Exploration of Digestive Diseases

Open Exploration

Open Access Perspective

Clinical applications of circulating tumor DNA (ctDNA) as biomarker in gastric cancer

Sunil Vitthalrao Jagtap[1*], Shubham S. Jagtap[2], Mohini S. Patil[1], Prayosha S. Thakkar[1]

[1]Department of Pathology, Krishna Vishwa Vidyapeeth "Deemed To Be University", Krishna Institute of Medical Sciences, Karad 415110, Maharashtra, India

[2]Department of Medicine, Krishna Vishwa Vidyapeeth "Deemed To Be University", Krishna Institute of Medical Sciences, Karad 415110, Maharashtra, India

***Correspondence:** Sunil Vitthalrao Jagtap, Department of Pathology, Krishna Vishwa Vidyapeeth "Deemed To Be University", Krishna Institute of Medical Sciences, Karad 415110, Maharashtra, India. drsvjagtap@gmail.com

Academic Editor: Jose C. Fernandez-Checa, Institute of Biomedical Research of Barcelona (IIBB), CSIC, Spain

Received: April 21, 2026 **Accepted:** June 16, 2026 **Published:** August 18, 2026

Cite this article: Jagtap SV, Jagtap SS, Patil MS, Thakkar PS. Clinical applications of circulating tumor DNA (ctDNA) as biomarker in gastric cancer. Explor Dig Dis. 2026;5:1005132. https://doi.org/10.37349/edd.2026.1005132

Abstract

Gastric cancer is one of the most prevalent malignancies of the gastrointestinal tract. Worldwide, it ranks as the fourth most commonly diagnosed cancer and the third leading cause of cancer-related mortality. A variety of diagnostic approaches are used for the detection of gastric cancer. Early diagnosis of gastric cancer is crucial, as timely treatment can significantly improve patient prognosis. Detection and monitoring of circulating tumor DNA (ctDNA) provide valuable clinical information while minimizing the need for invasive procedures, such as tissue biopsy. These ctDNAs have been identified as reliable and accurate biomarkers for gastric cancer. The application of ctDNA in gastric cancer plays a significant role in the early diagnosis, detection, and monitoring of minimal residual disease, as well as in the clinical management of advanced-stage disease.

Keywords

liquid biopsy, biomarkers in gastric cancer, next-generation DNA sequencing, gastric cancer, ctDNA

Introduction

Gastric cancer is one of the most common cancers worldwide and is responsible for approximately 800,000 deaths annually [1]. It has third leading cause of cancer-associated mortality worldwide. Despite improvements in treatment modalities for gastric cancer, the prognosis for advanced cases following curative resection remains poor [2].

Preoperative circulating tumor cells (CTCs) are a prognostic indicator in gastric cancer and also valuable for predicting progression-free survival [3]. CTCs and circulating tumor DNA (ctDNA) serve as complementary liquid biopsy modalities in gastric cancer for disease monitoring, prognostication, and therapeutic decision-making. While ctDNA demonstrates higher sensitivity for detecting tumor-specific

genetic alterations and minimal residual disease, CTCs provide valuable information regarding metastatic potential and tumor cell biology.

The study presents a significant theoretical advancement and identifies potential novel insights in gastric cancer findings: CTCs-positive status was significantly associated with aggressive clinicopathological features, including advanced tumor stage and metastasis. CTCs in gastric cancer are malignant cells that detach from the primary tumor and enter the bloodstream. These cells are considered important precursors of metastasis and play a significant role in cancer progression.

The detection of CTCs provides a non-invasive "liquid biopsy" approach that can be used for prognosis assessment, treatment monitoring, and evaluation of disease progression in patients with gastric cancer. Studies have shown that the presence of CTCs is associated with poorer survival outcomes and an unfavorable prognosis.

