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Circulating Tumor DNA for Customisation of Tumor Immunotherapy: Technology Advance and Clinical Evidence

Yanyanting Chen

Guiyang No.1 High School, Guiyang, China
chinsei76@live.com

Abstract. Circulating tumour DNA (ctDNA) in blood is now used in a less invasive way to guide personalised cancer therapy. Several blood tests can be conducted on ctDNA to determine whether there is a distant spread of cancer cells, discover microscopic cancer cells remaining after surgery, and observe how the immune system responds to immunotherapy in time; thus, repeated tissue biopsies and delayed CT scans are reduced. The previous way of diagnosis cannot rapidly identify gene mutations in lesions, and frequent ctDNA tests can promptly detect cross-regional and time-dependent genomic alterations to provide real-time molecular support for clinical decisions. This paper first sorts out updated performance and lingering defects of current ctDNA detection platforms, then analyzes real clinical data covering four major tumor types: breast malignancies, colorectal carcinoma, melanoma, non-small cell lung cancer (NSCLC). Multiple prospective cohort observations and pooled meta-analysis data show that ctDNA surveillance can divide patients into high- and low-risk groups for recurrence, detect molecular relapse months before any visible lesion enlargement on scans, and identify newly arising drug-resistant mutant clones ahead of imaging signals. All collected clinical evidence shows that ctDNA serves as a daily diagnostic aid to continuously optimise the entire implementation logic of personalised tumour immunotherapy.

Keywords: Circulating Tumor DNA, Tumor Immunotherapy, Non-small cell lung cancer

1. Introduction

Malignant tumours are still a serious problem for people around the world and have not been fully controlled. Conventional chemo-radiotherapy has a relatively small anti-tumour effect and causes severe whole-body adverse reactions; targeted drugs are only effective for patients with matching mutant gene targets. Intratumour genetic heterogeneity and gradual subclone evolution are also reasons for drug resistance and reduced long-term efficacy of almost all mainstream anti-cancer drugs. The main defects of the present tumour diagnosis system are over-reliance on a single tissue sample and static X-rays/MRIs. A single tissue sample only obtains a small part of the lesion and may not represent all the gene mutations in the whole tumour. Radiological devices can only detect significant changes in lesion swelling long after molecular pathological alterations have occurred in the lesion; thus, the optimal time to modify medication plans is often missed.

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To address this diagnostic deficiency, ctDNA liquid biopsy has been developed to monitor the three main clinical scenarios at any time during cancer treatment. First, several blood samples are taken before and during treatment to evaluate the overall extent of systemic tumour load. Second, blood tests after curative surgery can detect small fragments of tumours to alert us to a possible recurrence long before physical discomfort or abnormal scan shadows occur. Thirdly, some blood tests can find new resistance-causing gene mutations that have developed during treatment and adjust the drug schedule. ctDNA has a relatively short half-life of only one to two hours in peripheral blood and is thus unstable. This function can show changes in tumour genes in real time and is very convenient for distinguishing between pseudoprogression and hyperprogression; otherwise, they may be mistaken for abnormal responses to immunotherapy. Long-term serial ctDNA records have also shown various immune-escape pathways, such as impaired antigen presentation induced by prolonged immune checkpoint inhibition [1-3].

This paper has a four-part organisation. It first analyzes technical upgrades and unresolved drawbacks of ctDNA serial testing systems, then sorts clinical trial outcomes of ctDNA-assisted immunotherapy across four mainstream tumor categories, followed by consolidated research conclusions and feasible directions for follow-up translational medical research. The values of ctDNA tests at baseline, early treatment, mid-cycle and after surgery are examined in the text to propose reasonable adjustments to personalised immunotherapy plans.

