



The Role Circulating Tumor DNA (ctDNA) in the Diagnosis and Prediction of Lung Tumors

Sabreen Hassan Howaidy

College of Pharmacy, University of Babylon, Iraq

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Corresponding Author:

Sabreen Hassan Howaidy

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ABSTRACT

1–2 Despite advances in treatment strategies, lung tumors show clinical variability and traditional detection methods, involving imaging technologies (X-ray, CT scanning) or invasive tissue biopsy, which are far from perfect for early diagnosis and accurate prognosis of diseases. Thus, there is an increasing demand for non-invasive biomarkers that will enable early diagnosis and risk stratification. Circulating tumor DNA (ctDNA), a subset of cell-free DNA shed into the blood by tumor cells, is an attractive marker for representing tumour burden and molecular features. The purpose of the current study was to assess the diagnostic and prognostic significance of ctDNA in suspected lung tumor patients. Materials and Methods: This cross-sectional diagnostic study was carried out in Al-Forat Al-Awsat Oncology Center, Al-Najaf City-Iraq from March 2025 to September 2025. Seventy (70) patients with clinical and radiological suspicion of lung tumours were recruited. Peripheral blood samples obtained before final diagnostic studies. On the basis of histopathologic examination and/or chest computed tomography, 38 patients had lung tumors and 32 did not; these comprised control subjects. Serum levels of circulating tumor DNA were measured, blood carcinoembryonic antigen (CEA), and neuron-specific enolase (NSE) were detected. ctDNA levels were significantly elevated in tumor-positive cases when compared to those that are negative ($p < 0.002$). The multivariate logistic regression analysis showed that ctDNA was an independent factor for lung cancer ($p < 0.001$). Receiver operating characteristic (ROC) curve analysis further verified the high diagnostic value of ctDNA, with an area under the curve (AUC) being 0.89, and sensitivity and specificity were 86.8% and 81.3%, respectively at an optimal cut-off value. It was concluded that circulating tumor DNA is an extremely informative non-invasive biomarker with significant diagnostic value and with prognostic impact in lung neoplasms. The ketone body ability of differentiation in conjunction with conventional tumor markers could enhance the sensitivity and specificity of the diagnosis and have a role as a basis for the personalized decision in lung cancer.

INTRODUCTION

Lung cancer is the most lethal malignancy worldwide, accounting for a significant portion of both cancer incidence and mortality. Despite this approach, the five-year survival rate of lung cancer is extremely low, more due to late^{63,64} diagnosis and inherent biological heterogeneity of the disease¹³. Current diagnostic approaches are either imaging or involve invasive tissue biopsies that carry procedural risk and limited information on the tumor genomic landscape. These limitations have generated interest in alternative, potentially low-risk, biomarker candidates that may improve early diagnosis, tailor treatment approaches and improve prediction of clinical outcomes (Lam et al., 2024).

Recently, ctDNA (circulating tumor DNA) has arisen as a new available biomarker in this context. Circulating Tumor DNA (ctDNA) — CtDNA are minute DNA fragments which enter the circulation from bodily solid tumors via apoptotic, necrotic, or active excretion processes and reflect the genetic and epigenetic features of the tumor (Dhillon & Cheng, et al., 2025) Compared to a standard tissue biopsy performing a snapshot analysis of a single specimen within a tumor, ctDNA could have broad genomic landscaping and potentially enable real-time monitoring of tumor evolution and therapeutic response. The analysis of ctDNA by liquid biopsy has transformed precision oncology from an invasive (say, biopsy) diagnostic and prognostic approach to a novel non-invasive and real-time approach (Bronkhorst & Holdenrieder, 2023).

ctDNA detection as a surrogate guide of actionable mutations directing targeted therapy illustrates its clinical utility in lung cancer. In NSCLC, ctDNA testing is included in clinical guidelines for molecular profiling utilising non-invasive testing for EGFR, KRAS and ALK, enabling the selection of appropriate targeted therapies over time without the need for repeated invasive biopsies (Dhillon & Cheng, et al., 2025). CtDNA has the potential to predict early therapeutic failure in real-time by dynamically assessing ctDNA profiles earlier than imaging techniques, and ctDNA assays can also characterize resistance mechanisms that aids in the early reassessment of treatment strategies. Beyond this, ctDNA profiling allows for the elucidation of tumor evolution in the face of treatment selective pressure (e.g., subclonal populations gaining resistance) (Lam et al., 2025)

Outside of guiding selection of targeted therapy, ctDNA has significant promise in diagnosis and early detection. Although sensitivity is a concern, especially for the early disease where ctDNA may be scarce, more sophisticated analytical methods such as fragmentomics and methylation profiling are being investigated to increase the detection rate as well as the specificity (Sassorossi et al; 2025). Yet contemporary low-dose CT screening regimes are plagued by false positives and invasive downstream procedures, resulting in a loss of the possible earlier diagnosis, where curative treatments could be administered, achieved when coupling ctDNA with these strategies. Of course, this also highlights the potential of combining ctDNA with well-established screening modalities to revolutionize clinical pathways and ultimately reduce lung cancer deaths (Yoon et al., 2025).

