Original Article

Response Assessment of Gefitinib Therapy in the Epidermal Growth Factor Receptor- Mutant Advanced Adenocarcinoma Lung at a Tertiary Care Center in North India

Anubhuti Singh, Anand Srivastava[1], Abhishek Verma[1], Rajiv Garg[1]

Department of Respiratory Medicine, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, Uttarakhand, [1]Department of Respiratory Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India

Abstract

Context: Oral tyrosine kinase inhibitors (TKIs) have been proven to improve response rates (RRs) and progression-free survival in a chemo-naïve setting in the epidermal growth factor receptor (EGFR)-mutant advanced lung adenocarcinoma patients in studies conducted in Western countries. Similar data from India are currently sparse. **Aims:** The aim is to study the epidemiological, clinical, and radiological profile of advanced-stage of lung adenocarcinoma patients harboring an EGFR mutation and to assess the response of TKIs in these patients. **Settings and Design:** This was a prospective observational study performed at a tertiary care hospital. **Materials and Methods:** A total of 40 advanced-stage lung adenocarcinoma patients who harbored an EGFR mutation and received an oral TKI (gefitinib) were included in the study and response was evaluated using the Response Evaluation Criteria for Solid Tumors. **Statistical Analysis Used:** Qualitative variables were compared using the Chi-square test/Fisher's exact test as appropriate. **Results:** A total of 30 (75%) patients had an exon 19 mutation and 3 (7.5%) patients had an exon 21 mutation. The overall RR to gefitinib was 57.5%. Eleven (27.5%) patients had partial response, 12 (30%) patients had stable disease (SD), and 6 (15%) patients had progressive disease. The RR was more favorable among females, rural residents, nonsmokers, patients having good performance score, and stage III disease. **Conclusions:** The overall RR to gefitinib was comparable to those reported in western studies but lower than those reported in Asian studies at our center.

Keywords: *Gefitinib, lung adenocarcinoma, response rate*

Introduction

Lung cancer is the most common cancer affecting humanity, and is the leading cause of cancer-related deaths. While worldwide lung cancer accounts for 13% of all new cancer cases, it constitutes 6.9% of all cases in India.[1] According to the GLOBOCAN 2012, it is the fourth most common cancer in India and it holding the second position among males and the sixth position among females.[2] Lung cancer is responsible for around 10% of all deaths due to cancer in India.[1]

Among the histological variants of lung cancer, nonsmall cell lung cancer (NSCLC) constitutes around 85%, whereas SCLC constitutes 15% of all cases. Squamous and adenocarcinoma are the two most prevalent cell types of NSCLC. While adenocarcinoma is more common worldwide, in India, there appears to be a conflict with different centers providing different data in the absence of a countrywide registry.

Till 2004, the treatment of all types of advanced NSCLC was similar, irrespective of histology. In 2004, there was a historic breakthrough when activating the epidermal growth factor receptor (EGFR) mutations were discovered in lung cancer.[3] EGFR is transmembrane receptors responsible for cellular functioning. On ligand binding, there is phosphorylation of receptor, which causes downstream signaling through tyrosine kinases, leading to cell maturation and differentiation. Lynch *et al*. reported that certain lung cancers have activating EGFR mutations (across exon 19–21). These mutant receptors do not require ligand binding for activation and thus cause unregulated cellular proliferation and growth. These activating mutations are commonly found in adenocarcinoma, female patients, never smokers, and patients of East Asian origin.[4]

How to cite this article: Singh A, Srivastava A, Verma A, Garg R. Response assessment of Gefitinib therapy in the epidermal growth factor receptor-mutant advanced adenocarcinoma lung at a tertiary care center in North India. Clin Cancer Investig J 2019;8:41-6.

