Clinical Oncology: Case Reports

Case Report

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Circulating Tumor Cells as Biomarkers for Relapse Detection in Rectal Cancer with Liver Metastasis: Insights from a Case Report

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Abstract

A 70-year-old female diagnosed case of rectal carcinoma, T3N2M0 received FOLFOX × 2 cycles followed by CAPOX × 2 cycles. She then underwent chemoradiation using Capecitabine as a radiosensitiser, followed by laproscopic tumor resection. The histopathology report showed Tumour Regression Grade 2 (TRG2) response. Subsequently, patient received 4 #CAPOX but developed grade 2 peripheral neuropathy, leading to modification in her treatment to Capecitabine alone for an additional 2 cycles. A whole-body Positron Emitted Tomography-Computed Tomography (PET-CT) scan at this stage showed no evidence of disease. However liquid biopsy test detected the presence of two Circulating Tumor Cells (CTCs). An MRI of the abdomen and pelvis was conducted revealing multiple live lesions (4 mm-6 mm) in segment IV/VIII of the liver, with no sign of local disease. To manage liver metastasis, the patient received 1 cycle of Folfiri while awaiting Selective Internal Radiotherapy (SIRT), followed by 5 cycles of Folfiri. Three years later, her PET scans are observed to be completely normal.

This case highlights the critical role of CTC as a biomarker for detecting Minimal Residual Disease (MRD) or relapse. Without CTC monitoring the liver metastasis-that was successfully treated with SIRT, would have likely been missed under the standard cancer care guidelines. As of today, the patient is completely disease free, underscoring the importance of thorough investigation based on advanced CTC liquid biopsy biomarkers in managing rectal cancer with liver metastasis.

Keywords: Circulating Tumor Cells (CTCs); Laproscopic tumor; Radiosensitiser; Lymph nodes; Biomarkers; Liver metastasis

Introduction

Colorectal Cancer (CRC) is the 3rd most common malignancies worldwide, and being a 2nd leading cause of cancer-related deaths, it has a significant impact on morbidity and mortality [1]. Despite advances in surgical and adjuvant therapies, metastatic progression and recurrence remains a major challenge. Recurrence rate of CRC range from 9% to 40%, depending on the stage of the disease [2]. Early-stage and locally advanced patients can greatly benefit from systematic treatment, if recurrence is timely diagnosed. However, current diagnostic standard of care, including PEC-CT imaging fails to detect MRD, and early recurrence [3]. In clinically disease-free patients the presence of MRD is often present in occult state. The occult disease or covert metastasis can result into untreatable metastatic recurrence to other parts of the body. The MRD refers to the small number of cancer cells that may persist in the body after primary treatment including tumor resection with curative intent, which may lead to micro-metastasis or recurrence. CTCs, are cancer cells that disimminate from the primary tumor and enter the bloodstream [4,5]. These cells, along with Circulating Tumor DNA (CTDNA) serve as a biomarker for disease progression, prognosis, and treatment response in CRC [6-8]. Numerous studies have demonstrated that the presence and quantity of CTCs in the blood correlate with poor prognosis in CRC patients [9,10].

High levels of CTCs are associated with an increased risk of recurrence and reduced overall survival. CTC enumeration before and after treatment can help stratify patients based on risk, guiding therapeutic decisions. The dynamic changes in CTC counts during and after treatment provide valuable insights into treatment efficacy. A decrease in CTCs post-treatment is typically associated with a favourable response, whereas stable or increasing CTC levels may indicate treatment resistance or early relapse [11]. This real-time monitoring can help clinicians adjust treatment strategies promptly. The detection of CTCs in patients who are clinically disease-free after treatment can indicate the presence of MRD. This early identification of MRD through CTC analysis can prompt closer surveillance and early intervention, potentially improving outcomes. Furthermore, CTC analysis can help distinguish between patients who may benefit from adjuvant therapy and those who can be spared from the overtreatment [12]. While CTCs offer great promise as a biomarker for MRD in CRC, there are several challenges.