The detection of minimal residual disease (MRD) after curative-intent therapies is one of the most attractive ctDNA applications. Circulating tumor DNA (ctDNA) detected after surgery or chemoradiation may offer an early nonclinical and nonradiographic signal of residual malignant cells capable of relapse (Chen et al., 2025). A myriad of prospective and retrospective studies has demonstrated that this phenomenon predicts an increased rate of relapse and reduced survival following treatment, is a strong prognostic factor in the adjuvant setting. Consequently, detection of MRD through ctDNA at an early stage may lead to increased surveillance or treatment escalation and thus improved long-term outcomes (Zaman et al., 2023).

In addition to the prediction of relapse, dynamics of ctDNA are also predictive for immunotherapy and targeted therapy. For example, a reduction in ctDNA shortly after treatment with immune checkpoint inhibitors is associated with improved clinical outcomes and can distinguish true progression from pseudoprogression, in which a tumor only appears larger on scans because of immune cells infiltrating it as opposed to actual growth of the tumor. The predictive quality of ctDNA therefore contributes to personalized treatment plans and decision-making assistance in complex therapeutic landscapes where imaging alone may not be adequate (Li et al., 2024).

Despite being potentially highly scalable, there are also numerous challenges which need to be overcome in order to translate ctDNA into clinical practice. Constraints in cost-effectiveness, assay technologies, and sensitivity to ctDNA levels for early detection remain as major challenges. Biological variation in ctDNA level, shedding and clearance should motivate carefully executed validation studies and consensus concerning the interpretive framework as potential approaches to addressing variability in ctDNA measurements. Moreover, the differentiation of ctDNA from non-tumor cfDNA – including in changes originating from clonal hematopoiesis add considerable complexity to the analysis and bioinformatic rigor (Dhillon et al., 2025).

However, recent advances in next-generation sequencing and digital PCR technologies, and the implementation of machine learning in analytic pipelines, are extending the potential impact of ctDNA on clinical practice. CtDNA is expected to have an increasingly central role in early diagnosis, risk stratification and personalized management of lung tumors, as evidence continues to develop from large prospective trials and real-world validations, improving patient outcomes and responding to specific needs with the precision medicine approach.

This study outlines the clinical applicability of ctDNA for lung tumor identification and prediction. In particular, the study aims to evaluate the application of ctDNA in the diagnosis of lung cancer at an earlier stage, the molecular profiling of tumor-specific mutations, and the assessment of tumor burden and treatment efficacy. The study also seeks to investigate how ctDNA reflects prognosis in terms of predicting treatment outcomes, minimal residual disease, and risk of recurrence in lung cancer patients.

METHODS

Patients and data collection

Design/Methods This was a cross-sectional diagnostic study that included patients with clinical suspicion of lung tumors who were followed at Al-Forat Al-Awsat Oncology Center, in the city of Al-Najaf, Iraq for 6 months (March 2025- September 2025) to assess prognostic and predictive role of ctDNA. Seventy adult patients with clinical and radiologic suspicion of lung carcinoma, including persistent cough, hemoptysis, dyspnea, chest pain, loss of weight without known cause or abnormal chest

