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When Blood Speaks Before the Scan: The Role of ctDNA in Real-time CRC Care

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Abstract

Background/Aim: Colorectal cancer (CRC) recurrence, especially in stage III disease, remains a clinical challenge. Circulating tumor DNA (ctDNA) has emerged as a minimally invasive biomarker for detecting minimal residual disease (MRD) and predicting recurrence. The Signatera assay is a personalized, tumor-informed ctDNA test reported in mean tumor molecules per milliliter (MTM/ml), offering dynamic monitoring beyond traditional mutant allele frequency methods. The objective of the current study was to demonstrate the clinical utility of Signatera in managing four patients with stage III CRC, particularly in detecting recurrence earlier than imaging and informing curative interventions.

Case Report: We conducted a retrospective case series of four patients with histologically confirmed stage III CRC who underwent curative-intent surgery, completed adjuvant chemotherapy, and received longitudinal Signatera ctDNA testing for at least 12 months. ctDNA was assessed every three months, and imaging was performed every six months or sooner if ctDNA became positive. We documented trends in ctDNA, recurrence patterns, imaging results, and treatment changes. All patients initially achieved a disease-free status. In all cases, ctDNA positivity preceded radiographic detection of recurrence. Each had isolated liver metastases, which were detected early and treated surgically. Post-surgical ctDNA clearance was associated with improved outcomes, and one patient remained ctDNA-negative without additional chemotherapy.

Conclusion: Serial ctDNA monitoring with Signatera enabled earlier detection of recurrence and guided timely interventions in stage III CRC. These findings support its clinical integration, pending further validation in prospective trials.

Keywords: Colorectal cancer, circulating tumor DNA, Signatera, recurrence, oligometastatic, liver metastasis, adjuvant chemotherapy.

Introduction

Colorectal cancer (CRC) ranks as the third most frequently diagnosed cancer and stands as the second leading cause of cancer-related deaths globally (1). For patients battling stage III CRC, the chances of recurrence are still relatively high, sitting between 30% and 50%, even with the advancements we've made in surgical methods and

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systemic chemotherapy (2). Traditionally, monitoring patients after treatment has involved a combination of imaging tests and checking serum carcinoembryonic antigen (CEA) levels; however, these methods often fall short in accurately detecting early recurrences (3). Recently, circulating tumor DNA (ctDNA) has emerged as a game-changing biomarker for detecting minimal residual disease (MRD) and predicting relapses in solid tumors, including CRC (4, 5). The Signatera assay from Natera, Inc. (Austin, TX, USA) is a personalized ctDNA test that pinpoints somatic variants unique to each patient's tumor (6). This assay is a tumor-informed circulating tumor DNA (ctDNA) test that uses whole-exome sequencing of the patient's resected tumor tissue to identify up to 16 clonal, tumor-specific somatic variants. Once identified, these variants are tracked in plasma samples using multiplex PCR and next-generation sequencing. This differs from traditional mutant allele frequency (MAF) reporting, as the Signatera assay summarizes tumor-specific ctDNA levels in Mean Tumor Molecules per milliliter (MTM/ml), enabling sensitive and dynamic monitoring of MRD and recurrence (Figure 1) (7). Fluctuations in ctDNA levels provide real-time insights into tumor burden and treatment effectiveness. Numerous studies have confirmed the clinical benefits of ctDNA in CRC. Notably, the CIRCULATE-Japan and GALAXY trials showed that a positive ctDNA result after surgery or adjuvant chemotherapy is a strong indicator of recurrence and correlates with a poorer prognosis (8, 9). A typical example from this series is shown in Figure 2, where a patient with stage IIIC CRC had no imaging evidence of recurrence after adjuvant chemotherapy; however, ctDNA was positive, prompting early follow-up. The early follow-up discovered a single liver metastasis, which was surgically resected. This demonstrates that ctDNA can detect recurrence before it appears on imaging.

On the contrary, patients who consistently test negative for ctDNA tend to enjoy excellent long-term outcomes and might be able to skip extended chemotherapy (10). This case series highlights the importance of incorporating ctDNA into the treatment strategy for stage III CRC. It discusses the benefits of ongoing ctDNA monitoring, which can identify issues before imaging, its role in oligometastatic disease, and how it can help guide treatment duration. Recent research findings support these insights and offer practical recommendations for informed clinical decision-making.

Case Report

Case 1. A 56-year-old non-Hispanic white man presented to the emergency department in February 2023 with nausea, vomiting, diffuse abdominal pain, and a 3-day history of constipation. Computed tomography (CT) imaging showed an obstructing apple-core lesion in the distal transverse colon. On February 19, 2023, he underwent emergent exploratory laparotomy with left colectomy and primary anastomosis. Histopathology demonstrated moderately differentiated invasive adenocarcinoma with T4aN2aM0 (stage IIIC) disease, with five of 13 lymph nodes positive. Lymphovascular and perineural invasion were present, and surgical margins were negative.