The rarity of CTCs in peripheral blood, particularly in early-stage disease or after curative surgery, makes their detection difficult. Moreover, the heterogeneity of CTCs, both within and between patients, complicates the interpretation of their clinical significance. The ongoing advancements in CTC detection and characterization are expected to enhance their clinical utility in CRC. Liquid biopsy platforms that combine CTC analysis with other biomarkers, such as ctDNA, are being explored to improve the sensitivity and specificity of MRD detection [13-15]. Additionally, integrating CTC analysis with imaging and other diagnostic tools may provide a more comprehensive assessment of disease status, guiding more precise and personalized treatment strategies.

Case Presentation

We report the case of a 70-year-old Indian female with a 20-year history of type II diabetes who presented in january 2020. Prior to her presentation, she experienced intermittent rectal bleeding for one year and developed constipation three months earlier. Upon examination, ileo-colonoscopy revealed a 10 cm circumferential, non-obstructive proliferative mass located 5 cm to 15 cm from the anal verge. A surgical biopsy confirmed moderately differentiated adenocarcinoma. Figure 1 shows the clinical timeline of the case presented here.

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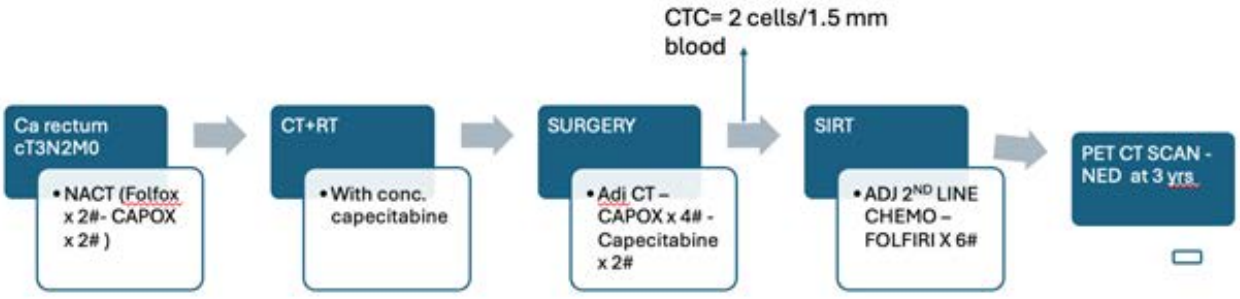

Figure 1: Schematics depicting Clinical timeline of the case.

An anterior and posterior plain contrast CT scan, performed on february 22, 2020, showed a circumferential growth involving a 6.3 cm segment of the rectum, with the distal end approximately 6 cm from the anal verge. The growth was associated with loss of fat planes with the uterus and the presence of multiple peri-rectal lymph nodes, the largest measuring 1 cm. Metastasis was noted in the lower mesenteric and left iliac lymph nodes (Figure 2). The liver, gallbladder, pancreas, bilateral adrenal glands, and renal system appeared normal, with no evidence of focal lesions, hydronephrosis, calculi, or mass lesions.

Based on radiological examinations,the patient was diagnosed with locally advanced rectal carcinoma (cT3N2M0). Following the primary diagnosis, she was treated with Neoadjuvant Chemotherapy (NACT). A chemo port was inserted, and the FOLFOX regimen (Oxaliplatin + Leucovorin + 5-FU) was administered from february 27, 2020, to march 16, 2020. After two cycles, the patient developed a severe reaction, leading to a switch to the CAPOX regimen starting with the third cycle on april 4, 2020. The patient successfully completed the fourth cycle of CAPOX on may 22, 2020.

