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HISTOPATHOLOGICAL PATTERNS OF LUNG CANCER ALONG WITH THE CLINICO-RADIOLOGICAL CORRELATION IN A TERTIARY CARE HOSPITAL IN PAKISTAN

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Abstract

Background: *Lung cancer, characterized by histological heterogeneity and significant clinico-radiological implications, remains the leading cause of cancer-related mortality worldwide.* ***Objectives:*** *The study was carried out to assess in lung cancer patients the histological patterns, radiological findings and biomarker expression.* ***Methods:*** *From March to September 2024, tertiary care hospitals in Rawalpindi undertook this cross-sectional study. Including 140 lung cancer patients in all, demographic, clinical, and histological data were gathered. Six biomarkers–TTF-1, UBE2C, MCM2, MCM6, FEN1, and TPX2–were immunohistochemically stained.* ***Results:*** *Patients' mean age was 62.4 ± 10.2 years; 58.6% of them were men. Among the patients, 69.3% smoked. The most often occurring histological subtype (35%), followed by papillary (21%) and solid patterns (18%), was acinar carcinoma. The most frequently observed radiological features were pleural effusion (19%) and mediastinal involvement (14%). TTF-1 (83.6%), MCM6 (77.1%), and MCM2 (73.6%), revealed high positive rates according to immunohistochemical investigation. Significant relationships between tumor proliferation and DNA repair were shown by biomarkers including FEN1 (65.7%) and UBE2C (72.1%).* ***Conclusion:*** *Acinar carcinoma was the most common histological subtype, with pleural effusion being the most frequently observed radiological feature. Especially TTF-1, high biomarker expression emphasizes its diagnostic and prognostic relevance in lung cancer. These results underlined the need of including molecular and histological data into customized therapy plans.*

INTRODUCTION

With its great frequency and poor prognosis, lung cancer is the primary cause of cancer-related death globally and presents a major public health issue. The histological variety of the disease greatly affects its clinical presentation, treatment plans and results [1]. Lung cancer can be mostly divided histologically into

two main forms: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [2-3]. With subtypes including adenocarcinoma, squamous cell carcinoma and giant cell carcinoma, NSCLC makes about 85% of all cases account for. Conversely, SCLC is more forceful and strongly connected with smoking. Correct diagnosis and individualized treatment plans depend on an awareness of these histological characteristics [3-6].

Lung cancer's clinical symptoms are sometimes vague and depend on tumor location, size and degree of metastases. Symptoms could range from dyspnea, hemoptysis and coughing to systemic ones including weight loss and tiredness [7-8]. Furthermore, the tumor's close proximity to the pleural cavity or mediastinum can cause problems such pleural effusion or superior vena cava syndrome. Apart from the respiratory system, lung cancer often presents with distinct radiological manifestations [9]. Tumor invasion into adjacent structures, pleural effusion, mediastinal involvement, and lymphadenopathy are frequently observed on imaging. These radiological findings play a crucial role in staging, prognosis, and guiding treatment decisions [10-11].

Recent studies have particularly examined the correlation between histopathological subtypes and clinico-radiological findings. Emerging data points to the influence of histopathological features on survival rates, therapeutic responses and probability of particular problems [12]. For example, SCC is more likely to present with central airway obstruction, while adenocarcinoma is frequently associated with peripheral lung lesions and distant metastases, including brain and bone involvement. SCLC, despite its chemosensitivity, often demonstrates rapid progression with a high likelihood of widespread metastasis, including pleural effusion, mediastinal involvement, and lymph node enlargement, as seen in imaging studies [13].

This study aimed to investigate the histopathological patterns of lung cancer and their clinico-radiological correlations, providing insight into imaging characteristics and their role in diagnosis and treatment planning.

Materials and Methods

Study Design and Setting

Over a six-month period from March 2024 to September 2024, tertiary care hospitals in Rawalpindi, Pakistan, carried out this cross-sectional study. The study sought to evaluate, in patients diagnosed with lung cancer, the histopathological features of the disease and their clinico- radiological features.

