RESEARCH ARTICLE

Clinico-pathology of Lung Cancer in a Regional Cancer Center in Northeastern India

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Abstract

Background: Globally, there have been important changes in trends amongst gender, histology and smoking patterns of lung cancer cases. Materials and Methods: This retrospective study was conducted on 466 patients with lung cancer who were registered in Regional Cancer Center, Regional Institute of Medical Sciences, Manipur from January 2008 to December 2012. Results: Most were more than 60 years of age (67.8%) with a male: female ratio of 1.09:1. Some 78.8% of patients were chronic smokers with male smoker to female smoker ratio of 1.43:1. Consumption of alcohol was found in 29.4%, both smoking and alcohol in 27.5%, betel nut chewing in 37.9% and tobacco chewing in 25.3%. A history of tuberculosis was present in 16.3% of patients. The most frequent symptom was coughing (36.6%) and most common radiological presentation was a mass lesion (70%). Most of the patients had primary lung cancer in the right lung (60.3%). The most common histological subtype was squamous cell carcinoma (49.1%), also in the 40-60 year age group (45.9%), more than 60 year age group (51.6%), males (58.1%) and females (41.8%). As many as 91.9% of squamous cell carcinoma patients had a history of smoking. About 32.5% of patients had distant metastasis at presentation with brain (23.8%) and positive malignant cells in pleural effusions (23.1%) as common sites. The majority of patients were in stage III (34.4%), stage IV (32.5%) and stage II (30.2%). Conclusions: Our analysis suggests that the gender gap has been narrowed such that about half of the patients diagnosed with lung cancer are women in this part of India. This alarming rise in female incidence is mainly attributed to an increased smoking pattern. Squamous cell carcinoma still remains the commonest histological subtype. Most of the patients were elderly aged and presented at locally or distantly advanced stages.

Keywords: Lung cancer - smoking - women - squamous cell carcinoma - northeast India

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Introduction

Lung cancer is mainly a disease of modern era and probably one of the most important health problems today. Globally, there have been important changes in incidence trends amongst men and women, histology and smoking patterns. According to National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 2010 report, lung cancer is the second most common cancer worldwide, in both males (accounting 15% of all cancer) and females (accounting 14% of all cancer) and it is the most common cause of cancer death worldwide (Longo, 2012). Compared to western population, epidemiological study shows there are increased prevalence of lung cancer in Indian population (Jagadish et al., 2009). In India, approximately 63,000 new lung cancer cases are reported each year (Ganesh et al., 2011). The latest National Cancer Registry programme (NCRP) 2010, has reported the highest age-adjusted incidence rates (AARs) of lung cancer in north-eastern region of India: Aizawl district (18.2/100000) followed by Imphal west district (18/100000) for males and AAR of 26.2/100000 in Aizawl district and 18/100000 in Imphal west district for females.

Based on our Hospital Based Cancer Registry (HBCR) 2012, lung cancer is the most common cancer in both males (19.7% of all cases) and females (15.1% of all cases). Lung cancer has been the most common malignancy in both males and females in our state for the past decade contributing approximately 16-20% of all malignancies. Lung cancer is almost exclusively a smoker's disease and both incidence and mortality are directly related to the degree of cigarette use that occurs in a population (Wingo et al., 1999). However, histopathological cell types may vary with the changes of social and other environmental factors (Becket, 1993). A concrete study on demographic pattern, clinico–radiological presentation, pathology characteristics with smoking and other forms of tobacco intake and alcohol consumption has not been reported till date from this region to the best of our knowledge.

We undertook this study to analyse the demographic pattern, clinico-radiological presentation, pathological characteristics and stage at presentation of lung cancer at

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Regional Cancer Centre, Regional Institute of Medical Sciences (RIMS) situated in Imphal, Manipur state, is the biggest referral Centre for the neighbouring North eastern states in India i.e. Nagaland, Mizoram, and bordering Myanmar.

