Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/57/20241262

Evaluation of traditional lung cancerdetection modalities and research and application of biomarkers in the early detection of lung cancer

Yue Ou

Yunkang School of Medical and Health, Nanfang College·Guangzhou, Guangzhou, 510900, China

oy370718@outlook.com

Abstract. At present, the cancer that kills people the fastest worldwide is lung cancer, and many lung cancer patients are found or detected at the late stage of lung cancer, which is very bad for the prognosis of the disease, and makes the mortality rate of the patients increase greatly. Therefore, the development of techniques for the early diagnosis and detection of lung cancer is imperative. At the moment, lung cancer can be detected early due to biomarkers. This review primarily outlines the many kinds of biomarkers and the conventional techniques for detecting and diagnosing lung cancer. In addition, bodily fluids' potential application as biomarker carriers in the detecting of cancer development and progression is mentioned in this review, the feasibility of non-invasive cancer diagnostic methods is analyzed, and the current status of the development of such diagnostic methods is summarized.

Keywords: lung cancer, early detection, body fluid, non-invasive diagnosis, biomarkers

1. Introduction

Lung cancer, one of the world's most common and fatal illnesses , is often diagnosed in advanced stages [1]. According to Goldberg et al., ealrl diagnosis of all lung cancers in the United States could reduce annual deaths by more than 70,000 per year [1]. According to Reem Nooreldeen and Horacio Bach, lung cancer will be the leading cause of cancer worldwide by 2050, accounting for half of all cases [2]. Therefore, early detection of lung cancer is urgent, as it allows for treatment with today's medical methods. Many studies have shown that lung cancer is usually symptomless in its early stages, and most patients are diagnosed with this disease at an advanced stage. As a result, the progression of the disease is often more advanced than it should be, leading to a poor prognosis, having a survival rate of below 20% following five years [3]. Accurate and effective early detection methods are needed. Nowadays, some detection methods have been proposed and applied to the early identification of lung cancer, while these techniques are never without limits, which lead to the error of the test results, affecting the accuracy of the test results. The current detection methods, whether traditional or early detection methods, make it difficult to avoid the immersion test, which has a certain impact on the patient's lesion and requires the assessment of the patient's indicators and his/her ability to bear before sampling the biopsy specimen for detection, which is a high-risk and costly detection method. Non-invasive detection methods are under development.

DOI: 10.54254/2753-8818/57/20241262

Numerous investigations have revealed that the application of lung cancer biomarkers as indicators of detection is a promising method. Therefore, a summary of the traditional detection methods, the methods of early lung cancer detection proposed by the current research frontiers, and an analysis of the advantages and disadvantages of each detection method will be conducive to the discovery of the advantages of the detection in different ways, and will serve as a basis and reference for future research in related fields.

2. Lung Cancer Incidence and Mortality

Lung cancer has among of the highest incidence and fatality rates in the globe in recent years. Jacques Ferlay et al. reviewed the sources of data and techniques employed in the 2020 GLOBOCAN cancer statistics published by the International Agency for Research on Cancer (IARC). The data showed that with non-melanoma skin cancer excluded, there were an estimated 19.3 million (95% uncertainly interval [UI]: 19.00-19.6 million) new cases of cancer globally in 2020. The cancer death rate was almost 10.0 million (95% [UI]: 9.7-10.2 million, 9.9 million excluding non-melanoma skin cancer). One of the most important finding was that the majority of cancer-related deaths (1.79 million deaths) were caused by lung cancer [4].

Rebecca L. Siegel et al. found that higher cancer deaths than breast, prostate, and pancreatic cancers combined, and 2.5 times higher than colorectal cancer (CRC), are expected to occur in America in 2022—1,918,303 new cases and 609,360 cancer deaths, including around 350 deaths every day. Thus, the primary cause of cancer-related mortality remained lung cancer. There were researches which illustrated state-by-state incidence rates of particular malignancies in the US from 2014 to 2018 and the morality rates for selected cancers in the US from 2015 to 2019 separately. The tables also reflect that both the cases and deaths of lung cancer were the most common [5].

