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Comparison of EGFR with Other Molecular, Demographic and Clinicopathologic Data in Nonsmall Cell Lung Carcinoma: A Study from Tertiary Cancer Centre from Western Part of India

Running Title

Comparison of EGFR with Other Molecular, Demographic and Clinicopathologic Data in Nonsmall Cell Lung Carcinoma

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Abstract: ***Most of non-small cell lung cancer (NSCLC) is a locally advanced or metastatic stage which is affiliated with constrained therapy option and poor prognosis at appearance. Approximately 30% of NSCLC tumors harbor a mutation in the epidermal growth factor receptor (EGFR) gene, with geographical variation in rates reported to be highest in Asia (38%) and lowest in Europe (14%). With tumor molecular genetics at the forefront of precision medicine, subclassification of NSCLC based on EGFR mutation status has been paramount for predicting response to EGFR targeted therapies in unresectable advanced and metastatic disease. Patients / Materials & methods: 100 cases of lung carcinoma were retrospectively studied from October 2019 to February 2021. These patients were identified on the basis of biopsy proven non small cell lung carcinoma or metastatic carcinoma in lung biopsy and EGFR detection was present. Results: Of the 100 cases who underwent the EGFR detection method, Total no of cases in which EGFR mutation is present is 17 (34%) and total no of EGFR wild type cases is 32 (64%) This study supports the finding of increased metastatic recurrence in patients with locally advanced EGFR mutated (70.5%) NSCLC undergoing definitive therapy as compared to wild type disease (50%).***

Keywords: Non-small cell lung cancer, NSCLC, Epidermal growth factor receptor, EGFR, wild type

1.Introduction

Lung cancer, most common type of cancer worldwide, impacting ~ 2.1million people and causing an estimated 1.7 million deaths each year, most of patients present in an advanced stage (stage IIIB and IV) at diagnosis, resulting in higher mortality rates[1, 2]. Lung cancer can be divided into small cell lung cancer (SCLC) ~15% of cases, and non-small cell lung cancer (NSCLC) ~85% of cases; histologic subtypes of NSCLC include adenocarcinoma ~40–50% of all lung cancer cases, squamous cell carcinoma ~25–30% of all lung cancer cases, and large cell carcinoma ~10–15% of all lung cancer cases[3, 4, 5]. The key molecule is epidermal growth factor receptor (EGFR); with an extracellular ligand-binding domain with tyrosine kinase activity. EGFR mutation harboured by~30% of non-small cell lung cancer (NSCLC) cases, with geographical variation highest in Asia (38%) and lowest in Europe (14%) [6, 7]. Subclassification of NSCLC done based on EGFR mutation for predicting response to EGFR targeted therapies in not resectable, advanced and metastatic disease[8]. This tertiary cancer hospital department aims to do the retrospective study on the role of EGFR in non small cell lung cancer to better understand the clinicopathological correlation of nsclc with EGFR mutated /wild type cases.

2.Materials and Methods

We retrospectively collected 100 cases of lung carcinoma who presented in the hospital from October 2019 to February 2021. These patients were identified on the basis of biopsy proven non small cell lung carcinoma or metastatic carcinoma in lung biopsy and EGFR detection was present. The patients who were lost to follow up or did not undergo treatment with curative intent at time of initial diagnosis were excluded. The demographic, clinical, and treatment details were retrieved from the patients' case records. The EGFR mutational status was assessed and correlated with the clinical and pathological parameters, including age, gender, smoking status, histology, stage of disease, treatment and response to therapy. This protocol was approved by the Institutional Ethics Committee (IEC).

Collection of patient samples: formalin-fixed, paraffin-embedded tissue (FFPET) specimens were collected for the EGFR detection methods.

Mutation analysis by RT-PCR: The TRUPCR® EGFR Kit is an in vitro diagnostic test intended for the qualitative detection of 32 somatic mutations in exons 18-21 (Table) of epidermal growth factor receptor (EGFR) gene from tumor tissue DNA (fresh, frozen or formalin fixed paraffin-embedded tissue) or liquid biopsy. Results are intended to aid the clinician in identifying patients with lung cancer who may benefit from treatment with EGFR tyrosine kinase inhibitors.

