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Editorial

# Liquid Biopsy: Open New Vista in the Diagnosis of Lung Cancer

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Carcinoma of lung is the most common neoplasm as well as leading cause of cancer related death in the Asian Pacific area accounting 1.38 million cancer deaths per year worldwide which is 17.8%. Since 1970s, the 5-year survival rate of lung cancer has remained unchanged at < 15%. In terms of incidence rates, lung cancer ranked fourth overall among the various types of cancer (excluding non-melanoma skin cancer) after breast, cervical, and oral cavity cancer [1,2]. Lung cancer is the most common cancer in men worldwide with an age-standardized rate (ASR) of 33.8 per 100,000, and it is the fourth most frequent cancer in women (13.5 per 100,000). Besides this in Indian males, lung cancer was the most common cause of cancer mortality, though the estimated lung cancer mortality among Indian females was ranking seventh behind breast, cervix, colorectal, ovary, stomach, and lip/oral cavity cancer. Unfortunately, most cases of the disease are not diagnosed in early stages, when the disease typically causes no symptoms. It's unclear how to predict when and whether these patients will progress and whether it makes sense to use treatments designed for patients with metastatic disease [1,3,4].

Late detection is an important factor for high mortality rates related to lung cancer. It has been reported that prognosis of lung cancer is robustly associated with the stage of cancer at the time of diagnosis, and 5-year survival rates range from 5% for stage IV cancers to 80% for stage I cancers, besides this patients with localized disease at diagnosis have a 5 year survival rate of 52%, however more than 52% of patients with distant metastasis at diagnosis have a 5 year survival rate of 3.6%, therefore improving the detection rate of early stage lung cancer is essential for improving the prognosis of lung cancer [1,3].

According to various published research in eminent journal, cytological methods in the diagnosis of neoplastic lesions of the respiratory tract has been considered as one of the most successful application. Flexible fiber -optic bronchoscope revolutionized respiratory cytology as technique like bronchial brushing, Broncho- alveolar lavage and bronchial biopsy became more easy, accessible and gained popularity, however bleeding is always a major concern when an airway lesion is biopsied. Pneumothorax occurs in 1 - 10% of cases of transbronchial biopsies. Besides this bronchial biopsy cannot be performed at certain anatomical locations (peripheral tumors) or in patients at risk of haemorrhage. Apart from this tissue biopsies, have their own significant pitfalls like, difficult to get a clear picture of a person's systemic disease burden, not enough tissue to do all the tests needed (According to experts, this happens in 25 percent of cases), genetics and thus the drug markers differ within one tumor or between different metastatic sites, tumor location or locations in the bone or liver make tissue biopsy dangerous or impossible as is the case for 31 percent of patients with lung cancer, and a patient is too sick to endure a stressful tissue biopsy [4-6].

Hence alternative methods for obtaining a diagnosis is need of time and advancements in bioinformatics and nanotechnology have brought the "liquid biopsy" - i.e. assessing the genetic material of tumor cells in the blood and urine - to the forefront. There are three major sources for the plasma liquid biopsy - 1) circulating tumor cells (CTCs), 2) cell-free nucleic acids (cfNA) and 3) extracellular vesicles (EVs).

Tumor cells (and their DNA) are released into the circulation as well as circulating- free tumor DNA (cfDNA) could be isolated and finally, the molecular test can be obtained. The majority of ctDNA is released from apoptotic or necrotic tumor cells, thus reflecting the genetic profile of a tumor. Liquid biopsy could overcome the clonal heterogeneity of tumour biopsy, as it provides a unique view of a tumor

tissue. Perhaps, non-invasiveness is the biggest advantage for liquid biopsy, and the procedure can be repeatedly performed during the treatment for the purpose of monitoring. Hence, ctDNA could be consider as a potential adjuvant method for tissue biopsies in diagnosis, prognostic, treatment response and resistance [7,8].

The development of liquid biopsies (LB) has changed substantially the care of patients with solid cancers, in particular late stage lung cancer patients. Addition of liquid biopsy to management of advanced lung cancer can have a strong impact at three different levels: 1) for the initial detection of actionable oncogenic drivers; 2) for the identification of resistance mutations in patients relapsing on targeted therapies; and 3) for the monitoring of the response to therapy and the prediction of the clinical outcome.

cfDNA, CTCs, TEPs, TECs, and tumor ES all show promise, although few are currently used clinically. Tumor cfDNA was discovered in 1948 and is partially composed of DNA fragments roughly 150 to 1,000 base-pairs long which form a ladder-like electrophoretic pattern of roughly 180 bp multimers, possibly indicating an apoptotic origin. Tumor cfDNA which is nuclear and/or mitochondrial in origin, is found in blood, lymph, milk, spinal fluid, urine, and saliva. It is less stable than cfDNA derived from non-tumor cells and is rapidly degraded by plasma nucleases, conferring a short half-life [9,10].

Presently several challenges must be met before the liquid biopsy can enter clinical practice, including 1) optimizing and standardizing sample gathering, 2) implementing uniform analytical procedures, 3) identifying the circulating analyte(s) most likely to yield useful information, and 4) performing the sufficiently large multi-center clinical trials necessary for validating specific analysis protocols [11,12].

However few eminent researchers alleged that liquid biopsies will never replace real biopsies, which are irreplaceable sources of information that cannot be obtained by any other means, such as tumor type and histology. Though, they offer all sorts of additional data that cannot be obtained in any other way. In patients who cannot be biopsied, or where biopsies do not have enough tissue, "liquid biopsy" is the only alternative to perform genetic testing for targeted therapy. Also, in patients with advanced disease, it is not feasible to obtain biopsies of every metastatic site while blood reaches both the primary tumor and the metastases, and materials coming from all can be found in a "liquid biopsy.

It was reported that the sensitivity of cfDNA detection has been more than 85% in patients with early stage NSCLC patients, suggesting that cfDNA may be a diagnostic and prognostic biomarker in this setting. In brief, cfDNA is a promising biomarker for the detection and follow-up of NSCLC patients as well as in clinical practice, cfDNA may serve as alternative for those patients who are unable to provide an accurate tissue-biopsy sample. It will also serve as invaluable source of information, complimentary to imaging, during the period of follow-up after surgery [13].

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