He initiated adjuvant therapy on April 5, 2023, receiving mFOLFOX6 for 12 planned cycles, completed on October 2, 2023. Treatment was generally well tolerated, with intermittent thrombocytopenia and chemotherapy-induced neuropathy managed with duloxetine. Surveillance CT scans in April and October 2023, and a colonoscopy in December 2023, showed no evidence of disease, and CEA levels remained normal.

ctDNA monitoring and recurrence. Serial Signatera ctDNA testing was performed during surveillance. Following an initial positive result after surgery (0.19 on March 20, 2023), ctDNA remained negative until April 2024, when levels increased to 1.59 and further to 19.28 by July 2024 (Figure 3), despite a negative CT scan three months earlier. Subsequent imaging revealed a new hepatic lesion measuring 21×15 mm. Positron emission tomography (PET)/CT on July 31, 2024, demonstrated hypermetabolic activity (SUV 11.5) in the caudate lobe, consistent with liver metastasis.

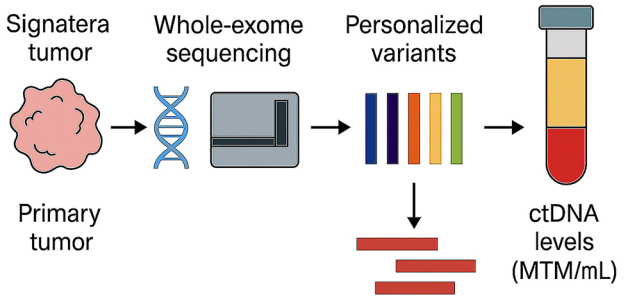

Figure 1. *Schematic of the tumor-informed Signatera ctDNA assay. Whole-exome sequencing of resected tumor tissue identifies up to 16 tumor-specific variants, which are subsequently tracked in plasma using multiplex polymerase chain reaction (PCR) and next-generation sequencing. ctDNA levels are reported in mean tumor molecules per milliliter (MTM/ml) for minimal residual disease and recurrence monitoring.*

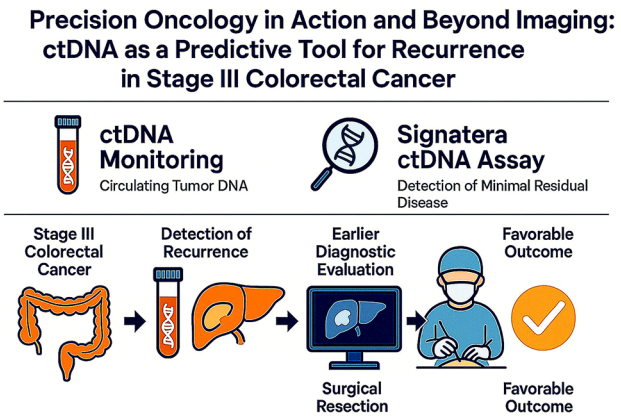

Figure 2. *Representative clinical course illustrating ctDNA-guided detection of recurrence in stage III colorectal cancer. Despite negative surveillance imaging after adjuvant chemotherapy, ctDNA positivity prompted early follow-up imaging, which identified a solitary liver metastasis amenable to surgical resection.*

Treatment and outcome. The patient underwent exploratory laparotomy, cholecystectomy, and partial liver lobectomy on August 9, 2024. Pathology confirmed moderately differentiated colorectal adenocarcinoma with negative margins. A postoperative seroma required drainage and resolved uneventfully. Given early recurrence, adjuvant FOLFIRI was initiated on October 16, 2024, for six cycles, and completed January 8, 2025. Follow-up ctDNA testing in October and December 2024 was negative, with low CEA levels and no evidence of recurrence on imaging. The patient remains clinically well under surveillance.

Case 2. A 60-year-old male was diagnosed with stage IIIC (pT4aN2aMx) sigmoid colon adenocarcinoma after presenting with hematochezia and left lower quadrant pain. Colonoscopy and biopsy confirmed moderately differentiated adenocarcinoma. Surgical pathology revealed that four of 45 lymph nodes were positive, with negative margins following left colectomy. Resection margins were negative after Da Vinci–assisted left transverse colectomy. There was no perineural or lymphovascular invasion. Pre-treatment PET/CT showed no metastatic disease and stable chronic pulmonary nodules.

