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Original Research Article

Correlating Liquid Biopsy Biomarkers with Histopathological Features for Early Detection of Lung Adenocarcinoma

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Name of Author:
Hafiz Abdul Basit Khan[1], Muhammad Usman Fazal[2], Seema Shafiq[3], Sania Ali Shah[4], Tehseen Tanveer[5], Javairia Riaz Masood[6]

Affiliation: *[1]Resident Internal Medicine, Medical Unit-1, Jinnah Hospital, Lahore, Pakistan*
[2]Trainee Medical Officer / Postgraduate Resident in Pulmonology Department, Saidu Group of Teaching Hospital (SGTH), Swat, Pakistan
[3]Assistant Professor, Oral Pathology, Islamic International Dental College & Hospital, Riphah International University, Islamabad, Pakistan
[4]Resident Histopathology, Aga Khan University Hospital, Karachi, Pakistan
[5]Medical Specialist, Department of General Medicine, KRL Hospital, Islamabad, Pakistan
[6]PGR General Surgery, Surgical A, Saidu Group of Teaching Hospitals, Swat, Pakistan

Corresponding Author: Hafiz Abdul Basit Khan,
Email: abdulbasitkhan962@gmail.com

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Abstract: ***Background:*** Lung adenocarcinoma is often diagnosed at an advanced stage due to its subtle early symptoms and limitations of conventional tissue biopsy. Objective: To evaluate the correlation between liquid biopsy biomarkers and histopathological characteristics of lung adenocarcinoma for potential use in early detection and tumor profiling. ***Methods:*** This observational analytical study was conducted at Jinnah Hospital Karachi and Agha Khan Hospital, Karachi from November 2023 to February 2025, included 75 patients with histopathologically confirmed lung adenocarcinoma. Blood samples were collected for analysis of circulating tumor DNA, circulating tumor cells, exosomal microRNAs, and specific gene mutations. Histopathological features including tumor grade, growth pattern, and lymphovascular invasion were assessed. ***Results:*** Circulating tumor DNA was detectable in 62 patients (82.7%), circulating tumor cells in 49 patients (65.3%), and elevated exosomal microRNA levels in 57 patients (76.0%). EGFR mutations correlated significantly with lepidic and acinar patterns ($p = 0.02$), whereas KRAS mutations were associated with solid and mucinous growth patterns ($p = 0.03$). Circulating tumor cells showed a significant association with lymphovascular invasion ($p = 0.01$). Elevated microRNA expression was more common among moderately and poorly differentiated tumors ($p = 0.01$). Circulating tumor DNA concentration correlated with tumor size ($r = 0.52$) and lymph node involvement ($r = 0.47$), while circulating tumor cell count correlated with distant metastasis ($r = 0.44$). ***Conclusion***: It is concluded that liquid biopsy biomarkers demonstrate strong correlations with important histopathological features of lung adenocarcinoma and may serve as valuable complementary tools for early detection and disease characterization.

Keywords: Lung adenocarcinoma, liquid biopsy, circulating tumor DNA, circulating tumor cells, exosomal microRNA, histopathology

INTRODUCTION

Lung adenocarcinoma remains one of the most pressing challenges in thoracic oncology, representing a substantial proportion of non–small cell lung cancer cases globally. Imaging and molecular diagnostics have improved over the last few years, but prognosis still relies on the stage at initial diagnosis, as early stages have improved prognosis and survival [1]. This is unfortunate, however, as the disease almost always