The study recommends integrating preoperative CTC testing into the clinical management of patients to improve risk stratification and guide personalized treatment strategies. We suggest that further prospective studies are warranted to validate the utility of optimizing the use of ctDNA. ctDNA has potential applications in gastric cancer. These will be very helpful for early gastric cancer screening and for detection of minimal residual disease [4]. ctDNA plays an important role in therapeutic monitoring following curative surgery, in the management of advanced disease, and in treatment decision-making. Compared with tissue-based next-generation DNA sequencing, ctDNA analysis provides a non-invasive and convenient approach for assessing the tumor genomic landscape [5]. In addition, can potentially overcome the challenges of tumor heterogeneity seen with tissue-based next-generation DNA sequencing. The combined analysis of CTCs and ctDNA aims to clarify the fundamental biological and clinical significance of their complementarity. In gastric cancer, CTCs provide comprehensive insights into tumor cell morphology, RNA and protein expression profiles, and can additionally be utilized for in vitro drug sensitivity assays and the establishment of patient-derived xenograft models, thereby offering significant value for functional studies. In contrast, ctDNA offers advantages in terms of broader genomic coverage and ease of detection. The integration of CTC and ctDNA analyses is not intended merely to improve detection rates, but rather to provide a multidimensional characterization of tumor biology by capturing complementary aspects of the disease, including genomic alterations and functional phenotypic features. Genotypically, both CTCs and ctDNA capture the high inter- and intra-tumoral heterogeneity of gastric cancer. ctDNA is genotype-focused with high-sensitivity mutation detection (e.g., *HER2*, *KRAS*) and thus useful for identifying targetable mutations.

ctDNA detection methods and potential applications in early gastric cancer

The presence of malignant cells in the bloodstream has been recognized for many years. Tumor cells release DNA fragments into the circulation, known as ctDNA. These tumor-derived components can be detected in patients with gastric cancer through a blood-based test referred to as a liquid biopsy. In gastric cancer, CTCs and ctDNA serve as valuable non-invasive biomarkers for liquid biopsy applications [6]. CTCs are promising minimally invasive biomarkers for tumor biology and metastasis. These biomarkers help assess the genetic profile of tumors, provide insight into the mechanisms of cancer development, and identify actionable mutations that may be targeted with specific therapies. They may also be used for the screening and clinical management of patients with gastric cancer. ctDNA has been recognized as an important prognostic biomarker across all stages of gastric cancer. Furthermore, quantification of ctDNA levels is valuable for identifying mechanisms of resistance to ongoing therapy and for predicting treatment response and disease progression. Thus, they will aid in early diagnosis, detecting minimal residual disease post-surgery, and predicting treatment response mainly in cases of targeted therapies like *HER2*/*ERBB2*, *HER2* overexpression or amplification, *MET* inhibitors, *PDL1*, and *FRGFR2* overexpression [7]. They also help in monitoring drug resistance for assessing prognosis. The combined CTC/ctDNA analysis shows high accuracy for predicting metastasis risk.

Measuring ctDNA levels and methylation patterns can identify gastric cancer up to four years earlier than standard imaging. Advanced techniques like next-generation sequencing and digital PCR have improved the sensitivity and specificity of ctDNA detection [8]. It also helps in response monitoring of a patient. A > 90% decrease in ctDNA levels after chemotherapy or immunotherapy initiation indicates a positive prognosis.

Clinical applications of ctDNA in gastric cancer

Liquid biopsy offers several advantages over conventional tissue biopsy, particularly due to its minimally invasive nature and ability to provide dynamic, real-time information about tumor biology. Unlike traditional tissue sampling, liquid biopsy can be performed repeatedly through a simple blood draw, making it a safer and more convenient approach for patients. In addition, it enables the early detection of cancer, facilitates continuous monitoring of disease progression and treatment response, and assists in the identification of emerging therapeutic resistance. These features make liquid biopsy a promising tool for personalized cancer management, especially in patients with gastric cancer. A blood-based ctDNA analysis is a non-invasive, cost-effective method that would be helpful to anticipate gastric cancer detection before the advanced stage. In clinical practice, it would contribute to a considerable reduction in cancer-related mortalities.