Sample Size

Considering 10% prevalence rate for lung cancer, WHO sample size calculator helped us to determine the sample size. Calculated sample size was 140 patients with the 95% confidence level and 5% margin of error.

Inclusion Criteria

- Patients eighteen years or above.
- Using biopsy or surgical specimen analysis, histopathological confirmation of the lung cancer diagnosis.
- Willing to take part, accompanied by informed permission acquired.

Exclusion Criteria

- Patients with insufficient medical records or dubious histological diagnosis.
- Other cancers or systemic illnesses unrelated to lung cancer.
- Patients on palliative care solely or reluctant to consent.

Data Collection

Medical record review, histological analysis and clinical examination taken together gathered data. Developed to guarantee consistency and comprehensiveness was a structured data collecting form. Among the gathered data were:

Age, gender, smoking history, occupational exposure, family cancer history—demographic information.

Clinically, symptoms include coughing, hemoptyzed dyspnea, weight loss and systemic indications.

Radiological Findings: Chest X-ray, CT scan, and PET-CT imaging were used to assess tumor size, lymph node involvement, pleural effusion, mediastinal invasion, and distant metastases.

Histopathological Information: Type, grade and stage determined using the most recent WHO classification of thoracic tumors.

Histopathological Analysis

All hematoxylin and eosin (H&E)-stained histological sections were examined for the existence and degree of histological development patterns. Defined using the 2004 WHO classification system with minor changes, the five patterns examined were lepidic, acinar, papillary, micropapillary, and solid:

Lepidic: Tumor cells growing along alveolar walls without stromal, vascular or pleural invasion.

Acinar: Tumor cells set in acini or tubules mimicking bronchial gland epithelium.

Papillary: Fibrovascular core and secondary branch tumors with papillae features

Micropapillary: Small papillary tufts of cells with peripheral nuclei and no fibrovascular core are micropapillary.

Solid: Tumor cells producing nests or sheets devoid of acini, tubules, or papillae nevertheless producing mucin.

Each pattern's percentage in the tumor was noted in five percent increments. Tumors were categorized as mixed if many patterns were seen and as pure if just one pattern was present. Additionally lymphovascular invasion and necrosis were analyzed.

Immunohistochemical Analysis

Immunohistochemical staining on formalin-fixed, paraffin-embedded tumor tissues analysis was thyroid transcription factor-1 (TTF-1) expression and biomarkers from the FILM signature (UBE2C, MCM2, MCM6, FEN1, and TPX2). Previously proven techniques were used for stainings five-micrometer tissue slices. Nuclear staining intensity (0, 1+, 2+, 3+) and extent (0%-100%) determined TTF-1 staining scores; the final score was computed by multiplying the two values (range 0–300). Summing the separate results for the five biomarkers produced the FILM signature index.

Ethical Considerations

The investigation was carried out under ethical standards specified in the Declaration of Helsinki. The Institutional Review Board of the cooperating tertiary care facilities granted ethical clearance. Every participant gave written informed permission, guaranteeing anonymity and voluntary participation.

Statistical Evaluation

SPSS program version 25.0 was used to examine data. Demographic, clinical, and histological variables were compiled using descriptive statistics. Means and standard deviations were determined for continuous data; frequencies and percentages were derived for categorical variables. Associations between histopathological patterns and clinico-radiological findings were assessed using independent t-tests and chi-square tests. Considered statistically relevant was p-value of 0.05.