He began adjuvant mFOLFOX6 on March 23, 2022, transitioning to 5-FU and leucovorin after oxaliplatin hypersensitivity in cycle 6. Treatment was tolerated with transient neutropenia managed by G-CSF. Serial CEA levels remained normal, and follow-up CT imaging through 2023 showed no progression. Colonoscopy in February 2023 was unremarkable.

ctDNA monitoring and recurrence. Signatera ctDNA testing from March to September 2022 was negative. In July 2024, ctDNA became positive (3.23 MAF) and confirmed in October 2024 (3.32 MAF), despite regular tumor markers and stable imaging. Subsequent CT imaging revealed a new 1 cm liver lesion (Figure 4), further characterized on MRI as a 2.0×1.7 cm enhancing mass consistent with metastasis.

Treatment and outcome. The patient underwent partial right hepatic lobectomy and cholecystectomy on December 6, 2024. Pathology confirmed a solitary metastatic lesion with negative margins. Recovery was uncomplicated aside from a localized port-site reaction. Due to prior oxaliplatin hypersensitivity, adjuvant FOLFIRI was planned to begin January 15, 2025. The patient remains under close surveillance.

Case 3. A 53-year-old Caucasian male presented with chronic epigastric discomfort and nausea refractory to

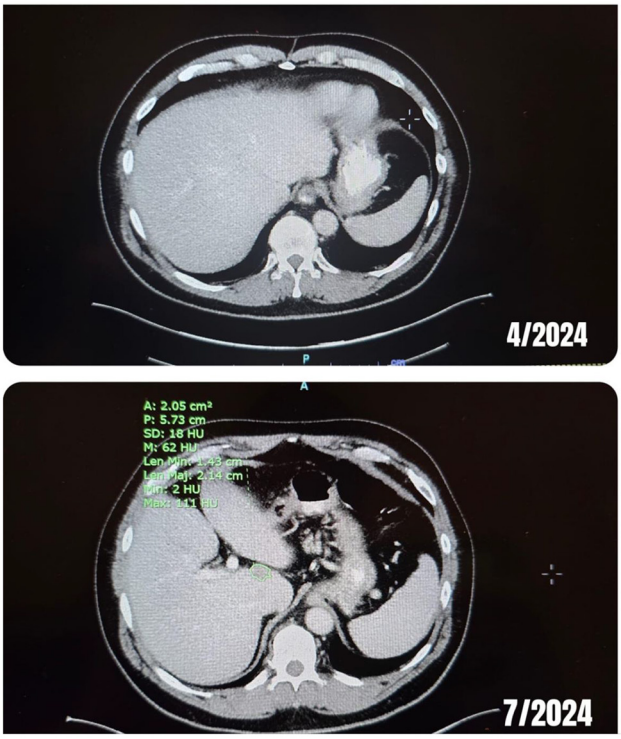

Figure 3. *Contrast-enhanced axial computed tomography (CT) images of the liver in Case 1. (A) No focal hepatic lesion is visible 4 weeks after completion of adjuvant chemotherapy. (B) Twelve weeks later, CT demonstrates a 2.1-cm hypoattenuating right hepatic lesion (arrow) detected after ctDNA positivity, consistent with oligometastatic recurrence subsequently managed with partial hepatectomy.*

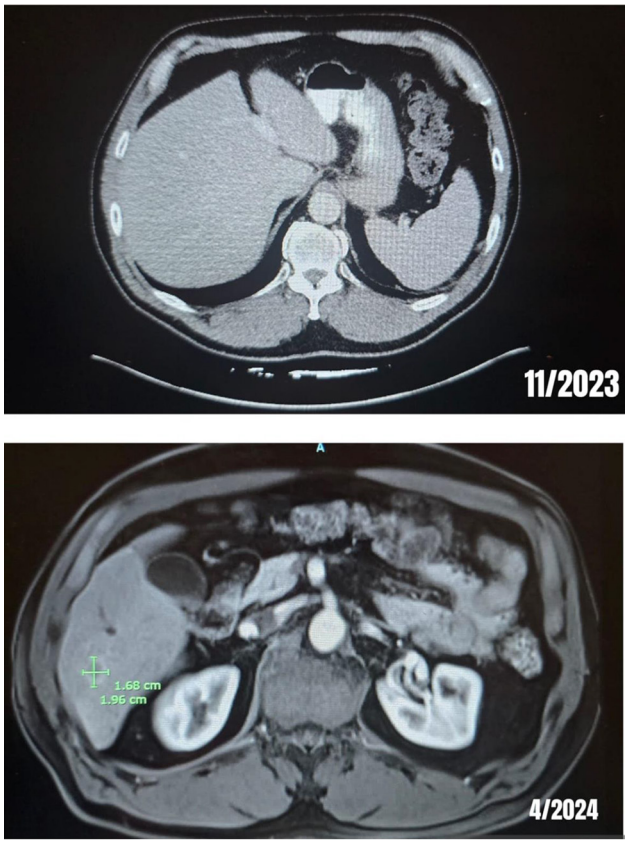

Figure 4. *Computed tomography (CT) images of the liver in Case 2. (A) Surveillance imaging after surgery and adjuvant chemotherapy shows no focal hepatic lesion. (B) Follow-up CT obtained after ctDNA positivity demonstrates a solitary segment VII liver metastasis (arrow), which was subsequently confirmed and resected.*