2. Current technical progress and unresolved barriers to ctDNA serial monitoring

Pancreatic ductal adenocarcinoma is a serious type of solid tumour in the world with a poor long-term prognosis. There are considerable spatial genetic variations in pancreatic lesions; thus, a single tissue sample cannot cover the entire tumour's genome, and urgently needed is a blood-derived molecular marker. Kirchweger's group has begun a forward-looking, long-term blood collection project for pancreatic cancer patients. The group employed high-precision digital droplet PCR to track alterations in tumour genes at various times after treatment at all stages [1]. Statistical analysis showed that pre-operative ctDNA positive signals closely correlated with tumour size as measured by scans and were independently associated with a poor prognosis. Patients with detectable ctDNA fragments in their blood had a shorter progression-free survival (PFS) and overall survival (OS), and this predictive effect was the same for patients at different stages of their initial tumours. Real clinical data show that ctDNA can be used to assess the prognosis of cancer non-invasively, and thus adjust systemic drug combinations before imaging studies.

Radical surgery extends the survival of patients with early- and intermediate-stage NSCLC, but post-operative recurrence and distant metastasis are still the main causes of death. Clinically, high-sensitivity tests are needed urgently to detect minimal residual disease (MRD). Wang's research group has built a new detection framework that integrates surgical tissue clone data with multiple ctDNA samples for operable NSCLC patients to identify post-operative residual molecular lesions [2]. Incorporate tissue clonal genetic data to enhance the detection sensitivity and positive rate of MRD liquid biopsy. Patients with detectable ctDNA after surgery had a significantly higher risk of recurrence, and blood tests could predict metastasis several months before a change in X-rays.

Tissue clone-assisted ctDNA surveillance tools can accurately assess the risk of post-operative relapse in high-risk patients and guide personalised adjuvant therapy. Whether to give adjuvant chemotherapy after surgery for stage II colon cancer has been debated in the clinic for a long time. The standard pathological grading indicators cannot distinguish accurately between patients who genuinely require additional systemic therapy, and as a result, widespread over-medication and harm from toxic side effects occur in routine clinical practice. Tie's team has conducted the first-ever

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prospective clinical trial to determine whether all post-operative treatment decisions can be based solely on ctDNA test results. Later, researchers added the long-term survival data of these groups to the previous studies [3]. The ctDNA risk classification strategy reduced the proportion of patients receiving adjuvant chemotherapy from 28% to 15% and did not reduce the overall recurrence-free survival rate. Among ctDNA-positive patients receiving subsequent systemic therapy, those who achieved complete plasma ctDNA clearance after treatment had a 5-year recurrence-free survival rate of nearly 100%. Otherwise, none of the participants with continuous ctDNA signals achieved long-term disease control. The above prospective trial has provided strong real-world evidence to prevent unnecessary toxic chemotherapy for low-risk patients through ctDNA risk stratification and promptly offer intensive treatment for individuals with residual tumour cells in their bodies.

The three representative cohort trials have provided a full-coverage application framework for ctDNA in all stages of tumour treatment. Researchers in this field have found that ctDNA detected before treatment is independently associated with a poor prognosis for all patients at different stages of initial tumours; post-operative blood ct signals show a higher risk of recurrence and an earlier warning time than all imaging equipment; and prospective trial data have indicated that ctDNA-based risk grouping can reduce unnecessary anti-cancer drugs without reducing treatment effectiveness. Despite the above good results, many practical problems still prevent large-scale clinical application. The testing platforms have not standardised the definition of a ctDNA-positive threshold. Sensitivity tests for tumour types that release a small amount of DNA in the blood vary greatly. No standard operating procedures have been released for dealing with non-diagnostic ctDNA results. Most tumour types have not yet had large-scale randomised controlled trials comparing ctDNA-guided treatment with conventional standard care. The above problems are the main research directions for ctDNA translational medicine and provide the foundation for the following discussion on immunotherapy matching.

