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REVIEW ARTICLE

AI-Powered Liquid Biopsy: The Future of Early Lung Cancer Detection

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ABSTRACT: Lung cancer is frequently asymptomatic in its early stages, causing it to progress silently to deadly stages in countless individuals; Consequently, this cancer is the leading cause of cancer-related deaths worldwide. Current methods to detect lung cancer are generally expensive and invasive; Biomarkers are complex to analyze, imaging methods are difficult to make accurate or powerful enough, and other methods like biosensors are too expensive. This paper aims to synthesize a faster and more accurate method of lung cancer detection to eliminate late-stage diagnosis and reduce lung cancer-related deaths. Liquid Biopsy (LB) combined with AI is the future of early LC detection: A non-invasive biopsy technique that is efficient, quick, and accurate. LB on its own is a powerful, prototypic tool that has slowly been emerging over the past decade; It utilizes a fluid sample from the patient and analyses it for CTCs and ctDNAs. This, combined with trained Artificial Intelligence, can significantly reduce the quantity of false positive and false negative cases that can occur in the analysis of LB. This AI-Powered Liquid Biopsy method, utilizing LB as an effective sample tool and AI as a powerful analysis tool, results in an effective diagnosis method for future lung cancer patients.

KEYWORDS: Disease Detection and Diagnosis, Algorithms, Artificial Intelligence, Liquid Biopsy, Lung Cancer.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. It can be classified into non-small cell lung cancer (NSCLC; accounting for 85% of cases) and small cell lung cancer (SCLC).[1,2] NSCLC can be further classified into subtypes such as large cell carcinoma, adenocarcinoma, and squamous cell carcinoma.[3] The primary cause of large cell lung cancer is smoking, but there can be other factors such as radon exposure, second-hand smoke, and genetic family history.[4] Lung cancer can cause persistent coughing, blood being coughed up, chest pain, shortness of breath, and unexpected weight loss.[5] The problem is that in early stages, lung cancer is mostly asymptomatic, so due to symptoms that can take a long time to start appearing, the condition might not be diagnosed until the cancer has reached a high stage.[6] Over 55% of lung cancer cases are diagnosed at Stage IV,[7] and by that point, it becomes extremely resource-heavy, time-consuming, and financially difficult to treat, along with a much higher chance of failure. Data shows that the 5-year survival rate for Stage I Lung cancer is between 68 and 92%, but when applied to Stage IV, that percentage drops to 10% at best, which shows how negatively impactful late diagnosis is.[2] This is why lung cancer is the leading cause of cancer deaths worldwide, so late diagnosis plays a big role in that problem.

One way to allow early detection of lung cancer is to expand access to low-dose CT scans, especially in high-risk families or areas.[8] However, another alternative way is to develop more non-invasive early detection methods (blood-based biomarkers, etc.), which will help prevent late diagnosis. These methods can be made further effective with modern advancements in artificial intelligence. In medical and research fields, it could be developed, adapted, and utilized to scan better and recognize early signs and already emerging lung cancer in certain patients. The advantage is that by avoiding late diagnosis, those with lung cancer can increase their chance of survival and lessen the financial and medical stress on them. Lung cancer can also show or be related to other conditions, so by detecting lung cancer early and eliminating it, other conditions can also be avoided.

This methodological review aims to expand upon a new and emerging form of lung cancer diagnosis – Liquid Biopsy - and how it can be combined with modern artificial intelligence to combat late and ineffective diagnosis in lung cancer patients. This is significant in this modern day, where late-detected lung cancer results in thousands of deaths each year.

The utility of using AI with Liquid Biopsy has been explored before – as seen by [9], which discusses the use of Liquid Biopsy and AI for ctDNA and CTC identification in a more general-tumor context – this study specifically focuses on the use of AI-powered liquid biopsy as a means to solve the issue of late-stage diagnosis in lung cancer: such a method of diagnosis can enable quicker (effectively more convenient and patient-friendly) analysis of an at-risk patient. The convenience does not repel at-risk patients, and the alleviated time-constraint aids in periodic diagnostics (close to 'real-time' monitoring). This is beneficial because regular monitoring of individuals who are at-risk of lung cancer can help identify symptoms early on and begin treatment before the dangerous consequences of lung cancer can occur.