treatment. Colonoscopy in December 2023 revealed a friable mass at the hepatic flexure, with biopsy confirming moderately differentiated adenocarcinoma. Imaging showed no metastatic disease. On January 4, 2024, he underwent robotic right hemicolectomy. Pathology demonstrated stage IIIB (pT4aN1bM0) disease with lymphovascular and perineural invasion, and two of 22 lymph nodes were positive; margins were negative. Molecular profiling showed intact mismatch repair (MMR), negative human epidermal growth factor receptor 2 (*HER2*) status, and a *KRAS* p.Gly12Asp mutation.

ctDNA monitoring and recurrence. ctDNA testing from February to May 2024 was negative. In August 2024, ctDNA became positive (1.4 MTM/ml), rising to 24.0 MTM/ml by October 2024, despite stable CEA and negative CT imaging. PET/CT in November 2024 (Figure 5) identified a hypermetabolic hepatic lesion measuring 1.4 cm, confirmed on MRI.

Treatment and outcome. The patient underwent central liver resection with cholecystectomy on December 12, 2024. Pathology confirmed metastatic adenocarcinoma with negative margins. Adjuvant FOLFIRI was initiated on January 22, 2025. ctDNA levels declined significantly, and follow-up CT in April 2025 showed no evidence of disease. The patient remains under close surveillance.

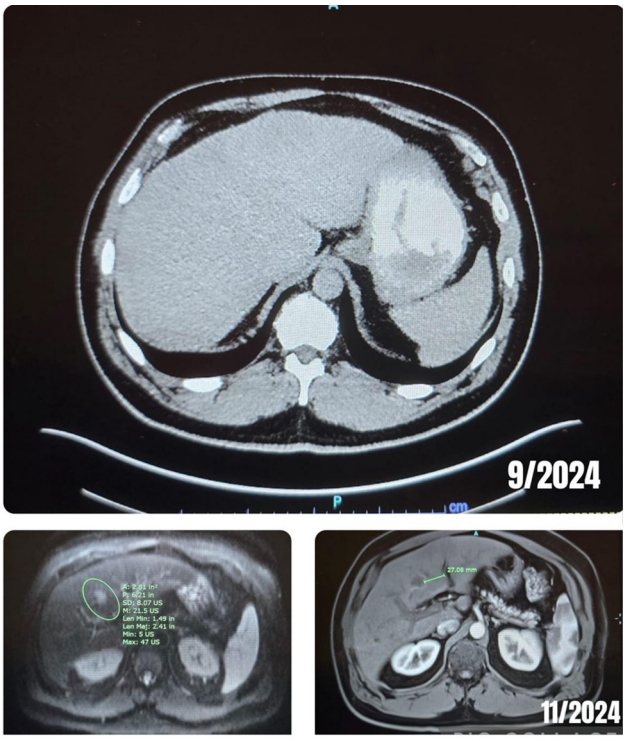

Figure 5. *Computed tomography (CT) images of the liver in Case 3. (A) Baseline post-adjuvant surveillance CT shows no evidence of recurrent disease. (B) Subsequent imaging obtained after persistent ctDNA positivity reveals a central hepatic lesion (arrow), later confirmed on MRI and surgically resected.*

