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RESEARCH ARTICLE

Early Onset Colorectal Cancer: Younger Patients, More Advanced Stage and Worse Postoperative Results: A Retrospective Review

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ABSTRACT

Aim: The incidence of colorectal tumors in young patients has been rising lately, and current investigations are directed to determine causes and prognosis of this type of patients. The objective of this publication is to analyze results of surgical treatment and tumor stages in young patients, and compare them to those in older individuals.

Method: A retrospective analysis of patients undergoing surgery for colorectal adenocarcinoma during 2015-2020 in a single institution was performed, dividing them into two categories: those younger than 50 years old, early onset colorectal cancer (EOCRC), and those on age for colorectal cancer screening, average onset colorectal cancer (AOCRC), focusing on disease stage and postoperative outcomes.

Results: Two hundred and seven patients were included, thirty-two in the EOCRC group. Median age was 42.10 years (SD= 5.74) and 65.38 years (SD= 7.19) respectively, dyslipidemia was more prevalent in AOCRC patients. EOCRC patients had more upper rectum (28.13 vs. 8%, p= 0,001) and transverse colon (21.88 vs. 10.29%, p=0.06) tumors, had higher rates of complications (43.75 vs. 28%, p=0.07) and reoperations (18.75 vs. 7.43%, p=0.04). Moreover, major complications were more frequent in younger patients. EOCRC had significantly more stage IV tumors (18.75 vs. 5.13 %, p=0,01), and 46.86% of these individuals had an advanced disease at the time of surgery.

Conclusion: EOCRC is diagnosed at more advanced stages of the disease and presents differences in tumor location. Complications including need of reoperation are more frequent in this group.

Keywords: Colorectal adenocarcinoma, early onset, screening strategies, colonoscopy, advanced stage

Introduction

Colorectal cancer (CRC) is the third cancer in incidence in both males and females worldwide, only outnumbered by breast and lung tumors. It is also the second cause of cancer related deaths [1].

Significant advances have been made in early diagnosis of CRC due to the development of population screening strategies performing exams which detect potentially neoplastic polyps at an early stage [2]. The most widely-used screening procedure is colonoscopy, and an association has been found between its implementation and a significant reduction in CRC incidence [3, 4]. According to current guidelines, the indication for screening colonoscopy is recommended for patients between 50-75 years old [5], average-onset of CRC (AOCRC).

On the other hand, there is a rising concern due to the increase in CRC among younger patients, a trend that has been formerly addressed as "Early Onset CRC" (EOCRC) [6]. Screening in patients from 45 to 49 years old is being considered as a Grade B recommendation by the US Preventive Service Task Force, although no definitive recommendation has been published since 2016.

Early diagnosis and treatment of these patients remain challenging, as they are not included in screening strategies, and consequently, they may consult at an advanced stage, usually when they are overtly symptomatic. It has been

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estimated that by 2030, the incidence rate for CRC will rise by 90 to 124%, in patients below 34 years of age [7, 8].

Even though some guidelines have already suggested that CRC screening should start earlier [9], the impact of this new tendency and the way to prevent development of tumors in this population remain unclear.

There is a paucity of studies comparing postoperative outcomes between patients with EOCRC and AOCRC; this could be explained by the assumption that AOCRC patients would have worse results due to their age. We sought to compare postoperative outcomes between EOCRC and AOCRC patients as well as to compare the tumor stage at the time of diagnosis

Materials and Methods

Study design and population

We undertook a cross-sectional study at an academic hospital in the city of Buenos Aires, Argentina. The study protocol was approved by our local ethics committee. The Surgery department's database was reviewed from January 2015 to May 2020. Patients who underwent colorectal surgery were identified; we excluded patients who received surgery for benign colorectal tumours as well as malignant tumours other than colorectal adenocarcinoma. We also excluded patients who were diagnosed with colorectal adenocarcinoma beyond 75 years of age.