Rebecca L. Siegel et al. said in 2023, the data for it was anticipated that American cancer mortality and new cases would be about 1,958310 and 609,820 respectively. There were a number of data points that estimated incidence of selected cancer by states in the US in 2023 (approximately 238,340 cases) and the deaths for selected cancers in the US in 2023 (about 127,070 cases) separately [6].

Some data also suggests that the total rate of lung cancer has a downward trend from year to year because of the lung cancer early diagnosis. Additionally beneficial to the prognosis and prevention of lung cancer is early detection of the disease mortality. Rebecca L. Siegel et al. put forward the idea that earlier diagnosis has a significant influence on the result of lung cancer. The survival rate of patients increases, with the 5-year relative survival rising to 33% for regional stage and 60% for localized stage diseases, from 6% for distant-stage disease [5]. Many factors, such as , smoking, age, genes and so on, can increase the risk of suffering from lung cancer. As such, Matthew B. Schabath and Michele L. Cote (2019) supposed that the only option for those who were at a high risk to improve survival was early detection [7]. Reem Nooreldeen and Horacio Bach (2021) said that the reasons why the most common cause of cancer-related deaths was lung cancer which were not to be found until the cancer had progressed to a severe stage [2].

3. Advantages and Disadvantages of Contemporary Approaches to Lung Cancer Diagnosis and Mechanism

3.1. Radiographic Screening

Reem Nooreldeen and Horacio Bach (2021) summarized that the results of some researches showed that with the help of low-does helical computed tomography (LDCT), the incidence of lung cancer decrease 20% in lung cancer as compared with the standard radiography screening. At the same time, the when the National Lung Screening Trial (NLST) compared yearly low-dose computed tomography (LDCT) screening versus traditional chest radiography, it was discovered that, after just three screening rounds, LDCT screening reduced the risk of lung cancer by 20% [8]. One of the advantages of LDCT is that compared with plain or conventional radiography screening, which is used to screen the whole lung, CT is more effective in screening the surrounding lesion around the lung. Spiral CT scanning can

DOI: 10.54254/2753-8818/57/20241262

continuously acquire data, so the screening time will be shorter with lower radiation exposure and the diagnosis accuracy of this technique is better than that of plain radiography. What's more, in just one or two breath holds, this technique can picture the entire chest, and this function can reduce artifacts that yield a more precise result in missing nodules that measure between 1 and 5 mm. Strong biomarkers would ideally enhance image-based screening in two ways [8]. The challenges of this technique are high cost and accessibility [2]. Reem Nooreldeen and Horacio Bach (2021) said that about 40% of all individuals enrolled in the National Lung Screening Trial's LDCT experienced at least one false positive result with a false-positive rate as high as 96%. The high rate of false positives can lead to high-cost screening and invasive diagnosis for patients. LDCT exists with the possibility of a false positive, so patients have to undergo an invasive check, which will increase the risk of surgery and complications. In other words, this technique cannot avoid the invasive check [2].

3.2. Sputum Examination

3.2.1. The Cytological Examination of Sputa. Although Cytological Examination of Sputa can aid in the identification of core tumors from the bigger bronchi, including small- and squamous-cell carcinomas, there are still some limitations to this technique. Small adenocarcinomas with a diameter of less than or equal to 2 cm can aid in the detection of central tumors from the bigger bronchi, including small-cell and squamous cell carcinomas, which are not visible in sputum samples, and these small adenocarcinomas originated from the airway ramifications. Based on the research of screening, the sensitivity of Cytological Examination of Sputa to early lung cancer is only 20% to 30%. Thus, the accuracy and sensitivity of this technique cannot be considered into the common detection of lung cancer [2].

3.2.2. Immunostaining. Immunostaining can deliver a better result than sputum cytology. Reem Nooreldeen and Horacio Bach (2021) mentioned that this detect method can predict two years before a clinical diagnosis of lung cancer X-ray and cytology-based. Other research found one of these antibodies (703D4), which was subsequently found to be capable of identifying the heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1 protein with higher sensitivity. And the study's findings demonstrated that compared with routine X-ray of the chest and sputum cytology, the sensitivity of the early identification of lung cancer, hnRNP A2/B1 was 2- to 3- fold [2].