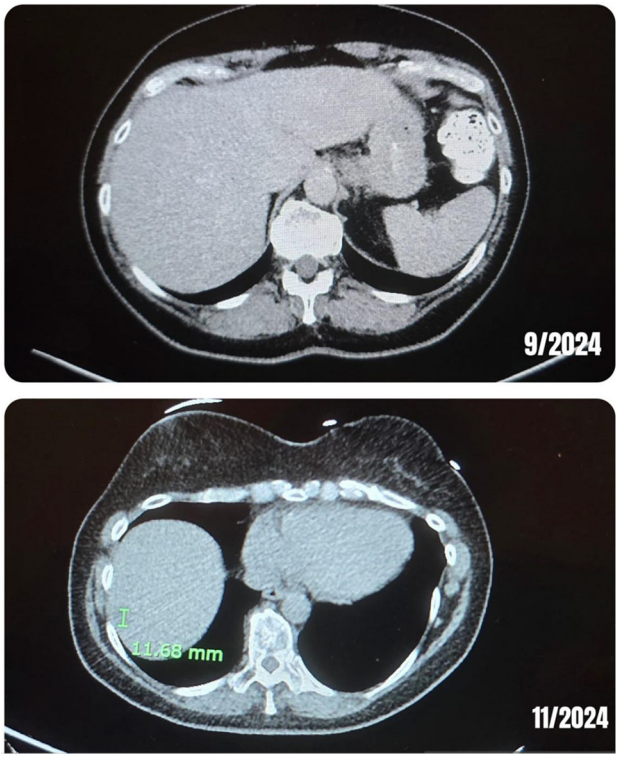

Figure 6. *Initial post-treatment computed tomography (CT) scans (A) and follow-up CT scans (B) at eight months are both negative for any evidence of disease. The serial surveillance imaging revealed no evidence of disease during the initial follow-up period. After the patient developed ctDNA positivity, subsequent PET/CT imaging detected a solitary hepatic metastasis, which was managed with surgical resection.*

Case 4. A 66-year-old Caucasian female was evaluated for iron-deficiency anemia detected on routine labs. Colonoscopy in June 2023 revealed an ulcerated hepatic flexure mass and rectal polyp, with biopsies confirming moderately differentiated adenocarcinoma and tubulovillous adenoma. Imaging showed no metastatic disease. She underwent robotic extended right hemicolectomy on June 28, 2023. Pathology revealed pT3N2a disease with lymphovascular and perineural invasion, and four of 21 lymph nodes were positive. Margins were negative, MMR was intact, and genetic testing was negative.

ctDNA monitoring and recurrence. She received seven cycles of adjuvant FOLFOX between August and November 2023. Serial ctDNA testing remained negative through May 2024, with normal CEA and imaging. In August 2024, ctDNA became positive and continued to rise by November 2024. PET/CT identified a solitary liver lesion (Figure 6).

Treatment and outcome. The patient underwent partial right hepatic lobectomy on December 9, 2024, with pathology confirming isolated metastatic disease. Postoperative recovery was uneventful. ctDNA became negative, and she completed six cycles of FOLFIRI by March 25, 2025. She remains without evidence of recurrence.

This case series presents the clinical course and management of four patients with stage III colorectal cancer monitored with ctDNA surveillance. Figure 7 summarizes the timeline of molecular recurrence, imaging findings, and interventions.

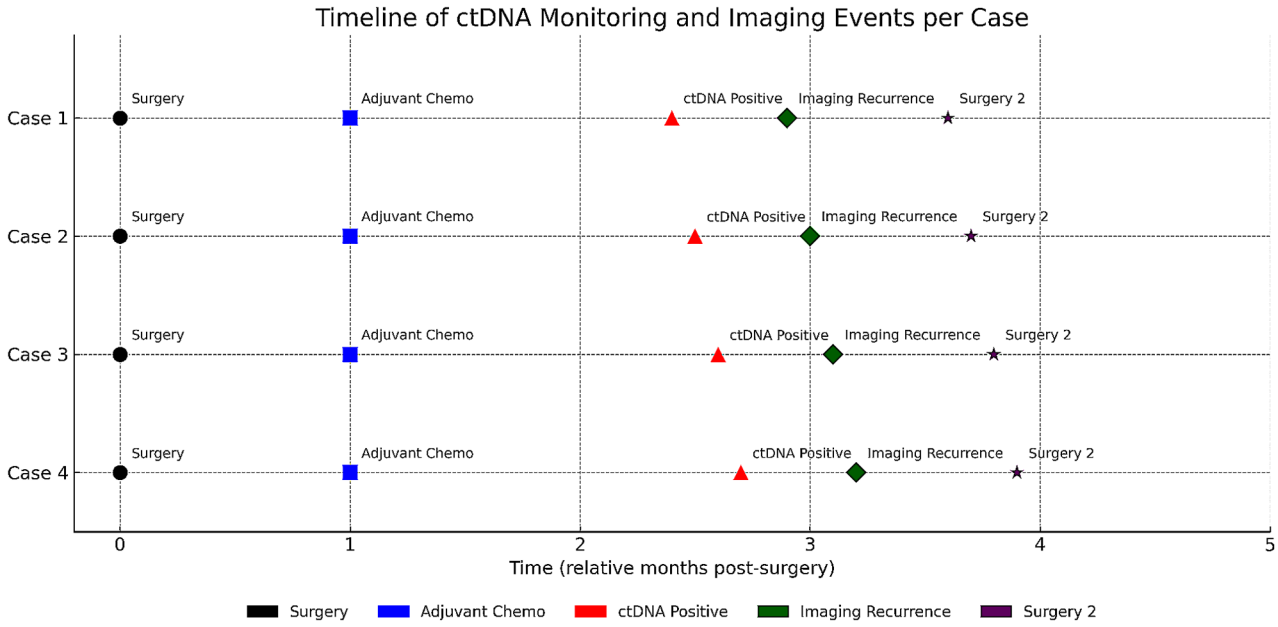

Figure 7. *Timeline of ctDNA monitoring, imaging, and treatment events in four patients with stage III colorectal cancer. The schematic depicts curative-intent surgery, adjuvant chemotherapy, ctDNA positivity, radiographic recurrence, and salvage intervention. In all cases, ctDNA positivity preceded radiographic detection of recurrence.*

