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Prevalence of Common Driver Mutations in Advanced Adenocarcinoma of Lung in a Tertiary Hospital of Nepal

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ABSTRACT

Background

Molecular testing of lung adenocarcinoma has become standard in clinical practice because the studies have shown that the use of targeted therapies increases the overall survival and quality of life in these patients. The primary aim of this study is to see the prevalence of common driver gene mutations (DGM) in advanced adenocarcinoma of lung in Nepalese population.

Methods

Retrospective collection of information regarding age, gender, and DGM in advanced lung adenocarcinoma was gathered covering the period from January 2022 to July 2023. Data was analyzed by using SPSS-20 using descriptive statistical tools in terms of frequency and percentage.

Results

Among 112 patients, 25% had Epidermal Growth Factor Receptor (EGFR) mutation, with exon 19 deletion being more prevalent (17 patients) compared to exon 21 L858R point mutation (nine patients). The occurrence of EGFR mutation was higher in males (14.29%) than in females (10.71%). Anaplastic Lymphoma Kinase (ALK)translocation was identified in six patients, while only one patient exhibited ROS1 rearrangement. Approximately 3% of patients did not undergo successful DGM tests due to insufficient tissue in the biopsy sample.

Conclusions

A quarter of patients diagnosed with advanced lung adenocarcinoma carry EGFR mutations. Sufficient tissue sampling is necessary to conduct driver mutation tests effectively.

Keywords: driver gene mutation; EGFR mutation; lung adenocarcinoma.

INTRODUCTION

Lung cancer stands as the leading cause of cancer-related mortality worldwide. According to the 2022 global cancer observatory (GLOBOCAN), it comprises 2.4 million newly diagnosed cases reported worldwide resulting in 1.8 million fatalities. Classification of lung cancer has transitioned from a simple differentiation between small-cell and non-small cell lung cancer (NSCLC) to a more detailed histologic subdivision of NSCLC into squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Adenocarcinoma of the lung constitutes roughly 40% of lung cancer cases and occurs frequently in nonsmokers. Out of numerous targetable mutations in DGM testing, EGFR, ALK, ROS1 are the most common mutations. The targetable mutations testing is very vital in advanced NSCLC as they have shown improvement in over all survival, quality of life and decreased adverse effects when compared with standard chemotherapy. Currently, targetable DGM are detected in around 20% of lung adenocarcinoma patients in Western regions and up to 60% in Asian populations. This study was carried out to determine the prevalence of common driver mutations because

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there are no studies from Nepal regarding the incidence of these mutations, with the exception of EGFR.

METHODS

A retrospective cross sectional study was conducted among all the patients with advanced adenocarcinoma of lung who underwent DGM testing which is the standard of care. It was conducted after taking institutional approval from National Academy of Medical Sciences, Bir hospital. Data related to age, gender and DGM in advanced adenocarcinoma of lung was collected between January 2022 and July 2023 from the file record. Non probablility convenience sampling technique were used for data collection. DGM testing was done using direct sequencing or Polymerase Chain Reaction (PCR) or Next gene sequencing (NGS) technique for the detection of EGFR mutations, fluorescent in situ hybridization (FISH)/PCR / NGS for ALK and FISH or NGS for ROS1 using Formalin Fixed Paraffin Embedded (FFPE) tissue samples. The tests were done by single sequencing technique or as part of target panel testing or NGS depending upon the biopsy sample and the patient's decision for test methods. All the DGM tests were done in outsourced laboratory as these tests are not available inhouse. EGFR, ALK and ROS 1 mutation reports were collected as these three are the most common tests done for DGM in Nepal due to easy availability of therapeutic drugs for these mutations, other uncommon mutations if done were collected as well. Collected data was analyzed by using SPSS-20 using descriptive statistical tools. In the descriptive statistics for the categorical variable frequency and percentage were calculated and then data was presented using pie chart and bar diagram.

RESULTS

There were 112 patients in total with an equal distribution of male and female, each comprising 56 patients. The mean age was 62 years (ranging from 30 to 90 years). All patients were of Nepalese descent. Majority of the patients were Janjati (42.8%), Newars from Kathmandu Valley followed by Brahmins/ Chhetris (35.7%).

Table 1. Demographics and frequency of driver gene mutations.

Variables	Frequency (%)
Age in years (Mean±SD)	62±13
Sex	
Male	56(50%)
Female	56(50%)
Ethnicity	
Brahmin/ Chhetri	40(35.7%)
Janjati	48(42.8%)
Dalit	14(12.5%)
Muslim	3(2.6%)
Others	7(6.4%)
EGFR mutation	
Exon19 deletion	17(15.18%)
Exon 20 insertion	1(0.89%0
Exon 21 L858R mutation	9(8.04%)
Exon 18 G719X and Exon 20 S768I	1(0.89%)
ALK translocation	
Detected	6(5.36%)
Not Detected	71(63.39%)
Not Done Due to tissue insufficiency	3(2.68%)
Not Done due to other reasons	32(28.57%)
ROS translocation	
Detected	1(0.89%)
Not Detected	74(66.07%)
Not Done Due to tissue insufficiency	3(2.68%)
Not Done Due to other reasons	34(30.06%)
MET exon 14 skipping	
Not Detected	57(50.89%)
Not Done Due to tissue insufficiency	3(2.58%)
Not Done Due to other reasons	52(46.43%)
BRAF mutation	
Not Detected	9(8%)
Not Done	103(92%)

EGFR mutation was the most prevalent DGM among various targeted mutations, accounting for approximately 25% of cases. All patients underwent EGFR mutation testing. Exon 19 deletion was the most frequent mutation, observed in 17 patients, followed by exon 21 L858R point mutation in nine patients. Rare mutations like exon 20 insertion, exon 18G719X, and exon 20 S768I point mutation were found in only one patient each. The incidence of EGFR mutation was higher in males (14.29%) compared to females (10.71%) in our study population. Among 77 patients who tested, six were found to have ALK translocation whereas ROS1 translocation was identified in only one out of 75 patients. MET gene amplification and BRAF V600E mutation were

evaluated in 57 and 8 patients respectively, but none showed positive results. Due to tissue insufficiency, ALK translocation, ROS1 rearrangement, and MET gene amplification tests couldn't be performed in three percentage of the total patients.