Address for correspondence:
Dr. Anand Srivastava, Department of Respiratory Medicine, King George's Medical University, Lucknow - 226 003, Uttar Pradesh, India.
E-mail: drsrianand@gmail.com

Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_6_19

Quick Response Code:

The discovery of EGFR mutations led to renewed interest in targeted therapy for lung cancer. Tyrosine-kinase inhibitors (TKIs) such as gefitinib and erlotinib are small-molecule inhibitors which bind to intracellular domain of EGFR, preventing autophosphorylation and downstream signaling. In comparison to conventional chemotherapy, EGFR-TKIs provide longer progression-free survival (PFS), a better quality of life and are better tolerated in EGFR-mutant lung cancer. TKIs are approved as both first and second line therapy as well as maintenance therapy in patients with advanced lung adenocarcinoma.

Although lung cancer has been extensively researched elsewhere in the world, research in India is still in its nascent stage. Limited data are available regarding incidence, histological and stage-wise distribution, chemotherapy response, mortality, and survival for lung cancer in general and adenocarcinoma in particular.

We conducted a prospective observational study at our tertiary care center to evaluate the clinico-epidemiological profile of advanced lung adenocarcinoma patients and response to gefitinib with the following aims and objectives:

- To study the epidemiological, clinical, and radiological profile of advanced lung adenocarcinoma patients harboring an EGFR mutation
- To study the response of gefitinib in these patients at 6 and 12 months and to assess the correlation of response rates (RR) to clinical parameters.

Materials and Methods

This was a prospective observational study carried out at the respiratory medicine department of a tertiary care center in North India. On the basis of a questionnaire, the basic demographic, clinical, radiological, and histological features of each patient were recorded. The diagnosis of lung adenocarcinoma was established by cytology or histopathology of samples obtained by computed tomography (CT)-guided transthoracic fine-needle aspiration (FNA) and/or biopsy, endobronchial biopsy or pleural biopsy (thoracoscopic and/or closed). The staging of disease was done using contrast-enhanced computed tomography (CECT) thorax with abdomen or ultrasonography of the abdomen and CT head whenever relevant according to the tumor, node, metastasis (TNM) eight staging. Patients having advanced disease (stage III and IV; according to the TNM eight staging) were included in the study.[5] The functional status of the patients was measured using the Eastern Cooperative Oncology Group (ECOG).[6]

Inclusion criteria

Newly diagnosed (chemo-naïve) advanced-stage (III and IV) lung adenocarcinoma patients harboring EGFR mutations who are receiving 250 mg oral gefitinib once daily were included.

Exclusion criteria

- Lung adenocarcinoma with unknown EGFR status
- Lung adenocarcinoma patients who have previously received or those who were receiving conventional chemotherapy were excluded.

The samples which were positive for adenocarcinoma were subjected to EGFR mutation analysis. Immune-histochemistry on the tissue sample was performed using cell signaling technology. The EGFR mutations in exon 19 were detected through E746-A750 deletion specific monoclonal antibodies while the EGFR mutation in exon 21 was detected through L858R mutant-specific monoclonal antibodies. This method for immune-staining for EGFR mutation-specific antibody has a sensitivity of 81.4% and a specificity of 97.5%.[7]

A total of 81 advanced-stage lung adenocarcinoma patients were diagnosed at our center over a period of 1 year. Of these, 40 patients who harbored EGFR mutation and were receiving gefitinib were included in the study.

After the initiation of gefitinib, the patients were followed up monthly by chest radiographs and clinical status. A CECT thorax was performed at 4, 6, and 12 months, and other relevant investigations were done whenever required. Based on CT, response was evaluated using Response Evaluation Criteria for Solid Tumors (version 1.1, 2009).[8]

Study protocol

Of 40 patients receiving gefitinib, 6 patients expired and 5 patients were lost to follow-up. Hence, the assessment was made for 29 patients at 6 months. Subsequently, out of these, 6 patients have completed 12 months of treatment and 2 patients have completed 18 months of treatment at the time of data compilation [Figure 1].

