The Potential Of Liquid Biopsies For Early Cancer Detection And Monitoring Treatment Response

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Abstract
The identification of tumor-derived components in biofluids, such as blood, by minimally invasive or non-invasive methods, known as liquid biopsy, is a groundbreaking technique with great promise for cancer care. Liquid biopsies are capable of effectively identifying genomic and transcriptomic changes, offering a more thorough understanding of the diverse tumor profile compared to tissue biopsies alone. Liquid biopsies have the potential to aid in the diagnosis, prognosis, and selection of therapy. They may also be used with existing monitoring tools to track the progression of illness and the response to treatment in real-time. Specifically, these tests may detect even small amounts of remaining illness, forecast the likelihood of disease development, and determine the reasons for treatment resistance. This enables more timely adjustments to treatment plans. This review compiles the latest information on the function and promise of liquid biopsies in diagnosing and monitoring cancer patients. The data presented highlight the advantages of liquid biopsies, demonstrating their potential to enhance the detection and monitoring of many kinds of tumors in the near future. Nevertheless, while there is increasing evidence to support the usefulness of these tools in cancer therapy, many constraints must to be addressed before they can be effectively integrated into standard clinical practice.

Keywords: cancer, liquid biopsies, diagnosis, prognosis, monitoring, cell-free DNA, circulating tumor cells, precision medicine.

1. Introduction

With the increasing prevalence of cancer worldwide, ongoing endeavors are being undertaken to enhance the detection and treatment of this illness. One of the primary difficulties in cancer treatment is the early detection of the disease [1]. Hence, the advancement of screening and early detection tests, along with the implementation of effective monitoring techniques, has significant significance in enhancing the effectiveness of treatments and minimizing cancer-related deaths [2]. Precision medicine has garnered significant interest in the realm of cancer [3]. Molecular profiling may be used to get a deeper understanding of the changes that occur throughout the development of tumors [4]. This helps in identifying biomarkers that can be used for diagnosis and prognosis, as well as in selecting therapies that take into account individual differences.

Despite being the current benchmark for tumor profiling, tissue biopsies have some drawbacks. They are invasive, dangerous, and not readily acquired for certain anatomical regions. Additionally, they provide a restricted view of the tumor profile. Tumors are really composed of many subpopulations of cells that possess distinct changes, making them heterogeneous entities. Furthermore, tumor cells have dynamic alterations in their genetic and epigenetic makeup throughout time, often as a response to therapeutic treatment. This leads to increased heterogeneity within the tumor and differences between the main tumor and its metastatic lesions. Therefore, the tissue samples that are confined in space and time are unable to accurately reflect the whole tumor characteristics, capture changes from various locations, and effectively track the evolution of the illness [7].

In recent years, oncology research has primarily focused on liquid biopsies, which involve detecting cancer-related components such as circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), RNA, extracellular vesicles (EVs), and tumor educated platelets (TEPs) in patients' biofluids. These biopsies provide valuable genomic, epigenetic, transcriptomic, and proteomic information about tumors and metastatic sites [8-15]. Liquid biopsies have the potential to enhance cancer screening, diagnosis, and prognosis. They can also improve the classification of diverse cancer types and provide more precise monitoring of patients. Additionally, liquid biopsies can assess treatment response and identify treatment-resistant clones [15-20]. This may be accomplished by the use of a minimally invasive treatment that can be performed several times throughout the evolution of the illness without causing harm to the patients. In addition, liquid biopsies provide a more comprehensive genetic analysis of the tumor, which accurately represents its heterogeneity [9].

Furthermore, they have the potential to detect aggressive clones that are spreading. This review aims to gather up-to-date research on the possibility of liquid biopsies for diagnosing and monitoring cancer patients, while also discussing the benefits and limits of this method.