Data extraction

The patients who fulfilled inclusion criteria were furtherly classified according to the age of CRC diagnosis into two groups: the EOCRC group included patients younger than 50 years and the AOCRC group included patients between 50 to 75 years. The medical history of each patient was reviewed and the following clinical comorbidity data was collected: hypertension, dyslipidaemia, diabetes mellitus, smoking, chronic obstructive pulmonary disease, chronic kidney disease, history of abdominal surgeries. The tumour location as well as tumour stage were recorded according to the American Joint Committee on Cancer guidelines [10]. Surgery charts were also reviewed, and the following information was retrieved for further analysis: whether surgery was urgent or not. Urgent surgery was defined as any surgical procedure that had to be performed secondary to a critical clinical condition of the patient, due to acute tumour complications: intestinal obstruction, haemorrhage or tumour perforation.

Laparoscopic approach, length of stay after surgery, postoperative complications classified as minor (Clavien-Dindo score I or II) or major (Clavien-Dindo score IIIb or higher) [11], assigned by one of the authors (AC) and confirmed by the Surgery Department Mortality and Morbidity Review Meeting, held on a weekly basis; need for reoperation, need for re-hospitalization 30 days after discharge and 30-day mortality were also retrieved for each patient.

Statistical analysis

Stata version was used for this purpose (v11.1, Statacorp, College Station, Texas USA). The categorical variables are described as percentages whereas numerical variables are described as median with their 25-75% interquartile range. We used the chi square test for the comparison of categorical variables and the Mann Whitney test for the comparison of continuous numerical variables. Odds Ratio (OR) with their 95% confidence intervals were calculated. A multivariable analysis using a logistic regression model was performed including all the variables compared with a p value of less than 0.1. _A p value below 0.05 was considered as statistically significant. Our primary outcome variable was overall complication prevalence. Other variables that were compared between EOCRC and AOCRC which showed a p value of less than 0.1 were also included in the logistic regression analysis.

Results

We reviewed the medical records of 545 patients who underwent colorectal surgery during the study period; 207 patients were finally included in the analysis, as shown in

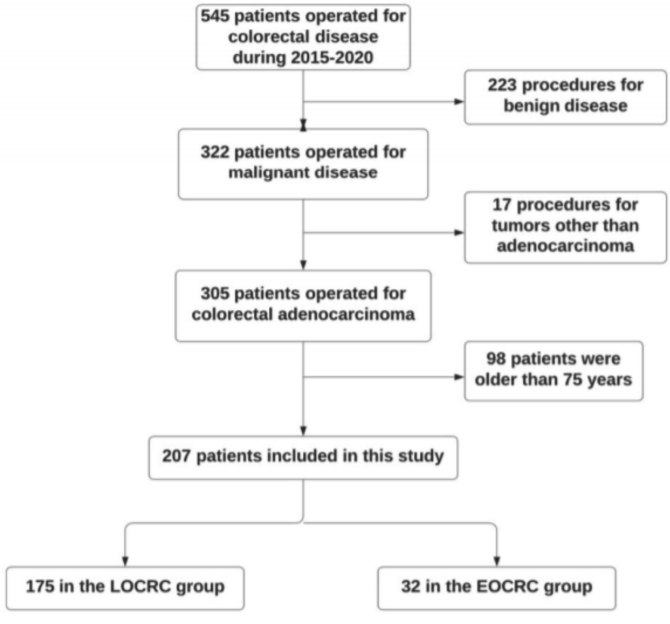

Figure 1. Selection process

Table 1 shows the main clinical characteristics of patients included. The median age was 42.10 (SD: 5.74) in the EOCRC group and 65.38 (SD: 7.19) in the elder group; 28% (9/32) of the patients included in the EOCRC were under 40 years of age. No differences were found regarding gender proportion in each group.

Symptomatic presentation also varied in both groups (**Table 2**). In the EOCRC group there were 6% (2/32) of the patients were diagnosed by screening methods, whereas 94% were diagnosed with a symptomatic presentation, five of them (15,6%) with an acute complication that involved urgent surgery procedure. On the other hand, on the AOCRC group 36,5% of the patients were diagnosed by screening methods, and only 6,8% underwent urgent surgery for acute complications.

Overall, 2/32 (6,25%) patients in the EOCRC cohort had a history of a first-degree family member with CRC. They were both diagnosed at an early stage subsequent to an early screening colonoscopy.

