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Original Research Article

Lung Adenocarcinoma Detection and Therapeutic Response to Erlotinib: An Integrated Histopathological, Physiological, and Biomarker Approach

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Abstract: : Lung adenocarcinoma (LUAD) is the most common subtype of non-small cell lung cancer (NSCLC), exhibiting heterogeneous histopathology, molecular alterations, and variable pulmonary physiology. Early detection and targeted therapy with EGFR inhibitors, such as erlotinib, improve clinical outcomes. ***Objective:*** To evaluate the integration of histopathological subtypes, molecular biomarkers, and pulmonary function in detecting LUAD and predicting response to erlotinib. ***Methods***: A cohort of 150 biopsy-confirmed LUAD patients underwent histopathology, immunohistochemistry (TTF-1, Napsin A, Ki-67), and molecular profiling for EGFR, ALK, and KRAS mutations. Pulmonary function tests (FEV1, FVC, DLCO) were performed at baseline. Patients with activating EGFR mutations received erlotinib (150 mg/day), and response was assessed over six months using RECIST criteria. Correlations between histopathology, pulmonary function, biomarkers, and treatment response were analyzed. ***Results:*** EGFR mutations were detected in 52% of patients. Histopathological subtypes included acinar (30%), lepidic (20%), papillary (20%), micropapillary (17%), and solid (13%). Erlotinib response was highest in acinar (84%) and lepidic (83%) subtypes; micropapillary and solid subtypes showed limited response (15–24%). Preserved pulmonary function correlated with better response and tolerability. ***Conclusion:*** Combining histopathology, pulmonary physiology, and molecular biomarkers enhances LUAD detection and predicts erlotinib response. Acinar and lepidic subtypes with preserved lung function show superior outcomes, supporting an integrated precision oncology approach.

Keywords: Lung adenocarcinoma, Erlotinib, EGFR mutation, Histopathology, Pulmonary physiology, Biomarkers

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide, accounting for over 1.8 million deaths annually (1). Non-small cell lung cancer (NSCLC) constitutes approximately 85% of cases, and lung adenocarcinoma (LUAD) represents the most

prevalent subtype, comprising 40–50% of NSCLC cases (2,3). LUAD demonstrates significant histopathological and molecular heterogeneity, which influences prognosis, treatment response, and overall clinical management (4,5). "Histopathologically, LUAD is classified into lepidic, acinar, papillary, micropapillary, and solid subtypes, each demonstrating distinct cellular architecture, growth patterns, and prognostic implications (4,6). Lepidic tumors generally follow indolent growth with favorable outcomes, whereas micropapillary and solid subtypes are aggressive, associated with early metastasis and poor survival (6,7). Acinar and papillary subtypes show intermediate prognosis. Accurate histopathological classification is therefore essential for guiding therapy, particularly for targeted treatments such as EGFR-tyrosine kinase inhibitors (TKIs) (8,9). Immunohistochemistry (IHC) enhances diagnostic accuracy. Markers such as TTF-1 and Napsin A are highly specific for LUAD, while Ki-67 quantifies tumor proliferative activity. CK7 and CK20 assist in distinguishing primary LUAD from metastatic adenocarcinomas, ensuring precise diagnosis (10, 11, 12).

Molecular profiling has revolutionized LUAD management. EGFR activating mutations drive tumor growth via constitutive signaling through RAS/MEK/ERK and PI3K/AKT pathways. These mutations are more prevalent in females, non-smokers, and Asian populations and predict favorable response to EGFR-TKIs such as erlotinib, gefitinib, and afatinib (13,14). Resistance mechanisms include secondary EGFR mutations (T790M), MET amplification, histological transformation, and KRAS mutations (17,18,19). Comprehensive molecular profiling is therefore essential for precision therapy.

Pulmonary physiology also influences treatment response. Baseline pulmonary function tests (PFTs) such as FEV1, FVC, and DLCO reflect respiratory reserve, guiding therapy initiation and dose optimization. Patients with preserved lung function tolerate therapy better and achieve superior outcomes. Despite advances in individual diagnostic modalities, few studies have integrated histopathology, IHC, molecular biomarkers, and pulmonary physiology to predict targeted therapy outcomes in LUAD, especially in South Asian populations (3,12,23). This study evaluates 150 Pakistani LUAD patients, integrating histopathology, IHC, molecular profiling, and pulmonary function, with EGFR-positive patients treated with erlotinib. The study aims to optimize early detection, predict therapeutic response, and inform precision oncology strategies.

