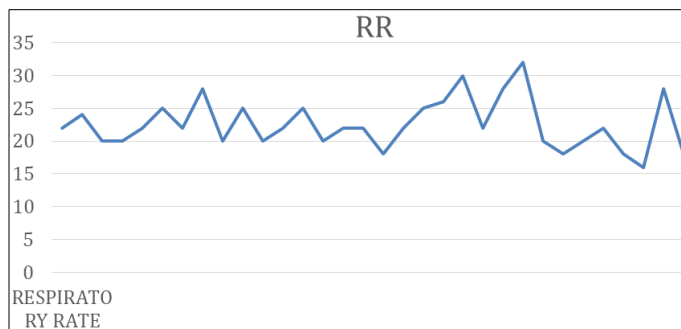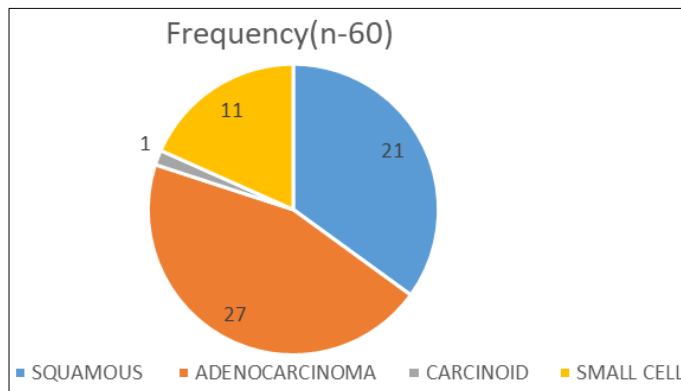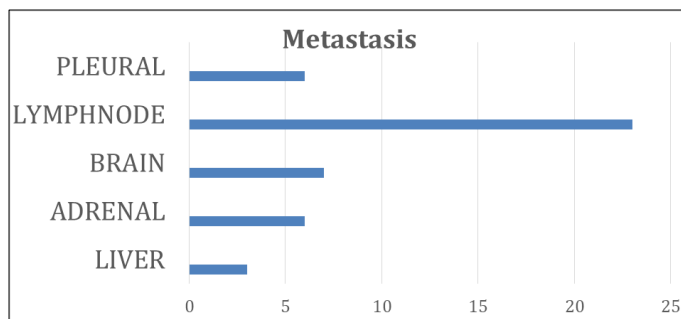**Fig 4:** Type of carcinoma

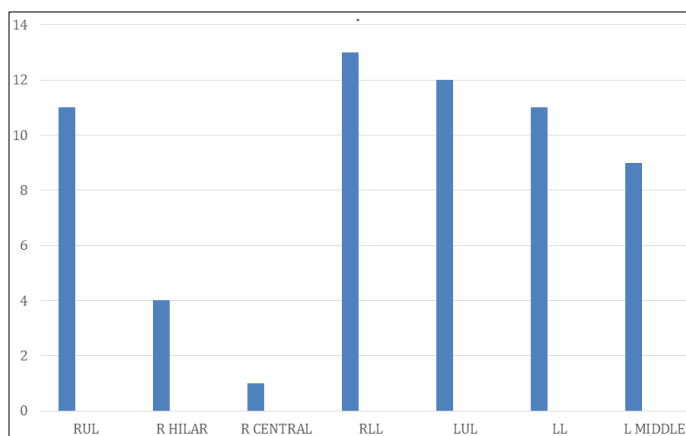**Fig 5:** Distant metastasis of primar lung cancer

Fig 6: Primary site of lung carcinoma

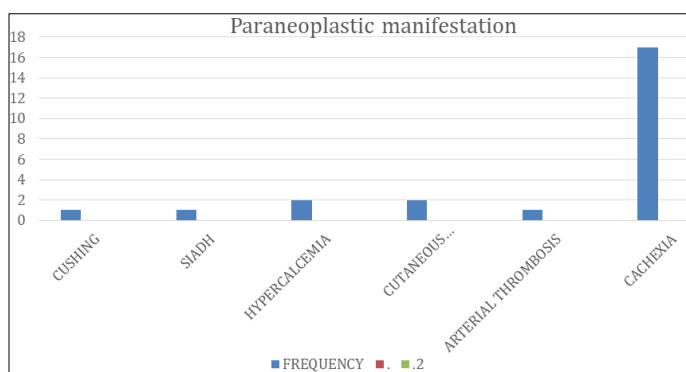**Fig 7:** Paraneoplastic manifestations

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