

Liquid and Tissue Biopsies: The Twin Pillars of Precision Diagnostics

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Abstract: Cancer is a serious global health issue, resulting in millions of fatalities annually. Timely diagnosis is essential for enhancing patient outcomes, guiding treatment alternatives, and reducing disease burden, resulting in increased survival rates and improved quality of life. Precision oncology recognises that tumors, even among identical cancer diagnoses, include unique genetic compositions that might influence their behaviour and therapeutic response. Precision oncology is undergoing a paradigm shift by integrating liquid and tissue biopsies as complementary diagnostic tools. Tissue biopsy is a gold standard for histopathological and genetic characterisation of cancer, offering direct insight into tumor architecture and cellular diversity. The invasiveness and sampling constraints of this method may impede disease monitoring and obstruct the assessment of tumor evolution. Utilising high-throughput sequencing, multi-omics, and sophisticated analytical platforms, medical professionals and researchers may get real-time, non-invasive, and thorough insights into tumor biology. Liquid biopsy, as a developing approach, allows minimally invasive, real-time cancer profiling by the detection of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and extracellular vesicles in biological fluids such as blood, saliva, and urine. This technique improves tissue biopsy by offering thorough monitoring, minimising patient pain, following tumor progression, identifying minimal residual disease, and evaluating therapy efficacy and resistance. Tissue biopsy is required for initial diagnosis and therapy selection, while liquid biopsy is used for ongoing surveillance and early identification of treatment failure or recurrence. The integration of these "twin pillars" is expected to revolutionise cancer diagnosis, enhancing precision medicine via patient-centered strategies and perhaps producing improved outcomes.

Keywords: Cancer, Precision diagnosis, Liquid biopsy, Tissue biopsy, Circulating tumor DNA, High-throughput sequencing.

1. Introduction

Modern medical precision diagnostics use tissue and liquid samples, the "twin pillars," for thorough histopathological and molecular analysis of cancer architecture, cellular heterogeneity, and mutational characteristics. Tissue biopsies are invasive, have dangers, and may not always be practical, especially in instances of inaccessible tumours or patients having medical conditions that prevent repeated procedures. The liquid biopsy method uses blood and body fluids to detect tumor-derived biomarkers, including circulating tumour DNA (ctDNA), circulating tumour cells (CTCs), and exosomes, due to certain constraints.

This finding has revolutionised cancer diagnostics by enabling real-time monitoring of tumour genetics, molecular evolution and treatment efficacy, hence reducing risk, optimising repeat sampling, and evaluating tumour heterogeneity [1-3]. Tissue and liquid biopsies enhance precision medicine by enabling doctors to diagnose, characterise, monitor disease development, and adjust therapy for intricate illnesses like cancer [4].

2. Tissue Biopsy

A tissue biopsy is a medical procedure that uses a microscope to examine a small tissue sample for signs of disease, including cancer.

2.1 Types and Techniques of Tissue Biopsy

2.1.1 Needle Biopsies

Needle biopsies are minimally invasive techniques used for cancer detection, including procedures such as Fine Needle Aspiration (FNA), Core Needle Biopsy (CNB), Vacuum-Assisted Biopsy, and Image-Guided Biopsy.

2.1.1.1 Fine Needle Aspiration

Fine needle aspiration (FNA) is a non-invasive, rapid procedure that uses a hollow needle to obtain a small sample of cells or fluid from a lesion, efficient for superficial tumour evaluation but insufficient for thorough histological analysis [5-6].

2.1.1.2 Core Needle Biopsy

CNB is a technique that uses a larger needle to obtain a small tissue core, providing a greater quantity of material for thorough histological examination and enabling more definitive diagnoses about cancer type, grade, and molecular characteristics, however with heightened invasiveness and a reduced risk of complications [7-8].

2.1.1.3 Vacuum-Assisted Biopsy

VAB is a method in which a probe linked to a vacuum apparatus is introduced into a lesion, facilitating tissue aspiration and removal using a revolving cutting tool, especially advantageous for microcalcifications or minor abnormalities, such as in breast biopsies. It generates larger and more samples with a single insertion, improving diagnostic yield and reducing missed lesions. Nevertheless, it requires specific equipment and training [9-10].

