ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 02 | February - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EGFR EXPRESSION IN NON-SMALL CELL LUNG CANCER AND ITS CLINIC-RADIOLOGICAL CORRELATION.

Clinical Radiology

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ABSTRACT

Introduction : Globally, in both sexes combined, lung cancer is the most commonly diagnosed cancer (11.6% of total cases) and the major cause of cancer deaths (18.4% of the total cancer deaths). In India, lung cancer is the 4th most commonly diagnosed cancer with 67,795 new cases and 63,475 cancer deaths in the year 2018 . With the recent global trends of increasing incidence and cancer related mortality of NSCLC in mind, we plan to study the prevalence and pattern of NSCLC along with the expression of EGFR and its correlation with various clinic-pathological parameters in Indira Gandhi Medical College Shimla, Himachal Pradesh as it is the tertiary care institute in Himachal Pradesh. **Materials and methods:** This is a hospital based cross-sectional observational study. The study population comprised of patients with operable and resectable NSCLC, who underwent lung biopsies between June 2017 to July 2018 at Indira Gandhi Medical College, Shimla. The samples for histopathology and immunohistochemical examination were collected from lung biopsy specimens which were endobronchial biopsy, transbronchial biopsy and peripheral lung biopsy. **Results** : Majority of the cases presented in the 6th and 7th decade of life. The mean age of presentation was 65.6 years. Histologically most of the tumors were SCC (57.3%), followed by ADC (33.3%), NSCLC (NOS) (8.0%) and LCC (1.3%). Majority of the tumors showed moderate degree of differentiation (77.9%) followed by poor differentiation (14.7%) and well differentiation (7.4%). EGFR positivity was seen in 61 (81.3%) cases.

KEYWORDS

INTRODUCTION

Globally, in both sexes combined, lung cancer is the most commonly diagnosed cancer (11.6% of total cases) and the major cause of cancer deaths (18.4% of the total cancer deaths) with incidence of 20,93,876 cases and 17,61,007 deaths in the year 2018. Among males, it is the most frequent cancer and leading cause of cancer associated mortality. In females, it is the 3rd and 2nd most common cancer in terms of incidence and mortality respectively[1].

In India, lung cancer is the 4th most commonly diagnosed cancer with 67,795 new cases and 63,475 cancer deaths in the year 2018[2]. This increase in number of cases has clearly surpassed the estimation of new cases of lung cancer annually to be 67,000 by the year 2020[3].

Lung cancer can be broadly classified into two major types; Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC comprising the majority (85%) of the lung cancers[4,5]. NSCLC is further subdivided into three main subtypes; Adenocarcinoma (ADC), Squamous cell carcinoma (SCC) and large cell carcinoma (LCC).Among NSCLC, ADC is the most common subtype comprising 40% cases followed by SCC (25-30%) and LCC (10-15%) [6].

Lung cancer is a heterogenous multifactorial disease[7]. Carcinogenesis is a multistep process which takes years to develop by evading the protecting mechanisms of the body like immune system, antioxidative system and DNA repair mechanisms[8,9]. Both major forms of the NSCLC (ADC and SCC) arise from their respective pre-malignant lesions. SCC of the lung starts as bronchial epithelial dysplasia to CIN to invasive cancer and ADC has atypical adenomatous hyperplasia as a premalignant lesion[4]. LCC is the diagnosis of exclusion as it lacks both glandular (ADC) and squamous (SCC) differentiation.

Although, there are many risk factors associated with lung cancer, smoking tobacco is beyond doubt the most important one, the cancer infact apparently being rare before the widespread use of tobacco[4]. With increasing prevalence of smoking, lung cancer has reached epidemic proportions in India[10]. Besides smoking, other risk factors which contribute to the development of lung cancer are: second hand smoke, environmental exposure (indoor and outdoor air pollution), underlying lung diseases (eg. HPV infection) and genetic factors[11].

NSCLC has been proven difficult to treat inspite of the major advances in the surgical techniques and systemic chemotherapy with resultant 5-year survival rate of only 5-15% (after the initial diagnosis) [12]. Owing to this dismal prognosis, advanced stage at diagnosis, limited surgical options and plateau of cytotoxic therapies, new treatment options are needed[13]. Nowadays, research is focused upon exploring the pathology of the lung cancer at the molecular level[14,15].