2. Liquid Biopsies for Diagnosis and Profiling of Tumors

At now, cell-free DNA (cfDNA) is a highly researched substance in liquid biopsies. The presence of both a sufficient amount and the integrity of cfDNA in the bloodstream has shown the capacity to differentiate between persons with cancer and those who are in good condition. Cancer patients often exhibit greater amounts of cfDNA compared to healthy individuals [17,21,22,23]. These levels seem to rise with the progression of the disease, particularly in advanced stages [17] and when metastasis occurs [24]. The elevated levels of cfDNA in these individuals are believed to be indicative of the enhanced release of genetic material from cancerous cells.

However, it is also possible that this phenomenon is caused by the impaired removal of circulating DNA by phagocytes [25]. Nevertheless, elevated cfDNA levels are not exclusive to cancer and have been seen in other clinical and non-pathological circumstances, such as exercise, trauma, and surgery [22]. This might impede their direct use in cancer detection. When it comes to integrity, cancer patients often exhibit more cfDNA fragmentation (less than 100 bp) compared to healthy individuals [22,23]. However, a research on thyroid carcinoma showed the opposite [21], highlighting the ongoing challenge of achieving the necessary sensitivity and specificity for accurate detection in these types of tests.

However, by examining specific changes in tumors such as single nucleotide variants (SNVs), insertions, deletions, copy number variations (CNVs), and methylation alterations, it is possible to detect tumor-derived DNA known as ctDNA within the overall pool of cfDNA. This method of cancer genotyping is more precise and therefore leads to more accurate diagnoses. Significantly, these (epi)genetic changes appear to be strongly consistent in blood ctDNA and in corresponding tumor tissues in various types of cancers, such as lung [17,26], breast, colorectal, pancreatic, liver, esophageal, gastric, and ovarian cancers [6,17,27,28]. These liquid biopsies are less intrusive and have lower risks compared to tissue biopsies. They may be utilized as an alternative when tissue biopsies cannot be conducted or when they do not yield sufficient high-quality DNA [17,24,26].

Since 2016, non-small cell lung cancer (NSCLC) patients who cannot supply tumor tissues have the option to be tested for EGFR mutations in their plasma. This may be done with the FDA-approved cobas EGFR Mutation Test v2 [29]. Subsequently, this regulatory organization has authorized other liquid biopsy tests that use plasma samples to identify certain gene mutations and rearrangements in individuals diagnosed with ovarian, lung, breast, and metastatic castration-resistant prostate cancers. These tests primarily serve as companion diagnostic tests to identify individuals who meet the criteria for targeted therapy [30].

Nevertheless, the correlation between changes detected in ctDNA and tumor tissues differs not only based on the specific kind of cancer [19], since various tumors have varying chances of releasing DNA into the circulation [20], but also based on the stage of the illness [17,26]. Indeed, the amounts of cfDNA are often reduced in the first phases, indicating that liquid biopsies have a restricted capacity for early cancer diagnosis [17,18]. However, advancements in technical sensitivity may potentially address these challenges [17]. While the use of liquid biopsies for cancer screening is not yet fully established, a liquid biopsy test that detects aberrant methylation of the SEPTIN9 gene in blood has previously received approval for colorectal cancer (CRC) screening [29]. Furthermore, ongoing research is also investigating the use of ctDNA-based blood tests to screen for several forms of cancer, such as ovarian, liver, stomach, pancreatic, and esophageal cancers, for which screening assays are currently unavailable [30].

3. Circulating tumor DNA (ctDNA)

Circulating tumor DNA (ctDNA) not only precisely reflects the genetic makeup of the tumor, but it also records the presence of different genetic variations within the tumor (tumor heterogeneity) [28]. This is especially important in cases of metastatic illness, when it may not be possible or practical to get several tissue samples. Additionally, doing repeated biopsies might raise costs and pose dangers to the patients. Accurately evaluating all areas where tumors are located is particularly crucial for identifying actionable alterations and, as previously stated, for determining which patients may benefit from targeted therapy [19,28]. However, ctDNA analysis may have poorer sensitivity in detecting some changes that are present in tumor tissues [19,31]. This is because these changes are diluted in a mixture of normal DNA [12,20] and may only be present in small groups of cells, resulting in lesser levels in the bloodstream [6,32]. Currently, liquid biopsies seem to serve as a supplementary rather than alternative method to tissue biopsies for diagnostic and profiling reasons.