Materials and Methods

We conducted a retrospective study using data base of 466 patients of primary lung cancer diagnosed in indoor and outdoor of the department of radiation therapy at Regional Cancer Centre, RIMS, Manipur, India from January 2008 to December 2012. All these patients were diagnosed on clinical, radiological and bronchoscopic examination. The diagnosis was confirmed pathologically in 454 (97.4%) cases by image guidance cytology or biopsy, bronchio-alveolar lavage and/or bronchoscopy guided biopsy and classified according to WHO histological classification of lung cancer (Travis, 2004). In the other 12 (2.6%) cases in whom the histo/cytological positivity could not obtained, clinico-radiological and endoscopic findings suggestive of malignancy were considered essential for inclusion in this study. The cases having doubts about primary origin, incomplete data or metastasis to the lung from other primary sites were excluded. Restaging was done according to AJCC staging system 7th edition based on the available clinical and radiological findings. The clinical records of the patients were reviewed in relation with age, sex, family history of lung cancer, medical history for chronic obstructive pulmonary disorder (COPD), bronchial asthma and emphysema, history of tuberculosis infection, smoking habits, consumption of alcohol, betel nut and tobacco chewing, clinical presentation, radiographic finding, pathological report and TNM stage. However, no quantitative relation of lung cancer and the duration and number of cigarette smoking was done. Due to lack of information on indoor pollution and occupational risk for lung cancer was not studied. Descriptive statistics was used for describing the data using SPSS version 20 and results were presented in percentage and simple frequency.

An approval from the Institutional Ethics Committee for research involving human subjects was obtained before the study was conducted. Confidentiality of the patient's identity was maintained.

Results

The study included 466 patients with a male to female ratio of 1.09:1. Distribution of age varied from 39 to 85 years. Maximum patients were found in the more than 60 years age group (67.8%) followed by 40-60 years (29.4%) and least in less than 40 years (2.8%). Nearly 73.9% of male and 61.3% of the female patients had age more than 60 years. Of 466 patients, family history of lung cancer was found in 5 (1.1%) patients. The medical history of COPD, bronchial asthma and emphysema was present in 6 (1.3%) patients. Most of the patients were chronic cigarette

Table 1. Histological Distribution and Demographic Factors

Variables		Squamous cell carcinoma	Adenocarcinoma	Small cell lung carcinoma	Undifferentiated carcinoma	Large cell carcinoma	Total (n=454)
Age (years)	<40	3 (1.3%)	7 (5%)	3 (4.4%)	0	0	13 (2.8%)
	40-60	61 (27.3%)	48 (34.3%)	20 (29.8%)	3 (42.8%)	1 (5.8%)	133 (29.2%)
	>60	159 (71.4%)	85 (60.7%)	44 (65.8%)	4 (57.2%)	16 (94.2%)	308 (68%)
	Total	223 (100%)	140 (100%)	67 (100%)	7 (100%)	17 (100%)	454 (100%)
Sex	Male	133 (58.1%)	60 (25.1%)	30 (12.5%)	3 (1.2%)	13 (3.1%)	239 (100%)
	Female	90 (41.8%)	80 (37.2%)	37 (17.2%)	4 (1.9%)	4 (1.9%)	215 (100%)
Smoking	Present	205 (91.9%	79 (56.4%)	52 (77.6%)	5 (71.4%)	16 (94.1%)	357 (78.7%)
	Absent	18 (8.1%)	61 (43.4%)	15 (22.4%)	2 (28.6%)	1 (5.9%)	97 (21.3%)
Alcohol	Present	72 (32.3%)	30 (21.4%)	23 (34.3%)	1 (14.3%)	6 (35.2%)	132 (29%)
	Absent	15 (67.7%)	110 (78.6%)	44 (65.7%)	6 (85.7%)	11 (64.8%)	322 (71%)
Both smoking and alcohol	Yes	208 (93.3%)	83 (59.3%)	53 (79.1%)	5 (71.4%)	16 (94.1%)	365 (80.4%)
	No	15 (6.7%)	57 (40.7%)	14 (20.9%)	2 (28.6%)	1 (5.9%)	89 (19.6%)
History of Tuberculosis	Yes	40 (17.9%)	23 (16.4%)	8 (11.9%)	2 (28.5%)	3 (17.6%)	76 (16.7%)
	No	183 (82.1%)	117 (83.6%)	59 (88.1%)	5 (71.5%)	14 (82.4%)	378 (83.3%)

