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Review Article

Next Generation of Colorectal Cancer Management: Integrating Omics, Targeted Therapies, and Smart Technologies

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Abstract

Colorectal cancer (CRC) remains a significant global health concern, with increasing incidence rates observed in young adults and Asian populations. Recent advancements in diagnostic tools, targeted therapies, and precision medicine approaches have revolutionized CRC management. This review aimed to summarize the latest developments in CRC diagnosis, treatment, and prevention, focusing on innovative technologies and personalized approaches. Advanced imaging techniques, including high-definition colonoscopy, virtual colonoscopy, and integrated PET-CT scans, have enhanced CRC detection and staging accuracy. Novel biomarkers such as circulating tumor DNA (ctDNA), microRNAs (miRNAs), and exosomes show promise for early diagnosis and treatment monitoring. Precision medicine employs molecular profiling to guide targeted therapies, including epidermal growth factor receptor (EGFR) inhibitors, V-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors, and immune checkpoint inhibitors. Anti-cancer metal ions such as platinum, ruthenium, and gallium compounds demonstrate efficacy through diverse mechanisms. The application of artificial intelligence (AI) in imaging analysis, pathology, and treatment planning enhances diagnostic accuracy and personalized care. Herbal and traditional medicines, including curcumin and green tea catechins, exhibit anti-tumor properties and potential synergistic effects with conventional therapies. Prevention strategies include lifestyle modifications, screening programs, and risk-based personalized approaches. Emerging technologies such as organoid engineering and nanomedicine, offer new avenues for drug discovery and targeted delivery. Integrating advanced diagnostic tools, targeted therapies, and personalized approaches has substantially improved CRC management. However, challenges remain in addressing tumor heterogeneity, drug resistance, and treatment accessibility. Future research should focus on validating emerging technologies and biomarkers through large-scale clinical trials to further enhance CRC prevention, diagnosis, and treatment outcomes.

Keywords: Colorectal cancer, Diagnostic tools, CRC prevention, CRC herbal medicine, Anti-CRC metal ions

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Background

Colorectal cancer (CRC) remains a major global health issue, accounting for a high number of new cases and deaths worldwide (1). While age is a major risk factor, incidence rates are rising in young adults (aged 20-29), with more advanced diseases. Rates are also increasing in Asia, largely due to changes in lifestyle and diet, though genetic factors impact differences between countries (2). Obesity is strongly correlated with an increased risk of colon cancer in obese men as seen in studies although its relationship in women requires further investigation. With over one million new cases and nearly 800 000 deaths each year worldwide, CRC poses a significant global health burden (4). Alarmingly, incidence rates are increasing in adults under 50, particularly in Asian countries, likely due to lifestyle changes such as unhealthy diets, obesity, smoking, and reduced physical activity. Providing comprehensive data on the global scale of CRC would underscore the

importance of advanced technologies and strategies to improve outcomes. Understanding how weight changes affect CRC risk can inform lifestyle recommendations as persistent obesity is significantly correlated with increased risk in both sexes. Thus, preventing obesity and weight gain may help reduce CRC incidence (3).

Inherited and environmental factors impact CRC development. Metabolic syndrome, characterized by central obesity and other comorbidities, represents a key modifiable risk factor. Lifestyle modifications significantly lower costs and risks compared to other strategies though the impact of healthy living with metabolic syndrome requires evaluation. CRC heterogeneity and late diagnosis due to the lack of non-invasive screening methods negatively impact prognosis, emphasizing the importance of early detection. The intestinal microbiome plays a crucial role in CRC development through metabolic and immune effects, representing a promising target (5). Figure 1 depicts CRC staging from localized to metastatic disease. Stage 0 involves cancer cells confined to the mucosa. Stage I indicates the submucosa and muscularis propria. Stage II shows cancer spread to surrounding tissue, and Stage III denotes lymph node involvement (6).

Common screening markers such as fecal occult blood, fecal transferrin, and serum carcinoembryonic antigen (CEA)/cancer antigen 19-9 (CA 19-9) have limitations in sensitivity, specificity, and their ability to detect non-bleeding lesions, necessitating the need for improved biomarkers for early CRC detection (7). Novel therapies aim to improve outcomes in advanced/metastatic CRC despite current treatment limitations. The combination of radiotherapy and immunotherapy requires further investigation to clarify its effectiveness. CAR T-cell therapy targeting CEA shows promise since over 80% of metastatic CRC patients overexpress this antigen, making it an important therapeutic target (8,9).

A comprehensive methodology section was implemented to ensure the validity and rigor of this study. The research process included a systematic literature review using electronic databases such as PubMed, MEDLINE, and the Cochrane Library. Inclusion criteria focused on peer-reviewed articles published between 2010 and 2024, addressing CRC management. Two independent reviewers screened titles, abstracts, and full texts, with disagreements resolved through consensus. Data extraction followed a standardized form, and study quality was assessed using appropriate tools (e.g., Cochrane Risk of Bias for RCTs). Evidence was graded using the GRADE approach, and expert consultation provided additional insights. Limitations, including potential language and publication bias, were acknowledged. This systematic approach ensures the study's reproducibility, transparency, and overall quality, providing a solid foundation for the presented findings.

