



Comparative Molecular Profiling of Tissue and Liquid Biopsy Using Next-Generation Sequencing in Treatment-Naïve Lung Carcinoma Patients: A Real-World Study

Running Title: Tissue vs Liquid Biopsy in Lung Cancer

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ABSTRACT

Background:

Tissue biopsy remains the gold standard for molecular profiling in lung cancers; however low tissue availability, tumor heterogeneity, and low cellularity can compromise genomic evaluations. Liquid biopsy has emerged as a surrogate modality for tissue, but its performance across histopathological subtypes and clinical stages requires real-world validation.

Methods:

This retrospective study included 270 newly diagnosed lung carcinoma patients who underwent NGS testing on tissue biopsy, liquid biopsy, or both. Specimens were comparatively evaluated for pathogenic alterations in cancer-associated genes, NCCN guideline targetable biomarkers and secondary co-mutations across histopathology stratification and clinical staging.

Results:

Pathogenic mutations were detected in a higher percentage for tissue than liquid biopsy (93% vs. 74%), whereas actionable alterations showed comparable detection rates (58% vs. 61%). Adenocarcinoma demonstrated the highest frequency of actionable alterations across both specimen types. Stage-wise analysis showed that pathogenic mutation detection in liquid biopsy increased from 67% in stage III to 82% in stage IV. The detection rate of guideline-based actionable alterations was highest in stage III/IV for liquid biopsy, and the detection of secondary mutations increased for liquid biopsy in metastatic disease. Overall concordance among both pairs was 65.5%, while 100% concordance was observed for targetable driver alterations in mutation-positive matched cases.

Conclusion:

Liquid biopsy demonstrated clinically relevant genomic profiling, particularly in advanced-stage lung cancer, with comparable detection of actionable biomarkers and complete concordance for targetable drivers in mutation-positive matched cases. These findings support its clinical utility as a complementary or alternative modality when tissue biopsy is limited.

KEYWORDS: Lung carcinoma, tissue biopsy, liquid biopsy, pathogenic mutations, guideline-approved biomarkers, secondary co-mutation, histopathology subtype, clinical staging.

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INTRODUCTION

Lung cancer is one of the leading causes of cancer-related death worldwide, whereas in India it accounts for 5.9% of all cancers and 8.1% of all cancer-related deaths. The main factor driving lung cancer is the use of tobacco and smoking, with India positioned among the top five countries in terms of consumption.¹ It's predicted that by 2040 the incidence of lung cancer in India will increase by 75.2% and death by 82.8%.² According to a global study (CONCORD-3) conducted in 61 countries, the 5-year survival rate in India is less than 10% compared to western countries³ and the reason for this may be due to a lag of 6 months from diagnosis of symptom to initiation of treatment. In India, the majority of cases are diagnosed at an advanced stage compared to an early, which accounts for only 3.5%-7.2%.⁴

The first diagnostic approach is the radiological imaging, which evaluates the lesions in the lungs followed by tissue biopsy

testing⁵. National Comprehensive Cancer Network (NCCN) guidelines for non-small cell lung cancer⁶ recommends targeted therapies/immunotherapies/chemotherapies based on positive biomarkers predictive tested via comprehensive molecular profiling and PD-L1 testing by IHC of the patients. Hence, tissue biopsy remains the gold standard biomarker analysis. However, certain challenges are faced upon tissue biopsy, such as anatomical accessibility, tumor heterogeneity, low cellularity issues, etc.

To overcome such challenges, the advancements in liquid biopsy have acted as a surrogate modality⁷. The major markers that are isolated from liquid biopsy are circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), tumor-derived extracellular vesicles (EVs), tumor-educated platelets (TEPs), and circulating free RNA (cfRNA)⁸. Tumor dynamics can be represented by ctDNA, as it reflects the somatic genetic alterations that reflect the entire tissue. Although ctDNA detection is very effective, it becomes challenging when the concentration is extremely low (<1%) due to low shredding of ctDNA⁹.