Table 2. Histological Distribution and Clinico-radiological Presentations

Variables		Squamous cell carcinoma	Adenocarcinoma	Small cell lung carcinoma	Undifferentiated carcinoma	Large cell carcinoma	Total (n=454)
Symptoms	Cough	79 (47.9%)	55 (33.3%)	22 (13.3%)	4 (2.4%)	5 (3%)	165 (100%)
	Dyspnoea	18 (33.3%)	25 (46.3%)	5 (9.3%)	1 (1.9%)	5 (9.3%)	54 (100%)
	Chest pain	19 (52.8%)	10 (27.8%)	6 (16.7)	0	1 (2.8%)	36 (100%)
	Haemoptysis	24 (77.4%)	2 (6.5%)	2 (6.5%)	0	3 (9.6%)	31 (100%)
	SVC syndrome	3 (27.3%)	3 (27.3%)	5 (45.4%)	0	0	11 (100%)
	Combined	80 (50.9%)	45 (28.7%)	27 (17.2%)	2 (1.3%)	3 (1.9%)	157 (100%)
Radiological presentation	Mass	167 (52.5%)	82 (25.8%)	51 (16%)	4 (1.3%)	14 (4.4%)	318 (100%)
	Collapse-consolidation	17 (56.7%)	9 (30%)	3 (10%)	0	1 (3.3%)	30 (100%)
	Pleural effusion	1 (7.1%)	12 (85.7%)	1 (7.1%)	0	0	14 (100%)
	Combined	38 (42.2%)	37 (41.1%)	12 (13.3%)	3 (3.3%)	2 (2.2%)	90 (100%)
Site of primary lung cancer	Right lung	138 (50.5%)	88 (32.2%)	34 (12.4%)	5 (1.8%)	8 (2.9%)	273 (100%)
	Left lung	85 (47.7%)	52 (29.2%)	30 (16.8%)	2 (1.1%)	9 (5.1%)	178 (100%)
	Both lungs	0	0	3 (100%)	0	0	3 (100%)

smokers (78.8%). The ratio of smokers to non-smokers was 3.7:1 and the ratio of male smokers to female smokers ratio was 1.43:1. The history of tuberculosis infection was found in 76 (16.3%) patients. The history of alcohol consumption was found in 137 (29.4%) patients with male: female ratio of 11.4:1. The combined smoking and alcohol consumption was seen in 128 (27.5%) patients, mainly male patients. The history of betel nut intake was seen in 177 (38%) patients with male: female ratio of 1.3:1. Tobacco chewing habits was found in 118 (25.3%) patients with male: female ratio of 2.2:1. Cough alone was the most common symptom found in (35.8%) patients followed by combined presentation (34.3%) invariably including cough, chest pain, dyspnoea, fever and others, dyspnoea (11.8%), chest pain (7.9%), haemoptysis (6.9%) and superior vena cava syndrome (SVCS) (2.4%). The most common radiological presentation was mass (70%) followed by combined presentation (20.3%), collapse-consolidation (6.7) and pleural effusion (3%). Right lung (60.3%) was most common site of primary site, followed by left lung (39.1%) and both lung (0.6%). Out of 454 histologically confirmed diagnoses, 223(49.1%) patients had squamous cell carcinoma, adenocarcinoma (30.8%), small cell lung carcinoma (14.8%), large cell carcinoma (3.7%) and undifferentiated carcinoma (1.5%). For less than 40 year, adenocarcinoma (53.8%) was commonest and for 40-60 years and more than 60 years age group, squamous cell carcinoma was commonest representing 45.9% and 51.6% respectively. Squamous cell carcinoma was commonest histological finding both in male (58.1%) and female (41.8%) patients, followed by adenocarcinoma seen in 25.1% male and 37.2% female patients. The commonest histology in patients with history of tuberculosis infection was squamous cell carcinoma (52.6%) and adenocarcinoma (30.2%). Nearly 91.9% of squamous cell carcinoma patients had history of smoking. The distant metastasis at presentation was seen in 151 (32.5%) patients with commonest site as brain (23.8%), followed by positive malignant cell in pleural effusion (23.1%), bone (18.4%), liver (15.7%), contralateral lung (9.5%), adrenal gland (1.3%) and multiple sites (8.1%). Most of the patients (63.9%) presented with T3 stage, followed by T2 stage (16.7%), T4 stage (15.4%) and T1 stage (4%). Among N staging, N0 (56.3%) was found to be commonest followed by N3 (22.4%), N2 (14.8%) and N1 (6.4%). Most of the patients had advanced stages at presentation with stage III (34.4%), stage IV (32.5%), stage II (30.2%) and stage I (2.9%).