3.Results

This is the retrospective study in which 100 cases were taken. Out of 100, 40 cases show very scanty DNA tissue or less number of tumor cells; so no result of EGFR possible & in 11 cases no proper work up present. out of the 49 cases, this study supports the finding of increased metastatic recurrence in patients with locally advanced EGFR mutated (70.5%) NSCLC undergoing definitive therapy as compared to wild type disease (50%). On follow up on Positron emission tomography-computed tomography, 2 cases show increase in size of lesion in follow up and 2 cases show decrease in size of lesion in EGFR mutated cases; while in EGFR wild type; five cases show decrease in size and one case show increase in size.

The majority in both groups received standard of care treatment, including cytotoxic platinum-based doublet therapy when needed and even based on stage. But of the cases which underwent EGFR mutation, EGFR inhibitors that is tyrosine kinase inhibitors are given in the definite therapy.

4.Discussion

Many centers across the world and in India have now incorporated evaluation of the EGFR mutation status in the initial management algorithm of NSCLC patients. The mutations in EGFR are associated with the ATP-binding site of tyrosine kinase domain which is targeted by tyrosine kinase inhibitors[9]. This led to the development of EGFR mutation targeted tyrosine kinase inhibitors (TKIs) in NSCLCs patients. However, majority of patients with EGFR mutation are found to be resistant (primary resistance) or gradually develop resistance (acquired resistance) after EGFR-TKI therapy[10]. In NSCLC patients with acquired resistance, T790M mutation is found in approximately 50%–60% of the cases[11]. Therefore, along with sensitizing EGFR mutation in exons 19 and 21, identifying the resistant mutation T790M is also important and critical for treatment-related decision-making[12]. Despite advances with unresectable disease, very little is known about the prognostic implications of EGFR mutation status in early and locally advanced NSCLC constraint to definitive therapy. Further investigation of molecular tumor markers, particularly EGFR, as a predictor of recurrence is required[8]. Moreover, various randomized trials also support the significance of performing EGFR mutation testing before the initiation of NSCLC treatment[13]. Several traditional methods such as immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and denaturing high-performance liquid chromatography (DHPLC) are available for EGFR mutation, but they provide limited information. More sensitive methods such as polymerase chain reaction (PCR)-based methods (reverse transcriptase-PCR [RTPCR], real-time PCR, quantitative PCR [qPCR], allele-specific PCR, etc.) are also available. In India, in NSCLC cancer cases EGFR mutation is detected by PCR-based methods and Sanger sequencing (SS) in about 20%–50% of cases [14]. The prevalence rates of EGFR mutations in NSCLC vary widely across different ethnicities. It has been reported to be in the rate of 10 – 15% in North Americans and Europeans, 26 – 30% in various East Asian series, including Chinese, Koreans, and Japanese[15-20] whereas, few studies from India have reported mutation rates varying from 35 to 51.8% [21-26]. Of the 100 cases who underwent the EGFR detection method, Total no of cases in which EGFR mutation is present is 17 (34%) and total no of EGFR wild type cases is 32 (64%). Mutations have been found to be highly co-existent with adenocarcinoma histology, women, and nonsmokers[2]. Mutations in EGFR, in our study, are found to be with most common histology pattern in both EGFR wild and mutated type are adenocarcinoma, higher in males than female with the non smoker category. According to a study done by Sandra P. D' Angelo, 31% percent of all EGFR mutations would be missed if testing were restricted to women, 40% would be missed if testing were restricted to persons who had never smoked, and 57% would be missed if testing were restricted to women who never smoked cigarettes[27]. In the reported literature, approximately 45 to 54% of EGFR mutations are in-frame deletions in exon 19, while approximately 40% of EGFR mutations are missense mutations in L858R in exon 21 and between 4 to 9% of the mutations were reported in exon 20[28] but the most common mutation seen in our study is EXON19, EXON 20 followed by exon 21.

