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A REVIEW ON COLORECTAL CANCER MANAGEMENT IN THE ERA OF PRECISION MEDICINE

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ABSTRACT
Colorectal cancer (CRC) continues to be a major global health concern, ranking among the top causes of cancer morbidity and mortality. Although advances in early detection, surgical techniques, chemotherapy, and targeted therapies have improved outcomes, therapeutic resistance and tumor heterogeneity remain significant barriers. Precision medicine driven by molecular profiling, next-generation sequencing, liquid biopsy technologies, and patient-specific treatment strategy is reshaping CRC management. This review explores the molecular mechanisms underlying CRC progression, highlights diagnostic approaches including genomics and biomarker testing, and evaluates conventional as well as targeted therapies. Furthermore, it discusses emerging concepts such as immunotherapy, nanomedicine and artificial intelligence, which hold promise for more personalized and effective interventions in the precision oncology era.

KEYWORDS: Chemotherapy, Diagnostics, Radiotherapy, Surgery, Signalling pathways, Nanomedicine etc.

1. INTRODUCTION

Colorectal cancer (CRC) is the third most frequently diagnosed malignancy and the second leading cause of cancer-related mortality worldwide.[1] Global statistics indicate over 1.9 million new cases and nearly 935,000 deaths annually.[2] The development of CRC is multifactorial, with lifestyle factors, hereditary syndromes, and environmental exposures contributing significantly to disease risk. Prognosis largely depends on the stage at diagnosis; while localized disease is highly treatable, advanced CRC is often associated with therapy resistance and poor survival rates.[3]

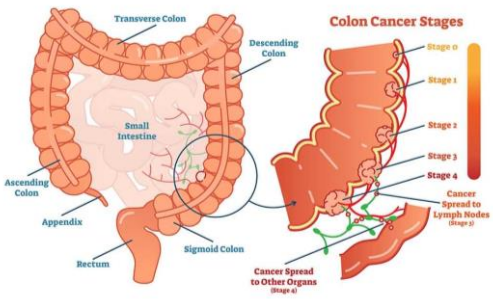

Fig. 1: Colon Cancer with different stages.

Historically, surgery, radiotherapy, and systemic chemotherapy have been the primary treatment strategies. However, with an enhanced understanding of CRC biology, clinical practice is shifting toward precision medicine, which emphasizes the integration of molecular and genetic information with clinical features to optimize treatment selection and improve patient outcomes.[4]

2. Molecular Pathogenesis of Colorectal Cancer

CRC arises through a stepwise process of genetic alterations and epigenetic changes that collectively disrupt normal cellular regulation.[5] The major molecular pathways implicated include chromosomal instability, microsatellite instability, CpG island methylator phenotype, and dysregulation of key signalling cascades.

2.1 Chromosomal Instability (CIN) Pathway

CIN represents the predominant route of CRC development, accounting for approximately 70% of cases. It is defined by large-scale chromosomal alterations and mutations in critical genes such as *APC*, *KRAS*, and *TP53*. Loss of *APC* function initiates adenoma formation, followed by activating mutations in *KRAS* and subsequent inactivation of *TP53*, culminating in carcinoma formation.[6]

2.2 Microsatellite Instability (MSI) Pathway

MSI results from defects in DNA mismatch repair (MMR) genes, including *MLH1*, *MSH2*, *MSH6*, and *PMS2*. MSI-high tumors occur in about 15% of sporadic CRC and in the majority of Lynch syndrome–associated cases.[7] Clinically, MSI-high CRCs are characterized by improved prognosis and enhanced responsiveness to immune checkpoint inhibitors, making MSI a critical biomarker in treatment decision-making.

2.3 CpG Island Methylator Phenotype (CIMP)

CIMP is an epigenetic subtype of CRC characterized by widespread hypermethylation of CpG-rich promoter regions, leading to silencing of tumor suppressor genes.[8] A common event is methylation-induced inactivation of *MLH1*, giving rise to sporadic MSI-high CRCs. CIMP is strongly associated with *BRAF^V600E* mutations, occurring in 60–80% of such tumors, and is frequently observed in the proximal colon, particularly in elderly and female patients. Clinically, CIMP-positive tumors often display mucinous or poorly differentiated histology and tend to have worse outcomes compared with CIMP-negative CRCs. Importantly, CIMP has therapeutic implications: it is linked with reduced sensitivity to anti-EGFR monoclonal antibodies, while DNA demethylating agents such as azacitidine and decitabine are under investigation as potential therapies for this CRC subset.