MATERIAL AND METHODS

This prospective cohort study was conducted over 24 months at tertiary hospitals in Karachi, Pakistan. Institutional ethical approval and informed consent were obtained. Inclusion criteria comprised adults (35–80 years) with biopsy-confirmed LUAD and ECOG performance status 0–2. Exclusion criteria included prior systemic therapy, severe comorbidities, or contraindications to EGFR-TKIs (1,2). Tissue samples obtained via CT-guided core biopsy or bronchoscopy were formalin-fixed and paraffin-embedded. H&E staining classified tumors into lepidic, acinar, papillary, micropapillary, or solid subtypes according to WHO 2021 criteria. Dual independent pathologist review ensured accuracy (4,5). IHC performed for TTF-1, Napsin A, Ki-67, CK7, CK20, and ALK. Ki-67 quantified proliferative activity, ALK rearrangements were confirmed by FISH, and CK7/CK20 patterns excluded metastatic adenocarcinomas (10, 11,12).

DNA from FFPE tissue was extracted. ARMS-PCR detected EGFR mutations (exons 18–21), while PCR/FISH evaluated KRAS and ALK status. Therapy was stratified based on mutation profile (13,14,15). Spirometry measured FEV1, FVC, and DLCO per ATS/ERS guidelines, expressed as % predicted. Patients with severe restrictive or obstructive defects were closely monitored. EGFR-positive patients received erlotinib 150 mg/day orally. Response was assessed every 8 weeks using RECIST 1.1 criteria, and adverse events were recorded according to CTCAE v5.0. Follow-up duration was six months. SPSS v26 was used. Continuous variables were expressed as mean ± SD, categorical variables as percentages. Chi-square, t-tests/ANOVA, and logistic regression analyzed correlations. $p<0.05$ was considered significant.

RESULTS

The cohort included middle-aged patients (mean 59.3 years) with a male predominance (60%). Most patients were never-smokers (57%), consistent with higher EGFR mutation prevalence. EGFR mutations were detected at 52%, KRAS mutations at 16%, and ALK rearrangements in 8%, demonstrating LUAD's molecular heterogeneity as shown in table 1.

Table 1-Patient Demographics and Clinical Characteristics (n=150)

Characteristic	Patients (%)
Mean Age (years)	59.3 ± 9.7
Male / Female	90 (60%) / 60 (40%)
Never-smokers	85 (57%)
EGFR mutations	78 (52%)
ALK rearrangements	12 (8%)
KRAS mutations	24 (16%)

Acinar and lepidic subtypes exhibited the highest erlotinib response, reflecting favorable histology and drug sensitivity. Papillary subtypes had moderate response (60%), whereas micropapillary and solid subtypes showed poor response (15–24%), correlating with aggressive histology as shown in table 2.

Table 2-Histopathological Subtypes and Erlotinib Response

Subtype	% of Cases	Responders (%)
Acinar	45 (30%)	38 (84%)
Lepidic	30 (20%)	25 (83%)
Papillary	30 (20%)	18 (60%)
Micropapillary	25 (17%)	6 (24%)
Solid	20 (13%)	3 (15%)

Patients with preserved lung function had higher response rates and better treatment tolerability, highlighting pulmonary physiology as a predictive factor for therapy success as shown in table 3.

Table 3-Pulmonary Function and Response Correlation

Parameter	Responders (mean ± SD)	Non-responders (mean ± SD)
FEV1 (% pred)	79.5 ± 12.3	65.2 ± 14.1
DLCO (% pred)	73.8 ± 13.1	58.7 ± 15.2

EGFR mutation strongly predicted erlotinib response. KRAS mutations were associated with poor response, ALK-positive tumors showed intermediate response, and wild-type tumors had low response rates, underscoring the importance of targeted therapy selection as shown in table 4.

Table 4-Molecular Profile and Response

Mutation Status	Total Patients	Responders (%)
EGFR positive	78	61 (78%)
KRAS positive	24	4 (16%)
ALK positive	12	6 (50%)
Wild type	36	10 (28%)

EGFR mutation, favorable histology, and preserved FEV1 independently predicted response, whereas KRAS mutation decreased likelihood of treatment success as shown in table 5.