Advanced Tools of Diagnosis for Colorectal Cancer

Early detection of CRC greatly improves the chances of successful treatment and survival. Currently, colonoscopy is recommended every ten years, but it is invasive and not feasible for whole-population screening. Other common stool-based tests have limited sensitivity to detect non-bleeding or early-stage lesions. This highlights the need for improved screening strategies such as advanced imaging techniques and biomarkers that can more accurately identify precancerous polyps and small malignant growths at curable stages. The diagnosis of CRC is a critical step in the management of the disease. Advances in diagnostic tools have led to improvements in the accuracy and speed of CRC diagnosis, as well as the ability to detect early-stage and precancerous lesions. Combining biomarkers tests with imaging tools is a potential improvement over the current standard of care for CRC, as it offers benefits based on patient and biological factors (10). This review will list several recent examples of diagnostic tools for CRC, including biomarkers tests and imaging tools as depicted in Figure 2 (11).

Advances in Imaging Tools

Imaging plays a critical role in CRC diagnosis and monitoring. Recent technological advances have improved

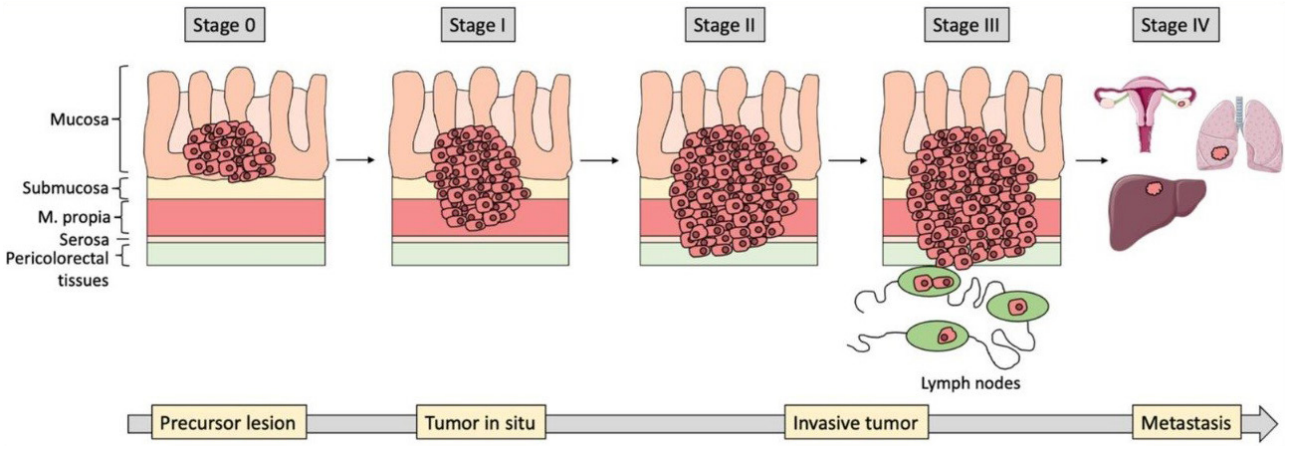

Figure 1. Different Classification Stages of Colorectal Cancer. Reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/) (6)

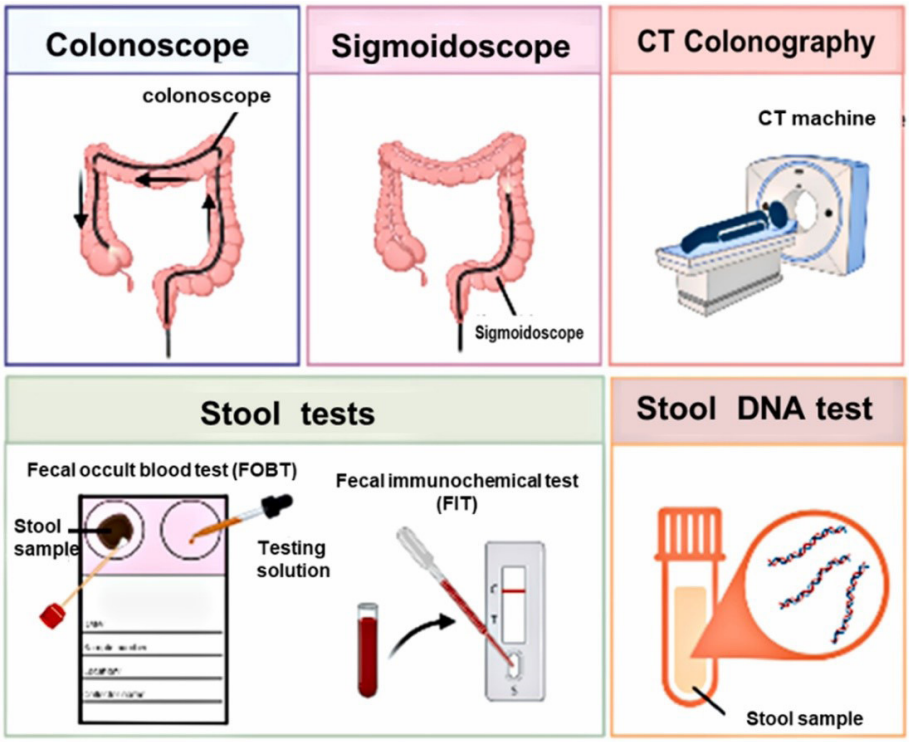

Figure 2. Various Techniques for the Early Detection of Colorectal Cancer. Reproduced under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/) (11)

accuracy, speed, and the ability to assess treatment response (12). Colonoscopy remains the gold standard for detecting polyps and CRC. High-definition colonoscopes and narrow-band imaging enhance visualization of lesions. Cap-fitted colonoscopes improve detection in the cecum. Virtual colonoscopy using computed tomography (CT) is now comparable to standard colonoscopy for detecting large polyps. CT colonography allows non-invasive whole-colon examination without sedation (13).

