ORIGINAL ARTICLE

doi.org/10.1590/S0004-2803.230302023-23

Early-onset colorectal cancer: an eleven-year analysis of clinicopathological characteristics at a tertiary healthcare center

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HIGLIGHTS

- The incidence of early-onset colorectal cancer (EO-CRC) has significantly increased worldwide, often leading to advanced disease at the time of diagnosis.
- This study investigates the clinicopathological characteristics of EO-CRC cases at an academic healthcare center in Spain.
- The majority of patients with EO-CRC were diagnosed between 40-49 years of age.
- Left-sided tumors were more common, and most patients were diagnosed at advanced stages.
- Moderately differentiated adenocarcinoma was the most frequent histological type, with 18.8% showing KRAS mutation and 11.9% showing BRAF mutation.

Received: 9 February 2023
Accepted: 13 June 2023

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
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ABSTRACT – Background – Early-onset colorectal cancer (EO-CRC) incidence has increased significantly worldwide in recent years, and these individuals frequently have advanced disease at the time of diagnosis. This study examines the clinicopathological characteristics of EO-CRC cases diagnosed at an academic healthcare center in Spain. **Methods –** A retrospective record review study of patients diagnosed with EO-CRC from 2010 to 2021 was performed. Clinical and pathological data were collected. **Results –** A total of 101 patients were included. The majority of cases (75.3%) were diagnosed in the age group between 40 and 49 years, specifically within the subgroup of 46–49 years. A family history of colorectal cancer was found in 23% of patients. Left-sided tumors were more common (43.6%), and most patients were diagnosed at advanced stages (34.7% at stage III and 32.7% at stage IV). The majority of patients (94.1%) were symptomatic, with rectal bleeding being the most prevalent clinical presentation. The most frequent histological type was moderately differentiated adenocarcinoma (44.6%). KRAS mutant tumors were found in 18.8% and BRAF mutant tumors in 11.9%. 67.3% had microsatellite stability. Tumor recurrence occurred in 24.8% of the patients, while 27.7% of the patients died. **Conclusion –** From 2010 to 2021, EO-CRC accounted for 3% of all colorectal cancer cases. To improve early diagnosis and treatment, physicians should maintain a high suspicion of red flag symptoms in young patients. To decrease EO-CRC morbidity and mortality, starting diagnostic screening tests at age 45 should be considered.

Keywords – Colorectal cancer; early-onset; young age; clinicopathological features.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in both sexes, with 1,931,590 new cases diagnosed in 2020 worldwide and representing the second leading cause of cancer-related death[1]. CRC incidence rates differ significantly across geographical regions. The highest rates have been reported in the Australasia region, with an estimated age-standardized incidence rate of 48.3 cases per 100,000 standard population, followed by high-income Asia-Pacific countries, where the incidence rate has been 44.6. Central Sub-Saharan Africa and South Asia, on the other hand, have the lowest rates, with 7.3 and 8.3 cases per 100,000 standard population, respectively[2]. With regard to mortality, there are also significant geographical variations. The age-standardized mortality rate was the highest in central Europe (23.6 per 100,000 standard population) and the lowest in South Asia (7.3 per 100,000 standard population)[2].

CRC is often diagnosed in elderly individuals, with a median age at diagnosis being 66 years in men and 69 years in women[3]. In this age group, the incidence is reported to have remained stable and even to have decreased in highly developed countries in the last years[4]. This is likely due to the expansion of screening programs and a better understanding of risk factors among the population[5]. Nevertheless, there has been a noteworthy increase in the incidence of CRC in the young population over the past years[6]. Since most countries do not offer screening programs for people under the age of 50, these patients are often diagnosed at an advanced stage of the disease[7].

Currently, it is still unknown whether early-onset colorectal cancer (EO-CRC) is a part of the spectrum of CRC in younger people or if it comprises tumors that are physiologically distinct from late-onset colorectal cancer (LO-CRC)[5]. Understanding the epidemiologic, clinical, microbial, and genetic features of EO-CRC is key to establishing new population health policies for the early diagnosis and treatment of these patients. This study is aimed to assess the clinicopathologic features of EO-CRC diagnosed in a single academic tertiary healthcare center in Spain.

METHODS

Study design

We conducted a retrospective record review of patients diagnosed with EO-CRC at *Hospital Clínico Universitario de Valladolid* (HCUV), Valladolid, Spain, between January 2010 and December 2021. HCUV is a public academic tertiary healthcare center. In the current study, all CRCs diagnosed before the age of 50 were considered EO-CRC. This cutoff has been used in most studies because the majority of screening programs worldwide start at this age[5]. The 8th edition of the American Joint Committee on Cancer (AJCC) TNM system was used to stage the patients[8]. The exclusion criteria included patients with carcinoid tumors, patients with inflammatory bowel disease and incomplete data in the electronic medical record.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of HCUV.