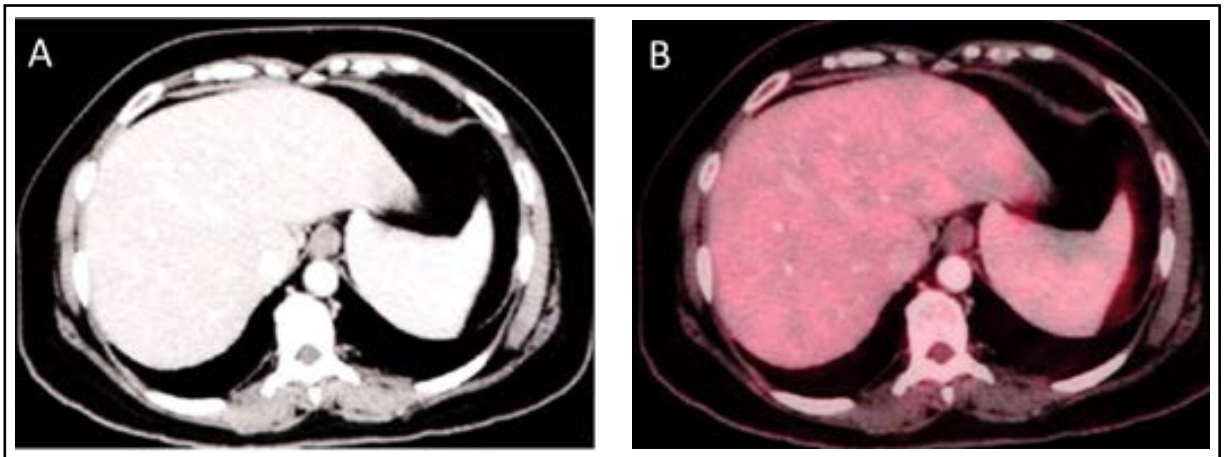

Figure 2: Schematics depicting Clinical timeline of the case.

Following the CAPOX treatment, a whole-body PET-CT scan was performed on june 10, 2020, to assess the treatment response. The scan showed FDG-avid circumferential growth involving thickening of the recto-sigmoidal colon with perirectal fat stranding (Figures 3 and 4). Presacral nodes exhibited reduced metabolic activity compared to the prior baseline examination, with no evidence of hypermetabolic activity elsewhere in the body. Overall, the PET-CT scan indicated a partial response to chemotherapy. To manage the residual disease, radiation therapy (50.4 Gy/28 fractions) was administered over six weeks, starting on june 18, and completed on august 5, 2020. Concurrent CAPECITABINE was given at a total dose of 1650 mg/m^2/day in two divided doses alongside the radiotherapy.

Subsequently, on september 22, 2020, the patient underwent laparoscopic anterior resection. Histopathological examination of the laparoscopic biopsy specimen (22 cm × 9 cm × 7 cm) revealed a tumor mass measuring 1 cm × 1 cm × 0.5 cm, located 16 cm proximally and 4 cm distally. Nodal infiltration was observed in 10 nodes, with the largest node measuring 1.5 cm × 1.5 cm. Microscopic examination indicated residual viable moderately differentiated adenocarcinoma with mucin secretion through the muscularis propria involving the subserosa. No lymphovascular emboli or perineural invasion was noted. The Circumferential Resection Margin (CRM) and resection margins were free of the tumor. Five out of ten examined nodes showed metastatic infiltration with perinodal extension. The overall histopathological impression indicated the presence of residual viable moderately differentiated rectal carcinoma with nodal metastasis. The tumor was classified as regressive with a TRG II.

During this period, the patient also underwent right ureteric reimplantation due to right hydronephrosis and ureteric stricture. On december 15, 2020, the patient underwent colostomy closure to restore normal bowel function and removal of the double J stent to ensure proper urinary function.

Following the colostomy closure, the patient received an additional three cycles of CAPOX chemotherapy (Cycle 6 on 7th january 2021, Cycle 7 on 28th january 2021, and Cycle 8 on 20th february 2021). The CAPOX regimen included reduced doses of capecitabine due to the patient's grade 3 peripheral neuropathy. Capecitabine treatment was continued to manage this condition.

To assess the therapy's effectiveness, a whole-body PET-CT scan was performed on 21st march 2021. The scan revealed no metabolic activity at the primary tumor site or anywhere else in the body, indicating an absence of metastatic disease. Encouraged by these results, we proceeded with a liquid biopsy to detect any residual disease at the molecular or cellular level.

