

ctDNA Predicts Relapse in Early Cancer, but Clinical Action Remains Unclear

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The detection of circulating tumour DNA (ctDNA) after curative-intent surgery for early-stage solid tumours strongly correlates with an increased risk of disease recurrence. However, the immediate clinical utility of this information, specifically whether it should prompt escalation of adjuvant therapy in ctDNA-positive patients, remains a significant dilemma for oncologists.

KEY TAKEAWAYS

- **The Pivot:** ctDNA offers a highly sensitive method for detecting minimal residual disease (MRD) post-surgery, improving prognostication beyond conventional imaging.
- **The Data:** Patients with detectable ctDNA post-surgery consistently demonstrate a significantly higher risk of relapse, with hazard ratios often ranging from HR 3.0 to 10.0 across various tumour types.
- **The Action:** While ctDNA is a powerful prognostic marker, current evidence does not support routine modification of adjuvant treatment strategies based solely on ctDNA status outside of clinical trials.

Minimal residual disease (MRD) after curative-intent surgery for solid tumours is a primary driver of disease recurrence. Traditional methods for detecting MRD, such as imaging and serum tumour markers, often lack the sensitivity to identify microscopic disease.¹ Circulating tumour DNA (ctDNA) analysis, which detects tumour-derived DNA fragments in the bloodstream, has emerged as a highly sensitive tool for MRD detection.² The presence of ctDNA post-surgery is consistently associated with an elevated risk of relapse across various cancer types, including colorectal, breast, lung, and gastric cancers.³ This prognostic capability has led to interest in using ctDNA to guide adjuvant therapy decisions.

What the studies show

Multiple prospective and retrospective studies have demonstrated the prognostic value of post-operative ctDNA. For instance, in stage II colorectal cancer, patients with detectable ctDNA after surgery exhibit a significantly higher risk of recurrence compared to ctDNA-negative patients. One meta-analysis reported a pooled hazard ratio for recurrence-free survival of HR 7.4 (95% CI 5.6 - 9.8) for ctDNA-positive versus ctDNA-negative patients.⁴ Similar observations have been made in early-stage breast cancer, where ctDNA detection post-surgery predicted recurrence with a hazard ratio often exceeding HR 5.0.⁵ In non-small cell lung cancer (NSCLC), post-operative ctDNA positivity has been linked to a 3- to 10-fold increased risk of relapse.⁶

The methodology for ctDNA detection typically involves next-generation sequencing (NGS) of plasma samples. This can include tumour-informed approaches, where a patient's primary tumour tissue is sequenced to identify somatic mutations, and then a personalised assay tracks these specific mutations in plasma. Alternatively, tumour-agnostic approaches

screen for a broader panel of cancer-associated mutations without prior tumour sequencing. The choice of assay impacts sensitivity and specificity, with tumour-informed methods generally offering higher sensitivity for MRD detection. Blood samples are usually collected at specific time points post-surgery, often several weeks after resection to allow for clearance of ctDNA from the surgical procedure itself. The half-life of ctDNA in circulation is short, typically hours, making it a dynamic marker of disease burden. This rapid clearance allows ctDNA levels to reflect the presence of active, proliferating tumour cells.

Despite this strong prognostic association, evidence supporting the use of ctDNA to escalate or de-escalate adjuvant therapy outside of a clinical trial setting is limited. Several ongoing randomised controlled trials are investigating ctDNA-guided adjuvant therapy. For example, trials in colorectal cancer are randomising ctDNA-positive patients to either standard adjuvant chemotherapy or intensified regimens, while ctDNA-negative patients may be considered for de-escalation or observation.⁷ Preliminary data from some of these trials suggest that ctDNA-guided de-escalation in ctDNA-negative patients may be safe, but definitive results on escalation strategies are still pending.⁸

The primary limitation is the absence of level 1 evidence from large, randomised controlled trials demonstrating that acting on ctDNA positivity improves patient outcomes (e.g., overall survival or disease-free survival) beyond standard-of-care adjuvant therapy. While ctDNA can identify patients at high risk of relapse, it is not yet clear whether intensifying treatment in these patients provides a clinical benefit that outweighs the potential toxicities.⁹ Furthermore, standardisation of ctDNA assays, including sensitivity, specificity, and optimal timing of sampling, remains an area of active research. The analytical sensitivity required to detect MRD means that false positives, though rare, could lead to unnecessary treatment, while false negatives could provide false reassurance.¹⁰ The clinical utility of ctDNA also depends on the specific cancer type and stage. For instance, in very early-stage cancers with low recurrence risk, the absolute benefit of intensified therapy based on ctDNA positivity might be modest, even if the relative risk is high. Conversely, in higher-risk early-stage cancers, the potential for benefit from targeted intervention might be greater. The cost-effectiveness of routine ctDNA testing and subsequent therapy modifications also requires careful consideration, particularly in healthcare systems with resource constraints. The integration of ctDNA into routine clinical practice will necessitate clear guidelines on patient selection, assay interpretation, and subsequent therapeutic algorithms, all supported by robust clinical evidence.

CLINICAL IMPLICATIONS

The enthusiasm surrounding ctDNA as a prognostic marker is understandable; it offers a level of sensitivity for detecting microscopic disease that conventional methods simply cannot match. However, the current clinical landscape for ctDNA is one of profound prognostic power without clear therapeutic direction. Oncologists are now faced with a highly accurate crystal ball that shows a high probability of relapse, but without a proven intervention to alter that outcome. Prescribing additional, potentially toxic, adjuvant therapy based solely on a ctDNA signal, absent robust randomised data demonstrating improved survival, is premature and potentially harmful. This is particularly relevant given the financial implications for healthcare systems and patients, as these advanced molecular tests are not inexpensive, and subsequent intensified treatments carry their own substantial costs.

Pharmaceutical companies and diagnostic developers are heavily invested in this space, and rightly so. The

potential for companion diagnostics to guide targeted therapies in the adjuvant setting is immense. However, the industry must prioritise the generation of definitive clinical trial data demonstrating a survival benefit from ctDNA-guided interventions, rather than simply marketing the prognostic utility. Guideline bodies like ASCO and ESMO will need to carefully weigh the emerging evidence, ensuring that any recommendations for ctDNA-guided therapy are grounded in improved patient outcomes, not just improved risk stratification. Without this, ctDNA risks becoming another piece of information that creates anxiety for patients and clinicians without offering a tangible solution.

For patients, the knowledge of ctDNA positivity can be a double-edged sword. While it offers a clearer picture of their individual risk, it also presents the psychological burden of knowing they are at high risk of recurrence, often without a clear, evidence-based treatment path to mitigate that risk. Until large-scale trials confirm that acting on ctDNA status improves survival, its use should largely remain within the confines of clinical research, where its true therapeutic potential can be rigorously evaluated.

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