Research has proven that EGFR, a 170 K dalton transmembrane receptor tyrosine kinase protein has emerged as a leading target for the treatment of patients of NSCLC[12]. Dysregulation/overexpression of EGFR leads to increased intracellular pathways activity leading to cellular (tumor) proliferation, invasion, angiogenesis and higher incidence of metastasis. Overexpression of EGFR is identified in 40-89% of NSCLC with highest rates seen in SCC (89%) followed by ADC (49%)[5,16].

Immunohistochemistry (IHC) is a standard method used to identify the presence of EGFR. Currently, scoring systems assist in determining the EGFR expression levels in tumor samples using internationally validated antibodies[17].

With the recent global trends of increasing incidence and cancer related mortality of NSCLC in mind, we plan to study the prevalence and pattern of NSCLC along with the expression of EGFR and its correlation with various clinic-pathological parameters in Indira Gandhi Medical College Shimla, Himachal Pradesh as it is the tertiary care institute in Himachal Pradesh.

Aims :

1. To know the prevalence and type of NSCLC lung in Indira Gandhi Medical College, Shimla.
2. To study EGFR expression in different types of NSCLC.
3. To assess the utility of EGFR expression in diagnosis and its correlation with clinico-pathological parameters in NSCLC.

MATERIALS AND METHODS :

This is a hospital based cross-sectional observational study. The study population comprised of patients with operable and resectable NSCLC, who underwent lung biopsies between June 2017 to July 2018 at Indira Gandhi Medical College, Shimla. The samples for histopathology and immunohistochemical examination were collected from lung biopsy specimens which were endobronchial biopsy,

transbronchial biopsy and peripheral lung biopsy. Paraffin embedded blocks of these patients were collected for histopathological and immunohistochemical examinations. The relevant clinical and clinico-pathological information of all these patients including gender, age, smoking, site of tumor, histological type and stage of the disease was recorded according to the proforma attached.

Inclusion Criteria

1. Patients of both sexes, irrespective of age diagnosed as primary Non-small cell lung cancer.
2. Patients willing to give informed consent.

Exclusion Criteria

1. Patients not willing to participate in the study.
2. Patients having recurrence of cancer.
3. Patients who have taken radio/chemo therapy.

Interpretation Of Ihc Score

Interpretation Was Done As Follows:

1. Immunoreactivity for EGFR was evaluated according to percentage of immunoreactive cells showing membrane and/or cytoplasmic staining, scoring was done as follows:
   0 - no / faint staining in < 10% of cells
1 + - faint staining in > 10% tumor cells
   2+ - moderate staining in > 10% of cells
   3+ - strong staining in >10% of cells
2. H-score: It is the product of the percentage of cancer cells positive for EGFR protein on the cell surface multiplied by the overall intensity of staining (ranging from 0-3+), producing a number from 0 to 300[17,5].

Statistical Analysis

The data was collected, cleaned and entered into electronic Microsoft Excel spreadsheet. After validation and resolving all the discordance with the help of original record, a final data base was prepared. The data was analyzed using appropriate statistical techniques.

RESULTS

The present study was conducted in the department of Pathology, Indira Gandhi Medical College and Hospital, Shimla, Himachal Pradesh. The study included 75 routine cases of lung cancer specimens biopsied by Department of Pulmonary Medicine and diagnosed in Pathology Department from June 2017 to July 2018. Relevant clinical detail of the patient was recorded and correlated with various pathological parameters which were further correlated with EGFR expression in the NSCLC cases using IHC staining.

- Most common age group involved was between 60 to 69 years of age comprising 31 (41.3%) cases, followed by 70 to 79 age group comprising 20 (26.7%) cases, 50 to 59 age group with 15 (20.0%) cases, 80 to 89 age group with 7 (9.3%) cases and least number of cases were present in less than 49 years of age group comprising 2 (2.7%) cases.
- Average age for males and females was 65.6 years. Out of 75 cases in our study, 59 (78.7%) were males and 16 (21.3%) were females. Male to female ratio for NSCLC in our study was approximately 3.7:1
- Most common presenting symptom was cough, seen in 67 (89.3%) cases. Chest pain was present in 29 (38.7%) cases. Least common symptom was of shortness of breath, seen in 19 (25.3%) cases.
- Out of 75 cases in our study, 55 (73.3%) cases were smokers and 20 (26.7%) cases were non-smokers. Smoker to non-smoker ratio was 2.8:1.
- Out of 59 males in our study 47 (79.7%) were smokers. Out of 16 females in our study 8 (50%) were smokers.

