RESEARCH PAPER

CORRELATION OF EGFR MUTATION STATUS WITH HISTOLOGICAL SUBTYPES OF LUNG ADENOCARCINOMA: A RETROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Purpose:

Lung adenocarcinoma is frequently driven by alterations in the EGFR gene and has significant therapeutic implications. This study aimed to govern the occurrence of EGFR mutations and gage their link with histological subtypes of lung adenocarcinoma, along with associated clinicopathological factors.

Design:

The present retrospective study comprised 120 patients who had been diagnosed with primary lung adenocarcinoma at a tertiary-level healthcare facility between January 2020 and December 2023. Histologic sub-typing was performed according to the WHO classification. EGFR mutation testing was steered using real-time polymerase chain reaction. Statistical analysis was performed to assess associations between EGFR mutation status, histological patterns, and clinical variables.

Results:

EGFR mutations were detected in 52 cases (43.3%). A predominance of mutations was noted in exon 19 deletions (53.8%) and L858R point mutations in exon 21 (38.5%). EGFR positivity test was drastically associated with female gender ($p=0.01$) and non-smoking status ($p=0.003$). Among histological subtypes, lepidic (62.5%) and acinar (55.2%) patterns showed higher mutation frequencies, whereas solid (21.4%) and micropapillary (25.0%) subtypes demonstrated lower prevalence. A significant correlation was found linking EGFR mutation status with histological subtype ($p=0.02$).

Conclusions:

EGFR mutations are prevalent in lung adenocarcinoma and show a significant association with specific histological subtypes, particularly lepidic and acinar patterns. Histomorphological assessment may serve as a useful surrogate indicator for EGFR mutation status in resource-limited settings, aiding therapeutic decision-making and improving patient outcomes.

Keywords: EGFR mutation, Lung adenocarcinoma, Histological subtypes, Lepidic, Acinar, Solid, Micropapillary, Exon 19 deletion, L858R.

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KEY MESSAGES BOX

What is already known on this topic

EGFR mutations are important therapeutic targets in lung adenocarcinoma and are known to be associated with certain clinical characteristics such as female gender and non-smoking status.

What this study adds

This study demonstrates a significant correlation between EGFR mutation status and specific histological subtypes, with higher mutation prevalence in lepidic and acinar patterns compared to solid and micropapillary subtypes.

How this study might affect research, practice or policy

Histological subtyping may help predict EGFR mutation status in settings where molecular testing is limited, thereby aiding early therapeutic decision-making and improving personalised cancer care.

INTRODUCTION

Lung cancer remains the leading factor responsible for deaths due to cancer worldwide, with lung adenocarcinoma representing the most common histological subtype.[1] Advances in molecular oncology have significantly transformed the management of lung adenocarcinoma, particularly with the identification of actionable driver mutations such as EGFR mutations.[2] These mutations not only play a pivotal role in tumourigenesis but also serve as critical determinants for targeted therapy, improving survival outcomes in selected patient populations.[3]

EGFR mutations are reported more frequently in females, non-smokers, and Asian populations, with exon 19 deletions and exon

21 L858R substitutions being the most prevalent.[4] The advent of tyrosine kinase inhibitors (TKIs) has revolutionised treatment strategies, offering improved response rates and progression-free survival compared to conventional chemotherapy.[5] First, second, and third-generation TKIs have further expanded therapeutic options, enabling more tailored and operative treatment approaches.[6] However, the advance of resistance mutations, such as T790M, continues to pose clinical challenges and necessitates ongoing molecular monitoring.

Despite the increasing availability of molecular testing, access remains limited in many resource-constrained settings due to cost, infrastructure, and technical expertise requirements. In such contexts, reliance on histopathological features and clinical parameters may provide initial insights into mutation status.[7] Identifying reliable morphological predictors could facilitate early treatment decisions, particularly where molecular diagnostics are delayed or unavailable.

Histopathological evaluation remains the cornerstone of lung adenocarcinoma diagnosis. The World Health Organization classification recognises distinct histological patterns, including lepidic, acinar, papillary, micropapillary, and solid subtypes, each with unique prognostic and biological characteristics.[8] Emerging findings suggest that these patterns may be not merely morphological variations but may reflect underlying molecular alterations.[8],[9] Lepidic and acinar patterns have been associated with higher EGFR mutation rates, while solid and micropapillary forms are often linked to aggressive clinical behaviour and poorer outcomes.[9],[10] Additionally, tumour heterogeneity within the same lesion may result in mixed histological patterns, complicating both diagnosis and molecular correlation.

