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**Title:** The clinical relevance of circulating tumour DNA in colorectal cancer

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Circulating tumour DNA (ctDNA) is a novel biomarker with significant translational utility in the treatment of colorectal cancer (CRC).[1] DNA is a representation of the genetic make-up of a tumour cell, and is usually found within its nucleus. Tumour proliferation involves significant tumour-cell shedding, which subsequently releases intra-nuclear tumour DNA into the bloodstream, detectable as circulating tumour DNA.[2] There has been a recent rapid development in the application of ctDNA in the treatment of several malignancies, including CRC.

In recent years, significant technological developments have been made, allowing for more sensitive detection, and enrichment of ctDNA in the plasma of patients either by polymerase chain reaction or next-generation DNA sequencing. These improvements deliver a level of accurate ctDNA measurement that makes clinical application possible. The level of ctDNA in plasma of patients with CRC is dependent on their tumour stage, with higher levels of ctDNA detected with more advanced disease. ctDNA has been found to be detected in up to 73% of patients with advanced CRC, and in more than 90% of patients with stage IV disease.[3] ctDNA dynamics has been shown to reflect tumour burden where levels of ctDNA have shown to be significantly reduced following curative resection of CRC, and are often undetectable.[4] The presence of ctDNA in such patients following curative surgery is defined as minimal residual disease, and has been shown in multiple studies to be associated with disease recurrence.[5-8]

In the landmark prospective observational multicentre Australian study of curatively resected Stage II CRC, the rates of minimal residual disease were found to be between 8 – 15%.[6] ctDNA

was detectable after surgery in 14 of 178 (7.9%) patients, with 11 of these 14 patients (79%) subsequently developing distant recurrence after a median follow-up of 27 months. Comparatively, only 16 of 164 patients who had undetectable ctDNA levels post-operatively developed distant recurrence; conferring an overall hazard ratio of 18 (95% confidence interval 7.9-40 p=0.001).[6] These findings have now been reproduced across multiple cohorts of CRC in several studies supporting the role of ctDNA being a possibly strong predictor of recurrence following curative surgery for CRC. Such encouraging findings suggest the current imprecise approach to selecting patients for adjuvant chemotherapy can be further refined to deliver the highest therapeutic benefit to high risk for distant recurrence.

These findings have also been correlated by rectal cancer studies, with post-operative ctDNA found to be a strong predictor of disease recurrence, independent of conventional clinicopathological risk factors, in patients who undergo curative resection for locally advanced rectal cancer following neoadjuvant chemoradiatherapy.[9,10] The benefits of adjuvant chemotherapy in such patients following curative rectal cancer resection have long been debated [11-13] despite the fact that approximately 30% of these patients develop distant metastases.[14] Findings from ctDNA studies suggest a role for ctDNA measurement post-operatively in appropriate selecting patients from this subset for adjuvant chemotherapy, based on their risk of recurrence.[15]

Additionally, ctDNA could play an important role in patient selection for curative surgery following neoadjuvant chemoradiotherapy for rectal cancer. It is estimated that 15 – 25% of

patients who undergo neoadjuvant chemoradiotherapy have a complete pathological response.[16] A rectal preservation approach may be suitable for these patients if they meet the appropriate criteria; a complete clinical response, and a confirmation that no residual tumour is left on endoscopic visualisation of the irradiated tumour bed, magnetic resonance imaging and/or positron emission tomography.[17] However, the uptake of such an approach has been limited, and due greatly in part to the high risk of local recurrence of rectal cancer.[17] Absence of ctDNA, or a significant reduction in ctDNA, following neoadjuvant chemoradiotherapy may be considered to be an additional surrogate marker of complete pathological response. This may preclude the need for curative surgery with the morbidity it entails in patients with low or absent ctDNA levels following neoadjuvant chemoradiotherapy, while maximising their oncological outcomes.

Finally, ctDNA is useful in monitoring the therapeutic response for metastatic CRC.[18] While imaging has traditionally been used for this purpose, utilising ctDNA to gauge therapeutic response carries the advantage of identifying these responses at an earlier stage. A 2015 study on patients with metastatic CRC found that a significant reduction in ctDNA measured just prior to the second cycle of chemotherapy (14 - 21 days following treatment onset) was correlated with a therapeutic response on computer tomography imaging at 8 – 10 weeks (Odds Ratio 5.25, 95% confidence interval 1.38-19.93, p=0.0016). Early ctDNA response in first-line chemotherapy can therefore be considered as a predictive factor of later radiologic response, and may allow for timely cessation of toxic chemotherapeutic regimens.

ctDNA is rapidly being validated for clinical utility, and has many possible clinical applications in the treatment of CRC. Crucially, ctDNA may predict the recurrence of CRC following curative resection, refine patient selection for curative rectal resection or adjuvant chemotherapy, and predict radiologic response to chemotherapy in metastatic CRC. As we wait for numerous randomised controlled trials investigating the role of ctDNA in tailoring adjuvant chemotherapy to mature, it is likely ctDNA will be a unique biomarker for daily clinical applicability.

| **Contributions** | **By which author** |
|---|---|
| Substantial contributions to the conception and design and interpretation of data | All authors |
| Drafting and revising the article | All authors |
| Final approval of the version to be published | All authors |

**Reference**


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