3.3. Bronchoscopy

White light bronchoscopy (WLB) is the most common technique used to diagnose lung cancer. However, this method exists a significant limitation on diagnosing pre-malignant lesions, and an expert bronchoscopist could only identify 29% of these cases. While fluorescence bronchoscopy may be able to help with this issue, there were some challenges in the detection of dysplasia. Thus, based on the mechanism that showed that dysplastic and malignant tissues exhibit lower autofluorescence signals than normal tissues, that is why the LIFE-lung Fluoresence Endoscopy was created. Although LIFE bronchoscopy has a high diagnostic sensitivity in detecting premalignant and early malignant lesions, the results are less specific, in other words there are more false positive results [2].

3.4. Lung Tissue Biopsies

Tissue biopsies are considered the gold standard for cancer diagnosis. Fiber optic bronchoscopy with or without transbronchial needle aspiration, endobronchial ultrasonography, image-guided trans-thoracic needle aspiration, mediastinoscopy, pleural fluid analysis (thoracentesis), thoracoscopy, and surgical techniques are among the many frequently used procedures in the diagnosis of lung cancer. However, the disadvantages of these methods were high cost, susceptibility to complications, and the need for larger samples [1]. Plasma testing has many advantages over biopsy as a test for common lung cancer NSCLC, such as being noninvasive, fast, and easily repeatable over time, but they can't be used as stand-alone testing for NSCLC patients since they can be less sensitive than tissue-based assays [9].

DOI: 10.54254/2753-8818/57/20241262

4. Types of Biomarkers of Cancer

4.1. Genetics and Epigenetic Biomarkers

4.1.1. P53. The P53 gene codes for a tumor suppression protein that is involved in various cell processes, such as cell cycle regulation, DNA repair, and apoptosis. Numerous P53 point mutations were discovered and assessed as potential indicators of NSCLC prognosis [3].

4.1.2. Epidermal growth factor reporters (EGFR). Some studies showed that about 62% of NSCLC cases had mutant versions of EGFR present or overexpressed. Furthermore, EGFR mutations have been linked to between 50% and 70% of lung cancer incidences in East Asia, suggesting that lung cancer biomarkers exist [3].

4.1.3. Ras Genes. The Ras family, which includes K-eas, H-ras, and N-ras, is in charge of producing proteins that are essential for signal transduction and cell division. Additional studies showed a high correlation between 78% of lung cancer patients and K-ras mutations. Furthermore, it has been demonstrated that circulating K-ras mutant proteins are significant prognostic and predictive indicators for lung malignancies [3].

4.1.4. Micro RNAs. MicroRNAs are RNA molecules containing 19–25 nucleotides that play significant roles in the silencing of genes. These tiny chemicals work by obstructing or damaging mRNA molecules, which ultimately suppresses the expression of those molecules. It has been demonstrated that these molecules have important roles in both the prognosis of cancer and cell development. They were also found to be relevant to various cancers' pathological parameters and this discovery showed that these molecules had the potential to be cancer biomarkers. MicroRNAs' existence in bodily fluids suggests they have the potential to be biomarkers for cancer diagnosis. These molecules may have opportunities for research breakthroughs in non-invasive detection of lung cancer [3].

4.2. Protein Based Biomarkers

While there are several established protein biomarkers for lung cancer, the presence of these biomarkers, and more specifically their expression level, varies significantly among different subtypes of the disease. The combination of some biomarkers succeeds in diagnosing excellent sensitivity and specificity in cases of lung cancer [3].

4.2.1. Carcinoembryonic Antigen (CEA). Several studies have shown a strong association between SSCLC survival and CEA values.

The research found a strong association between NSCLC and CEA levels. According to additional research, the prognosis following surgery is worse the higher the serum CEA level. The higher the value, the poorer the prognosis after surgery.Nowadays, CEA levels are taken into account in addition to other markers including CA 15-3, CCAT2, and AFP for a more accurate forecast [3].