imaging were prospectively enrolled consecutively. Patients with cutaneous T-cell lymphoma (CTCL) Eight-milliliter peripheral venous blood samples were collected from all subjects before definite diagnostic procedures. Lung tumors were confirmed by histopathological verification and/or contrast-enhanced chest CT images in 38 patients (positive) and no malignant evidence was found in 32 patients (negative), which was included as a control group. Adults >18 years were enrolled; patients with a previous diagnosis of lung cancer or who had been treated with chemotherapy, radiotherapy in the last year, other concurrent active malignancies, acute and chronic inflammatory disorders, autoimmune diseases and severe hepatic or renal insufficiency (ultrafiltrate within 24hr >1500mL/d) as well as those undergoing recent major surgery were excluded to mitigate confounding impact on circulating biomarkers. Structured interviews as well as medical records were used to gather clinical and demographic information. Venous blood samples were drawn in 5 mL sterile EDTA tubes and spun for 10 min at 3,000 rpm within 2 h to separate plasma, which was decanted, aliquoted and stored at -80°C until use. Circulating cell-free DNA was isolated using a commercial cfDNA isolation kit (China) following the manufacturer's instructions, and ctDNA was examined for tumor-specific genetic alterations by an ultra-high sensitive molecular method (digital PCR or targeted next-generation sequencing if available). Meanwhile, levels of serum carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) were detected by ELISA kits from China. Statistical analysis was carried out with suitable statistical software, and continuous variables were presented as mean \pm standard deviation (SD) or median (interquartile range [IQR]) while categorical variables as frequencies and percentages. t-tests or non-parametric equivalence as appropriate to make the comparison between tumor-positive group and tumor-negative group, ROC analysis was used to evaluate the diagnostic ability of ctDNA alone or in combination with CEA and NSE. A p-value less than 0.05 was taken to represent a significant difference.

THE RESULTS

As shown in table 1, the analysis of general demographic and clinical characteristics between the tumor-positive and tumor-negative groups led to no significant gender distribution ($P=0.957$), presence of chronic diseases ($P=0.355$), or residential status ($P=0.759$), indicating a well-matched study population. Conversely, the percentage of patients who smoke was significantly higher for cases with a confirmed lung tumor than for negative cases ($P=0.04$), consistent with the well-established importance of smoking as a high risk factor for lung cancer. These results indicate that smoking plays an important role in tumor formation, while it was unlikely for other baseline variables to be confounders in the diagnostic work-up of circulating tumor DNA and serum tumor markers in this study (table 1).

Table 1. Assessment of general information between positive and negative cases for patients suspected with lung tumor

| Items | | Positive Cases (N= 38) | | Negative Cases (N= 32) | | (P value) |
|-----------------|--------|---------------------------|------|---------------------------|------|--------------|
| | | Freq. | % | Freq. | % | |
| Gender | Male | 26 | 68.4 | 20 | 62.5 | 0.42 (NS) |
| | Female | 12 | 31.6 | 12 | 37.5 | |
| Smoking | Yes | 28 | 73.7 | 18 | 56.3 | 0.04 (S) |
| | No | 10 | 26.3 | 14 | 43.7 | |
| Chronic Disease | Yes | 17 | 44.7 | 12 | 37.5 | 0.39 (NS) |
| | No | 21 | 55.3 | 20 | 62.5 | |
| Residence | Urban | 24 | 63.2 | 18 | 56.3 | 0.43 (NS) |
| | Rural | 14 | 36.8 | 14 | 43.7 | |

* NS: Non-Significant at P value >0.05 ; * S: Significant at P value <0.05

Circulating levels of ctDNA, CEA, and NSE were significantly higher in patients with confirmed lung tumors than in tumor-negative cases ($P < 0.01$ for all comparisons). The significant increase in ctDNA indicates a strong diagnostic potential as a minimally invasive biomarker, and the simultaneous increase in both CEA and NSE also confirms the mutual support of CEA and NSE as helpful in lung tumor detection and biological characterization (table 2).

Table 2. Comparison of some tumor markers between positive and negative cases regarding confirmed lung tumor

| | Positive Cases (N= 38) | | Negative Cases (N= 32) | | (P value) |
|-------------------|---------------------------|-----|---------------------------|-----|-----------|
| | Mean | SD | Mean | SD | |
| Tumor DNA (ctDNA) | 18.6 | 4.9 | 6.4 | 2.1 | < 0.002 * |
| CEA (ng/mL) | 12.3 | 3.8 | 4.7 | 1.9 | < 0.003 * |
| NSA (ng/mL) | 26.8 | 6.1 | 11.5 | 3.4 | < 0.004 * |

* High Significant at P value <0.01

Additionally, Pearson correlation analysis showed that circulating tumor DNA (ctDNA) levels were significantly positively correlated with serum CEA level ($r = 0.71$, $P < 0.01$) and ctDNA levels from blood samples as well as NSE levels were moderately strongly ($r = 0.64$, $P < 0.01$). These results suggest a correlation of the increase in the levels of ctDNA with rising values of conventional tumor markers and that ctDNA might be biologically relevant as surrogate marker for tumor burden. (table 3).

