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Increasing Incidence of Early Onset Locally Advanced Colorectal Cancer: Does Adjuvant Treatment Has a Clinical Improvement?

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Abstract

The global prevalence of early-onset colorectal cancer (EO-CRC) has exhibited a notable upward trend, thereby emerging as a significant concern within the realm of public health. The clinical, genetic, molecular, and histological characteristics of this condition indicate that it may be a separate entity, exhibiting a higher level of aggression. Nevertheless, it appears that both genetic and environmental risk factors play a role in the observed epidemiological change in the incidence of colorectal cancer (CRC). Further evidence is required to elucidate the aetiology of EO-CRC and to formulate effective screening and management approaches. The management of colorectal cancer in young adults is an unmet clinical need, given that the disease may result in the greatest loss of years of life in this demographic upon diagnosis. The incidence of colorectal cancer (CRC) in people under 50 has been rising annually since early 1990 at a rate of 2%. Since the frequency of CRC has been declining overall, the rise in the disease's incidence among young adults is especially concerning. The primary tumour of early-onset colorectal cancer (CRC) is located on the left side of the colon and is associated with poorer cell differentiation, a higher prevalence of signet ring cell histology, and an advanced stage at diagnosis. 20% of patients have familial colorectal cancer (CRC), and about 30% of patients have tumours containing mutations that cause hereditary cancer predisposing syndromes. 20% of patients have familial colorectal cancer (CRC), and about 30% of patients have tumours containing mutations that cause hereditary cancer predisposing syndromes.

Keywords: early onset, colorectal cancer, adjuvant treatment

Introduction

Over the past 20 years, there has been a notable increase in the incidence and mortality of colorectal cancer (CRC) in young people, especially in Western countries. Increased exposure to risk factors such as a Western-style diet, obesity, physical inactivity, and the use of antibiotics during pregnancy and childhood are among the possible causes. While distal tumour location, poor differentiation, and advanced stage at diagnosis appear to be

more common biologic characteristics, stage-specific survival was found to be similar in older patients. Nonetheless, population-based cancer registries and retrospective analyses account for the majority of today's knowledge. It is largely unknown whether the outcomes for early-onset (EO)-CRC and later-onset (LO)-CRC differ under the conditions of particular modern interventions. Furthermore, it is unclear if managing EO-CRC differently from managing LO-CRC is necessary. Since there are comparatively fewer cases than in the older population, there is limited evidence from randomised control trials.[1]

Currently, there is no widely accepted consensus in the literature or guidelines, so it is necessary to define "EO-CRC," or "young adult CRC," precisely. When defining non-pediatric oncology, all colorectal cancers (CRCs) diagnosed before the screening age—which is less than 50 years old—are usually included. This age, which is established by cost-effective evaluations of the healthcare system's long-term viability, is when the majority of screening programs start. In contrast, Adolescent and Young Adult (AYA) Oncology includes patients with colorectal cancer who were diagnosed between the ages of 15 and 29. In the context of some AYA clinical trials, the Children's Oncology Group has raised the age limit to 50 years old. The literature is also inconclusive about what defines a "very EO-CRC," with definitions that vary greatly from one another. Consequently, non-specific epidemiologic screening or clinical trial accrual criteria are used to define age groups among patients with colorectal cancer.[2,3,4]

Epidemiology Perspective

For unclear reasons, the number of cases of early-onset colorectal cancer (CRC), which affects people under 50, has been rising globally, particularly in high-income nations. Exposure to possible risk factors like a western-style diet, obesity, physical inactivity, and increased use of antibiotics, particularly during the early stages of life from pregnancy to adolescence, are plausible theories explaining this rise. These exposures may influence the gut microbiota and host immunity in addition to causing genetic and epigenetic changes in colorectal epithelial cells. Early-onset colorectal cancers (CRCs) differ from later-onset CRCs in their clinical, pathological, and molecular characteristics. Furthermore, more life-course cohort studies covering the ages of early life to young adulthood that are integrated with prospective biospecimen collections, omics biomarker analyses, and the molecular pathological epidemiology approach are required in order to fully understand the aetiology of early-onset colorectal cancer (CRC) and to guide the development of effective prevention, early detection, and therapeutic strategies. [5]