In several studies the comparative analysis among the tissue and liquid biopsy data has shown that the overall concordance of the mutation detection rate is in the range of 85% to 95%^{10,11}. In the absence of tissue biopsy, 42% of cases have shown actionable markers by the liquid biopsy specimen¹⁰. Hence, liquid biopsy is likely to be considered in routine practice in the absence of tissue biopsy. But still certain percentages of liquid biopsies show the negative results, which again leads to a dilemma upon the use of targeted therapies. Thus, we performed an analysis of real-world patient data to evaluate the role of liquid biopsy across histopathology subtypes and clinical stages. This study focused on distribution of molecular pattern including molecular evolution in tissue and liquid biopsy based on histopathology and clinical stages, to understand in brief which factors show prominent concordant results.

METHODOLOGY

This retrospective study identified 270 lung carcinoma patients whose tissue biopsy and liquid biopsy Next- Generation Sequencing (NGS) testing was requested as a routine clinical management. The inclusion criteria for this study were for those patients who are newly diagnosed for lung carcinoma.

Sample Collection and Processing

From these 270 patients, 186 patient's formalin-fixed paraffin embedded (FFPE) tissue biopsy, 55 patient's liquid biopsy in Streck tube was collected and 29 patients both tissue biopsy and liquid biopsy specimen was collected simultaneously before initiating treatment. All the samples underwent NGS processing. The genomic DNA was isolated from FFPE tissue specimens with tumor volume of >20% using commercially available QIAamp DNA FFPE Advanced kit ((QIAGEN, Cat. No. 56604). Peripheral blood was collected in Cell-Free DNA BCT and plasma separation was performed by centrifugation and circulating tumor DNA (ctDNA) was isolated using commercially available QIAamp minElute ccfDNA DNA kit (QIAGEN, Cat No. 55284). The extracted DNA was subjected to quality-control assessment using the Agilent 4200 TapeStation to determine the DNA Integrity Number (DIN). Samples meeting the laboratory-validated quality criteria (DIN >1.5) for FFPE DNA and cfDNA quality threshold >80%¹² and genomic DNA with 260/280 ratio in range on 1.8 to 2 were considered suitable for downstream NGS library preparation. The concentration of DNA isolated is determined on Qubit 4.0 fluorometer (ThermoFisher Scientific, Waltham, MA, USA).

Next-Generation Sequencing Analysis

Sequencing libraries are prepared using OncoIdx platform¹³. Libraries with unique indexes are then pooled (multiplexed) into a single sequencing run using UMIs. Pooled libraries are loaded onto the sequencing platform. Next generation sequencing is performed using Illumina NextSeq 2000 platform (Illumina, San Diego, CA, USA) in a paired-end fashion (150 × 2) using clinically relevant gene enriched panels. The panels are custom designed to target the coding as well as non-coding regions of the relevant genes. These panels are clinically validated targeted gene panels designed for lung carcinoma molecular profiling. Sequencing analysis included assessment of clinically relevant driver alterations and actionable genomic variants, including mutations, insertions/deletions, copy number alterations, and gene fusions where applicable.

The Bioinformatic processing of data is achieved through custom designed pipeline which is optimized to detect single nucleotide variants (SNV), Copy number variants (CNVs), Insertions and deletions (InDels), Fusions, and Microsatellite instability (MSI). Post-NGS analysis involves trimming the adapter and barcode sequences from the raw FastQ files upon thorough quality assessment (QA tests). Trimmed sequences are then aligned with the Genome Reference Consortium Human Build 38 (GRCh38) reference genome for further processing as detailed in the following sections. Only pathogenic and likely pathogenic variants with adequate sequencing quality metrics were included in the final analysis. The variants with uncertain significance were excluded from the study.