4.2.2. Neuron-specific Enolase (NSE). The other prevalent lung cancer biomarker, neuron-specific enolase (NSE), was discovered to be elevated in the serum of patients with small cell lung cancer (SCLC). At this point, NSE is regarded as one of the most accurate biomarkers with a high diagnostic yield in SCLC cases. While monitoring the NSE as a marker in SCLC is enough for diagnosis, it is preferable to take into account additional biomarkers, such as CEA and CYFRA 21-1, in addition to this enzyme in order to achieve reliable detection in NSCLC [3].

4.2.3. Annexin A2 (ANXA2). The 36 kDa protein known as annexin A2 has been found to be a new and effective biomarker for lung cancer. It gained recognition as a lung cancer biomarker due to its notable rise in the disease's early stages. Current research found that, compared with healthy people, patients' levels of ANXA2 in serum were higher. In another experiment, heat shock protein 60 (HSP60) and

DOI: 10.54254/2753-8818/57/20241262

ANXA2 as a novel combination of lung cancer biomarkers showed significant improvements in lung cancer early diagnosis. All of the above illustrates that ANXA2 is promising in early lung cancer detection [3].

4.2.4. Serum Amyloid A1 (SAA1). This protein is regarded as one of the acute phase proteins, exhibiting high levels of expression in response to various severe conditions, infections, and traumas. Some experiments have shown that lung cancer patients have higher levels of SAA1, and that SAA1 levels in samples from cancer patients are fourteen times higher than in healthy people compared to normal people. It demonstrated a notable advancement in the early identification and diagnosis of lung cancer [3].

4.2.5. Breath and Volatile Organic Compound (VOC) Analysis. Every intracellular pathophysiological fluctuation has an impact on cellular metabolism and, consequently, on the products that are expelled, such as volatile organic compounds (VOCs). Breath volatile organic compounds (VOCs) may be an indicator of the body's biochemical state for lung cancer as well as lung disorders for which the patient has already received evaluation, such as asthma or chronic obstructive pulmonary disease. Phillips and colleagues, almost 20 years ago, found a possible correlation between breath composition and lung cancer with the analysis of 108 individuals. Furthermore, Phillips, using a model of 30 volatile organic compounds (VOCs), lung cancer was detected with a sensitivity of 84.5% and a specificity of 81.0% in a research involving breath samples from 193 lung cancer patients and 211 healthy controls. GC-MS has shown to be a helpful analytical method for identifying particular biomarkers in breath, but because of its complexity, long processing time, requirement for trained operators, and expensive cost, its potential application as an early diagnostic tool is limited. Furthermore, a number of studies show that it is extremely challenging to pinpoint a particular molecule that is associated with lung cancer. Rather, the ability to detect cancer depends on the relative amounts of many substances. These factors led the researchers to concentrate their efforts on novel techniques that were more easily accessible and economically viable [7].

4.2.6. Tumor Exosomes. Exosomes are a type of nanoscale extracellular vesicles (30–150 nm) that can infiltrate blood, plasma, and urine, among other bodily fluids. They are released from their parent cells. As a novel class of cancer biomarker, tumor exosomes have emerged as a viable marker for non-invasive early cancer diagnosis. Growing evidence has shown that tumor exosomes play important roles in the spread and progression of cancer by delivering abundant malignant bioinformation, including particular RNAs and proteins for facilitating intercellular communication. However, because of the characterization of exosomes, it is currently very difficult to identify tumor exosomes with good sensitivity and selectivity due to their small size and low concentration in bodily fluids. Therefore, it is imperative to devise dependable and efficient methodologies for the direct extraction and examination of exosomes related to cancer in intricate biological specimens, particularly in authentic hematic samples. This endeavor is anticipated to yield novel pathways for non-invasive, preemptive cancer diagnostics.