Magnetic resonance imaging (MRI) provides high-resolution soft tissue imaging of the entire colon and rectum. Diffusion-weighted MRI analyzes water molecule movement to distinguish tumors from normal tissue. MR enterography assesses Crohn's disease activity and complications such as strictures or abscesses. MR colonography may one day replace CT colonography (14). Integrated positron emission tomography (PET)-CT scans, which combine anatomical and metabolic data, improve staging accuracy. Novel PET tracers target specific tumor pathways. For example, fluorodeoxyglucose (FDG)-PET assesses glucose metabolism, while 18F-fluorothymidine measures cellular proliferation (15,16).

Endoscopic techniques enhance traditional endoscopy. Narrow-band imaging improves the visualization of mucosal patterns. Confocal laser endomicroscopy and optical coherence tomography provide real-time histology at a cellular level. Endoscopic ultrasound evaluates bowel wall layers and nearby organs or lymph nodes (17). Novel promising techniques include 3D sonography for rectal tumors, elastography for measuring tissue stiffness, photoacoustic tomography for imaging angiogenesis, and thermal ablation using high-intensity focused ultrasound to destroy tumors (18). Integration of imaging with genomics, blood-based markers and artificial intelligence (AI) may ultimately enable highly accurate, non-invasive diagnosis, and personalized management of CRC. Continuous technological advances will further improve CRC detection and treatment (19).

Advances in Biomarker Tools for Monitoring and Diagnosis of Colorectal Cancer

Various classes of biomarkers hold promise for CRC management. Genomic and epigenetic alterations, as well as microsatellite instability (MSI), can predict tumor behavior and guide targeted therapies. Proteomic and glycomic profiling may reveal biomarkers for early detection, while metabolomics can uncover metabolic pathways implicated in CRC. Circulating biomarkers such as ctDNA, miRNAs, and exosomes show potential for non-invasive liquid biopsies. Together, these multilayered biomarkers aim to improve cancer screening, surveillance, and personalized care. Biomarkers, defined as measurable molecular or cellular alterations, play a pivotal role in the monitoring, diagnosis, and prognostication of CRC. These biomarkers can inform treatment selection strategies and facilitate patient outcome predictions. DNA methylation, an epigenetic modification involving the addition of methyl groups to cytosine residues in DNA, has emerged as a promising biomarker for CRC. Aberrant methylation patterns such as hypermethylation of specific genes like MLH1 and CDKN2A, have been associated with disease progression and poor prognosis. DNA methylation may be utilized in conjunction with other biomarkers, including MSI and tumor mutational burden (TMB), to

enhance the prediction of treatment response. However, the clinical implementation of DNA methylation as a CRC biomarker necessitates standardized measurement protocols, addressing the potential for false positives and further large-scale validation studies (20).

Circulating tumor cells (CTCs), which are cancer cells that have detached from the primary tumor and entered the bloodstream, have been explored as potential biomarkers for CRC. However, their heterogeneity, along with factors such as tumor size and location, may limit their reliability as biomarkers (21). The fecal immunochemical test (FIT) is a non-invasive, cost-effective, and user-friendly screening tool that detects the presence of human hemoglobin in stool samples, indicating potential CRC or other gastrointestinal conditions. FIT has exhibited high sensitivity and specificity for detecting early-stage CRC and has been shown to reduce CRC mortality rates and detect precancerous lesions. Moreover, it is recommended as a primary CRC screening tool by several national and international organizations (22).

TMB, a measure of the number of mutations in cancer cell DNA, has emerged as a promising biomarker for CRC. High TMB is associated with increased sensitivity to immunotherapy, and CRC patients with high TMB often exhibit better response rates to checkpoint inhibitors. TMB may be used in combination with other biomarkers such as MSI and programmed death-ligand 1 (PD-L1) expression to enhance the prediction of immunotherapy response and monitor disease progression (23). Liquid biopsy, a non-invasive method for detecting cancer-related biomarkers in body fluids, has shown promise for the diagnosis and monitoring of CRC. Liquid biopsy can detect various biomarkers, including CTCs, cell-free DNA (cfDNA), RNA, miRNAs, proteins, and exosomes, in blood, urine, or other bodily fluids. This approach provides valuable information on disease progression, treatment response, and prognosis (24).

