

A significant study on EGFR mutations in lung carcinomas

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ABSTRACT

Background: Lung cancer is one of the leading causes of cancer related deaths among both men and women. Non-small cell lung carcinomas comprises the majority (about 75%) of lung cancers, has proven difficult to treat due to poorly understood pathological mechanism. Recent advances in cell signalling pathways that control cell survival have identified genetic and regulatory aberrations that suppress cell death, promote cell division and induce tumorogenesis. One such discovery is that of epidermal growth factor receptor. Overexpression of EGFR has been reported and implicated in pathogenesis of many human malignancies including Non- small cell carcinoma of lung.

Aims And Objectives; To study EGFR expression by immunohistochemistry in diagnosed cases of Non- small cell carcinomas of lung at our institute.

To determine the value of EGFR test by IHC in predicting response to targeted therapy and clinical outcome.

Materials and Methods: A retrospective and prospective study of bronchial biopsies diagnosed as Non-small cell carcinoma for a duration of two years with their expression to EGFR immunohistochemistry marker at our institute and these patients response to the targeted therapy.

Results: Out of twenty nine (29) cases of lung malignancies majority were Non -small cell carcinomas- twenty seven cases (27), of which adenocarcinomas were seventeen (17) cases topped the list, followed by squamous cell carcinomas (5) cases, malignant epithelial lesions (3) cases and poorly differentiated carcinomas (2) cases. Small cell carcinomas were two (2) cases. Fifteen cases of non-small cell carcinomas cases showed EGFR mutations and twelve patients were started on the targeted therapy of Gefitinib and Erlonitib. All twelve of them showed good response to chemotherapy.

Conclusions: Most of the Non-small cell carcinomas of lung have EGFR mutations especially all adenocarcinomas in non-smokers. The clinical outcome of patients could be predicted. There is significant response to targeted chemotherapy.

Keywords: Lung, Cancer, Epidermal, Growth, Factor.

Introduction

Lung cancer is one of the leading causes of cancer related deaths among both men and women.⁽¹⁾ Non-small cell lung carcinomas comprising the majority (about 75%) of lung cancers, have proven difficult to treat due to poorly understood pathological mechanism. ^(2,3)Recent advances in cell signaling pathways that control cell survival have identified genetic and regulatory aberrations that suppress cell death, promote cell division and induce tumorogenesis. One such discovery is that of epidermal growth factor receptor. EGFR is a transmembrane receptor tyrosine kinase protein expressed in normal epithelial, mesenchymal and neurogenic tissue. EGFR over expression is related to cancer proliferation and has been implicated in pathogenesis of many human malignancies including Non -small cell carcinoma of lung. ^(4,5) Gefitinib is the first molecular target agent for lung cancer which inhibits

tyrosine kinase of the epidermal growth factor receptor. Erlotinib provides survival benefit in a phase III trial for chemotherapy for Non-small cell lung carcinomas. Studies identified somatic mutations in EGFR gene around the region encoding the ATP-binding pocket of the receptor's tyrosine kinase domain which increases sensitivity of tumour cells to gefitinib. ^(6,7)

Aims and Objectives

To study EGFR expression by immunohistochemistry in diagnosed cases of Non -small cell carcinomas of lung at our institute.

To determine the value of EGFR test in predicting response to targeted therapy and clinical outcome

Materials and Methods

A retrospective and prospective study of lung biopsies diagnosed as Non- small cell carcinomas in two years

(2017-2018) period with their expression to EGFR - IHC marker at our institute and those with positive expression, their response to the targeted therapy.

The patients were followed post therapy for a duration of ten years. The response to therapy was assessed in retrospective cases based on patients' condition and disease free survival gained. Clinical characteristics and treatment details were collected from the patient's medical records.