Recently, Donaldson and Park's study [9] showed that ctDNA in blood plasma has become a promising cancer biomarker. In patients with localized disease, qualitative and quantitative analysis of cell-free DNA (cfDNA) and ctDNA has the potential to provide valuable information regarding the risk of cancer recurrence and metastatic spread [10]. Preoperative positivity for CTCs is linked to more aggressive tumor characteristics, including greater depth of invasion (higher T-stage) and the presence of distant metastases. ctDNA has emerging clinical applications across the entire continuum of gastric cancer management. These applications include early cancer screening, preoperative assessment, postoperative surveillance, treatment response monitoring, early detection of recurrence, and management of advanced-stage disease. High levels of pre-surgical ctDNA are associated with higher-grade histology, advanced T-stage, and increased mortality risk.

ctDNA analysis provides a minimally invasive approach for real-time evaluation of tumor dynamics and molecular alterations, thereby supporting personalized treatment strategies and improving disease monitoring in patients with gastric cancer.

ctDNA analysis can identify genetic mutations, copy number variations, and methylation patterns (e.g., in genes like *SOX17*, *RUNX3*, and *TFPI2*) to track cancer progression, assess tumor heterogeneity, and predict response to targeted therapies [11].

Multi-modal approaches in early gastric cancer detection, monitoring and prognostic evaluation

The integrated and multi-modal approaches to improve detection by a combination of CTCs, ctDNA, protein markers, genomics, transcriptomics, proteomics, and AI-enhanced advanced imaging are coming up for precise diagnostic strategies in gastric cancers. Approaches such as combining ctDNA mutation analysis with protein tumor markers (e.g., CA-125, CEA [carcinoembryonic antigen]) enhance detection sensitivity for early-stage cancers. DNA methylation is a key epigenetic change in various cancers [12]. Epigenetic changes in gastric cancer often occur early in tumor development. It contributes to carcinogenesis by silencing tumor suppressor genes through hypermethylation and, in some cases, by activating oncogenes [13]. Studies indicate that ctDNA methylation profiles can detect gastric cancer early and distinguish it from benign lesions. Methylation-based ctDNA assays generally offer greater sensitivity for early detection of gastric cancer. Validated methylated loci, including *RASSF1A, CDH1,* and *SALL3*, are commonly hypermethylated in gastric cancer and demonstrate high specificity as diagnostic biomarkers.

A study by Li et al. [14] demonstrated that, despite the limited number of established therapeutic targets in gastric cancer, ctDNA analysis is valuable for detecting genomic alterations that may guide the selection of more personalized treatment strategies. Similarly, Lengyel et al. [15] highlighted the emerging role of liquid biopsy in gastric cancer, emphasizing that ctDNA has significant clinical utility in prognostic prediction, assessment of treatment response, early disease detection, identification of patients eligible for targeted therapies, and, more recently, selection of candidates for immunotherapy. Emerging evidence indicates that ctDNA monitoring aids in differentiating pseudoprogression from true disease progression during immune checkpoint inhibitor therapy in gastric cancer.

Recent studies in 2025 and 2026 have highlighted that detecting CTCs and ctDNA in peritoneal lavage fluid rather than just blood offers the highest accuracy (up to 85%) for predicting peritoneal metastasis. A recent study by Zhao et al. [16] provided innovative insights into gastric cancer and outlined future research directions through the application of single-cell RNA sequencing. This advanced transcriptomic approach enables high-resolution characterization of tumor heterogeneity, identification of distinct cellular subpopulations, and a deeper understanding of the tumor microenvironment, thereby offering new perspectives for precision oncology and the development of targeted therapeutic strategies. Rays et al. [17] observed that in metastatic gastric cancer, selecting patients for immunotherapy in second and subsequent lines remains challenging. In gastric cancer, emerging research is focusing on integrating ctDNA with additional biomarkers, such as circulating non-coding RNAs (including miRNAs, circRNAs, and lncRNAs) and DNA methylation patterns, to improve diagnostic accuracy and detection sensitivity [18, 19]. Preliminary results of PanSeer, a noninvasive blood test based on ctDNA methylation, demonstrate the detection of cancer in 95% of asymptomatic individuals who were later diagnosed with cancer [20]. Changes in ctDNA levels serve as a dynamic indicator of tumor burden during neoadjuvant chemotherapy or chemoimmunotherapy [21]. A rapid reduction or complete clearance of ctDNA following surgery or during neoadjuvant treatment is strongly associated with a favorable pathological complete response and improved long-term survival outcomes. In contrast, detection of ctDNA after surgery is linked to reduced recurrence-free survival. In advanced gastric cancer, ctDNA also plays an important role in monitoring response to targeted therapies [22].