Exosomes, small extracellular vesicles secreted by cells, have been identified as potential biomarkers for CRC due to their ability to carry and transfer cargo such as proteins, nucleic acids, and lipids. Several studies have reported the presence of exosomes containing specific proteins, miRNAs, and other molecules such as the protein CD133 and the miRNA miR-21 in CRC patients, which may serve as potential biomarkers for early detection and disease monitoring (25). Similarly, ctDNA, which is released into the bloodstream by cancer cells, can provide valuable information on disease progression, treatment response, and prognosis when detected through liquid biopsy (26).

miRNAs, small non-coding RNA molecules that regulate gene expression, have been implicated in CRC pathogenesis, and their detection in blood or other bodily fluids using liquid biopsy has been promising for early cancer diagnosis and prognostic assessment. Several miRNAs such as miR-21, miR-29a, and miR-92a have been associated with disease progression and treatment response in CRC patients (27). Protein biomarkers such as CEA, CA 19-9, and cancer antigen 125 (CA 125) have been used for disease monitoring and surveillance in CRC patients. Additionally, novel protein biomarkers, including those involved in angiogenesis (e.g., angiopoietin-2), apoptosis, and immune regulation, have also been proposed for CRC (28-32).

Epigenetic biomarkers such as aberrant DNA methylation patterns and histone modifications have been observed in CRC cells and may serve as potential biomarkers for disease diagnosis, prognosis, and treatment response prediction (33). Metabolomic biomarkers, characterized by the measurement of small molecules or metabolites in biological samples, can provide insights into dysregulated biochemical pathways and cellular processes in CRC. Alterations in amino acid metabolism, lipid metabolism, and gut microbiota-derived metabolites have been identified as potential biomarkers for CRC diagnosis and prognosis (34-36).

Multi-gene panels, consisting of several genes associated with CRC development and progression, such as APC, KRAS, TP53, and BRAF have been developed for risk assessment, prognosis, and treatment selection in CRC patients (37-41). Immune biomarkers, including tumor-infiltrating lymphocytes, PD-L1 expression, MSI, TMB, and cytokine levels, are being increasingly studied in CRC as they may provide valuable insights into diagnosis, prognosis, and treatment decisions, particularly for immunotherapy (42-46).

Gut microbiome-based biomarkers such as fecal microbial signatures, gut microbial metabolites, microbial genes, and microbial diversity have been identified as potential biomarkers for CRC and may facilitate diagnosis, prognosis, and treatment decisions. Specific microbial signatures such as changes in the abundance of *Fusobacterium nucleatum*, *Bacteroides fragilis*, and *Prevotella* species, as well as gut microbial metabolites such as trimethylamine-N-oxide, have been associated with an increased risk of CRC (47). Proteomics-based biomarkers, identified through large-scale analysis of proteins in biological samples, have shown promise for CRC. Altered expression or post-translational modifications of proteins involved in key cellular processes such as cell cycle regulation (e.g., Survivin), apoptosis, and metabolism have been linked to CRC pathogenesis and progression (48-50).

Glycomics-based biomarkers focus on alterations in glycan structures and their expression levels, which have been observed in CRC cells and may serve as potential biomarkers for disease diagnosis, prognosis, and treatment. Abnormal glycosylation patterns such as increased fucosylation and sialylation and decreased galactosylation and N-acetylglucosamine branching have been associated with CRC progression, and changes in serum glycan patterns have been proposed as potential biomarkers for disease detection and monitoring (51-54). Metastasis-associated biomarkers, including proteins (e.g., epithelial cell adhesion molecule, EpCAM), miRNAs

(e.g., miR-21, miR-29a), and CTCs, have been identified in CRC. These biomarkers may provide valuable information on the metastatic potential of CRC cells and contribute to the development of targeted therapies and treatment decision-making (55-59).

Despite significant progress in biomarker research, numerous challenges remain for clinical application. Large-scale validation studies are still needed to confirm accuracy and reproducibility. Standardized measurement techniques must be established to ensure quality control. Addressing sources of error such as false positives is also crucial for diagnostic reliability. Regulatory processes can be lengthy, and the associated costs are substantial. Widespread integration into treatment decisions will require overcoming these hurdles through well-designed testing and rigorous evidence.

Advances in Histopathology Tools for Monitoring and Diagnosis of Colorectal Cancer

Histopathological analysis of biopsy and surgical specimens remains essential for CRC diagnosis and staging. Recent technological advances are improving accuracy and efficiency (60). Digital pathology enables high-resolution whole-slide imaging, telepathology for an expert consultation, and integration with other data such as sequencing results. Digital images can be rapidly shared, permanently archived, and analyzed using AI. Whole genome sequencing from biopsy samples causes the early diagnosis of Lynch syndrome and helps predict prognosis (61).

Immunohistochemistry improves tumor grading by detecting markers associated with growth, invasion, and metastasis. For example, immunohistochemistry for MLH1, MSH2, and MSH6 proteins evaluates for Lynch syndrome, while PD-L1 expression predicts immunotherapy response. Multiplex imaging allows simultaneous visualization of several markers on a single slide (62). Molecular pathology helps with diagnosis and prognosis. Next-generation sequencing evaluates mutations in oncogenes and tumor suppressor genes to predict recurrence and guide targeted therapies. DNA methylation analysis detects epigenetic changes in genes like MGMT and MLH1, while mRNA or miRNA expression profiling links molecular subtypes to clinical behaviors (63).