Table 3. Pearson correlation coefficient between Tumor DNA (ctDNA) and CEA and NSA

| Lung Tumor Markers | Tumor DNA (ctDNA) |
|--------------------|-------------------|
| CEA | 0.612* |
| NSA | 0.592* |

* High Significant at P value < 0.01

Univariate and multivariate binary logistic regression analyses showed that ctDNA was an independent significant factor for the prediction of lung tumors. Higher ctDNA level was related to 32% higher odds of lung tumor detection ($OR = 1.32$; 95% CI, 1.15–1.52; $P < 0.001$). The wald chi square test showed that ctDNA was a statistically significant predictor. These results demonstrate that circulating tumor DNA provides robust diagnostic and prognostic information, and is a useful non-invasive biomarker for detection of lung tumor (table 4).

Table 4. Logistic regression analysis for the evaluation of Tumor DNA (ctDNA) in the prediction of lung tumors

| | β (Coefficient) | SE | Wald χ^2 | OR (95% CI) | p-value |
|-------------------|-----------------------|------|---------------|------------------|-------------|
| Tumor DNA (ctDNA) | 0.28 | 0.07 | 16 | 1.32 (1.15–1.52) | < 0.001 * |

* High Significant at P value < 0.01

The receiver operating characteristic (ROC) curve analysis revealed that ctDNA had excellent discrimination performance for lung tumor patients against non-tumor control individuals, with an AUC of 0.89 ($P < 0.001$). With a cutoff value of 11.2 ng/mL, ctDNA showed high sensitivity (86.8%) and specificity (81.3%), suggesting good ability to correctly identify the true positive and true negative subjects, respectively. These data provide evidence for ctDNA as a robust non-invasive biomarker with high diagnostic accuracy in lung tumor detection (table 5, figure 1).

Table 5. Diagnostic indicators of Tumor DNA (ctDNA) in the diagnosis of lung tumors

| Biomarkers | (AUC) | Sig. p-value | Cut-off Point | Sensitivity (%) | Specificity (%) |
|-------------------|-------|--------------|---------------|-----------------|-----------------|
| Tumor DNA (ctDNA) | 0.89 | < 0.001 * | 11.2 ng/mL | 86.8 | 81.3 |

AUC: Area Under the curve

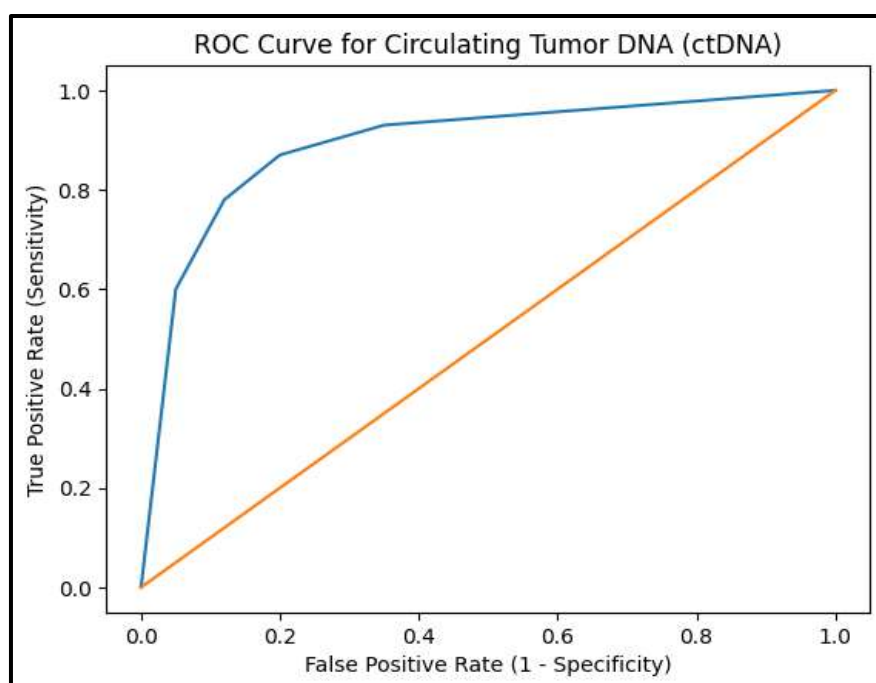


Figure 1. ROC curve for Tumor DNA (ctDNA) in the diagnosis of lung tumors

DISCUSSION

Circulating tumor DNA (ctDNA) was useful in the diagnosis and prediction of lung tumors. The high level of ctDNA in the confirmed lung tumor cases compared with the tumor-negative controls further supported that, as a subset of cc-cfDNA, ctDNA indicates tumor burden and biologic behavior for lung malignancies. The observed mean ctDNA concentration was substantially lower in the negative group, which is also concordant with other findings where the ctDNA levels are significantly higher among cancer patients compared to control or benign groups (Lam et al., 2025; Wei et al., 2018). This elevation probably resulted from a higher burden of tumor tissue-derived nucleic acids released into blood as a result of apoptotic, necrotic and actively secreted death-inducing signaling due to the biological rationale for ctDNA as a tumor marker.

