INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND DENTAL HEALTH
(ISSN: 2454-4191)
www.ijmsdh.org (2026)

Received: 18 December 2025
Revised: 27 January 2026
Accepted: 22 February 2026
Published: 08 March 2026

Page No - 07-14
DOI - 10.55640/ijmsdh-12-03-02

Article Citation: Jasim, Z. M., & Shemran, K. A. (2026). Histological Alterations, Diagnosis and Therapeutic Approaches of Colorectal Cancer: A Review Article. International Journal of Medical Science and Dental Health, 12(03), 07-14. https://doi.org/10.55640/ijmsdh-12-03-02

Histological Alterations, Diagnosis and Therapeutic Approaches of Colorectal Cancer: A Review Article

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Abstract

Colorectal cancer (CRC) is one of the most common cancers and a major public health burden leading to cancer-related morbidity and mortality throughout the world. Its induction is a multistaged process which includes genetic and epigenetic mutations, and complicated environmental/lifestyle interactions. Histologically, CRC is mainly adenocarcinoma that develops from dysplastic transformation of the colonic epithelium and has known variants which affect prognosis and response to treatment. The cumulative effect of architectural distortion, cellular irregularities, invasive extension beyond muscularis mucosae and through the surrounding lymphovascular channels to form metastases describes disease progression. Early diagnosis is paramount for survival. Diagnostic work up includes screening tools, including fecal occult blood test and colonoscopy, followed by histo-pathological diagnosis and radiologic staging. Molecular diagnostics for mutation analysis and microsatellite instabilty status have provided additional clarification to categorization and treatment strategy in recent years. Therapies for CRC are dependent on the stage, as local disease is resected surgically and treatment there-after administered. The introduction of adjuvant and neo-adjuvant systemic chemotherapy, radiotherapy (especially for rectal cancer), new targeted biologic agents, and as of late immune therapy have transformed the management of both metastatic and locally advanced disease. Identification of target therapy according to the molecular tumor profile is essential to patients who respond to this treatment. In conclusion, the

histopathological features of CRC and early diagnosis options and modern therapeutic opportunities should be combined to best control colorectal cancer as well as additional new research approaches in response to worldwide diseases.

Keywords: Cerebrospinal Fluid, Chromosomal Instability, Colorectal Cancer

Introduction

Cerebrospinal fluid (CSF) is an unique biological fluid that performs several crucial tasks for the structural, chemical and physiological homeostasis of the central nervous system. As it courses through the ventricles and subarachnoid space, CSF also plays a role in mechanical protection of the brain and spinal cord by serving as a transport medium for nutrients, waste products, and immune surveillance of the central nervous system. Because of the immediate proximity to neural tissue and its relative biochemical stability, CSF offers a unique access point into both normal brain function as well as disease processes affecting the nervous system (Spector & Johanson, 2007). From the biochemical point of view CSF is a tightly regulated ultrafiltrate of plasma, to which it resembles selectively transported at choroid plexus level rather than being absorbed by simple diffusion. The composition of ISF is strikingly different from blood, with lower protein content, unique electrolytes profiles and CNS metabolites, neurotransmitter breakdown products and signalling molecules. These biochemical characteristics are indicative of a healthy blood–brain and blood–CSF barriers, which are known to be disrupted in many neurological diseases (Abbott et al., 2010).

CSF has several physiological roles such as IC pressure control, cerebral homeostasis and glymphatic clearance. The newly discovered glymphatic system highlights the importance of CSF as it relates to mediating convective exchange between CSF and ISF, an activity responsible for clearing away metabolic waste materials including amyloid-β and tau proteins. Dysfunction in CSF circulation and clearance has been implicated in neurodegenerative conditions such as Alzheimer's disease, highlighting an active role for the fluid beyond its passive 'cushion'. These observations have reframed longstanding notions of CSF physiology and emphasized its role in brain health over the long term (Iliff et al., 2012).