Table 3 shows the comparison of the main surgical features. Postoperative complications were numerically more frequent among EOCRC patients (43.75% vs 28%, p=0.07), with a significantly higher need for re-intervention among these subjects (18.75% vs. 7.43%, p=0.04). Furthermore, most of these events in younger patients were major complications (64.29%). Six patients required re-operation for surgery related complications: two patients due to haemoperitoneum, one due to evisceration, one due to bowel obstruction and two patients due to major anastomotic leaks. Other three patients with anastomotic leakage were managed successfully with percutaneous drainage. In the AOCRC group most of the complications were minor (62.27%), mainly urinary infection and postoperative ileus.

There were no deaths in the EOCRC group within the first three months. In the AOCRC group, five patients (2,8%) died within 30 days of surgery: one postoperative myocardial infarction, two pneumonias, and two presented metastatic disease a month after surgery.

Table 1. Patient characteristics

	EOCRC patients (N=32) %(n)	AOCRC (N=175) %(n)	OR (IC95%)	P
Age (median, range)	42.10 (28-49)	65.38 (50-75)	N/A	0.20
Gender (% male)	50 (16)	48 (84)	1.08 (0.51-2.30)	0.83
LOCATION				
Right colon	15.63 (5)	25.71 (45)	0.57 (0.20-1.57)	
Hepatic flexure	3.13 (1)	5.71 (10)	0.53 (0.06-4.33)	
Transverse colon	21.88 (7)	10.29 (18)	2.44 (0.92-6.51)	
Splenic flexure	3.13 (1)	3.43 (6)	0.91 (0.10-7.85)	
Left colon	6.25 (2)	8 (14)	0.76 (0.16-3.56)	
Sigmoid colon	18.75 (6)	29.71 (52)	0.55 (0.21-1.41)	
Upper rectum	28.13 (9)	8 (14)	4.50 (1.70-11.91)	
Middle rectum	0	6.29 (11)	N/A	
Lower rectum	3.13 (1)	2.86 (5)	1.38 (0.15-12.82)	
COMORBIDITIES				
Hypertension	31.25 (10)	49.14 (86)	0.47 (0.21-1.06)	0.06
Diabetes	3.13 (1)	14.86 (26)	0.18 (0.02-1.44)	0.07
Dyslipidemia	9.38 (3)	33.71 (59)	0.20 (0.05-0.71)	0.006
Smoking	40.63 (13)	41.71 (73)	0.95 (0.44-2.06)	0.91
Chronic pulmonary obstructive disease	6.25 (2)	7.43 (13)	0.83 (0.17-3.88)	0.81
Chronic kidney disease	0 (0)	1.71 (3)	N/A	0.45
Neoadjuvant therapy	15.63 (5)	4.57 (8)	3.86 (1.15-12.94)	0.01
Previous abdominal surgery	46.88 (15)	56.57 (99)	0.67 (0.31-1.44)	0.31

The EOCRC group of patients received more urgent procedures for complicated tumors. No differences were found regarding surgical approach.

Table 4 describes the comparison of tumour stage between the two groups: EOCRC showed a significantly higher proportion of patients diagnosed with a stage-IV CRC (18.75% vs 5.13%, p=0.01). Moreover, 64% of patients in the older group were operated for early tumours (stages 0, I or IIA of the AJCC classification), whereas 46.86% of the younger cohort had advanced disease (stages IIB or more of the AJCC classification) at the time of the operation.

On multivariable analysis, location of the tumour at the upper rectum as well as tumour stage were significantly different between EOCRC and AOCRC patients (**Table 5**).

Table 2. Presenting Symptoms

	EOCRC (%,n/N)	AOCRC (%,n/N)
Screening (n,%)	6 (2/32)	36,5 (64/175)
Non-specific abdominal pain	18 (6/32)	13,7 (24/175)
Symptomatic Anemia	15,6 (5/32)	8,5 (15/175)
Change in bowel habit	31,2 (10/32)	19,4 (34/175)
Hematochezia	3,1 (1/32)	3,6 (6/175)
Late symptoms (asthenia, weight loss)	9,3 (3/32)	11,4 (20/175)
Acute complications (hemorrhage, bowel obstruction, perforated tumor)	15,6 (5/32)	6,8 (12/175)

We found a higher proportion of patients with upper rectum tumors in the EOCRC group (28.13 vs. 8%, p=0.001). There were also more tumors in the transverse colon among these subjects. We did not find significant differences in terms of comorbidities among groups, except for dyslipidemia, which was more frequent in the AOCRC group (33.71% vs 9.38%, p=0.006). Neoadjuvant therapy requirement was significantly higher in the EOCRC group (15.63% vs 4.57%, p=0.01), which is consistent with the fact that this group of patients presented with more advanced tumors .