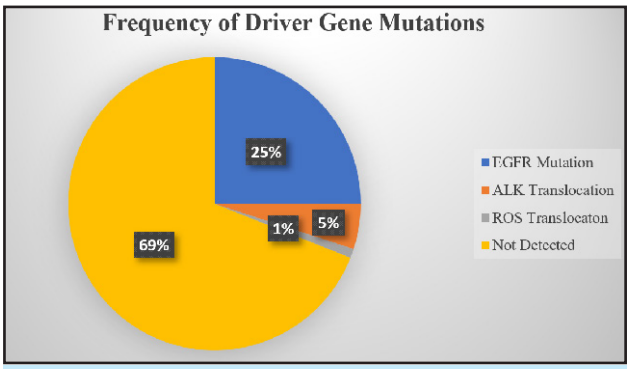

Figure 1. Frequency of driver mutations in advanced lung adenocarcinoma.

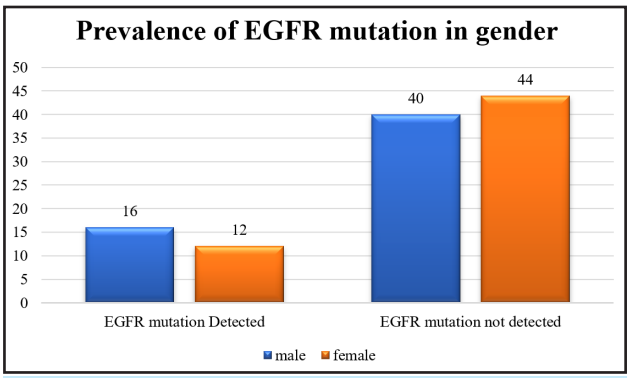

Figure 2. Prevalence of EGFR mutation in gender.

DISCUSSION

In our study, we discovered that around a quarter of patients carry an EGFR mutation. In a meta-analysis conducted by Gupta. V et al., EGFR positivity was observed in 36.9% of patients, with a higher prevalence among females (42.2%) compared to males (26.5%). However, in our study, we found a higher prevalence of EGFR mutation in males (14.29%) than females (10.17%). Exon 19 deletion emerged as the most frequent among all other locations of EGFR mutation, a trend consistent with our findings. EGFR mutations when occur have great therapeutic benefit, so they should be offered in all cases of adenocarcinoma lung regardless of gender. As per Tarigopula. A et al., the most commonly identified molecular driver mutation in advanced lung adenocarcinoma was EGFR (34.1%), followed by ALK rearrangement (11.1%) and ROS1 rearrangement (2%). However, the prevalence of oncogenic driver mutations was comparatively lower in our study. Nearly 30% of patients in our study did not undergo ALK and ROS1 rearrangement tests, while 3% lacked sufficient tissue for testing. These factors might explain the lower prevalence of ALK and ROS rearrangements observed in our study. Inadequate tissue for sampling is a major problem during DGM testing which highlights the importance of obtaining enough tissue during diagnostic procedures. Sharma. M et al. found the BRAFV600E mutation in 6 out of 260 patients, while Song. Y et al. reported MET exon 14 skipping in 0.9% of patients and MET amplification in 0.78% of patients. However, in our study, none of the patients exhibited BRAF V600E or MET gene mutations. However many of our patients did not undergo testing either due to inadequate tissue sample or financial constraints to testing as all the tests are done out of pocket expenditure by the patients. In the study by Gurung. B et al., EGFR mutations were detected in 36% of non-small cell lung carcinoma, including adenocarcinoma cases. Exon 19 mutations were predominant at 55%, followed by exon 21 mutations at 37%. No mutations were noted in exon 18, and while males had a higher overall malignancy rate, EGFR mutations were more prevalent in females. In contrast, our study identified EGFR mutations in around 25% of cases, with exon 19 deletions being the most common. We also observed rare mutations in exons 20 and 18, which were absent in Gurung et al.'s study. Additionally, our study showed a higher incidence of EGFR mutations in males. In the study by Vuong. LD et al., the mutation rates for EGFR, ALK, ROS1, RET, and MET genes were higher at 44.6%, 7.9%, 3.0%, 3.0%, and 2.0%, respectively. In our study, the mutation frequencies were relatively lower, with EGFR at 25%, ALK at 5%, and ROS1 at 1%. Notably, we did not detect any mutations in RET and MET genes among our patients. According to guidelines for management of advanced adenocarcinoma lung, testing for DGM is deemed necessary. However, in reality, conducting DGM frequently presents difficulties, such as limited tissue sample availability, access to testing and financial

constraints for the patients. Even though NGS is the preferred method for testing DGM, we still rely mostly on single gene testing due to lack of access to these testing in Nepal as well as very high costs.

CONCLUSIONS

The commonest driver gene mutations are EGFR accounting for 25% followed by ALK and ROS. The presence of these driver mutations in advanced lung adenocarcinoma significantly influences prognosis and treatment decisions. Hence, it is essential to perform molecular testing in all diagnosed patients to enable customized treatment strategies based on their molecular profile. However, challenges like tissue insufficiency hindered comprehensive testing in some cases.

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