Colorectal Cancer: A Comprehensive Review

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Abstract: Colorectal cancer (CRC) is one of the most significant malignancies affecting the gastrointestinal tract and continues to pose a major global public health challenge. Despite advances in screening, diagnostic modalities, and therapeutic strategies, CRC remains among the leading causes of cancer-related morbidity and mortality worldwide. Recent epidemiological trends reveal a concerning rise in CRC incidence among young adults, a shift influenced by multiple factors including genetic susceptibility, Westernized dietary habits, sedentary lifestyles, increasing obesity rates, and environmental exposures. CRC often develops silently, with early stages presenting minimal or nonspecific symptoms, contributing to delayed diagnosis and higher rates of advanced-stage disease at presentation. The burden of CRC varies considerably across regions and income groups, with high-income countries demonstrating better survival outcomes due to organized screening programs and advanced healthcare services, while low- and middle-income countries continue to face challenges such as delayed presentation, limited diagnostic resources, and inadequate screening coverage. Clinically, CRC may present with rectal bleeding, changes in bowel habits, abdominal discomfort, anemia, or weight loss, but these symptoms frequently overlap with benign conditions, complicating early detection. Colonoscopy remains the gold standard for diagnosis and screening, enabling direct visualization, biopsy, detection of synchronous lesions, and early intervention. Advances in imaging techniques—particularly high-resolution magnetic resonance imaging (MRI), computed tomography (CT), and endorectal ultrasound—have significantly improved local staging accuracy and guided decisions regarding neoadjuvant therapy. Modern treatment approaches, including total mesorectal excision (TME), targeted therapy, immunotherapy, and total neoadjuvant therapy, have transformed management outcomes, particularly for rectal cancer. However, the emergence of chemotherapeutic drug resistance remains a major barrier to effective treatment, with many patients experiencing reduced drug responsiveness, ultimately leading to treatment failure. The objective of this review is to consolidate current knowledge on the epidemiology, etiological factors, clinical presentation, diagnostic challenges, and evolving therapeutic strategies related to colorectal cancer, while emphasizing the increasing incidence among young adults and highlighting the critical need for early detection, improved screening programs, and comprehensive management approaches. By integrating existing evidence and identifying persistent gaps in understanding and care delivery, this review aims to support ongoing efforts to reduce the global burden of colorectal cancer and improve patient outcomes.

Keywords: Cancer, colorectal, colon, rectum, tumor, CRC, mortality

I. INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies of the gastrointestinal tract and remains a major public health challenge worldwide. According to the GLOBOCAN 2020 report, CRC ranks among the top three most frequently diagnosed cancers globally and is one of the leading causes of cancer-related deaths. It accounts for nearly 10% of all cancer cases and 9.4% of cancer-related mortality, with an estimated 1.9 million new cases and over 935,000 deaths annually. CRC represents approximately 13% of all malignant tumors and is the second most common cancer among women and the third among men. The burden of colorectal cancer continues to increase globally, reflecting significant changes in lifestyle, diet, and population aging, posing a substantial challenge to healthcare systems due to the high costs of diagnosis, treatment, and long-term management.

The incidence and mortality of CRC exhibit striking geographic variation. The highest age-standardized incidence rates are observed in highly developed

regions such as North America, Western Europe, Australia, and New Zealand, whereas the lowest are found in Africa and South-Central Asia. These disparities are largely attributed to differences in dietary habits, lifestyle behaviors, genetic predisposition, socioeconomic conditions, and access to organized screening and healthcare services. Populations consuming a Western-style diet rich in red and processed meat, high-fat foods, and low in fruits, vegetables, and fiber demonstrate a significantly higher risk of colorectal cancer compared to those following traditional or plant-based diets. In addition, sedentary behavior, obesity, tobacco smoking, and excessive alcohol consumption are recognized as major modifiable risk factors. Genetic and hereditary syndromes, such as Lynch syndrome (hereditary non-polyposis colorectal cancer) and familial adenomatous polyposis (FAP), further contribute to increased susceptibility.

In India, the overall incidence of colorectal cancer remains relatively low compared to Western nations; however, the trend is steadily rising, especially in urban areas where lifestyle and dietary patterns are shifting toward Westernization. According to national cancer registries, CRC ranks among the top ten cancers in India, with an increasing incidence among younger adults under 50 years of age. The age-adjusted incidence rate (AAR) for colon cancer in Indian males is approximately 4.4 per 100,000 and for rectal cancer is 4.1 per 100,000, while in females it is slightly lower. Although these figures may seem modest, the country's large population translates these rates into a significant disease burden, emphasizing the urgent need for effective screening, preventive strategies, and early diagnosis. Regional data from the Sher-i-Kashmir Institute of Medical Sciences (SKIMS) indicate that colorectal cancer ranks among the top five cancers in both sexes, with an increasing trend in rectal cancer cases, particularly among urban and semi-urban populations.

