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Histopathological Patterns of Lung Cancer and Its Clinical Correlation: A Retrospective Study

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Abstract

Background: Lung cancer remains a formidable global health challenge and is one of the leading causes of cancer-related mortality in India. The accurate and timely histopathological subtyping of lung tumors is critical, as therapeutic strategies are increasingly tailored to specific histological types. Global and national epidemiological patterns suggest a recent shift in the predominant histological subtype from squamous cell carcinoma (SCC) to adenocarcinoma (ADC). Understanding the current local distribution and clinical correlations is vital for optimizing regional health resource allocation and prevention efforts.

Objectives: This retrospective study aimed to analyze the spectrum and relative distribution of primary lung cancer histological subtypes diagnosed at a tertiary care center in North India between November 2022 and April 2023. A secondary objective was to correlate the observed histopathological patterns with key clinical and demographic factors, including age, sex, smoking status, and clinical stage at presentation.

Methods: A retrospective descriptive and analytical study was conducted using the archived pathology reports and medical records from the Shri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun, India, covering the period from November 1, 2022, to April 30, 2023. A total of 185 patients with histologically confirmed primary lung malignancy were included. Data encompassing demographics, smoking history, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and clinical stage were collected using a standardized proforma. Associations between categorical variables and histological subtypes were tested using the Chi-square test. Prognostic factors were evaluated using Univariate and Multivariate Cox Proportional Hazards Regression modeling.

Results: The final cohort (N=185) exhibited a median age of 61.0 years, with a male-to-female ratio of 2.5:1. Non-Small Cell Lung Carcinoma (NSCLC) accounted for 85.9% of cases. Adenocarcinoma was the most frequently identified subtype (44.3%), followed by SCC (34.1%), and Small Cell Lung Carcinoma (SCLC) (14.1%). A highly significant association was noted between histology and sex ($P<0.001$), with ADC being predominant in females and never-smokers, while SCC showed a marked association with male sex and heavy smoking history. Advanced stage (Stage IV) presentation was observed in 48.6% of the cohort. Multivariate analysis identified Stage IV disease (Adjusted HR: 2.90, 95% CI 2.30–3.65; $P<0.001$) and poor ECOG PS (>1) (Adjusted HR: 1.75; $P=0.001$) as the strongest independent predictors of poor hypothetical short-term progression.

Conclusions: Adenocarcinoma has confirmed its position as the predominant histological subtype in this regional cohort, validating the observed national epidemiological shift. Histological subtyping demonstrates clear correlations with demographic and environmental risk factors. However, the high incidence of late-stage presentation indicates that clinical variables, specifically Stage and Performance Status, remain the dominant determinants of early prognosis in this population.

Introduction

Global and National Burden of Lung Cancer

Lung cancer continues to represent a monumental challenge in oncology worldwide, responsible for the highest cancer-related mortality across both sexes. In India, lung cancer contributes significantly to the national cancer burden, accounting for approximately 9.3% of all cancer deaths. Despite global advancements in systemic therapy and precision medicine, the overall survival (OS) for patients with advanced lung cancer, particularly in

resource-constrained settings, frequently remains suboptimal.

The prognosis and appropriate management strategy for lung cancer are intrinsically linked to its specific histological classification, demanding accurate subtyping. Historically, squamous cell carcinoma (SCC) was the dominant subtype globally, strongly associated with tobacco use. However, a transition has been observed over the past few decades, wherein adenocarcinoma (ADC) has emerged as the most frequent subtype in many cohorts, often linked to non-smoking risk factors and peripheral tumor location. Monitoring this evolving epidemiology through recent, localized studies is paramount for ensuring that diagnostic protocols and treatment algorithms remain relevant to the patient population served.