ctDNA testing in gastric cancer faces challenges in clinical application, particularly regarding its low shedding in early-stage disease, which limits sensitivity. Another is related to the lack of standardization in pre-analytical and analytical methods, such as optimal timing for blood draws and utilization of specialized tubes to reduce pre-analytical variability. Clonal Hematopoiesis of Indeterminate Potential (CHIP) is an important age-related challenge in the application of cfDNA assays for cancer detection, especially in older individuals at risk for gastric cancer, which introduces false-positive variants [23].

Despite remarkable progress in surgical techniques, chemotherapy, and targeted therapies, the survival rates for patients diagnosed with advanced gastric cancer remain disappointingly low, so future research directions are appreciated.

Conclusion and future directions

In gastric cancer, ctDNA is emerging as a highly promising liquid biopsy biomarker for diagnosis, minimal residual disease detection, prognosis, treatment monitoring, and precision therapy selection. The ctDNA is often more abundant and stable in the blood than the rare and fragile CTCs. The ctDNA potentially has higher sensitivity in detection and real-time monitoring of tumor dynamics and treatment response. The integrated and multi-modal approaches to improve detection by a combination of ctDNA, CTCs, protein markers, genomics, transcriptomics, proteomics, and AI-enhanced advanced imaging are being developed for precise diagnostic strategies in gastric cancers. Future advances are focused on enhancing sensitivity in low-shedding tumors, integrating methylation profiling, and using ctDNA-guided adaptive therapy strategies to increase the intensity of patient care in gastric cancer.

Abbreviations

CEA: carcinoembryonic antigen

cfDNA: cell-free DNA

CHIP: Clonal Hematopoiesis of Indeterminate Potential

CTCs: circulating tumor cells

ctDNA: circulating tumor DNA

Declarations

Author contributions

SVJ: Conceptualization, Formal analysis, Writing—original draft, Writing—review & editing. SSJ: Conceptualization, Formal analysis, Writing—original draft, Writing—review & editing. MSP: Formal analysis, Writing—review & editing. PST: Formal analysis, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Publisher's note

Open Exploration maintains a neutral stance on jurisdictional claims in published institutional affiliations and maps. All opinions expressed in this article are the personal views of the author(s) and do not represent the stance of the editorial team or the publisher.

References

1. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol. 2019;14:26–38. [DOI] [PubMed] [PMC]
2. Uguztemur E, Oztürk B. Impact of Treatment Modalities on Locally Advanced Gastric Cancer-Real-World Data. Curr Oncol. 2025;32:463. [DOI] [PubMed] [PMC]
3. Li Z, Song M, Han S, Jin C, Yang J. The prognostic role of circulating tumor cells in gastric cancer: A meta-analysis. Front Oncol. 2022;12:963091. [DOI] [PubMed] [PMC]

