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Postoperative Circulating Tumor DNA as a Marker of Molecular Residual Disease in Stage II–III Colorectal Cancer: A Systematic Review

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ABSTRACT

Postoperative recurrence remains a major challenge in stage II–III colorectal cancer (CRC) despite curative-intent surgery and adjuvant chemotherapy. Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for detecting molecular residual disease (MRD) and for recurrence surveillance. This systematic review evaluated the prognostic utility of postoperative ctDNA in stage II–III CRC. Methods: A systematic review was conducted according to PRISMA guidelines, using PubMed/MEDLINE, Scopus, Web of Science, the Cochrane Library, and Google Scholar to identify studies published between 2015 and 2026. Eligible studies involved adults with stage II–III CRC undergoing curative-intent surgery and evaluated postoperative ctDNA in relation to recurrence or survival outcomes. Eight studies involving 1,557 patients were included. Postoperative ctDNA positivity was consistently associated with significantly increased recurrence risk and inferior oncologic outcomes, with reported hazard ratios ranging from 3.8 to 50.76. Serial ctDNA monitoring enabled recurrence detection approximately 5–10 months earlier than conventional imaging or carcinoembryonic antigen surveillance. Most studies demonstrated that ctDNA-guided management reduced the use of adjuvant chemotherapy without compromising recurrence-free survival. Postoperative ctDNA demonstrates strong prognostic value as a biomarker of MRD in stage II–III CRC and may facilitate more individualized postoperative surveillance and treatment strategies.

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INTRODUCTION

Colorectal cancer (CRC) remains a major global health burden and is currently the third most commonly diagnosed malignancy and the second leading cause of cancer-related mortality worldwide (H. Chen et al., 2025; Lukman et al., 2024; Roshandel et al., 2024). Advances in screening, surgery, and systemic therapy have occurred, but postoperative recurrence remains a major challenge, particularly in stage II–III disease, where about 15–30% of patients develop recurrence despite curative-intent resection and adjuvant chemotherapy (Khan et al., 2025; Ozluk et al., 2026). The prognosis of CRC remains highly stage-dependent, with survival declining substantially once recurrent or metastatic disease develops (H. Chen et al., 2025). Thus, improving postoperative risk stratification and early detection of residual disease has become a central focus in contemporary colorectal oncology.

Curative-intent surgery remains the cornerstone of treatment for localized stage II–III CRC. However, postoperative management presents substantial challenges. Conventional clinicopathological parameters, such as TNM staging, lymphovascular invasion, tumor grade, and mismatch repair status, offer only indirect estimates of recurrence risk and are insufficient to accurately identify patients with molecular residual disease (MRD) (Hsieh et al., 2026; Kotani et al., 2023; Ozluk et al., 2026). Standard surveillance, including carcinoembryonic antigen (CEA), computed tomography (CT), and endoscopic evaluation, also has limited sensitivity for early recurrence and has not consistently led to meaningful survival improvements (Krell et al., 2024; Nguyen et al., 2024). These limitations have intensified interest in biomarkers capable of detecting occult residual disease with greater precision and enabling more individualized postoperative management.

Liquid biopsy has emerged as a promising strategy in precision oncology, enabling minimally invasive and dynamic assessment of tumor biology. Among available liquid biopsy biomarkers, circulating tumor DNA (ctDNA), the tumor-derived fraction of circulating cell-free DNA, has gained considerable attention in CRC (H. Chen et al., 2025; Ozluk et al., 2026). ctDNA contains tumor-specific genomic and epigenomic alterations and demonstrates rapid clearance kinetics, enabling real-time assessment of tumor burden and postoperative MRD status (H. Chen et al., 2025). Emerging evidence indicates that postoperative ctDNA positivity is strongly associated with recurrence risk, inferior disease-free survival (DFS), recurrence-free survival (RFS), and overall survival (OS) in stage II–III CRC (Diergaarde et al., 2025; Grancher et al., 2022). In addition, serial ctDNA surveillance has demonstrated the ability to detect recurrence several months earlier than conventional radiologic assessment (Holz et al., 2025; Nguyen et al., 2024). These findings suggest that ctDNA may redefine postoperative surveillance and facilitate risk-adapted therapeutic strategies in CRC management.