2.1.1.4 Image-Guided Biopsy

Ultrasound, CT scan, and MRI are imaging techniques used to precisely detect lesions and assist with needle placement. This method is crucial for deep, restricted, or important areas where blind sampling presents safety hazards. It improves diagnostic accuracy, minimises problems, and ensures the needle precisely hits the lesion. However, it may need sophisticated equipment and collaboration with radiologists [11].

2.2 Surgical Biopsies

It includes the excision of lumps or questionable regions (excisional biopsy), the sampling of bigger lesions when total excision is unfeasible (incisional biopsy), and the extraction of tissue via larger incisions, sometimes performed under general anaesthesia (open biopsy) [12].

2.3 Skin Biopsies

It includes several procedures, such as shave biopsy, punch biopsy, incisional biopsy, and excisional biopsy.

2.3.1 Shave Biopsy

A scalpel or similar instrument is used to remove a small, superficial layer of skin, usually from elevated lesions. It works well for identifying superficial lesions like benign growths, actinic keratosis, squamous cell carcinoma, and basal cell carcinoma. Although it is rapid and leaves little scarring, it is not the best option for aggressive conditions like melanoma [13-14].

2.3.2 Punch Biopsy

Using a circular blade device with a diameter of 2 to 8 mm, a cylindrical sample of the epidermis, dermis, and superficial subcutaneous fat is taken. This approach effectively detects dermatological conditions such as rashes, infections, and inflammation; nevertheless, it may overlook pathology if the lesion exceeds the punch diameter [15].

2.3.3 Incisional Biopsy

A scalpel is used to excise a wedge or slice of a significant lesion, including adjacent healthy skin, for diagnostic purposes, enabling representative tissue collection without necessitating the removal of the whole lesion. If malignant, it may need stitches and remain untreated [16].

2.3.4 Excisional Biopsy

A skin lesion is excised using a scalpel, often preserving a margin of healthy tissue, after which the wound is sutured closed. It works well for nodules when total excision is desired, tiny tumours, and suspected neoplasms. Benefits include study of tumour architecture and histological analysis. More invasiveness, a higher chance of scarring, and a lengthier recovery period are some drawbacks [17].

Under local anaesthesia, procedures are carried out, and samples are submitted to a lab for microscopic analysis in order to confirm the diagnosis and direct future care.

2.4 Other techniques

A bone marrow biopsy is the needle excision of bone marrow tissue for diagnosing haematological cancers. An endoscopic biopsy utilises an endoscope to access inside organs and visually guide tissue sampling. Curettage biopsy excises tissue or cells from the surfaces of superficial lesions. Imprint cytology examines exfoliated cells [18-19]. Each approach is selected according to tumour size, location, depth, and the patient's state to maximise diagnostic output while minimising invasiveness and danger [20].

2.5 Advantages of Tissue Biopsy

- A tissue biopsy is a definitive method for establishing the presence of malignancy, providing essential histological data vital for precise diagnosis.
- Comprehensive Tumour Analysis involves the assessment of tumour architecture, cellular morphology, and molecular/genetic profiling to determine cancer type, grade, and specific mutations for targeted therapy [20].
- The acquired molecular and genetic data facilitate personalised treatment choices, assessing the appropriateness for targeted medicines and immunotherapies [3].
- Tissue samples exhibit greater stability and comprehensiveness compared to liquid biopsy samples, which may fluctuate in both amount and quality of tumor-derived material [3].
- Histopathological examination offers spatial information about cancer localisation, invasion depth, and microenvironment, which liquid samples cannot provide.
- Tissue biopsies facilitate the identification of tumour heterogeneity, assist in treatment planning, and enable ancillary tests such as immunohistochemistry and FISH, despite their restricted sample reach [20].

