

Long Non-Coding RNAs in the Early Detection of Colorectal Cancer Recurrence: A Narrative Review

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Abstract

Despite major advances in surgery, chemotherapy, and surveillance strategies, colorectal cancer (CRC) recurrence remains a critical clinical challenge. Early detection of relapse significantly improves the chances of successful intervention; however, currently available biomarkers such as carcinoembryonic antigen (CEA) lack sufficient sensitivity and specificity (1,13). In recent years, long non-coding RNAs (lncRNAs) have emerged as key regulators in cancer biology (2,3). Growing evidence supports their role in tumor progression, metastasis, and therapy resistance (3,14). Importantly, several lncRNAs have shown potential as minimally invasive biomarkers for detecting CRC recurrence. This narrative review summarizes current evidence regarding the biological functions of lncRNAs in CRC and evaluates their emerging role in the early detection of disease relapse

Keywords: Colorectal cancer, Cancer recurrence, Long non-coding RNA (lncRNA), HOTAIR, MALAT1, CCAT1

Introduction

Colorectal cancer remains one of the most commonly diagnosed malignancies worldwide and a leading cause of cancer-related mortality. Although curative resection combined with adjuvant therapy can achieve favorable outcomes in early-stage disease, recurrence occurs in a substantial proportion of patients (1). Detecting recurrence at a subclinical stage is crucial, as early therapeutic intervention directly impacts survival.

Current surveillance strategies rely on imaging studies, colonoscopy, and serum biomarkers such as CEA (13). While helpful, these tools often fail to detect minimal residual disease (MRD) or micrometastatic relapse at an early stage. Consequently, there is a pressing need for more sensitive, non-invasive biomarkers capable of identifying recurrence before radiologic progression becomes evident.

Long non-coding RNAs (lncRNAs), transcripts longer than 200 nucleotides with limited protein-coding potential, have emerged as important regulators of gene expression and epigenetic

modulation (2,4). Over the past decade, lncRNAs have transitioned from being considered transcriptional “noise” to recognized drivers of oncogenic pathways (3). Their cancer-specific expression patterns and relative stability in circulation make them attractive candidates for biomarker development.

Biological Basis of lncRNA Function in Colorectal Cancer

The oncogenic relevance of lncRNAs lies in their ability to modulate multiple layers of gene regulation.

First, lncRNAs can interact directly with chromatin-modifying complexes, altering histone marks and transcriptional programs (6,16). Through these interactions, they influence the expression of tumor suppressor genes and oncogenes.

Second, many lncRNAs function as competing endogenous RNAs (ceRNAs), acting as molecular sponges for microRNAs (5,15). By sequestering tumor-suppressive miRNAs, they indirectly upregulate pro-metastatic or pro-survival genes.

Third, lncRNAs can bind transcription factors, scaffold protein complexes, or modulate mRNA stability and translation (2,3). These multilayered regulatory effects contribute to epithelial–mesenchymal transition (EMT), invasion, metastasis, and resistance to chemotherapy—key biological processes underlying CRC recurrence.

Key lncRNAs Associated with CRC Recurrence

HOTAIR

HOTAIR (HOX transcript antisense RNA) is among the most extensively studied oncogenic lncRNAs. In colorectal cancer, elevated HOTAIR expression has been associated with advanced stage and poor prognosis (7). Mechanistically, HOTAIR recruits polycomb repressive complex 2 (PRC2), leading to epigenetic silencing of tumor suppressor genes (6,7).

Higher circulating or tumor tissue levels of HOTAIR have been correlated with increased risk of recurrence in CRC patients (8). These findings suggest that HOTAIR may serve as both a prognostic marker and a potential indicator of disease relapse during follow-up.

MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) plays a pivotal role in cell migration and metastatic dissemination (9). In CRC and other solid tumors, MALAT1 overexpression has been linked to enhanced EMT and shorter disease-free survival (9,10).

Elevated MALAT1 expression in primary tumors appears to predict early relapse. Its detectability in plasma and extracellular vesicles further supports its potential role in non-invasive longitudinal monitoring.

CCAT1

Colon cancer–associated transcript 1 (CCAT1) is highly expressed in colorectal tumors and located near the MYC oncogene locus (11). CCAT1 promotes tumor proliferation and metastasis through MYC-driven signaling pathways.

High CCAT1 expression has been associated with increased recurrence rates, particularly in stage II and III CRC patients (11). Its relative tumor specificity enhances its potential clinical utility.

Circulating and Exosomal lncRNAs

A particularly promising avenue involves circulating lncRNAs packaged within extracellular vesicles or exosomes. These vesicles protect RNA molecules from degradation, enabling stable detection in blood samples (12).

Liquid biopsy–based assessment of lncRNAs offers several advantages, including non-invasive sampling, feasibility of repeated measurements, and potential integration with other biomarkers such as circulating tumor DNA and CTCs (12). Such approaches may allow earlier detection of molecular relapse before radiologic changes become evident.

Clinical Implications

The clinical application of lncRNAs in CRC recurrence detection can be envisioned in several scenarios:

- 1. Risk Stratification After Surgery**

lncRNA expression profiles may help identify patients at high risk of recurrence who could benefit from intensified surveillance or adjuvant therapy (7,8).

- 2. Monitoring Minimal Residual Disease (MRD)**

Serial measurement of circulating lncRNAs could complement established tumor markers and emerging ctDNA assays (12,13).

- 3. Therapeutic Decision-Making**

Certain lncRNAs are associated with chemoresistance or altered signaling pathways, potentially guiding personalized treatment strategies (3,14).

Challenges and Limitations

Despite promising data, several barriers remain.

There is currently a lack of methodological standardization in RNA extraction, normalization strategies, and quantification techniques, contributing to variability across studies (2,16). Many investigations are retrospective and involve limited patient cohorts. Moreover, the biological heterogeneity of CRC suggests that single-marker approaches may not fully capture recurrence risk.

Large-scale, multicenter prospective studies are required before lncRNA-based assays can be integrated into routine surveillance protocols.

Future Perspectives

Future recurrence monitoring strategies will likely involve multi-omic integration. Combining lncRNA signatures with circulating tumor DNA, epigenetic markers, and clinicopathological features may significantly enhance predictive accuracy.

Artificial intelligence–driven predictive models incorporating lncRNA panels could refine individualized recurrence risk assessment. Additionally, mechanistic studies may transform certain lncRNAs from passive biomarkers into active therapeutic targets (3,14).

Conclusion

Long non-coding RNAs represent a promising frontier in the early detection of colorectal cancer recurrence. Their involvement in critical oncogenic pathways (3,6), cancer-specific expression patterns (7,11), and detectability in circulation (12) position them as attractive candidates for non-invasive monitoring.

Although substantial validation and methodological harmonization are still required, accumulating evidence suggests that lncRNAs may become integral components of precision surveillance strategies in colorectal cancer.

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