Research

Clinico-pathological Profile of Lung Cancer among Smokers Versus Non-Smokers: Experience at Single Tertiary Care Center from India

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Abstract

Smoking was solely considered as the major commonest risk factor for lung cancer. But now rising prevalence of lung cancer is observed among non-smokers also. 10-25% of the diagnosed cases of lung cancer are never smokers in their life. Clinical picture, risk factors, histological characters and hence prognosis differs strikingly among smokers and never smokers. In the present study, we aimed to compare clinical profile of lung cancer among smokers versus never smokers.

Cases of histopathologically confirmed lung cancer were analyzed for demographic, clinical and pathological characteristics. Out of 110 cases, 64 were smokers and 46 had never exposed to tobacco-smoke in their life. Among non-smokers, majority was of females with adenocarcinoma. Maximum patients were presented in advanced stages III and IV.

Lung cancer among non-smokers is a unique clinical entity with different demographic, clinical and pathological characteristics. Presentation at the advanced stage is a major concern in the management of the disease. Even though, tuberculosisis frequent respiratory disease in India, clinicians should have high level of suspicion for early diagnosis and treatment of lung cancer.

Key words: Lung Cancer; Smokers; Non-Smokers; Adenocarcinoma; Squamous Cell Carcinoma

Introduction

Lung cancer is one of the commonest and important cause of cancer related mortality worldwide. Its prevalence is rising in India also, with reported incidence of new 63000 cases per year [1]. It's a life threatening condition because mostly patients present with the advanced stage of the disease. Clinical profile, histological picture and epidemiological distribution of lung cancer are presenting with varied trends among males and females. Smoking was solely considered as the major commonest risk factor for lung cancer. But now rising prevalence of lung cancer is observed among non-smokers also. 10-25% of the diagnosed cases of lung cancer are never smokers in their life [2]. Other causes identified are second hand smoke, air pollution, active smoking of other tobacco products and exposure to carcinogens like asbestos, pesticides, combustion products, radon, radiation therapy during occupational, environmental and medical exposure [3].

The physician Fritz Lickint from Germany established link between association of smoking and lung cancer for the first time in 1929 [4]. As men predominantly follow smoking practices, there was male preponderance for development of lung cancer. But with the changed profile of lung cancer, significant number of cases does not have history of smoking. With the social awareness programs for prevention of smoking, there might be increased prevalence of lung cancer among never smokers. Hence lung cancer has become prevalent now among females also. Especially never smokers group comprise of females predominantly with adenocarcinoma. Clinical picture, risk factors, histological characters and hence prognosis differs strikingly among smokers and never smokers. In the present study, we aimed to compare clinical profile of lung cancer among smokers versus never smokers.

Material and methods

Present cross sectional study was conducted in the Oncology unit of United CIIGMA Hospital. Patients with confirmed diagnosis of lung cancer were included in the study. Informed consents were obtained from all enrolled participants. Demographic data including age, sex, personal habits of smoking (current and ex-

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smokers), tobacco chewing, alcoholism, occupational history was recorded through detailed questionnaire. Every patient was interviewed to obtain personal history with respect to duration, frequency per day, type and pattern of smoking. Past medical history about tuberculosis, chronic obstructive pulmonary disease, exposure to radiation therapy or any other occupational carcinogens was recorded. Anthropometric parameters body weight (Kg), height (m) were recorded and Body Mass Index (BMI) was calculated as Weight (Kg)/ Height (m2). Presenting symptoms of the cases were recorded. After thorough clinical examination with diagnostic work up, patients were categorized stage wise. Depending upon histopathology and stage, treatment was planned along with the schedule of follow up for monitoring.

Routine diagnostic work up included complete blood examination, liver and renal function profile, chests X ray, Computed Tomography (CT) scan. In patients with pleural effusion, we tap the effusion to prepare cellblock. Different investigations like CT guided biopsy, bronchoscopic brushing and PET-CT is done in lung cancer patients to confirm histopathological diagnosis and to stage the malignancy. Rarely bone marrow examination is also advised. In cases with axillary and supraclavicular lymphadenopathy, fine needle aspiration cytology or biopsy is done.