Despite these promising developments, several important challenges continue to limit the integration of ctDNA into routine clinical practice. Considerable heterogeneity exists regarding assay platforms, sampling timing, mutational panels, ctDNA thresholds, and tumor-informed versus tumor-agnostic approaches, limiting direct comparison across studies and reducing the generalizability of findings (Khan et al., 2025; Ozluk et al., 2026). In addition, biological factors such as tumor burden, histologic subtype, and metastatic site may influence ctDNA shedding and detection sensitivity, potentially leading to false-negative results in low-volume disease (H. Chen et al., 2025). Although ctDNA has demonstrated strong prognostic utility, its role as a predictive biomarker for guiding adjuvant treatment escalation or de-escalation remains incompletely established (Ozluk et al., 2026). Furthermore, previous reviews have

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generally evaluated ctDNA across heterogeneous CRC stages or broader clinical applications, with limited emphasis on the specific role of postoperative ctDNA as an MRD biomarker in stage II–III CRC (Krell et al., 2024; Vojjala et al., 2025).

Given the rapidly expanding evidence and the rising clinical relevance of ctDNA-guided postoperative management, a focused synthesis of the current literature is timely and necessary. This systematic review evaluates the prognostic utility of postoperative ctDNA as a marker of molecular residual disease in patients with stage II–III colorectal cancer undergoing curative-intent surgery. By synthesizing contemporary evidence on recurrence prediction, survival outcomes, and surveillance utility, this review clarifies the current clinical role of postoperative ctDNA and identifies key limitations, evidence gaps, and future directions for integration into precision colorectal oncology.

METHODS

Search Strategy

This systematic review followed the Cochrane Handbook for Systematic Reviews of Interventions. Reporting was structured to conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A comprehensive electronic search was conducted across PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, and Google Scholar. Controlled vocabulary and free-text keywords were used based on three domains: circulating tumor DNA (ctDNA), molecular residual disease (MRD), and colorectal cancer.

Search strings were constructed with Boolean operators (AND/OR). Terms included: “circulating tumor DNA” OR ctDNA, “molecular residual disease” OR MRD, “colorectal cancer” OR “colon cancer” OR “rectal cancer,” and “postoperative” OR “post-surgical” OR “curative surgery.” Additional terms such as “recurrence,” “disease-free survival,” “recurrence-free survival,” and “surveillance” were included to improve sensitivity. No restrictions were placed on the ctDNA assay platform or surveillance protocol. The search included studies from 2015 to 2026 and was limited to English articles. The final literature search was conducted in March 2026. Reference lists of eligible studies and relevant reviews were also manually screened to identify additional studies. This review protocol was not prospectively registered.

Table 1. Keywords for Search Strategy

Database	Search Terms Used
PubMed/MEDLINE	("circulating tumor DNA" OR ctDNA) AND ("molecular residual disease" OR MRD OR "minimal residual disease") AND ("colorectal cancer" OR CRC OR "colon cancer" OR "rectal cancer") AND (postoperative OR postsurgical OR "curative surgery" OR resection) AND (recurrence OR relapse OR prognosis OR surveillance OR "disease-free survival" OR "recurrence-free survival" OR "overall survival")
Scopus	TITLE-ABS-KEY(("circulating tumor DNA" OR ctDNA) AND ("molecular residual disease" OR MRD OR "minimal residual disease") AND ("colorectal cancer" OR CRC OR "colon cancer" OR "rectal cancer") AND (postoperative OR postsurgical OR surgery OR resection) AND (recurrence OR relapse OR surveillance OR prognosis OR "disease-free survival"))

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Database	Search Terms Used
Web of Science	TS=(("circulating tumor DNA" OR ctDNA) AND ("molecular residual disease" OR MRD OR "minimal residual disease") AND ("colorectal cancer" OR CRC OR "colon cancer" OR "rectal cancer") AND (postoperative OR postsurgical OR surgery OR resection) AND (recurrence OR relapse OR surveillance OR prognosis OR "disease-free survival"))
Google Scholar	("circulating tumor DNA" OR ctDNA) "colorectal cancer" postoperative recurrence surveillance "molecular residual disease"
Cochrane Library	("circulating tumor DNA" OR ctDNA) AND ("molecular residual disease" OR MRD) AND ("colorectal cancer" OR "colon cancer" OR "rectal cancer") AND (postoperative OR surgery OR resection) AND (recurrence OR surveillance OR "disease-free survival")

Study Selection

All records found were exported to reference management software. Duplicate articles were removed. Two reviewers independently screened titles and abstracts, then assessed full texts according to predefined criteria. Only original observational and interventional studies were included. These comprised prospective cohort studies, retrospective cohort studies, longitudinal surveillance studies, and randomized controlled trials. Eligible studies had to meet three criteria: (1) involve adults with stage II–III colorectal cancer who underwent curative-intent surgery; (2) evaluate postoperative circulating tumor DNA (ctDNA) as a marker of molecular residual disease (MRD) or recurrence risk; and (3) report oncologic outcomes such as recurrence, disease-free survival (DFS), recurrence-free survival (RFS), overall survival (OS), or recurrence surveillance performance.

