Editorial

Why Liquid Biopsy is a Paradigm Shift in Clinical Oncology

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ABSTRACT

Liquid biopsy (LB) represents a transformative advance in clinical oncology, offering a minimally invasive, dynamic, and highly sensitive approach to cancer diagnosis, prognosis, and treatment monitoring. Unlike conventional tissue biopsy, LB evaluates circulating tumor DNA and other biomarkers in blood and body fluids, enabling early detection of malignancies and real-time assessment of tumor dynamics. This review highlights the evolution, applications, advantages, and challenges of LB, particularly in the Indian healthcare context where timely and accessible cancer diagnostics remain a pressing need.

Keywords: Liquid biopsy, Circulating tumor DNA, Precision oncology, Non-invasive cancer diagnosis

INTRODUCTION

The registry of new patients of various cancer types in Tata Memorial Hospital alone is approximately 75,000/year. The World Cancer Report said that according to the estimated cancer burden in India in 2018, there were about 1.16 million new cancer cases, 784,800 cancer deaths, and 2.26 million 5-year prevalent cases in India's population of 1.35 billion. Projections suggest that this figure will increase to 1.70 million by 2035. Approximately 87% of these patients seek medical attention in advanced stages of disease. This contributes to India's very high mortality-incidence ratio of 0.68, which is substantially higher than that of high-income countries. In addition to late-stage presentation, other factors that likely contribute to poor cancer outcomes in India include limited health system infrastructure, a scarcity of oncologists, and patients' inability to afford cancer treatment.

Cancers of the oral cavity and lungs account for over 25% of cancer deaths in males, and cancer of the breast and oral cavity accounts for 25% of cancers in females. As seen in the diagram [Figure 1], the top five cancers in men and women account for 47.2% of all cancers; the mortality rate of these cancers can be significantly reduced or prevented if screened, diagnosed, and treated at an early stage. In this era of personalized medicine, there is a huge unmet need for early diagnosis and early treatment protocols, particularly in solid tumors. The crude cancer incidence rate was highest in Kerala and Mizoram, followed by Haryana, Delhi, Karnataka, Goa, Himachal Pradesh, Uttarakhand, and Assam.

Early detection is the holy grail of cancer management. In clinical oncology, the current clinical practice for diagnosis and treatment decisions is based on methods such as tissue biopsy, imaging techniques (computed tomography [CT], magnetic resonance imaging, or positron emission tomography scans), and cytology. The information gained from these approaches is static in time, coarse-grained because they provide little detail at the molecular/genomic level about the underlying cancer. During a particular tissue biopsy, the surgeon may or may not capture the precise tumor

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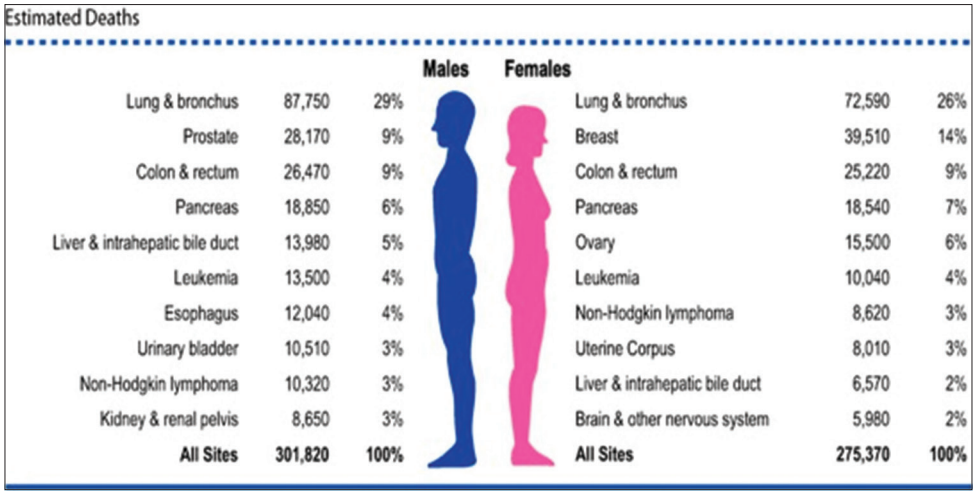

Figure 1: GLOBOCAN report for 2022 estimates million cancer-related deaths worldwide

cells in the tissue sections captured for histopathology/ morpohology, which then determines the next steps for treatment. Further, these surgical tissue biopsies cannot be iterative given the patient's frailty, tolerance for invasive procedures, costs, etc. The presence of interpatient tumor heterogeneity complicates treatment decisions. However, tissue biopsy remains the gold standard in diagnosing the various histopathology types and subtypes of solid tumors.