The limitations of currently investigated methods for exosome determination, most of which are limited by cumbersome sample handling techniques, and the difficulty of these methods to selectively detect tumor exosomes, have seriously hampered their widespread application in complex biological systems. There are also newer strategies that have excellent performance, but most of them require the use of ultracentrifugation to enrich exosomes. Technologies based on aptamers, cholesterol, and antibodies have now been cleverly suggested for the quantitative analysis and collection of tumor exosomes. Specifically, they can recognize and bind the biomarkers on the surface of malignant exosomes. Among them, aptamers and antibodies have a high affinity for tumor-derived exosomes. It's significant to note that, in comparison to antibodies, aptamers have superior qualities of chemical stability, ease of synthesis, and affordability. The following problems with conventional electrochemical exosome assays exist, notwithstanding the tremendous evolution that has been attained. First of all, the

DOI: 10.54254/2753-8818/57/20241262

immobilization of probes on an electrode surface is a necessary step in these conventional electrochemical assays, which is not only time-consuming and laborious but also inevitably prevents the exosome and probe from being recognized effectively, severely restricting the improvement of the detection sensitivity. Secondly, the capacity of exosomes to be captured could be restricted due to their specific kind of aptamer or antibody recognition. Finally, the majority of these reported electrochemical biosensors only measure the change in the single-peak current signal output, which is susceptible to environmental disturbances that are unavoidable and can lead to false-positive readings.

Limin Yang, Xuehan Yin et al. have created a ratiometric immobilization-free electrochemical sensing technology that allows them to accurately extract tumor exosomes from their intricate biological surroundings and quantify them directly. More importantly, the new method shows good feasibility for clinical sample analysis as it can directly detect tumor exosomes in human serum samples in a complicated sample medium [10].

5. Conclusion

Since lung cancer patients are usually detected at an advanced stage of the disease, which can be a major obstacle to treatment and prognosis, early detection methods are crucial. The limitations of traditional tests, such as their high cost, low detection rate, increased pressure at the patient's lesion, and increased risk of lesions due to invasive and radiological methods, underscore the need for more effective methods to bring the research on early-stage lung cancer detection to maturity. Many clinical trials have demonstrated the promise of biomarkers as an early detection modality in the present. However, further research on biomarkers for lung cancer also requires the help of biosensors, and the application of biomarkers for early lung cancer detection and the development of lung cancer biomarkers are faced with various challenges. This will not only improve early detection rates but also contribute to better treatment outcomes for lung cancer patients in the future.

References

[1] Gasparri R, Romano R, Sedda G, et al. Diagnostic biomarkers for lung cancer prevention [J]. Journal of breath research, 2018, 12(2): 027111.

[2] Nooreldeen R, Bach H. Current and future development in lung cancer diagnosis [J]. International journal of molecular sciences, 2021, 22(16): 8661.

[3] Roointan, Amir; Ahmad Mir, Tanveer; Ibrahim Wani, Shadil; Mati-ur-Rehman, ; Hussain, Khalil Khadim; Ahmed, Bilal; Abrahim, Shugufta; Savardashtaki, Amir; Gandomani, Ghazaal; Gandomani, Molood; Chinnappan, Raja; Akhtar, Mahmood H (2018). Early detection of lung cancer biomarkers through biosensor technology: a review. Journal of Pharmaceutical and Biomedical Analysis

[4] Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: An overview [J]. International journal of cancer, 2021, 149(4): 778-789.

[5] Siegel R L, Miller K D, Fuchs H E, et al. Cancer statistics, 2021 [J]. Ca Cancer J Clin, 2021, 71(1): 7-33.

[6] Siegel R L, Miller K D, Wagle N S, et al. Cancer statistics, 2023 [J]. Ca Cancer J Clin, 2023, 73(1): 17-48.

[7] Schabath M B, Cote M L. Cancer progress and priorities: lung cancer [J]. Cancer epidemiology, biomarkers & prevention, 2019, 28(10): 1563-1579.

[8] Seijo L M, Peled N, Ajona D, et al. Biomarkers in lung cancer screening: achievements, promises, and challenges [J]. Journal of Thoracic Oncology, 2019, 14(3): 343-357.

[9] Pennell N A, Arcila M E, Gandara D R, et al. Biomarker testing for patients with advanced non–small cell lung cancer: real-world issues and tough choices [J]. American Society of Clinical Oncology Educational Book, 2019, 39: 531-542.

[10] Yang L, Yin X, An B, et al. Precise capture and direct quantification of tumor exosomes via a highly efficient dual-aptamer recognition-assisted ratiometric immobilization-free electrochemical strategy [J]. Analytical Chemistry, 2020, 93(3): 1709-1716.