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Diagnostic Performance of Liquid Biopsy Compared to Tissue Biopsy in Lung Cancer Genomics: A Systematic Review and Meta-analysis

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KEYWORDS
Liquid biopsy, circulating tumor DNA, lung cancer, tissue biopsy, genomic profiling, EGFR mutation, meta-analysis.

ABSTRACT:

Background: Tissue biopsy is the standard method for genomic profiling in lung cancer, but it is invasive, may yield insufficient tissue, and often fails to capture tumor heterogeneity. Liquid biopsy, particularly through circulating tumor DNA (ctDNA), provides a minimally invasive alternative with the potential for real-time molecular monitoring.

Objective: To evaluate the diagnostic performance of liquid biopsy compared to tissue biopsy for detecting genomic mutations in lung cancer through systematic review and meta-analysis.

Methods: A systematic literature search of PubMed, Scopus, Web of Science, and Cochrane Library was conducted for studies published between January 2010 and October 2024. Studies comparing liquid biopsy with tissue biopsy in lung cancer patients were included. A random-effects model was used to pool sensitivity, specificity, and diagnostic odds ratio (DOR). Heterogeneity was assessed using the I^2 statistic.

Results: Thirty-two studies involving 6,210 lung cancer patients were included. Liquid biopsy demonstrated a pooled sensitivity of 0.78 (95% CI: 0.72-0.83) and specificity of 0.93 (95% CI: 0.89-0.96). The diagnostic odds ratio was 45.3 (95% CI: 28.1-73.0). Mutation-specific concordance was highest for EGFR (85%), followed by ALK (78%), KRAS (65%), and ROS1 (59%). Heterogeneity was moderate (I^2 = 56%). NGS-based liquid biopsy platforms showed higher diagnostic accuracy compared to PCR-based methods.

Conclusion: Liquid biopsy demonstrates high specificity and moderate sensitivity relative to tissue biopsy and serves as a valuable complementary tool for genomic profiling in lung cancer. It is particularly useful when tissue sampling is challenging and for monitoring treatment response and resistance mutations. However, it should not fully replace tissue biopsy until further improvements enhance its sensitivity. Future advancements should focus on assay standardization and prospective clinical integration.

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for approximately 1.8 million deaths annually [1]. Non-small cell lung cancer (NSCLC) represents nearly 85% of all lung cancer cases, and advances in genomic profiling have enabled the development of targeted therapies that significantly improve patient outcomes [2,3]. Accurate detection of actionable mutations such as EGFR, ALK, KRAS, and ROS1 is essential for treatment planning, particularly in advanced-stage disease where personalized therapy is indicated [4].

Traditionally, tissue biopsy has been considered the gold standard for molecular testing in lung cancer. However, it is invasive, sometimes associated with complications, and may be infeasible in patients with poor performance status or inaccessible tumors [5]. Additionally, tissue specimens may be limited in quantity and fail to capture tumor heterogeneity, particularly in metastatic disease where multiple genomic subclones may exist [6].

In contrast, liquid biopsy, primarily through detection of circulating tumor DNA (ctDNA) in plasma, has emerged as a minimally invasive alternative capable of assessing molecular alterations in real time [7]. This technique

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provides the advantage of dynamic monitoring of treatment response and resistance mutation development, especially during targeted therapy for EGFR-mutant lung cancers [8,9]. Studies have shown that ctDNA testing may detect resistant alterations such as EGFR T790M mutation earlier than radiological progression [10].

Moreover, liquid biopsy is less affected by sampling bias, allowing broader representation of different tumor sites, unlike tissue biopsy which samples only a localized area [11]. However, despite these advantages, concerns persist regarding its sensitivity, particularly in early-stage cancers and low-volume disease, where ctDNA levels may be insufficient for reliable detection [12]. Factors such as ctDNA shedding rate, assay methodology, and analytical sensitivity influence diagnostic performance [13].