Results

Comprising 140 lung cancer patients overall with the mean age of 62.4 ± 10.2 years, with the cohort of 82, the study comprised 58.6% of men and 41.4% of women, While 43 non-smoking patients (30.7%) reported, smoking was common among most of the patients—97 individuals (69.3%). Stage III was the most often occurring (46, 32.9%), followed by Stage II (39, 27.9%), Stage I (28, 20.0%), and Stage IV (27, 19.3%), according to patient distribution across the IASLC (International Association for the Study of Lung Cancer). With 67 patients (47.9%) in stages T1–T2 and 73 (52.1%) in stages T3–T4 TNM staging displayed virtually equal distribution. While most (81, 57.9%) did not receive further treatment, 59 patients—42.1%—were given adjuvant therapy. Of 48 cases (34.3%), necrosis was noted; of 92 cases (65.7%), no necrotic alterations were seen. Likewise, lymphovascular invasion was found in 44 individuals (31.4%) but it was missing in 96 cases (68.6%). With regard to occupational exposure, 63 patients (45.0%) said they had the history of occupational risk factors while 77 patients (55.0%) said they did not. Only 14 patients (10.0%), had a family history of cancer; the rest (126, 90.0%) reported no such history (Table 1).

Across all six biomarkers examined, immunohistochemical staining found substantial positive rates. At 83.6% (117 patients, $p = 0.021$), TTF-1 displayed the greatest positive rate indicating its important expression in lung cancer tissues. In 72.1% (101 patients, $p = 0.037$) and 73.6% (103 patients, $p = 0.037$), respectively, UBE2C and MCM2 were positive, thereby stressing their roles in

tumor growth. Strong nuclear positivity in 77.1% of cases (108 patients, p = 0.018) was shown by MCM6; FEN1 was positive in 65.7% (92 patients, p = 0.049), implying its involvement in DNA repair systems in tumor cells. Reflecting its varied expression in lung cancer, TPX2 revealed the lowest positive rate at 62.9% (88 patients, p = 0.050) (Table 2).

Six main biomarkers' were representative immunohistochemistry staining in lung cancer tissue samples in our study. Strong nuclear staining of TTF-1 (a) indicated great positivity and its relevance in the diagnosis of lung cancer. Granular nuclear positivity shown by UBE2C (b) reflects its role in cell cycle control. MCM2 (c) underlined nuclear staining in proliferative areas and its correlation with tumor growth. Strong nuclear staining of MCM6 (d) emphasized its importance in processes of cellular replication. Positive nuclear staining in glandular structures by FEN1 (e) conformed to its function in DNA repair systems. Finally, TPX2 (f) showed focal nuclear and cytoplasmic staining, which reflected its role in spindle assembly during mitosis. These trends together emphasized the several biological functions of these biomarkers in pathophysiology of lung cancer (Figure 1).

Frequency of histological patterns and radiologically based clinical observations in lung cancer patients revealed that among the histological subtypes, acinar carcinoma was the most common (35%), followed by papillary (21%) and solid (18%), patterns; micropapillary and mixed patterns were less common. Radiologically, the most often seen complications—indicating notable tumor progress—were pleural effusion (20%) and mediastinal involvement (13%). Reflecting the several imaging presentations of lung cancer, ground-glass opacity (12%), lung nodules (15%), and lymphadenopathy (14%) were also often found (Figure 2).

Table 1: Demographic and clinical characteristics

Characteristic	Categories
All Tumors, N	140
Age, years Mean ± SD	 62.4 ± 10.2
Sex Male Female	 82 (58.6) 58 (41.4)
Smoking Status Smokers Non-smokers	 97 (69.3) 43 (30.7)
IASLC Stage Stage I Stage II Stage III Stage IV	 28 (20.0) 39 (27.9) 46 (32.9) 27 (19.3)
TNM Stage T1-T2 T3-T4	 67 (47.9) 73 (52.1)
Adjuvant Therapy Yes No	 59 (42.1) 81 (57.9)
Necrosis Present Absent	 48 (34.3) 92 (65.7)
Lymphovascular Invasion Present	 44 (31.4)

Absent	96 (68.6)
Occupational Exposure Yes No	 63 (45.0) 77 (55.0)
Family History of Cancer Yes No	14 (10.0) 126 (90.0)

