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Incidence of colorectal cancer in young patients

Incidência de câncer colorretal em pacientes jovens

Fábio Guilherme C. M. de Campos, TCBC-SP[1]; Marleny Novaes Figueiredo[1]; Mariane Monteiro[1]; Sérgio Carlos Nahas, TCBC-SP[1]; Ivan Cecconello, ECBC-SP[1].

A B S T R A C T

Sporadic colorectal cancer (CRC) is traditionally diagnosed after de sixth decade of life, although a small percentage of cases are diagnosed in patients under 40 years of age, and incidence is increasing. There exists a great volume of controversy regarding clinical outcome of young patients diagnosed with colorectal cancer (CRC) when compared to elder counterparts. Our aims were to evaluate the rate of CRC in young patients, to review the pertaining literature and to discuss outcomes and clinical prognosis. A retrospective review involving patients with CRC was undertaken, focusing on age at diagnosis. The information extracted from this literature review showed a trend towards a decreased incidence in older people with an opposite effect among adolescents and young adults. Moreover, biological aggressiveness in young adults diagnosed with CRC has not been fully recognized, although it is usually diagnosed later and in association with adverse histological features. Besides that, these features don't affect outcome. These apparent increase in CRC incidence among young patients during the last decades raises the need for a greater suspicious when evaluating common symptoms in this group. Thus, educational programs should widespread information for both population and physicians to improve prevention and early diagnosis results.

Keywords: *Colorectal Neoplasms. Age. Incidence. Young Adult. Prognosis.*

INTRODUCTION

Colorectal cancer (CRC) is the commonest malignancy in the gastrointestinal tract and the third leading cause of cancer associated death in the world. Usually, CRC is thought as a common disease affecting old people, with most cases diagnosed during the 5th and 6th decades and a higher prevalence among men[1]. Therefore, it is often thought of as a disease of the elderly, what makes screening not usually recommended for those individuals younger than 50 years, considered to have an average risk of carcinogenesis.

The definition of what age would be considered young for a patient developing CRC is controversial. In an interesting retrospective study, O'Connell *et al*.[2] collected data on 6425 patients from 55 manuscripts in the literature. While the majority of articles (n=37) defined "young" those patients under 40 years of age, four articles (7%) focused attention on patients younger than 35 years, 14 articles (25%) looked at patients before 30 years and only one article looked at patients before 25 years.

According to the literature, a non-worthless fraction of CRC patients are diagnosed before 40 years in approximately 0.8 to 14.6%[3]. Furthermore, recent publications have documented a disproportional increase in CRC incidence among young people[4]. Especially within this young group, one recognizes the need to investigate if the malignancy represents an apparent sporadic CRC or if it is associated with some form of hereditary CRC (mainly Familial Adenomatous Polyposis or Lynch Syndrome) or inflammatory bowel disease.

Attempts to describe clinical, pathological and molecular features in young patients have reached controversial conclusions regarding tumour grade and disease stage at diagnosis. So far, there is no consensus if age should be considered an adverse independent prognostic factor if other features such as topography and staging are considered together. However, it is commonly accepted that diagnosis in young patients is always difficult, because both patient and the doctor usually don't give credit to the presenting symptoms, leading to a frequent unfavorable outcome of the disease[5].

1 - Colorectal Surgery Division (Gastroenterology Department). Hospital das Clinicas (HC-FMUSP), Faculty of Medicine, São Paulo University of Medical, Sao Paulo State, Brazil.

The present study is based on literature review and aims to discuss some relevant issues within this context, such as clinicopathological features, prognosis and the need for earlier detection.

EPIDEMIOLOGY OF CRC

It is widely known that lifetime risk is around 5% and risk increases with age, where more than 90% occurring in people aged 50 and over. For this reason, current guidelines recommend screening after this age for people with no risk factors associated with the disease[6].