Statistical tools employed

The data were entered into MS Excel spreadsheet and analysis was performed using Statistical Package for Social Sciences software version 21.0, manufactured by IBM,

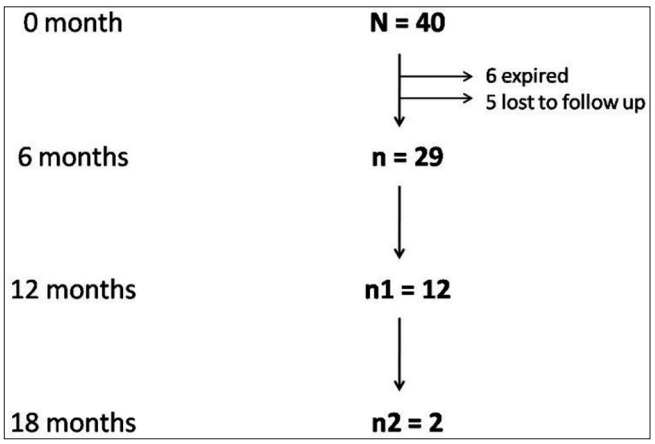

Figure 1: Study protocol

USA. Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean and standard deviation. Qualitative variables were compared using the Chi-square test/Fisher's exact test as appropriate. A value of $P < 0.05$ was considered statistically significant.

Results

The age of patients varied from 34 to 78 years, with a mean age of 55.95 years. The male-to-female ratio was 1.2:1 [Table 1]. Around two-thirds of patients (60%) were from a rural background, with the majority of males being farmers (42.5%) and all the females being homemakers. Nearly 57.5% of patients were nonsmokers, whereas 42.5% were smokers.

The common symptoms reported by the patients were cough (70%), dyspnea (70%), and chest pain (67.5%). A few patients reported hemoptysis (12.5%) and hoarseness of voice (15%). Fever was a chief complaint in 32.5% of patients. As far as performance status is concerned, maximum number of patients were in the ECOG functional grade 2 (50%) at the time of diagnosis, followed by grade 3 (37.5%) and grade 4 (12.5%).

Regarding radiological features, all the tumors were unilateral, with more preponderance to the left side (57.5%) [Table 2]; three-fourths of the tumors (75%) were peripheral. Nearly 77.5% of patients had the presence of pleural effusion and 25% of patients had evidence of distant metastasis at the time of diagnosis. Being peripheral, the majority (70%) of patients were diagnosed through transthoracic FNA and biopsy, 20% were diagnosed through closed pleural biopsy and 5% each through thoracoscopic pleural biopsy and endobronchial biopsy. Majority (87.5%) of patients were diagnosed in stage IV, 10% in stage IIIB, and 2.5% in stage IIIA.

On mutation analysis, 30 (75%) patients had an exon 19 mutation and 3 (7.5%) patients had an exon 21 mutation. In 7 (17.5%) patients, the exon analysis could not be performed due to the small sample size and the EGFR mutation was only quantitative.

- On response evaluation at 6 months, the overall RR was 57.5%. Eleven patients either expired or were lost to follow-up. The remaining 29 patients were assessed. 11 (27.5%) patients had partial response (PR), 12 (30%) patients had stable disease (SD), and 6 (15%) patients had progressive disease (PD). The patients having progressive disease were switched over to conventional chemotherapy depending on the performance status
- On evaluation at 12 months, out of six patients, 3 patients had SD, 2 patients had PR, and one patient had PD
- At 18 months, one patient had SD and one had PR.

The RR was more favorable among females, rural residents, nonsmokers, patients having good performance score and stage III disease; while it was poorer among patients having pleural effusion, distant metastasis and stage IV disease; although, these figures were no statistically significant [Figure 2 and Table 3].