Rectal cancer, which constitutes nearly one-third of all colorectal malignancies, is anatomically defined as a tumor whose lower margin lies within 15 cm of the anal verge, as determined by rigid sigmoidoscopy or MRI. Although traditionally grouped with colon cancer under the broad classification of CRC, rectal cancer differs in several crucial aspects, including anatomical location, patterns of spread, lymphatic drainage, surgical challenges, and response to therapy. Its fixed position within the confines of the pelvis, close to vital structures such as the bladder, uterus, prostate, and sacrum, makes surgical excision technically demanding and increases the risk of positive circumferential resection margins and local recurrence. Consequently, rectal cancer is now regarded as a distinct clinical and pathological entity, requiring specialized diagnostic and therapeutic strategies.

Over the past few decades, advances in imaging techniques, surgical procedures, and multimodal treatment approaches have substantially improved rectal cancer outcomes. The introduction of total mesorectal excision (TME), first described by Heald et al. in 1982, revolutionized rectal cancer surgery by ensuring complete removal of the mesorectal envelope, thereby reducing local recurrence rates and improving survival. High-resolution magnetic resonance imaging (MRI) has emerged as the gold standard for local staging, providing detailed assessment of tumor extent, circumferential resection margins (CRM), and involvement of adjacent structures. The use of preoperative MRI, along with endorectal ultrasound (ERUS) and computed tomography (CT), enables precise staging and guides decisions regarding neoadjuvant treatment. The incorporation of neoadjuvantchemoradiotherapy (CRT) and, more recently, total neoadjuvant therapy (TNT) has further enhanced local control, achieved tumordownstaging, improved R0 resection rates, and facilitated organ-preserving approaches such as local excision or the "watch-and-wait" strategy in complete responders. These developments have contributed to a marked decline in local recurrence rates—now under 10%—and an improvement in five-year overall survival exceeding 70% in well-resourced centers.

The etiology of rectal cancer is multifactorial, resulting from the interplay between genetic predisposition, environmental influences, and inflammatory conditions of the bowel. Lifestyle factors such as high intake of red and processed meats, low dietary fiber, obesity, and physical inactivity have been strongly associated with increased risk. In contrast, diets rich in fruits, vegetables, and whole grains appear to have a protective effect. Chronic

inflammatory bowel diseases, particularly ulcerative colitis and Crohn's disease, significantly increase the risk of colorectal malignancy, depending on the duration, extent, and severity of inflammation. Inherited genetic syndromes, such as Lynch syndrome and FAP, account for approximately 5–10% of CRC cases and often present at an earlier age.

Clinically, rectal cancer often presents with nonspecific or subtle symptoms such as rectal bleeding, altered bowel habits, abdominal discomfort, anemia, or unexplained weight loss. Because these symptoms may mimic benign anorectal disorders like hemorrhoids or irritable bowel syndrome, diagnosis is frequently delayed, leading to more advanced-stage presentation. In 15–30% of cases, patients may present as surgical emergencies due to complications such as intestinal obstruction, perforation, or severe bleeding, which are associated with worse prognosis and higher perioperative morbidity. Early detection through careful clinical evaluation—including digital rectal examination, colonoscopy, and imaging—is therefore essential for improving patient outcomes. Colonoscopy remains the gold standard for diagnosis, allowing direct visualization, biopsy, and detection of synchronous lesions.

Accurate staging remains critical in the management of rectal cancer and is best achieved through the Tumor-Node-Metastasis (TNM) classification system developed by the American Joint Committee on Cancer (AJCC). This staging framework provides a standardized approach for assessing disease extent, guiding treatment planning, and predicting prognosis. With the integration of advanced imaging, multidisciplinary management, and evolving therapeutic strategies, the outlook for rectal cancer patients has improved considerably. Nevertheless, in low- and middle-income countries, delayed presentation, limited access to specialized care, and lack of widespread screening programs continue to pose significant barriers to optimal outcomes.

The incidence and mortality of colorectal cancer (CRC) continue to rise in developing nations among both males and females, although high-income countries still report comparatively higher overall rates. Upper-middle–income countries show the highest burden, contributing 45.94% of global incidences and 49.37% of deaths. In contrast, high-income countries report slightly lower incidence rates (42.43%) compared with upper-middle–income countries; however, their mortality is markedly lower (36.40%), likely due to advanced healthcare services and better treatment access (Figure 4). Together, high-income and upper-middle–income countries account for over 88% of global CRC incidence and more than 85% of CRC-related deaths.

