International Journal of Clinical Case Reports, 2026, Vol.16, No.1, 1-10
http://medscipublisher.com/index.php/ijccr

Research Article Open Access

Early Clinical Applications, Pitfalls, and Imaging Integration of ctDNA-MRD in Early-Stage Solid Tumors

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International Journal of Clinical Case Reports 2026, Vol.16, No.1 doi: 10.5376/ijccr.2026.16.0001
Received: 16Nov., 2025
Accepted: 21 Dec., 2026
Published: 03 Jan., 2026

Preferred citation for this article:
Xu H., 2026, Early clinical applications, pitfalls, and imaging integration of ctDNA-MRD in early-stage solid tumors, International Journal of Clinical Case Reports, 16(1): 1-10 (doi: 10.5376/ijccr.2026.16.0001)

Abstract This study explores the latest advancements in circulating tumor DNA (ctDNA) testing and discusses the clinical significance of ctDNA-based minimal residual disease (ctDNA-MRD). As a liquid biopsy marker, ctDNA-MRD can capture the signals of trace residual diseases at the molecular level and is gradually being used to assess the risk of recurrence and guide follow-up management. Numerous studies have shown that patients with positive ctDNA test results after treatment are more likely to experience recurrence and have poorer survival outcomes. In many cases, the changes in ctDNA prece de imaging findings, providing doctors with earlier reference for adjusting treatment plans and follow-up strategies. In practical applications, ctDNA-MRD also has certain limitations. Factors such as individual biological differences, low ctDNA release levels, clonal hematopoiesis interference, and differences in detection platforms can all affect the accuracy of the results, potentially leading to false negatives or false positives. If one relies too heavily on a single test result, it may result in insufficient or excessive treatment. ctDNA is suitable for dynamic monitoring, while imaging is still indispensable for locating lesions. The combined application of the two is considered a more reliable approach. With further clinical validation, ctDNA-MRD is expected to gradually evolve fro m a predictive indicator to a more practically meaningful decision support tool.

Keywords Circulating tumor DNA; Minimal residual disease; Early-stage solid tumors; Molecular relapse; Imaging integration

1 Introduction

In the treatment of early-stage solid tumors, determining whether the disease has been completely cured has always been a challenge. Even after surgery or systemic treatment, there may still be residual malignant cells at the molecular level in the body, which is what we commonly refer to as minimal residual disease (MRD). These lesions are difficult to detect clinically, but they may eventually lead to cancer recurrence or metastasis (Pantel and Alix-Panabières, 2024). Currently, the recurrence rate of early-stage solid tumors is still not low, which indicates that traditional imaging examinations and serum markers are not sensitive enough in monitoring molecular-level residual lesions.

Over the years, high-throughput sequencing and error correction technologies have become increasingly mature, and the sensitivity of circulating tumor DNA (ctDNA) detection has also significantly improved. Therefore, micro-residual disease assessment based on ctDNA (ctDNA-MRD) has become an important alternative indicator for evaluating molecular residual disease (Semenkovich et al., 2023; Quinn et al., 2025). Many prospective studies and systematic reviews have confirmed that if ctDNA remains positive after radical treatment, the risk of recurrence and death for patients will significantly increase, and this positive signal often appears earlier than imaging abnormalities or clinical symptoms. In various solid tumors, ctDNA signals can predict the risk of recurrence 4 to 12 months in advance, and its prognostic value is very stable (Zhu et al., 2023; Zheng et al., 2024).

However, there are still many challenges to be addressed in the practical clinical application of ctDNA-MRD. For instance, there are differences in results among different detection platforms, and the criteria for positive determination are not uniform. Moreover, there is currently no mature framework that can effectively integrate it with imaging, clinical pathological indicators (Boukouris et al., 2025). Imaging is crucial for lesion localization, but its sensitivity in detecting minor lesions is limited; while ctDNA can better reflect the overall tumor burden and clonal evolution. The complementarity of their time and information aspects can improve the accuracy of