Data collection

Data were obtained from electronic medical records of HCUV. Information collected included patient clinical demographic data, family history of CRC and known genetic syndromes (including Lynch syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, and juvenile polyposis syndrome), clinical presentation, interval from the onset of symptoms to diagnosis, tumor location, stage, histology, microsatellite stability status, KRAS and BRAF mutations, treatment information (including surgery, systemic therapy, and radiotherapy), recurrence, and mortality.

Statistical analysis

In the case of a normal distribution, continuous variables were expressed as mean ± standard deviation (SD) while they were expressed as the median and interquartile range in a nonnormal distribution. Categorical variables as frequencies and proportions. Joinpoint regression analysis was used to examine whether changes in the temporal trend were statistically significant. The analysis included two maximum joinpoints and 4499 Monte Carlo permutation tests. The segmental annual percent change (APC) and the

overall average annual percent change (AAPC) were calculated, along with their 95% confidence intervals (95% CIs). The statistical analyses were conducted using IBM® SPSS® Statistics 21.0 and the Joinpoint Regression Program, Version 4.9.1.0 (Statistical Research and Applications Branch, National Cancer Institute).

RESULTS

During the period from January 2010 to December 2021, a total of 3126 individuals were diagnosed with CRC, of whom 101 (3%) were under the age of 50. Of these patients, 51 (50.5%) were male. The median age at diagnosis was 46 years. The age group of 46 to 49 years was the most prevalent, comprising 50.5% of the sample. Regarding lifestyle habits, 14.9% of patients consumed alcohol, and 29.7% smoked. Among the patient cohort, 22.8% had a family history of CRC, but only 5.0% had a known hereditary cancer-predisposing syndrome, all of which were cases of Lynch syndrome. Baseline patient characteristics are summarized in TABLE 1.

TABLE 1. Baseline characteristics.

Variables	n=101
Median age, (IQR)	46 (40.5–49.0)
Age group (years), n (%)	
<30	1 (1)
30–35	11 (10.9)
36–40	13 (12.9)
41–45	25 (24.8)
46–49	51 (50.5)
Sex, n (%)	
Male	51 (50.5)
Female	50 (49.5)
BMI, mean (± SD)	29.3 (±5.8)
Diabetes mellitus, n (%)	10 (9.9)
Hypertension, n (%)	19 (18.8)
Alcohol consumption, n (%)	15 (14.9)
Smoking, n (%)	30 (29.7)
Family history of CRC, n (%)	23 (22.8)
Known genetic syndrome, n (%)	5 (5.0)

IQR:interquartile range; SD: standard deviation; BMI: body mass index; CRC: colorectal cancer.

The number of cases of EO-CRC diagnosed per year showed fluctuations throughout the study period. In 2018, there were a total of 14 cases, representing the highest number of cases in a single year and comprising 5.6% of all CRC cases diagnosed that year. In contrast, 2017 had the lowest number of cases with only four cases, comprising 1.5% of all CRC cases diagnosed that year (FIGURE 1). A joinpoint regression analysis revealed three trends throughout the study. The first trend was a decrease of 3.8% per year from 2010 to 2016 (APC -3.8; 95%CI -18.8 to 14.1; *P*=0.56). This was followed by a rise of 19% per year from 2016 to 2019 (APC 19.0; 95%CI -56.5 to 225.5; *P*=0.65), and then a more pronounced decline of 24% per year (APC -24.0%; 95%CI -72.2 to 107.9; *P*=0.49) from 2019 to 2021. Over the entire period 2010-2021, the number of new cases of EO-CRC decreased by 2.3% per year (AAPC -2.3; 95%CI -23.3 to 24.4; *P*=0.85). However, the previous trends were not statistically significant (FIGURE 2).

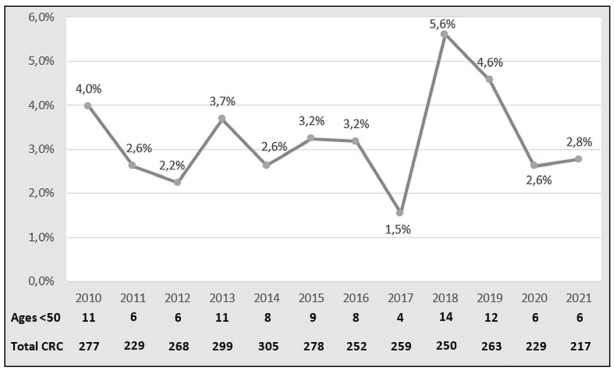

FIGURE 1. Percentage of new cases of early-onset colorectal cancer during the period 2010–2021.
CRC: colorectal cancer.