Line of treatment: Patients received the treatment as per our departmental protocol with multidisciplinary team approach. In case of localized lesions without spread, neo-adjuvant chemotherapy and surgical resections were the line of treatment. Patients with progressive disease received chemotherapy depending upon their histological subtype. In squamous cell carcinoma, Paclitaxel and Carboplatin as first line and Gemcitabine and Oxaliplatin were offered as second line of chemotherapy treatment. The patients with adenocarcinoma received Pemetrexed and Carboplatin with oral tyrosine kinase inhibitors. This was followed by maintenance dose of Pemetrexed. Some patients received combined chemotherapy and radiotherapy according to stage and grade of the disease. Terminally ill patients received palliative chemotherapy and best supportive treatment.

Statistical Analysis

Data was entered and analyzed using SPSS software (SPSS for windows, version 16). Mean, standard deviations and frequency (%) were calculated. p values were calculated to find out the difference in variables among smokers and non-smokers. Less than 0.05 is considered as statistically significant, 0.001 as highly significant and more than 0.05 is statistically insignificant.

Results

Total 110 diagnosed cases of lung cancer were included in the study. Out of them, 64 cases were smokers and 46 were never smokers with male to female proportion 76:34. Among non-smokers, 30 were female while among smokers, 62 were male. Mean age for all cases was 52.67 years (+/-8.94). Mean age of females was 39.34 years (+/-5.4) while that of males was 59.45 years (+/-8.65). Out of 110 cases, 56 patients had positive past history of tuberculosis and 24 had COPD. **(Insert Table 1,2,3)**

Discussion

Lung cancer carries a greater mortality than other cancers because majority of patients get diagnosed in late stage. At this advanced stage, surgical intervention is not amenable. Chemotherapy and radiotherapy remain the only therapeutic modalities in such patients. As reflected in the various tables, our patients presented in stages III and IV commonly. Non-smokers presented with different demographic, clinical and histological subtypes.

One of the massive, population based prospective study compared age, sex and race specific lung cancer mortality in more than 940000 white and African American adults who were non-smokers at the time of enrollment is the Three-Prefecutre cohort study in Japan conducted by Thun et al. Findings of this study reported that lung cancer mortality was higher among never smokers men than women and higher among African American women than white women [3]. Marugame et al studied lung cancer death rates by smoking status among 88153 Japanese in 10-year prospective follow up study. They reported lower death rates among smokers in comparison with non-smokers regardless age and sex [5]. One of Indian study reported smokers to non-smokers ratio as 3.9:1. They found maximum cases of squamous cell carcinoma among smokers, while adenocarcinoma was more prevalent among females and non-smokers [6]. Previous Indian studies described squamous cell carcinoma as the commonest histological type, but now trend is shifting towards adenocarcinoma. It may be because of rising prevalence of lung cancer among non-smokers and females [7-9]. Bhadke et al reported 42.55% non-smokers lung cancer cases in their study from rural area India. Adenocarcinoma was the most frequent histopathological type and maximum patients presented with stage IV [10].

Noronha V and colleagues studied epidemiological patterns and clinical profile with focus on the differences between non-smokers and smokers. Out of 489 patients, 52% were non-smokers. Maximum cases were diagnosed in stage III with predominately histological subtypes of adenocarcinoma followed by squamous cell, large cell and other. They concluded that in India also, prevalence of lung cancer is rising mong non-smokers in parallel with global trend of rise in adenocarcinoma [11]. Kumar et al analysed 266 cases of lung cancer from West Bengal state of India. They observed squamous cell carcinoma as the most frequent histological subtype presenting in stages III and IV and majority smokers [12]. Malik and colleagues analysed 434 cases of lung cancer. They reported 70% current or former smokers, majority with bidi smoking. Adenocarcinoma was the commonest histologic type with male preponderance [13].

Apart from well-established risk factors, key molecular alterations have been proposed as chief oncologic drivers in lung carcinogenesis among cases never exposed to tobacco and smoke. Such molecular alterations may be responsible for unique clinico-pathological profile of never smokers patients. Significant genomic and epigenomic alterations have been documented among never smokers lung cancer patients like mutations in tyrosine kinase domain of epidermal growth factor receptor (EGFR) gene and

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Table 1: demonstrates demographic data of the patients.