Results

Out of twenty nine (29) cases of lung malignancies majority were non-small cell carcinomas (27) -93% and small cell carcinomas were two (2) cases- 7%. (FIG:1) Out of (27) non-small cell carcinomas there were seventeen (17) adenocarcinomas - 63% which topped the list, followed by squamous cell carcinomas (5) 18% , malignant epithelial lesions (3) 11% and poorly differentiated carcinomas(2) 7 %. (FIG:3)There were 14 males (52%) and 13 females(48%) of 27 Non-small cell lung carcinomas.(FIG:2)

15 cases (55.5%) of non-small cell carcinomas showed over expression to EGFR marker and 12 patients were started on the targeted therapy of Gefitinib or Erlonitib. (TABLE:1) Majority of adenocarcinomas -10 cases (67%), 4 (27%) of squamous cell carcinoma and 1 (7%) of malignant epithelial lesion were positive for EGFR marker. There was good response to treatment in nine patients (75%) of adenocarcinoma and three (25%) of squamous cell carcinoma . All of them were nonsmokers.

There were two interesting cases which presented with distant metastasis and that showed good response to Erlotinib and gefitinib. One was a 51yr old male patient with histopathology report of Infiltrating moderately differentiated adenocarcinoma with desmoplastic stroma.

PET CT & Whole body scan of the patient showed oligometastasis in brain with extracranial disease , diagnosed as right lung carcinoma with brain secondaries. MRI Brain showed 2.5x2.3cm lesion in left occipital lobe with perilesional edema suggestive of metastasis. CECT scan chest showed a small heterogeneous lesion 3x2.8 cms in size in the apical segment of right upper lobe with spiculated margins and enlarged perihilar lymph nodes. Genomic alterations showed EGFR positive hot spot mutations. The drug approved was Erlotinib/gefitinib. The treatment given was Erlotinib.

The second interesting case was of 48yr old female with histopathological report left lung invasive adenocarcinoma lepidic predominant type. Pleural fluid for analysis showed white blood cell count-1350 cells/cumm and Pleural fluid cytology show adenocarcinoma deposits. CT Chest showed consolidation in the left lower lobe, Multiple small nodular lesions in bilateral lung parenchyma-Metastases, collapse of left lower lobe and left pleural effusion .Ultra sound abdomen showed left pleural effusion. FDG PET-CT SCAN of Chest shows a lobular mass lesion of 4.2x3.1cm size in left lower lobe and superior segment with adjacent scarring. Patient was diagnosed as Non-small cell carcinoma with adrenal and bone metastasis. EGFR Hotspot mutations was positive. Treatment given was gefitinib

Discussion

Non -small cell carcinomas accounted for majority of lung carcinomas and some of our patients presented with advanced disease at the time of diagnosis in our study.⁽⁸⁾Adenocarcinoma is one of the most common histological subtypes of NSCLC. ^(9,10) Molecular profiling of tumor samples from patients with NSCLC has identified

TABLE 1

| | AGE/SEX | CLINICAL DETAILS | HISTOPATHOLOGY DIAGNOSIS | EGFR MARKER |
|----|---------|---|-----------------------------|-------------|
| 1 | 60YR/F | Cough With Expectoration/Positive | Adenocarcinoma | Positive |
| 2 | 62YR/F | Cough With Expectoration | Adenocarcinoma | Positive |
| 3 | 48YR/F | Cough With Expectoration,Chest Pain | Adenocarcinoma-Lepidic Type | Positive |
| 4 | 51YR/M | Cough With Expectoration | Adenocarcinoma | Positive |
| 5 | 53YR/F | Cough With Expectoration | Adenocarcinoma | Positive |
| 6 | 71YR/M | Cough With Expectoration | Adenocarcinoma | Positive |
| 7 | 64YR/M | Cough With Expectoration | Adenocarcinoma | Positive |
| 8 | 58YR/F | Cough With Expectoration,Chest Pain | Adenocarcinoma | Positive |
| 9 | 55YR/F | Cough With Expectoration Shortness Of Breath | Adenocarcinoma Papillary | Positive |
| 10 | 73YR/M | Cough With Expectoration Shortness Of Breath | Adenocarcinoma | Positive |

