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Original Article

Incidence and trend of Carcinoma Lung among women and use of oral TKI – A Single Institution Based Study

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Abstract
Lung cancer is the most common cancer of men in India, whereas it is 2nd most common in women in India as per Globocon 18 data. Smoking tobacco is the principal risk factor for causation of lung cancer. However causation of carcinoma lung in women is not clearly defined. In the present observational study we have investigated the causal risk factors of carcinoma lung among female patients especially below 60 years of age group. As part of management, trend of usage of Tyrosine Kinase Inhibitor (oral TKI) in female lung cancer patients was also investigated, with outcome. There is lack of epidemiological data on Lung cancer among women from India as well as outcome of Oral Tyrosine kinase inhibitor (TKI) or Epidermal growth factor receptor inhibitor (EGFR) in female carcinoma lung.
Keywords: *India, Lung cancer, oral Tyrosine kinase inhibitor (TKI), Epidermal growth factor receptor (EGFR).*

Introduction

Lung cancer used to be thought of as a man's disease, but women now account for almost half of new cases and deaths from lung cancer. The changing epidemiological trend in India is not investigated anywhere. Based on estimates for 2011, 48% of more than 221,000 people diagnosed with lung cancer were women and 45% of 157,000 who died from lung cancer were women [1]. According to Globocan (2012) estimate of lung cancer in India would indicate that, incidence of lung cancer in India is 70,275 in all ages and both sexes. The estimated lung cancer mortality among Indian females was 15,062 [2]. In male it ranked second while in females it was sixth in terms of cancer incidence. As more women began to smoke, the number of deaths from lung cancer increased very dramatically among women — by more than 60% between 1950 and 1997[3]. In our country 40% of women who develop lung cancer have never touched a cigarette Twenty years after stopping, the risk of developing lung cancer drops only by half. In addition, exposure to second-hand smoke at home,

work or other environments, including childhood exposures, can cause lung cancer in women who have never smoked themselves. Smoking among Indian women is seen often in two classes of women – one who live in village, associated with agricultural and household works and another who live in metro cities, working in IT sector or any other private firms. Even female students are also nowadays addicted to smoking for a virtual reason to reduce stress. A meta-analysis of 41 studies showed the environmental tobacco exposure carries a relative risk of developing lung cancer of 1.48 in males and 1.2 in females[4].

Apart from smoking, other risk factors include exposure to carcinogenic chemicals, second hand smoking, air pollution, lung infections, burning of coal in houses and family history. Environmental tobacco smoke exposure during childhood is strongly associated with the risk of developing lung cancer (odds ratio 3.9, 95% CI 1.9-8.2) [5]. Recent studies suggest infection with the Human Papilloma Virus (HPV) may also play a critical role in developing lung cancer[6]. Tobacco-associated head and neck cancers (tongue, mouth, or pharynx, hypo pharynx and larynx) constituted about 20% of the total cancers in West Bengal. In various surveys in Kolkata, 27.5% adult men and 18% women were found to be ever-chewers. Kolkata has one of the highest prevalence of lung cancer alongside Delhi, because of the severe air pollution[7,8]. In India, the most predominant histopathological subtypes of primary bronchogenic carcinoma were squamous cell carcinoma at 35.1% and adenocarcinoma at 30.8%. Adenocarcinoma is the predominant type in female 40.68%, particularly in non-smokers. Bronchoalveolar carcinoma is a rare type of lung cancer, very rarely found in women. Incidence of Bronchoalveolar Carcinoma (BAC) is increasingly worldwide, mainly among younger, non-smoking women[9]. In this observational study, Adenocarcinoma was the most common type of lung cancer found in women, whereas, men were most likely to develop squamous cell carcinoma in lung. It is assumed that estrogen plays a critical role in developing and progression of lung cancer. Women who have their ovary removed surgically before menopause or women who with hormone replacement therapy after menopause are more prone to develop lung cancer. On the contrary, using of birth control pills is associated with lower risk of developing lung cancer[10].