In addition to blood, many additional biofluids, including urine, cerebrospinal fluid (CSF), and gastric washes, have been shown to contain ctDNA [7,23,28,32]. Tumors of different types of cancer may come into closer contact with various fluids, resulting in increased quantities of ctDNA in those fluids compared to blood [23]. Urinary ctDNA has been identified in bladder cancer [23,32] as well as other urothelial tumors [23]. In addition, transrenal DNA, which is the DNA cleared from the circulation by the kidneys, has been found in non-urological cancers such NSCLC and CRC [28]. Importantly, urine ctDNA exhibits cancer-specific mutations, CNVs, and methylation changes that closely match those seen in tumor tissues [23,33]. Considering the complete lack of invasiveness in collecting urine, the use of urine for liquid biopsies shows great promise. This non-invasive method improves patient compliance for repeated sample for diagnosis or follow-up, making it especially advantageous [34]. However, despite the apparent positive relationship between plasma and urine cfDNA levels [35,36], the ability to identify mutations in pee is often more restricted compared to blood [34].

CSF, or cerebrospinal fluid, is an important source of information for studying brain cancers, particularly gliomas. It serves as an alternative to surgical tissue biopsies. Significantly, ctDNA obtained from cerebrospinal fluid (CSF) has also shown the presence of mutations, copy number variations (CNVs), and structural rearrangements that are consistent with the tumor [32].

Aside from ctDNA, liquid biopsies may also be used to explore additional components with diagnostic potential, including messenger RNA (mRNA) and micro-RNAs (miRNAs) [4,37]. Malczewska et al. conducted a study where they analyzed gene expression in the blood of patients with bronchopulmonary carcinoid (BPC) tumors. They found that the levels of specific gene transcripts were significantly higher in these patients compared to healthy individuals. This difference in gene expression allowed them to differentiate between patients with metastatic disease and those with localized disease. Crucially, there found a strong correlation between gene expression in tumor tissue and blood [4]. Similarly, the levels of several miRNAs are often changed in cancer patients, which may be used to identify miRNA signatures that have the potential to be used for diagnosis and prognosis [38,39].

Tumors and their surrounding environment secrete miRNAs, which may be found in the circulation either in ribonucleoprotein complexes or enclosed inside extracellular vesicles (EVs) [39]. Specifically, the patterns of circulating miRNA seem to be consistent with those of tumor tissues [37]. Nevertheless, miRNAs that are integrated into extracellular vesicles (EVs) seem to make up just a tiny portion of the miRNAs found in the bloodstream and exhibit unique diagnostic capabilities [38].

Exosomes include exoDNA, which is a reliable source of information.

Unlike cfDNA, exoDNA is less likely to degrade and is produced from alive cells. As a result, exoDNA is likely to provide a more accurate reflection of tumor-driving mutations compared to ctDNA, which comes from apoptotic and necrotic cells [32]. Unlike exosomes, which originate from internal compartments, tumor-associated microparticles (taMPs) are vesicles generated from the cell membrane and exhibit cell surface markers characteristic of their origin. The presence of cancer markers epithelial cell adhesion molecule (EpCAM) and CD147 in taMPs was shown to be exclusive to cancer patients, suggesting their potential application in diagnostics. Furthermore, these double-positive tumor-associated macrophages (taMPs) exhibited a strong correlation with the amount of tumor present in colorectal cancer (CRC) [40].

4. Conclusion

To summarize, while liquid biopsies currently have some limitations, they possess significant promise to enhance clinical treatment in the field of cancer. Specifically, this biopsy method has possibilities for enhancing the monitoring of cancer patients throughout therapy and might be beneficial in complementing existing diagnostic and tumor profiling approaches in the near future.

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