Studies were excluded if they were narrative reviews, systematic reviews, meta-analyses, or conference abstracts without full-text availability. Editorials, expert opinions, case reports, animal studies, and laboratory-only investigations were also excluded. Studies involving unresectable or metastatic colorectal cancer without curative-intent surgery were not considered. Studies focused on non-colorectal cancers or non-postoperative ctDNA uses were excluded. The study selection process will be shown with a PRISMA flow diagram.

Table 2. PICO Framework

Population (P)	Intervention/Exposure (I)	Comparison (C)	Outcome (O)
Adults with stage II–III colorectal cancer undergoing curative-intent surgery	Detectable postoperative circulating tumor DNA (ctDNA-positive) as a marker of molecular residual disease	Undetectable postoperative circulating tumor DNA (ctDNA-negative)	Recurrence, disease-free survival (DFS), recurrence-free survival (RFS), overall survival (OS), and recurrence surveillance performance

Data Extraction

Two reviewers independently extracted data using a standardized form. Variables included authors, publication year, country, study design, patient population, sample size, cancer stage, ctDNA assay

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platform, timing of ctDNA assessment, follow-up duration, and reported oncologic outcomes. Specific ctDNA-related variables included assay method (such as droplet digital PCR, targeted next-generation sequencing, or tumor-informed assays). Timing of postoperative blood collection, surveillance interval, ctDNA positivity rates, and recurrence lead-time compared to imaging or CEA monitoring were recorded. Outcome measures included recurrence rate, disease-free survival, recurrence-free survival, overall survival, hazard ratios (HR), odds ratios (OR), and recurrence detection performance. Significant differences were expected in ctDNA assay methods, surveillance protocols, and outcome measures. For this reason, findings were synthesized descriptively without meta-analysis. When possible, prognostic effect estimates such as HRs and confidence intervals were compared narratively across studies.

Methodologic Quality Assessment

Two reviewers independently assessed the methodological quality of the included studies. Cohort and observational studies were rated using the Newcastle-Ottawa Scale (NOS), which covers selection, comparability, and outcome. Randomized controlled trials were evaluated with the Cochrane Risk of Bias tool. Disagreements were resolved through discussion and consensus. Results from the methodological quality and risk-of-bias assessments will be summarized descriptively, in accordance with PRISMA recommendations.

RESULTS

The database search identified a total of 1.617 records. After removal of 786 duplicate records, 831 studies underwent title and abstract screening, with eight studies meeting inclusion criteria for the final review. The literature demonstrated that postoperative circulating tumor DNA (ctDNA) positivity was strongly associated with increased recurrence risk following curative-intent colorectal cancer surgery. Several studies also found that serial ctDNA monitoring enabled earlier recurrence detection compared to traditional radiologic surveillance or carcinoembryonic antigen (CEA) monitoring.