Statistical analyses

Statistical analyses (chi-square test) were performed using R script (Version 4.4.3, The R Foundation, Vienna, Austria) and genetic aberrations in the form of bar diagram using Microsoft excel. All hypotheses were two sided and p <0.05 was considered statistically significant.

RESULTS

A total of 270 patients with histologically confirmed lung carcinoma were included in this retrospective study. The comprehensive baseline demographic and clinical features are summarized in Table 1. The study population demonstrated male predominance of 60% and 40% being female with median age of 64 years (range 27-90).

Histopathological subtyping revealed that adenocarcinoma (82%) was the predominant subtype compared to squamous cell carcinoma (11%) and lung carcinoma, not otherwise specified (NOS) (7%). The clinical staging information showed the largest proportion of the cohort belong to stage IV disease (54%) followed by stage III (10%) and then early-stage disease (Stage I/II) (9%) and for the remaining 27% cases the staging data was unavailable.

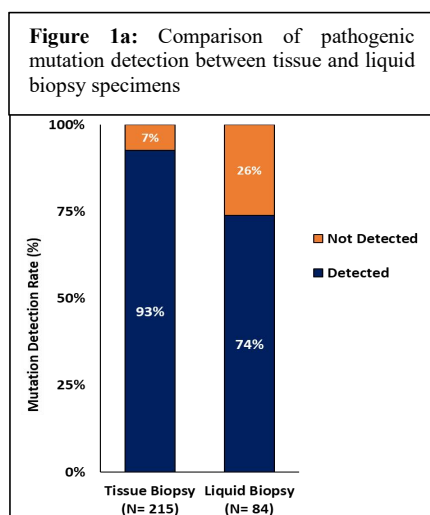
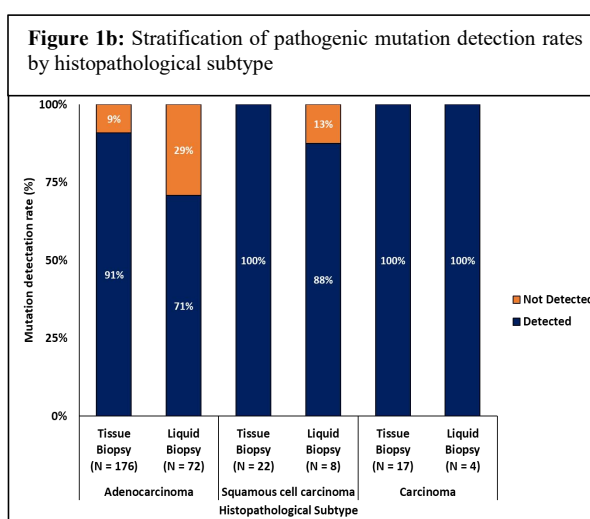
The molecular diagnostic testing was done on tissue biopsy in 186 cases (69%), liquid biopsy in 55 cases (20%), and matching concurrent specimens (both tissue and liquid biopsy) were analyzed in 29 cases (11%).

Table 1. Baseline demographic and clinicopathological characteristics of the study population (N = 270).

Characteristics	Category	n (%)
Age, years	Median (Range)	64 (27–90)
Gender	Male	163 (60)
	Female	107 (40)
Histology	Adenocarcinoma	222 (82)
	Squamous cell carcinoma	28 (11)
	Lung carcinoma (NOS)	20 (7)
Stage	I/II	23 (9)
	III	28 (10)
	IV	145 (54)
	Unknown	74 (27)
Specimen type	Tissue biopsy	186 (69)
	Liquid biopsy	55 (20)
	Both specimens	29 (11)

3.1. Comparative pathogenic mutation rate detection in Tissue v/s Liquid Biopsy for cancer-causing genes

Across 270 patients, the molecular profiling was executed on 215 tissue and 84 liquid biopsy specimens. The first primary analysis evaluated the diagnostic yield and detection rate of pathogenic mutations in cancer causing genes across both specimens. Tissue biopsy demonstrated a significantly higher overall pathogenic mutation compared with liquid biopsy (93% vs. 74%; $p < 0.001$) (Figure 1a).