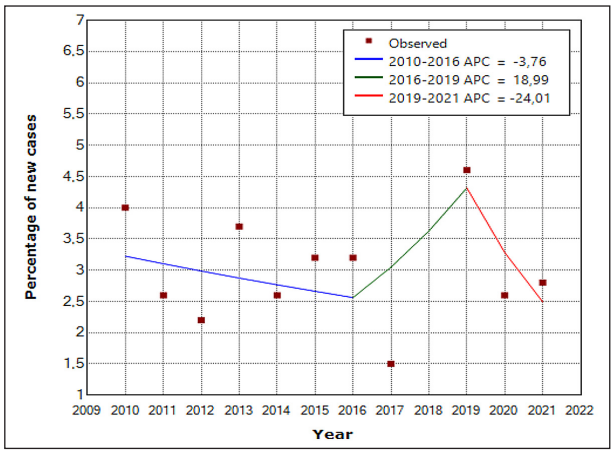

FIGURE 2. Annual Percent Change (APC) in the incidence of early-onset colorectal cancer during the period 2010–2021.

TABLE 2 illustrates that the majority of patients in this study presented with rectal bleeding (32.7%), followed by intestinal obstruction (19.8%). The median time from clinical presentation to diagnosis was 6.5 weeks. A small number of patients (5.9%) were asymptomatic at the time of diagnosis and were identified through an early screening colonoscopy due to a positive family history of colorectal cancer (CRC). Nearly 88% of the patients were considered for surgical resection of the primary tumor. Urgent surgery was required in 18 (17.8%) cases. The primary tumor was most frequently located in the left and sigmoid colon (43.6%). A significant proportion of patients (67.4%) were diagnosed at an advanced stage of the disease, with 34.7% at stage III and 32.7% at stage IV. At the time of diagnosis, 22 patients had a single site of metastasis, with the liver being the most common location. On the other hand, 11 patients presented with multiple metastasis sites.

Moderately differentiated adenocarcinoma was the most frequently observed histological type, comprising 44.6% of all cases. Mucinous adenocarcinomas accounted for 14.9% and signet ring cell carcinomas for 4% of the cases. In terms of molecular characteristics, KRAS mutant tumors were found in 19 patients (18.8%), and BRAF mutant tumors were present in 12 patients (11.9%). A majority of the patients (67.3%) had microsatellite stability. A comprehensive summary of the pathological and molecular findings can be found in TABLE 2. It was observed that 24.8% of the patients experienced tumor recurrence over the course of the study, while 27.7% of the patient cohort died.

TABLE 2. Clinicopathological features.

Variables	n=101
Clinical presentation, n (%)	
Bleeding	33 (32.7)
Obstruction	20 (19.8)
Weight loss	17 (16.8)
Iron-deficiency anemia	11 (10.9)
Abdominal pain	10 (9.9)
Asymptomatic	6 (5.9)
Constipation	3 (3.0)
Diarrhea	1 (1.0)
Interval from clinical onset to diagnosis (weeks), median (IQR)	6.5 (1.0–16.0)
Primary tumor resection, n (%)	89 (88.1%)
Urgent surgery, n (%)	18 (17.8)
Tumor location, n (%)	
Right/transverse	30 (29.7)
Left/sigmoid	44 (43.6)
Rectal	27 (26.7)
AJCC staging, n (%)	
I	10 (9.9)
II	23 (22.8)
III	34 (34.7)
IV	33 (32.7)
Number of metastasis sites at diagnosis, n (%)	
1	22 (21.8)
≥2	11 (10.9)
Histology, n (%)	
Well differentiated ADC	19 (18.8)
Moderately differentiated ADC	45 (44.6)
Poorly differentiated ADC	18 (17.8)
Mucinous ADC	15 (14.9)
Signet ring cell carcinoma	4 (4.0)
Angiolymphatic invasion, n (%)	20 (19.8)
Perineural invasion, n (%)	22 (21.8)
Surgical margins, n (%)	
Free	60 (67.4)
Compromised	29 (32.5)
KRAS status, n (%)	
Wild type	56 (55.4)
Mutant	19 (18.8)
Non-tested	26 (25.7)
BRAF status, n (%)	
Wild type	60 (59.4)
Mutant	12 (11.9)
Non-tested	29 (28.7)
MSS, n (%)	
Stable	68 (67.3)
Unstable	14 (13.9)
Non-tested	19 (18.8)
Adjuvant chemotherapy, n (%)	70 (69.3)
Neoadjuvant chemoradiotherapy, n (%)	5 (5.0)
Tumor recurrence, n (%)	25 (24.8)
Mortality, n (%)	28 (27.7)

IQR: interquartile range; AJCC: American Joint Committee on Cancer; ADC: adenocarcinoma; MSS: microsatellite stability status.