Table I presents patient demographics, treatment, recurrence site, and ctDNA dynamics in the four included cases. Figure 8 demonstrates overlapping ctDNA patterns across all four patients, showing a clear lead time between ctDNA positivity and radiographic recurrence. In each case, ctDNA elevation preceded imaging-detected metastasis by several weeks, highlighting its value as an early molecular marker of recurrence. This early detection enabled timely imaging and curative interventions, including metastasectomy. These findings underscore the importance of serial ctDNA surveillance in high-risk stage III colorectal cancer, as molecular recurrence consistently preceded radiologic evidence.

Discussion

This case series illustrates the role that ctDNA surveillance, particularly with the Signatera assay, plays in the post-treatment management of stage III CRC. Historically, recurrence surveillance has relied on radiographic imaging studies and serum CEA levels, both of which have limitations in sensitivity and specificity, particularly in identifying subclinical recurrences or MRD (4, 5). The assay of ctDNA, a dynamic and sensitive biomarker, provides a molecular window into tumor biology and has quickly become an essential adjunct to standard imaging, becoming a standard aspect of oncology practice.

One of the standout findings from the three patients with ctDNA-detected recurrences was the early detection of oligometastatic liver lesions. We reaffirm that ctDNA molecular recurrence preceded radiographic recurrence in all four cases by a median of 2.94 months (Figure 9). This crucial lead time enabled timely imaging, surgical interventions, and the initiation or continuation of systemic therapies before the disease had a chance to spread significantly. By incorporating ctDNA surveillance into the clinical workflow, healthcare providers could initiate curative-intent treatments at a point where traditional imaging might not have prompted such actions (11). These findings are consistent with those of Reinert *et al*., who demonstrated that ctDNA positivity occurs months before radiographic recurrence and that, in

Table I. *Summary of clinical characteristics, treatments, and ctDNA trends.*

Case	Age/Sex	Stage	Primary tumor location	Initial chemo	ctDNA recurrence	Recurrence site	Salvage surgery	Post-surgery chemo	ctDNA Status post-surgery and post-chemotherapy
1	56/M	IIIC	Distal transverse colon	mFOLFOX6 x12	Yes	Liver	Partial lobectomy	FOLFIRI x6	Undetectable post-surgery; remained 0.00 MTM/ml after chemo
2	60/M	IIIC	Sigmoid colon	FOLFOX → 5FU/LV	Yes	Liver	Right lobectomy	FOLFIRI x6	Dropped from 1.12 MTM/ml to 0.00 MTM/ml post-chemo
3	53/M	IIIB	Hepatic flexure	FOLFOX + chemoRT + FOLFOX	Yes	Liver	Central resection	FOLFIRI ongoing	Decreasing trend: 0.85 → 0.42 → 0.18 MTM/ml
4	66/F	IIIB	Hepatic flexure	FOLFOX x7	Yes	Liver	Right lobectomy	FOLFIRI x6	Became undetectable post-surgery; sustained 0.00 MTM/ml

patients who have undergone resection, relapse can be predicted with accuracy (4).

These results align with findings from prospective trials like CIRCULATE-Japan, which showed that a positive ctDNA result after curative treatment is strongly linked to a higher risk of relapse and a poorer prognosis (8). Moreover, the GALAXY study emphasized the role of ctDNA as a predictor of recurrence and its potential to guide personalized therapy adjustments, whether that means escalating or de-escalating treatment (9). Additionally, the DYNAMIC-II studies, which used ctDNA-informed therapy in stage II CRC using the Safe-SeqS platform, demonstrated that ctDNA positivity was independently associated with increased recurrence risk and influenced decisions regarding adjuvant therapy (12). The BESPOKE CRC trial, a prospective multi-arm, multi-center study of the Signatera assay in stage III CRC, also reported the prognostic value of post-surgery ctDNA positivity and its utility in optimizing treatment interventions (13). In comparison, the DYNAMIC-III studies in stage III colon cancer showed no improvements in recurrence-free survival (RFS) when adjuvant chemotherapy was determined by ctDNA status, highlighting the continued need to define predictive utility in this setting (14). Hazard ratios from these trials reinforce the finding that ctDNA positivity following curative-intent treatment is associated with a significantly increased risk of recurrence, often preceding radiographic detection by several months (15).