Histomorphological analysis with virtual microscopy captures features that may be missed by the unaided eye. Digital slide scanners, combined with AI, can automatically assess angiogenesis, margin status, tumor budding, and lymphocytic infiltration. Quantitative analysis of histological patterns through machine learning may eventually support standardized tumor grading (64). Ex vivo and in vitro organoid cultures, developed from patient biopsies, recapitulate disease and preserve inter-tumor heterogeneity for personalized drug testing. Patient-derived organoids, combined with genetic analysis of the original tumor, provide a robust platform for precision oncology approaches (65). Continued integration of molecular diagnostics with high-throughput tissue analysis techniques will allow comprehensive characterization of CRC from small biopsy samples, guiding treatment in the era of personalized medicine (66).

Treatment Through Precision Medicine and Targeted Therapies

Several important targeted therapies have emerged for CRC. Epidermal growth factor receptor (EGFR) inhibitors block the EGFR, which is often overexpressed in tumors. BRAF inhibitors target tumors with BRAF mutations. Anti-angiogenic agents such as bevacizumab inhibit vascular endothelial growth factor (VEGF) to curb tumor growth. Immunotherapies like pembrolizumab help immune cells attack MSI-high or PD-L1 positive cancer cells. Describing the molecular markers that guide the use of each therapy could help illustrate the promise of precision medicine approaches. The field of precision medicine and targeted therapies has significantly transformed the treatment landscape for CRC in recent times. One of the most promising advancements in precision medicine for CRC involves using biomarkers to identify patients who are likely to respond favorably to specific treatment modalities. The effective management of CRC depends on several factors, including the stage and anatomical location of the tumor, as well as the overall health status of the patient. The treatment approach typically involves a combination of surgical intervention, radiation therapy, chemotherapy, targeted therapy, and immunotherapy (67).

- Surgical resection is the primary treatment modality for early-stage CRC, where the tumor and surrounding tissue are removed to prevent further spread of the cancer to other regions. In cases where the cancer has metastasized to nearby lymph nodes, these lymph nodes may also be excised during surgery (68).
- Radiation therapy, which uses high-energy beams to destroy cancer cells, is commonly employed alongside surgery or chemotherapy to address more advanced stages of CRC (69).
- Chemotherapy involves the administration of drugs designed to kill cancer cells and is typically utilized in combination with surgery or radiation therapy to manage more advanced stages of CRC. Depending on the stage of the cancer, chemotherapy may be administered before or after surgical intervention (70).
- Targeted therapy uses drugs that specifically target molecules implicated in the growth and metastatic spread of cancer cells. These therapies can be useful in treating advanced CRC that has not responded to other treatment modalities (71).
- Immunotherapy involves the use of drugs that stimulate the immune system to recognize and attack

cancer cells. Immunotherapy can be employed to treat advanced CRC that has not responded to other treatment approaches. Additionally, palliative care can be provided to alleviate symptoms and improve the quality of life for patients with advanced CRC (72-74).

Examples of Precision Medicine and Targeted Therapies for Colorectal Cancer

Precision medicine and targeted therapies have significantly advanced the treatment landscape of CRC. These approaches harness specific molecular targets involved in the pathogenesis and progression of CRC tumors. EGFR inhibitors such as cetuximab and panitumumab block the activity of the EGFR, a protein that is overexpressed in many CRC tumors. These agents have demonstrated efficacy in patients whose tumors exhibit EGFR overexpression (75,76).

BRAF inhibitors, including vemurafenib and dabrafenib, target the mutated BRAF protein found in a subset of CRC tumors. By blocking the activity of the mutated BRAF, these inhibitors can effectively treat patients with BRAF-mutant tumors (77). Mitogen-activated protein kinase (MEK) inhibitors, including trametinib and cobimetinib, modulate the activity of MEK, a protein kinase involved in the mitogen-activated protein kinase (MAPK) signaling pathway, which is frequently dysregulated in CRC (78).

Anti-angiogenic agents (e.g., bevacizumab and ramucirumab) inhibit VEGF, a key mediator of tumor angiogenesis. By disrupting the formation of new blood vessels that supply nutrients to the tumor, these agents can impede the growth of CRC tumors (79). Fibroblast growth factor receptor (FGFR) inhibitors, exemplified by infigratinib and pemigatinib, target the FGFR family of proteins, which are involved in cell signaling and growth processes. These inhibitors have shown efficacy in tumors with mutations in the FGFR gene (80).

Human epidermal growth factor receptor 2 (HER2) inhibitors (e.g., trastuzumab and lapatinib) block the activity of the HER2, a protein that is overexpressed in a subset of CRC tumors. These agents can be effective in patients with HER2-positive CRC (81).

Immune checkpoint inhibitors (e.g., pembrolizumab and nivolumab) are a form of immunotherapy that targets checkpoint proteins on immune cells, which cancer cells exploit to evade immune surveillance. By blocking these proteins, these inhibitors allow the immune system to recognize and attack cancer cells (82).