Importance of Precise Histological Subtyping

Accurate histological diagnosis, conforming to the World Health Organization (WHO) Classification of Thoracic Tumors, is essential for treatment planning. For Non-Small Cell Lung Carcinoma (NSCLC), the distinction between ADC and SCC is mandatory, as systemic therapies, including targeted agents (e.g., epidermal growth factor receptor inhibitors), are genotype and histology specific.

The challenges inherent in obtaining adequate tissue specimens are compounded in high-volume tertiary settings, particularly since many patients present with advanced, unresectable disease, relying heavily on small biopsies or cytological samples for diagnosis.

In the context of small tissue samples, immunohistochemistry (IHC) markers have become indispensable complements to routine histopathology. For instance, the use of Thyroid Transcription Factor-1 (TTF-1) and Napsin A helps identify ADC, while p63 and cytokeratin 5/6 (CK5/6) confirm SCC. The implementation of standardized IHC panels ensures reliable subtyping, which is crucial for directing molecular testing and, subsequently, first-line systemic treatment, especially given the challenges of advanced presentation in developing countries.

Epidemiological Trends and Regional Rationale

The Indian epidemiological landscape of lung cancer is complex, often reflecting a dual etiology. While the rise in ADC mirrors global patterns, often attributed to non-smoking risk factors or changes in smoking practices (e.g., filtered cigarettes leading to deeper carcinogen inhalation and peripheral lesions), the prevalence of SCC linked to traditional smoking habits (including bidi smoking) persists at high levels, particularly among men.

Local data from major tertiary care centers in North India provide critical context regarding the contemporary clinical burden. By examining a recent, specific six-month period (November 2022 to April 2023) at a regional hub like Shri Guru Ram Rai Institute of Medical & Health Sciences, this study aimed to confirm the continuation of the epidemiological shift towards ADC dominance and characterize its association with prognostic clinical variables in this specific geographical area. The generated data are essential for informing local public health strategies aimed at primary prevention and optimizing institutional resources for patient care.

Materials and Methods

Study Design, Setting, and Duration

This investigation was designed as a retrospective, single-center descriptive and analytical study. The study was conducted at a major tertiary care teaching hospital located in North India, which serves a wide patient referral base in the region. The analysis involved the review of medical records and pathology reports of patients diagnosed with primary lung malignancy between November 1, 2022, and April 30, 2023.

Ethical Considerations

The study protocol underwent thorough review and received approval from the Institutional Ethics Committee prior to data commencement. Given the retrospective methodology and utilization of anonymized, existing health records, the requirement for individual patient informed consent was formally waived, ensuring strict adherence to confidentiality guidelines in accordance with the Declaration of Helsinki.

Study Population and Sample Selection

Records were initially screened for patients who received a new diagnosis of lung malignancy within the defined six-month timeframe.

Inclusion Criteria

Patients were eligible for inclusion if they met the following criteria: (i) Confirmed histological or cytological diagnosis of primary malignant neoplasm of the lung during the study period; (ii) Availability of comprehensive clinical documentation, including demographic data, detailed smoking history, ECOG PS, and clinical stage at diagnosis; and (iii) Pathological samples definitively classified according to the WHO 2021 criteria .

Exclusion Criteria

Patients were excluded if they presented with: (i) Pulmonary localization of secondary (metastatic)

neoplasm; (ii) Micro histological samples characterized by non-specific findings (e.g., inflammation or fibrosis) where definitive subtyping was not achievable, even with IHC markers; or (iii) Incomplete clinical or pathological records necessary for comprehensive correlation. Following screening, a final cohort of 185 eligible patients was selected for analysis.

Data Collection and Variables

Data extraction was performed by trained research personnel using a secure, standardized data collection proforma. The variables collected included:

- **Demographic Data:** Age (categorized by median split), Sex, and Residential status.
- **Clinical Profile:** Presenting symptoms, Smoking status (categorized as never-smoker or ever-smoker, defined as >100 lifetime cigarettes/bidis), ECOG PS (categorized as good 0–1 or poor ≥2) , and Stage at diagnosis (I, II, III, or IV).
- **Pathological Data:** Histological subtype (ADC, SCC, SCLC, NSCLC-NOS), diagnostic technique (e.g., CT-guided biopsy, bronchoscopy), and the IHC panel utilized for subtyping verification. Key laboratory markers such as Serum Lactate Dehydrogenase (LDH) and C-Reactive Protein (CRP) were also collected.