Changes in the composition and flow of CSF are important from a pathophysiologic point of view also for many neurological diseases. Inflammatory and infectious diseases, such as multiple sclerosis, bacterial meningitis and viral encephalitis, are known to display changes in cellular composition, immunoglobulin levels and cytokine profiles found in CSF. There are likewise more subtle biochemical changes in the CSF that precede the onset of clinical symptoms in neurodegenerative diseases--evidence of early neural damage and synapse loss. On the other hand, these disease-induced changes in fact emphasize the potential of CSF as both a diagnostic platform and means to understand pathogenesis (Blennow & Zetterberg, 2018). From the clinical point of view, cerebrospinal fluid is still of vital importance in neurology. A cerebrospinal fluid (CSF) test including cell count (leukocytes and erythrocytes), protein measurement, determination of glucose concentration and microscopic analyses is indispensable for the characterization of CNS infections, haemorrhage, demyelinating processes and malignancy. After analogous routine parameters, CSF disease-specific molecular biomarker determination Too made it into routine diagnostic algorithms, especially for neurodegenerative and autoimmune diseases. For instance, CSF amyloid-β, total-tau and phosphorylated tau constitute Alzheimer's disease itself by definition, making the use of CSF-biomarkers for precision neurology ever more common (Jack et al., 2018).

However, The analysis of CSF has gotten increasing importance for treatment monitoring and as a biomarker tool fulfilled in pharmaceutical research. As most CNS active drugs have to infiltrate a restrictive barrier, CSF profiling represents an important source of information to evaluate compound penetration, target engagement and pharmacodynamics. Intrathecal drug delivery also utilizes the CSF pathways in order to obtain high local concentrations with relatively low systemic toxicity, notably in oncological and pain therapies. These methods also reveal the translational potential of CSFs research (Pardridge, 2016).

This review aims to achieve this knowledge by gathering and presenting all aspects related to the biochemistry, pathophysiology and clinical applications of CSF. The aim of this review is to reconcile classical concepts with recent experimental progress, and proposed a better definition of its complex role in health and disease showing that it will not remain confined within the walls of research but should mature into applications as diagnostic or therapeutic tools.

Histological Alterations of Colorectal Cancer

Colorectal (CRC) cancer exhibited several divisional subtypes defined by any possible morphological changes given their relative "spread", but they relate to the same pathways for

morphogenesis. The histopathological examination that depends on testing of tissues is not only the current gold standard for diagnosis of CRC but also necessary for precise estimate prognosis. The architectural and cytological features of CRC supplies valuable information regarding the malignant potential, control of metastatic pathways as well as response to treatment (Bosman et al., 2010).

Normal Architecture of the Colon and Dysplasia

Normal colonic mucosa comprises the crypts of Lieberkühn (orderly deranged tubular glands) lined by columnar epithelial cells, goblet and enteroendocrine cells. From the mucosa to the muscle layer, right colonic glands show a regular cellular differentiation and unchanged polarity along their whole extension. The transition from normal epithelium to colorectal cancer (CRC) is a multistep process involving sequenced mechanisms of dysplastic transformation. During this process, affected cells show architectural distortion, cellular and nuclear enlargement, hyperchromatic and increased mitotic figures finally culminating in loss of polarity (Duan et al., 2020). There is evidence of both histologic and cytologic dysplasia in colonic adenomas. Low-grade dysplasia is composed of mild glandular crowding and nuclear stratification, whereas high-grade dysplasia shows complex glandular architecture, such as cribriform patterns and significant architectural distortion, with severe nuclear atypia and frequent mitotic figures. Altogether, these changes are representative of a continuum of genetic instability that is tightly correlated with malignant progression (Fenoglio-Preiser et al., 2008).

Adenocarcinoma and Glandular Architecture

Tumor glands are frequently irregular, back-to-back with inset by luminal necrosis and desmoplastic stromal response (WHO Classification of Tumours Editorial Board, 2019). Tumor Grading Formation of Gland is the Index of the Differentiation of Tumor. Well-differentiated tumours maintain well-formed glandular structures, which progressively begin to lose between moderate differentiation and are less associated with poorly-differentiated carcinoma. Poorly differentiated/undifferentiated tumors are associated with more aggressive cancer behaviors, high stage at diagnosis and bad prognosis (Nagtegaal et al., 2020).