The third most prevalent cause of cancer worldwide in both men and women is colorectal cancer. According to epidemiologic data, nutrition and other modifiable risk factors can reduce the incidence of colon cancer by around half. In order to determine whether diet can be a feasible intervention, this article examines earlier research on certain foods and their association with colorectal cancer. The development of colorectal cancer is significantly influenced by diet. Consumption of many foods and nutrients has been linked to the risk of colorectal neoplasia in recent decades, according to findings from substantial epidemiologic and experimental research. Red meat and processed meat have been tied to an increased risk of colorectal cancer, while calcium, fiber, milk, and whole grains have been linked to a decreased risk. There is strong evidence that vitamin D, folate, fruits, and vegetables may have chemopreventive effects. Additionally, foods and nutrients may interact as a dietary pattern to affect the risk of colorectal cancer. Colorectal carcinogenesis is probably influenced by diet through a number of interrelated pathways. These include the direct impact on inflammation and immunological response, as well as the indirect effects of obesity and overnutrition-related risk factors for colorectal cancer.

The gut microbiome of healthy people and those with colon cancer differs, according to some recent research. The relationship between pathobionts and symbionts in the development of colon cancer has been better understood because to research on animals. Although there isn't a single causative organism for colorectal cancer (CRC), there is compelling evidence that age-related changes in microbiota, an increase in some bacteria (such as fusobacterium members and Bacteroides/Prevotella), and a decrease in beneficial bacteria all affect the development of adenoma or cancer. Further studies will help us comprehend procarcinogenic and anticarcinogenic pathways and provide guidance on

how to rationally manipulate the microbiota using probiotics, prebiotics, or dietary changes.

Individuals with inflammatory bowel disease (IBD) face a 10%-15% elevated risk of getting colorectal cancer (CRC), a prevalent condition associated with significant economic burdens in developed nations.

The current standard for staging patients with colorectal cancer is the American Joint Committee on Cancer/Union for International Cancer Control tumor, node, metastasis (TNM) approach. For both individuals with early-stage and severe disease, this technique offers the best predictive information. It is less accurate in predicting the course of the disease for patients with intermediate disease levels. Consequently, more prognostic indicators are required to enhance the treatment of afflicted individuals. Ideal indicators are easily evaluated on tumor slides stained with hematoxylin and eosin, making them widely relevant.

More than 70% of individuals with colorectal cancer (CRC) report experiencing pain. It is still a dreaded and crippling side effect of cancer and cancer-related therapies. Intravenous, oral, or topical medicines are among the various choices available for managing pain in colorectal cancer. The nociceptive, neuropathic, and/or psychogenic pain components should all be addressed in order to treat the entire spectrum of pain. Many people are not satisfied with the pain management that is currently available, and incorrect use can lead to a number of issues. Future therapies should therefore prioritize pain relief while simultaneously minimizing potential adverse effects. This article discusses new and exciting advances in the treatment of colorectal cancer, both pharmaceutical and non-pharmacological.

The preoperative sensitivity for the identification of minuscule foci of hematogenously or regionally metastatic colorectal cancer has been greatly enhanced by advances in imaging technology. Unfortunately, this information has not resulted in ongoing linear improvements in patient survival, and it may even cause some cases to be falsely upstaged. These are two problems with colorectal cancer imaging. The widespread use of real-time image guidance during surgical procedures may provide a solution to both problems. This could pave the path for fluorodeoxyglucose PET/CT to be widely used for colorectal cancer patients' initial staging.

II. CANCER DRUG RESISTANCE AND ITS CHALLENGES

Germline abnormalities involving mutations in the adenomatous polyposis coli (APC) gene, DNA mismatch repair genes, K-ras, or p53 lead to uncontrolled cellular proliferation and progression to colorectal cancer (CRC), often aligning with specific stages of tumor development. These mutated genes produce dysfunctional proteins that fail to carry out normal regulatory roles, allowing damaged DNA to replicate unchecked and accumulate additional genetic alterations, eventually resulting in a malignant phenotype. Because these molecular changes are not apparent during the early stages of CRC, early detection remains difficult, contributing to the high mortality associated with the disease. Beyond the challenge of early diagnosis, additional obstacles exist in clinical assessment. Accurate pre-operative staging and imaging techniques capable of identifying lymph node involvement and micro-metastases remain limited, directly influencing treatment planning and patient outcomes.