The liquid biopsy, focused on Circulating Tumor Cells (CTCs), was conducted using the DCGI-approved OncoDiscover test developed by Actorius Innovation and Research in Pune. This highly sensitive and minimally invasive assay required only 1.5 ml of the patient's blood. CTCs were isolated using magnetic nanoparticles coated with anti-EpCAM antibodies, which specifically target cancer cells of epithelial origin. These CTCs were magnetically captured, processed and confirmed through immunofluorescence using automated fluorescence imaging (Zeiss Axioscope Z1). The assay identified two CTCs in the patient's blood sample, suggesting the presence of residual disease undetectable by PET-CT. Figure 5 shows representative image of a CTC isolated from peripheral blood of this patient.

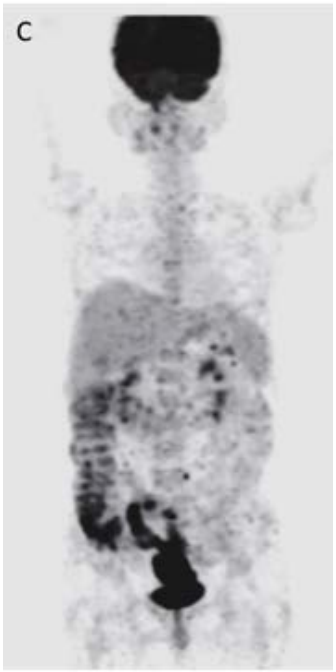

Figure 3: Whole body-PET scan indicating hypermetabolic activity of rectal segment and multiple perirectal metastatic nodes.

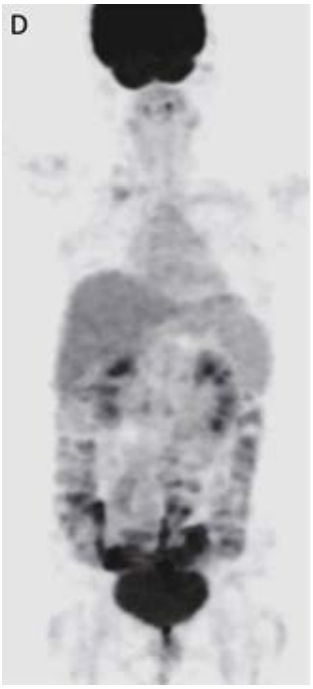

Figure 4: Whole body PET scan showing partial response to CAPOX treatment.

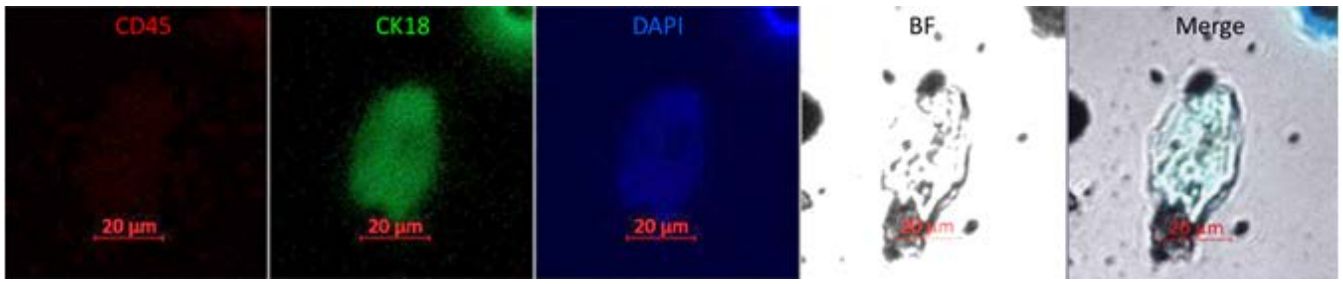

Figure 5: Representative image of a CTC isolated from peripheral blood of the patient. Single CTC showing absence of CD 45 expression (left panel image, red channel), presence of cytokeratin 18 (CK18, green channel, second panel from the left) and a well-defined nucleus (middle panel). Brightfield (second panel from the right) and merged (right panel image) images of the same fluorescence channels.