MSI-targeted therapies (e.g., pembrolizumab) are designed to treat MSI-high CRC tumors, which exhibit a high mutational burden and are more responsive to immune checkpoint inhibitors, especially after failing chemotherapy (83). Wnt signaling pathway inhibitors, including vantictumab and ipafricept, target components of the Wnt pathway, a crucial signaling cascade involved in the development and progression of CRC (84). Phosphoinositide 3-kinase (PI3K) inhibitors (e.g., alpelisib and idelalisib) modulate the activity of the PI3K signaling pathway, which plays a pivotal role in CRC tumorigenesis (85).

Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors (e.g. palbociclib and abemaciclib) target the CDK4/6, which are involved in regulating the cell cycle (86). Poly (ADP-ribose) polymerase (PARP) inhibitors, including olaparib and rucaparib, inhibit the PARP, an enzyme involved in DNA repair mechanisms. These agents have shown efficacy in tumors with defective DNA repair pathways such as those harboring BRCA gene mutations (87). Bromodomain and extraterminal (BET) inhibitors, including i-BET762 and JQ1, target BET proteins, which regulate gene expression. Preclinical studies demonstrated that BET inhibitors can be effective in treating CRC (88).

Heat shock protein 90 (HSP90) inhibitors, such as ganetespib and onalespib, modulate the activity of the HSP90, which is crucial for stabilizing proteins essential for cancer cell growth and survival (89). Antibody-drug conjugates (ADCs) such as trastuzumab emtansine (Kadcyla®) combine an antibody that targets a specific protein on cancer cells with a cytotoxic payload. By delivering the toxic agent directly to cancer cells while minimizing off-target effects, ADCs were found to be effective in treating CRC (90).

RNA interference (RNAi) therapies such as patisiran and givosiran employ small RNA molecules to silence specific genes involved in the development and progression of CRC. While approved for other indications, RNAi therapies are currently under investigation for treating CRC (91). Epigenetic therapies, exemplified by azacitidine and decitabine, target enzymes that modify the structure of DNA and histones, leading to changes in gene expression patterns. Preclinical studies have highlighted the potential of epigenetic therapies in managing CRC (92,93).

Several Biological Challenges in Treating Colorectal Cancer

Tumor heterogeneity, both within and between patients, can limit the identification of optimal treatment regimens. Cancer cells can also develop resistance to targeted drugs through various mechanisms, reducing therapy effectiveness over time. Additionally, reliable biomarkers to predict drug responses are challenging to detect consistently in clinical samples (94-98).

Moreover, precision therapies face practical barriers. Targeted drugs have high development and manufacturing costs, restricting their availability. There is limited clinical evidence for many drugs regarding their safety and efficacy in humans. Identifying optimal combination treatments is challenging and may require individualized approaches. The regulatory approval process can also be time-consuming for novel therapies. Some therapies cause significant toxicities, which may preclude their use in some high-risk patients. Furthermore, patient selection for personalized care additionally requires extensive biomarker testing (99-101). Tumor heterogeneity

presents significant challenges, as markers predictive of response can vary between patients and evolve over time. Cancer cells may also develop resistance to targeted therapies through different mechanisms. To address these challenges, combination regimens that integrate multiple drugs, immunotherapy, and radiation are being evaluated. Additionally, continuous biomarker monitoring through liquid biopsies may allow for adaptive treatment approaches that adjust therapies based on signs of resistance.

Anti- Colorectal Cancer Based Metal Ions

Certain metal ions have demonstrated promising anti-cancer activity against CRC, and their anti-tumor mechanisms are an active area of research driving the development of novel ion-based therapeutics (102). Platinum complexes such as cisplatin are widely used in chemotherapy but often lead to drug resistance. Next-generation orally administered platinum drugs are designed to overcome this resistance. For example, carboplatin and oxaliplatin form platinum-DNA adducts that hinder replication and transcription in rapidly dividing CRC cells (103-105). Ruthenium complexes exhibit anti-CRC effects via multiple mechanisms, with lower toxicity compared to platinum. NAMI-A inhibits metastasis by reducing tumor cell adhesion and invasion. KP1019 induces apoptosis and cell cycle arrest. Oral ruthenium drugs are currently in clinical trials, with significant responses observed (104). Gold compounds exhibit anti-proliferative effects on CRC cells. Auranofin, a gold-phosphine complex, disrupts thioredoxin reductase, which is critical for maintaining redox balance and supporting cell survival. Additionally, triapine-gold conjugates enhance the efficacy of radiotherapy by preventing DNA damage repair in hypoxic tumor regions, thereby improving treatment outcomes (105-106).

Gallium salts demonstrate broad-spectrum anti-tumor properties. Gallium maltolate is well-tolerated both orally and intravenously, where it disrupts iron transport in CRC cells and triggers mitochondrial apoptosis. This iron deprivation subsequently induces ferroptosis cell death (107). Selenium compounds elevate reactive oxygen species in CRC cells beyond tolerable levels, causing oxidative stress-mediated apoptosis. Phenylselenocysteine and ebselen were found to inhibit CRC growth with fewer side effects compared to 5-fluorouracil (108-109).