Surgery remains the primary treatment for CRC, particularly for stage 0 to stage II disease. More advanced stages often require adjuvant chemotherapy, targeted therapy, or a combination of modalities in addition to surgical intervention. However, one critical challenge involves determining the appropriate role of laparoscopic resection in patients with low rectal cancer. As CRC cases continue to rise, standardized, widely applicable surgical techniques must be refined, which has implications for both procedural approaches and clinical training. Postoperative management and prognosis are significantly supported by detailed pathological evaluation of resected tumor specimens. Nevertheless, difficulties persist in evaluating and reporting these samples, either due to limitations of existing diagnostic criteria or the ongoing incorporation of new pathological concepts. High-quality pathology reporting is essential to ensure accurate prognosis and effective patient management.

Another major barrier to successful CRC treatment is the development of drug resistance. Although recent advancements in chemotherapy have improved

survival in patients with advanced CRC, resistance to chemotherapeutic regimens remains a critical issue. Despite response rates that may reach 50% with modern systemic therapies, most CRC patients ultimately develop resistance, reducing drug efficacy and frequently resulting in treatment failure.

III. DISCUSSION

The rising incidence of colorectal cancer (CRC) among young adults is a growing global concern. Although CRC has been considered a disease of older adults, recent evidence shows that more young people are being diagnosed, often at more advanced stages. This is mainly because early symptoms—such as bleeding per rectum, abdominal discomfort, or changes in bowel habits—are commonly mistaken for minor conditions, leading to delays in diagnosis. Since routine screening is not recommended for younger individuals, many cases remain undetected until the disease has progressed.

Young adults with CRC often show more aggressive tumor types and advanced disease at the time of presentation. While genetic factors such as Lynch syndrome and familial adenomatous polyposis contribute to some cases, many young patients do not have a family history. This suggests that lifestyle changes, Western-type diets, physical inactivity, obesity, and environmental exposures may also play an important role in the increasing burden of CRC. In regions like Kashmir, unique dietary habits and environmental conditions may influence disease patterns, but research from this region is limited, highlighting the need for more local studies.

Another major challenge is achieving early and accurate diagnosis. Colonoscopy remains the most effective tool for detecting CRC and identifying additional lesions, yet it is underused in younger populations due to low clinical suspicion. Improving awareness among both healthcare providers and the general population is essential to encourage timely evaluation of symptoms.

Treatment of CRC has improved significantly due to better imaging, surgical techniques, and multimodal therapies. However, drug resistance continues to be a major obstacle, especially in advanced stages, reducing the effectiveness of chemotherapy and targeted therapies. Young patients, who often present with aggressive disease, may be particularly affected by this issue.

Overall, the increasing number of CRC cases among young adults emphasizes the need for early recognition of symptoms, wider use of diagnostic tools like colonoscopy, and improved awareness of risk factors. More research is needed—especially in regions such as Kashmir to understand local patterns, identify high-risk groups, and develop strategies for early detection and prevention. Strengthening healthcare access and promoting healthy lifestyle practices are essential steps toward reducing the rising burden of colorectal cancer in young populations.

IV. CONCLUSION

Although colorectal cancer (CRC) has been widely studied, there is still much to learn about how this cancer begins, progresses, and responds to treatment, making further research essential. The incidence of CRC is rising, especially among young adults, and early detection remains one of the most effective ways to improve outcomes. Colonoscopy is a very important screening tool, particularly for people over 40 years of age, even when there is no family history, because CRC-related deaths increase significantly after this age, and detecting cancer at an early, curable stage greatly improves survival. Bleeding per rectum is the most common presenting symptom, often followed by changes in bowel habits, which makes endoscopic evaluation a crucial step in identifying suspected cases. Colonoscopy also helps detect additional lesions that may occur at the same time in different parts of the colon. Since CRC can develop due to many different causes and the type of cancer may vary depending on which gene is mutated, treatment must be personalized, guided by a clear understanding of the underlying genetic changes. Surgery continues to be the main and most effective treatment for CRC, and in young patients, outcomes are strongly linked to whether the surgery is done with curative intent or for palliation. In many cases, surgery should be radical and supported by adjuvant therapy whenever possible to achieve the best prognosis. At the same time, researchers are exploring natural compounds and newly developed chemical agents as possible additional treatments that could improve patient survival and quality of life. Despite the advancements, there remains a strong need for more studies focused

on early diagnosis, prevention, and management of CRC, especially among young adults, to ensure better outcomes in the future.

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