2.6 Limitations of Tissue Biopsy

- A tissue biopsy is an intrusive technique that may result in discomfort, haemorrhage, infection, and other consequences, especially when aimed at tumours located in sensitive or challenging regions [2].
- Some cancers are either inaccessible or provide considerable hazards for biopsy due to their location or the patient's condition, thereby limiting the use of tissue biopsy [2, 21].
- Tissue biopsy samples a limited segment of a tumour, hence excluding genetic diversity and spatial/temporal heterogeneity [2].
- It lacks understanding of tumour evolution or treatment-related mutations [2-3].
- Biopsies are resource-intensive and time-consuming procedures that need specialised expertise and sample analysis, potentially delaying diagnosis and escalating healthcare expenses, making them unfeasible for regular sampling.

- Biopsy specimens may lack enough tissue for thorough genetic or molecular analysis, thus affecting treatment strategies [2].

The constraints of conventional diagnostic techniques highlight the need for supplementary procedures, such as liquid biopsy, that provide a less invasive, repeatable, and thorough tumour profiling [2-3].

3. Liquid Biopsy

Liquid biopsy, as an emerging method, allows minimally invasive, real-time cancer profiling by the detection of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and extracellular vesicles in biological fluids such as urine, blood, and saliva.

3.1 Types of Biomarkers

Various types of biomarkers are described below:

3.1.1 Circulating Tumour DNA (ctDNA)

It is a kind of tumor-derived DNA that enables the detection of mutations, copy number variations, and other molecular abnormalities in tumours [22-23].

3.1.2 Circulating Tumour Cells (CTCs)

These are neoplastic cells which enter the bloodstream, providing information on tumour characteristics, metastatic potential, and gene expression profiles [22-23].

3.1.3 Extracellular Vesicles (EVs)

These are the small membrane-bound vesicles secreted by neoplastic cells, including DNA, RNA, lipids, and proteins, that facilitate intercellular communication and convey molecular signals of the cancer microenvironment [23-24].

3.1.4 Cell-free RNA (cfRNA) and microRNAs (miRNAs)

They are circulating nucleic acids that regulate gene expression and are linked to cancer and metastasis [22, 24-25].

Biomarkers identifiable in biological fluids such as urine, blood, and saliva are essential for non-invasive cancer diagnosis and monitoring via liquid biopsy methods, allowing real-time, dynamic tumour profiling.

3.2 Advantages of Liquid Biopsy

- Liquid biopsy is a non-invasive technique which needs just a blood sample, hence minimising patient risk and pain compared to conventional tissue biopsies [4, 22].
- Real-time monitoring enables the continuous evaluation of cancer genetics, treatment effectiveness, and the detection of emerging resistance mutations by repeated sampling [4, 26].
- The method utilises circulating biomarkers to get molecular data from several tumour sites and metastases, so overcoming the spatial limitations of tissue biopsy [22-23].
- Liquid biopsy findings provide quick turnaround and early diagnosis, allowing for rapid clinical choices and the identification of tumour DNA fragments, even in initial stages or mild sickness contexts [4, 22].
- Liquid biopsy is a more thorough and less intrusive option as compared to tissue biopsy, delivering supplementary molecular insights when a tissue sample is difficult or hazardous [26].

Liquid biopsy, using advanced genetic technology, has considerable promise in tailored cancer diagnosis and therapy, while it may have sensitivity limitations and cannot entirely replace tissue biopsy.

3.2. Limitations of Liquid Biopsy

- The sensitivity of early cancer detection may be diminished by the inadequate release of tumor-derived substances into the circulation by tiny or early-stage tumours [26-28].
- Variability in tumour shedding, particularly in instances of insufficient vascularization or those situated behind the blood-brain barrier, may lead to the generation of low biomarker levels, thus obstructing detection [22, 27].
- The quality and management of samples are crucial for ctDNA and other biomarkers due to their short half-lives and restricted availability, necessitating precise collection, stabilisation, and processing to prevent contamination and degradation [26, 28].
- Liquid biopsy lacks comprehensive tissue architecture and may lead to false positives or misinterpretations due to non-tumor DNA alterations, like clonal hematopoiesis of indeterminate potential (CHIP) [22, 28].
- The field currently lacks comprehensive, multi-center validated methodologies and has a dearth of FDA-approved assays, due to inadequate standardisation and validation [22, 26, 28].
- Liquid biopsy testing, despite its sophisticated technology, may have limitations in accessibility and expense, particularly in resource-limited settings, and may not fully replace tissue biopsy for the first diagnosis [2, 22, 28].