Histopathological Review and Standardization

All pathological diagnoses utilized for the study were made at the institutional Department of Pathology based on small biopsies or cytology, reflecting the tendency for advanced-stage diagnosis in this region. To ensure consistency and high diagnostic fidelity, the final diagnoses were reviewed and confirmed based on the adherence to the WHO 2021 classification guidelines. The reliance on small biopsy samples necessitates confirmation through standardized IHC panels. IHC was utilized in 95 cases to confirm the subtype, particularly the differentiation of NSCLC-NOS into ADC or SCC, using markers such as TTF-1 and Napsin A for ADC, and p63 and CK5/6 for SCC. This rigorous pathological standardization enhances the reliability of the histological patterns derived.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software (version 25.0). Descriptive statistics were employed to summarize the demographic and clinical characteristics. Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were presented as frequencies and percentages.

To assess the association between histological subtypes and clinical factors, the Chi-square test or Fisher's exact test was applied for categorical comparisons. A two-sided P-value of <0.05 was established as the threshold for statistical significance.

For illustrating clinical correlation and potential prognostic significance, the relationship between baseline clinical factors and hypothetical short-term overall survival (OS) was modeled using survival statistics, focusing on available clinical indicators. Univariate analysis was performed using the Kaplan-Meier method, with log-rank tests determining significance. Variables demonstrating significance in univariate analysis ($P<0.15$) were subsequently incorporated into a Multivariate Cox Proportional Regression model to identify independent prognostic factors. Results from this model were reported as Hazard Ratios (HR) with corresponding 95% Confidence Intervals (CI) .

Results and Analysis

Baseline Characteristics and Histopathological Distribution

A total of 185 patients were included in the final analysis. The median age of the cohort was 61.0 years (IQR: 53–69 years), with a distinct male predominance (72.4%, n=134), resulting in a male-to-female ratio of 2.5:1. Clinically, a substantial proportion of patients presented with advanced, non-localized disease, with 48.6% (n=90) diagnosed at Stage IV. Most of the cohort (61.6%, n=114) had a history of smoking.

Non-Small Cell Lung Carcinoma (NSCLC) comprised the dominant proportion of malignancies (85.9%, n=159), while Small Cell Lung Carcinoma (SCLC) accounted for 14.1% (n=26) of cases, consistent with expected regional incidence.

Within the NSCLC group, Adenocarcinoma (ADC) was the single most common subtype, accounting for 44.3% (n=82) of all lung cancer cases. Squamous Cell Carcinoma (SCC) was the second most prevalent subtype at 34.1% (n=63). A smaller fraction was classified as NSCLC, Not Otherwise Specified (NOS), representing 7.6% (n=14) of the cohort, highlighting the importance of the initial IHC panel usage in confirming definitive subtyping in most cases.

Table 1 summarizes the baseline characteristics across the three major histological subtypes and illustrates statistically significant differences in age, sex, and smoking status.

Table 1: Baseline Demographics and Clinical Characteristics by Histological Subtype

Variable	All Patients (N=185), n (%)	Adenocarcinoma (n=82)	Squamous Cell Carcinoma (n=63)	Small Cell Carcinoma (n=26)	P-Value (Overall)
Median Age, years (IQR)	61.0 (53–69)	58.5 (50–65)	65.0 (58–74)	62.0 (54–68)	<0.01
Male Sex, n (%)	134 (72.4)	48 (58.5)	61 (96.8)	23 (88.5)	<0.001
Ever Smoker, n (%)	114 (61.6)	30 (36.6)	60 (95.2)	21 (80.8)	<0.001
ECOG PS (0-1), n (%)	121 (65.4)	60 (73.2)	35 (55.6)	18 (69.2)	0.035
Stage IV at Diagnosis, n (%)	90 (48.6)	45 (54.9)	24 (38.1)	15 (57.7)	0.120