Several studies have attempted to establish correlations between histologic sub-types and EGFR mutation status;[11],[12] however, findings have been conflicting, perhaps due to differences in study design, sample size, and population characteristics. Furthermore, data from developing countries, where the burden of lung cancer is substantial and resources are often limited, remain relatively scarce. Understanding these correlations in diverse clinical settings is essential for improving the generalisability of findings and enhancing clinical applicability.

In this context, the present study aims to evaluate the prevalence of EGFR mutations and to analyse their correlation with histological subtypes of lung adenocarcinoma. Additionally, the study seeks to assess the relationship between EGFR mutation status and clinicopathological parameters. By integrating morphological and molecular data, this study aspires to contribute to more accurate prediction models and support personalised treatment strategies in lung cancer management

MATERIALS AND METHODS

Study Design and Setting

This study retrospectively examined data collected over four years at a tertiary-level teaching hospital from January 2020 to December 2023. The study was approved by the Institutional Ethics Committee, and all procedures were carried out in accordance with ethical standards (781/04/2026/PG/SRB/SMCH). Throughout the study, all necessary steps were implemented to safeguard patient confidentiality.

Study Population

A total of 120 patients diagnosed with primary lung adenocarcinoma were included. This was a time-bound study, and all eligible cases available during the study period (January 2020 to December 2023) were included without prior sample size calculation. Cases were identified from the hospital pathology database. Inclusion criteria comprised histologically confirmed lung adenocarcinoma with available tissue samples for molecular analysis. Patients with inadequate tissue samples, prior history of malignancy, or incomplete clinical data were excluded.

Data Collection

Relevant clinicopathological details, including age, gender, smoking status, tumour characteristics, and staging, were documented from medical records. All data were anonymised prior to analysis.

Histopathological Evaluation

Formalin-fixed, paraffin-embedded tissue-material segments were stained with haematoxylin and eosin and reviewed independently by two experienced pathologists.[13] Tumours were classified according to the World Health Organization classification of lung tumours into lepidic, acinar, papillary, micropapillary, and solid subtypes.[8] In cases with mixed patterns, the predominant subtype was recorded.

EGFR Mutation Analysis

DNA was extracted from tumour tissue samples using standard protocols. EGFR mutation testing was performed using real-time polymerase chain reaction (RT-PCR) targeting common mutations in exons 18-21, including exon 19 deletions and exon 21 L858R substitutions.[14] Quality control measures were applied to ensure accuracy and reproducibility of results.

Statistical Analysis

Data analysis was carried out with IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Frequencies and percentages were used to describe categorical variables, while continuous variables were reported as mean ± standard deviation. The association between EGFR mutation status and clinicopathological variables was assessed using the chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 120 patients with histologically confirmed lung adenocarcinoma were included in the study. The mean age of the study population was 58.4 ± 10.6 years (range: 32-78 years). There was a slight male predominance, with 68 males (56.7%) and 52 females (43.3%). Among the patients, 65 (54.2%) were smokers, while 55 (45.8%) were non-smokers as shown in table 1

Table 1. Baseline Clinicopathological Characteristics

Variable	Number (n=120)	Percentage (%)
Age (mean ± SD)	58.4 ± 10.6	-
Gender (Male)	68	56.7
Gender (Female)	52	43.3
Smokers	65	54.2
Non-smokers	55	45.8

EGFR Mutation Profile

EGFR mutations were found in 52 out of 120 cases, yielding an overall mutation frequency of 43.3%. The most widespread mutation subtype was exon 19 deletion (28 cases, 53.8%), followed by exon 21 L858R mutation (20 cases, 38.5%). Less frequent mutations included exon 18 mutations (2 cases, 3.8%) and exon 20 insertions (2 cases, 3.8%). The overall data has been summarised in table 2

Table 2. EGFR Mutation Spectrum

Mutation Type	Number (n=52)	Percentage (%)
Exon 19 deletion	28	53.8
Exon 21 (L858R)	20	38.5
Exon 18 mutation	2	3.8
Exon 20 insertion	2	3.8

Association with Clinicopathological Variables

EGFR mutation positivity was significantly higher in females (61.5%) compared to males (29.4%) (p=0.01). Similarly, non-smokers demonstrated a significantly higher mutation rate (60.0%) compared to smokers (29.2%) (p=0.003).