Discussion

Although primary lung cancer in India was rare in early part of 20th century (Nath and Grewal, 1935), later an increasing trend in its incidence was recognised by Vishwanathan et al. (1962), who analysed 1570 cases admitted during 1955-59 in several teaching hospitals of Delhi, Lucknow, Calcutta, Mumbai and Chennai. Now with increasing prevalence of smoking, lung cancer has reached an epidemic proportion in India (Bahera and Balamugesh, 2004). Lung cancer remains a major health problem in Manipur state (18% of all cancers) and other neighbouring states like Mizoram and Nagaland. In our present study, most of the patients of primary lung cancer belonged to more than 60 years age group with male to female ratio of 1.09:1 signifying it as disease of old age nearly equally prevalent in both sexes in this region. Our results are contrary to other Indian studies that reported male to female ratio to vary from 5.76:1 to 6.7:1 (Bahera and Balamugesh, 2004), 7.9:1 (Rajasekaran et al., 1993) and 8.4:1 (Tippanna et al., 1999). However, most studies in other parts of the globe that have reported that the incidence of lung cancer among women is on rise (Bal, 2001; Charles, 1991). The dramatic increase of lung cancer among women all over the world is attributed to increase in cigarette consumption that is a well known major risk factor for the development of lung cancer (Peter, 1993; Bal, 2001; Mghfoor and Perry, 2005). In the current study, 88.5% of male patients and 68% of the female patients had history of smoking with male smoker to female smoker ratio of 1.43:1. Globally, an estimated 85% of lung cancers in men and 47% in women are attributable to tobacco smoking (Peto, 1994). Majority were chronic cigarette smoker. As per our HBCR 2012, lung cancer ranks first among both males with 16.4% and females with 14% of all tobacco related cancers indicating lung cancer exclusively a smoker's disease. The increased prevalence of lung cancer in Manipur state is mainly due to high smoking pattern in both male and female. The traditional use of unventilated coal-fuelled stoves and fire wood for cooking, fumes for frying vegetables, less ventilated house, less electricity supply and second hand smoke may contribute significantly for indoor pollution risk for lung cancer especially in females of this region. The proportion of lung cancer incidence among the non-smokers is 21.2%, which correlates with other studies in India (Rajasekaran et al., 1993; Gupta et al., 1998; Prasad et al., 2004). Although the role of hereditary factors in lung carcinogenesis is not well established, in our study only

Table 3. Histological Presentation and Site of Metastasis at Presentation

Variables	Squamous cell carcinoma	Adenocarcinoma	Small cell lung carcinoma	Undifferentiated carcinoma	Large cell carcinoma	Total (n=454)
Brain	16 (32%)	11 (15.9%)	9 (34.6%)	0	0	36 (23.8%)
Positive malignant cell in pleural effusion	5 (10%)	26 (37.7%)	2 (7.7%)	0	2 (40%)	35 (23.1%)
Bone	10 (20%)	10 (14.5%)	7 (27%)	0	1 (20%)	28 (18.4%)
Liver	9 (18%)	11 (15.9%)	4 (15.4%)	0	0	24 (15.7%)
Contralateral lung	6 (12%)	6 (8.7%)	1 (3.8%)	0	1 (20%)	14 (9.5%)
Adrenal gland	1 (2%)	0	1 (3.8%)	0	0	2 (1.3%)
Multiple sites	3 (6%)	5 (7.2%)	2 (7.7%)	1 (100%)	1 (20%)	12 (8.1%)
Total	50 (100%)	69 (100%)	26 (100%)	1 (100%)	5 (100%)	151 (100%)