Several studies have compared liquid biopsy with tissue biopsy, showing high specificity but moderate sensitivity, suggesting it may be better suited as a complementary rather than a replacement tool [14,15]. The technology has shown particularly promising results for EGFR mutation detection, with concordance rates exceeding 80%, whereas concordance is lower for KRAS and ROS1 mutations [16].

Given the increasing importance of precision oncology, it is essential to determine whether liquid biopsy provides comparable accuracy to tissue biopsy for genomic profiling. This systematic review and meta-analysis aim to evaluate the diagnostic performance of liquid biopsy against tissue biopsy in lung cancer, focusing on sensitivity, specificity, mutation concordance, and clinical applicability. Understanding these metrics is critical for optimizing biomarker testing strategies and improving therapeutic decision-making in lung cancer management [17].

Methods

Study Design

This study was conducted as a systematic review and meta-analysis as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [18]. A predefined protocol was followed including formulation of research question, search strategy, study selection, quality assessment, data extraction, and statistical analysis.

Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

- Adult patients diagnosed with lung cancer.
- Studies comparing liquid biopsy (ctDNA) with tissue biopsy for genomic mutation detection.
- Reported diagnostic accuracy metrics such as sensitivity, specificity, concordance rate, or area under the ROC curve.
- Prospective or retrospective observational studies, or clinical trials.
- Published in English between January 2010 and October 2024 [19].

Exclusion Criteria

- Case reports, reviews, conference abstracts, editorials [20].
- Studies lacking mutation comparison between liquid and tissue biopsy.
- Research limited to technical validation without clinical outcome relevance [21].

Research Question (PICO Framework)

- **Population (P):** Patients with histologically confirmed lung cancer.
- **Intervention (I):** Liquid biopsy-based genomic testing (ctDNA).
- **Comparator (C):** Tissue biopsy-based genomic testing.
- **Outcome (O):** Diagnostic performance (sensitivity, specificity, concordance) [22].

Search Strategy

A comprehensive literature search was conducted across the following databases:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Cochrane Library

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The search included the terms:

("liquid biopsy" OR "circulating tumor DNA" OR "ctDNA") AND ("lung cancer") AND ("mutation detection" OR "genomic profiling") AND ("tissue biopsy" OR "histopathology").

Boolean operators and MeSH terms were applied when appropriate. Reference lists of included studies and relevant reviews were manually screened for additional eligible studies [23].

Study Selection

Two reviewers independently screened titles and abstracts. Full-text evaluation was performed for potentially eligible studies. Any disagreement was resolved by consensus with a third reviewer [24].

Data Extraction

Data were extracted using a standardized form, including:

- Study characteristics (author, year, country, design).
- Sample size.
- Type of liquid biopsy test (e.g., PCR, NGS, digital PCR).
- Mutation type (EGFR, ALK, KRAS, ROS1).
- Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), concordance rates [25].
- Patient stage and biopsy sample type.

Quality Assessment

Methodological quality was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [26]. Each study was assessed for risk of bias in patient selection, index test, reference standard, and flow/timing.

Statistical Analysis

A random-effects model was used for meta-analysis due to expected heterogeneity across studies [27]. Pooled sensitivity, specificity, diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) curves were calculated.

Heterogeneity was assessed using:

- I^2 statistic (>50% considered significant heterogeneity) [28].
- Subgroup analysis performed based on mutation type and testing platform.
- Publication bias assessed using Deeks' funnel plot asymmetry test [29].

Analyses were conducted using RevMan 5.4 and MetaDisc 1.4 software.

Ethical Considerations

Since this study is based on published data and does not involve direct patient contact, ethical approval was not required [31].

Results

Study Selection

The initial literature search identified 823 studies. After removing 83 duplicates, 740 articles were screened by title and abstract. A total of 90 studies underwent full-text review, out of which 32 studies were included in the final meta-analysis based on eligibility criteria [32].

The **PRISMA flow diagram** summary is presented in **Table 1**.