During the past decades, there is a trend in decreasing the incidence of CRC in older people with an opposite effect among adolescents and young adults[7,8], a change that has been attributed to an inadequate screening and lifestyle risk factors related to obesity and diet profile[9].

Recent data from the National Cancer Institute (NCI) revealed that here has been a steady decline in the incidence of CRC in patients aged 50 years or older, but the opposite trend has been observed for young adults. For patients 20 to 34 years, the incidence rates of localized, regional, and distant colon and rectal cancers have increased. An increasing incidence rate was also observed for patients with rectal cancer aged 35 to 49 years[10]. Similar results came from the Surveillance Epidemiology and End Result (SEER) database (from 2000 to 2008), that detected a 10% overall increase in CRC, mainly in those <50 years of age, versus a 20% decrease in those >50 years of age[11].

Since Bacon and Sealy[12] published, in 1939, one of the earliest retrospective article focusing CRC in the young, different aspects regarding its incidence and clinicopathological features have been reported. In a review of in the literature, CRC in the "young" population represented approximately 7% of the total number of CRC patients in the 55 selected articles[2]. These authors found smaller figures in West countries, emphasizing that the higher rates reported in developing countries were due, in part, to the higher population of younger people in these countries. Regarding gender distribution, most studies found no significant difference, with a cumulative total of 2,554 men (51.4%) and 2,497 women (48.6%).

The NCI database from 2004-2008 revealed that the median age at CRC diagnosis was 70 years; in young people, CRC rates varied from 0.1% before 20 years to 1.1% between 20 and 34 and 3.8% between 35 and 44. The annual incidence increases from ten cases per million at age 20 years to 100 cases per one million at the age of 45 years. However, after reaching the age fifty, it is estimated that about one in 2,000 people will develop colorectal cancer per year. The chances of becoming a CRC sufferer rise accordingly every year after. After age 65, this rate increases to almost three in 1,000[11].

In the literature, most publications only report the incidence of CRC in patients with less than 40 years of age[2,3,5]. As may be noted in table 1, the published series present great variation due to biases associated with single-institution experiences and referral centers.

A publication from the American Cancer Society[13] showed that the overall incidence per 100,000 individuals has increased during 1992-2005 among adults from 20 to 49 years by 1.5% per year in men and 1.6% per year in women. The highest increases occurred in patients among 20-29 years of age with 5.2% and 5.6% increase for man and women, respectively. In this study, the authors also found that rates increased in each 10-year age grouping (20-29, 30-39, and 40-49 years) among non-

Table 1. *Incidence of CRC in patients with less than 40 years of age.*

Author	Local	% CRC in young
Chen *et al.*, 1999	Taiwan	10.1%
Alici *et al.*, 2003	Istanbul	18%
De Silva *et al.*, 2000	Sri Lankan	19.7%
Isbister *et al.*, 1992	Saudi Arabia	23%
Smith *et al.*, 1989	United States	2.8%
Adloff *et al.*, 1986	France	3.0%
Keating *et al.*, 2006	New Zealand	5.5%
Soliman *et al.*, 1997	Egypt	35.6%
Singh *et al.*, 2002	Nepal	28.6%

Hispanic Whites. Furthermore, this incidence increase was predominantly driven by rectal cancer, which increased 3.5% per year in men and 2.9% per year in women over the 13-year study interval.

In a retrospective study using data from the Surveillance Epidemiology and End Results (SEER) Cancer Registry, Meyer *et al*.[14] identified 7,661 colon and rectal cancer patients under age 40 years between 1973 and 2005. After calculating the change in incidence over time for colon and rectal cancers, the researches described that while colon cancer rates remained flat, rectal cancer rates have been increasing. Between 1984 and 2005, rectal cancer rate rose 3.8% per year. This finding led the authors state that "in young people presenting with rectal bleeding or other common signs of rectal cancer, endoscopic evaluation should be considered in order to rule out a malignancy". They also suggested that more frequent endoscopic evaluation could decrease the documented delay in diagnosis among young people. But, as the overall incidence of rectal cancer is relatively low, the authors did not advocate for a change in screening guidelines.

