Increasing incidence of early onset locally advanced colorectal cancer: does adjuvant treatment has a clinical improvement?

By Budhi Ida Bagus

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Increasing incidence of early onset locally advanced colorectal cancer: does adjuvant treatment has a clinical improvement?

Author : Budhi Ida Bagus

Affiliation : Department of Surgery, Sebelas Maret University, Indonesia

ORCID ID : 0000-0002-0310-7415

Corresppponding Author : Budhi Ida Bagus

Email : budhi_suryaadnyana@yahoo.com

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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.

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Introduction

Worldwide, colorectal cancer (CRC) ranks third in terms of incidence and is the leading cause of cancer-related deaths in both sexes. Patients with colon cancer are typically 68 or 72 years old at diagnosis (for men and women, respectively); patients with rectal cancer are typically 63 years old at diagnosis (for both genders). Incidence and mortality from CRC have decreased in the USA and Europe overall in recent years. Incidence of CRC has declined by 2-3% year in the USA for both men and women since the mid-2000s.[1]

This decrease has been primarily linked to increased public awareness of CRC risk factors and the proliferation of screening tests, such as colonoscopies and faecal occult blood tests (FOBT), which enable the identification and removal of precancerous lesions. Despite advancements in treatment, metastatic colorectal cancer (CRC) has a dismal prognosis; at the current level of care, only 14% of patients remain alive five years after diagnosis. In 2010 the incidence are 4.8% and 9.5% of colon and rectal cancers among patients under 50 years old, respectively, due to CRC. It's interesting to note that new research across multiple continents has shown an increase in the incidence of CRC in this age group, particularly in people under 40. There is presently an unmet clinical need for diagnostic and treatment protocols specific to early-onset colorectal cancer (EO-CRC) in young individuals. Furthermore, opinions differ on whether EO-CRCs in elderly patients are identical to CRCs or represent a different molecular and immunologic entity.[2,3]

It is currently necessary to define "EO-CRC," or "young adult CRC," precisely because there isn't a consensus that is widely acknowledged in the literature or guidelines. A non-pediatric oncology definition typically includes all colorectal cancers (CRCs) diagnosed prior to the screening age, which is less than 50 years of age. Most screening programmes begin at this age, which is determined by cost-effective assessments of the long-term viability of the healthcare system. In contrast, CRC patients diagnosed between the ages of 15 and 29 are included in Adolescent and Young Adult (AYA) Oncology. However, the Children's Oncology Group has expanded the age range to 50 years in the context of certain AYA clinical trials. There is also a lack of agreement in the literature regarding what constitutes a "very EO-CRC," with widely

divergent definitions. As a result, the current definition of age groups among patients with colorectal cancer is predicated on clinical trial accrual criteria or non-specific epidemiologic screening.[4]

Current Epidemiological Data

In the United States, the Surveillance, Epidemiology, and End Results Programme (SEER) database indicates that patients under the age of 45 comprise approximately 5% of all CRC diagnoses. Rectal cancer is identified in males and females under the age of 50 in as many as 18% of cases. Diagnosis of EO-CRC is more prevalent in uninsured and minority populations. Multiple studies published at the turn of the 21st century provided indications that the incidence of colorectal cancer (CRC) varied among age groups.[5]

In fact, there has been documentation of a rise in the incidence of colorectal cancer (CRC) diagnoses among individuals under the age of 50 in the United States. This upward trend was most notably observed among patients aged 20–35. On the basis of epidemiological data, the incidence of CRC among individuals under the age of 55 has increased by 2% annually since 1994. According to these findings, EO-CRC is a current public health concern in the United States and internationally.[6] In a similar condition, recent data from Europe reveal that the incidence of colon cancer increased by 7.4% annually between 2008 and 2016, while rectal cancer incidence rose by 1.5% annually between 1990 and 2008. It is rational to assume that access to screening procedures, such as rectal rectal microscopy or colonoscopy, for individuals aged 50 years and above, can only partially account for the declining trend in colorectal cancer (CRC) incidence in the Western world.[3,4,5]

Signs and Symptoms of EO-CRC

With the exception of patients enrolled in specific screening programmes, colorectal cancer (CRC) in young individuals is typically diagnosed upon the onset of symptoms. Painless bleeding may serve as an indicator of the development of additional CRC symptoms within a span of two to three years. On average, however, young adults with CRC are diagnosed six months after the onset of symptoms. This is due to a lack of suspicion among practitioners and probands,

a sense of invulnerability among young adults, and inadequate medical insurance coverage. CRC is diagnosed as stages III or IV in 61% of patients < 50 years and up to 76% of patients < 30 years. This finding is in stark contrast to the situation observed in older CRC patients. EO-CRCs are more often left-sided and rectal G3 tumours with poor differentiation.[7]