Table 1: Demographic profile and clinical status

	n (%)
Gender	
Male	22 (55)
Female	18 (45)
Residence	
Urban	16 (40)
Rural	24 (60)
Smoking status	
Smoker	17 (42.5)
Nonsmoker	23 (57.5)
Biomass fuel exposure	
Yes	16 (40)
Nos	24 (60)
History of ATT intake	
Yes	14 (35)
No	26 (65)
Performance status (ECOG)	
0-2	20 (50)
3-4	20 (50)

ECOG: Eastern Cooperative Oncology Group, ATT: Antituberculosis treatment

Table 2: Radiological (computed tomography) features

Features	*n* (%)
Site	
Right	42.5 (17)
Left	57.5 (23)
Central	25 (10)
Peripheral	75 (30)
Pleural effusion	
Yes	77.5 (31)
No	22.5 (9)
Distant metastases	
Yes	25 (10)
No	75 (30)

Discussion

In this study, the age of patients varied from 34 to 78 years, with a mean age of 55.95 years. This result is similar to national figures according to the GLOBOCAN 2008 which reported the mean age at diagnosis among patients with lung cancer in India to be 54.6 years during the period of 1985–2001.[9]

The gender-wise distribution among the patients in our study was almost equal (male: female = 1.2:1). Noronha *et al.* analyzed the demographic data collected from 489 Indian lung cancer patients. They reported a male-to-female ratio of 3.5:1.[10] Over the last three decades, adenocarcinoma has remained the predominant tumor type among females; explaining the preponderance of females in our study.[11]

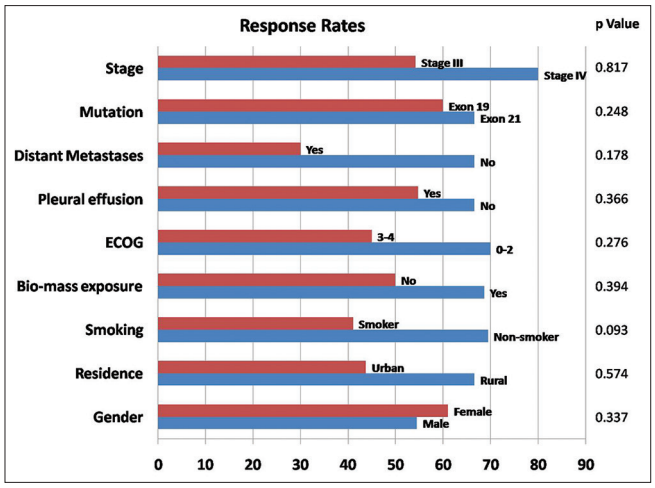

Figure 2: Association of response rates with variables

In this study, 57.5% of the patients were nonsmokers (which include those who have never smoked and those who have smoked <100 cigarettes/bidis in their lifetime). This is in accordance with other studies which state that lung adenocarcinoma is more common in nonsmokers.[12] Noronha *et al*. reported that 52% of lung cancer patients were nonsmokers.[10] Worldwide, among nonsmokers; lung cancer is the 7th leading cause of cancer mortality.[13]

Another common risk factor for lung cancer among Indian patients, especially those from a rural background is biomass fuel exposure. Biomass fuel includes wood, coal, dung cakes, etc. These constitute a cooking means in around 60% of Indian homes and most of this is done on an open fire.[14] About 40% patients in the study had this exposure. Only those patients were included who had direct exposure to smoke, i.e., women who cook on chulhas and men who are exposed to burning fuel because of the kitchen being inside the house. Emissions from house-hold coal combustion are labeled as Group 1 and biomass combustion as Group 2A carcinogen, according to the International Agency for Research on Cancer (IARC 2006).[15]

Surprisingly, 35% of patients in the study had a history of anti-tuberculosis treatment (ATT) intake, either in the past 1 year or were taking ATT at the time of diagnosis of lung cancer. Out of this, only two patients had any evidence of pulmonary or pleural tuberculosis (TB). This implies that around 1/3rd patients were incorrectly diagnosed with TB and were prescribed ATT, leading to a substantial delay in diagnosis. Agarwal *et al*. similarly reported that out of 195 cases of lung cancer, 40% of patients had taken ATT; although, only 5% of patients had co-existent TB and cancer.[16] They also stated that the mean delay in diagnosis of lung cancer in such patients was 3.2 months.