Discussion

Despite current efforts to understand the causes underlying EOCRC, most of the reasons for this new presentation remain unclear [12]. Many of these patients do not show the traditional risk factors for CRC (such as smoking) [13, 14] and even though familial predisposition is detected in up to 25% of these patients, most of the tumours seem to be sporadic [15, 16]. These findings are similar to those described in our cohort, where no significant differences were found related to comorbidities.

Irrespective of the underlying cause of this new tendency among CRC affecting younger individuals, it represents a major concern for the medical community, due to the fact that the incidence of tumors in the colon and rectum have significantly decreased lately in older patients, whereas it has been rising in patients under 50 years of age [17].

The present study found some interesting results related to the differences between the two groups.

Table 3. Operative data

	EOCRC (%, n/N)	AOCRC (%, n/N)	OR (IC95%)	P
Urgent procedure (ostomy)	15.63 (5/32)	6.86 (12/175)	2.51 (0.81-7.78)	0.09
Non-urgent surgery	84.38 (27/32)	85.71 (150/175)	0.90 (0.31-2.56)	
PROCEDURE				
Open	28.13 (9/32)	22.86 (40/175)	1.32 (0.56-3.09)	0.55
Laparoscopic	62.50 (20/32)	67.43 (118/175)	0.80 (0.36-1.76)	
Laparoscopic converted to open	9.38 (3/32)	9.71 (17/175)	0.90 (0.24-3.27)	
Hospitalization (Days)	6 (4-16)	5 (3-29)	N/A	0.39
Complications	43.75 (14/32)	28 (49/175)	2 (0.91-4.36)	0.07
Minor complications	35.71 (5/14)	63.27 (31/49)	3.10 (0.86-11.18)	
Major complications	64.29 (9/14)	36.73 (18/49)	0.32 (0.09-1.16)	
Surgical site infection	12.50 (4/32)	12 (21/175)	1.04 (0.33-3.29)	0.93
Anastomotic fistula	0 (0/27)	6.13 (10/163)	N/A	0.16
Re operation rate	18.75 (6/32)	7.43 (13/175)	2.87 (1-8.34)	0.04

Table 4. Tumor stage

Stage	EOCRC (%, n/N)	AOCRC (%, n/N)	OR (IC95%)	P
0	9.38 (3/32)	10.86 (19/175)	1.18 (0.33-4.25)	0.80
I	31.25 (10/32)	20.57 (36/175)	0.57 (0.25-1.32)	0.182
IIA	12.5 (4/32)	32.57 (57/175)	3.38 (1.11-10.27)	0.02
IIB	3.12 (1/32)	2.86 (5/175)	0.91 (0.10-8.11)	0.934
IIC	3.12 (1/32)	0 (0/175)	N.A	0.02
IIIA	6.25 (2/32)	6.29 (11/175)	1.00 (0.21-4.79)	0.99
IIIB	12.5 (4/32)	14.86 (26/175)	1.22 (0.39-3.78)	0.728
IIIC	3.12 (1/32)	6.86 (12/175)	2.28 (0.28-18.34)	0.424
IVA	6.25 (2/32)	3.42 (6/175)	0.53 (0.10-2.78)	0.44
IVB	12.50 (4/32)	1.71 (3/175)	0.12 (0.02-0.60)	0.002

Table 5. Multivariable analysis

Transverse colon location	1.63 (1-8.74)
Upper rectum location	4.48 (1.55-12.93)
Neoadjuvant therapy	2.54 (0.60-10.74)
Postoperative complications	1.23 (0.43-3.48)
Reoperation rate	1.53 (0.38-6.17)
AJCC stage IIA	0.33 (0.10-1)
AJCC stage IVB	5.15 (1.02-28.39)
Hypertension	0.32 (0.09-1.02)
Type II Diabetes	0.22 (0.1-1.13)

Firstly, young patients seem to have tumors predominantly in the upper rectum and transverse colon. Previous studies found that CRC was more frequent in the distal colon and rectum [18, 19], and this finding has led to suggest sigmoidoscopy as a screening strategy for these patients. However, such diagnostic methods would not be useful for patients with transverse and right colon tumors, which in our cohort account for approximately 50% of all patients.