Role of Artificial Intelligence in Diagnosis and Treatment of Colorectal Cancer

AI is being increasingly applied to improve various aspects of CRC care. Deep learning applied to endoscopy videos and radiology images can help achieve more accurate and early detection of lesions. Neural networks assist pathologists in analyzing biopsy slides and identifying diagnostic and prognostic markers. Machine learning also supports treatment planning by comparing patient tumors to past similar cases. Additionally, AI expedites drug discovery by screening databases to propose novel targets and simulate drug interactions. AI technologies are playing an increasingly pivotal role in CRC management. Machine learning applied to medical imaging data significantly aids in early detection and precise tumor staging. For instance, deep learning algorithms analyze endoscopy videos to identify precancerous polyps with greater accuracy than human experts (110).

When trained on large clinical datasets, AI assists pathologists in analyzing digitized biopsy slides. Neural networks can classify histopathological images, pinpointing diagnostic and prognostic features such as infiltrating margins or tumor budding. Whole slide imaging, combined with machine vision, automates cancer grading to ensure consistency in pathology assessments (111). Furthermore, genomic and molecular profiling generates vast amounts of biomarker data, and AI mining of integrated multi-omic profiles helps discover novel molecular subtypes and predictors of clinical outcomes. Non-invasive liquid biopsies use machine learning to detect rare circulating biomarkers in blood or stool samples (112).

AI-powered decision support tools help physicians develop personalized treatment plans. Deep learning models evaluate a patient's complete medical record, comparing their tumor characteristics to prior similar cases. These algorithms recommend the most effective therapies and predict potential side effects based on a patient's medical history, lifestyle, and genomic profile (113). During treatment, AI continuously monitors patients for complications or signs of disease recurrence, analyzing imaging, blood tests, and electronic health records to detect early signs such as abnormal CA 19-9 levels. This enables earlier intervention to improve survival outcomes (114).

AI also accelerates drug discovery. Machine learning screens vast databases to propose new drug targets based on genomic profiling of patient responses. Computer models simulate drug interactions to predict both effectiveness and toxicity before human trials (115). Several innovative technologies hold promise to further advance CRC management. Virtual and augmented reality enables surgeons to visualize patient anatomy and rehearse procedures using personalized 3D images. Digital twins continuously track individual health by merging multi-omic data with digital biomarkers from lifestyle patterns. This continuous monitoring can enable earlier intervention. These emerging fields empower personalized diagnosis and treatment planning through immersive digital reconstruction of patient-specific information.

Herbal and Traditional Medicine as Anti-colorectal Cancer

Plants have long been used in traditional medicine systems worldwide to treat cancer. Ongoing research is exploring their anti-CRC mechanisms and therapeutic potential

(116). Curcumin, the active compound in turmeric, inhibits CRC cell proliferation through antioxidant and anti-inflammatory effects. It downregulates various oncogenic pathways and sensitizes tumors to chemotherapy. Multiple clinical trials demonstrate curcumin's safety and efficacy when used in combination with standard CRC treatments (117).

Green tea catechins such as epigallocatechin gallate (EGCG) induce apoptosis in CRC cells and reduce metastasis. EGCG intake is associated with lower CRC incidence in epidemiological studies. Clinical research investigates its synergy with immune checkpoint inhibitors (118). Resveratrol, derived from grapes and berries, exhibits anti-tumor properties through sirtuin activation and mTOR pathway suppression. It enhances chemosensitivity and reduces toxicity by protecting normal cells from damage. Early trials indicated that resveratrol supplements are beneficial when combined with 5-fluorouracil (118-120).

Ginger compounds (e.g., 6-gingerol and 6-shogaol) exert antiproliferative effects on CRC cells through p53 activation and suppression of cyclooxygenase-2 and tumor necrosis factor alpha expression. They inhibit angiogenesis and sensitize resistant tumors. Patients consuming ginger extracts display better responses to post-surgical chemotherapy (121). Other natural products under active investigation include phytochemicals from mangosteen, pomegranate, cinnamon, and mushrooms, which induce apoptosis, block invasion, or boost immunity against CRC cells. Multi-targeted herbal formulations exhibit anti-cancer synergy superior to single agents with minimal side effects (122).

Prevention and Personalized Medicine of Colorectal Cancer

CRC prevention involves lifestyle modifications, screening programs, and personalized approaches based on individual risk profiles. A diet high in fruits, vegetables, and whole grains, while limiting red and processed meat intake, helps maintain a healthy gut microbiome, and reduce inflammation associated with CRC risk. Regular physical activity and avoiding smoking and excessive alcohol consumption also promote gut health (123). Screening programs allow for the detection and removal of precancerous polyps before they progress to cancer. Colonoscopy every 10 years remains the gold standard, but non-invasive stool-based tests such as FOBT and FIT enable population-level screening. New methods under study include blood biomarker tests, breath biomarkers, and capsule endoscopy (124). Genetic testing can identify hereditary syndromes such as Lynch syndrome and familial adenomatous polyposis, which confer extremely high lifetime CRC risk. At-risk individuals undergo more frequent screening or preventive surgery. Genome sequencing personalized by ancestry can also predict common variant-associated risks (125).