advances with no symptoms, and standard diagnostic practices only reveal it when there is already local invasion or when it has metastasised [2]. Liquid biopsies have emerged as one of the most transformative diagnostic tools of our time, as traditional biopsy methods, which are the only option when it comes to confirming diagnosis and molecular profiling, have significant downsides, including procedural invasiveness, sampling errors, the inability to capture the totally different microenvironments of the tumour, and the amount of risk involved [3]. Innovations in technology and diagnostic tools have led to a more accurate and safer diagnosis than traditional methods [4]. Liquid biopsies provide a less invasive diagnostic technique and can detect and assess the entire tumour circulation in microenvironments [5]. Specifically, these diagnostics focus on the circulating tumour DNA, exosomes, microRNAs, and the circulating tumour cells that capture, in real time, the cellular landscape of a tumour by monitoring the molecular changes and the tumour behaviour [6]. Whereas a tissue biopsy is a small sample that incorporates a temporal and spatial bias, a liquid biopsy is a more accurate and informative technique that captures signals from multiple microenvironments, which demonstrates a more diverse tumour heterogeneity [7]. This specific benefit positions liquid biopsy as a potential method for the detection of cancer at earlier stages, tracking outcomes of treatment, identifying residual cancer cells, and predicting a return of the disease [8]. Nonetheless, there is a need for robust validation against other diagnostic methodologies, specifically historical and standard pathology, before the use of liquid biopsy in research can materialise into day-to-day clinical practice [9]. Such pathology reports may provide pivotal details that include, but may not be limited to, tumour morphology, aberrant growth, changes in cellular composition, lymphatic and vascular system invasiveness, levels of cell division, and the tumour's differentiative character [10]. These factors comprise tumour pathology (grading and/or staging) and tumour prognosis. For the full potential of liquid biopsy research to be achieved, the questions arise as to whether or not the selected toxins are in the blood and whether or not the toxins accurately represent or predict the pathology of the tumour [11]. This relative predictor value is possibly the only factor that will confirm the validity of the liquid biopsy and facilitate its use in first-instance screening for early detection in asymptomatic patients [12]. There is newly published research that suggests a probable link, and therefore a subsequent and functional prediction, to liquid biopsy and the broader molecular profile and biopsy report detail in lung adenocarcinoma. For instance, there lie EGFR changes in the circulating tumour cell DNA that may correlate to other lepidic growth patterns, whereas KRAS changes seem to be more fit with invasive mucinous adenocarcinomas [13]. There is an association with an event of high circulating tumour cell counts, which tends to correlate with more aggressive forms of the tumour and poorer survival [14]. There are exosomes and microRNA factors that are known to drive epithelial-mesenchymal transition, which facilitate tumour microenvironment changes, and metastasis; all of which are changes that are known to pathology. Although there are likely positive associations in the literature, evidence is still in its infancy, and is confounded by issues such as small sample sizes, methodological issues, and biomarker heterogeneity [15].

Objective

To evaluate the correlation between liquid biopsy biomarkers and histopathological characteristics of lung adenocarcinoma for potential use in early detection and tumor profiling.

METHODOLOGY

This observational analytical study was conducted in the Department of Pulmonology and Pathology at – Jinnah hospital Karachi and Agha khan hospital Karachi from November 2023 to February 2025-. A total of 75 patients diagnosed with lung adenocarcinoma were included in the study. Non-probability consecutive sampling was used to recruit eligible participants. Patients presenting with suspected or confirmed lung adenocarcinoma and undergoing both tissue biopsy and liquid biopsy assessment were evaluated.

Inclusion Criteria

- Adults aged 18 years and above
- Histopathologically confirmed lung adenocarcinoma
- Availability of liquid biopsy sample (blood-based) collected before any treatment
- Patients who consented to participate

Exclusion Criteria

- Patients with other lung malignancies or mixed histological types
- Those who had received chemotherapy, radiotherapy, immunotherapy, or targeted therapy before sample collection
- Inadequate tissue sample or degraded liquid biopsy sample
- Patients with severe comorbidities making sample collection unsafe

Data Collection Procedure

After obtaining institutional ethical approval, written informed consent was taken from all participants. Body and demographic information, clinical history, smoking history, and imaging data were recorded on a standard form. Individual peripheral blood samples were taken. After liquid biopsy assessment, tumour