Table 2: Immunohistochemical analysis results

Biomarker	Positive Staining (%)	p-value
TTF-1	117 (83.6)	0.021*
UBE2C	101 (72.1)	0.037*
MCM2	103 (73.6)	0.026*
MCM6	108 (77.1)	0.018*
FEN1	92 (65.7)	0.049*
TPX2	88 (62.9)	0.050*

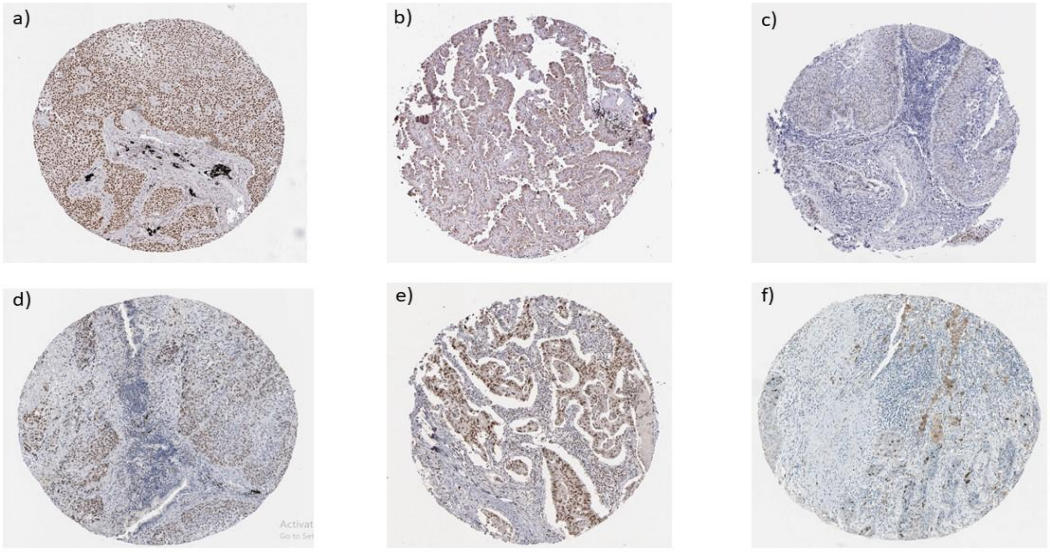

Figure 1: Representative immunohistochemical staining images of six biomarkers in lung cancer tissue samples.
(a) TTF-1: Nuclear staining indicating positive expression.
(b) UBE2C: Nuclear positivity with granular distribution.
(c) MCM2: Nuclear staining in proliferative regions.
(d) MCM6: Distinct nuclear staining with high intensity.
(e) FEN1: Positive nuclear staining in glandular structures.
(f) TPX2: Focal nuclear and cytoplasmic staining.