DOI: 10.36838/IJHSR815.63

Methodology

The objective of the study is to synthesize a theoretical approach using Liquid-Biopsy as a robust data sampling tool and Artificial Intelligence as a powerful analysis tool to detect lung cancer early, before it advances. This paper is strictly a secondary literature review; No original clinical or experimental data were collected, and all referenced data are extracted from existing online studies from databases such as PubMed and research papers found on tools such as Scispace. Data gathering was focused on peer-reviewed journal articles, papers, and clinical studies published between 2019 and 2024. Keywords such as "Lung Cancer" and "Liquid Biopsy" were used to narrow down clinical studies, and out of the 17 found, the 4 most relevant publications were used for their focus on the biomarkers used in LB and their effectiveness. The material used in this review consisted mainly of primary scientific sources, used to supplement evidence of the benefits of Liquid Biopsy. Data was reviewed and put together, then information regarding the topic was extracted and used to construct the evidence. Due to being a non-experimental, entirely literature-based review, this paper did not utilize any physical tools, materials, or biological samples. No ethical considerations were reviewed.

Discussion

Importance of Early Detection in Lung Cancer:

In 2022 alone, there were 2.5 million new cases of lung cancer globally.[10] Lung cancer can develop silently and without any symptoms, meaning it can reach higher stages without the affected individual noticing at all.[11] In stage I and II, the survival rate can range from 50-70%, but in stage III, that drops to 13-36%, with stage IV being even worse at 3-9%.[2] Catching lung cancer early, before it advances too far, is crucial to ensure better survival. This means that reliable and affordable screening methods are needed so that more people can get tested and catch lung cancer early.

Current or Standard Methods of Detection:

Present-day non-invasive methods to diagnose lung cancer utilize many approaches that rely on imaging technologies and biomarkers, allowing for these methods to enhance early detection and improve patient outcomes. This advancement symbolizes a shift away from more invasive approaches.

Imaging:

Optical Imaging methods, such as Fluorescence Imaging (FI) and bioluminescence imaging (BLI), are cost-efficient and moderately accurate when it comes to detecting anomalies. FI uses a variety of fluorophores to highlight molecular structures in the body – and unlike other methods, it is capable of real-time imaging, which eliminates the need for post-processing and image reconstruction. BLI allows molecular and cellular processes to be converted into chemical energy into light through enzymes (such as photoproteins) with luciferin substrates. This method is set back by its limited penetration depth, which only maxes at centimeters; This makes it ineffective when dealing with deep tumors. BLI is a universally harnessed technology that converts detected bioluminescence, precisely pinpointing cancer.[12,13]

Biosensors & Biomarker Analysis:

Biomarkers are chemicals or substances in the body that point to a disease or tumor. Diagnosis working with biomarkers is gaining attention, and the development of more advanced techniques is being used to find genetic alterations such as BRAF and epidermal growth factor receptors. PCR (Polymerase Chain Reaction) methods, Sanger sequencing, and pyro sequencing are other techniques used to identify biomarkers of NCSLC. Most biomarker analysis techniques fundamentally work the same: DNA/RNA is extracted from something in the body, then profiled, then matched to a disease or already-known tumor.[14] Sputum – a substance produced in the respiratory system – is an example of what can be analyzed for biomarkers, potentially pointing to lung cancer.[15] However, biomarkers can get complex, especially when it comes to the analysis of profiled DNA/RNA.