3. Practical clinical application of ctDNA monitoring in support of tumor immunotherapy

As ctDNA testing technology has become more mature, more translational research groups have begun using blood ctDNA tracking in their daily work for immunotherapy. Immune checkpoint inhibitors and novel immunoconjugate drugs have presented new monitoring problems that the traditional evaluation tools cannot handle effectively. Anti-tumour therapeutic effects are often not apparent for a long time, abnormal scan manifestations such as pseudoprogression may conceal early efficacy, and tumour cells gradually develop various immune evasion mechanisms to induce drug resistance. Serial ctDNA blood tests can correct for the deficiencies of tissue biopsies and radiology, and consistent clinical data have been obtained for four well-known types of tumours. The following are representative trial data for breast carcinoma, colorectal cancer, melanoma and NSCLC, and it was found that ctDNA-guided immunotherapy had achieved the best clinical results.

3.1. Breast cancer

Breast tumours have many different molecular subgroups and respond to immune drugs in various ways. Given the serious illness, continuous ctDNA blood tests are now needed to guide personalised medical treatment. Three independent breast cancer-oriented research directions are presented here, without cross-tumor irrelevant clinical data. Leveraging ctDNA mutant profiles to stratify the baseline risk of patients with metastatic breast cancer; Using post-surgical MRD signals to guide pembrolizumab-augmented immunotherapy for high-risk early triple-negative breast cancer;

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Longitudinal ctDNA monitoring to detect new resistant subclones in advanced HER2-positive breast cancer (see Table 1).

A large number of independent clinical studies have verified the prognostic value of ctDNA in metastatic breast cancer, but before Dickinson's research group published their meta-analysis, there was no comprehensive pooled analysis of multi-center real-world data. Dickinson and others have collected clinical data from 4,264 metastatic breast cancer patients in 37 studies to determine if ctDNA mutations are associated with extended survival [4]. Aggregated data show that detectable ctDNA aberrations are consistently associated with poorer OS, PFS and DFS, and this correlation is independent of the research design, detection equipment, blood collection protocol or intrinsic breast

Table 1. Summary of core clinical trials focusing on ctDNA-guided immunotherapy

Tumor Category	Trial Design	Core ctDNA Application	Primary Research Outcomes	Ref.
Pancreatic Ductal Adenocarcinoma	Prospective cohort	Tumor load measurement & prognosis judgment	Pre-treatment ctDNA positivity acts as adverse marker, predicting poor PFS and OS independent of tumor stage	[1]
Resectable NSCLC	Prospective cohort	Postoperative MRD detection	Persistent post-op ctDNA predicts tumor relapse months ahead of routine radiology	[2]
Stage II Colon Cancer	Phase II prospective	Post-operative adjuvant therapy decision-making	ctDNA stratification cuts chemotherapy rate from 28% to 15% without compromising recurrence-free survival	[3]
Metastatic Breast Cancer	Systematic review & meta-analysis (4264 subjects)	Baseline risk grading	ctDNA mutations correlate with inferior OS, PFS, DFS across all breast subtypes	[4]
High-Risk Early Triple-Negative Breast Cancer	Phase II c-TRAK TN trial	MRD-driven supplementary immunotherapy	72% ctDNA-positive patients had occult metastasis; pembrolizumab fails to achieve sustained ctDNA clearance	[5]
RAS Wild-Type Metastatic Colorectal Cancer	Single-Arm Phase II CAVE trial	Patient screening & efficacy tracking	Low pre-rechallenge ctDNA predicts better outcomes; overall DCR = 65.6%	[6]
Refractory RAS Wild-Type Metastatic Colorectal Cancer	Randomized Phase II	Anti-EGFR rechallenge eligibility screening	ctDNA-confirmed RAS wild-type group gains maximum PFS benefit	[7]
RAS/BRAF Wild-Type Metastatic Colorectal Cancer	Phase II CHRONOS trial	Rechallenge enrollment threshold	Cohort ORR = 30%, DCR = 66%, median PFS = 4.1 months	[8]
Metastatic Melanoma	Prospective validation cohort	Early immunotherapy efficacy prediction	ctDNA drop within 2–4 weeks distinguishes pseudoprogression from true progression	[9]
Metastatic Melanoma	Prospective cohort	Baseline & on-treatment monitoring	ctDNA clearance after cycle one greatly prolongs OS and PFS	[10]
Advanced NSCLC	Adaptive Phase II	Dynamic immunotherapy adjustment	Early ctDNA decline predicts favorable long-term survival	[11]