Over a period of 1 year, a total of 81 advanced lung adenocarcinoma patients were diagnosed at our center. Of these, 40 (49.38%) were found to have EGFR mutation and were included in the study. Doval *et al*. enrolled 500 lung adenocarcinoma patients from six centers across India.[17] They found that 32.8% of patients were positive for EGFR mutation. Various Indian studies have reported the prevalence of EGFR mutation in lung cancer between 25% and 50%.[18-21]

Table 3: Association between response rate and clinical variables

Variables	Response rates	*P*
Gender		
Male	54.5	0.817
Female	61.1	
Residence		
Rural	66.6	0.248
Urban	43.75	
Smoking status		
Nonsmoker	69.5	0.178
Smoker	41.1	
Biomass fuel exposure		
Yes	68.7	0.366
No	50.0	
ECOG grade		
0-2	70.0	0.276
3-4	45.0	
Presence of pleural effusion		
No	66.6	0.394
Yes	54.8	
Presence of distant metastases		
No	66.6	0.093
Yes	30.0	
Mutation in exon		
21	66.6	0.574
19	60.0	
TNM stage		
III	80.0	0.337
IV	54.28	

ECOG: Eastern Cooperative Oncology Group, TNM: Tumor, node, and metastasis

In this study, 75% of patients had an exon 19 mutation and 7.5% of patients had an exon 21 mutation. In 17.5% of patients, the exon analysis could not be performed due to small sample size and the EGFR mutation was only qualitative. None of the patients had a co-existence of both exon 19 and 21 mutations. In the data collected from 907 Indian lung adenocarcinoma patients, Chougule *et al*. reported 50% of patients having exon 19 mutation, 42% having exon 21 mutation, and 3% having exon 20 mutation.[20] In another study conducted by Bhatt *et al*. among 104 histologically confirmed NSCLC, 80% of patients had exon 19 mutation.[22] In this study, we found no association between exon, age, and gender. Similarly, Bhatt *et al*. found no significant association between exon, histology, age, and gender.[22]

On response evaluation of gefitinib at 6 months, the majority (57.5%) of patients had a favorable

response (either SD or PR, 15% had PD, and 27.5% of patients either expired or were lost to follow-up, thus the overall RR was 57.5%. Various studies have been conducted globally using EGFR TKIs as first-line treatment for EGFR-mutant patients. Among these, the RRs from Japanese and Chinese studies have been encouraging, with RR of 73.7% and 83% reported by Maemondo *et al*. and Zhou *et al*., respectively.[23,24] On the other hand, European studies such as EURTAC (*Rosell et al*., 2011)[25] and American studies (Sequist *et al*., 2008)[26] have reported comparatively lower RR of 58% and 55%, respectively. Going by this trend, our study compares with European and North American statistics rather than Asian data as was previously thought.

No significant association was found between gender and response to Gefitinib therapy in our study. A similar study conducted in China (n = 33) also found no association between female gender and response to TKIs.[27] Previous studies have found female gender to be a positive predictor for response to TKIs in lung adenocarcinomas.[28,29]

As compared to smokers (10%–20%), nonsmokers have 40%–60% incidence of harboring EGFR mutation.[30,31] TKIs have been consistently shown to have favorable response in nonsmokers.[32] in our study also, RR was more favorable in nonsmokers; although, the data were not statistically significant.

Choi *et al*. conducted a retrospective study among 130 patients of stage IV adenocarcinoma harboring EGFR mutations.[33] They evaluated the CT features in these patients which favor a positive response to TKIs. They found that patients with pleural effusion, pleural metastasis or both tend to have shorter -PFS. Our findings resonate with this study as we found a poorer response in patients with pleural effusion or distant metastases.