Biosensors are the different techniques used to detect biomarkers in order to profile them. Conductive Metal-Organic Framework (MOF) sensors have porous structures that are sensitive to certain biomarkers. Nucleic Acid Aptamer Sensors utilize binding capabilities to detect proteins and acids related to tumors. Finally, Nano-Field-Effect Transistor sensors utilize measuring molecules (biomarkers) by measuring the electrical current change. These methods are held back by restrictions such as high cost and being prone to degradation.[16]

History of Liquid Biopsy in a Clinical Setting, Current Stage, and Expected Future:

Liquid Biopsy is an extremely effective technique to diagnose tumors, especially lung cancer. What sets it apart from imaging techniques is that it returns usable data, which can be analyzed using tools such as AI.[17,18] The advantages of this would be increased pattern recognition, faster diagnosis speeds, more accuracy, and more precision. LB is also a new technique, with the term first being used in 2010.[19] The usage situations for LB can range a lot: from blood to many other fluids, it can be utilized, making it a technique that is applicable in many situations. LB is conceptually straightforward; a sample is taken (usually non-invasive and quick), it is fed into a machine which detects CTCs or ctDNA, and the results are seen by a doctor. AI makes this result-analysis part much quicker, more efficient, and accurate, resulting in an LB-AI method that is fast and accurate. The AI is also much cheaper to operate than paying a human doctor around the clock.[20,21] Over the past decade, LB has moved from a research phase to an almost clinical phase. In 2013, the first LB test was approved by the FDA. In the following couple of years, more and more approvals were passed for increasing the applications of LB. This increasing list of approvals has caused more clinical use of LB; however, due to it being a fairly new method, there are still restrictions and a lack of standards to be addressed.[22]

Liquid Biopsy for the Non-Invasive Early Detection of LC:

Liquid biopsy is a test where bodily fluids are taken and analyzed for biomarkers indicating the presence of a tumor, in this case, lung cancer. As the cancer gets larger and larger, little pieces of (CTCs and ctDNA) break off and end up in the bloodstream, and this is what liquid biopsy detects. A CTC is a cell from the cancer circulating in the bloodstream, and ctDNA is a part of the DNA of the cancer cells. Liquid biopsy is different from a normal biopsy in that, instead of testing the tumor tissue itself, it tests for evidence of such a tumor, making it much less invasive and safe.[23-27]

Cell-free DNA (cfDNA) is a category of DNA pieces that are naturally present in the bloodstream, created because of standard processes in the body. Healthy individuals naturally possess cfDNA at 10ng/mL or less. ctDNA is included in this class of DNA and is effectively absent in cancer-free persons. Additionally, the genetic makeup of the ctDNA reflects an exact copy of the tumor, giving an insight into its various traits.[28] Distinguishing the ctDNA from the larger group of cfDNA is what enables cancer identification.

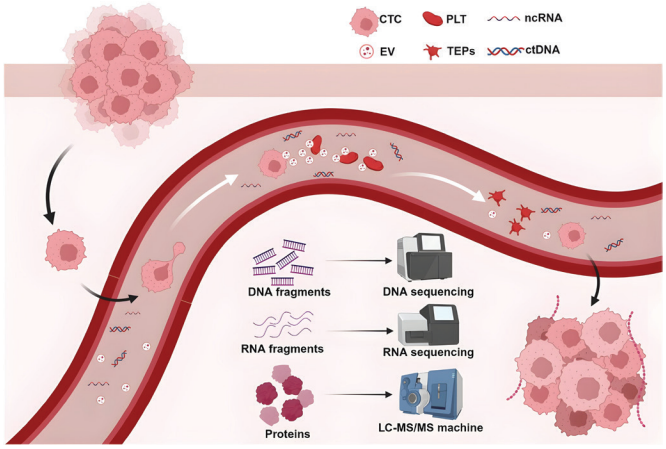

Figure 1: Liquid Biopsy Markers. A detailed diagram showing how different samples are taken, then separated into their individual parts, and then analyzed for biomarkers. Adapted from "Liquid biopsy in cancer: current status, challenges and future prospects," by W. Li, X. J. Liu, J. S. Wang, *et al.*, 2024, *Signal Transduction and Targeted Therapy, 9*(1), p. 134. https://doi.org/10.1038/s41392-024-02021-w. CC BY 4.0.