2.4 Key Signalling Pathways in Colorectal Cancer

Multiple oncogenic pathways drive CRC progression, often overlapping and contributing to tumor heterogeneity.[9]

2.4.1 Wnt/β-Catenin Pathway

Mutations in *APC* disrupt the degradation of β-catenin, allowing its nuclear accumulation and transcriptional activation of oncogenic targets such as *MYC* and *CCND1*. Nearly 90% of CRCs exhibit aberrations in this pathway, making it a central feature of disease biology. While therapeutic targeting is difficult due to pathway complexity, approaches such as β-catenin/TCF inhibitors and tankyrase inhibitors are in development.

2.4.2 MAPK Pathway (KRAS and BRAF Mutations)

Mutations in *KRAS* (~40% of CRC) and *BRAF* (~10%, predominantly *V600E*) activate the MAPK signalling cascade, promoting uncontrolled proliferation. These mutations predict resistance to anti-EGFR therapies. Targeted approaches include KRAS^G12C inhibitors (sotorasib, adagrasib) and combination strategies using BRAF inhibitors (encorafenib) with EGFR antibodies, which have shown clinical benefit in BRAF-mutant CRC.

2.4.3 PI3K/AKT/mTOR Pathway

Alterations in *PIK3CA* and loss of *PTEN* activity stimulate PI3K/AKT/mTOR signalling, enhancing tumor growth and survival. Such mutations occur in 15–20% of CRC cases and often coexist with MAPK alterations. While mTOR and PI3K inhibitors are under evaluation, single-agent efficacy remains limited due to compensatory pathway activation. Current strategies are exploring dual inhibition of PI3K and MAPK signalling.

2.4.4 TGF-β/SMAD Pathway

In healthy epithelium, TGF-β exerts tumor-suppressive effects through growth inhibition and apoptosis. In CRC, mutations in *SMAD4* and *TGFBR2* abrogate this function, facilitating tumor progression. At advanced stages, TGF-β may paradoxically promote metastasis via epithelial-to-mesenchymal transition (EMT). Therapeutic efforts aim to selectively modulate TGF-β signalling to exploit its dual roles in CRC.

3. Precision Diagnostics in CRC

Accurate molecular characterization of CRC is fundamental to precision oncology.

3.1 Next-Generation Sequencing (NGS): NGS provides comprehensive profiling of tumor genomes, enabling detection of actionable mutations in genes such as *KRAS*, *NRAS*, *BRAF*, and *PIK3CA*. Clinical panels like Foundation One and Onco Panel have been integrated into routine practice to inform treatment strategies.[10]

3.2 Liquid Biopsies: Non-invasive assays detecting circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomal RNA allow dynamic monitoring of minimal residual disease, treatment response, and emergence of resistance mutations.[11] This approach complements tissue biopsy by capturing tumor heterogeneity in real time.

3.3 Immunohistochemistry (IHC) and MSI Testing: IHC is routinely employed to assess MMR protein expression, while PCR and NGS-based assays confirm MSI status. Identification of MSI-high tumors is particularly relevant as these patients derive significant benefit from immune checkpoint blockade.[12]

4. Conventional Treatment Approaches

Traditional therapeutic modalities remain the foundation of colorectal cancer (CRC) management, particularly for patients diagnosed at an early or locally advanced stage. Surgery, chemotherapy, and radiotherapy are the mainstays, often employed in an integrated, multimodal fashion depending on tumor location, staging, and molecular subtype. While these approaches have significantly improved survival over past decades, challenges such as recurrence, toxicity, and treatment resistance continue to limit long-term outcomes.

4.1 Surgery

Surgical resection represents the primary curative strategy for localized CRC. In early-stage tumors (Stages I and II, without high-risk features), complete excision of the primary lesion with negative margins often provides long-term disease control and, in many cases, cure.[13] The introduction of laparoscopic and robotic-assisted colectomies has transformed the surgical landscape, offering minimally invasive options associated with reduced postoperative pain, shorter hospital stays, faster recovery, and cosmetic advantages, while maintaining oncologic equivalence with open surgery.

For rectal cancer, the adoption of total mesorectal excision (TME) has become the gold standard. TME involves en bloc resection of the rectum and mesorectal envelope, including lymph nodes and surrounding fat, significantly reducing local recurrence rates. Advances in imaging and preoperative chemoradiotherapy have further improved resectability and functional outcomes.

In metastatic CRC, surgery also retains an important role. Selected patients with liver- or lung-limited metastases may undergo metastasectomy, which can achieve prolonged survival and, in rare cases, complete cure. This aggressive surgical approach is often combined with perioperative chemotherapy to maximize disease control. However, the effectiveness of surgical strategies is constrained by the stage of disease at diagnosis, as many patients present with disseminated or unresectable tumors.