Mucinous and Signet Cell Carcinomas

CRC comprises several histological subtypes with different biological and prognostic relevance. Mucinous adenocarcinoma Mucinous adenocarcinoma is characterised by the presence of pools of extra-cellular mucin that accounts for >50% of tumour volume. Under the microscope, tumour cells float in lakes of mucin with inflammatory infiltrates as often illustrated. It is more frequently related to a proximal-colon vedgetation, microsatellite instability (MSI), and low response to standard chemotherapy (Hugen et al., 2014). SRCC is an unusual but aggressive variant with characteristic features of intracellular mucin displacing the nucleus to the periphery resulting in signet-ring cell appearance. These tumours usually show diffuse infiltration of the bowel wall, few glands and early peritoneal seeding. Histopthologically– Signet ring cell carcinoma prognosis is very bad, and usually its stage at diagnosis is advanced (Bosman et al., 2010).

Budding of Tumor and Changes at the Invasive Front

One of the most significant clinically applicable histological features in CRC is tumor budding, which is defined by the presence of single or small cell clusters (≤ 4 Tumor Cells) at the invasive margin. Tumor budding is a histologic manifestation of EMT and is closely correlated to lymphovascular invasion, nodal metastases, and poor outcome (Lugli et al., 2017). High TB is currently recognized as an additional independent poor prognostic factor, and reporting of esophageal cancer with TB and GC has increasingly become routine practice (Nagtegaal et al., 2020).

Inflammatory Infiltrates and Immune Landscape

The pathologic of CRC frequently shows some subsets of infiltration between inflammatory cells in the tumor and stroma. Tumor-infiltrating lymphocytes (particularly CD8+ cytotoxic T cells) are more abundant in MSI-high tumors and associated with favorable prognosis. The tumor may show Crohn's-like lymphoid aggregates at invasion margins histologically. In contrast, poor immune-infiltrated tumors more frequently have features of immune escape and worse patient outcome. Assessment of immune histologic features is more crucial than ever in the era of immunotherapy, which has reawakened interest in the relationship between histology and response to therapy (Galon et al., 2016).

Histological Correlates of Molecular Pathways

Histological alterations in CRC go hand in hand with certain molecular pathways. CIN pathway type tumors are histologically more similar to typical adenocarcinoma, whereas MSI-high TCCAs commonly demonstrate a large mucinous and poorly-differentiated component along with marked lymphocytic infiltrate (Fearon, 2011).

Clinical and Diagnostic Significance

Histology is important in detecting, staging and predicting prognosis. Tumor depth of invasion LVI, PNI and histological grade of malignancy, as well as cell types, all have different consequences for patients' other treatment strategies; this information should be recognized in order to avoid making treatment decisions without an understanding of the disease situation. However, though molecular tests is advancing, histopathology as a scientific channel into the structure and life mechanics of cells is an indispensable supplement to molecular profiling (Chen et al., 2021).

Diagnostic Techniques of Colorectal Cancer

Detection of colorectal cancer (CRC) is essential to minimize disease-related mortality and enhance patient survival. Due to the insidious development of CRC clinical symptoms in which pans may still remain asymptomatic, a combination of screening tests encompassing endoscopy, imaging however have discovered polymorphisms that are not present in healthy populations but this can be applied only on sample sumo and molecular analysis is known as an effective diagnostic strategy. These strategies allow detection, staging, prognostic stratification, and planning of intervention (Dekker et al., 2019).

Stool-Based Screening Tests

Stool-based tests are a non-invasive approach to CRC screening and currently constitute the primary CRC screening modality in average-risk populations. Guaiac-based FOBT (gFOBT) and FIT are the two types of fecal occult blood testing (FOBT) that can detect occult blood in stool samples. FIT has largely replaced gFOBT because it is more sensitive and specific for lower GI bleeding and does not require dietary restrictions (Lee et al., 2014). Stool-based tests, although convenient and inexpensive, do not allow anatomical localisation and following a positive test have to be followed by colonoscopy.

Combined multitarget stool DNA testing combines occult blood with molecular markers (eg, KRAS mutation, abnormal DNA methylation). This method increases sensitivity for advanced adenomas and stage I CRC, but at the expense of increased costs and false positive rates compared to FIT (Imperiale et al., 2014).