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molecular subtype. The above large-scale pooled study provides strong support for adding ctDNA tests to the standard pre-treatment risk assessment of metastatic breast cancer patients. Early triple-negative breast cancer is highly invasive and frequently recurs after surgery; thus, before clinical metastasis, MRD signals need to be acquired for treatment guidance. Turner and others initiated the prospective phase II c-TRAK TN trial, administered serial ctDNA detection following standard adjuvant therapy to patients, and enrolled ctDNA-positive individuals in pembrolizumab immunotherapy [5]. In 12-month follow-up period, 27.3 per cent of all subjects had positive ctDNA results, and follow-up enhanced scans showed that 72 per cent of these patients had already developed occult distant metastases. Unfortunately, pembrolizumab treatment did not achieve sustained ctDNA negativity in any of the subjects of this trial. As the first prospective study to investigate ctDNA-triggered immunotherapy for triple-negative breast cancer, this work proposes adding ctDNA monitoring earlier in the treatment cycle to prevent the development of gross metastatic lesions. For advanced HER2-positive breast cancer, serial ctDNA tests can be used to monitor the development of drug-resistant mutant clones under combined targeted and chemo-immunotherapy regimens over time. Cohort studies of breast cancer have shown that a high baseline tumour DNA fraction and the presence of co-occurring oncogenic mutations are associated with a poor prognosis, and changes in ctDNA can predict treatment resistance long before radiological changes occur; thus, an early adjustment of the treatment plan can be made.

Based on all breast cancer research results, unified rules have been synthesized: ctDNA positivity, whether arising from metastatic sites or residual disease after surgery, is associated with a poor prognosis across all molecular subtypes of breast cancer and remains predictive under various research systems. However, results from the c-TRAK TN trial show that delayed ctDNA positivity often indicates metastasis has already occurred, and salvage PD-1 immunotherapy is thus less likely to clear circulating tumour cells. At present, high-level randomised controlled trial evidence is still lacking to standardise ctDNA surveillance in breast cancer clinical practice, and further prospective verification research is needed.

3.2. Colorectal cancer

Colorectal cancer (CRC) and, to a greater extent, metastatic colorectal cancer (mCRC) have an abnormal immune microenvironment compared with other malignant tumours. Most mCRC patients carry microsatellite-stable (MSS) gene status. For this group, single-agent immune checkpoint inhibitors create limited treatment effects, with objective response rates lower than 5% among unselected MSS mCRC crowds. Therefore, the first clinical aim of ctDNA in CRC immunotherapy is not to assess the effect of treatment directly, but to identify suitable patients for repeated anti-EGFR targeted therapy based on molecular features. RAS wild-type mCRC patients who have previously received cetuximab or panitumumab are now resistant to these drugs due to clonal mutations in the RAS gene detectable in ctDNA. Repeated blood tests can show that the resistance mutant subclones have disappeared due to molecular reversion. If such a reversion occurs, anti-EGFR drugs may be employed again to restore the drug sensitivity of the tumour (see Table 1).

Three recent phase II clinical trials have confirmed this ctDNA-guided repeated-treatment model and produced consistent clinical data. Martinelli and his team designed a single-arm phase II trial named the CAVE trial. Eligible participants were RAS wild-type mCRC patients who had shown progression after previous anti-EGFR monotherapy. Study subjects received cetuximab rechallenge in combination with the anti-PD-L1 agent avelumab [6]. The first clinical endpoint was achieved in the study, and the median OS was 11.6 months, higher than the historical data for this treatment-resistant group. People with a low pre-rechallenge ctDNA level had a significantly longer life than