1.1% of patients had family history of lung cancer with first degree relativeness. This was contrary to one Indian study, reporting 21.2% of patients with family history of cancer (Bhaskarapillai et al., 2012), however the types of familial cancer association was not specified. More genetic studies are required to establish the hereditary risk for lung cancer. Family history of cancer is well accepted as an important risk factor for the development of several of the more common cancers (Offit and Brown, 1994).Although the risk of lung cancer in patients with COPD, bronchial asthma and emphysema are established (De Torres et al., 2011), our study reported only 1.3% of significant medical history of mentioned lung disorders. This may be related to poor health care facility in most hilly region of the state, ignorance and poor medical attention seeking. The history of alcohol beverages consumption mainly in form of local made beer and spirits are present in 51.2% of male patients may be potential risk factor for lung cancer independent of smoking as described in other studies (Eva et al., 1999; Elisa et al., 2001). About 27.5% of the patients had both smoking and alcohol consumption history, suggesting the possibility of synergistic effect in these set of patients (Steven et al., 2000).The higher prevalence betel nut intake was observed in 40.9% male and 34.6% female compared to other Indian study which had 15.1% and 12.5% in male and female respectively (Bhaskarapillai et al., 2012). Tobacco chewing is mainly risk factor for oral cancer and inconsistent with lung cancer (Boffetta et al., 2005a; 2008b), likewise our study had 25.9% of total patients with such history. The most common clinical presentation in our study was cough alone followed by combined symptoms including fever, dyspnoea, chest pain and haemoptysis, which were similar to results found in other studies (Hyde et al., 1974; Bruce, 1993; Rajasekaran et al., 1993; Bahera and Balamugesh, 2004; Khan et al., 2006). SVC syndrome was seen in 2.4% of the cases mostly involving small cell lung carcinoma patients. The most common radiological presentation seen in present study was mass followed by combined presentation, collapse-consolidation and pleural effusion; similar to reports published in Indian literature (Bahera and Balamugesh, 2004; Khan et al., 2006; Jagadish et al., 2009). Majority (60.3%) of our patients had a disease in right lung which is consistent with other reports (Weiss et al., 1982; Charles and Templeton, 1993; Khan et al., 2006). About 32.5% of our patients had distant metastasis at presentation with commonest site as brain, followed by malignant cell positive pleural effusion, bone mainly vertebra, liver, contralateral lung and adrenal gland. Multiple distant metastases at presentation were recorded in 8.1% patients. The distant involvement in our analysis is different from other Indian studies (Rajasekaran et al., 1993; Khan et al., 2006; Malik et al., 2013). However our results correlates well with one western study in which brain was reported as the most common distant metastasis involvement in Non-small cell lung carcinoma (Leslie et al., 1996). Brain metastases are detected in about 10% of SCLC patients at the time of presentation and are subsequently diagnosed during life in another 20-25%, with an increasing likelihood of development seen with lengthening survival (Komaki et al., 1981). The predilection for distant sites may be associated with tumour characteristics of lung cancer. In our study, squamous cell carcinoma is the most common histological type in both the sexes. The relative frequency of adenocarcinoma and small cell lung carcinoma is relatively higher in females as compared to male and in younger patients. Squamous cell carcinoma still remains the commonest cancer in this region similar to reports from other literature in India (Kapoor et al., 1993; Rajasekaran et al., 1993; Bahera and Balamugesh, 2004; Jagadish et al., 2009; Shiekh et al., 2010;). However, our results are contrary to recently published studies suggesting adenocarcinoma more prevalent in India now (Noronha et al., 2012; Malik et al., 2013). Patients with history of tuberculosis were commonly associated with squamous cell carcinoma and adenocarcinoma, which is similar to one other study (Liang et al., 2009). Squamous cell carcinoma of lung was high prevalent in smokers and old age group in present study. Most of the patients in the present study presented in locally advanced or distantly advanced stages. This delay in presentation may be attributed to poor knowledge of the disease, less medical attention seeking, ignorance, misdiagnosis, poor referral to speciality centres and lack of preventive measures. In the series from west as well as from India, it is reported that 50-70% cases of NSCLC and up to 2/3rd of SCLC usually present in advanced stage (Becket, 1993; Govindan et al., 2006; Grivaux et al., 2011; Malik et al., 2013).

In conclusion, our analysis suggests that the gender gap has been narrowed such that about half of the patients diagnosed with lung cancer are women in this part of India. This alarming rise in women incidence is mainly attributed to increased smoking pattern in females. Squamous cell carcinoma still remains the commonest histological subtype. Most of the patients were elderly aged and presented in locally or distantly advanced stages. Early detection and early treatment to reduce the morbidity and mortality associated with lung cancer in addition to imparting awareness on harmful effects of smoking and how to prevent the disease to general population is the need of this region.

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