sequenced DNA, circulating tumour cells, exosomal markers, and pertinent micro RNAs were evaluated. Biopsy tissue samples were processed in the pathology lab, stained with haematoxylin and eosin, and reviewed for histologic tumour grade, subtype, invasion, lymphovascular invasion, and other tissue molecular changes. For the available liquid biopsy, more than one validated molecular technique was used depending on the liquid biopsy markers. For other molecular technique markers, PCR-based assays, immuno-assays and/or liquid biopsy targeted assays with next generation sequencing were used. For all sampled patients, liquid biopsy biomarker profiles were compared with their corresponding tissue histopathologic findings to determine the lower tissue histopathologic finding and liquid biopsy biomarker correlation. A purpose-built data entry sheet was developed for all results to minimise data recording errors. The research primarily aimed to evaluate the linkage of sampled venous blood to the tumour and main histopathologic findings, primarily tumour grade, tumour pattern, and lymphovascular invasion. The research secondarily aimed to discover markers that may be useful for early diagnosis of the condition.

Statistical Analysis

Data were analyzed using SPSS version 26. Quantitative variables were presented as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Associations between liquid biopsy biomarkers and histopathological features were assessed using chi-square tests for categorical variables and independent t-tests or Mann-Whitney U tests for continuous variables, depending on data distribution. Correlation analysis was performed using Pearson or Spearman coefficients. A p-value of <0.05 was considered statistically significant.

RESULTS

Data were collected from 75 patients, mean age of the participants was 59.3 ± 10.8 years. Statistics reveal there were 46 men (61.3%) and 29 women (38.7%). A history of smoking revealed 43 of the patients were smokers (57.3%) and 32 were non-smokers (42.7%). The majority of patients had advanced disease stages, with 48 of the patients (64.0%) having stage III–IV disease and 27 patients (36.0%) stage I–II disease. Concerning the distribution of the biomarkers, 62 patients (82.7%) had detectable circulating tumour DNA, 49 patients (65.3%) had circulating tumour cells, and 57 patients (76.0%) had elevated levels of exosomal microRNAs. From the presented data, 21 patients (28.0%) were shown to have EGFR mutations, 14 patients (18.7%) had mutations in KRAS, and 6 patients (8.0%) had rearrangements in ALK. The results of histopathological examination revealed that 44 patients (58.7%) had moderately differentiated tumours, 23 patients (30.7%) had tumours that were poorly differentiated, and 8 patients (10.7%) had tumours that were well differentiated. Of the patients, 39 (52.0%) showed lymphovascular invasion. Of the patients, the most predominant growth patterns were 27 with acinar (36.0%), 20 with solid (26.7%), 18 with lepidic (24.0%), and 10 with mucinous growth patterns (13.3%).

Table 1: Baseline Characteristics of Patients (N = 75)

Variable	Value
Age (years)	59.3 ± 10.8
Gender	
Male	46 (61.3%)
Female	29 (38.7%)
Smoking status	
Smoker	43 (57.3%)
Non-smoker	32 (42.7%)
Disease stage	
Stage I–II	27 (36.0%)
Stage III–IV	48 (64.0%)
Biomarker values	
Circulating tumor DNA detectable	62 (82.7%)
EGFR mutation	21 (28.0%)
KRAS mutation	14 (18.7%)
ALK rearrangement	6 (8.0%)
Circulating tumor cells detectable	49 (65.3%)
Elevated exosomal microRNA levels	57 (76.0%)
Tumor grade	
Well differentiated	8 (10.7%)
Moderately differentiated	44 (58.7%)
Poorly differentiated	23 (30.7%)

Lymphovascular invasion	39 (52.0%)
Predominant growth pattern	
Lepidic	18 (24.0%)
Acinar	27 (36.0%)
Solid	20 (26.7%)
Mucinous	10 (13.3%)

EGFR mutations demonstrated a strong association with lepidic or acinar patterns, with 16 of 21 patients (76.2%) showing this correlation (p = 0.02). KRAS mutations were more frequently associated with solid or mucinous tumor morphology, observed in 10 of 14 patients (71.4%), with a significant p-value of 0.03. Circulating tumor cells showed a significant relationship with lymphovascular invasion, present in 34 of 49 patients (69.4%) who were positive for circulating tumor cells (p = 0.01). Elevated exosomal microRNA levels were significantly associated with higher tumor grade, as 41 of 57 patients (71.9%) with elevated microRNAs had moderate or poor differentiation (p = 0.01).