| | AGE/SEX | CLINICAL DETAILS | HISTOPATHOLOGY DIAGNOSIS | EGFR MARKER |
|----|---------|-----------------------------|-------------------------------|-------------|
| 11 | 73YR/M | Cough With Expectoration | Adenocarcinoma Papillary Type | Positive |
| 12 | 65YR/F | Chest Pain ,Cough | Adenocarcinoma | Positive |
| 13 | 39YR/F | Cough | Adenocarcinoma | Positive |
| 14 | 35YR/F | Right Side Pleural Effusion | Adenocarcinoma Mucinous | Positive |
| 15 | 45YR/M | Cough | Adenocarcinoma | Positive |

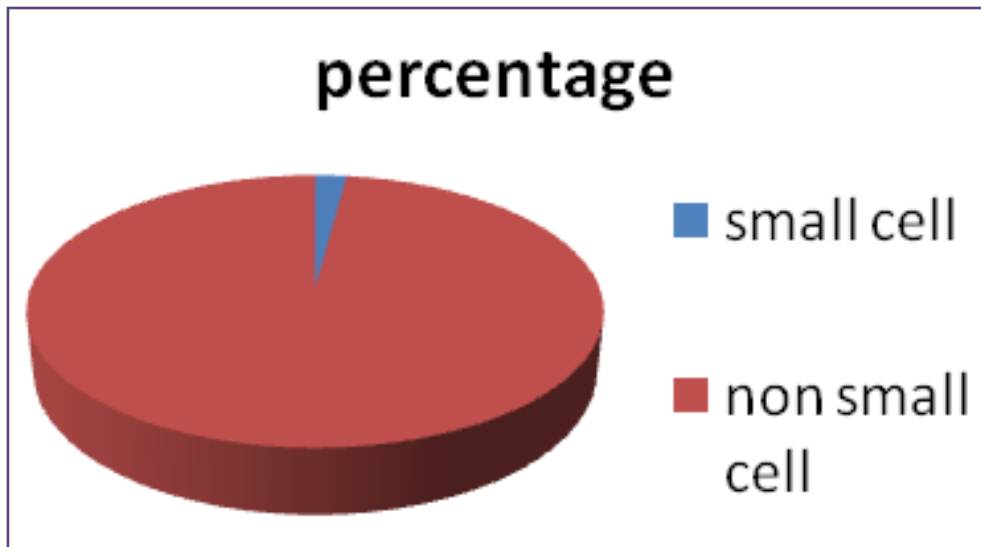


Fig. 1: PERCENTAGE OF SMALL CELL CARCINOMAS/NON SMALL CELL CARCINOMAS.