Currently molecular testing in lung cancer has become mandatory, is part of all management guidelines globally and is easily available. Depending on the molecular-pathological sub-type and stage of the disease, irrespective of sex, lung cancer can be treated with Surgery, Chemotherapy, Radiation Therapy or a combination of these treatments or oral biological therapy. Survival rate for lung cancer in women is better than that in men. Like breast cancer, Lung cancer, especially in younger age group, also should be discussed with special context. It had been seen that in Tata Memorial Hospital in Mumbai between August 2011 to December 2012, that overall genetic mutation rate in lung carcinoma was 23.2% with a higher mutation rate in females as compared to males(29.8% vs. 20%) [11].

The present retrospective observational study focused on the demographic factors (gender, age, smoking etc.) related to its causal incidence of female lung cancer and trend of use of EGFR inhibitor, oral TKI like Gefitinib or Erlotinib and Crizotinib in female adenocarcinoma cases as part of management with its outcome.

Methods

In the present observational study, we investigated the causal risk factors of carcinoma in lung in all female patients who were registered or admitted in our healthcare centre from June 2014 to June 2017 for their recommended treatment. Data obtained from the clinical history taking and follow-up findings which include some specific questionnaire consisted of sociodemographic information, clinical and smoking history, information mainly current smoking status

(whether participants were current, former, or never smokers), smoking frequency, quitting time in relation to cancer diagnosis, and as a proxy for secondhand smoking exposure, whether additional household members and close associates were smokers, no of pack of cigarette or bidis used by them with duration, smoking cessation, and occupancy with duration in same room with smoker or not etc. Type of cancer and time since diagnosis were also noted. The management details of all attending patients were observed, specially use of oral TKI in adenocarcinoma cases. Only female lung carcinoma patient's data were evaluated in this study.

Observational findings

According to our last 3 years observation, no. of lung cancer cases investigated was 195. An odd number of cases 123 were male and 72 cases were female with lung cancer. Forty cases were registered at our OPD as female carcinoma lung below 60 years of age from June 2014 to June 2017.

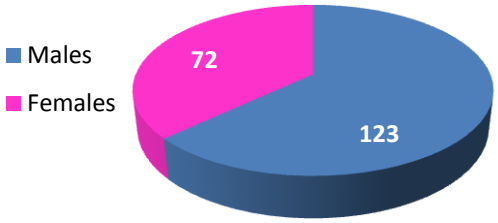

Fig 1: Sex predilection (n=199)

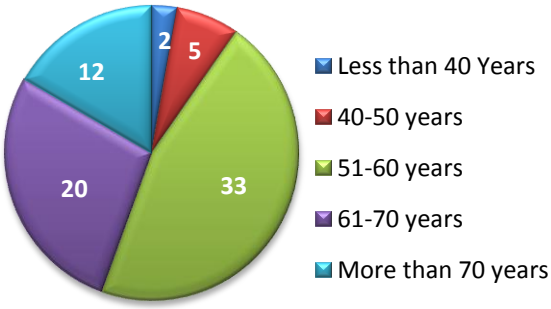

Fig 2: Age Distribution (n=72)

Among 72 cases, 48 females were with adenocarcinoma, 16 with squamous cell carcinoma, 5 cases with small cell carcinoma and 3 cases with adeno-squamous cell carcinoma and poorly differentiated carcinoma. Surprisingly among 72 cases, 40 cases were below the age group of 60 years. Among 40 cases of female lung cancer, below the age 60 years, 28 cases and above 60 years, 20 cases were with adenocarcinoma

Table 1: Distribution of Histological Types

Histological Type	Number of cases
Squamous Cell Carcinoma	16
Adenocarcinoma	48
Small Cell Carcinoma	5
Poorly Differentiated Carcinoma	2
Adenosquamous Carcinoma	1