Choi *et al*. also reported that the patients having exon 19 deletion are more sensitive to TKI therapy.[34] Kosaka *et al*. also reported that although the RR of each mutation group was different (93% for exon 19 and 75% for exon 21), there was no difference in overall survival between these two groups of patients.[34] We also did not find any statistically significant difference in RR according to exon.

In the present study, the RR was more favorable among females, rural residents, nonsmokers, patients having good performance score, and stage III disease; while it was poorer among patients having pleural effusion, distant metastasis, and stage IV disease; although, these figures were not statistically significant.

This study had certain shortcomings. The number of patients was small to generalize the results to the whole population. Since the patients were enrolled at different points of time, at the time of compilation of data, only few patients had completed 12 and 18 months of treatment. Furthermore, survival data (PFS and OS) could not be evaluated because the duration of the study was small.

Conclusions

We found an overall RR of 57.5% to Gefitinib, lesser than figures reported by Asian studies and comparable to European and American studies. We also noted that the RR was more favorable among females, rural residents, nonsmokers, patients having good performance score, and stage III disease; while it was poorer among patients having pleural effusion, distant metastasis and stage IV disease. Further studies enrolling a larger number of patients are mandated to consolidate or refute these findings. A nation-wise registry for advanced lung adenocarcinoma would be insightful for a broader perspective regarding lung cancer patients in India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Malik PS, Raina V. Lung cancer: Prevalent trends and emerging concepts. Indian J Med Res 2015;141:5-7.
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, *et al*. GLOBOCAN 2012 Cancer Incidence and Mortality Worldwide: IARC Cancer base No. 11. Lyon, France: International Agency for Research on Cancer; 2013.
3. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
4. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 2007;7:169-81.
5. Rami-Porta R, Bolejack V, Giroux DJ, Chansky K, Crowley J, Asamura H, *et al*. The IASLC lung cancer staging project: The new database to inform the eighth edition of the TNM classification of lung cancer. J Thorac Oncol 2014;9:1618-24.
6. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
7. Kawahara A, Taira T, Azuma K, Tominaga M, Hattori S, Kawahara M, *et al.* A diagnostic algorithm using EGFR mutation-specific antibodies for rapid response EGFR-TKI treatment in patients with non-small cell lung cancer. Lung Cancer 2012;78:39-44.
8. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
9. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.
10. Noronha V, Dikshit R, Raut N, Joshi A, Pramesh CS, George K, *et al.* Epidemiology of lung cancer in India: Focus on the differences between non-smokers and smokers: A single-centre experience. Indian J Cancer 2012;49:74-81.