Table 2: Association between Liquid Biopsy Biomarkers and Histopathology

Biomarker	Associated Feature	Value	p-value
EGFR mutation	Lepidic or acinar pattern	16 of 21 (76.2%)	0.02*
KRAS mutation	Solid or mucinous pattern	10 of 14 (71.4%)	0.03*
Circulating tumor cells	Lymphovascular invasion	34 of 49 (69.4%)	0.01*
Elevated exosomal microRNA	Moderate or poor differentiation	41 of 57 (71.9%)	0.01*

*Significant at $p < 0.05$

Circulating tumor DNA concentration showed a moderate positive correlation with tumor size (r = 0.52) and lymph node involvement (r = 0.47). Circulating tumor cell count demonstrated a correlation with distant metastasis (r = 0.44).

Table 3: Correlation Analysis between Biomarkers and Tumor Burden

Parameter	Correlation Value (r)
Circulating tumor DNA vs tumor size	0.52
Circulating tumor DNA vs lymph node involvement	0.47
Circulating tumor cell count vs distant metastasis	0.44

In stage I–II disease, circulating tumor DNA was detectable in 18 of 27 patients (66.7%), circulating tumor cells in 13 patients (48.1%), and elevated microRNA expression in 15 patients (55.6%). EGFR mutations were present in 10 patients (37.0%), while KRAS mutations were less frequent at 4 patients (14.8%). In contrast, stage III–IV disease showed substantially higher biomarker positivity. Circulating tumor DNA was detectable in 44 of 48 patients (91.7%), circulating tumor cells in 36 patients (75.0%), and elevated microRNA expression in 42 patients (87.5%). EGFR mutations were present in 11 patients (22.9%), while KRAS mutations occurred in 10 patients (20.8%).

Table 4: Distribution of Liquid Biopsy Biomarkers across Disease Stages (N = 75)

Disease Stage	Biomarker	Value
Stage I–II (n = 27)	Circulating tumor DNA detectable	18 (66.7%)
	Circulating tumor cells detectable	13 (48.1%)
	Elevated microRNA expression	15 (55.6%)
	EGFR mutation	10 (37.0%)
	KRAS mutation	4 (14.8%)
Stage III–IV (n = 48)	Circulating tumor DNA detectable	44 (91.7%)
	Circulating tumor cells detectable	36 (75.0%)
	Elevated microRNA expression	42 (87.5%)
	EGFR mutation	11 (22.9%)
	KRAS mutation	10 (20.8%)

Circulating tumor DNA was detectable in 38 smokers (88.4%) and 24 non-smokers (75.0%), although this difference was not statistically significant (p = 0.12). Circulating tumor cells were significantly more common in smokers, found in 32 of 43 patients (74.4%), compared to 17 of 32 non-smokers (53.1%), with a p-value of 0.04. Elevated exosomal microRNA levels were slightly more frequent in smokers (81.4%) than non-smokers (68.8%), but without statistical significance (p = 0.19). EGFR mutations were more common in non-smokers, present in 13 patients (40.6%) compared to 8 smokers (18.6%), with a significant p-value of 0.03. KRAS mutations were more frequent among smokers, observed in 12 of 43 patients (27.9%), whereas only 2 of 32 non-smokers (6.3%) had them, yielding a significant p-value of 0.01.

Table 5: Comparison of Biomarker Positivity Between Smokers and Non-Smokers (N = 75)

Biomarker	Smokers (n = 43)	Non-smokers (n = 32)	p-value
Circulating tumor DNA detectable	38 (88.4%)	24 (75.0%)	0.12
Circulating tumor cells detectable	32 (74.4%)	17 (53.1%)	0.04*
Elevated exosomal microRNA	35 (81.4%)	22 (68.8%)	0.19
EGFR mutation	8 (18.6%)	13 (40.6%)	0.03*
KRAS mutation	12 (27.9%)	2 (6.3%)	0.01*