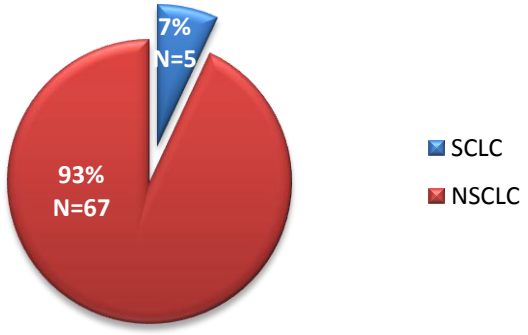

Fig 3: Broad Classification of Type of Lung cancers at presentation

Interestingly, 14 adenocarcinoma cases and 7 squamous cell carcinoma cases had clinical history of smoking, mainly prevalent in rural areas. Their clinical history depicted that, affected individuals were mainly associated with agricultural activities being exposed to active smoking like bidi, burnt smoke of dried leaves. About 35 cases had history of passive smoking, among them 23 cases were proven to be Adenocarcinoma, rest 12 cases were of other types. 9 cases had past history of Tuberculosis, who developed adeno carcinoma later.

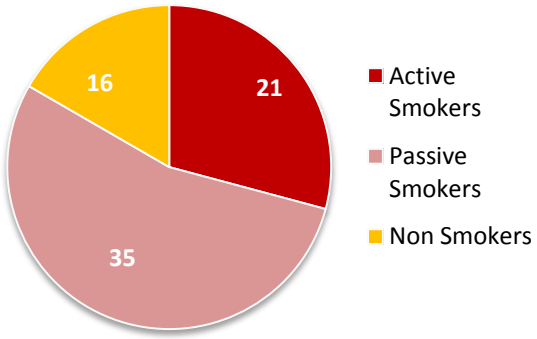

Fig 4: Smoking patterns at presentation

About 16 cases had no history of exposure to any causative factors. Among 16 cases, 2 small cell carcinoma, 11 adenocarcinoma, 2 squamous cell carcinoma, 1 poorly differentiated carcinoma cases were not exposed to any known etiological cause or factor. Majority of the cases (61 out of 72 cases, 84.72%) were with locally advanced (stage llB, lllA, IIIB disease), only 11 (15.72%) cases were with metastatic disease since presentation. All were treated with Chemotherapy with or without Radiotherapy, either with curative or palliative intent. Patients locally advanced stage were treated with Chemo-Radiotherapy protocol and metastatic disease with Palliative chemotherapy with or without Palliative Radiotherapy. According to our institutional protocol, locally advanced cases, sequential Chemo-Radiotherapy was given rather than concomitant Chemo-Radiotherapy due to logistic issue and patients' nutritional status. Among 67 Non-small cell lung carcinoma patients, 40 were histologically proven by core needle biopsy or cell block preparation from aspirated pleural fluid, rest were CT scan guided cytologically proven only. Of these 40 cases, 32 cases were Adenocarcinoma, rest 8 cases were of Squamous cell type. Trucut needle biopsy with EGFR mutation study was not possible in all cases due to technical and/or financial reason. Among 32 histology and pleural fluid cell block proven Adenocarcinoma cases, 6 (18.75%) cases were Epidermal growth factor receptor(EGFR) mutation positive in driver oncogene, mainly with Exon 19 deletion. These 6 cases with EGFR mutation received Oral TKI either primarily in metastatic settings (3/6), or as further lines of therapy in advanced stage disease (3/6). There were only 27 cases as cytology proven, among them 16 malignant case were reported as "compatible with Adenocarcinoma", for rest 11 cases no subtype of NSCLC were mentioned. Among them 6 (out of 16 compatible with adenocarcinoma of total 27 FNAC proved cases) were never exposed to smoking. These 6 cases were taken for oral TKI on the basis of previous well known phase III multi-centric trial.[12.13.14.]. Without further EGFR mutation study (due to logistic and financial issues), oral TKI was used out of desperation in these cytology proven cases as 3rd line therapy, where 2 lines of chemotherapy failed and performance status did not allow the use of any further line of chemotherapy and 2 out of 6 showed clinical benefits with indirect evidence of maculo-papular rash in body and incidence of diarrhea. Oral TKI either Gefitinib or Erlotinib gave significant benefit among 8 non-smoker adenocarcinoma patients, among them 6 cases were histologically proven, 2 were with only cytology proof**.** Average 2yrs 8 months was calculated survival benefit in 2 patients. Three patients with histological proven Adenocarcinoma, EGFR non-mutated were positive for EML4 (echinoderm microtubule associated protein like 4) ALK (anaplastic lymphoma kinase) fusion, treated with Crizotinib [(16.17)]. Maximum survival benefit with Crizotinib user in 2 metastatic Adenocarcinoma patients were 1year 8 months and 11 months as 1st line therapy, 1 patients died within 6 months, in whom Crizotinib was used as 3rd line, after treatment with 2 lines of chemotherapy.