4.2 Chemotherapy

Chemotherapy remains central to systemic management, both in the adjuvant setting (post-surgical) and in advanced disease. The fluoropyrimidine 5-fluorouracil (5-FU), introduced more than five decades ago, continues to serve as the backbone of chemotherapy regimens. 5-FU exerts its cytotoxic effect by inhibiting thymidylate synthase, an enzyme crucial for DNA synthesis, thereby impairing tumor proliferation. Its activity is enhanced by leucovorin (folinic acid), which stabilizes the 5-FU–thymidylate synthase complex.

To further improve efficacy, 5-FU is combined with other cytotoxic agents such as oxaliplatin or irinotecan. The most widely used regimens include:

- FOLFOX (5-FU, leucovorin, oxaliplatin): standard in the adjuvant treatment of Stage III CRC and as first-line therapy in metastatic disease.
- FOLFIRI (5-FU, leucovorin, irinotecan): a preferred regimen in advanced CRC.
- FOLFOXIRI (combination of 5-FU, oxaliplatin, and irinotecan): used selectively in fit patients with metastatic disease to maximize tumor response.

Despite these advances, toxicities such as diarrhoea, mucositis, neutropenia, and peripheral neuropathy (notably with oxaliplatin) limit tolerability. Furthermore, chemoresistance—both intrinsic and acquired—remains a critical barrier. Mechanisms of resistance involve alterations in drug transport, enhanced DNA repair, metabolic adaptations, and evasion of apoptosis.[14] Nevertheless, chemotherapy continues to serve as the foundation upon which targeted agents and immunotherapies are integrated.

4.3 Radiotherapy

The role of radiotherapy in CRC is context-dependent. For colon cancer, its application is limited due to the mobility of the colon and risks of radiation-induced bowel toxicity. Conversely, in rectal cancer, radiotherapy is pivotal in local disease management.

Preoperative chemo radiotherapy (CRT), typically involving fluoropyrimidines combined with pelvic irradiation, is standard for locally advanced rectal tumors (T3/T4 or node-positive). This approach offers multiple benefits:

- Tumor down staging and improved resectability.
- Higher rates of sphincter-preserving surgeries, particularly in low rectal cancers.
- Reduced local recurrence compared with postoperative radiotherapy.

Current research is exploring innovations such as short-course radiotherapy, dose intensification, and integration with immune checkpoint inhibitors to optimize outcomes while minimizing toxicity.[15]

5. Targeted Therapies

The advent of targeted therapy has revolutionized CRC management, reflecting a shift from non-specific cytotoxic chemotherapy to molecularly guided treatment. By exploiting key genetic and signalling aberrations, targeted therapies provide more precise tumor inhibition with the potential for improved efficacy and reduced systemic toxicity.

5.1 Anti-EGFR Therapy

The epidermal growth factor receptor (EGFR) is a critical regulator of proliferation and survival in epithelial malignancies. Monoclonal antibodies cetuximab and panitumumab bind the extracellular domain of EGFR, blocking ligand interaction and inhibiting downstream signalling via the MAPK and PI3K/AKT pathways. Clinical benefit is confined to patients with RAS wild-type tumors, as activating KRAS or NRAS mutations lead to constitutive downstream signalling, rendering EGFR inhibition ineffective.[16] Combining anti-EGFR therapy with chemotherapy (e.g., FOLFIRI + cetuximab) has demonstrated improved response rates and overall survival in metastatic CRC. However, resistance often emerges, mediated by EGFR mutations, HER2 amplification, or activation of bypass signalling cascades.

5.2 Anti-VEGF Therapy

Angiogenesis is essential for tumor progression and dissemination, with VEGF serving as its primary driver. Bevacizumab, a monoclonal antibody against VEGF-A, and ramucirumab, an inhibitor of VEGFR-2, have become integral components of metastatic CRC therapy. When combined with chemotherapy, these agents extend progression-free survival (PFS) and overall survival (OS).[17] Nevertheless, they are associated with significant adverse events, including hypertension, proteinuria, bleeding, and thromboembolic complications, necessitating vigilant patient monitoring.

5.3 BRAF and MEK Inhibitors

Approximately 10% of CRC patients harbour BRAF mutations, predominantly the V600E variant, which is associated with poor outcomes. Early trials with BRAF inhibitors such as vemurafenib yielded limited efficacy due to compensatory EGFR activation. A significant breakthrough came with combination regimens, particularly encorafenib (BRAF inhibitor) + cetuximab (anti-EGFR), which demonstrated improved survival in BRAF^V600E-mutant CRC and subsequently received FDA approval.[18] Ongoing trials are assessing triplet strategies (BRAF + MEK + EGFR inhibition) to further enhance response rates.