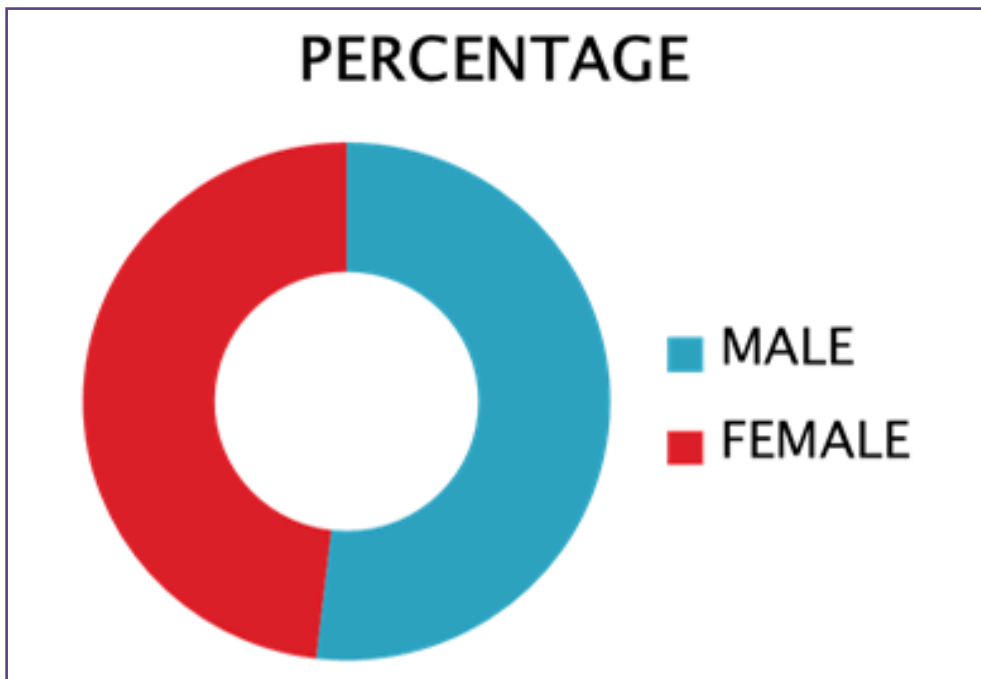


FIG. 2: PERCENTAGE OF MALE TO FEMALE RATIO.

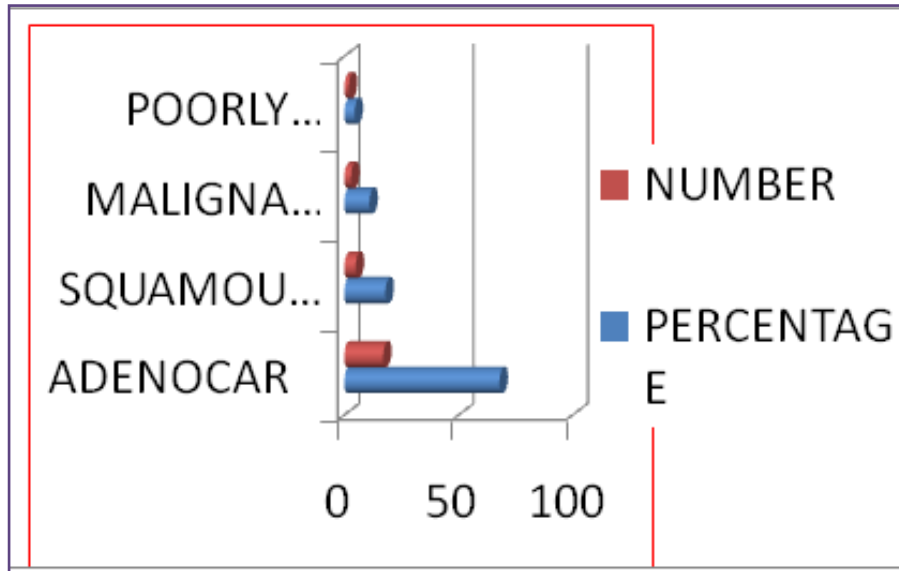


FIG. 3: TYPE OF NON SMALL CELL CARCINOMAS.