DISCUSSION

EO-CRC, once considered a rare condition, has been shown to have an increasing incidence globally, with rates rising at approximately 2% per year since the 1990s. Predictions suggest that by 2030, EO-CRC will account for 10% of colon cancer cases and 22% of rectal cancer cases in the United States[5,9]. Data from national and regional cancer registries in Europe also indicate an average increase of 7.9% per year in incidence for individuals aged 20 to 29 from 2004 to 2016, 4.9% per year for those aged 30 to 39 from 2005 to 2016, and 1.6% per year for those aged

40 to 49 from 2004 to 2016[10]. These estimations emphasize the magnitude of the issue and its potential impact on public health globally. EO-CRC is increasingly being recognized as a significant public health concern[5]. As a result, there has been a growing interest in studying the epidemiologic, clinical, and genetic features of this disease.

In the current study, it was observed that the majority of EO-CRC cases (75.3%) were diagnosed in the age group between 40 and 49 years, specifically within the subgroup of 46–49 years. This is consistent with the results of previous research, including a multicenter prospective cohort study conducted in Spain by Perea et al., which included 220 patients with EO-CRC, and a retrospective record review study by Silva et al. that involved 781 patients and was carried out in Brazil[7,11]. Therefore, it is plausible that this patient population would derive benefit from screening strategies that start at age 45, in accordance with the most recent recommendations of The American Cancer Society[12].

Our study found a rise in the number of new cases of EO-CRC between 2016 and 2019, which is supported by earlier research that highlighted an increase in the incidence of this condition worldwide. It is noteworthy that there was a sudden drop in the number of new cases during the biennium 2020–2021, which can be attributed to the effect of the COVID–19 pandemic on the diagnosis of CRC since fewer diagnostic tests were performed during this time[13]. As an example, during the pandemic in Spain, the diagnosis of CRC in screening programs dropped from 33.3 to 5.2%[14]. This drastic reduction in new cases due to an external cause may explain the absence of a significant trend change throughout the study period, which could potentially affect the AAPC estimate.

In this study it was found that nearly 23% of patients with EO-CRC had a family history of CRC. Chen et al. reported a higher likelihood of a family history of CRC among individuals with EO-CRC (24.9%) compared to those with LO-CRC (16.8%)[15]. We also found that at the time of diagnosis, the majority of patients in the present cohort (94.1%) presented with symptoms, with rectal bleeding being the most prevalent clinical presentation. These findings align with previous research, which has illustrated that individuals diagnosed with EO-CRC tend to present with symptoms, particularly haematochezia, while those with LO-CRC are more likely to be identified incidentally through screening tests[16].

Another noteworthy finding from the current study was the high proportion of patients who were diagnosed at advanced stages (67.4%), as previously reported in the literature. Abdelsattar et al. noted that, in comparison to patients with LO-CRC, those with EO-CRC had a relative risk (RR) of 1.37 for regional and 1.58 for distant metastases[17]. A study conducted by You et al. found that a greater proportion of young patients diagnosed with rectal cancer (59.4%) presented with advanced stages III or IV of the disease, compared to the older patient cohort where the percentage of advanced stages was 46.4%[18]. Further investigation is required to identify whether a delay in diagnosis or biological variations are responsible for these findings, which are not yet completely understood[19].

With regard to histologic features, it is interesting to note that most patients in this cohort had moderately differentiated tumors, which differs from several earlier studies where a greater proportion of poorly differentiated neoplasms was reported among patients with EO-CRC[20,21]. On the other hand, approximately 4% of the patients in the current study had signet ring cell carcinoma, a subtype characterized by the presence of signet-ring cells comprising over 50% of the tumor area. This uncommon histological subtype of CRC, accounting for nearly 1% of all cases, has been associated with a poorer prognosis compared to classical adenocarcinomas[22]. This is due to a number of pathological characteristics, such as a high rate of positive surgical margins, an increased risk of vascular invasion and lymph node involvement, an invasive growth pattern, and decreased expression of adhesion molecules such as E-cadherin and β-catenin, which leads to decreased cell-cell adhesion and thus increases metastatic potential[23-25]. Patients with EO-CRC have been found to have a higher incidence of this CRC subtype, accounting for 3–13% of cases, particularly in patients under the age of 30[5].