The proportion of young patients with EOCRC (15% of all patients with CRC tumors) is similar to that presented by other authors [20], even though other studies have found a significantly lower incidence of EOCRC when compared to the group of elder patients [21].

Our EOCRC group showed a higher proportion of postoperative complications and consequently, a higher proportion required reoperation. Publications about comparison of CRC surgery-associated morbidities young and older patients are scarce, and results are controversial. Hanna et al. presented a study involving 15.957 patients (10% were classified as EOCRC, which is similar to our group) comparing surgical results [22]. They found that, even though young patients had more advanced disease, this group seemed to have better surgical outcomes including less short-term complications, shorter hospital length of stay and lower 30-day mortality.

Another study reported a comparison of 7538 patients operated for rectal cancer, looking for differences between young and elder patients [23]. Even though they found that young patients had a lower 30-day complication rate and shorter hospital stay, these differences lacked statistical significance on the multivariate analysis.

Another study including 162 patients with rectal cancer also failed to show different postoperative outcomes between the two groups [24]. In our study, young patients had worse postoperative results, which can be partially explained by the fact that they had more advanced tumors.

Diagnosis of advanced stage CRC among younger patients has already been extensively described in many papers addressing EOCRC [12, 15, 25, 26]. Furthermore, the American Cancer Society screening guidelines have suggested that young people are 58% more likely to get diagnosed too late. The American Gastroenterological Association has recently submitted new guidelines addressing EOCRC and the importance of performing diagnostic procedures to young patients who present with symptoms that could suggest the presence of colorectal neoplasia (such as rectal bleeding and weight loss, among others) [27]. It has also stated the importance of considering certain aspects of these patients that must be handled differently than in elder patients (for example, the necessity of preserving fertility in young women subjected to neoadjuvant therapy for advanced rectal cancer). However, we believe that studying only the symptomatic patients might prove to be insufficient because symptoms

usually arise when the disease is advanced, and therefore, have worse prognosis, with an overall 5-year survival higher than 90% when diagnosed with localized disease, but less than 12% when they have distant metastases [28].

Other authors have linked the impact of family history-based screening strategies for early detection of EOCRC [29]. However, as previously mentioned, this will probably be of little help, as most tumors in this population are sporadic. In our experience, two of the patients had a history of a direct relative with colorectal tumors, and both were diagnosed at an early stage of the disease.

A further study of this cohort should be focused in the analysis of molecular features of tumors in young patients. A recent publication by Willauer et all. addressing such matters found that tumors in EOCRC patients seem to be molecularly different from those found in the elder population, and even more, that differences might be found between different age ranges in the young [30]. Similar findings were published by other authors as well [31, 32]. Adding these tumor characteristics to what we found in the results of surgery might help us to better understand the behavior of the disease and consequently, find answers to current questions.

This study has limitations. First of all, its retrospective nature and it was conducted in a single academic center. Additionally, it may be underpowered due to the relatively low number of EOCRC patients. However, the differences showed in terms of the distribution of the disease as well as tumor stages and postoperative complications have not been fully described between EOCRC and AOCRC patients, as stated before. Consequently, these findings become relevant and encourage further studies on these subjects. To our knowledge, it is the first study on this matter in Latin-American patients, which may show a distinct behavior in terms of CRC natural history.

In conclusion, EOCRC patients showed some distinct features in terms of disease location, tumor stage and postoperative complications when compared to AOCRC patients. More studies on the behavior and natural history of CRC among young subjects are needed.

Availability of data and material. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval. This paper was approved by the ethics committee of the institution and written consent was provided by all the patients involved. Permission is granted to reproduce material of other sources.

Consent to participate. Freely-given, informed consent to participate in the study has been obtained from all participants in the present study.

Consent for publication. Consent for relevant data publication was obtained from all individual participants included in the study.

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