The stratification based on tumor histopathological subtypes demonstrated that the pathogenic mutation detection rate in tissue biopsy was maintained constant across all lineages: adenocarcinoma (91%), squamous cell carcinoma (100%) and lung carcinoma NOS (100%). Conversely for liquid biopsy the detection rate got fluctuated by subtype capturing pathogenic variants in 71% of adenocarcinoma, 88% of squamous cell carcinoma and 100% in Lung carcinoma NOS (Figure 1b).

Another stratification based on clinical stages demonstrated a wider diagnostic gap in locally advanced (stage III) disease where tissue detection was 95% and liquid biopsy detection was 67% for pathogenic mutations. In metastatic disease (Stage IV), the

detection of pathogenic mutations in liquid biopsy increased the sensitivity to 82% narrowing the gap with tissue with 89% (Figure 1c).

Figure 1c: Stratification of pathogenic mutation detection rates by clinical stage

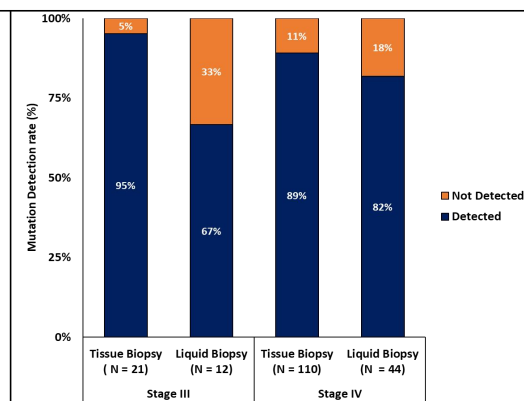
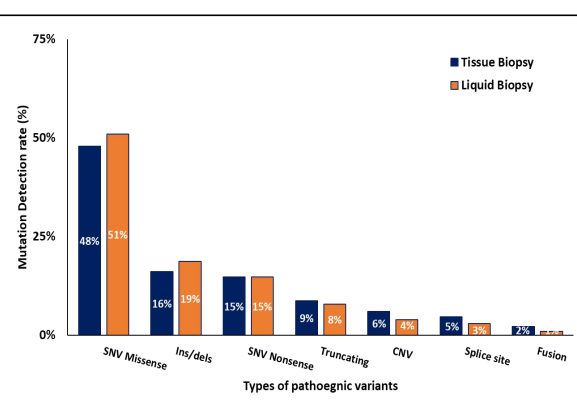


Figure 1d: Distribution of pathogenic mutation types across specimens



The types of pathogenic mutations identified in both the specimen types displayed exceptional structural consistency regarding variant type distributions single nucleotide variants (SNV), missense alterations predominated (48% tissue v/s 51% liquid), followed by insertions/deletions (16% v/s 19%) and SNV nonsense mutations (Figure 1d). The remaining variant landscape were of lower frequencies but showed similar distributions in both tissue as well as liquid biopsies.

3.2. Comparison of Clinically Actionable (Targetable) vs. Non-Targetable Mutations in Tissue v/s Liquid Biopsy

The pathogenic mutations identified in our initial analysis were further stratified into targetable (actionable) mutations and non-targetable mutations based on the NCCN guidelines approved biomarkers. Within pathogenic mutations detected, the prevalence of targetable driver genes was highly congruent between both specimen types; 58% in tissue v/s 61% in liquid biopsy ($p = 0.67$; Figure 2a).

Figure 2a: Comparison of clinically targetable v/s non-targetable pathogenic mutations.