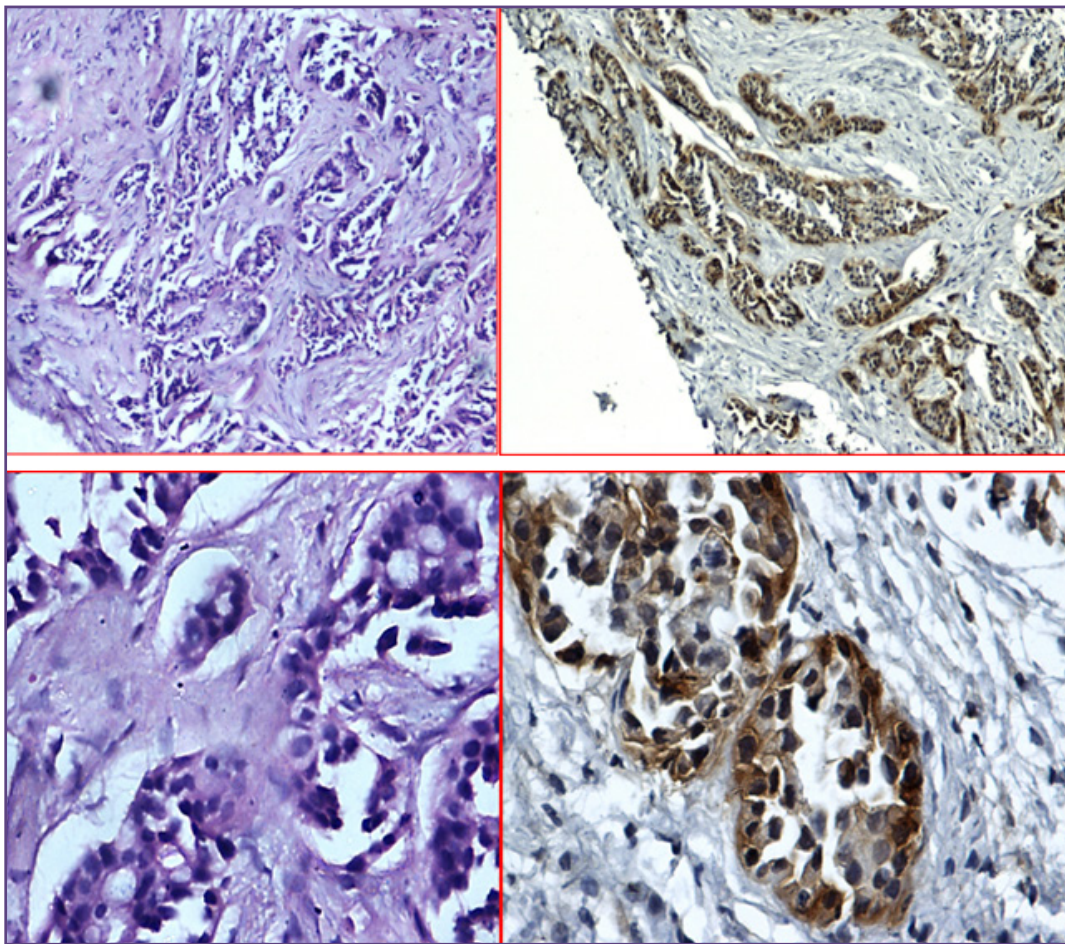


Plate 1: a,b,c,d-Adenocarcinoma H&E stain 10x,40x,EGFR stain in 10x, 40x

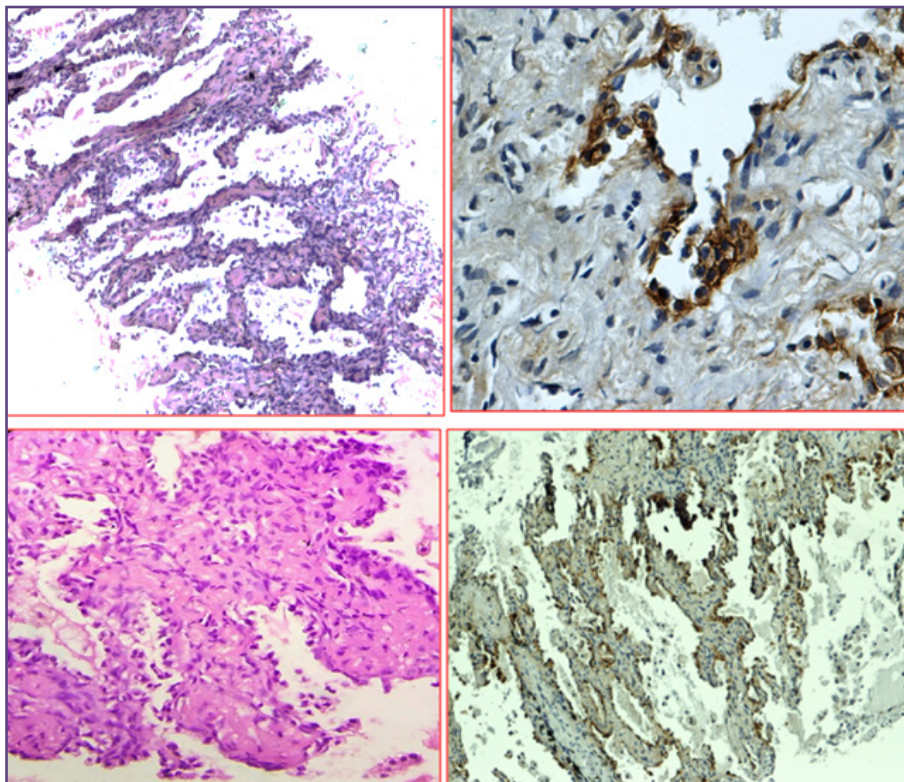