We have analyzed all data on December2017, survival and response according to RECIST criteria and Kaplan Meier survival analysis, taking cases till June 2017 year wise. Among 22 female lung cancer cases registered from June 2014 to May 2015, 3 cases presented de-novo metastatic disease. Among all 4 patients are living till the date of analysis, on oral Gefitinib/Erlotinib.

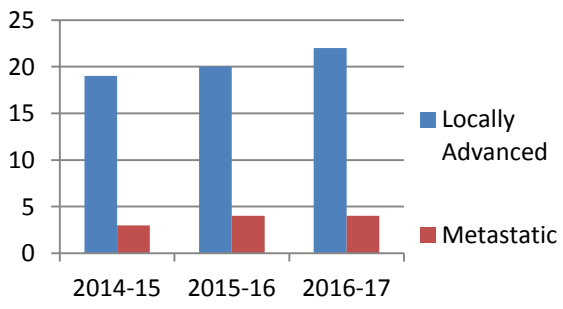

Fig 5: Year wise and Stage wise presentation of lung cancer

Among 24 cases registered between June 2015 to May 2016, 4 cases were with metastasis at presentation. About 10 cases are living till date of analysis, 6 on complete remission or stable disease,4 on oral TKI as salvage therapy for progressive disease. Between June 2016 to May 2017, 26 cases of Female carcinoma lung were registered, 4 patients with metastasis at presentation. Only 8 cases could not complete planned treatment with chemotherapy later kept on oral TKI, 4 metastatic patients primarily taken for oral TKI. They are surviving with stable disease, with total 16 patients were living at the time of analysis.

We assessed whether women and men differ in their susceptibility to lung cancer in data that we extracted from the hospital registry. The women were at significantly higher risk of adenocarcinoma and lower risk of large-cell lung cancer than the men in our cohorts. National Cancer Institute has reported that compensatory changes in smoking patterns, including depth of inhalation and puff frequency, reduce any theoretical benefit of lower-tar cigarettes. Although these reports are largely reassuring, we cannot claim to have compared men with women who have precisely the same epithelial exposures to tobacco carcinogens. The few results from previous prospective studies[18,19] on comparative risks of lung cancer at older ages, including some among former smokers, show no hint of effect modification by sex, although it should be acknowledged that exposure data and numbers are limited. Similarly, for possible differential sex effects across histology, neither the prospective data of Prescott et al [13] nor the meta-analysis of Khuder et a·[14] suggest any excess risk of adenocarcinoma among women. Our direct research findings lend little support to the notion of modification of the tobacco effect by sex, but they are neither sufficiently precise nor complete enough to conclusively argue the case for equal risk of lung cancer for men and women who experience identical smoking exposure, despite the fact of alarming number of incidence of lung cancer in younger women but their response to treatment is encouraging.