Endoscopic Techniques

Currently, colonoscopy is the best test for detection and prevention of CRC. It permits complete visualization of the colon mucosa, identification of preneoplastic lesions, biopsy and polypectomy. Colonoscopy has high sensitivity for CRC and advanced adenomas and is the main diagnostic tool after positive screening tests (Rex et al., 2017). Flexible sigmoidoscopy, testing the distal colon, is a complementary test but detects proximal lesions poorly. Such approaches are especially relevant in high-risk populations with factors such as inflammatory bowel disease (IBD) that may require the life-long use of medications known to be hepatotoxic, or management of complex comorbid medical conditions (Dekker et al., 2019).

Radiological Imaging Modalities

Radiological imaging has only a supplemental function for the diagnosis of CRC, especially concerning tumor stage and metastasis detection. Cross-sectional imaging: abdominal CT is standard practice for evaluating the extent of disease, lymph node involvement and distant metastases. CT colongraphy (CTC; virtual colonoscopy) is a non-invasive modality for patients who cannot undergo, or are unwilling to have, conventional colonoscopy, but is a non-therapeutic examination (Pickhardt et al., 2011). In rectal cancer, pelvic MRI is particularly useful as it provides a high-resolution image of the pelvis and enables an accurate evaluation of tumor invasion, circumferential resection margin involvement and meso-rectal fascia involvement. These are also important for preoperative planning and prognostic assessment. These cases that conceal metastatic disease or recurrence can be identified by positron emission tomography combined with Computed Tomography (Beets-Tan et al., 2018).

Histopathological Diagnosis

The definitive diagnosis of CRC is histopathologic examination of biopsy or surgical material. Analysis of tissue has two purposes: It confirms that the tumor is malignant, and determines its histopathologic type, grades it and tells how invasive or noninvasive it is. Immunohistochemistry (IHC) is commonly used to assess the MMR proteins, with possible detection of MSI. There are treatment implications (diagnostic, prognostic and therapeutic) of MSI testing and especially with regards to immunotherapy perspective (Boland & Goel, 2010).

Molecular and Genetic Diagnostic Techniques

Molecular detection has been introduced for CRC testing. Currently available technologies for mutation profiling of genes in this pathway, including KRAS, NRAS, BRAF and PIK3CA among others include both polymerase chain reaction (PCR)-based methods and next generation sequencing (NGS). These alterations dictate the selection of targeted agents and predict response to anti-epidermal growth factor receptor (EGFR) therapies (Van Cutsem et al., 2016). Liquid biopsy methods, such as analysis of circulating tumor DNA (ctDNA), are an emerging technology for non-invasive diagnosis and monitoring. ctDNA tests can identify minimal residual disease, measure treatment response and diagnose relapse early. While currently developing, such approaches have the potential to be incorporated in day-to-day clinical practice (Siravegna et al., 2017).

Emerging Diagnostic Approaches

Recent breakthroughs of artificial intelligence (AI) have further promoted the diagnostic capability in CRC, especially for endoscopy and imaging. AI-facilitated colonoscopy systems increase ADRs by minimizing the operator-dependence variability. Furthermore, proteomic and metabolomic profiling of blood, stool and tissue samples are under development as new diagnostics markers but these need more validation before widespread clinical application (Misawa & Kudo, 2025).

Therapeutic Approaches of Colorectal Cancer

The treatment of colorectal cancer (CRC) has developed enormously in the last few decades, transforming from a predominantly surgical disease into a multimodal individualized therapeutic approach. Therapeutic management is guided by tumor stage, anatomical site of origin, molecular profile and patient-related factors with curability being the primary objective in early stages of disease and prolonged overall survival (OS) while keeping quality of life intact as a goal in advanced stages (Dekker et al., 2019).

Surgical Management

Surgery is still the mainstay of curative treatment in localized CRC. Radical resection of the tumor with sufficient lymph node dissection could be enough for early-stage colon cancer. Resection is based on the location of the tumor and consists of a segmental resection with drainage lymph node dissection. Minimally invasive techniques, i.e., laparoscopic as well robotic-assisted procedures have shown oncological equivalence compared to open surgery and lower postoperative morbidity with quicker recovery (Veldkamp et al. 2005). In rectal carcinoma, the surgical treatment is challenging because of its anatomical limitations and local recurrence. TME remains the standard surgical approach and has resulted in a considerable reduction in rates of local recurrence as well as increased survival rates. Local excision methods may be an option for certain early rectal cancers, especially when used in conjunction with neoadjuvant treatment (Heald et al., 1998).