This study has several limitations that must be taken into account. First, there might be information bias due to the retrospective nature of the study. Se-

cond, this was a single center study, therefore, data on the regional epidemiology of the disease was not available, which may limit the generalizability of the present results in the region. Finally, our center did not have the availability of wide-ranging genomic tests in order to assess the presence of alterations in genes that have been reported to be related to sporadic EO-CRC, such as BMF7, LEF1, MET, RAD21CLC, and IFNAR1[26,27]. Due to these limitations, future multi-center studies that include data from various regions could provide a more comprehensive understanding of clinicopathological features of EO-CRC.

In summary, our results illustrated that 3% of all CRC diagnosed from 2010 to 2021 were in patients under the age of 50. Despite not being statistically significant, there was an increase in in the number of EO--CRC prior to the impact of the COVID-19 pandemic in the number of diagnostic tests performed. Most of these patients were symptomatic and presented with advanced stages of the disease. Therefore, in order to performed early diagnostic work-up procedures to rule out CRC and provide prompt and appropriate treatment, physicians should maintain a high likelihood of suspicion in young patients presenting with red flag signs and symptoms such as lower gastrointestinal bleeding and weight loss. Furthermore, it is important to consider ways to improve early detection strategies, such as starting diagnostic screening tests at age 45 rather than the traditional age of 50, in order to decrease EO-CRC morbidity and mortality.

Authors' contribution

Involved in the conception, analysis of data and draft of the manuscript: Piñerúa-Gonsálvez JF and Zambrano-Infantino RC. Involved in the acquisition of data: Piñerúa-Gonsálvez JF, Rizzo-Rodríguez MA, and Dueñas-Diez A. Revised manuscript critically for important intellectual content: Fernández-Salazar L. All authors contributed to the article and approved the submitted version.

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Piñerúa-Gonsálvez JF, Zambrano-Infantino RC, Rizzo-Rodríguez MA, Dueñas-Diez A, Fernández-Salazar L. Câncer colorretal de início precoce: uma análise de onze anos das características clinicopatológicas em um centro de saúde terciário. Arq Gastroenterol. 2023;60(3):315-21.

RESUMO – Contexto – A incidência de câncer colorretal de início precoce (CCR-IP) tem aumentado significativamente em todo o mundo nos últimos anos, e esses indivíduos frequentemente apresentam doença avançada no momento do diagnóstico. Este estudo examina as características clinicopatológicas dos casos de CCR-IP diagnosticados em um centro de saúde acadêmico na Espanha. **Métodos** – Realizado um estudo retrospectivo de revisão de prontuários de pacientes diagnosticados com CCR-IP de 2010 a 2021. Dados clínicos e patológicos foram coletados. **Resultados** – Foram incluídos um total de 101 pacientes. A maioria dos casos (75,3%) foi diagnosticada na faixa etária entre 40 e 49 anos, especificamente dentro do subgrupo de 46 a 49 anos. Histórico familiar de câncer colorretal foi encontrado em 23% dos pacientes. Tumores do lado esquerdo foram mais comuns (43,6%), e a maioria dos pacientes foi diagnosticada em estágios avançados (34,7% no estágio III e 32,7% no estágio IV). A maioria dos pacientes (94,1%) apresentava sintomas, sendo o sangramento retal a apresentação clínica mais prevalente. O tipo histológico mais frequente foi adenocarcinoma moderadamente diferenciado (44,6%). Tumores com mutação KRAS foram encontrados em 18,8% e tumores com mutação BRAF em 11,9%. 67,3% apresentavam estabilidade de microssatélites. A recorrência do tumor ocorreu em 24,8% dos pacientes, enquanto 27,7% dos pacientes morreram. **Conclusão** – De 2010 a 2021, o CCR-IP representou 3% de todos os casos de câncer colorretal. Para melhorar o diagnóstico precoce e o tratamento, os médicos devem manter uma alta suspeita de sintomas de alerta em pacientes jovens. Para diminuir a morbidade e a mortalidade do CCR-IP, a consideração de iniciar exames de triagem diagnóstica aos 45 anos deve ser considerada.

Palavras-chave – Câncer colorretal; início precoce; idade jovem; características clinicopatológicas.

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