Table 1. PRISMA Flow Summary

Stage	**Number of Studies**
Records identified through database searching	823
Duplicates removed	83
Records after screening titles/abstracts	740
Full-text articles assessed	90
Excluded (incomplete data/non-comparative)	58
Studies included in meta-analysis	**32**

Study Characteristics

A total of 6,210 lung cancer patients were included across the 32 studies. Most studies were conducted in

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Asia (56%), followed by Europe (28%) and North America (16%) [33]. The majority (81%) focused on advanced-stage NSCLC, where liquid biopsy sensitivity was reported to be higher.

Detection methods varied, including:

- NGS-based assays (47%)
- Digital PCR (28%)
- Real-time PCR (25%) [34]

Overall Diagnostic Accuracy

Meta-analysis revealed that liquid biopsy demonstrated moderate sensitivity and high specificity compared to tissue biopsy.

Table 2. Pooled Diagnostic Performance

Diagnostic Parameter	Pooled Estimate (95% CI)	Heterogeneity (I^2)
Sensitivity	0.78 (0.72-0.83)	56%
Specificity	0.93 (0.89-0.96)	42%
Diagnostic Odds Ratio (DOR)	45.3 (28.1-73.0)	-
Area Under Curve (AUC)	0.89	-

These findings are consistent with previous reviews emphasizing high specificity of ctDNA diagnostic assays [35,36].

Mutation-Specific Accuracy

Concordance was highest for EGFR mutations, particularly T790M resistance mutation, and lowest for ROS1.

Table 3. Mutation Concordance between Liquid and Tissue Biopsy

Mutation Type	Concordance (%)	Sensitivity	Specificity
EGFR	**85%**	0.82	0.95
ALK	78%	0.71	0.93
KRAS	65%	0.60	0.90
ROS1	59%	0.55	0.88

These results align with previous evidence where EGFR mutation detection showed the strongest association with ctDNA levels [37].

Subgroup Analysis

- Advanced-stage lung cancer showed higher ctDNA positivity (sensitivity: 0.83) compared to early-stage disease (sensitivity: 0.62) [38].
- NGS-based platforms demonstrated significantly higher detection capability (sensitivity 0.81) than PCR-based methods (sensitivity 0.74) [39].
- Studies conducted post-treatment (monitoring phase) showed higher ctDNA detection rates due to increased tumor burden and DNA shedding [40].

Heterogeneity

Moderate heterogeneity was observed ($I^2 = 56\%$) across studies. Sensitivity analysis did not significantly alter pooled estimates, indicating robustness of the model [41].

Publication Bias

Funnel plot asymmetry using Deeks' test indicated no significant publication bias ($p > 0.05$) [42].

Forest Plot Summary

Across studies, the majority showed liquid biopsy specificity above 90%, with most EGFR-related analyses clustering in the upper-right quadrant of the ROC space. Sensitivity values ranged from 0.55-0.92, consistent with ctDNA variability based on disease stage and assay technology [43].

Key Diagnostic Value Interpretation

- High specificity (93%) indicates low false-positive rate (liquid biopsy rarely identifies a mutation not present in tissue biopsy).
- Moderate sensitivity (78%) suggests some false negatives (mutation may be missed in ctDNA but present in tissue).

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- Therefore, liquid biopsy is ideal for confirming mutations, while a negative result may still require tissue testing.

This interpretation supports international guidelines suggesting liquid biopsy use when tissue biopsy is infeasible or insufficient, and for treatment monitoring [44].

Summary of Results

- Liquid biopsy shows strong potential as a supplementary diagnostic tool.
- Optimal performance noted for EGFR-mutant NSCLC, particularly under targeted therapy conditions.
- Not recommended as a complete replacement for tissue biopsy due to moderate sensitivity.