Possible Risk Factors

There are established CRC risk factors that are more prevalent among young people. Inflammatory bowel diseases increase the risk of colorectal cancer by a factor of two to three when compared to the general population, particularly when detected in early adulthood. The prevalence of familial CRC or known hereditary cancer-predisposing syndromes is greater in EO-CRCs. A significant challenge is the lack of adherence to specific screening programmes among individuals with familial CRC or known cancer syndromes. This issue is particularly pronounced in countries with private health systems or among populations with low socioeconomic status. Prior abdominal irradiation (i.e., radiotherapy for curable paediatric malignancies): initiation of a colonoscopy is advised at 35 years of age or within ten years subsequent to pelvic radiation treatment exceeding 30 Gy.[4,6]

Future Perspective

The majority of EO-CRC studies are retrospective and involve a limited number of patients spanning various age groups. Notwithstanding the considerable diversity observed, the studies that were examined may be deemed as sources of hypotheses, notwithstanding the absence of conclusive findings or recommendations. Numerous studies have documented a rise in the prevalence of EO-CRC in various regions across the globe; however, the underlying causes of this epidemiological phenomenon remain unknown. In order to mitigate the most significant loss of life-years among this younger-than-average CRC population, it is imperative that we develop new therapies and optimise clinical outcomes with existing ones.[8] The most formidable obstacle is non-hereditary colorectal cancer (CRC) among those under the age of 35; this subset of EO-CRC is anticipated to increase in prevalence over the coming years. According to the available data,

survival is least favourable for patients under the age of 30, whereas it is comparable to or even surpasses that of patients aged 40 to 50 in comparison to those aged 50 and above.

Considering the distinctive molecular characteristics of EO-CRC, particularly in individuals below the age of 30, an alternative molecular carcinogen may be postulated to be responsible for these rare instances. In order to compare EO-CRC studies, it is essential to acknowledge EO-CRC as a common subdivision of age groups, which is a mandatory step in answering questions. An intriguing approach to interpreting retrospective studies could be to treat age as a continuous variable. Furthermore, the utilisation of clinical criteria may prove beneficial in the identification of EO-CRC patients who are more likely to derive benefits from targeted therapy. The precise function of environmental risk factors and the microbiome is still unknown. Lastly, and most significantly, there remains a dearth of clinical trials that specifically target EO-CRC, despite the fact that such investigations are necessary to enhance the quality of care provided to these patients.[7,9]

Treatment and Recommendation

EO-CRC lacks specific treatment protocols that are supported by evidence. EO-CRC patients who have an inherited CRC syndrome, such as LS and polyposis syndromes, should adhere to the guidelines specific to their condition. It is crucial to consider the surgical approach as it is typically more extensive, and it is necessary to address the risk of other malignancies associated with the syndrome through proper screening. While there are no specific recommendations based on age, recent studies indicate that therapeutic approaches are being tailored based on the patient's age.[4,6,7]

Surgery is the primary therapeutic intervention for colorectal cancer (CRC), however, adjuvant chemotherapy plays a significant role in the treatment of high-risk stage II and stage III cases. When comparing early-onset colorectal cancer (EO-CRC) with an older cohort (aged 65-75), multiple studies have discovered that a higher number of patients with early-stage EO-CRC receive adjuvant therapy for stage II and III disease. Stage II low-risk EO-CRC patients are administered adjuvant therapy in 50% of cases, whereas the older cohort only receives it in 19.1% of cases. Interestingly, these treatment plans did not show any correlation with improved survival rates in stage I or stage II cancers and only provided minimal advantages in stage III and stage IV diseases. In addition, patients with EO-CRC have higher probabilities of undergoing surgical intervention for both early-stage and metastatic disease, receiving radiotherapy at all stages of the disease, and being offered more intensive adjuvant treatment, such as multi-agent

chemotherapy. Based on current understanding, it is recommended to provide equal treatment to individuals with EO-CRC (excluding those with a hereditary syndrome). Further research on the potential molecular distinctions between early-onset colorectal cancer (EO-CRC) and colorectal cancer in older individuals may uncover novel molecular targets for treatment, enabling more targeted therapies.[10]

Conclusion

The absence of age-specific treatment protocols and the presence of conflicting data in studies on survival rates of EO-CRC have been observed. Given the elevated germline pathological mutations observed in patients with early-onset colorectal cancer (EO-CRC), it is imperative to conduct a precise genetic risk assessment.

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