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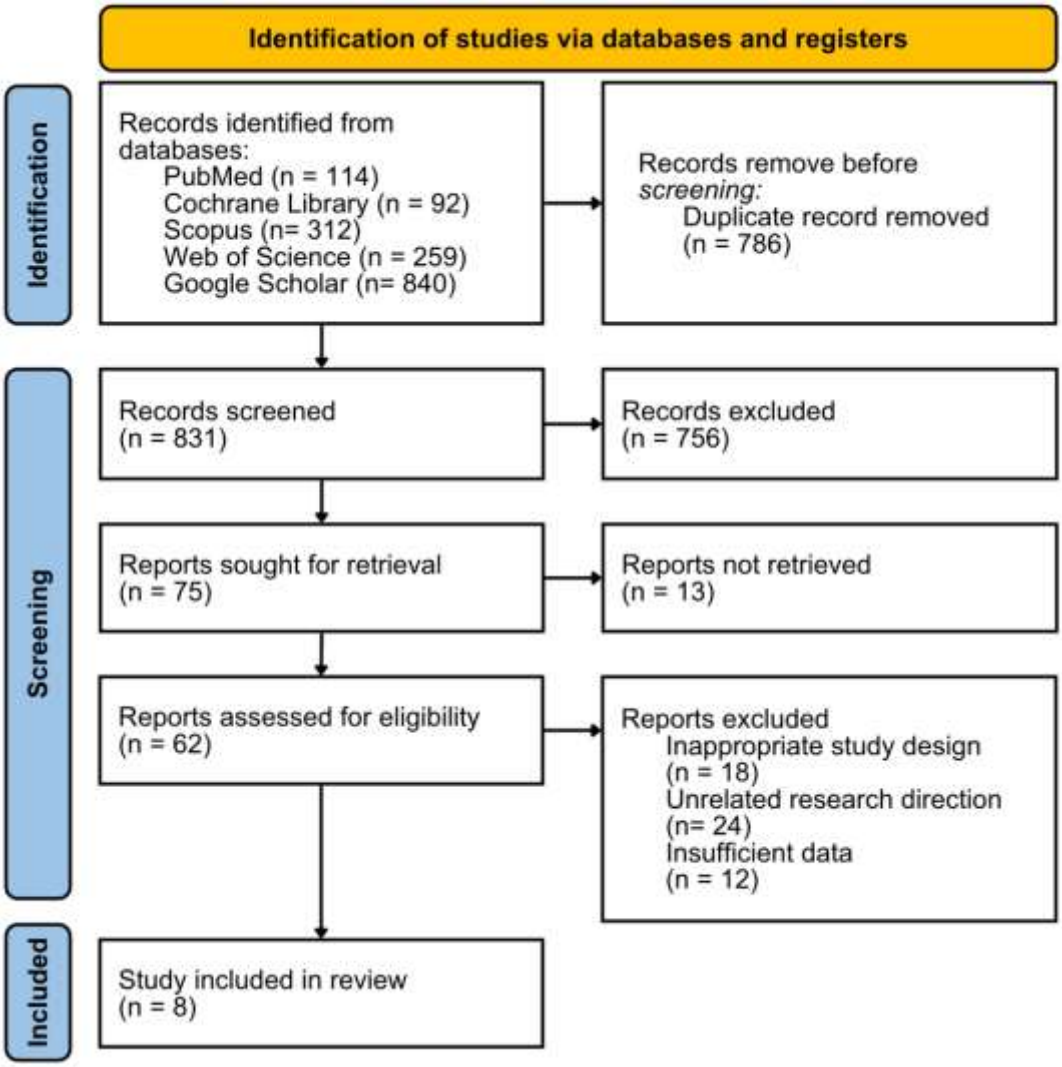

Figure 1. PRISMA flowchart.

A total of eight studies were included, comprising 1.557 patients overall. The included studies were published between 2016 and 2026 and were conducted across Australia, New Zealand, China, Denmark, Spain, and France. Most studies employed prospective cohort designs, while one study was a phase II randomized controlled trial. The study populations predominantly consisted of patients with stage II–III colorectal cancer undergoing curative-intent surgery, although one study evaluated patients undergoing resection of colorectal liver metastases (CRLM). ctDNA analysis was primarily performed using tumor-informed sequencing strategies, including next-generation sequencing (NGS), multiplex-PCR NGS, and droplet digital PCR (ddPCR)-based assays. Timing of ctDNA assessment varied across studies, including postoperative sampling, post-adjuvant chemotherapy evaluation, and longitudinal surveillance protocols. Detailed study characteristics are summarized in Table 3.

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Table 3. Characteristics of Included Studies Evaluating Postoperative Circulating Tumor DNA in Stage II–III Colorectal Cancer

Study	Country	Study Design	Population	Sample Size	Disease Stage	ctDNA Assay Platform	Timing of ctDNA Assessment	Follow-up Duration
Tie et al., 2019(Tie et al., 2019)	Australia	Prospective multicenter cohort	Patients undergoing curative resection followed by adjuvant chemotherapy	96	Stage III colon cancer	Tumor-informed personalized sequencing assay	Postoperative and post-adjuvant chemotherapy	3 years
Tie et al., 2022(Tie et al., 2022)	Australia/New Zealand	Phase II randomized controlled trial	Patients undergoing curative-intent surgery	455	Stage II colon cancer	Tumor-informed ctDNA-guided assay	4–7 weeks postoperatively	Median 37 months
Chen et al., 2021(G. Chen et al., 2021)	China	Prospective multicenter observational study	Patients undergoing curative-intent surgery	240	Stage II–III colorectal cancer	425-gene targeted next-generation sequencing panel	Preoperative, postoperative day 3–7, post-adjuvant chemotherapy, and surveillance	Up to 24 months
Henriksen et al., 2022(Henriksen et al., 2022)	Denmark/Spain	International prospective multicenter cohort	Patients treated with curative-intent surgery with or without adjuvant chemotherapy	168	Stage III colorectal cancer	Multiplex-PCR next-generation sequencing using patient-specific SNVs	Postoperative, during adjuvant chemotherapy, and surveillance	Up to 3 years
Benhaim et al., 2021(Benhaim et al., 2021)	France	Prospective multicenter cohort	Patients undergoing curative surgery	184	Stage II–III colorectal cancer	Droplet digital PCR with mutation and methylation markers	Preoperative, immediate postoperative, and longitudinal surveillance	3–4 years
Grancher et al., 2022(Grancher et al., 2022)	France	Retrospective matched cohort	Patients enrolled from the PRODIGE 13 trial following curative resection	134	Stage II colorectal cancer	Tumor-guided digital PCR following NGS profiling	Postoperative only	Median 6.5 years
Li et al., 2022(Li et al., 2022)	China	Prospective observational cohort	Patients receiving surgery followed by adjuvant chemotherapy	165	Stage III colon cancer	197-gene targeted sequencing combined with CMS classification	Pre-chemotherapy and post-chemotherapy	Not explicitly reported
Reinert et al., 2022(Reinert et al., 2022)	Denmark	Prospective longitudinal cohort	Patients undergoing curative-intent resection for colorectal liver metastases	115	Resectable colorectal liver metastases	Tumor-specific droplet digital PCR	Day-30 postoperative and serial surveillance	Up to 3 years