In response to the CTC findings, we decided to closely monitor the patient and performed an anterior and posterior MRI examination. The MRI results (Figure 6) showed no evidence of residual or recurrent lesions at the anastomotic site. However, multiple ill-defined lesions were unexpectedly discovered in liver segments VIII and IV, measuring approximately 4 mm-6 mm. These lesions exhibited restricted diffusion and enhancement during the portal venous phase. Other abdominal structures, including the pancreas, appeared normal and free of focal lesions.

Given the MRI findings, we initiated second-line chemotherapy, ad-ministering one cycle of FOLFIRI on 1st April 2021. To target the liver lesions more effectively, the patient was recommended for SIRT, which was conducted on 15th April 2021 at Tata Memorial Hospital in Mum-bai. Following SIRT, the patient received an additional five cycles of FOLFIRI.

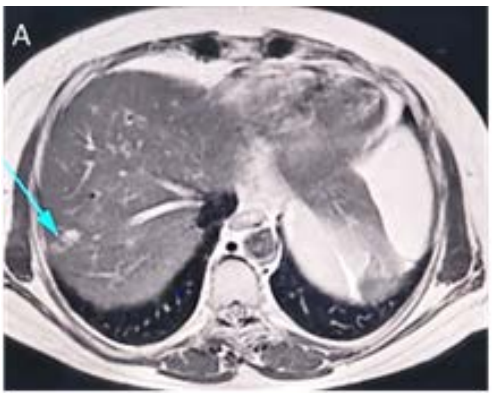

Figure 6: MRI image of the hepatic region clearly indicating the presence of metastatic lesions (pre-embolization).

Upon completing FOLFIRI treatment, a follow-up whole-body PET-CT scan in january 2022 showed normal metabolic activity, with no hypermetabolic lesions in the liver or other abdominal areas, including the colectomy regions (Figures 7 and 8). OncoDiscover CTC detection test performed thereafter did not show presence of any CTC in blood. A recent PET-CT scan in july 2024 also confirmed normal metabolic parameters with no signs of hypermetabolic activity. OncoDiscover CTC test results were negative, indicating the patient to be completely disease free at a cellular level.

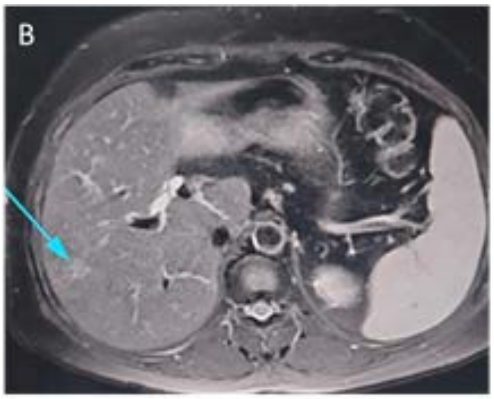

Figure 7: Post-embolization, SIRT and FOLFIRI treatment MRI image showing disappearing metastatic lesions.

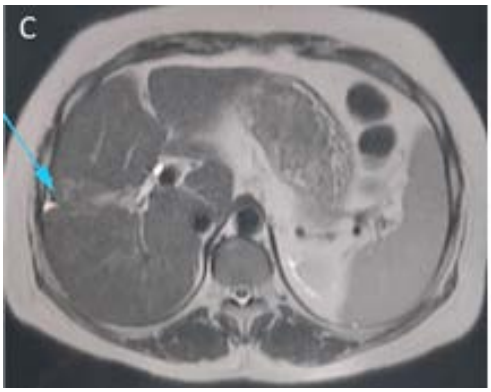

Figure 8: Post treatment MRI showing the lesion-free status of the liver along with reduced perihepatic fluid, and abdominal regions, suggesting patient to be disease free.