Studies Conducted on Liquid Biopsy:

Table 1 below observes 4 studies reviewed that utilize Liquid Biopsy and/or another technique to gauge the effectiveness and usefulness of LB. A majority of these studies use ctDNA and/or CTCs as the primary LB component, which are parts of the tumor that break off and fall into the bloodstream, like the process shown in Figure 1. These studies make use of other techniques that are already firmly established in the clinical setting alongside LB, and this allows for a reasonable comparison between the two techniques in order to gain an understanding of the effectiveness of LB.

Table 1: Different studies done with LB. *Each study utilizes Liquid Biopsy to measure biomarkers; Alongside LB, a reputable and reliable diagnosis method is performed concurrently. The results are compared, and the relative practicality and efficacy of LB are determined. The results can be quantitative, allowing for quantification of benefits.*

Study ID#	Biopsy Component	Purpose/Goal	Other Detection Methods Used
NCT05255133[29]	ctDNA	The goal of the study is to see the value of ctDNA in patients with tumors, use imaging to detect the disease, and then correlate the amount of ctDNA with tumor progression, proving how ctDNA can be used to detect tumors.[29]	Imaging/MRI
NCT04223492[30]	ctDNA/CTCs	The goal of the study is to utilize both MRI and liquid biopsies to get an accurate diagnosis of the tumor. The MRI will show visual qualities of the tumor, while the ctDNA from the liquid biopsy will give a usable value related to the growth of the tumor, allowing for a precise diagnosis.[30]	MRI
NCT03479099[31]	ctDNA/CTCs	The goal is to use liquid biopsy to analyze blood samples for CTC and ctDNA, which would make lung cancer evident.[31]	None
NCT05462795[32]	Pulmonary Nodules	The goal of this study is to use liquid biopsy for those at risk of lung cancer, those post-operation for lung cancer, and those who are perfectly healthy (control group) in order to gauge the effectiveness of the liquid biopsy test.[32]	CT Screening

Study NCT05255133 shown above is a clinical experiment done to gauge the qualitative value that the amount of ctDNA holds. Their format is to use an established diagnosis method, then use it to measure tumor growth alongside ctDNA values. By observing how ctDNA increases in count in proportion to tumor growth, a quantitative measure of ctDNA's value can be obtained.[29]

Study NCT04223492 shown above is a clinical experiment done to combine both Liquid Biopsy and multi-parametric MRI scanning to get an accurate diagnosis of breast cancer tumor size and potency. The MRI part is visual; It will allow the scientists to see a visual model of the size, shape, and other physical qualities of the tumor. The LB will allow scientists to see any biomarkers (in this study, CTCs and ctDNA) and get data on the tumor's effects and its genetic makeup.[30]

Study NCT03479099 shown above is a clinical experiment geared towards using Liquid Biopsy and assessing the utility it carries in the diagnosis of primary lung cancer. It utilizes CTCs and ctDNA as the biomarkers for analysis. This study is the only one to mention using tumor tissue samples for analysis specifically.[31]

Study NCT05462795, shown above, is focused on using Liquid Biopsy for early non-small lung cancer detection. CT screening will be run on pulmonary nodules, then biopsied, and the accuracy of the biopsy, combined with the correlation between its results and the CT screening, will be recorded. The study also aims to use LB to distinguish between pulmonary modules that are malignant and benign.[32]

The analysis portion of liquid biopsy is done by doctors who have to work with its complexity. This could lead to often returning false-positive or false-negative results about the patient(s).[33] To eliminate the shortcomings of liquid biopsy analysis, AI or trained artificial intelligence can be employed in order to more quickly and accurately analyze liquid biopsy data and come up with better and more precise results.[34,35]