Abbreviations: ACT, adjuvant chemotherapy; CMS, consensus molecular subtype; CRLM, colorectal liver metastases; CRC, colorectal cancer; ctDNA, circulating tumor DNA; NGS, next-generation sequencing; SNV, single-nucleotide variant.

Across included studies, postoperative ctDNA assessment was consistently evaluated as a marker of molecular residual disease (MRD) and recurrence risk following curative-intent colorectal cancer surgery. Most studies compared outcomes between patients with detectable postoperative ctDNA and those with undetectable ctDNA. The principal outcomes included recurrence-free survival (RFS), disease-free survival (DFS), recurrence risk, recurrence kinetics, and surveillance performance. While methodological approaches differed regarding assay platform, timing of blood sampling, and surveillance intervals, there

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was substantial consistency in the prognostic framework applied across studies, supporting the role of ctDNA as a biomarker of residual disease burden after surgery (Table 4).

Table 4. PICO Framework of Included Studies.

Study	Population (P)	Intervention/Exposure (I)	Comparator (C)	Outcome (O)
Tie et al., 2019(Tie et al., 2019)	Stage III colon cancer after curative surgery	Detectable postoperative ctDNA	Undetectable postoperative ctDNA	Recurrence-free interval
Tie et al., 2022(Tie et al., 2022)	Stage II colon cancer after curative surgery	ctDNA-guided adjuvant management	Standard clinicopathologic management	Recurrence-free survival and adjuvant chemotherapy utilization
Chen et al., 2021(G. Chen et al., 2021)	Stage II–III colorectal cancer after curative surgery	Positive serial postoperative ctDNA	Negative serial postoperative ctDNA	Recurrence-free survival and recurrence detection
Henriksen et al., 2022(Henriksen et al., 2022)	Stage III colorectal cancer treated with curative intent	Detectable postoperative or post-adjuvant chemotherapy ctDNA	Undetectable ctDNA	Recurrence risk and recurrence kinetics
Benhaim et al., 2021(Benhaim et al., 2021)	Stage II–III colorectal cancer after curative surgery	Detectable postoperative ctDNA	Undetectable postoperative ctDNA	Time to recurrence
Grancher et al., 2022(Grancher et al., 2022)	Stage II colorectal cancer after curative resection	Positive postoperative ctDNA	Negative postoperative ctDNA	Disease-free survival and overall survival
Li et al., 2022(Li et al., 2022)	Stage III colon cancer receiving adjuvant chemotherapy	Positive ctDNA before or after chemotherapy	Negative ctDNA	Recurrence-free survival
Reinert et al., 2022(Reinert et al., 2022)	Resected colorectal liver metastases	Positive serial ctDNA during surveillance	Negative serial ctDNA	Relapse detection and recurrence risk

Abbreviations: ctDNA, circulating tumor DNA.

The prognostic performance of postoperative ctDNA was consistently significant across included studies. Tie et al. demonstrated that postoperative ctDNA positivity was associated with increased recurrence risk, with hazard ratios (HRs) of 3.8 postoperatively and 6.8 following adjuvant chemotherapy. Similarly, Chen et al. reported markedly elevated recurrence risk among ctDNA-positive patients, with postoperative HRs reaching 10.98 and surveillance HRs of 32.02. Henriksen et al. further demonstrated that persistent ctDNA positivity after adjuvant chemotherapy was associated with very high recurrence risk (HR

50.76) and enabled recurrence detection with a median lead-time of 9.8 months before conventional imaging. Additional studies supported the prognostic utility of serial ctDNA surveillance.