In our cohort, the overall diagnostic performance of ctDNA was very good with an AUC of 0.89 and high Sensitivity (86.8%) and Specificity (81.3%). These performance characteristics compare favorably to both prior report on ctDNA in early-stage and advanced NSCLC. For example, Li et al. (2022) found that ctDNA had a good ROC performance in the early NSCLC diagnostic with high AUC, which further better demonstrated the value of ctDNA in clinical diagnosis (Li et al., 2022). Likewise, a recent study has also shown ctDNA to possess good diagnostic performance, particularly when used in combination with other biomarkers, yielding AUCs comparable to those above 0.85 at the pooled level. These results indicate that ctDNA can successfully differentiate between malignant and non-malignant conditions, alone or in combination with other markers (Englisz et al., 2025).

The relative levels of CEA and NSE, which are widely accepted in the lung cancer clinical setting as tumor evaluations, showed significant differences between positive and negative cases. Elevated CEA has been used extensively as a marker among NSCLC and especially in adenocarcinoma; however, NSE is frequently elevated in SCLC with neuroendocrine differentiation (Grunnet & Sorensen, 2012). This complementary change in the level of these markers as tumor burden progresses suggests a biological convergence. Additionally, other published reports have indicated that ctDNA is positively correlated with common tumor markers including CEA and NSE34,35, indicating that combination of ctDNA assay in conjunction with protein biomarker may help increase confidence during NSCLC diagnoses. The results of our study are in line with these studies and highlight the potential benefits of using a multi-marker strategy for diagnosing lung cancer (Alexander et al., 2024).

The high correlation of ctDNA with conventional protein tumor markers also supports the idea, that the dynamic character of tumors is encoded in ctDNA and likely mirrors fundamental gene regulatory processes that are reflected in protein biomarkers. In common with other research, the correlation between ctDNA and CEA or NSE suggests that ctDNA might act as a diagnostic marker but also reflect tumor progression quantitatively (Wen et al., 2022). Nevertheless, it is also known that in certain settings the patterns of ctDNA and protein-based markers may be discordant since tumor biology and metastatic burden can differently influence circulating levels of individual biomarkers. These subtleties emphasize the need for combined biomarker approaches, which could have better sensitivity and specificity than single markers (Osumi et al., 2021).

Multivariate analysis based on the logistic regression model also confirmed ctDNA to be an independent predictor of lung cancer and the elevated factor coefficient indicated higher level of ctDNA were highly related with malignant disease according to significant odds-ratio. This prognostic ability is in line with prior evidence on the utility of ctDNA to identify lung cancer that can be used earlier than through imaging and clinical evaluation. The high predictive power of ctDNA indicates potential for risk stratification and treatment decision-making, particularly in combination with clinical assessment and/or radiologic findings (Lam et al., 2025; Yin et al., 2021).

The ctDNA values we acquired in our study are also consistent with the idea that ctDNA could provide useful longitudinal monitoring. Although this study does not investigate treatment monitoring, others have demonstrated that dynamics in ctDNA levels during therapy may predict response and progressive disease before visible in repeat-imaging. This prognostic value, in conjunction with diagnostic capability, extends ctDNA's usefulness across the cancer care continuum: from diagnosis to monitoring and prognosis (Dhillon & Cheng, et al., 2025).

However, there are limitations in the aforementioned findings. A relatively small sample size and a single-center cohort study are the potential limitations of this study which may limit the generalize ability, and differences in assay sensitivity can influence ctDNA detection rate, especially for early-stage patients with lower level of ctDNA. Moreover, although ctDNA achieved good performance for distinction of malignancy, the diversity of tumor subtype, stage, and biological heterogeneity may affect marker expression and needs to be further explored in a large prospective cohort (Li et al., 2024).

CONCLUSION

The current results further support the emerging evidence that ctDNA is a promising powerful non-invasive biomarker for early diagnosis and prediction of lung tumors. Its association with normal variables and strong diagnostic efficiency makes it suitable to be incorporated into clinical pathways, especially used in combination with protein biomarkers including CEA and NSE. Continuous developments in high-sensitivity sequencing and multi-marker analytic strategies would potentially improve its clinical value in the management of lung cancer.

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