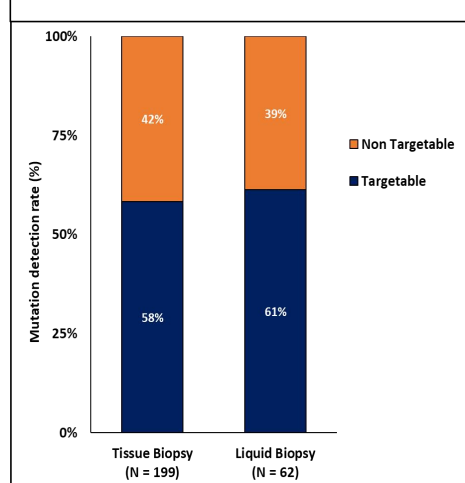
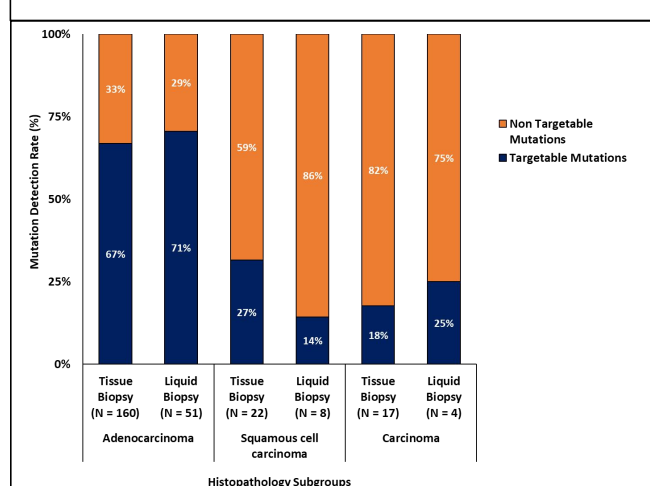


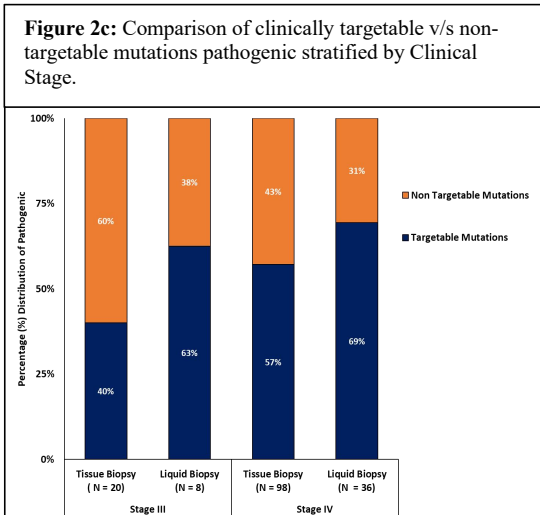
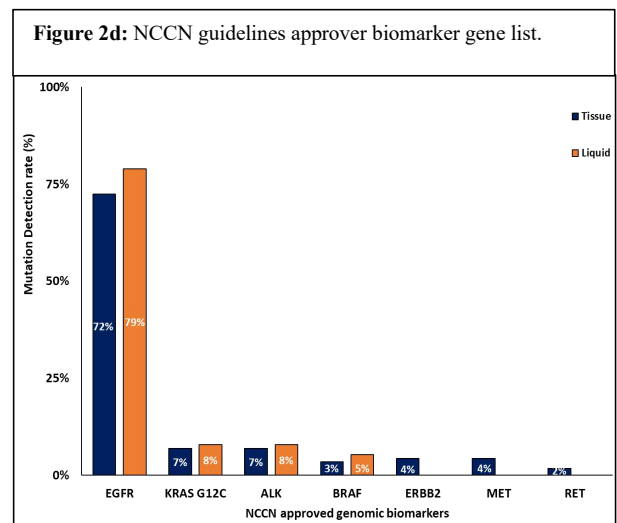
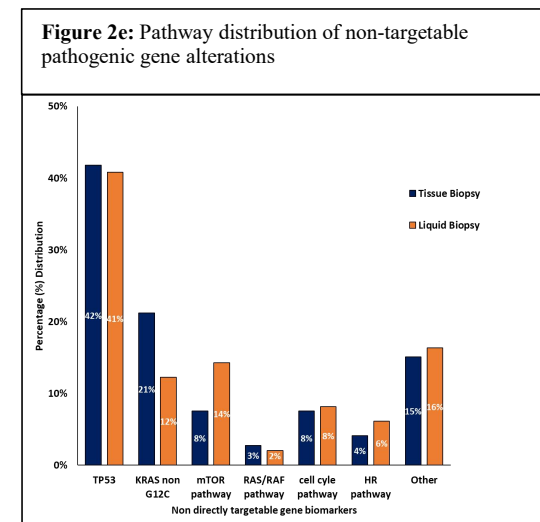
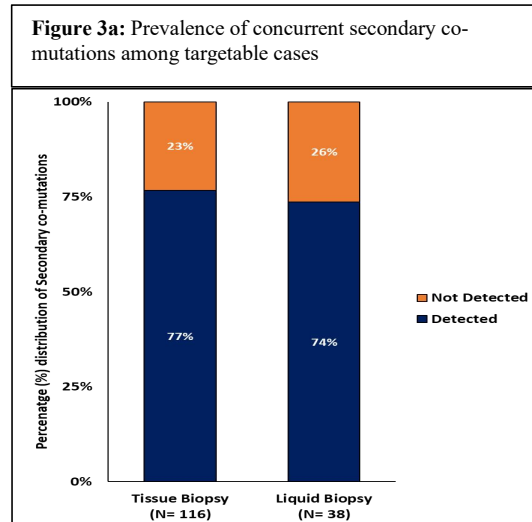
Figure 2b: Comparison of targetable v/s. non-targetable pathogenic mutations stratified by histopathology.