No statistically significant relation between EGFR mutations and stage of the disease was found in this study, suggesting the possibility that EGFR mutation is an early event in the pathogenesis of lung adenocarcinoma[29]. The same inference was also drawn from the study by Tang et al. who had tested the presence of EGFR mutation in histologically normal bronchial epithelium from lung adenocarcinoma and found that normal bronchial epithelium present within the tumor frequently contained the same EGFR mutation as seen in the tumor tissue[30].

In the univariate analysis of patients treated with EGFR-TKIs, brain metastasis, bone metastasis, liver metastasis and Pleural effusion (PE) were all associated with poorer Progression free survival (PFS) and Overall Survival (OS) times. Furthermore, in the multivariate analysis, bone metastasis was associated with a poorer PFS time and brain metastasis was associated with a poorer OS time[31]. Between 30 and 40% of patients with lung cancer develop bone metastases during the course of their disease[32]. Brain metastases are a frequent complication of NSCLC, with 25–40% of patients developing brain metastases during the course of their disease, often within the first 2 years

following the diagnosis of the primary tumor [32, 33]. The risk of brain metastasis was increased in *EGFR*-mutated tumors at the time of diagnosis, as well as during the postoperative course of the disease. Compared with patients with wild-type tumors, patients with *EGFR*-mutated tumors exhibited more widespread brain lesions[34]. In our study, most common metastasis was seen in bone (especially vertebral mets) followed by brain, adrenal, and even presentation in supraclavicular lymph nodes.

The extent of lymph node involvement in NSCLCs is the most important prognostic factor and influences treatment strategy[35]. NSCLC with lymph node metastasis is more likely to develop recurrence and metastasis after surgical resection and have a shorter survival time after recurrence[36]. It is necessary to test the gene status of NSCLCs after resection with regional lymph node metastasis [37]. In this study, mediastinal lymph adenopathy is present in both the EGFR wild type and mutated type cases which includes pre carinal, sub carinal lymph nodes also.

ALK fusions occurred more frequently in young patients and the incidence of ALK fusions was higher in EGFR wild-type patients than that of the EGFR mutation patients (44) and it appeared to be associated with a higher risk of progression, recurrence and metastases[38, 39]. In this study of EGFR wild type cases, 20 cases show ALK show immunonegativity and Median age of EGFR mutated and a wild type case is 62 year.

ROS1 fusions were more prevalent in patients with poor differentiation[37]. In this study, even 4 cases show ROS positivity that belongs to the poorly differentiated adenocarcinoma category.

The latest version of the National Comprehensive Cancer Network reported NSCLC patients could benefit from immunotherapy when TPS was over 1% [40]. For example, when TPS ≥ 50%, PD-1/PD-L1 antibody combined with chemotherapy is the best choice for ACC and PD-1/PD-L1 antibody alone is the best choice for SCC. When TPS during 1% to 49%, PD-1/PD-L1 antibody combined with chemotherapy is prior to PD-1/PD-L1 antibody alone for both ACC and SCC. When TPS < 1%, PD-1/PD-L1 antibody combined with chemotherapy is better than chemotherapy alone for both ACC and SCC[41]. In this study also, Correlation of PDL1 was seen. Out of 17 EGFR mutated cases, 5 cases show PDL1 positivity and 2 show negativity in EGFR mutated cases.

5.Conclusion

This study supports the finding of increased metastatic recurrence in patients with locally advanced EGFR mutated (70.5%) NSCLC undergoing definitive therapy as compared to wild type disease (50%).

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Contribution Details

Contribution	*Author*
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Design	Dr Anjali Sharma, Dr Simran Gilhotra
Definition of intellectual content	Dr Anjali Sharma
Literature research	Dr Simran Gilhotra
Clinical studies	Not applicable
Experimental studies	Not applicable
Data acquisition	Dr Simran Gilhotra
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Table: Showing BMCHRC Data of EGFR from Oct 2019 to Feb 2021