5.4 PI3K/AKT/mTOR Inhibitors

The PI3K/AKT/mTOR pathway is frequently dysregulated in CRC due to PIK3CA mutations or PTEN loss, driving tumor survival, growth, and therapy resistance. Multiple agents targeting this axis are under investigation, including:

- PI3K inhibitors (e.g., alpelisib, buparlisib).
- AKT inhibitors (e.g., capivasertib).
- mTOR inhibitors (e.g., everolimus, temsirolimus).

While preclinical results are promising, clinical efficacy has been modest, partly due to pathway redundancy and cross-talk with the MAPK cascade.[19] Current strategies are exploring rational combination therapies, such as PI3K and MEK co-inhibition, to overcome resistance and improve outcomes.

6. Immunotherapy in Colorectal Cancer

Immunotherapy has transformed the treatment paradigm for several malignancies, including melanoma and lung cancer, and is now an area of active exploration in colorectal cancer (CRC). However, its efficacy in CRC is strongly influenced by the underlying molecular subtype of the disease.

6.1 Immune Checkpoint Inhibitors

Checkpoint inhibitors targeting programmed cell death protein 1 (PD-1), such as pembrolizumab and nivolumab, have received FDA approval for patients with microsatellite instability–high (MSI-H) or deficient mismatch repair (dMMR) CRC.[20] These tumors exhibit a high mutational burden, producing numerous neoantigens that enhance immune recognition, which explains their responsiveness to immunotherapy. In contrast, microsatellite-stable (MSS) tumors, which account for the majority of CRC cases, typically display low immunogenicity and remain refractory to these agents, highlighting the need for alternative strategies.

6.2 Combination Immunotherapy Strategies

To overcome the limited scope of checkpoint inhibitor efficacy, several combination regimens are being evaluated in clinical trials.[21] These include pairing PD-1/PD-L1 inhibitors with chemotherapy, anti-angiogenic agents (such as bevacizumab), or targeted therapies to modulate the tumor microenvironment and enhance immune infiltration. Combinations with MEK inhibitors, radiation, or vaccines are also being tested to broaden the benefit to MSS tumors. Early results indicate that synergistic approaches may partially overcome resistance mechanisms and extend immunotherapy benefits beyond MSI-H CRC.

6.3 Cancer Vaccines and Adoptive Cell Therapies

Beyond checkpoint inhibitors, innovative immunotherapeutic modalities are under investigation. Cancer vaccines, such as dendritic cell–based vaccines, aim to stimulate immune responses against tumor-associated antigens (e.g., CEA, MUC1). In addition, adoptive cell therapies, particularly chimeric antigen receptor (CAR) T-cell therapy, are being engineered to recognize CRC-specific targets. Although promising in hematologic cancers, CAR-T therapy in CRC faces challenges such as tumor heterogeneity, antigen escape, and an immunosuppressive tumor microenvironment.[22] Nonetheless, ongoing clinical studies are optimizing target selection and improving persistence of engineered immune cells.

7. Emerging Technologies in CRC Management

7.1 Artificial Intelligence (AI)

AI is rapidly becoming a cornerstone of precision oncology in CRC. Deep learning models integrated into colonoscopy platforms improve adenoma detection rates

and reduce missed lesions, thereby enhancing early diagnosis. Additionally, AI-driven algorithms can analyse radiomic and genomic datasets to predict treatment outcomes, stratify patients by risk, and identify drug repurposing opportunities.[24] These tools are expected to significantly reduce inter-observer variability and support clinical decision-making.

7.2 Nano medicine

Nanotechnology provides innovative solutions for CRC therapy by enabling targeted delivery of chemotherapeutics, RNA molecules, and imaging agents. Nanoparticles can preferentially accumulate in tumor tissue due to the enhanced permeability and retention (EPR) effect, reducing systemic toxicity. For instance, liposomal formulations of 5-fluorouracil and siRNA-loaded nanoparticles directed against oncogenic drivers such as KRAS are under active development.[25] Furthermore, multifunctional nanoplatforms allow simultaneous drug delivery, real-time imaging, and immune modulation, paving the way for next-generation precision therapeutics.

7.3 Organoids and Patient-Derived Xenografts (PDXs)

Patient-derived organoids (PDOs) and xenograft models have emerged as powerful preclinical tools for personalized oncology. PDOs, grown from patient tumor biopsies, replicate the molecular and histological features of CRC, enabling rapid ex vivo drug screening and prediction of clinical response. Similarly, PDX models, where human tumors are implanted into immunocompromised mice, allow for in vivo evaluation of therapeutic strategies and biomarker discovery.[26] These platforms bridge the gap between laboratory research and clinical practice, accelerating drug development and guiding individualized therapy selection.