*Significant at $p < 0.05$

DISCUSSION

The findings of this study demonstrate that liquid biopsy biomarkers show meaningful and clinically relevant correlations with key histopathological features of lung adenocarcinoma. The 82.7% presence of circulating tumour DNA, along with the 76% presence of elevated exosomal microRNA, highlights the importance of conducting liquid biopsies. The identification of these biomarkers serves as the first evidence to indicate the presence of a tumour, especially with the presence of a tumour. One of the most important findings of this research is the presence of multiple ethological and histological growth patterns, along with specific tumour DNA mutations. Lepidic and acinar growth patterns have been associated with the strong presence of EGFR, whereas solid and mucinous patterns were correlated with the presence of KRAS. There have been similar findings in molecular pathology where EGFR mutant tumours have a lower aggressive behaviour, and KRAS mutant tumours have a more invasive phenotype, again providing more evidence of the existence of circulating tumour DNA, tumour profiling, and histology prediction [16]. Circulating tumour cells were spotted in 65.3% of patients and indicated a statistically significant association with lymphovascular invasion. This correspondence supports the established idea that circulating tumour cells mirror the tumour's capability to penetrate and spread from the primary site. Patients with detectable circulating tumour cells experienced a significantly greater presence of lymphovascular invasion, suggesting a more aggressive disease phenotype [17]. This correlation indicates that circulating tumour cell quantification could be an early and less intrusive indicator of the tumour's capability to invade and spread. Furthermore, exosomal microRNAs also exhibited strong correlations with more advanced tumour grade. In this endeavour, 71.9% of patients with high microRNA levels were noted to have moderately or poorly differentiated tumours. This aligns with the increasing data that exosomal microRNAs, especially those that regulate pathways like epithelial–mesenchymal transition, angiogenesis, and cellular stress responses, may correlate to the tumour's biological aggressiveness. Additionally, the findings reinforce the significance of microRNA profiling in the selection of patients exhibiting the rapid advancement of the disease [18]. Positive correlations between circulating tumour DNA, tumour size, and lymph node involvement, and circulating tumour cells and distant metastasis were sustained, according to correlation analyses. These results corroborate with other reports suggesting an increase in volume of tumour circulating biomarkers in response to an increase in passive tumour mass [19]. The correlation coefficients in this study provide evidence suggesting that liquid biopsy alone, without imaging complements, could provide value in determining the extent and/or early stage of disease. Moreover, the distribution of liquid biopsy biomarkers, including circulating tumour DNA, circulating tumour cells, and elevated microRNA, stage I to II, was significantly and profoundly lower than that of stage III to IV, where these markers were considerably more detectable [20]. This correlates with the biological behaviour of lung adenocarcinoma, where late-stage tumours shed more DNA into the circulatory system. Though biomarker detection in the early stage was lower than that of later stage disease, the volume of early stage patients with circulating biomarkers on detection demonstrates significant promise in liquid biopsy for advanced stage disease and supports the notion liquid biopsy could provide substantial value for early disease detection [21,22]. The study correlates with the evidence suggesting tumour-related biology liquid biopsy biomarkers correlated with more conventional histopathological parameters in a clinically significant manner. Liquid biopsy's capability of revealing molecular changes, reflecting the tumour's grade and potential to invade, and mirroring growth patterns, shows its capability as an auxiliary tool for the early detection, risk stratification, and monitoring of lung adenocarcinoma. Since liquid biopsy is minimally invasive and can be repeated to capture tumour heterogeneity, expanding its use into clinical workflows could help improve diagnostic precision and inform tailored approaches to patient care, particularly in instances in which sampling tissue is unsafe or impractical.

CONCLUSION

It is concluded that liquid biopsy biomarkers show strong and clinically meaningful correlations with key histopathological features of lung adenocarcinoma, supporting their potential role in early detection and biological characterization of the disease. Circulating

tumor DNA, circulating tumor cells, and exosomal microRNAs demonstrated significant associations with tumor grade, growth patterns, lymphovascular invasion, and overall tumor burden. Specific mutations such as EGFR and KRAS reflected distinct histological behaviors, while circulating tumor cell presence corresponded with more invasive and advanced disease.

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