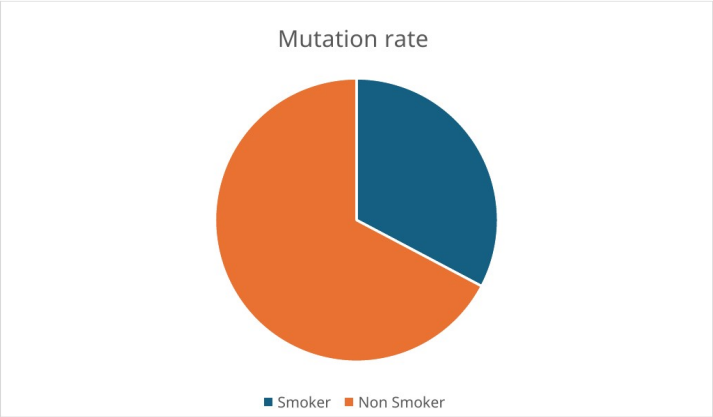

Figure Comparison of EGFR mutation frequency between smokers and non-smokers.

EGFR mutation positivity was significantly higher in females compared to other gender (61.5% vs 29.4%; $\chi^2 = 6.63$, $p = 0.01$), as shown in Table 3. Similarly, non-smokers demonstrated a significantly higher frequency of EGFR mutations compared to smokers (60.0% vs 29.2%; $\chi^2 = 10.02$, $p = 0.003$), as illustrated in Table 4.

Table 3. EGFR Mutation vs Gender

	EGFR Positive	EGFR Negative	Total
Male	20	48	68
Female	32	20	52
Total	52	68	120
$\chi^2 = 6.63$, $p = 0.01$			

Table 4. EGFR Mutation vs Smoking Status

	EGFR Positive	EGFR Negative	Total
Smokers	19	46	65
Non-smokers	33	22	55
Total	52	68	120
$\chi^2 = 10.02$, $p = 0.003$			

Histological Subtypes and EGFR Mutation

Among histological subtypes shown in Table 5, acinar pattern was the most common (48 cases, 40.0%), followed by solid (28 cases, 23.3%), lepidic (16 cases, 13.3%), papillary (14 cases, 11.7%), and micropapillary (14 cases, 11.7%).

Table 5. EGFR Mutation vs Histological Subtypes

Histological Subtype	Total Cases	EGFR Positive	Percentage (%)
Lepidic	16	10	62.5
Acinar	48	26	55.2
Papillary	14	6	42.9
Solid	28	6	21.4
Micropapillary	14	4	25.0

EGFR mutation frequency varied significantly across subtypes. Lepidic (62.5%) and acinar (55.2%) subtypes showed higher mutation prevalence, whereas solid (21.4%) and micropapillary (25.0%) subtypes demonstrated lower rates. The association

between histological subtype and EGFR mutation status was statistically significant (p=0.02).

DISCUSSION

Lung adenocarcinoma continues to represent a major clinical challenge due to its heterogeneous biological behaviour and variable response to therapy.[1] In recent years, the adoption of molecular diagnostics within everyday clinical practice-transformed the management paradigm, particularly with the identification of actionable mutations such as EGFR.[6],[15] The present study was undertaken to explore the relationship between EGFR mutation status and histological subtypes of lung adenocarcinoma, with an emphasis on identifying potential morphological correlates that may assist in predicting mutation status in routine clinical settings.

In this study, EGFR mutations were perceived in 43.3% of cases, which is steady with previously testified frequencies in Asian populations, where mutation rates typically range between 30% and 50%.[16],[17] This relatively high prevalence underscores the clinical importance of routine EGFR testing in patients with lung adenocarcinoma, particularly in regions with similar demographic characteristics. The predominance of exon 19 deletions and exon 21 L858R mutations observed in our cohort aligns with existing literature, as these mutations are known to constitute the majority of EGFR alterations and are associated with favourable responses to tyrosine kinase inhibitors.[18],[19]

A significant association was observed between EGFR mutation positivity and female gender, as well as non-smoking status. These findings corroborate earlier studies that have consistently demonstrated a higher prevalence of EGFR mutations among females and never-smokers.[20] The underlying biological mechanisms for this association remain incompletely understood but may involve differences in tumour biology, hormonal influences, and environmental exposures. From a clinical perspective, these associations can serve as useful indicators for prioritising molecular testing in resource-limited settings.

One of the key findings of this study is the significant correlation between EGFR mutation status and histological subtypes of lung adenocarcinoma. Lepidic and acinar patterns exhibited higher mutation frequencies, whereas solid and micropapillary subtypes were associated with lower mutation rates. These observations are in agreement with several previous studies, which have suggested that well-differentiated tumour patterns are more likely to harbour EGFR mutations,[21] while poorly differentiated and aggressive subtypes tend to show lower mutation prevalence. This relationship may reflect underlying differences in tumour differentiation pathways and molecular evolution.