The histopathological based stratification analysis confirmed that guidelines approved actionable gene mutations were concentrated with adenocarcinoma lineage for both specimens (67% in tissue; 71% in liquid biopsy) types. However, in other lineages such as squamous cell carcinoma and lung carcinoma (NOS) non-targetable mutations were identified in higher percentage compared to targetable mutations in both specimen types (Figure 2b)

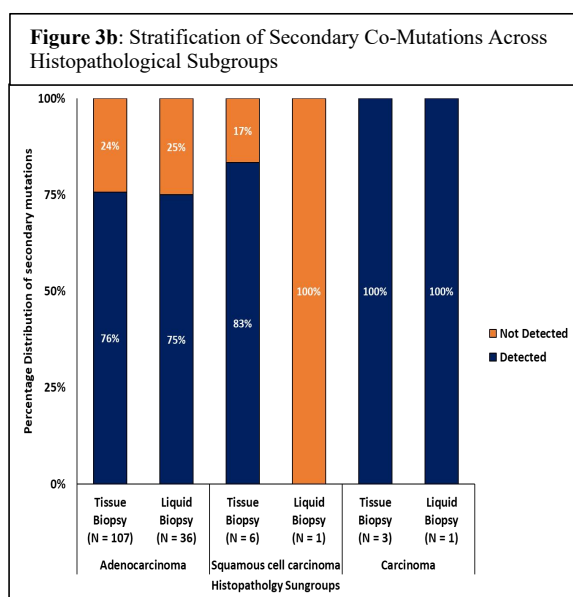
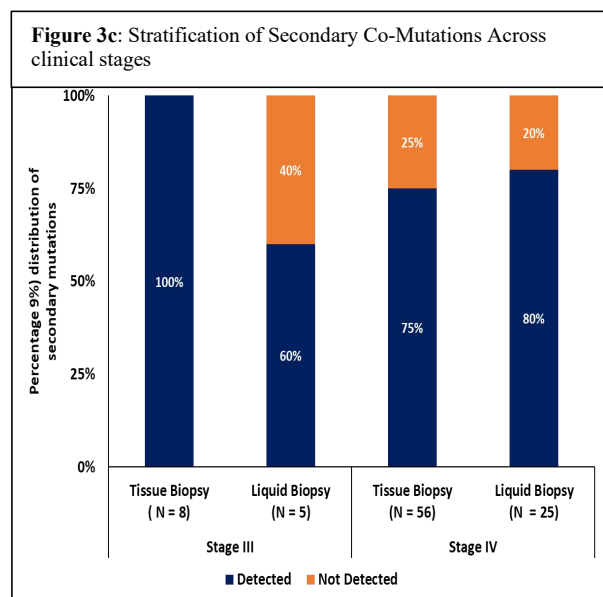
Another stratification based on clinical stages revealed that liquid biopsy captured higher proportion of targetable drivers than tissue in both stage III (63% v/s 40%) and stage IV (69% v/s 57%). Irrespective of specimen type stage IV demonstrated higher frequency of targetable mutations compared to stage III (Figure 2c). The dominant actionable gene mutation identified was EGFR in both specimens (72% in tissue; 79% in liquid biopsy) while the KRAS G12C and ALK rearrangements demonstrated parallel frequencies in both specimen types (7% in tissue v/s 8% in liquid biopsy) (Figure 2d). The dominant non-targetable mutation identified in both specimens was TP53 (42% in tissue; 41% in liquid biopsy), however non G12C KRAS mutations