8. Challenges and Future Perspectives

Despite significant progress, multiple challenges hinder the full realization of precision medicine in CRC:

- Therapy Resistance: Both targeted therapies and immunotherapies face intrinsic and acquired resistance. Tumor heterogeneity, compensatory signalling pathways, and clonal evolution drive therapeutic failure, necessitating rational combination regimens and next-generation inhibitors.
- Expanding Immunotherapy Benefits: While MSI-H tumors respond well to checkpoint inhibitors, the majority of patients with MSS CRC derive minimal benefit. Research is focused on enhancing immunogenicity in MSS tumors through oncolytic viruses, radiotherapy, and immune-modulating agents.
- Integration of Multi-Omics Data: Incorporating genomic, transcriptomic, proteomic, and metabolomic profiles into routine practice remains a challenge. Advances in computational biology and AI will be critical to convert complex datasets into actionable clinical insights.
- Access and Equity: The availability of precision diagnostics and targeted therapies is uneven across the globe, particularly in low- and middle-income countries. Bridging this gap requires cost-effective technologies, broader clinical trial inclusion, and global health policy reforms.[27]

In summary, the future of CRC management lies in the integration of immunotherapy, emerging technologies, and multi-omics-driven precision medicine. Addressing therapeutic resistance, expanding the applicability of immunotherapies, and ensuring equitable access to advanced diagnostics and treatments will be pivotal in improving global outcomes for colorectal cancer patients.

9. CONCLUSION

The advent of precision medicine has transformed CRC management, offering molecularly guided therapies, immunotherapeutic options, and real-time monitoring using liquid biopsies. While challenges remain, integration of AI, nanomedicine, pharmacogenomics, and personalized therapeutic strategies holds the promise of significantly improving survival and quality of life in CRC patients.

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REFERENCES

1. Sung H, et al. Global cancer statistics 2021. *CA Cancer J Clin*. 2021.
2. Siegel RL, et al. Colorectal cancer statistics, 2023. *CA Cancer J Clin*. 2023.
3. Dekker E, et al. Colorectal cancer. *Lancet*. 2019.
4. Dienstmann R, et al. Consensus molecular subtypes and the evolution of precision medicine in CRC. *Nat Rev Cancer*. 2017.
5. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell*. 1990.
6. Kinzler KW, Vogelstein B. Lessons from hereditary CRC. *Cell*. 1996.
7. Boland CR, et al. MSI in colorectal cancer. *Gastroenterology*. 2010.
8. Toyota M, et al. CpG island methylator phenotype. *PNAS*. 1999.
9. Guinney J, et al. CRC subtypes. *Nat Med*. 2015.
10. Frampton GM, et al. NGS in precision oncology. *Nat Biotechnol*. 2013.
11. Diaz LA, Bardelli A. Liquid biopsies. *J Clin Oncol*. 2014.
12. Hause RJ, et al. MSI diagnosis and therapy. *Nat Med*. 2016.
13. Fleshman J, et al. Laparoscopic colectomy. *NEJM*. 2007.
14. André T, et al. Chemotherapy in CRC. *NEJM*. 2004.

15. Sauer R, et al. Preoperative chemoradiotherapy. *NEJM*. 2004.
16. Van Cutsem E, et al. Cetuximab and panitumumab. *NEJM*. 2009.
17. Hurwitz H, et al. Bevacizumab in CRC. *NEJM*. 2004.
18. Kopetz S, et al. BRAF inhibition in CRC. *NEJM*. 2019.
19. Dienstmann R, et al. PI3K pathway in CRC. *Clin Cancer Res*. 2015.
20. Le DT, et al. Pembrolizumab in MSI-high CRC. *NEJM*. 2015.
21. Overman MJ, et al. Nivolumab + ipilimumab in CRC. *Lancet Oncol*. 2018.
22. Zhang C, et al. CAR-T therapy in CRC. *J Hematol Oncol*. 2019.
23. Amstutz U, et al. Pharmacogenomics in CRC. *Clin Pharmacol Ther*. 2018.
24. Byrne MF, et al. AI in colonoscopy. *Gastroenterology*. 2020.
25. Xiao B, et al. Nanomedicine in CRC. *Adv Drug Deliv Rev*. 2021.
26. Vlachogiannis G, et al. Patient-derived organoids. *Science*. 2018.
27. Prasad V, et al. Precision oncology challenges. *Nat Rev Clin Oncol*. 2016.