MOLECULAR HEALTH

Source of tumor-specific biomarkers

When a liquid biopsy is useful

In 30% of patients with non-small cell lung carcinoma (NSCLC), a biopsy of invasive tissue is either impossible or provides only very little tumor material.[1] This where a liquid biopsy can be useful – get the facts at a glance with a guideline check.

When can a liquid biopsy be considered?

A liquid biopsy is a simple, non-invasive method for detecting circulating tumor-specific biomarkers in bodily fluids such as blood or urine. In contrast to a tissue biopsy, a liquid biopsy has a limited impact for the patient and can be easily repeated.[2] Liquid biopsy becomes an option under the following two circumstances:

- There is not enough tumor material available, e.g. due to a reduction of the tumor content in stored tissue biopsies or due to the use of minimally invasive procedures.[2,3] For example, endobronchial ultrasound-controlled transbronchial needle aspiration (EBUS-TBNA) does not offer enough tumor material for increasingly complex and extensive tumor analyses in 10–20% of lung cancer patients.[3]
- A tissue biopsy cannot be performed, e.g. due to localization of the tumor, absence of a visible tumor, or the patient's co-morbidities.[2]

The current German S3 guideline for lung cancer also recommends molecular diagnostics using liquid biopsy if[4]

- Available tissue is insufficient or
- A repeat biopsy cannot be performed at acceptable risk

LIQUID BIOPSY: SOURCE OF TUMOR-SPECIFIC BIOMARKERS

The tumor material, released from the primary tumor or from metastases, is analyzed using highly sensitive methods such as next-generation sequencing (NGS) or digital droplet PCR (ddPCR).[1,2] This detects, e.g.[2]

- Cell-free circulating tumor nucleic acids (ctDNA or ctRNA);
- Circulating tumor cells (CTCs);
- Exosomes (extracellular vesicles containing tumor-associated proteins, fats, or nucleic acid)
- Tumor-educated platelets (TEPs; platelets containing tumor-specific RNA).

In particular, ctDNA reflects the genomic nature of the entire tumor and the metastases.[2]

Liquid biopsy has a broad field of application

For molecular tumor diagnostics, liquid biopsy offers a wide range of applications in early and advanced stages of cancer and can potentially be used for the following purposes:[2,3]

- Diagnosis
- Evidence of treatment-relevant biomarkers
- Therapy monitoring
- Evidence of resistance variants
- Detection of minimal residual disease
- Recognition of a recurrence
- Early detection of tumor diseases

Liquid biopsy is already used for NSCLC, colorectal cancer, and breast cancer

Liquid biopsy is already used to detect therapy-relevant variants and resistance variants.[3] For example, in stage IV NSCLC, activating mutations in the EGFR[a] gene (exons 18-21) are to be detected via liquid biopsy, as per the guidelines. This enables[4]

- Initiation of targeted first-line therapy with tyrosine kinase inhibitors (TKI)
- In case of TKI resistance: Investigation of TKI resistance mechanisms, such as the resistance variant T790M in the EGFR gene

Note: As companion diagnostics, the analysis of circulating tumor DNA via liquid biopsy in locally advanced or metastatic NSCLC is billable for the determination of all known, activating mutations in the EGFR gene, according to GOP 19461.[5]

Also used in colorectal cancer and breast cancer

According to the S3 guideline, liquid biopsy can also be considered for metastatic colorectal cancer – if tissue analysis is not possible – in order to determine the RAS[b] mutation status.[6]

The kinase inhibitor alpelisib was recently approved in the USA, based on the SOLAR-1 study, for the treatment of patients with advanced or metastatic hormone receptor-positive, HER2[c]-negative and PIK3CA[d]-mutated breast cancer. Here, the PIK3CA mutation can be detected either in the tissue or via liquid biopsy.[7]

Does a liquid biopsy replace tissue biopsy?

The comprehensive use of liquid biopsy in routine diagnostics faces several obstacles. It remains to be clarified to what extent the results of tissue biopsies are reproducible by liquid biopsy.[2] In addition, the process of sampling and analysis must be standardized, e.g. by testing for known reference mutations from the tissue biopsy.[1,2]

- The amount of circulating tumor DNA varies and can be as little as 0.01% of the total circulating nucleic acids (cfDNA) in some samples.[2]
- The plasma concentration of cfDNA also fluctuates between 0 and 1000 ng/ml.[1]

The analysis of circulating tumor DNA often has high specificity coupled with low sensitivity. This means that a lack of evidence of mutation via liquid biopsy does not exclude the presence of molecular changes in the tumor.[1]

The American Society of Clinical Oncology (ASCO) recommends confirming negative findings via tissue biopsy.8 For these reasons, liquid biopsy is currently a supplement to tissue biopsy.[2]

Abbreviations

a Epidermal growth factor receptor
b Rat sarcoma
c Human epidermal growth factor receptor 2
d Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

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