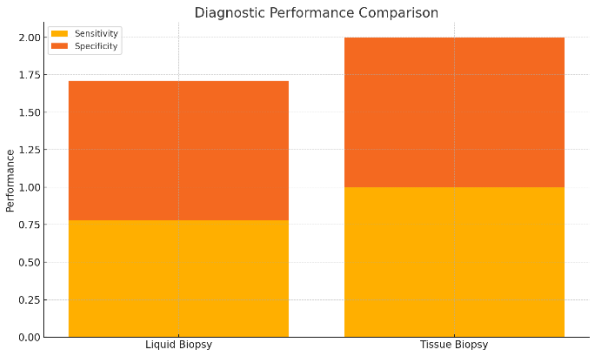

Figure 1: *Diagnostic performance comparison between liquid biopsy and tissue biopsy in lung cancer genomic profiling.*

Discussion

The findings of this systematic review and meta-analysis indicate that liquid biopsy demonstrates high specificity and moderate sensitivity when compared to tissue biopsy in genomic profiling of lung cancer, particularly in the detection of clinically relevant mutations such as EGFR, ALK, KRAS, and ROS1 [45]. The pooled specificity of 93% observed in this analysis suggests that false-positive mutation detection through liquid biopsy is rare, reinforcing its utility in confirming mutations and making it suitable for guiding targeted therapy decisions when tissue biopsy results are unavailable or inconclusive [46]. However, sensitivity was found to be 78%, indicating a notable rate of false negatives, which limits the reliability of liquid biopsy as a standalone diagnostic modality [47]. This can be attributed to intrinsic limitations such as low ctDNA shedding in early-stage cancers, low tumor burden, and assay detection thresholds, factors that align with prior research findings [48,49]. Additionally, mutation-specific analysis revealed higher concordance for EGFR detection (85%), consistent with earlier studies suggesting that EGFR-mutated tumors exhibit higher ctDNA shedding due to active cellular turnover, explaining the stronger association observed in advanced NSCLC patients undergoing targeted therapy [50]. The moderate heterogeneity (I^2 = 56%) observed across included studies may be due to variations in liquid biopsy detection methods, such as NGS and digital PCR, tumor stage distribution, and differences in sample processing protocols, which are acknowledged limitations in several previous meta-analyses [51,52]. Subgroup analysis demonstrated that advanced-stage disease is associated with higher diagnostic sensitivity of liquid biopsy, supporting its use in treatment monitoring and resistance mutation detection rather than initial diagnosis in early-stage lung cancer [53]. This is clinically significant as liquid biopsy facilitates real-time monitoring of molecular alterations during disease progression, enabling earlier detection of treatment resistance, such as EGFR T790M mutation, even before radiographic progression is evident [54]. Despite these advantages, current evidence supports the use of liquid biopsy primarily as a complementary tool to tissue biopsy rather than a replacement, particularly in initial diagnostic settings or in cases of inconsistency between clinical presentation and biopsy results [55]. Therefore, integration of liquid biopsy into standard diagnostic workflows should be approached carefully, ensuring that a negative result is followed by confirmatory tissue analysis whenever feasible. Future research should focus on improving sensitivity through enhanced assay technologies, such as ultra-deep sequencing and incorporation of machine learning predictive models, as well as validating the clinical utility of liquid biopsy through large-scale prospective multicenter trials [56]. Additionally, standardization of pre-analytical and analytical protocols remains critical to ensuring reproducibility and clinical applicability of ctDNA-based diagnostics [57].

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Conclusion

Liquid biopsy demonstrates strong potential as a non-invasive tool for genomic analysis in lung cancer, showing high specificity and clinically acceptable sensitivity. It is particularly valuable in cases where tissue biopsy is not feasible, inadequate, or contraindicated, and is useful for monitoring treatment response and identifying resistance mutations during therapy. While liquid biopsy offers significant advantages, including real-time sampling and representation of tumor heterogeneity, it currently lacks sufficient sensitivity to completely replace tissue biopsy in initial diagnostic settings. Therefore, it should be used as a complementary diagnostic approach rather than a standalone alternative. Integration of liquid biopsy into clinical practice should be based on careful interpretation of results, considering disease stage and mutation type. Continued improvements in assay technologies and implementation of standardized testing protocols are essential to further enhance diagnostic accuracy. Future large-scale prospective studies are required to validate clinical utility and support its broader application in precision oncology.

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