was identified in higher frequency in tissue (21%) compared to liquid biopsy (12%) and conversely the mTOR pathway associated gene alterations were identified higher in liquid biopsy (14%) compared to tissue (8%) (Figure 2e).



3.3.Prevalence of Secondary Co-Mutations within the Clinically Targetable Cohort

The presence of secondary mutations along with targetable mutations were highly concordant in both specimen types (77% in tissue v/s 74% in liquid biopsy) (Figure 3a). The histopathological stratification revealed secondary co-mutations are well characterized in adenocarcinoma with equal distribution among both specimen types (76% tissue v/s 75% liquid biopsy), however another lineage the size of specimen were compromised to determine the true results (Figure 3b)



The clinical stage wise stratification to understand the presence of secondary co-mutations revealed that tissue biopsy retained its sensitivity for co-mutational clones in stage III (100% tissue v/s 60% liquid biopsy), whereas liquid biopsy captured the enhanced clonal yield in stage IV (80% liquid v/s 75% tissue biopsy) (Figure 3c)

The presence of secondary co-mutations along with the targetable/ actionable mutations impact the treatment response. To evaluate whether the locally advanced stage or metastatic diseases co-relate with the presence of secondary co-mutations, the subgroup analysis was done across stage III and stage IV within the actionable mutation's presence along with secondary co-mutations in tissue and liquid biopsies.

The presence of secondary co-mutations along with targetable mutations in stage III was 100% (n= 8/8) but in stage IV the percentage was reduced to 75% (n= 42/56) for the tissue biopsies. Conversely the secondary co-mutations detected in liquid biopsy for stage III was 60% (n= 3/5) which increased to 80% (n= 20/25) in stage IV disease. These findings stated that although the tissue biopsy retains the absolute sensitivity for co-mutation sub-clones in localized disease, but in metastatic disease the liquid biopsy demonstrated an enhanced yield of secondary alterations reflecting its exceptional capability to identify the multi-clonal systemic molecular landscape.

3.4.High-Resolution Concordance Analysis of Matched Concurrent Specimens

An internal validation analysis of plasma cell free DNA (cfDNA) against solid tumor sequencing was conducted on a highly controlled cohort of 29 patients who underwent simultaneous liquid and tissue biopsies. Overall pathogenic mutations captured by both specimen types was 65.5% (n= 19/29) concordant, whereas the remaining 34.5% (n= 10/29) patients showed tissue-isolated mutation profile only whereas the liquid biopsy fell below the limit of detection or were absent.