Plate 2:e,f,g,h lepidic adenocarcinoma H&E 10x,40x, EGFR stain 10 x,40x.

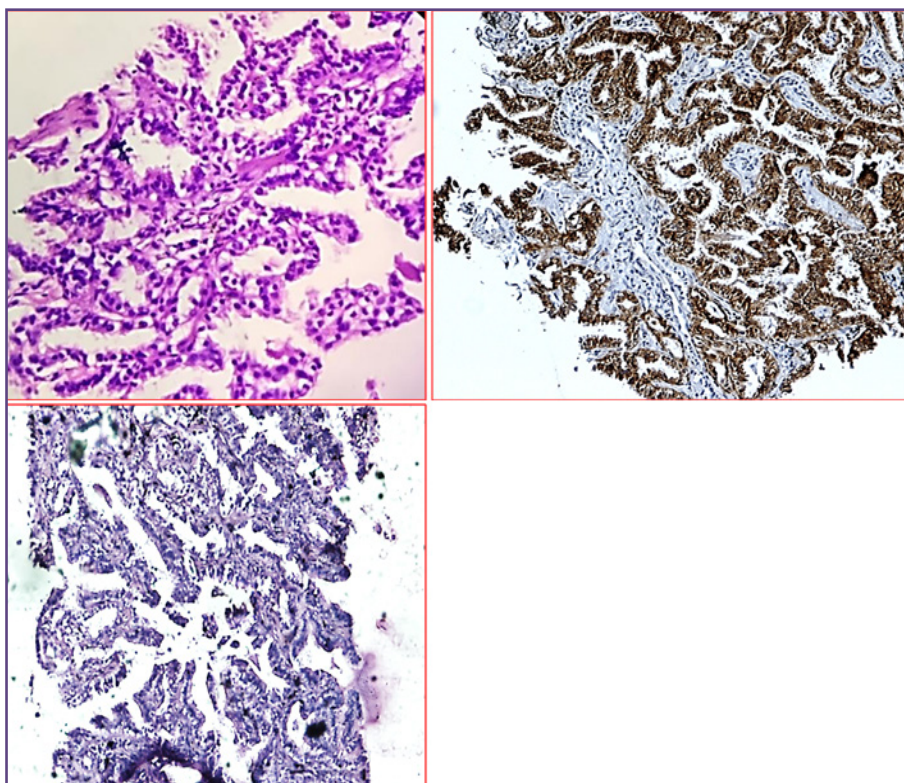
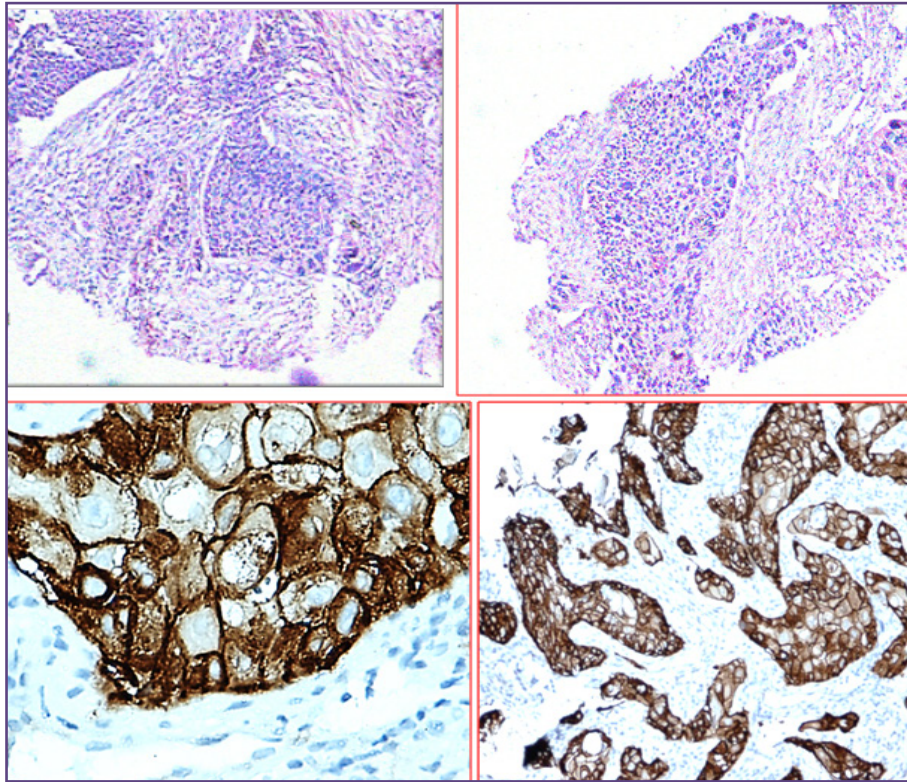