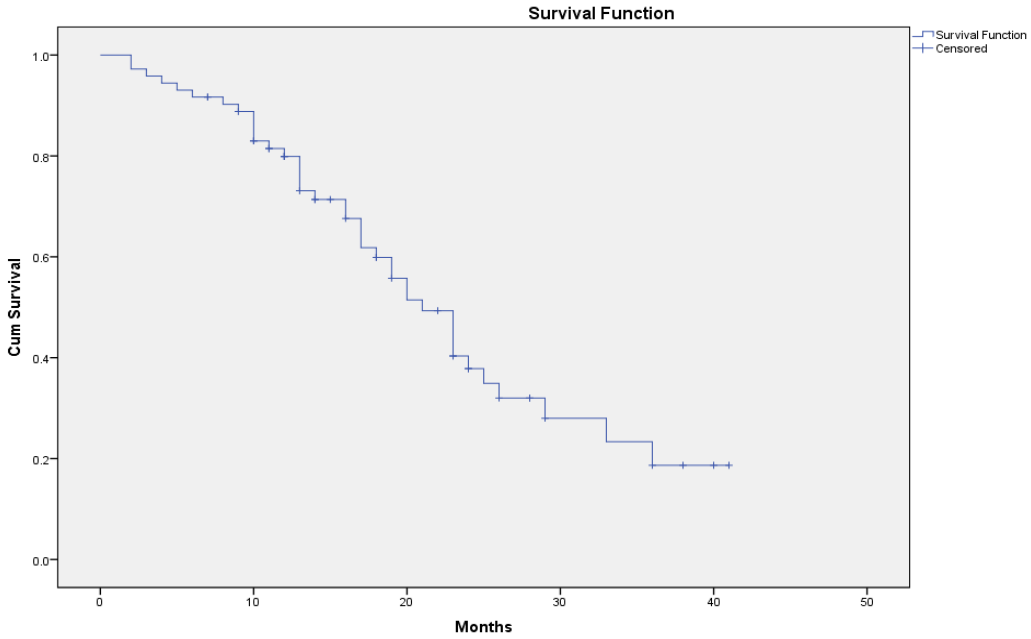

Fig 6: Kaplan Meier Survival Plot of Female patients with Lung Carcinoma

Discussion

The number of female Lung cancer is increasing though incidence of smoking is not directly related in most of the cases. Lung cancer is young aged female is more aggressive and sometimes they present in advanced stage as suspicion on lung cancer diagnosis is less. Recently recognized novel gene mutation such as EGFR (epidermal

growth factor receptor mutations are largely limited to never smokers or light smokers and this gene is responsible for the clinical efficacy of Gefitinib ,an oral Tyrosine kinase inhibitor. Non small cell Carcinoma Lung with the EML4 (echinoderm microtubule associated protein like 4) ALK (anaplastic Lymphoma Kinase) fusion gene is also more likely to occur in never smokers, adenocarcinoma histology is expressed to benefit from ALK inhibitor. The use of oral TKI in this observational cohort is mainly in EGFR mutation positive population, mainly with Exon 19 mutation, few with unknown EGFR status, without further option for chemotherapy. The response rate was better in EGFR mutated group, best response noted when oral TKI was used upfront.

Due to some logistic reason biopsy and EGFR mutation study were not possible in all cases, even proper counseling of the patients were done. Among 72 female carcinoma lung cases, irrespective of histology and other confounding factors, 11.11% (8/72) cases showed clinical benefit with oral TKI, in our study. Our result is similar to well known studies[16,17], highest oral TKI receiving female Carcinoma Lung case surviving more than 20 months ,that too in metastatic setting…

Causative factors for Female Lung cancer to be investigated deeply specially in molecular level as smoking is not not always associated.. As incidence of female lung carcinoma is increasing, more epidemiological data to be evaluated in future to prevent the incidence and to search causative factors of lung carcinoma among female

Inference

Our observation identified that, female lung cancer patients of < 60 years of age, tolerated the recommended treatment slightly better than by elderly age group and progression free survival are not different from male counterpart. Oral TKI is a very good option for adenocarcinoma, female non smoker (both active and passive) cases. Preferably Biopsy with EGFR mutation study should be done all Non small cell non squamous cell ca, cases. Without molecular markers specially EGFR activating mutation study those patients only continue oral TKI, who have shown clinical benefit.

No financial conflict of interest.

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