The lepidic pattern, in particular, demonstrated the highest rate of EGFR mutation positivity in our study. This finding is noteworthy, as lepidic-predominant adenocarcinomas are generally associated with better prognosis and less aggressive behaviour.[22] The strong association with EGFR mutations further supports the hypothesis that these tumours may arise through distinct molecular pathways. Similarly, the acinar subtype, which was the most common histological pattern in our cohort, also showed a relatively high mutation frequency, reinforcing its clinical relevance.[23]

In contrast, the solid and micropapillary subtypes demonstrated lower rates of EGFR mutation. These subtypes are often associated with more aggressive clinical behaviour, higher rates of metastasis, and poorer prognosis.[24] The lower prevalence of EGFR mutations in these patterns suggests that alternative oncogenic drivers may play a more prominent role in their pathogenesis.[9] This highlights the need for broader molecular profiling in such cases to identify other actionable targets.

Another important consideration is tumour heterogeneity, which can significantly impact both histological classification and molecular analysis. Many lung adenocarcinomas exhibit mixed histological patterns, and sampling limitations may lead to underrepresentation of certain components.[11] This may, in turn, affect the observed correlation between histology and mutation status. In our study, the predominant histological pattern was used for classification; however, it is important to recognise that minor components may also carry clinical and molecular significance.

The findings of this study have important practical implications, particularly in settings where access to molecular testing is limited. Histopathological evaluation is widely available and relatively cost-effective, and the identification of specific morphological patterns associated with EGFR mutations may provide a useful adjunct in clinical decision-making.[12],[14] While histology cannot replace molecular testing, it can serve as a valuable screening tool to identify patients who are more likely to benefit from targeted therapy.

Furthermore, the integration of histological and molecular data may enhance personalised treatment strategies. For instance, patients with lepidic or acinar predominant tumours may be prioritised for EGFR testing and targeted therapy, whereas those with solid or micropapillary patterns may require more comprehensive molecular profiling. Such an approach could optimise resource utilisation and improve treatment outcomes, particularly in low- and middle-income countries.

Despite its strengths, this study has certain limitations that should be acknowledged. The retrospective design may be associated with inherent biases, including selection bias and incomplete data. The sample size, although adequate for preliminary analysis, may limit the generalisability of the findings. Additionally, the study was conducted at a single centre, and the results may not be representative of other populations with different demographic and environmental characteristics.

Another limitation is the use of targeted molecular testing for EGFR mutations alone, without assessment of other potential driver mutations such as ALK, ROS1, or KRAS. Comprehensive genomic profiling could provide a more complete understanding of the molecular landscape of lung adenocarcinoma and its correlation with histological features. Future studies incorporating next-generation sequencing may offer deeper insights into these relationships.

Moreover, interobserver variability in histopathological classification may influence the reproducibility of results. Although efforts were made to minimise this by involving experienced pathologists, the subjective nature of morphological assessment remains a challenge. Standardisation of histological evaluation and incorporation of digital pathology tools may help improve consistency in future studies.

Future research should focus on larger, multicentric studies to validate these findings across diverse populations. Prospective studies with integrated molecular and morphological analysis would be particularly valuable in establishing robust predictive models. Additionally, exploring the role of artificial intelligence in correlating histological patterns with molecular alterations may represent an exciting avenue for advancing precision oncology.

In conclusion, this study demonstrates a significant association between EGFR mutation status and histological subtypes of lung adenocarcinoma, with higher mutation prevalence observed in lepidic and acinar patterns. These findings highlight the potential role of histopathological evaluation as a supportive tool in predicting EGFR mutation status, particularly in resource-limited settings. Integrating morphological and molecular approaches may enhance personalised treatment strategies and contribute to improved clinical outcomes in patients with lung adenocarcinoma.

CONCLUSION

This study demonstrates a significant association between EGFR mutation status and histological subtypes of lung adenocarcinoma, with higher mutation prevalence observed in lepidic and acinar patterns compared to solid and micropapillary subtypes. EGFR mutations were also found to be more common in females and non-smokers, reinforcing established

clinicopathological correlations. These findings highlight the potential utility of histomorphological assessment as a supportive tool in predicting EGFR mutation status, particularly in resource-limited settings where access to molecular diagnostics may be limited. Integrating histopathological evaluation with molecular testing can facilitate timely therapeutic decision-making and optimise personalised treatment strategies. Further large-scale, multicentric studies incorporating comprehensive molecular profiling are warranted to validate these findings and enhance their clinical applicability.

DATA AVAILABILITY STATEMENT

The data underlying this study are available from the corresponding author upon reasonable request. All relevant data supporting the findings of this study are included within the article.

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