Benhaim et al. observed significantly shorter time to recurrence among patients with detectable postoperative ctDNA, while Grancher et al. demonstrated associations between ctDNA positivity, recurrence, and mortality in stage II colorectal cancer. Li et al. reported improved recurrence prediction when ctDNA analysis was combined with molecular subtype stratification. In patients undergoing resection of colorectal liver metastases, Reinert et al. demonstrated that postoperative ctDNA positivity predicted relapse earlier than standard imaging-based surveillance. Collectively, the included studies consistently supported postoperative ctDNA as a clinically meaningful biomarker for molecular residual disease detection and recurrence surveillance following curative colorectal cancer surgery (Table 5).

Table 5. Prognostic Performance and Clinical Implications of Postoperative ctDNA in Colorectal Cancer

Study	Main Findings	Statistical Results	Clinical Implications
Tie et al., 2019(Tie et al., 2019)	Postoperative ctDNA positivity was strongly associated with recurrence following curative surgery	Postoperative HR 3.8; post-adjuvant chemotherapy HR 6.8	Established ctDNA as a marker of molecular residual disease
Tie et al., 2022(Tie et al., 2022)	ctDNA-guided management reduced adjuvant chemotherapy utilization without compromising recurrence-free survival	ACT use: 15% vs. 28%; 2-year RFS: 93.5% vs. 92.4%	Demonstrated feasibility of ctDNA-guided therapeutic de-escalation
Chen et al., 2021(G. Chen et al., 2021)	Serial ctDNA positivity strongly predicted recurrence during surveillance	Postoperative HR 10.98; surveillance HR 32.02	Supported longitudinal ctDNA monitoring for early recurrence detection
Henriksen et al., 2022(Henriksen et al., 2022)	Persistent ctDNA positivity after adjuvant chemotherapy was associated with markedly increased recurrence risk	Post-adjuvant chemotherapy HR 50.76; median lead-time 9.8 months	Suggested utility of ctDNA in treatment-response assessment and surveillance
Benhaim et al., 2021(Benhaim et al., 2021)	ctDNA positivity during postoperative surveillance predicted shorter time to recurrence	Immediate postoperative HR 3.22; surveillance HR 5.0	Confirmed prognostic value of longitudinal ctDNA surveillance
Grancher et al., 2022(Grancher et al., 2022)	Postoperative ctDNA positivity was associated with recurrence and mortality in stage II disease	Adjusted OR for recurrence 11.13; adjusted HR for mortality 3.15	Reinforced prognostic utility of ctDNA in stage II colorectal cancer
Li et al., 2022(Li et al., 2022)	Combined ctDNA and molecular subtype stratification improved recurrence prediction	Pre-chemotherapy HR 5.54; post-chemotherapy HR 3.27	Demonstrated integration of ctDNA with molecular risk stratification
Reinert et al., 2022(Reinert et al., 2022)	ctDNA positivity after colorectal liver metastasis resection predicted relapse earlier than conventional imaging	Postoperative HR 7.6; surveillance HR 4.3	Suggested ctDNA as an adjunct surveillance biomarker following CRLM surgery

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Abbreviations: ACT, adjuvant chemotherapy; CMS, consensus molecular subtype; CRLM, colorectal liver metastases; CRC, colorectal cancer; ctDNA, circulating tumor DNA; DFS, disease-free survival; HR, hazard ratio; MRD, molecular residual disease; OR, odds ratio; RFS, recurrence-free survival.

Methodological quality assessment was performed using the Newcastle–Ottawa Scale (NOS) for cohort studies and the Cochrane Risk of Bias tool for the randomized controlled trial. Overall, most observational studies demonstrated satisfactory-to-good methodological quality, with strengths including prospective design, longitudinal follow-up, and standardized recurrence assessment. However, several limitations were identified, including heterogeneity in ctDNA assay platforms, variability in timing of postoperative blood collection, differences in surveillance protocols, and incomplete adjustment for potential confounding variables. Despite these limitations, the overall body of evidence consistently supported the prognostic value of postoperative ctDNA across diverse clinical settings.

The available evidence suggests that postoperative ctDNA represents a promising biomarker for molecular residual disease detection and recurrence risk stratification in stage II–III colorectal cancer following curative-intent surgery. Serial ctDNA monitoring may provide clinically relevant lead-time advantages over conventional surveillance modalities and facilitate more individualized postoperative management strategies. Although heterogeneity in ctDNA methodology and surveillance timing currently limits standardization, the consistency of prognostic findings across studies supports the growing clinical role of ctDNA-guided surveillance in colorectal cancer management.