Variables	Smokers (n=64)	Non-smokers (n=46)	P value
Age (years)	57.87+/-7.68	40.43+/-5.43	0.000** (HS)
Sex Male: Female	62:2	16:30	0.04 (S)
H/o tuberculosis	31 (49%)	16 (35%)	0.08 (NS)
H/o COPD	21 (33%)	21 (46%)	0.09 (NS)
Second hand smoking		28 (61%)	
Occupational exposure	4 (6%)	7 (15%)	
H/o Radiation treatment	0	0	
Family H/o cancer	17 (26%)	20 (43%)	0.04 (S)
BMI (kg/m^2)	21.43 (+/-2.45)	22.87 (+/-2.98)	0.076 (NS)

HS- highly significant, NS- Non-significant, S- significant

Table 2: shows stage-wise distribution of the cases.

Stage	Smokers n=76	Non-smokers n= 34
Stage I	6 (8%)	2 (6%)
Stage II	15 (20%)	5 (15%)
Stage III	32 (42%)	11 (32%)
Stage IV	23 (30%)	16 (47%)

Table 3: represents clinical profile of the cases.

Variables	Smokers n=76	Non-smokers n=34
Presenting symptoms		
Cough	70 (92%)	21 (62%)
Expectoration	62 (82%)	15 (44%)
Weight loss	58 (76%)	19 (56%)
Breathlessness	62 (82%)	18 (53%)
Haemoptysis	32 (42%)	12 (35%)
Chest discomfort	50 (66%)	29 (85%)
Non-specific symptoms	70 (92%)	30 (88%)
Hoarseness of voice	12 (15%)	5 (14%)
Histologic types		
Squamous cell carcinoma	30 (%)	1 (2%)
Adenocarcinoma	46 (%)	33 (98%)
Lesions-		
Collapse	20 (26%)	7 (20%)
Mass	29 (38%)	18 (53%)
Pleural effusion	18 (23%)	8 (21%)
Combined lesions	47 (61%)	21 (62%)
Site of tumor		
Right lung	48 (62%)	18 (53%)
Left lung	24 (31%)	8 (21%)
Bilateral	4 (5%)	8 (21%)

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Location of tumor		
Upper zone	23 (30%)	10 (29%)
Middle zone	36 (47%)	8 (23%)
Lower zone	10 (13%)	7 (20%)
Combination	7 (9%)	9 (26%)
Lymphadenopathy	55 (72 %)	27 (79 %)
Metastasis	23 (30%)	16 (47%)

EML4- ALK fusion [14]. Never smokers may have inherited risk for development of lung cancer [15]. Next generation sequencing studies found relatively small number of genomic mutations among never smoker lung cancer. While higher number of mutations are found among smokers due to mutagenic field effect of tobacco-smoke exposure [16,17]. Non-smoking state is the strongest clinical predictor of therapeutic response from EGFR tyrosine kinase inhibitors [18].

In India tuberculosis and COPD are additional important and most frequent respiratory conditions. So patients of lung cancer in the initial stages remain undiagnosed and usually receive treatment for these conditions. This causes diagnosis of lung cancer with advanced stage with metastasis resulting in poor outcome. Rawat et al reported that majority of cases of lung cancer are misdiagnosed as tuberculosis, so delayed presentation and diagnosis by average 4-6 months of duration [19]. Singh et al reported 20% of cases received wrongly anti-tuberculosis therapy with median duration of 4.46+/-3.15 months [20].

Lung cancer is the leading cancer killer that imposes huge socioeconomic burden on the healthcare system. Smoking is one of the most important established cause of lung cancer. It has been reported that men smokers are 23 times and women smokers are 13 times more likely to have lung cancer in comparison with never smokers. But prevalence is rising among never smokers also. Never smokers with exposure to second hand smoke have 20-30% chance of getting lung cancer. Second hand smoke is an involuntary exposure to tobacco smoke which has been designated as known human carcinogen. Side stream and exhaled mainstream smoke contain more than 50 chemical carcinogens. Even low level of exposure also may cause harm to people [21]. Presence of multiple risk factors like smoking, occupational exposure to carcinogens, air pollution increases risk by several times.

Conclusion

Lung cancer among non-smokers is a unique clinical entity with different demographic, clinical and pathological characteristics. Presentation at the advanced stage is a major concern in the management of the disease. Even though, tuberculosis is frequent respiratory disease in India, clinicians should have high level of suspicion for early diagnosis and treatment of lung cancer. Acquisition of history about smoking status is at the utmost importance for better outcome of lung cancer. In future population based studies to identify risk factors among non-smokers are urgently warranted.

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