Serial number	Features	EGFR Mutated	EGFR Wildtype
1	No. of cases	17 (34%)	32 (64%)
2	AGE (median age: 62) <62 >62 (In years)	 13 (76%) 4 (23%)	 15 (42%) 16 (50%
3	SEX (MALE-M, FEMALE-F)	 11 6	 27 5
4	H/O SMOKING	3 CASES 14 non smokers	16 CASES 16 non smokers
5	MOST COMMON SYMPTOM	COUGH: 5 CASES Other symptoms: chest tightness, backache	COUGH: 12 CASES Other symptoms: chest tightness, backache
6	HISTOLOGY ADENOCARCINOMA (Fig 1) SQUAMOUS CELL CARCINOMA (Fig 2) Others	 12 2 3	 24 4 4
7	STAGE 1 2B 3B 4	 0 1 2 8	 0 0 2 19
8	NODAL STATUS MEDIASTINAL LYMPH NODE OTHER No lymphadenopathy	 7CASES 2 CASES 8 cases	 20 CASES 1 CASE 10 cases
9	SIZE OF LESION <3CM >3-<=5 >5-<=7 >7 CM	 1 6 3 1	 1 8 4 9
10	LATERALITY RIGHT LEFT BILATERAL	 13 4 0	 18 10 3
11	METASTASIS (bone> adrenal >brain)	12 (70.5%)	16 (50%)
12	PDL1 POSITIVITY NEGATIVITY	 5 2	 7 8
13	FOLLOW UP INCREASE IN SIZE	 2	 1

	DECREASE IN SIZE	2	5
14	ALK POS ALK NEG	- -	0 20
15	ROS POS ROS NEG	- -	4 14
16	EGFR MUTATION (Fig3) EXON 18 EXON 19 EXON 20 EXON 21	 1 7 7 2	

Figures:

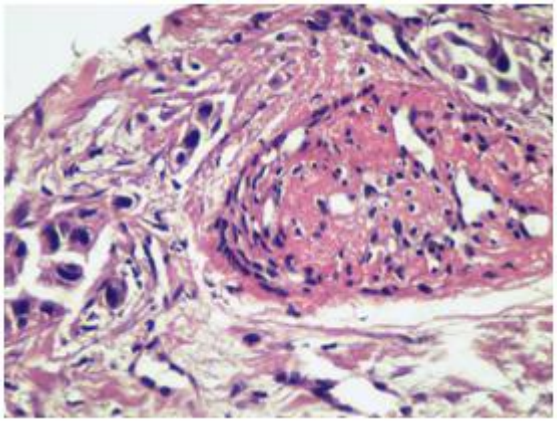

Figure 1: Adenocarcinoma

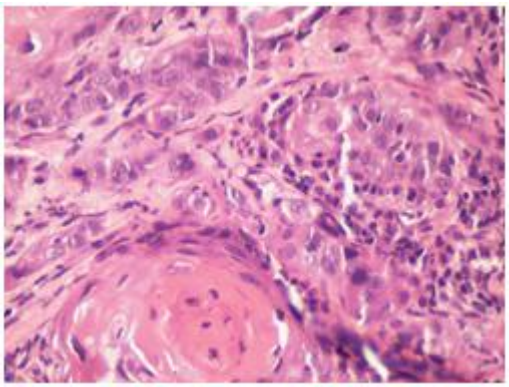

Figure 2: Squamous cell carcinoma

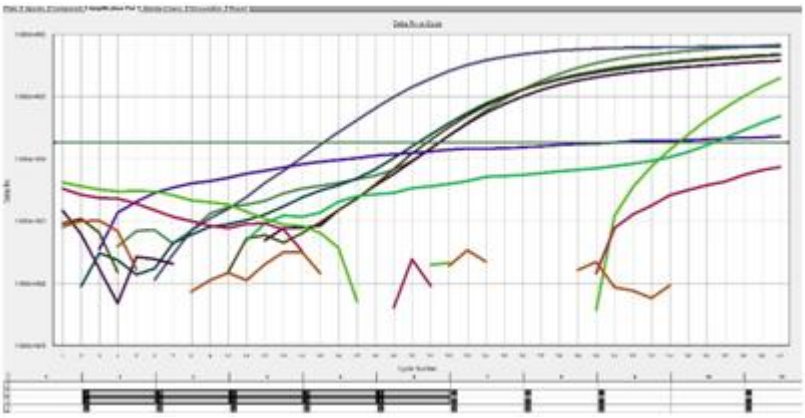

Figure 3: EGFR graph