Discussion

This systematic review demonstrates that postoperative circulating tumor DNA (ctDNA) is consistently associated with increased recurrence risk and inferior oncologic outcomes following curative-intent surgery for stage II–III colorectal cancer (CRC). Across the included studies, ctDNA positivity after surgery or after adjuvant chemotherapy was strongly predictive of recurrence, with hazard ratios ranging from 3.8 to 50.76, depending on the timing of assessment and the surveillance interval (G. Chen et al., 2021; Henriksen et al., 2022; Tie et al., 2019, 2022). These findings were consistently observed across diverse populations and assay platforms, including next-generation sequencing (NGS), multiplex PCR-NGS, and droplet digital PCR (ddPCR). Collectively, the available evidence supports the use of postoperative ctDNA as a robust biomarker of molecular residual disease (MRD) and for recurrence surveillance in localized CRC.

The strong prognostic performance observed across studies likely reflects the biological ability of ctDNA to directly identify occult residual tumor burden following curative-intent resection (Masfarré et al., 2021). Unlike conventional clinicopathological risk factors, ctDNA provides real-time molecular evidence of persistent disease activity (G. Chen et al., 2021; Ozluk et al., 2026). This concept was consistently demonstrated in prospective cohorts. Tie et al. demonstrated that postoperative ctDNA positivity in stage III colon cancer was associated with significantly inferior recurrence-free interval following surgery and after adjuvant chemotherapy (Tie et al., 2019). Similarly, Chen et al. reported markedly elevated recurrence risk among ctDNA-positive patients during postoperative and surveillance phases, while Henriksen et al. showed that persistent ctDNA positivity after adjuvant chemotherapy was associated with recurrence rates approaching 80% (Henriksen et al., 2022). Importantly, multivariable

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analyses in several studies demonstrated that ctDNA remained independently prognostic even after adjustment for established clinicopathological variables, supporting its role as a direct surrogate marker of residual tumor burden rather than merely a correlate of high-risk disease (G. Chen et al., 2021; Diergaarde et al., 2025).

Another important finding across the included literature was the consistent lead-time advantage of serial ctDNA monitoring over conventional surveillance modalities. Several studies demonstrated that ctDNA positivity preceded radiologic recurrence detection by approximately 5–10 months (G. Chen et al., 2021; Henriksen et al., 2022; Nguyen et al., 2024). Henriksen et al. reported a median lead time of 9.8 months before conventional imaging, whereas Chen et al. demonstrated a mean lead time of approximately 5 months during surveillance (G. Chen et al., 2021; Henriksen et al., 2022). Nguyen et al. additionally demonstrated that longitudinal ctDNA monitoring predicted recurrence with very high sensitivity and specificity and identified relapse approximately 8 months earlier than standard surveillance approaches (Nguyen et al., 2024). These findings are clinically important because conventional postoperative surveillance using carcinoembryonic antigen (CEA), computed tomography (CT), and endoscopy frequently fails to identify recurrence at a sufficiently early stage for optimal therapeutic intervention (Krell et al., 2024). The ability of ctDNA to identify molecular recurrence before radiologic progression suggests that ctDNA-guided surveillance may enable earlier intervention and potentially improve long-term oncologic outcomes.

The findings of this review also highlight the emerging role of ctDNA in guiding adjuvant treatment decision-making. Current postoperative management strategies for stage II–III CRC rely predominantly on clinicopathological risk stratification, which incompletely reflects true residual disease burden (Ozluk et al., 2026). Several included studies suggested that ctDNA-positive patients derive the greatest prognostic benefit from intensified surveillance and potentially escalated adjuvant chemotherapy, whereas ctDNA-negative patients may avoid unnecessary treatment-related toxicity (Henriksen et al., 2022; Tie et al., 2019). The landmark DYNAMIC trial further demonstrated that a ctDNA-guided management strategy reduced the use of adjuvant chemotherapy without compromising recurrence-free survival in stage II colon cancer (Tie et al., 2022). These findings support the growing concept of ctDNA-guided precision oncology, in which postoperative management is individualized according to molecular residual disease status rather than clinicopathologic criteria alone.