The usefulness of ctDNA extends beyond simply detecting recurrences. For instance, in one case, a patient showed persistent ctDNA positivity even when there was no visible sign of disease on scans, which led to the decision to continue chemotherapy past the usual six-month mark. In addition, another patient with consistently harmful ctDNA levels was able to safely reduce their therapy, cutting down on toxic side effects while still keeping their remission intact. These clinical choices are supported by findings from the DYNAMIC trial and other research, which suggest that treatment decisions based on ctDNA can help avoid unnecessary chemotherapy without compromising patient outcomes (10, 16). Similarly, a patient with persistent ctDNA negativity was able to safely discontinue chemotherapy early to minimize toxicities while controlling the disease.

The utility of ctDNA extended beyond recurrence detection to influencing surgical decision-making. Our findings also support the use of ctDNA to guide the surgical removal of oligometastatic disease, especially in the liver. Removing liver metastases in CRC has been linked to better survival rates, particularly when done in cases with limited disease (17). Given the early detection of molecular recurrences using

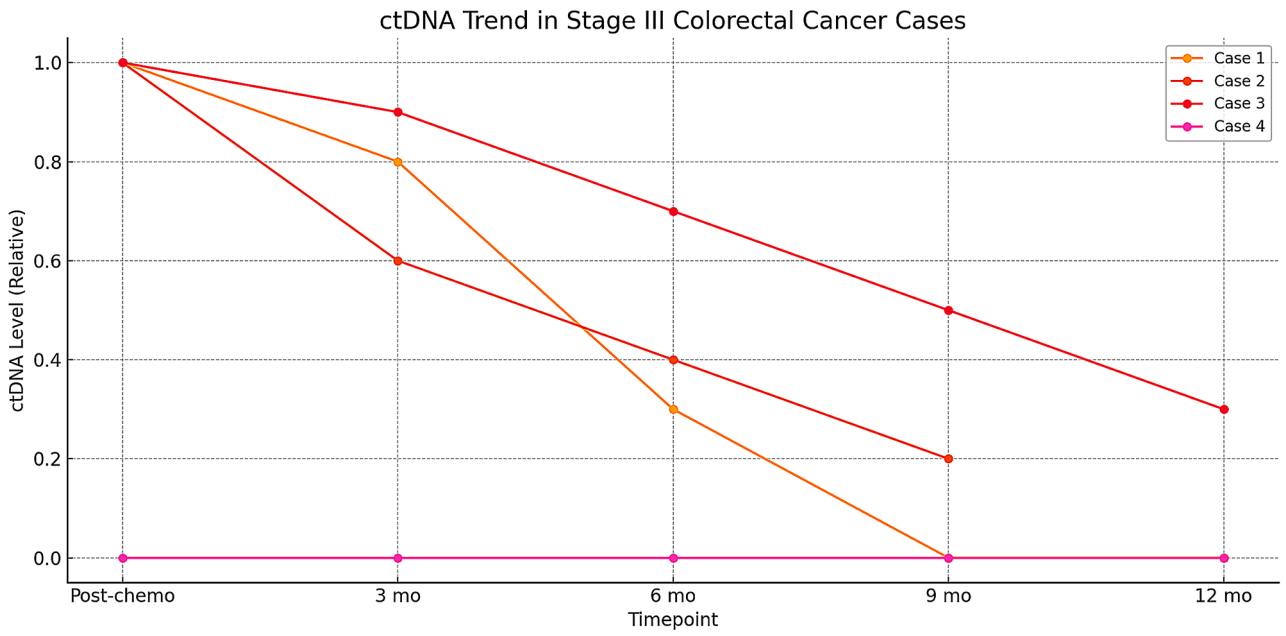

Figure 8. *Longitudinal ctDNA trends in four patients with stage III colorectal cancer. In each case, ctDNA elevation preceded radiographic confirmation of recurrence, underscoring the value of serial molecular surveillance for early detection of oligometastatic disease.*