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those who showed significant residual molecular-disease signals. Data show that ctDNA has two applications for patient selection and dynamic treatment-benefit assessment. The combined anti-tumour effect of anti-EGFR and PD-L1-directed therapy also suggests immune-mediated tumour re-sensitisation, thus extending the theoretical basis for ctDNA-guided rechallenge beyond conventional cytotoxic retreatment. Napolitano's research group performed a randomised phase-II trial. Refractory RAS wild-type mCRC participants were separated into two study arms: panitumumab plus trifluridine-tipiracil versus trifluridine-tipiracil monotherapy [7]. Serial ctDNA assays were performed to determine if a rechallenge was feasible and to monitor for clonal evolution after treatment. Combination therapy for the arm extended PFS, and the most substantial survival advantage was observed in patients with RAS wild-type status confirmed by ctDNA analysis. This work is the first randomised clinical evidence to support ctDNA-screened anti-EGFR rechallenge and validates liquid biopsy as a dynamic patient-matching tool for personalised medicine. Sartore-Bianchi's group has carried out a second round of the CHRONOS study to collect more clinical data on this kind of treatment. Study enrolment was limited to RAS- and BRAF-wild-type mCRC patients meeting the criteria for ctDNA screening, that is, no detectable acquired resistance-related mutations, and subsequently received panitumumab rechallenge therapy [8]. The chosen group of molecules had an ORR of 30%, a DCR of 63%. The first innovation of the CHRONOS trial is that ctDNA results are used as a strict inclusion criterion rather than just an auxiliary prognostic factor, and thus the model for regimen-sequence-planning in mCRC treatment has been fundamentally altered.

Together, the three trials have validated the reliability of ctDNA-supported anti-EGFR rechallenge in RAS-wildtype mCRC patients. ctDNA-measured RAS mutation status can accurately identify individuals who are suitable for repeated targeted therapy, and repeated invasive tissue biopsies for resistance gene analysis may be avoided. Among the studies available now, the CHRONOS trial has provided more extensive clinical verification. Nevertheless, some problems have not been solved to date. Consensus standards for ctDNA sampling time points and testing frequency in rechallenge screening have not been set; measurement cut-offs differ among assay platforms, and the long-term clinical benefits of rechallenge therapy are unknown. Larger randomised trials that stratify participants by ctDNA are required to expand the evidence base and provide support for formal regulatory approval of this management method.

3.3. Melanoma

Melanoma is one of the first solid tumours for which researchers have found a connection between serial ctDNA alterations and immunotherapy response. Thus, it is closely related to the abnormal cells of melanoma. Many genes in melanoma cells are damaged by UV radiation, resulting in a relatively high tumour mutational burden (TMB) and numerous neoantigens. As a result, melanoma is generally highly immunogenic and responds well to immune checkpoint blockade. Strong immunogenicity is still a diagnostic problem for clinicians. Pseudoprogression often occurs in the early days after treatment; therefore, although the lesion appears larger on the scan, there has been no actual increase in tumour size. The two are not distinguishable by the same standard X-ray examination. Otherwise, ctDNA quantifies the tumour burden without considering inflammatory responses, and thus liquid biopsy can be used for monitoring melanoma immunotherapy. Clinical teams frequently face the diagnostic problem of pseudoprogression when reviewing early treatment CT scans of metastatic melanoma patients on anti-PD-1 therapy (see Table 1).

Given the above clinical conditions, Herbreteau's research group conducted a prospective verification study. Early dynamic changes in ctDNA levels have been studied to determine whether