Davis *et al*.[8] evaluated the rates of change in CRC incidence within the SEER database (1987-2006), reporting that people older than 50 had decreasing incidences, and colon and rectal cancer increased 56% and 94%, respectively. They also noted a higher incidence across age groups 20-49 years in 2006 than in 1987. Most significantly, the highest increase (67%) occurred from age 40-44 (from a low of 10.7 per 100,000 in 1988 to 17.9 per 100,000 in 2006).

These findings have raised the question to consider age-based colonoscopic screening beginning at age 40. This is especially true for men, as they have a higher risk of developing advanced neoplasia at any age when compared to women, and an earlier screening might detect more asymptomatic pre-neoplastic and neoplastic colonic lesions[15].

In this context, the perspective of establishing aggressive diagnostic efforts in young patients presenting rectal bleeding is supported by the idea that age may influence clinicopathological features and outcome of CRC[16,17]. For decades, a more aggressive biological behaviour has been attributed to CRC in young patients, who are diagnosed in more advanced stages. Young age has also been considered a predictor of poor survival[7]. However, investigation of these features in sporadic tumors occurring in young patients have led to controversial results, as there are studies reporting that they have similar histopathological features and rates of advanced stage when compared to older patients[18,19].

CLINICAL AND PATHOLOGICAL CHARACTERISTICS IN YOUNG PATIENTS

The literature discloses many publications focusing on CRC age-related disparities regarding delayed diagnosis, tumor biology, recurrence rates, treatment and outcomes. A worse prognosis is usually attributed to the finding of a more advanced disease among younger patients. In this regard, most comparative studies focusing clinicopathological features and survival have shown that the young patients also present more commonly with stages III or IV disease[20,21] although it is not clear whether the prognosis differs stage for stage from older individuals[2,17,22]. In some series, advanced stage is the only independent prognostic variable [23, 24]. Furthermore, there has been documented a greater prevalence of mucinous[20,25] or less differentiated tumors[26,27] in this group. Although mucinous tumors represent 10-16% of all colorectal adenocarcinomas, they occur in 20 to 64%of young individuals[3,21,26].

In a study comparing 59 patients younger than versus 416 older than 40 years during a 20-years period, Ganapathi *et al*.[17] found a higher frequency of tumors with poor differentiation (43% *vs*. 16%, p<0.001), T4 stage (47% *vs*. 30%, p=0.005) and vascular invasion (VI; 38% *vs*. 29%, p=0.13) in the younger group. Multivariate analysis showed T4 status (p=0.001) and vascular invasion (p=0.002) as independent prognostic factors for overall survival and T4 status (p=0.004) as independent factor influencing disease-free survival.

When comparing clinical and histopathological parameters of 244 patients aged 50 years or less with

1,718 patients aged more than 50 years, Schellerer *et al*.[28] found that although young patients present with more aggressive histopathological subtypes and less early stages, cancer-related survival was not less favorable. Similar findings were found in series comparing only patients with rectal cancer, reporting poorer histological differentiation, more advanced pathologic stage and no difference in long-term survival[22].

However, a study using a prospective database from Taipei Veterans General Hospital[29] identified 69 patients with mean age of 33.5 years, and the elderly group consisted of 253 patients with mean age of 83.4 years from 2001 to 2006. Younger patients had a higher incidence of mucinous cell type (14.5% *vs*. 6.3%, p=0.05), poorly differentiated adenocarcinoma (26.1% *vs*. 6.3%, p<0.001) and more advanced disease (82.6% *vs*. 41.9%, P<0.001). The comparison of prognosis in these groups with different onset ages revealed that the young had poorer disease-free survival (67.2% *vs*. 79.3%, p=0.048), and cancer-specific survival (44.1% *vs*. 73.1%, p<0.001).