Probiotics, which supplement beneficial gut bacteria, modify epithelial cell proliferation and reduce cancer-causing compounds produced by pathological microbiota. Prebiotics selectively nourish helpful microbes. Fecal microbiota transplantation is used to treat recurrent C. difficile infection and may also prevent CRC. Chronic inflammation drives oncogenesis, so anti-inflammatory nutraceuticals offer promising potential. Curcumin, resveratrol, and EGCG target inflammation-related transcription factors to exert chemopreventive effects. Various clinical trials assess their efficacy and safety as long-term supplements (126). Multi-targeted approaches tailored using a patient's molecular and clinical profile optimize prevention strategies. As healthcare evolves to become more predictive, preventive, and personalized, CRC incidence and mortality rates will decline significantly (127).

Future Directions and Emerging Technologies

CRC management continues to advance rapidly through new technologies that push the frontiers of science. Promising areas primed to transform patient care in the coming years include immunotherapies, nanomedicine, and organoid engineering. Adoptive cell therapies utilizing genetically engineered T cells or natural killer cells have demonstrated efficacy against advanced CRC. Combination strategies that integrate immunotherapies with targeted agents and radiation therapy further improve response rates. Emerging checkpoints beyond PD-1/PD-L1 are also enhancing anti-tumor immunity (128).

Nanocarriers enable the precise delivery of drugs, genes, and imaging agents to tumors, facilitating personalized multi-modal therapies. Theranostic nanoparticles monitor treatment responses in real-time. Nanodelivery technologies address solubility challenges, protect cargoes from degradation, and actively target cancer cells via surface functionalization (129). 3D bioprinting builds complex tumor models for accelerated drug discovery. Patient-derived organoids implanted in mice create avatars for preclinical testing. Organs-on-chips better simulate human physiology than cell cultures alone. Transplanting engineered organ modules may one day regenerate diseased tissues (130).

Virtual reality and augmented reality enable surgeons to visualize and rehearse procedures on highly realistic 3D anatomical reconstructions. Digital twins continually track individual patient health, integrating multi-omic data with digital biomarkers mined from lifestyle patterns (131). AI and machine learning are transforming diagnostics, drug development, and clinical decision support. Big data on AI can identify novel therapeutic targets, repurpose approved agents, and predict optimal treatment combinations based on molecular profiles (132). The integration of advanced technologies in CRC management is progressing, with AI-assisted colonoscopy, liquid biopsies, and precision medicine platforms being increasingly adopted across various healthcare settings.

Case studies demonstrate improved polyp detection rates and treatment outcomes. Cost-effectiveness analyses suggest long-term benefits despite the initial high costs. However, challenges remain, including implementation expenses, the need for specialized training, and reimbursement issues. The future of CRC management will likely involve integrating multiple technologies for comprehensive care. Ongoing clinical trials and health economic studies are crucial to fully evaluate the impact of these integrated approaches. As evidence grows and technologies evolve, broader adoption is expected, ultimately enhancing patient outcomes and potentially more efficient healthcare delivery in CRC management.

Conclusion

The integration of advanced imaging techniques, biomarker testing, and histopathological analyses has significantly improved the accuracy and efficiency of CRC diagnosis and monitoring. Precision medicine and targeted therapies have revolutionized CRC treatment by focusing on specific molecular pathways and biomarkers, thereby improving patient outcomes and enabling personalized care. Anti-cancer metal ions such as platinum, ruthenium, gold, gallium, and selenium compounds have shown promising anti-tumor effects through various mechanisms, opening up new avenues for drug development. AI and machine learning have played a crucial role in early detection, tumor staging, treatment planning, and drug discovery for CRC. Herbal and traditional medicines, including curcumin, green tea catechins, resveratrol, and ginger compounds, have demonstrated anti-cancer properties and potential synergistic effects when with conventional therapies. Additionally, prevention strategies, including lifestyle modifications, screening programs, and personalized approaches based on risk profiles, are crucial for reducing CRC incidence and mortality. However, challenges such as tumor heterogeneity, drug resistance, biomarker identification, high cost, and regulatory hurdles need to be addressed to fully realize the potential of these cutting-edge approaches.

Recommendations

1. Conduct large-scale multi-center clinical trials to further validate the efficacy and safety of promising targeted therapies, anti-cancer metal ions, and herbal medicines when used in combination with standard treatments for CRC.
2. Invest in the development of robust biomarker panels and liquid biopsy technologies for early detection, monitor treatment response monitoring, and guide personalized therapy selection for CRC patients.
3. Foster interdisciplinary collaborations between researchers, clinicians, and industry partners to accelerate the clinical translation of emerging technologies such as nanomedicine, organoid engineering, and AI into clinical practice for CRC management.
4. Establish standardized protocols and guidelines for the integration of AI and machine learning algorithms into diagnostic and treatment decision-making processes for CRC, ensuring ethical and equitable implementation.
5. Encourage public-private partnerships and funding initiatives to support the development and accessibility of precision medicine approaches, targeted therapies, and innovative drug delivery systems, especially for CRC patients in underserved and resource-limited settings.
6. Promote patient education and awareness campaigns that emphasize the importance of lifestyle modifications, adherence to screening guidelines, and participation in clinical trials for CRC prevention and treatment.
7. Conduct long-term epidemiological studies and post-marketing surveillance to monitor the safety, efficacy, and potential adverse effects of emerging CRC therapies, ensuring ongoing improvement and refinement of treatment protocols.

Competing Interests

None.

Ethical Approval

Not applicable.

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