CTC or CEA: Choosing Reliable Markers for Metastatic Colorectal Cancer

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Colorectal cancer (CRC) represents one of the most common causes of disease and death globally. CRC ranks as the third most commonly diagnosed malignancy, and approximately 10% of all global cancer cases.[1,2] In 2022, more than 1.4 million of new CRC cases were reported globally, and this incidence is predicted to rise an estimated 3.2 million cases by 2040.[2] Interestingly, CRC has shown a shifting incidence toward younger age groups. In the United States, approximately 18,000 new cases are diagnosed in individuals under 50 years of age.[3]

The clinical manifestations of CRC include persistent changes in bowel habits, abdominal pain, hematochezia, anemia, and weight loss.[4] Several risk factors are known to contribute in CRC development, including a family history of colorectal cancer, diets high in red or processed meat, smoking, excessive alcohol consumption, sedentary lifestyle, and elevated body mass index.[5] Diagnosis of CRC generally involves a combination of clinical evaluation, endoscopic procedures, and histopathological confirmation via biopsy. Radiological imaging and laboratory investigations further support disease staging and treatment planning.[6] However, early-stage CRC frequently remains asymptomatic, leading to late presentation in a substantial proportion of patients

Clinically, about 15–30% of patients present with metastatic disease at the first time of diagnosis. Moreover, 20–50% of patients with localized CRC are risk of developing distant metastases during the course of their illness.[7] These findings underscore the critical importance of early detection and timely intervention in improving survival outcomes. Limited access to effective screening programs in many regions also contributes to delays in diagnosis and worsened prognoses.[8] Among the various cancer biomarkers investigated, Circulating Tumour Cells (CTCs) and Carcinoembryonic Antigen (CEA) gaining attention for their roles in monitoring of cancer metastases and recurrence especially in colorectal cancer.[9]

CIRCULATING TUMOUR CELLS (CTCS)

Circulating Tumour Cells (CTCs) are malignant cells that detach from the primary tumour and enter the bloodstream.[9] Their presence was first reported in 1869 by Ashworth, who identified tumour-like cells in the blood of a patient with metastatic cancer.[10] Over the past decade, CTCs have gained recognition as a "real-time liquid biopsy" for solid tumours. Compared with traditional tissue biopsy, CTC analysis is minimally invasive, can be repeated over time, and provides dynamic insights into tumour biology and disease progression.[11]

Despite their potential, detecting CTCs remains technically challenging due to rare in the bloodstream and are highly fragile.[11] Nevertheless, their presence in the circulation is closely linked to the metastatic process. When tumour cells intravasate into the bloodstream, they may adhere to distant tissues and initiate the formation of secondary metastatic sites. Thus, the detection of CTCs serves not only as a marker of tumour cell dissemination but also as a predictor of disease progression and prognosis. Patients with higher CTC counts generally have poorer survival outcomes compared with those with lower counts.[12]

Several studies have demonstrated a positive correlation between CTC levels and tumour progression, even in patients without overt metastases. Specifically, higher CTC counts are often associated with advanced tumour stage (T and N classification), larger tumour size, and lower histological differentiation. For instance, patients with ≥5 CTCs per 2 mL of peripheral blood have been shown to have a greater likelihood of distant metastasis than those with <5 CTCs.[13]

CTCs exhibit marked heterogeneity, encompassing epithelial, mesenchymal, and hybrid phenotypes.[12] This phenotypic diversity adds complexity to understanding their metastatic potential, as each subtype may differ in its capacity for survival, adaptation, and tissue invasion. Within the harsh and immune-surveilled environment of the bloodstream, platelets play a crucial role in protecting CTCs.[12] Clinically, thrombocytosis has been associated with poorer outcomes in CRC patients, reflecting its role in promoting CTC persistence and metastatic dissemination.

CARCINOEMBRYONIC ANTIGEN (CEA)

Carcinoembryonic Antigen (CEA) is a glycoprotein first isolated from human colorectal carcinoma tissue in 1965 by Gold and Freedman.[14] It functions primarily in cell adhesion and normally produced in gastrointestinal tissues during fetal development. In healthy non-smokers, serum CEA levels are typically low (0–3 ng/mL), while levels up to 5 ng/mL in smokers.[15] Elevated CEA concentrations can also occur in several benign conditions as well as in malignancies of the gastrointestinal tract, lungs, and breasts.[16]

In CRC, serum CEA serves as one of the most widely used biomarkers for disease monitoring. As a non-invasive, inexpensive, and safe blood test.[17] CEA measurement is commonly employed in follow-up assessments to detect recurrence or monitor response to therapy.[15,18] Nevertheless, it has limited sensitivity and specificity for early-stage disease and should not be used as a standalone screening tool.

Current clinical guidelines recommend assessing serum CEA levels prior to initiating therapy and at three-month intervals during active treatment. Importantly, measurement should not be performed too early specifically within four to six weeks before starting a new therapeutic regimen since certain chemotherapeutic agents may cause transient, misleading elevations in CEA levels.[19]

OTHER BIOMARKER

Beyond CTC and CEA, other biomarkers have been identified to play crucial roles in the diagnosis and therapeutic management of CRC. Circulating tumor DNA (ctDNA) has emerged as a rapidly advancing biomarker with significant potential in CRC management. It serves not only as a diagnostic and prognostic tool but also as a means for therapeutic monitoring, including the detection of minimal residual disease (MRD).[20]

In metastatic CRC, studies have demonstrated that ctDNA exhibits a sensitivity of 87.2% in detecting clinically relevant KRAS mutations, with a specificity of 99.2%, highlighting its high accuracy in identifying actionable genetic alterations.[21] The BRAF gene, which encodes a serine-threonine kinase protein that regulates the MAPK signaling pathway downstream of KRAS, has been recognized as an important prognostic biomarker and potential therapeutic target in CRC.[22] Meanwhile, KRAS mutations, occurring in approximately 30–40% of CRC cases, are associated with poor clinical outcomes and resistance to anti-EGFR therapies, underscoring their clinical relevance in guiding treatment decisions.[23]

CONCLUSION

Combining both CTC and CEA as biomarkers to monitor CRC development to either metastases and recurrence might become an alternative to prevent further mortality and morbitdities in patients with CRC. While CEA provides valuable information on tumor burden and treatment response, CTCs offer deeper molecular and cellular insights into tumor dynamics and metastatic potential.

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