High-income nations have seen a stable or declining incidence of colorectal cancer (CRC) over the past 20 years, while low- and middle-income nations with historically lower CRC rates have seen an increase in CRC incidence. Red and processed meat, alcohol, obesity, inflammatory bowel disease (IBD), a family history of colorectal cancer (CRC), and genetic variants that predispose to the disease are among the established risk factors for CRC. Conversely, protective factors include the use of aspirin, high systemic vitamin D levels, high folate intake, and physical activity. The incidence of CRC with an early onset has been rising in many countries during the past few decades, affecting both men

and women. Incidence of early-onset CRC changed by an average of 4.0% per year in New Zealand and 2.8% per year in Canada and Australia. During 2004–2016, the average annual percent changes in the incidence of early-onset CRC were 1.6% for people in the 40–49 age group, 7.9% for those in the 20–29 age group, and 4.9% for those in the 30-39 age group. When combined, early-onset colorectal cancer (CRC) affects a considerable portion of the younger adult cancer burden.[3,4,5]

Relatively few epidemiological studies prospectively examined exposure data obtained prior to CRC diagnosis, whereas the majority of case-control studies looked at potential risk factors for early-onset CRC. The case-control studies have revealed several potential risk factors for early-onset colorectal cancer (CRC), such as male sex, race (particularly Black and Asian ethnicities), alcohol consumption, family history of CRC, weight loss of at least 5 kg (within five years prior to colonoscopy), consumption of processed meat, and inflammatory bowel disease (IBD). Conversely, the use of aspirin along with increased consumption of citrus fruits, vegetables, fish, β-carotene, vitamin C, vitamin E, and folate have been linked to a decreased risk of CRC with an early onset.[3,5,6]

Symptoms and Signs of EO-CRC

The most common site of early-onset CRCs is the rectum (35-37%), with distal colon (25-26%) and proximal colon (22-23%) following in that order.1,30, while the rectum, distal colon, and proximal colon are the sites of approximately 29%, 27%, and 29% of CRCs diagnosed in individuals aged 50 years or older (hereafter referred to as later-onset CRCs). The effect sizes of specific risk factors and their associations with later-onset CRC appear to vary based on the anatomic site. For example, the associations between colon cancer and BMI were more pronounced than those between rectal cancer and waist circumference. The associations between height and physical inactivity were limited to colon cancer. Conversely, smoking was significantly more closely associated with rectal cancer than with colon cancer. Nevertheless, it is uncertain whether these distinctions continue to be present in cases of colon and rectal cancer diagnosed before the age of 50. Epidemiological analyses should be conducted stratified by colorectal subsites, given the significant increase in early-onset rectal cancer compared to early-onset colon cancer incidence. Patients with early-onset CRC were more likely to be diagnosed at an advanced stage (stage III-IV) than those with later-onset CRC. Compared to older patients, patients with CRC who developed symptoms at an early age experienced a significantly longer time to diagnosis and a longer duration of symptoms. Synchronous and metachronous CRC have been linked to early-onset CRC. In patients with early-onset CRC, delayed diagnosis and advanced stage at diagnosis may be influenced by a lack of screening, an underappreciation of symptoms, a reluctance to seek medical care, and a lower awareness of CRC.

With the exception of patients registered in prescribed screening programmes, colorectal cancer (CRC) in young individuals is typically identified when symptoms first manifest. Asymptomatic bleeding can serve as a dependable indicator of the development of additional symptoms of colorectal cancer within a period of two to three years. The usual assessment period for detecting colorectal cancer (CRC) in young adults is six months

following the initial manifestation of symptoms. It is possible to attribute this phenomena to a lack of scepticism among practitioners and probands, a belief in invincibility among young adults, and inadequate medical insurance coverage. Approximately 61% of patients under the age of 50 and up to 76% of patients under the age of 30 are diagnosed with colorectal cancer (CRC) at stages III or IV. This finding sharply differs from the pattern observed in elderly patients diagnosed with colorectal cancer. Early-onset colorectal cancers (EO-CRCs) are primarily left-sided and rectal G3 cancers named for their insufficient differentiation.[7]