4. Mencel J, Slater S, Cartwright E, Starling N. The Role of ctDNA in Gastric Cancer. Cancers (Basel). 2022; 14:5105. [DOI] [PubMed] [PMC]
5. Businello G, Galuppini F, Fassan M. The impact of recent next generation sequencing and the need for a new classification in gastric cancer. Best Pract Res Clin Gastroenterol. 2021;50–51:101730. [DOI] [PubMed]
6. Ma L, Guo H, Zhao Y, Liu Z, Wang C, Bu J, et al. Liquid biopsy in cancer current: status, challenges and future prospects. Signal Transduct Target Ther. 2024;9:336. [DOI] [PubMed] [PMC]
7. Kim IH. Emerging Targets for Systemic Treatment of Gastric Cancer: HER2 and Beyond. J Gastric Cancer. 2024;24:29–56. [DOI] [PubMed] [PMC]
8. Aravanis AM, Lee M, Klausner RD. Next-Generation Sequencing of Circulating Tumor DNA for Early Cancer Detection. Cell. 2017;168:571–4. [DOI] [PubMed]
9. Donaldson J, Park BH. Circulating Tumor DNA: Measurement and Clinical Utility. Annu Rev Med. 2018; 69:223–34. [DOI] [PubMed]
10. Chen W, Yan H, Li X, Ge K, Wu J. Circulating tumor DNA detection and its application status in gastric cancer: a narrative review. Transl Cancer Res. 2021;10:529–36. [DOI] [PubMed] [PMC]
11. Xia JY, Aadam AA. Advances in screening and detection of gastric cancer. J Surg Oncol. 2022;125: 1104–9. [DOI] [PubMed] [PMC]
12. Jagtap SV, Jagtap SS. Methylation of *BRCA1* promoter in sporadic breast cancer. Indian J Med Res. 2023;158:85–7. [DOI] [PubMed] [PMC]
13. Fu DG. Epigenetic alterations in gastric cancer (Review). Mol Med Rep. 2015;12:3223–30. [DOI] [PubMed] [PMC]
14. Li TT, Liu H, Yu J, Shi GY, Zhao LY, Li GX. Prognostic and predictive blood biomarkers in gastric cancer and the potential application of circulating tumor cells. World J Gastroenterol. 2018;24:2236–46. [DOI] [PubMed] [PMC]
15. Lengyel CG, Hussain S, Trapani D, El Bairi K, Altuna SC, Seeber A, et al. The Emerging Role of Liquid Biopsy in Gastric Cancer. J Clin Med. 2021;10:2108. [DOI] [PubMed] [PMC]
16. Zhao CF, Li QW, Ye SY, Chen LW, Xu ZF. Innovative insights and future research directions in gastric cancer through single-cell RNA sequencing. World J Gastrointest Oncol. 2025;17:103808. [DOI] [PubMed] [PMC]
17. Rays A, Fedyanin M, Popov D, Pokataev I, Lyadova M, Zhukova L, et al. Immune checkpoint inhibitors in patients with advanced gastric cancer: a multi-institutional retrospective real-world study. Explor Dig Dis. 2025;4:100568. [DOI]
18. Deng Q, Jiang B, Yan H, Wu J, Cao Z. Circulating tumor cells in gastric cancer: developments and clinical applications. Clin Exp Med. 2023;23:4385–99. [DOI] [PubMed]
19. Jiang C, Zhang J, Wang W, Shan Z, Sun F, Tan Y, et al. Extracellular vesicles in gastric cancer: role of exosomal lncRNA and microRNA as diagnostic and therapeutic targets. Front Physiol. 2023;14: 1158839. [DOI] [PubMed] [PMC]
20. Chen X, Gole J, Gore A, He Q, Lu M, Min J, et al. Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. Nat Commun. 2020;11:3475. [DOI] [PubMed] [PMC]
21. Liu Z, Shi Z, Jiang W, Shen Z, Chen W, Shen K, et al. Circulating tumor DNA analysis for prediction of prognosis and molecular insights in patients with resectable gastric cancer: results from a prospective study. MedComm (2020). 2025;6:e70065. [DOI] [PubMed] [PMC]
22. Sahwan O, Batha L, Jamal F, Sonbol MB. Circulating Tumor DNA (ctDNA) in Gastroesophageal Adenocarcinoma (GEA): Evidence and Emerging Applications. Cancers (Basel). 2025;17:3692. [DOI] [PubMed] [PMC]
23. Krishnan T, Solar Vasconcelos JP, Titmuss E, Vanner RJ, Schaeffer DF, Karsan A, et al. Clonal Hematopoiesis of Indeterminate Potential and its Association with Treatment Outcomes and Adverse Events in Patients with Solid Tumors. Cancer Res Commun. 2025;5:66–73. [DOI] [PubMed] [PMC]