Chemotherapy

Both in the adjuvant setting as well as for mCRC, systemic chemotherapy is pivotal. In patients with stage III colon cancer and high-risk stage II disease, adjuvant chemotherapy decreases the risk of recurrence and enhances overall survival. Standard regimens contain typically fluoropyrimidines (5-fluorouracil or capecitabine) in combination with oxaliplatin, e.g., following FOLFOX or CAPOX protocols (Andre et al., 2020). In the setting of metastatic CRC, chemotherapy is part of palliative care with goals to provide extended survival and symptom control. The combination with FOLFIRI (irinotecan-containing) or FOLFOX has become standard practice and is typically selected based on patient fitness, tumour burden, and previous therapies. Maintenance approaches and treatment de-escalation are increasingly used in an attempt to balance efficacy with toxicity (Van Cutsem et al., 2016).

Radiotherapy

The treatment of rectal cancer emphasis on radiotherapy. Neoadjuvant chemoradiotherapy or short-course radiotherapy is indicated for patients with locally advanced

rectal cancer in an attempt to downstage the tumor, facilitating resection and reducing locoregional recurrence. Preoperative radiother- apy has shown better local control than the postoperative approach. Palliative radiotherapy Palliative radiotherapy may be used in advanced or metastatic disease to relieve symptoms of pain, bleeding or obstruction. Another modification is the advent of new radiation methods, such as IMRT, which increased targeting accuracy and reduced surrounding tissue toxicity (Sebag-Montefiore, et al. 2009).

Targeted Therapy

The advent of molecular targeted agents has dramatically altered the treatment environment for metastatic CRC. Agents that inhibit tumor angiogenesis, which include bevacizumab and other anti-vascular endothelial growth factor (VEGF) agents, frequently are administered in conjunction with chemotherapy resulting in enhanced progression-free survival (PFS) (Hurwitz et al., 2004). Anti-epidermal growth factor receptor (EGFR) monoclonal antibodies such as cetuximab and panitumumab are active in patients with RAS wild-type tumors. Molecular testing for KRAS and NRAS mutations is therefore a prerequisite preceding treatment with EGFR-targeted therapy. BRAF-mutated CRC also constitutes a separate entity that will necessitate combining targeted therapies to address intrinsic resistance (Van Cutsem et al., 2016).

Immunotherapy

Immunotherapy has proven to be a very effective therapy for the subset of CRC patients that presents with MSI-H or dMMR tumors. Immune checkpoint inhibitors including programmed death-1 (PD-1) inhibitors pembrolizumab and nivolumab have shown durable responses and preferable survival benefits over chemotherapy among this subgroup of patients. Despite these achievements, the majority of CRCs are microsatellite stable (MSS) and have limited responsiveness to immunotherapy. Current studies target combination strategies to maximize immunogenicity in MSS tumors (Le et al., 2015).

Local Therapies for Metastatic Disease

Local ablative therapies may have curative potential in a subset of patients with oligometastatic disease, including liver or lung metastases. In selected cases, survival advantages have been demonstrated following local treatment with surgical metastasectomy, radiofrequency ablation and stereotactic body radiotherapy. (Adam et al., 2015).

Conclusion

Colorectal cancer (CRC) represents a significant global health burden and imposes a high cost to the healthcare systems around the world. It is lined by a variety of molecular changes, pathways for tumorigenesis and histological subtypes, which affect the progression of disease and consequently the prognosis at diagnosis. Progress in our knowledge of its pathophysiology has made it possible to perform more accurate risk stratification and develop useful biomarkers. The advent of sophisticated diagnostic outlets, such as endoscopy, has enhanced the opportunity for early detection and accurate staging of colonic carcinoma. From the clinical point of view, treatment strategies for CRC have moved forwards from surgery alone to a multimodality therapy including chemotherapy, radiotherapy, targeted molecular therapy and immune based-regimens based on specific tumor biological features. Recognition of unique molecular patterns, focus on early diagnosis, and adoption of risk-reduction strategies for patients with colon cancer are thus key concepts that continue to be ripe for further investigation and clinical debate.

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