Current Perspective

Most EO-CRC studies are retrospective and include a small number of patients from the different age groups. Despite the significant diversity noted, the reviewed studies can be regarded as sources of hypotheses, despite lacking definitive findings or recommendations. A multitude of studies have recorded an increase in the occurrence of EO-CRC in different parts of the world; yet, the fundamental factors contributing to this epidemiological phenomenon are still unidentified. To reduce the disproportionately high loss of life-years in this younger-than-average CRC population, it is crucial that we advance the development of new treatments and enhance the effectiveness of current ones.8 Among those under the age of 35, the most significant challenge is non-hereditary colorectal cancer (CRC); this specific group of EO-CRC is expected to have a higher incidence in the next years. Based on the existing data, the survival rate is the lowest for patients who are younger than 30 years old. However, it is similar to or even higher for patients between the ages of 40 and 50 compared to these aged 50 and older. Given the unique molecular features of EO-CRC, especially in those under 30 years old, it is possible to hypothesise that another molecular carcinogen is implicated in these uncommon cases. To effectively compare EO-CRC studies, it is crucial to recognise EO-CRC as a shared categorisation of age groups. This is an obligatory prerequisite for addressing enquiries successfully. To interpret retrospective studies, one could adopt an interesting strategy of considering age as a continuous variable. Moreover, the use of clinical criteria can be advantageous in identifying EO-CRC patients who are more likely to benefit from precision therapy. A precise understanding of the role of environmental risk factors and the microbiome remains elusive. Finally, and of utmost importance, there is a scarcity of clinical trials that expressly focus on EO-CRC, despite the need of such studies to improve the standard of care served to these patients.[7,9]

Current Recommendation for EO-CRC

EO-CRC does not have explicitly defined treatment protocols that are backed by empirical evidence. Patients with early-onset colorectal cancer (EO-CRC) who have a hereditary colorectal cancer (CRC) syndrome, such as LS and polyposis syndromes, should follow the guidelines tailored to their specific condition.[8.] The surgical approach must be carefully evaluated due to its generally more extensive nature, and it is imperative to mitigate the risk of other malignancies linked to the syndrome by thorough screening. Despite the absence of explicit age-based recommendations, recent research suggests

that therapeutic strategies are being customised according to the age of the patient. Although surgery is the main treatment for colorectal cancer (CRC), adjuvant chemotherapy is crucial in managing high-risk stage II and stage III cases. Numerous studies have shown that a greater proportion of patients with early-stage early-onset colorectal cancer (EO-CRC) receive adjuvant treatment for stage II and III disease when compared to an older group (aged 65-75).[6,7] The administration of adjuvant therapy is observed in 50% of Stage II low-risk EO-CRC patients, while the older group only receives it in 19.1% of cases. Notably, these treatment strategies did not demonstrate any association with enhanced survival rates in stage I or stage II malignancies and only offered limited benefits in stage III and stage IV disorders. Furthermore, individuals diagnosed with early-onset colorectal cancer (EO-CRC) are more likely to have surgical procedures for both early-stage and metastatic disease, receive radiation therapy at all disease stages, and be provided with more intensive adjuvant therapy, such as multi-agent chemotherapy. Given the present knowledge, it is advisable to offer equitable treatment to persons with EO-CRC, except those with a hereditary syndrome. Additional investigation into the possible molecular differences between early-onset colorectal cancer (EO-CRC) and colorectal cancer in older persons could reveal new molecular targets for therapy, facilitating more precise and focused drug interventions.[10]

Conclusion

There is a lack of treatment protocols tailored to specific age groups and inconsistent data in studies on survival rates of early-onset colorectal cancer (EO-CRC). Multimodality treatment still has an impact on them. The adjuvant treatment might have an important role on the clinical outcome of this age specific group of colorectal cancer patients and the possibility of using the targeted therapy also.

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