Table 1: Histological Subtypes In Nsclc (n=75)

Subtype	No. of cases	Percentage (%)
SCC	43	57.3
ADC	25	33.3
LCC	1	1.3
NSCLC (NOS)	6	8.0

- Out of 75 cases in our study, majority of cases were of SCC, comprising 43 (57.3%) cases.
- Out of total 75 cases in our study, grade of tumor differentiation was ascertained in 68 cases (SCC and ADC). Among these 68 cases, majority of the cases, 53 (77.9%) showed moderate degree of differentiation. Poor differentiation was seen in 10 (14.7%) cases. Only 5 (7.4%) cases showed well differentiation.
- Immunohistochemical staining for EGFR was done on tumors diagnosed as NSCLC [its subtypes and NSCLC (NOS)]. Tumor cell cytoplasmic membrane staining was used to define the positivity as 1+. 2+, 3+ on the basis of >10% tumor cells showing light, moderate and strong staining respectively.
- Percentage of tumor cells showing positivity was used to calculate the H-score using the formula: H-score = 1 x (percentage of 1+ cells) + 2 x (percentage of 2+ cells) + 3 x (percentage of 3+ cells) giving the score of 0-300. H-score is basically used as a marker to predict the outcome/survival benefit for the use of various chemotherapeutic agents in patients of the lung cancer. There is less literature on the use of H-score, and in present study we tried to find the correlation between H-score and various clinico-pathological parameters.
- Out of 75 cases in our study, 61 (81.3%) cases showed positivity for EGFR. 14 (18.7%) cases were negative for EGFR staining.

Table 2: EGFR Cytoplasmic Membrane Immunostain Scoring In NSCLC (n=75)

Score	No. of cases	Percentage (%)
Score- 0	14	18.7
Score- 1+	28	37.3
Score- 2+	24	32.0
Score- 3+	9	12.0

- Out of 75 cases in our study, majority of the cases, 28 (37.3%) showed EGFR positivity score 1+. 24 (32.0%) cases showed EGFR positivity score 2+. EGFR positivity score 3+ was seen in 9 (12.0%) cases. EGFR staining was negative in 14 (18.7%) cases.

3: EGFR expression and its correlation with Smoking in NSCLC

Out of 55 smokers in our study, 47 (85.5%) showed EGFR expression while 8 (14.5%) were negative for EGFR staining. Among 20 non-smokers in our study, 14 (70%) showed EGFR expression while 6 (30%) were negative for EGFR staining.There was no statistically significant correlation between EGFR expression and smoking in NSCLC (p-value= 0.179).

4: EGFR expression and its correlation with subtype in NSCLC

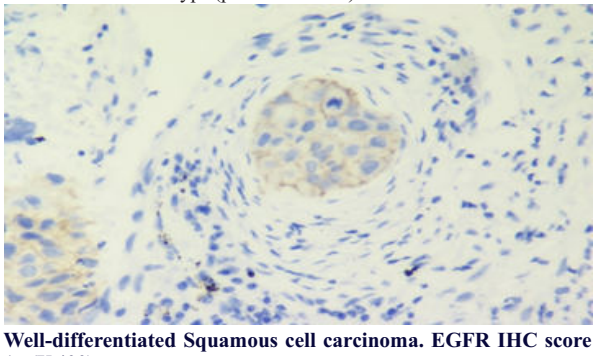
- Out of 43 cases of SCC, 38 (88.4%) showed EGFR IHC positivity while 5 (11.6) were negative for EGFR expression. Among 25 cases of ADC, 19 (76%) showed EGFR IHC positivity while 6 (24%) were negative for EGFR expression. 1 (100%) case of LCC showed EGFR expression. 50% of cases diagnosed as NSCLC (NOS) were positive for EGFR expression.There was no statistically significant correlation of EGFR expression with subtype in NSCLC (p-value= 0.113).