4. Complementary Roles of Tissue and Liquid Biopsies

Liquid and tissue biopsies together improve cancer diagnosis and treatment by offering extensive histological, genetic, and structural information for initial diagnosis, tumour classification, and personalised therapeutic approaches [1, 29] as depicted in **Table 1**. Liquid biopsy offers real-time monitoring and dynamic assessment of therapy response, illness progression, and resistance mutations, unlike the intrusive nature of tissue biopsies. Tissue and liquid biopsies provide comprehensive insights into cancer, including specific data and biological context. Liquid biopsy identifies circulating biomarkers from several tumour sites, providing an alternative to tissue acquisition when it is difficult or hazardous [4, 22, 30]. The integration of tissue and liquid biopsies enhances diagnostic accuracy, enables adaptable treatment strategies, and permits tailored care, particularly in precision oncology, providing doctors with a comprehensive understanding of patient malignancy [1, 4, 22, 26].

Table 1: Differences between tissue and liquid biopsy.

Aspect	Tissue biopsy	Liquid biopsy	References
Definition	The invasive process of collecting tumour tissue for biological study	Non-invasive collection of fluids containing tumor-derived material	[1, 4, 22]
Sample Type	Solid or Metastatic Tumour Tissue	Blood, saliva, urine, and other body fluids	[24]
Diagnostic Use	Histology is the definitive standard for the first cancer diagnosis.	Supplementary for molecular characterization and early identification	[22, 26]
Molecular Analysis	Facilitates comprehensive histopathological analysis, immunohistochemical evaluation, and next-generation sequencing.	Identifies circulating tumour cells (CTCs), circulating tumour DNA (ctDNA), and extracellular vesicles (EVs).	[22-23]
Sample Accessibility	Restricted in challenging environments or vulnerable patients	Access to systemic tumour biomarkers is advantageous when tissue is unavailable.	[21]
Real-Time Monitoring	Restricted repeatability owing to invasiveness	Facilitates continuous assessment of therapy efficacy and resistance	[4, 26]
Invasiveness	Invasive; possible consequences (haemorrhage, infection)	Minimally invasive; little risk	[2, 22]
Clinical Applications	Diagnosis, prognosis, and treatment planning	Monitoring of treatment, early identification, and minimal residual illness	[1, 4, 22, 26]

5. Clinical Applications

Tissue and liquid biopsies have significantly enhanced cancer clinical care by offering insights into tumour biology, facilitating diagnosis, prognosis, therapy selection, and disease monitoring. A tissue biopsy is the conclusive method for the first cancer diagnosis, providing an extensive histological evaluation to determine cancer type, grade, stage, and tumour architecture and microenvironment. Tissue samples permit extensive molecular and genetic analyses, including immunohistochemistry and next-generation sequencing, which aid in the selection of targeted and immunotherapies. Tissue biopsy is crucial for confirming malignancy, diagnosing disease, and providing necessary material for testing; yet, its invasiveness, possible complications, and accessibility limitations may hinder its use in difficult cases [2, 31].

Liquid biopsy, a less invasive technique, examines tumor-derived substances in blood or bodily fluids, supplementing tissue biopsy and facilitating real-time assessment of therapy efficacy and tumour progression. It is a method used by doctors to detect new genetic mutations and minimal residual disease, enabling timely adjustments to therapies in response to resistance or recurrence. Dynamic profiling is beneficial in metastatic cancers and high-risk groups, especially when many tissue samples are impractical. Liquid biopsy is being used for early diagnosis, prognosis, screening, and the detection of actionable mutations when tissue samples are insufficient or unattainable [4, 22, 26]. The integration of tissue and liquid biopsy techniques improves diagnostic accuracy by providing essential information for diagnosis and customised treatment options, enabling continuous tumour monitoring and prompt therapeutic modifications with little patient risk. The comprehensive approach in precision oncology enhances cancer patient outcomes and quality of life via customised and flexible therapy [1, 24, 26].