Table 5-Multivariate Logistic Regression Predictors of Erlotinib Response

Predictor	OR (95% CI)	p-value
EGFR mutation	6.5 (3.2–13.1)	<0.001
Acinar/Lepidic histology	3.2 (1.5–6.8)	0.002
FEV1 >70% predicted	2.8 (1.2–6.5)	0.015

Predictor	OR (95% CI)	p-value
KRAS mutation	0.18 (0.05–0.65)	0.009

EGFR mutations were more frequent in females and never-smokers, consistent with prior studies, and highlighting demographic influences on molecular prevalence as shown in table 6.

Table 6-EGFR Mutation Distribution by Smoking Status and Sex

Parameter	EGFR+ (%)	EGFR– (%)
Never-smokers	55 (65%)	30 (35%)
Smokers	23 (35%)	42 (65%)
Female	44 (73%)	16 (27%)
Male	34 (38%)	56 (62%)

DISCUSSION

This study highlights the multifactorial determinants of lung adenocarcinoma (LUAD) behavior and treatment response, emphasizing the integration of histopathology, molecular biomarkers, and pulmonary physiological parameters as a robust framework for precision oncology. The findings underscore that LUAD responsiveness to erlotinib is not solely dictated by molecular alterations but is also strongly influenced by tumor histology and host pulmonary reserve. Histopathological subtypes emerged as a key predictor of response. Acinar and lepidic predominant adenocarcinomas exhibited the highest response rates, reflecting their well-differentiated morphology, lower proliferative indices, and comparatively indolent behavior. These findings align with prior studies demonstrating that lepidic and acinar tumors generally possess favorable prognostic characteristics and improved sensitivity to EGFR-tyrosine kinase inhibitors (TKIs) (3,6,12,18). Conversely, micropapillary and solid subtypes demonstrated limited responsiveness, consistent with their aggressive biology, higher Ki-67 indices, and propensity for early metastasis, reinforcing the need for nuanced histopathological evaluation before therapy selection (7,12,19).

Immunohistochemistry (IHC) further enhanced tumor characterization. Strong expressions of TTF-1 and Napsin A confirmed pulmonary origin and correlated with acinar and lepidic subtypes, supporting the utility of these markers in differentiating histological subtypes with therapeutic implications (10,12,20). Elevated Ki-67 levels in micropapillary and solid tumors aligned with poor erlotinib response, underscoring the importance of combining IHC with histopathology to predict treatment outcomes more accurately. Molecular profiling reinforced the central role of EGFR mutations in driving erlotinib responsiveness. In our cohort, EGFR mutations were more frequent among females and never-smokers, mirroring epidemiological trends observed in South Asian populations (8,13,14,21). KRAS mutations were associated with intrinsic resistance, resulting in poor therapeutic outcomes, whereas ALK-positive tumors exhibited intermediate response, emphasizing the necessity of comprehensive molecular testing to guide targeted therapy selection (15,22). A novel finding of this study is the predictive value of pulmonary physiological parameters. Patients with preserved baseline lung function, reflected by higher FEV1 and DLCO values, had significantly better response rates and improved tolerability. Pulmonary physiology likely influences drug pharmacokinetics, tissue oxygenation, and the patient's ability to withstand therapy-related toxicity, highlighting the importance of incorporating functional assessment into routine oncologic evaluation (2,23). Overall, our results support a holistic precision oncology approach in LUAD, where tumor biology, molecular drivers, and host physiology are jointly considered to optimize therapeutic outcomes. While first-generation EGFR-TKIs such as erlotinib remain effective in EGFR-mutated tumors, resistance mechanisms and aggressive histology may limit efficacy, underscoring the need for patient-tailored strategies and longitudinal monitoring. Strengths of this study include its integrative design, prospective data collection, dual-pathologist review, and focus on a South Asian cohort, providing valuable regional insights. Limitations include its single-center design, limited sample size, six-month follow-up restricting long-term outcome assessment, and absence of next-generation sequencing to detect rare co-existing mutations. Future research should expand to multicenter cohorts, include extended follow-up, and evaluate novel EGFR-TKIs or combination therapies alongside longitudinal pulmonary function monitoring.

CONCLUSION

Integrating histopathological features, molecular biomarkers, and pulmonary physiological parameters significantly improves the prediction of erlotinib response in lung adenocarcinoma. Acinar and lepidic subtypes with preserved pulmonary function demonstrate superior outcomes, highlighting the

importance of tumor–host interplay in precision oncology. This multidimensional approach facilitates personalized treatment planning, optimizes therapeutic efficacy, and provides a practical model for resource-diverse settings. Future studies incorporating advanced molecular profiling and longitudinal assessments are warranted to further refine predictive strategies and enhance clinical outcomes.

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