Similarly, a study from the British Columbia Cancer Agency showed that 78 (0.47%) patients among 16,732 treated during a 20-year period were younger than 30 years of age. Data from 62 of these patients displayed 49% and 27% in stages III and IV, respectively. In this young cohort, the 5-year survival appeared inferior to that expected, although 5-year survival among patients with stage IV disease was observed to be higher than expected[16].

Thus, the majority of young patients usually present with later stages tumors at diagnosis, data confirmed by two reviews[2,30]. Moreover, it has been considered a rare disease in very young patients (below 20 years of age)[31,32]. Due to that, it has been questioned that the diagnosis in advanced stages is a result of less diagnostic efforts directed towards an apparent healthy group. However, in a series published by our group, there was no difference regarding symptoms duration (13.8 *vs*. 14.5 months; p=0.5) between the young and control groups[3]. Another fact that may decrease clinical suspicion of malignancy is that symptoms are commonly credited to benign anorectal diseases and a positive family history of CRC is referred by less than 27% of young patients[16].

Regarding the anatomical distribution, it has been documented that CRC in young people is confined to a topography distal to the splenic angle of the colon in more than 80% of the cases, which is why they usually determine rectal bleeding, abdominal pain, fecal changes and mucorrhea.

IMPORTANT GENETIC ASPECTS

In a recent review article regarding young colorectal patients, Ciarrocchi and Amicucci[33] concluded that colon carcinoma in young adults appears to be a distinct disease characterized by biological aggressiveness, but prognosis is not worse due to a better performance status at time of surgical intervention. CRC carcinogenesis occurs over a number of years and is related to combination of gene alterations and two separate destabilizing pathways (chromosomal instability and intragenic mutation)[34]. However, the spectrum of somatic mutations contributing to the pathogenesis of CRC is likely to be far more extensive than previously appreciated, with individual lesions harboring an average of nine mutant genes each. In addition, each tumor studied had a distinct mutational gene signature[35].

Microsatellite instability (MSI) is considered a hallmark of the mutator pathway in colorectal carcinogenesis, being found in 15% of sporadic CRC and in a higher percentage of young patients (<45 years). Most of the remaining CRC may follow the classic suppressor pathway. MSI occurs from the mutational inactivation of the DNA mismatch repair genes (hMSH2 and hMLH1 in Lynch Syndrome), as well as from epigenetic inactivation of hMLH1 in sporadic CRC. Although mutator pathway (including microsatellite instability, hMLH1 promoter methylation, and hMSH2 and hMLH1 mutation patterns) has been implicated in younger-age-onset colorectal carcinogenesis, many tumors may evolve from different genetic events other than hMSH2 and hMLH1 mutations frequently identified in Lynch Syndrome[36].

Thus, it is not surprising that cancers that emerge from different mutational pathways should differ clinically. Previous case-control studies reported that 58%[37]and 47%[38] of CRC in patients 35 years of age or younger and 40 years of age or younger, respectively, had high-frequency MSI. In an interesting study within 124 young (<50 years old) people in Hong Kong population (recognized to have an unusually high incidence of CRC in the young), Ho *et al*.[39] found that the MSI incidence increased significantly with decreasing age at diagnosis. For those aged 30 to 49, MSI tumors were located mainly at the proximal colon, while they tended to be at the distal large bowel. However, for exceptionally young patients (<30 years), this observation suggested a differential activity of the MMR pathway in colorectal carcinogenesis in different age groups.

FINAL CONSIDERATIONS

After summarizing the available data regarding CRC in young patients, it is possible to abstract important information from the present review. Within this group, CRC is usually diagnosed later, when an advanced disease leads to a poorer prognosis. As an apparent increase in the CRC incidence in young is still ongoing, a higher suspicious diagnostic criteria is necessary when evaluating young patients with common symptoms. Moreover, educational and preventive programs should provide consciousness information about alert symptoms.