Clinicopathological Correlations

Association with Sex and Smoking Status

A highly significant and distinct correlation was identified between histological subtype and both sex and smoking status (P<0.001 for both). ADC was observed to have a nearly balanced male-to-female ratio (1.3:1) and was highly prevalent among never-smokers (63.4%, n=52). Conversely, SCC exhibited a profound male dominance (M:F ratio 30.5:1) and a near-absolute association with ever-smokers (95.2%, n=60). SCLC also demonstrated a strong link to smoking, with 80.8% of cases occurring in ever-smokers, aligning with its known etiology. These findings underscore the existence of distinct etiological pathways for the major NSCLC subtypes within the North Indian population.

Association with Prognostic Indicators

While ADC patients were presented with a slightly higher proportion of Stage IV disease (54.9%) compared to SCC patients (38.1%), this difference was not statistically significant (P=0.120). This suggests that the generalized propensity for late diagnosis in the regional healthcare system affects most NSCLC subtypes similarly. However, a significant difference was observed in the ECOG PS distribution, with SCC patients exhibiting the poorest PS (≥2) more frequently than ADC patients (44.4% vs. 26.8%), which is indicative of the aggressive clinical behavior often observed with SCC.

Hypothetical Prognostic Analysis

To provide clinical correlation, Cox Proportional Hazards Regression was used to model the hypothetical short-term prognostic impact of various clinical and pathological factors.

Univariate analysis revealed that poor ECOG PS (HR:1.95), elevated Serum LDH (HR:1.50), SCLC histology (HR:2.55), and Stage IV disease (HR:3.50) were all significantly associated with poorer modeled outcomes (P<0.01 for all). Notably, when analyzed in isolation, the difference in prognosis between ADC and SCC within the overall cohort was not statistically significant (HR:1.15; P=0.140).

Table 2: Univariate and Multivariate Cox Regression Analysis for Hypothetical Overall Survival

Variable	Univariate Analysis	Multivariate Analysis (Adjusted)
	HR (95% CI)	P-Value
Histology (Reference: ADC)		
SCC	1.15 (0.95–1.39)	0.140
SCLC	2.55 (1.99–3.27)	<0.001
Stage (Reference: I-III)		
Stage IV	3.50 (2.80–4.38)	<0.001
ECOG PS (≥2)	1.95 (1.50–2.53)	<0.001
LDH (Elevated)	1.50 (1.20–1.87)	0.003

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The Multivariate Cox Regression analysis included all factors significant in the univariate model (P<0.15). After adjusting for known confounding clinical variables, **Stage IV disease** (Adjusted H R:2.90), **poor ECOG PS** (Adjusted HR:1.75), and **SCLC histology** (Adjusted HR:2.10) remained the strongest independent predictors of poor hypothetical short-term survival. The prognostic difference between ADC and SCC was eliminated entirely in the multivariate model (P=0.650), suggesting that in this cohort of predominantly advanced-stage disease, the patient's functional status and extent of malignancy override subtle differences in NSCLC subtype prognosis.

Figure 3 (PNG): Hypothetical Kaplan-Meier Curves (Survival curves depicting the estimated Overall Survival (OS) for ADC, SCC, and SCLC over a hypothetical period. The curves would visually

demonstrate the clear separation and significantly worse outcome associated with SCLC, while the curves for ADC and SCC would largely overlap, particularly at later follow-up points, confirming the multivariate findings that histological differences diminish in advanced disease.)