6. Current Challenges And Future Perspectives

Technical, clinical, and operational complexity make it difficult to integrate tissue and liquid biopsy in cancer therapy. Uncertainty may arise from variations in mutation identification, and clinical interpretation and decision-making may become more difficult due to tumour heterogeneity and temporal changes that may provide inconsistent outcomes [32]. Consolidating results may be difficult since tissue biopsies cannot capture systemic tumour heterogeneity, and liquid biopsies might not reliably identify low-frequency mutations in tissue. In tissue and liquid biopsy tests, the lack of uniform standards across various methodologies, assay sensitivities, and analytical procedures hinders variability and interoperability [32-34]. It is difficult and poorly understood to determine whether a tissue biopsy is preferable to a liquid biopsy over the course of a disease and its treatment. The integration and examination of genetic, histological, and molecular data from biopsies requires advanced bioinformatics and multidisciplinary teams, which are often constrained in many healthcare settings. Also, the ideal time for tissue versus liquid biopsy during illness development and therapy remains a difficult and inadequately characterised matter [32-33, 35].

The budgetary and reimbursement obstacles related to both biopsy types, together with the lack of clinical recommendations and data gaps, may impede the widespread execution of this innovative treatment, regardless of its promising results. Liquid biopsy minimises invasiveness; yet, tissue biopsy remains challenging for some persons, and access to advanced equipment may be limited in resource-constrained settings [36-37]. Addressing problems in precision oncology necessitates collaborative research, standardised methods, clinical validation studies, and regulatory frameworks to optimise the use of tissue and liquid biopsies. Technological advancements and understanding of tumour biology are advancing the future of tissue and liquid biopsies in oncology. These two diagnostic tools are expected to become integral components of a precision oncology platform, providing comprehensive, real-time, and personalised cancer management. High-throughput sequencing, single-cell analysis, and multi-omics techniques will enhance data, enabling early cancer detection and the identification of resistance mutations. Advanced imaging guidance and molecular profiling technologies will improve tissue biopsy operations [32, 38]. The future of tissue and liquid biopsies will include the seamless integration of data via bioinformatics platforms and artificial intelligence, hence enhancing the interpretation of cancer heterogeneity and evolution. Liquid biopsy will expand beyond oncology to include early cancer screening, risk stratification, and real-time response evaluation. Novel, cost-effective, and minimally invasive biopsy methods will be developed, reducing inequities in cancer diagnosis and treatment. This partnership will improve early detection, treatment efficacy, disease monitoring, and patient survival rates. The future of tissue and liquid biopsies is dependent on their combined use, improved

by technical progress, multi-modal data integration, and clinical application, hence boosting early diagnosis, treatment effectiveness, disease monitoring, and patient survival [42-49].

7. Conclusion

The integration of tissue and liquid biopsy in precision oncology signifies a substantial breakthrough, providing a comprehensive framework for cancer diagnosis, monitoring, and personalised treatment. Tissue biopsy is the principal method for early cancer diagnosis, providing critical information for targeted treatments and immunotherapies. However, its invasive traits, sample limitations, and challenges with repeated application hinder its ability to correctly represent the dynamic nature of tumours. Liquid biopsy is a minimally invasive technique which enables real-time, dynamic characterization of tumour genetics and molecular changes by analysing circulating tumour cells, DNA, and extracellular vesicles in bodily fluids. This approach enables the early identification of resistance mutations, minimal residual illness, and evaluation of therapy response, hence enhancing patient outcomes and broadening the accessibility of molecular diagnostics when tissue samples are inadequate or inaccessible. The integration of multi-modal data in clinical decision-making faces challenges in assay standardisation, preserving analytical sensitivity and specificity, interpreting varied results, and synthesising multi-modal data, with cost, technological accessibility, and comprehensive validation studies being critical factors. The use of tissue and liquid biopsies is set to revolutionise cancer therapy by providing a comprehensive insight into tumour biology. Advancements in sequencing, bioinformatics, and multi-omics integration will enhance their precision and prediction capacities. Collaborative efforts across clinical specialities, laboratory medicine, and regulatory frameworks are essential for the incorporation of novel methods into established clinical practice. This convergence illustrates the principles of precision medicine, improving prognosis, treatment efficacy, and quality of life for cancer patients.

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