The finding of a CRC in young patients raises not only diagnostic challenges, but also management issues. When dealing with a young patient, it is worthy to separate sporadic CRC from those originating from hereditary syndromes such as Lynch Syndrome or Familial Adenomatous Polyposis. However, even for CRC patients under 40 years of age, the prevalence of positive family history of cancer is under 27%[40]. It is well recognized that young CRC patients associated with hereditary syndromes have an increased metachronous cancer rate after colonic partial resection. Thus, an adequate preoperative approach should identify this select group in order to deliver appropriate surgical decision regarding the colectomy extent and familial surveillance.

In the case of sporadic cancers, there exist suggestions to consider a more extended colectomy in the management of patients under 50 years of age. However, performance of an extended colectomy in this group is not always associated with improvement in disease-free survival or mortality, besides the 3% occurrence of metachronous cancer[41]. This fact explains why most surgeons would not alter surgical decision without a proof of genetic disease. In this situation, factors such as health conditions, quality of sphincter muscles, opportunity and willing to adopt long-term follow-up, and mainly the existence of affected relatives may help the surgeon to choose the best option case by case, after offering the patient complete information. This is what happened with our second patient, who was treated by total colectomy.

Consequently, the issue of age at diagnosis naturally raises the discussion of performing genetic testing (IHC, MSI) before treatment, although there is no agreement to offer preoperative investigation based only in this criteria, without a suggestive family history or the presence of other histological risk factors for Lynch Syndrome[42]. Even knowing that most surgeons would not change their surgical decision in the absence of a genetic evaluation, it is right to suppose the opposite when facing a young patient that developed a CRC on the basis of a genetic mutation.

Even today, most RCC appear sporadically dependent on several factors such as diet, obesity, intestinal microbiota, alcohol intake, smoking, and germ or somatic mutations. In young people, the participation of genetic mechanisms is greater and, in order to increase the effectiveness of CRC detection at an earlier age, young adults should know the effects and criteria of screening through advertising campaigns. Clarification in primary medical care sectors, emphasis on the subject in undergraduate medical courses and enhancement of public laws should also be remembered.

Then, the data and all this controversy presented here bring support to suggest a modification in current recommendations, as there is an opportunity to improve medical and population education regarding CRC risks.

RESUMO

O câncer colorretal (CCR) esporádico é tradicionalmente diagnosticado após a sexta década de vida, embora uma pequena porcentagem de casos seja diagnosticada em doentes abaixo dos 40 anos de idade, e a incidência está aumentando. Existe uma grande controvérsia a respeito da evolução clínica de doentes jovens portadores de CCR em comparação aos mais idosos. Os objetivos deste estudo foram avaliar a prevalência de CCR em doentes jovens, rever a literatura pertinente e discutir suas características mais importantes nesta faixa etária. Para tanto realizou-se revisão da literatura envolvendo doentes com CCR com foco na idade ao diagnóstico. A informação extraída da revisão de literatura demonstrou uma tendência de redução da incidência em pessoas mais idosas com efeito oposto em adolescentes e adultos jovens. Sua agressividade biológica ainda não foi claramente reconhecida, embora seja usualmente diagnosticado mais tardiamente e em associação com características histológicas adversas. Apesar disso, estas características não afetam a evolução. Este aparente aumento na incidência de CCR entre pacientes jovens durante as últimas décadas levanta a necessidade de uma maior suspeita diagnóstica na avaliação de sintomas comuns neste grupo. Assim, programas educacionais devem disseminar informação tanto para população como para médicos a fim de melhorar a prevenção e o diagnóstico precoce.

Descritores: Neoplasias Colorretais. Idade. Incidência. Adulto Jovem. Prognóstico.

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Mailing address:
Fábio Guilherme C. M. de Campos
E-mail: fgmcampos@terra.com.br