From the 19 patients who exhibited the pathogenic mutations in both modalities showed 100% concordance for identifying targetable mutation in both specimens. 12 cases (63.2%) demonstrated identical guideline approved targetable driver mutations in both specimens whereas both specimens synchronously confirmed non- targetable mutations in remaining 7 cases (36.8%).

DISCUSSION:

Within a large clinical cohort of lung carcinoma patient, this study demonstrated a robust, real- world comparative evaluation between formalin fixed paraffin embedded (FFPE) tissue and plasma cell-free (cfDNA) liquid biopsy specimens based on NGS platform using a comprehensive gene panel. Our findings demonstrated that for disease at diagnosis the tissue biopsy remains the gold standard for identifying predictive biomarkers of lung carcinoma, along with that liquid biopsy has achieved a highly comparable results in capturing targetable oncogenic driver mutation and secondary mutations especially in advanced stages.

The detection of pathogenic mutations is a pivotal to identify the tumor biology in the patients. In our study the comparative analysis showed that tissue biopsy presented with higher pathogenic mutation detection rate compared to liquid biopsy. However, in 26% cases where liquid biopsy showed no mutations detection (NMD) it becomes difficult to distinguish between true and false negative results. The tumor fraction plays an important role to identify the true negative results as it quantifies the presence of ctDNA levels in blood¹⁴. In the negative liquid biopsy specimens, the samples whose tumor fraction was less than 20-25% reflex tissue biopsy testing was recommended and cases showed tumor fraction of >25% were considered as true negative mutations¹⁵. Although liquid biopsy showed less pathogenic mutation detection rate but the identification of actionable mutations according to NCCN approved guidelines was 2% higher in liquid biopsy compared to tissue biopsy. Our study showed that the liquid biopsy had higher sensitivity for EGFR mutation and other non NCCN approved gene alterations identified in mTOR, Homologues recombinant (HR), cell cycle pathways¹⁶.

The literature studies have shown that Lung squamous cell carcinoma (LUSC) and Lung adenocarcinoma (LUAD) show differences in the target gene, targetable treatments, and clinical efficacy. The higher frequency targetable genes such as EGFR and KRAS in LUAD are identified in less than 5% cases of LUSC¹⁷. Similar to this in our study, the targetable genes are identified in higher percentage in LUAD compared to LUSC considering both specimen modalities indicating no statistical significance among specimens (p>0.05).

Comparing to the prospective study which showed the increase in pathogenic mutation rate from 82% in stage III to 89% in stage IV¹⁸; our study also demonstrated for the rise in detecting actionable mutations in liquid biopsy from stage III (63%) to stage IV (69%). Compared to tissue biopsy, the liquid biopsy presented with more actionable mutations which emphasizes its potential use in early detection of targetable markers and disease monitoring which underscores its role as transformative tool in lung carcinoma cases.

We observed an overall 65.5% of concordance among plasma and tissue specimens in our study within advanced stage lung cancer. This is consistent with other reported studies which also showed 65% concordance in mutations between tissue and plasma specimens^{18,19}.

CONCLUSION

This study provides a comprehensive comparative evaluation of FFPE tissue and ctDNA liquid biopsy using comprehensive gene panel on NGS platform for large cohort of lung carcinoma patients. The advantage of this study is that it interpreted the comparative results considering all the parameters which is based on NCCN approved biomarkers, the type of pathogenic variants, histopathology subgroups and the clinical stages. The liquid biopsy has shown its higher sensitivity in terms of NCCN approved biomarker, histopathology subgroup and in advanced clinical stage IV lung cancer. Hence at baseline liquid biopsy can be an alternative approach in the advanced and metastatic disease only if the tissue biopsy is not available, which is also concordant to literature published in European Society for Medical Oncology (ESMO) and International Association for the

Study of Lung Cancer (IASLC).

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