WHAT IS LIQUID BIOPSY

The existence of liquid biopsy was first demonstrated in 1948 by Mandel and Metais. During programmed cell death (apoptosis) and necrosis, the dead cells are engulfed by macrophages and other scavenger cells (phagocytosis). However, when macrophage phagocytosis is exhausted, there is an increased nucleosome (shed DNA fragments) amount released into the bloodstream. Liquid biopsy (LB) has the ability to detect cancer biomarkers in blood and malignant body fluids earlier than conventional methods such as tissue biopsy. These "shed DNA" fragments are the circulating-free tumor DNA (cfDNA). During tumor necrosis, shedding of nucleosomes by malignant tumors results in the release of ctDNA along with cfDNA. This ctDNA causes changes in the genomic sequence (genetic mutations) within the patient's normal genes. The circulation of ctDNA through the lymph and blood circulation spreads the disease to other organs – and is termed "metastasis."

The genomic profiling of plasma-shed ctDNA is an emerging multimodal diagnostic tool for the therapeutic approach in clinical oncology. Their presence can be analysed using plasma, urine, saliva, and other malignant body fluids, such as cerebrospinal fluid, pleural effusion, pericardial, and ascitic fluids, which are close to the tumor.

For tissue biopsy, a larger team of CT scan, interventional radiologist, on-site pathologist, technician to make blocks, pathologist, molecular pathologist, or molecular biologist is essential, whereas for LB the essential team is just a phlebotomist, molecular pathologist, or biologist. In tissue, only 18% of patients get their complete tissue genotyping; however, this number can greatly improve by performing a liquid biopsy. A cross-sectional observation study regarding patients and their physicians' willingness to wait for a driver mutation report on the tissue biopsy is just 35%. In lung cancer, there are several procedural complications of CT-guided biopsy, of pneumothorax, pneumothorax with a need for intervention, pulmonary hemorrhage, hemoptysis with spontaneous hemostasis, and hemothorax, and hence LB (partial invasive procedure) testing, predominantly overcomes all these complications.

SIGNIFICANCE OF LIQUID BIOPSY TESTING

The highly dynamic clonal evolution of the tumor over time warrants longitudinal surveillance of the molecular landscape of the tumor. This cannot be efficiently achieved with tissue biopsy samples alone and requires an alternative approach. Due to the rapid turnover rate of tumors, tumor materials such as nucleic acids, vesicles, and viable cells are constantly released into

the circulation. Liquid biopsy can be used to frequently assess the dynamic molecular landscape of tumors with the least cost or discomfort to the patient (Figure 2).

CHALLENGES OF LIQUID BIOPSY

Liquid biopsy ctDNA has an approximately 86% chance of positive detection across all solid tumor types. It is a promising biomarker in advanced/metastasis cancer disease. However, a negative liquid biopsy test result may not indicate the absence of tumor oncogenes. Hence, here a tissue biopsy analysis is recommended. LB can also be challenging in the early stages of cancer because of low ctDNA levels in the body fluids. The presence of mutations in plasma does not establish that these mutations originate from a particular cancer and does not establish its histologic type and subtype. ctDNA reflects the genome of dying tumour cells and not the existing tumor cells or resistant population, and hence cannot provide the exact origin of the mutation.