From a technical perspective, most included studies utilized tumor-informed ctDNA approaches, which generally demonstrated strong prognostic performance across postoperative and surveillance settings. Tumor-informed assays leverage patient-specific somatic mutations identified from tumor tissue sequencing to improve analytical sensitivity and specificity for MRD detection (G. Chen et al., 2021; H. Chen et al., 2025). This may explain the consistently high hazard ratios reported across prospective cohorts. Furthermore, serial ctDNA analysis appeared to provide additional prognostic information beyond single postoperative measurements by enabling dynamic assessment of treatment response, ctDNA clearance, and recurrence kinetics. Henriksen et al. additionally demonstrated distinct ctDNA growth-rate patterns associated with survival outcomes, suggesting that quantitative ctDNA dynamics may further refine postoperative risk stratification (Henriksen et al., 2022).

An important strength of this systematic review is its focused evaluation of postoperative ctDNA specifically as a marker of molecular residual disease in stage II–III CRC, rather than broadly evaluating

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ctDNA across heterogeneous disease stages or metastatic settings. Most previous reviews have discussed ctDNA in broader CRC contexts, including metastatic disease, treatment monitoring, and molecular profiling, whereas the present review specifically synthesized evidence on postoperative MRD detection and recurrence surveillance following curative-intent surgery. In addition, this review incorporated contemporary prospective multicenter cohorts and randomized evidence, including the DYNAMIC trial, thereby providing a clinically relevant overview of ctDNA-guided postoperative management strategies. The inclusion of studies evaluating serial ctDNA monitoring, post-adjuvant chemotherapy assessment, and surveillance kinetics also allowed comprehensive evaluation of ctDNA beyond single postoperative measurements (Tie et al., 2022).

Despite these promising findings, several limitations currently restrict widespread clinical implementation of postoperative ctDNA surveillance. Considerable methodological heterogeneity exists across studies regarding assay platforms, gene panels, sampling intervals, postoperative timing, surveillance schedules, and ctDNA positivity thresholds (G. Chen et al., 2021; H. Chen et al., 2025; Khan et al., 2025). Such variability limits direct comparison between studies and complicates standardization of ctDNA-guided management algorithms. In addition, biological factors such as low tumor burden, mucinous histology, and limited tumor shedding may contribute to false-negative ctDNA results (G. Chen et al., 2021). While ctDNA has consistently demonstrated strong prognostic utility, its predictive role in determining which patients will definitively benefit from treatment escalation or de-escalation remains incompletely established (Ozluk et al., 2026; Parikh et al., 2021). Most included studies were observational cohort studies, and although methodological quality was generally satisfactory, residual confounding and selection bias cannot be entirely excluded. Furthermore, the relatively limited number of randomized trials and the absence of pooled quantitative meta-analysis in the present review may restrict definitive conclusions regarding effect magnitude and comparative clinical utility across different ctDNA platforms.

Future research should prioritize prospective randomized trials evaluating ctDNA-guided therapeutic strategies, particularly regarding adjuvant chemotherapy escalation, de-escalation, and surveillance optimization. Ongoing studies such as CIRCULATE, COBRA, PEGASUS, and BESPOKE CRC are expected to provide important evidence regarding the integration of ctDNA-guided management into routine colorectal oncology practicE (Bartolomucci et al., 2025; Kasi et al., 2021; Nakamura et al., 2024). In addition, further standardization of pre-analytical and analytical ctDNA methodologies, including blood collection timing, assay harmonization, and surveillance intervals, will be essential for broader clinical implementation. Emerging approaches integrating ctDNA dynamics with molecular subtyping, radiologic assessment, and artificial intelligence-based risk modeling may further enhance postoperative precision oncology strategies in CRC.

Overall, available evidence indicates that postoperative ctDNA has substantial clinical potential for MRD detection and recurrence risk stratification in stage II–III CRC. Serial ctDNA monitoring consistently demonstrated strong prognostic value and meaningful lead-time advantages over conventional surveillance modalities. Although methodological standardization and prospective interventional validation remain necessary, ctDNA-guided postoperative management represents a promising step toward more individualized and biologically informed colorectal cancer care.

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CONCLUSION

Postoperative circulating tumor DNA (ctDNA) demonstrates strong and consistent prognostic utility as a biomarker of molecular residual disease (MRD) in patients with stage II–III colorectal cancer following curative-intent surgery. The available evidence indicates that postoperative and serial ctDNA positivity are closely associated with increased recurrence risk, inferior survival outcomes, and earlier relapse detection compared with conventional surveillance strategies. Emerging data also suggest that ctDNA-guided approaches may improve postoperative risk stratification and facilitate more individualized adjuvant treatment and surveillance decisions. However, current evidence remains limited by heterogeneity in ctDNA methodologies, sampling timing, and surveillance protocols, highlighting the need for further prospective and standardized studies before widespread clinical implementation can be fully established.

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