5: IHC H-score

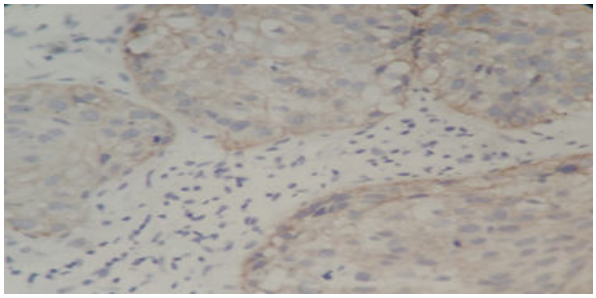
- Out of 75 cases, H-score of < 200 was seen in 56 cases and ≥ 200 was seen in 19 cases.

6: H-score and its correlation with Subtype in NSCLC

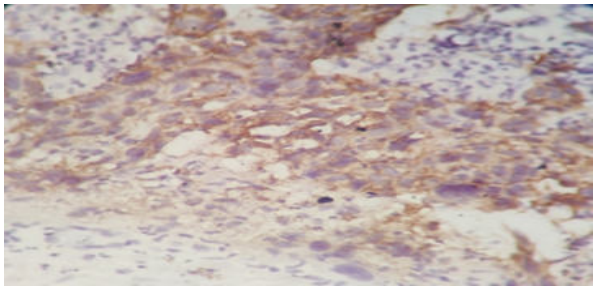
- Out of 43 cases diagnosed as SCC, 31 (72.1%) had H-score of <200 and 12 (27.9%) had H-score of ≥ 200.
- Among 25 cases diagnosed as ADC, 21 (84%) had H-score of <200 and 4 (16%) had H-score of ≥ 200. 1 (100%) case of LCC had H-score of ≥ 200. Out of 6 cases diagnosed as NSCLC (NOS), 4 (66.7%) had H-score of <200 and 2 (33.3%) had H-score of ≥ 200. There was no statistically significant correlation between H-score and NSCLC subtype (p-value= 0.217).



Well-differentiated Squamous cell carcinoma. EGFR IHC score 1+ (X 400)



Well-differentiated Squamous cell carcinoma. EGFR IHC score 2+ (X 400)



Moderately-differentiated Adenocarcinoma. EGFR IHC score 3+ (X 400)

DISCUSSION

Lung cancer remains the major cause of cancer related morbidity and mortality accounting for more deaths than any other cancer[18].

Contrary to the past correlation of smoking with mainly SCC, now ADC is becoming more common even among the smokers. This increased correlation of ADC with smoking is due to the introduction of lower yield–filtered cigarettes and deeper inhalation leading to more peripheral distribution of carcinogens of smoke in the lungs[11].

As most of the patients are diagnosed at the advanced stage of the disease, there is an urgent need of better understanding of the lung cancer pathogenesis which will facilitate the earlier diagnosis and its earlier treatment with improved prognosis[17,19]. Newer techniques such as IHC and molecular technology have helped a lot to gather the information about tumorigenesis. Research has revealed that lung cancer originates from dysregulated cellular proliferation which pushes normal cells to undergo malignant transformation[20].

EGFR is a key molecule in the lung cancer pathology which promotes cancer initiation and progression. It is expressed more abundantly in the malignant tissue rather than its normal counterpart[21]. EGFR dependant activations of Ras/MAPK and PI3K/AKT pathways are the culprits providing pro-prolifirative signaling, thus promoting cellular multiplication and attenuates apoptosis in NSCLC[20].

Extensive workup has been done on understanding the lung cancer pathology and its relation with the various clinical parameters including the expression of EGFR in NSCLC. In the present study majority of the patients of NSCLC were in 6th and 7th decade of life with male to female ratio of 3.7:1. Cough was the major symptom present in the patients. Majority of the patients were smokers.

There was no statistically significant correlation between EGFR expression as well as H-score with various clinico-pathological parameters. EGFR expression is used for targeted therapy.

Hence to conclude we would like to say that there is need for standardization of EGFR staining protocol, including the use of a particular/specific antibody.

There is also a need of standardization of EGFR scoring method for the evaluation and reproducibility of IHC staining results. The need of larger studies with long term follow-up to see the prognostic value of EGFR expression in patients with NSCLC is also needed.

Conflicts Of Interest :

There is no conflicts of interest in the present study.

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