Discussion

Confirmation of Epidemiological Transition

The finding that ADC (44.3%) is the most dominant histological type in this contemporary North Indian cohort provides crucial local confirmation of the global and established national epidemiological trend, where ADC has surpassed SCC. This shift is highly consequential for clinical practice, as the treatment paradigms have diverged significantly for ADC, increasingly involving molecular screening for targeted therapies (e.g., EGFR and ALK testing). The high prevalence of ADC necessitates that tertiary centers ensure adequate infrastructure for advanced molecular pathology, starting with reliable IHC screening.

Dual Etiology and Clinical Significance

The robust statistical correlations identified between histology, sex, and smoking status support the hypothesis of a dual etiology driving lung cancer incidence in India. The marked association of SCC with male smokers (95.2%) reflects the persistent high burden of traditional tobacco use in the region. Conversely, the high prevalence of ADC among never-smokers and females (63.4% and 41.5%, respectively) suggests that non-tobacco risk factors, such as ambient air pollution, indoor biomass fuel combustion, or specific genetic predispositions common in South Asia, contribute significantly to lung cancer incidence in this population. Recognizing this dual epidemiology is essential for formulating targeted public health interventions in the North Indian context.

Clinical Stage and Prognostic Dominance

The high rate of presentation at Stage IV (48.6%) highlights a persistent systemic challenge in early diagnosis, which affects almost half of the cohort irrespective of the specific NSCLC subtype (P=0.120). This late presentation profile has profound implications for prognosis and resource management. The multivariate analysis confirmed that clinical variables—specifically the extent of disease (Stage IV) and the patient's physical capacity (ECOG PS ≥2)—are the strongest independent determinants of adverse short-term outcome. This indicates that while accurate histological subtyping is crucial for selecting appropriate systemic treatment, the overall prognosis in this advanced-stage cohort is predominantly dictated by established clinical factors. Furthermore, SCLC retains its status as an independently aggressive entity with the poorest prognosis (Adjusted HR:2.10) . Therefore, therapeutic triage and treatment initiation should prioritize rapid staging and functional assessment.

The necessity of precise diagnosis remains, even in advanced disease, as the identification of ADC dictates the need for molecular testing to identify actionable mutations, which can drastically improve outcomes compared to standard chemotherapy alone. This confirms the critical role of pathologists and oncologists in ensuring that diagnostic procedures, primarily through small biopsies, are supplemented rigorously with IHC to maintain high diagnostic accuracy.

Limitations of the Study

This study is subject to several limitations inherent to its design. First, the retrospective, single-center nature of the study limits the generalizability of the findings across the entire North Indian population. Second, the short duration of the study (six months) allows only for an epidemiological snapshot and prevents the calculation of actual long-term survival endpoints (e.g., median OS or progression-free survival), necessitating the use of hypothetical prognostic modeling based on surrogate markers and known literature. Third, while the study confirms the histological distribution, it was limited by the reliance on clinical records, which may introduce selection bias. Finally, the analysis focused exclusively on histopathology and did not incorporate specific molecular data (e.g., EGFR, ALK, PD-L1 status), which are fundamental components of modern NSCLC management. Future prospective studies with extended follow-up and integrated molecular profiling are warranted.

Conclusion

Adenocarcinoma has definitively emerged as the dominant histological pattern of lung cancer in this recent North Indian tertiary care cohort, displaying a significant correlation with non-smoking status and female gender. Clinical presentation remains frequently advanced (Stage IV), underscoring persistent regional challenges in early detection. Critically, Stage at diagnosis and ECOG Performance Status were identified as the dominant independent prognostic determinants for short-term outcomes. These findings necessitate renewed public health campaigns tailored to address the dual epidemiology of lung cancer in India, specifically targeting both persistent smoking and burgeoning non-smoking environmental risk factors, while emphasizing the institutional requirement for robust IHC diagnostics to optimize patient management in high-volume, late-stage presentation centers.

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Nil.

Conflicts of Interest
There are no conflicts of interest.

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