DOI: 10.36838/IJHSR815.63

Liquid Biopsy with AI:

Liquid Biopsy on its own is already a powerful tool for diagnosing Lung Cancer – and other tumors – effectively. Unlike imaging techniques such as MRI, Liquid Biopsy returns tangible, usable numerical data in the form of ctDNA and CTC detection in the blood. AI takes liquid biopsy to another level: by theoretically utilizing it to analyze liquid biopsy results and ctDNA counts, AI can be used for ultra-refined pattern recognition of patterns of correlation across multiple different patients and tests.[9] AI has already been utilized in oncology for biopsy applications such as the Galleri Test, a diagnosis that utilizes AI to detect 'methylation patterns' in cfDNA.[36]

AI can be used to detect the specific genomic differences in ctDNA and cfDNA shed from normal physiological processes. It can analyze patterns and genomes that are specific to an individual and determine what sequences appear healthy or evidence of a tumor.[37]

Table 2: Benefits of AI in Liquid Biopsy. *The Liquid Biopsy has many different qualities that determine its practicality. Liquid Biopsy with AI can expand upon these greatly, reducing shortcomings and increasing effectiveness. The table qualitatively expands upon this, clearly showing the benefits and changes.*

Qualities of Liquid Biopsy	Without AI	With AI
Time to analyze data	The time to analyze data by human doctors can take a while, especially when dealing with multiple sets of data across multiple patients.	An AI program trained to compute liquid biopsy data with ctDNA and CTC can crunch test results from hundreds of patients within minutes or even seconds.
Pattern recognition	When doctors and researchers analyze results, it can be very easy for patterns and correlations between two factors to go right over their heads.	Even when fed with extremely large amounts of data, AI can recognize scrutinized patterns across patient data (e.g., correlation between ctDNA values and another factor).
Accuracy	Human error is frequent and unavoidable; even the most talented and well-trained doctors are prone to making mistakes in their analysis.	Artificial Intelligence can make mistakes. However, when trained for one specific task (LB data analysis), it can be honed to be extremely accurate.
Precision with smaller data values	Liquid Biopsy works with ctDNA and CTC, which come in small amounts. This leads to many, many sets of data with small numbers that are hard to work with, and the overall computation path can cause mistakes.	Being a computer model, AI can easily do calculations and observations using the largest and smallest numbers and still be extremely precise.

Table 2 above demonstrates the different 'factors' or 'stats' of a diagnosis technique that make it effective and practical. Each row is a different aspect of diagnosis, and the following columns have a qualitative description of the benefits of using AI and LB against using LB with just human analysis.

■ Conclusion

Lung cancer is asymptomatic in nature and leads to many late diagnoses and, in turn, the deaths of many patients around the world. LB is a powerful emerging technique that analyzes bodily fluids for biomarkers, yet it is held back by data analysis errors. AI is the tool to solidify the LB data analysis, so by combining LB and AI, a new, powerful diagnosis technique can be synthesized. This method of quick, non-invasive diagnosis is crucial to improving early detection accuracy and saving patients all around the world. AI-Powered Liquid Biopsy represents the future of early lung cancer detection; A reliable yet affordable path to reducing late-stage diagnosis. There are aspects not covered in this paper: experimental data, specific AI models, and cost-benefit have not been gauged yet. Future recommendations for further advancement on this topic would be to perform real-world, clinical studies and obtain experimental/quantitative data on the benefits of AI analysis. Specific AI model(s) have not been pinpointed yet, and a process to train them has not been discussed. Studies on the cost-benefit analysis between human pay and AI running costs should be performed as well, in order to gain more understanding of the possible utility of AI with Liquid Biopsy.

■ Acknowledgments

I would like to thank Professor Prahlad Parajuli, Professor Kay Diaz, and Professor Virgel Torremocha for their guidance and mentorship during this writing process.

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DOI: 10.36838/IJHSR815.63