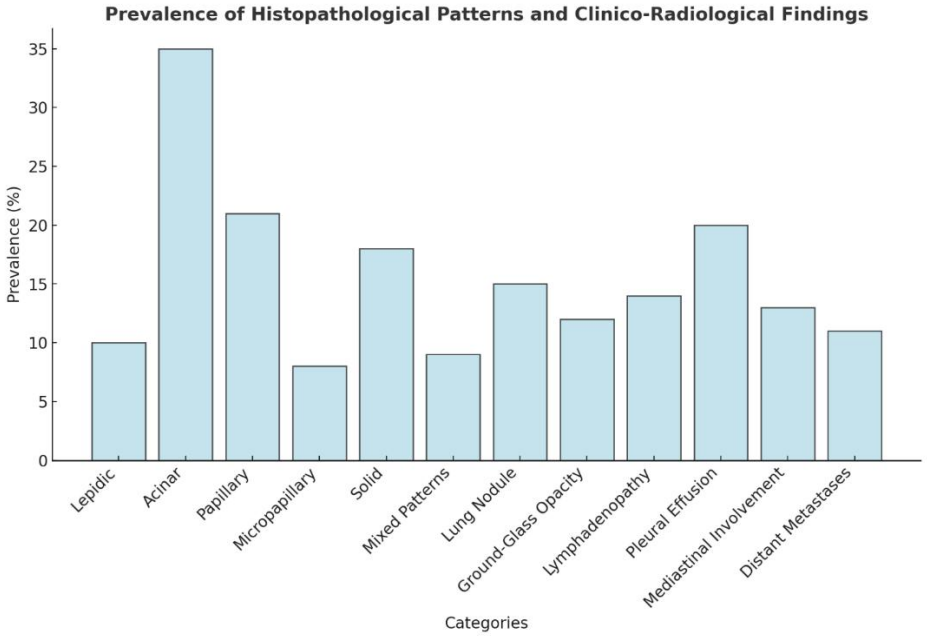

Figure 2: Prevalence of histopathological patterns and clinico-radiological findings

Discussion

Our study investigated demographic traits, histological patterns, clinico-radiological results and biomarker expression in lung cancer patients. The outcomes determined the pathophysiology of lung cancer, its clinical presentation and possible diagnostic markers.

Our cohort's mean age was 62.4 years, in line with earlier studies showing that lung cancer mostly affects elderly persons. The male preponderance (58.6%) is in line with world trends, whereby higher smoking rates among males greatly influence the risk of lung cancer. In our study, 69.3% of patients smoked; this is similar to results of the study, where smoking accounted for over 60% of lung cancer cases worldwide [14-15]. Thirty-7% of patients, however, were nonsmoking, which emphasizes the need of looking at other possible causes including occupational exposure and environmental toxins [16]. Finding in line with past research on NSCLC, acinar carcinoma (35%) was the most common among the histological subtypes followed by papillary (21%) and solid (18%) patterns. The preponderance of acinar carcinoma underlines its clinical and pathological relevance in lung cancer diagnosis and prognosis.

Consistent with results of the researcher, who noted frequent pleural involvement in advanced lung cancer, pleural effusion (20%) appeared as the most often seen radiological consequence in terms of clinico-radiological associations [17-18]. Reflecting the usual imaging patterns of lung malignancies, also seen were mediastinal involvement (13%), lymphadenopathy (14%), and lung nodules (15%). Furthermore observed were ground-glass opacity (12%) and distant metastases (11%), which underline the need of imaging in determining tumor spread and directing therapy recommendations. These findings underline the need of combining radiography and histology for exact therapy and staging of lung cancer.

High TTF-1 (83.6%) expression was found by immunohistochemical investigation, therefore confirming its function as a main diagnostic marker for lung cancer [19]. Furthermore showing considerable positive to support their role in tumor growth and poor prognosis were UBE2C (72.1%), MCM2 (73.6%), and MCM6 (77.1%). These results line up with past studies [17-20]. Suggesting their possible as therapeutic targets in lung cancer, the expression of FEN1 (65.7%) and TPX2 (62.9%) emphasizes their further importance in DNA repair and mitotic control.

Our results complement study, which also noted acinar carcinoma as the main subtype in lung adenocarcinoma [21]. Prior investigations supported by the high frequency of pleural effusion and mediastinal involvement show that these consequences are rather common in lung cancer

progression. Furthermore in line with past research stressing their diagnostic and prognostic relevance is the increased expression of TTF-1 and UBE2C [22].

Though our research offers insightful analysis, some restrictions should be admitted. Being cross-sectional, it does not prove causal links between radiological characteristics, histological patterns, and biomarker expression. Larger sample sizes and molecular analysis in future longitudinal studies could assist to clarify the processes behind biomarker expression and their function in tumor development and therapy response.

Conclusion

This study highlights acinar carcinoma as the most prevalent histological subtype of lung cancer, along with significant clinico-radiological findings, particularly pleural effusion and mediastinal involvement. The high expression of biomarkers such as TTF-1, UBE2C, MCM2, and MCM6, as revealed by immunohistochemical analysis, underscores their diagnostic and prognostic significance. These findings emphasize the importance of integrating molecular, histopathological, and radiological data in lung cancer management, paving the way for personalized treatment strategies and improved clinical outcomes.

Conflict of Interest

None.

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