In normal subjects, the concentration of plasma cfDNA ranges from < 10 ng/mL to more than 100 ng/mL. The half-life of cfDNA is between 16 min and 2.5 h. In cancer patients, ctDNA represents a small proportion of total cfDNA, varying from <0.1% to over 10% according to the tumor burden, cancer stage, cellular turnover, and response to therapy. For the accurate analysis of downstream pathways of genomics, an algorithm of plasma separation and extraction of ctDNA has to be implemented meticulously. In case of in-house sample analyses, the sample can be drawn in a routine K2 EDTA vacutainer, whereas the sample that is transported to a reference laboratory has to be collected in special vacutainers (Streak, PAX gene, etc.) having a larger stability of 48 h, to prevent the plasma from degrading. Once the sample reaches the laboratory, it is very important to separate out the plasma within 2 h and store at −80°C till the cfDNA is extracted. For genomic profiling, the samples are processed on a next-generation sequencing platform. It is an unmet need for the samples to be sent out only to a certified (NABL/CAP) laboratory, which can then provide a final report outlining the detected genomic alterations.

In terms of time management, the reporting of genomic profiling is much faster than tissue biopsy (7 days vs. 15 days), and since liquid biopsy bypasses all the surgical procedures, it is highly cost-effective.

I at Tata Memorial Hospital pioneered liquid biopsy testing in India, particularly in lung cancer. Because of the site and size of the tumor in lung cancer, "tissue is the issue," and hence detection of driver oncogenic mutations in liquid biopsy becomes more advantageous over tissue biopsy."

With the advent of high throughput technology and with several notable studies in cancer, testing of liquid biopsy (plasma ctDNA) is becoming more popular to identify somatic driver actionable mutations, and predictive and prognostic biomarkers in various cancer tumors in the oncology clinic. Further, LB can also be effectively used to monitor the efficacy of tyrosine kinase inhibitor treatments and to evaluate resistance mechanisms in the human body. The biomarkers other than plasma ctDNA liquid biopsy include ctDNA, circulating tumor cells, exosomes, tumor-derived RNA, and tumor-educated platelets. The analyses of these biomarkers are still being researched, and have not yet been approved for routine testing.

A wider adoption of liquid biopsy techniques in India could detect cancer much earlier, reduce the burden on the limited cancer hospitals while saving a lot of lives – all at much lower patient costs.

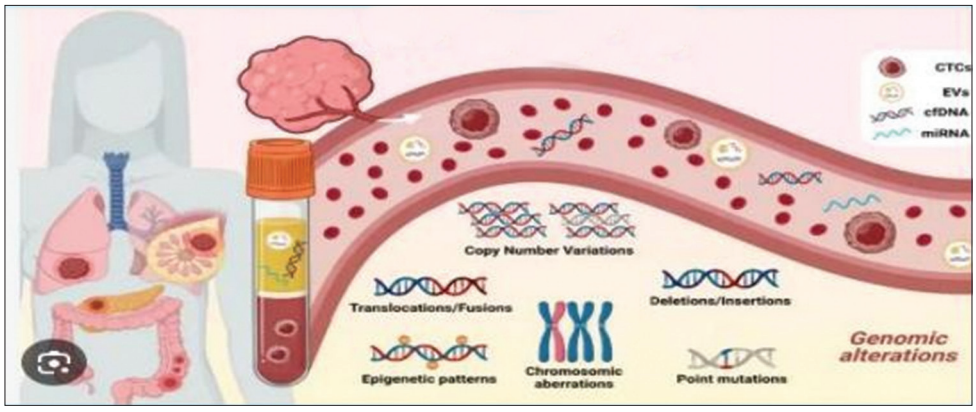

Figure 2: Schematic diagram of liquid biopsy and its components

Hence to conclude, LB is similar to tissue biopsy, less invasive and safer for patients, less tedious to perform, requires less manpower than tissue biopsy, and has also shown a high concordance (96.96%) between tissue biopsy and ctDNA for oncogenic driver mutations, showing a false negative rate of only around 3% which is acceptable. Thus, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the assay, such as 91.1%, 100% 100%, 95.6%, and 97%, respectively, have made liquid biopsy testing more acceptable in clinical precision oncology.[1]

CONCLUSION

Liquid biopsy offers a reliable, less invasive, and dynamic diagnostic option for the detection and molecular profiling of solid tumors. It overcomes several limitations of tissue biopsy, particularly in advanced and metastatic cancers. With high concordance rates for actionable mutations and its potential to monitor treatment response and resistance mechanisms, LB represents a pivotal step towards precision oncology in India. Wider adoption and infrastructure development for liquid biopsy could substantially improve early cancer detection and outcomes nationwide.

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