Plate 3:i,j,k Papillary adenocarcinoma H&E stain 10x,EGFR stain 10 x stain.



late 4:l,m,n,o :Squamous cell carcinoma 10x,40x,H&E stain, EGFR stain 40x,10x.

epidermal growth factor receptor mutations in more than 50% of cases in various studies. ^(11,12)

Three land mark trials in year 2004 showed that lung adenocarcinomas with mutated EGFR had significant responses to gefitinib and erlotinib.⁽¹³⁾ Other phase III clinical trials with chemotherapy of erlotinib or gefitinib in NSCLC patients showed a survival improvement for patients with EGFR mutations.⁽¹⁴⁾

Overall response rates to tyrosine kinase inhibitors in adenocarcinomas with mutations in EGFR are in the range of 65-90% in other studies.⁽¹⁵⁾ 75% of squamous cell and 90% adenocarcinomas showed response to tyrosine kinase in our study. High response rates to tyrosine kinase inhibitors with EGFR mutations is seen in adenocarcinoma, non-smoker and Japanese patients similar to our study.⁽¹³⁾

Tumours with amplified EGFR are more likely to have a significant component of solid growth, association between EGFR amplification. Studies reported certain morphologic characteristics that appear to be associated EGFR mutations have better responses to tyrosine kinase inhibitors. These include adenocarcinoma with a non-mucinous bronchioloalveolar component, hobnail cell type, as well as papillary and micropapillary patterns.^(14,15)

Papillary and non mucinous bronchioloalveolar type in our study showed good response to chemotherapy.

Conclusions

Most of the Non-small cell carcinomas of lung have EGFR mutations especially all adenocarcinomas in non-smokers. The clinical outcome of patients could be predicted. There is significant response to chemotherapy especially to TKIs.

Abbreviations

NSCLC-Non- small cell lung carcinomas, EGFR-Epidermal growth factor receptor,TKIs- tyrosine kinase inhibitors.

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