Discussion

In this report, we present a compelling case of a 70-year-old patient diagnosed with stage III rectal cancer, a common subtype of colorectal cancer. The significance of this case lies in the detection of Minimal Residual Disease (MRD) at the cellular level through Circulating Tumor Cells (CTCs) via liquid biopsy, even when the patient was deemed clinically 'disease-free' based on radiological assessments. Advanced colorectal cancer, particularly in stages III and IV, has a notorious tendency for distant metastasis, especially to the liver, making it difficult to manage [16]. The five-year survival rate for such cases remains dismally low at 13%, largely due to metastatic relapse, which often remains undetected until it becomes unmanageable with curative treatments [17]. Thus, early detection of relapse or residual disease before the onset of metastasis is critical after completing curative treatments.

Liquid biopsy has emerged as a powerful tool for monitoring disease relapse and detecting MRD at molecular and cellular levels [18-20]. Both CTCs and ctDNA are blood-based biomarkers with significant prognostic value and are effective in monitoring therapy responses [21]. The presence of CTCs or ctDNA is strongly correlated with clinical outcomes, including survival and disease progression [22]. Detecting plasma ctDNA or CTCs in Colorectal Cancer (CRC) patients after surgery, or chemotherapy strongly suggests the presence of MRD [23].

In this particular case, we highlight the utility of CTCs in detecting MRD in a patient with locally advanced stage III rectal cancer. The patient underwent Neoadjuvant Chemotherapy/Radiation Therapy (NACT/RT) followed by surgery and systemic chemotherapy. Radiological evaluations indicated no detectable malignant lesions, suggesting a disease-free status. However, CTC analysis conducted post-treatment was positive, indicating the presence of the disease in an occult stage. This prompted CTC-guided close monitoring of the patient, leading to subsequent MRI analysis, which revealed possible liver metastasis. The metastasis was managed with chemotherapy and Selective Internal Radiation Therapy (SIRT). Following the completion of therapy, the patient has remained off treatment without any signs of recurrence, and routine CTC analyses have shown no presence of CTCs, suggesting the patient is currently disease-free.

CTC and ctDNA-based liquid biopsies are rapidly gaining traction in clinical settings due to their superiority over traditional radiological imaging in detecting MRD at the cellular and molecular levels [14]. Numerous clinical trials and ongoing research strongly support the use of ctDNA and CTC-guided monitoring in CRC patients for MRD detection. For instance, the Dynamic trial, which involved stage II colon cancer patients, demonstrated the benefits of ctDNA-guided therapy approaches for stratifying patients based on their risk of recurrence [24]. Additionally, ctDNA-guided approaches reduced the risk of overtreatment with adjuvant chemotherapy without compromising recurrence-free survival. Similarly, the MIRACLE trial, which involved resectable CRC patients with liver metastasis, underscored the utility of ctDNA and CTCs for prognosis and peri-hepatic recurrence monitoring [25]. While preoperative detection of CTCs and ctDNA did not correlate with relapse-free survival, postoperative detection was prognostic for relapse-free survival, further emphasizing the role of these biomarkers in identifying patients at risk of recurrence and in stratifying those who may not require additional therapy.

Although our case report strongly demonstrates the utility of CTCs for guided monitoring and informed treatment decisions, it requires further validation through case-controlled clinical trials. Additionally, our findings are limited to the detection and enumeration of CTCs, as downstream molecular characterization was not possible due to the scarcity of detected CTCs in the patient. Nevertheless, our findings clearly indicate the potential of CTCs as markers for MRD and therapy response in patients with locally advanced resectable CRC.

Conclusion

In this case report we demonstrate the utility of CTC as a sensitive marker to detect MRD. CTCs play a crucial role in the context of MRD in colorectal cancer, offering a valuable biomarker for prognosis, treatment monitoring, and early detection of recurrence. Despite the challenges in their clinical application, CTCs hold great potential to transform the management of CRC by enabling more personalized and effective treatment approaches. As technology advances, the integration of CTC analysis into routine clinical practice may become a reality, significantly improving outcomes for patients with colorectal cancer.

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