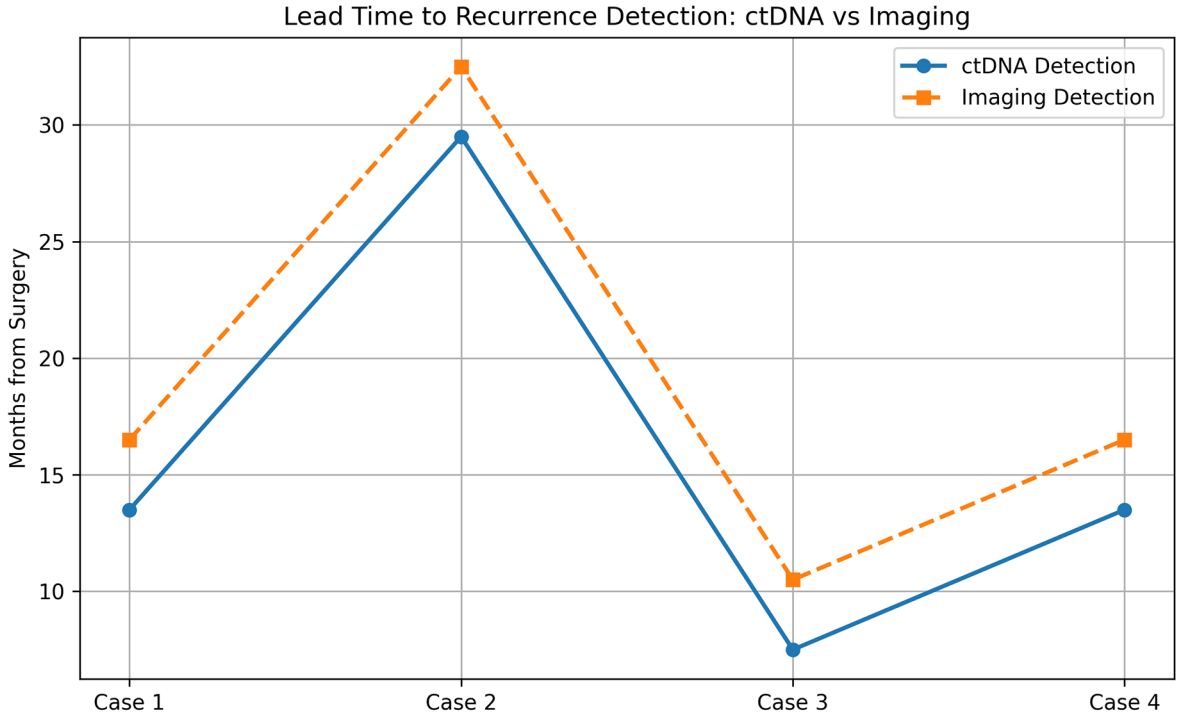

Figure 9. *Lead time between ctDNA positivity and radiographic recurrence detection. The bar graph compares the interval from molecular recurrence to imaging-confirmed recurrence, demonstrating earlier detection by ctDNA surveillance.*

ctDNA, resectable lesions can be precisely localized before further progression or dissemination. This advantage highlights ctDNA's capacity to identify a timing for curative intervention that might be overlooked by standard monitoring methods (4).

Moreover, ctDNA served as a crucial biomarker for determining treatment response and disease progression. For patients undergoing chemotherapy or who have undergone surgery, trends in ctDNA levels closely correspond with clinical and radiologic outcomes. When levels decreased, a therapeutic response and significant stability were predicted; when levels rose, recurrence was predicted, consistent with findings in the literature regarding the prognostic value (11, 16). These findings align with recent data on RAS mutation dynamics tracked by ctDNA in metastatic CRC, which emphasized the temporal heterogeneity of mutations and the clinical value of serial plasma monitoring (18).

Integrating ctDNA into standard care presents various obstacles, despite its promise. Current hindrances include access to testing, test pricing, turnaround time, and differences in clinician experience with molecular surveillance. Furthermore, it has not been determined when and how often to test ctDNA, and it is likely that this varies by treatment type and disease stage. While retrospective series and observational data (such as ours) are promising predictors of ctDNA value, randomized, prospective, stratified studies are needed to provide consensus-based clinical practice recommendations.

Looking ahead, ctDNA will emerge as a staple in precision oncology, particularly when used alongside other modalities. Radiomics, imaging enhanced with artificial intelligence (AI), and immune profiling, in conjunction with ctDNA, will provide a broader picture of the disease's evolution. Further research will also be needed on the use of ctDNA in immunotherapy and targeted therapy situations, where early markers of response are difficult to measure (19, 20).

Conclusion

Serial ctDNA testing with Signatera offers vital insights into how diseases like stage III CRC can recur and how patients respond to treatment. This approach paves the way for more personalized interventions. By incorporating this test into everyday clinical practice, we could revolutionize the way we manage CRC, making recurrence monitoring more precise, timely, and less invasive. As shown in this case series, ctDNA-guided surveillance not only detects recurrences earlier but also enables targeted surgical options for oligometastatic disease, potentially improving survival. Thus, our results support the prognostic use of ctDNA in CRC surveillance. Its predictive role in curative decision-making remains investigational and requires further randomized trials to validate these findings.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

NS drafted the manuscript; EL contributed review and grammatical corrections; HL provided hematology-oncology expertise and critical revision. All Authors approved the final manuscript.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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