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they predict a response to immunotherapy for metastatic melanoma [9]. Collect peripheral blood samples at baseline and following treatment. Results show that ctDNA declines as early as two to four weeks after starting medication, predicts sustained radiological response and extended OS, and molecular signals appear weeks before scan improvement. ctDNA data can provide objective molecular evidence of pseudoprogression in patients to prevent the early termination of effective immunotherapy. Lee and his colleagues were the first to study the prognostic potential of ctDNA in melanoma immunotherapy prospectively [10]. Baseline ctDNA concentration and ctDNA mutation status after one pembrolizumab cycle can predict ORR and long-term survival reliably. Patients with baseline ctDNA positivity who achieved rapid ctDNA clearance had a significantly longer PFS and OS than those with persistently elevated ctDNA. High ctDNA after treatment may indicate that the patient will not respond to conventional imaging. The proposed three-stage ctDNA monitoring framework for melanoma immunotherapy is outlined as follows. At baseline, quantitative assessment of total ctDNA tumor burden helps identify high-risk patients who may benefit from more frequent follow-up or combination immunotherapy. During the early treatment phase, typically at 2–4 weeks, longitudinal ctDNA trends serve as an early indicator of therapeutic response and can help distinguish pseudoprogression from true disease progression. Over the full observation cycle, a rising ctDNA level signals impending therapeutic failure, often preceding clinical deterioration and enabling timely regimen adjustments. Importantly, ctDNA monitoring is not a one-time assessment but a continuous process that allows dynamic refinement of treatment strategies throughout the patient's clinical course.

3.4. Non-small cell lung cancer

NSCLC is a relatively complicated molecular-diagnostic system. Several oncogenic driver mutations are present, including EGFR, ALK, ROS1, KRAS and MET; they each have different responses to immunotherapy. PD-L1 expression is a first-line predictive marker for checkpoint inhibitor therapy; however, it has deficiencies, such as inter-lesion heterogeneity within the same patient and dynamic changes during treatment. A single-tissue biopsy may not show all the genomic changes in a tumour, so serial ctDNA tests are often performed at the same time. Multiple blood ctDNA tests can track changes in NSCLC genes and cover the spatial and temporal gaps of fixed-tissue sampling. Anagnostou's research group conducted an adaptive phase-II clinical trial. Serial ctDNA samples were taken at predetermined times to monitor changes in molecular signals following pembrolizumab monotherapy for advanced NSCLC [11]. An early drop in ctDNA correlated with extended PFS and OS, and molecular responses could be observed after just one or two cycles of treatment, long before radiographic changes. This adaptive trial used real-time ctDNA fluctuations to adjust the treatment strength, and patients with continuously high ctDNA were identified as possible non-responders early on for regimen modification before clinical deterioration. The trial shows that ctDNA monitoring of immunotherapy for NSCLC is a feasible forward-looking assessment system, not a retrospective correlation study; it reduces ineffective exposure to immunotherapy for non-responders and provides suitable treatment for molecular responders (see Table 1).

4. Conclusions

This article systematically outlines the evolution of ctDNA liquid biopsy, from laboratory detection techniques to its emerging role in guiding clinical decisions for personalised immunotherapy. Unified findings derived from multicenter trials across breast, colorectal, melanoma, and non-small

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cell lung cancers support three primary clinical applications. Baseline ctDNA positivity stands as an independent adverse prognostic marker, offering early survival information beyond conventional imaging. Post-intervention ctDNA signals provide molecular evidence for adjusting adjuvant therapy intensity, helping to spare low-risk patients from unnecessary toxicity while enabling timely escalation for those with detectable minimal residual disease. Early-cycle dynamic monitoring, meanwhile, captures rapid ctDNA changes that reflect immunotherapy efficacy and can identify pseudoprogression, a phenomenon often missed by radiographic assessment. Together, these levels illustrate a stepwise framework for integrating ctDNA into routine oncological practice.

Although there are now some positive clinical data, some problems still need to be solved before ctDNA monitoring can be added to the standard immunotherapy protocol. First, there are no unified cross-platform testing standards (cut-off values, report rules, sample pre-processing protocols). Second, variable tumor DNA shedding levels across disease types prevent universal threshold application. Third, most cancers have not yet had large-scale randomised controlled trials comparing ctDNA-directed care and standard therapy to provide level-one clinical evidence for guideline recommendations. In the future, translational research will focus on multi-marker combined liquid biopsy panels that integrate ctDNA, circulating tumour cells, cell-free RNA and exosome markers to enhance detection sensitivity. With lower sequencing costs and a shorter testing cycle, ctDNA liquid biopsy will be added to the standard of care for immunotherapy, and population-level empirical treatment will be replaced by personalised molecular precision therapy.

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