11. Egleston BL, Meireles SI, Flieder DB, Clapper ML. Population-based trends in lung cancer incidence in women. Semin Oncol 2009;36:506-15.
12. Toh CK, Gao F, Lim WT, Leong SS, Fong KW, Yap SP, *et al.* Never-smokers with lung cancer: Epidemiologic evidence of a distinct disease entity. J Clin Oncol 2006;24:2245-51.
13. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers – A different disease. Nat Rev Cancer 2007;7:778-90.
14. Prasad R, Singh A, Garg R, Giridhar GB. Biomass fuel exposure and respiratory diseases in India. Biosci Trends 2012;6:219-28.
15. Bruce N, Dherani M, Liu R, Hosgood HD 3rd, Sapkota A, Smith KR, *et al*. Does household use of biomass fuel cause lung cancer? A systematic review and evaluation of the evidence for the GBD 2010 study. Thorax 2015;70:433-41.
16. Agarwal A, Agarwal PK, Tandon R, Singh S, Singh L, Sharma S. Pulmonary tuberculosis as a confounder for bronchogenic carcinoma due to delayed and misdiagnosis. Indian J Community Health 2013;25:438-44.
17. Doval D, Prabhash K, Patil S, Chaturvedi H, Goswami C, Vaid A, *et al*. Clinical and epidemiological study of EGFR mutations and EML4-ALK fusion genes among Indian patients with adenocarcinoma of the lung. Onco Targets Ther 2015;8:117-23.
18. Noronha V, Prabhash K, Thavamani A, Chougule A, Purandare N, Joshi A, *et al.* EGFR mutations in Indian lung cancer patients: Clinical correlation and outcome to EGFR targeted therapy. PLoS One 2013;8:e61561.
19. Veldore VH, Rao RM, Kakara S, Pattanayak S, Tejaswi R, Sahoo R, *et al.* Epidermal growth factor receptor mutation in non-small-cell lung carcinomas: A retrospective analysis of 1036 lung cancer specimens from a network of tertiary cancer care centers in India. Indian J Cancer 2013;50:87-93.
20. Chougule A, Prabhash K, Noronha V, Joshi A, Thavamani A, Chandrani P, *et al.* Frequency of EGFR mutations in 907 lung adenocarcioma patients of Indian ethnicity. PLoS One 2013;8:e76164.
21. Sahoo R, Harini VV, Babu VC, Patil Okaly GV, Rao S, Nargund A, *et al.* Screening for EGFR mutations in lung cancer, a report from India. Lung Cancer 2011;73:316-9.
22. Bhatt AD, Pai R, Rebekah G, Nehru GA, Dhananjayan S, Samuel A, *et al*. Clinic-pathologic features of non-small cell lung cancer in India and correlation with EGFR mutational status. Indian J Cancer 2013;50:94-101.
23. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
24. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, *et al.* Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
25. Rosell R, Gervais R, Vergnenegre A, Massuti B, Felip E, Cardenal F, *et al*. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomized trial. J Clin Oncol 2011;29:7503a.
26. Sequist LV, Martins RG, Spigel D, Grunberg SM, Spira A, Jänne PA, *et al.* First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol 2008;26:2442-9.
27. Chen L, Chen R, Zhu Z, Zhang Y, Wen Z, Li Y, *et al.* Predictive factors associated with gefitinib response in patients with advanced non-small-cell lung cancer (NSCLC). Chin J Cancer Res 2014;26:466-70.
28. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T, *et al.* Mutations of the epidermal growth factor receptor gene in lung cancer: Biological and clinical implications. Cancer Res 2004;64:8919-23.
29. Satouchi M, Negoro S, Funada Y, Urata Y, Shimada T, Yoshimura S, *et al.* Predictive factors associated with prolonged survival in patients with advanced non-small-cell lung cancer (NSCLC) treated with gefitinib. Br J Cancer 2007;96:1191-6.
30. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, *et al.* Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 2005;97:339-46.
31. Zhang Y, Kang S, Fang W, Hong S, Liang W, Yan Y, *et al.* Impact of smoking status on EGFR-TKI efficacy for advanced non-small-cell lung cancer in EGFR mutants: A meta-analysis. Clin Lung Cancer 2015;16:144-510.
32. Mitchell P, Mok T, Barraclough H, Strizek A, Lew R, van Kooten M, *et al*. Smoking history as a predictive factor of treatment response in advanced non-small-cell lung cancer: A systematic review. Clin Lung Cancer 2012;13:239-51.
33. Choi CM, Kim MY, Lee JC, Kim HJ. Advanced lung adenocarcinoma harboring a mutation of the epidermal growth factor receptor: CT findings after tyrosine kinase inhibitor therapy. Radiology 2014;270:574-82.
34. Kosaka T, Yatabe Y, Onozato R, Mitsudomi T. Analysis of the relationship between mutation of the epidermal growth factor receptor and response to gefitinib treatment in patients with recurrent lung cancer after pulmonary resection; updated analysis. J Thorac Oncol 2007;2:s724.