DOI: 10.4274/tjcd.galenos.2021.2021-3-1
Turk J Colorectal Dis 2021;31:174-181

RESEARCH ARTICLE

Early-Onset Colorectal Cancer in Younger Patients with a More Advanced Stage and Worse Postoperative Results: A Retrospective Review

Daha İleri Evre ve Daha Kötü Postoperatif Sonuçlara Sahip Genç Hastalarda Erken Başlangıçlı Kolorektal Kanser: Retrospektif Bir İnceleme

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ABSTRACT

Aim: The incidence of colorectal tumors in young patients has been rising lately, and current investigations focus on the causes and prognosis in these patients. The objective of this publication is to analyze the results of the 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. Patients were divided into two categories, early-onset colorectal cancer (EOCRC) (younger than 50 years old) and average-onset CRC (AOCRC) (those on age for CRC screening), focusing on disease stage and postoperative outcomes.

Results: Two hundred and seven patients were included: 32 in the EOCRC group and 175 in the AOCRC group. The median age was 42.10 years [standard deviation (SD) =5.74] and 65.38 years (SD =7.19), respectively. Dyslipidemia was more prevalent in the AOCRC group. The EOCRC group had more tumors in the upper rectum (28.13% vs. 8%; p=0.001) and transverse colon (21.88% vs. 10.29%; p=0.06) and 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. The EOCRC group had significantly more stage IV tumors (18.75% vs. 5.13%; p=0.01), and 46.86% of patients in this group had an advanced disease at the time of surgery.

Conclusion: Patients in the EOCRC group are diagnosed at more advanced stages and show differences in tumor location. Complications including the need for reoperation are more frequent in this group.

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

ÖZ

Amaç: Son zamanlarda genç hastalarda kolorektal tümör insidansı artmakta olup, güncel araştırmalar bunun nedenlerini ve prognozunu belirlemeye yöneliktir. Bu derlemenin amacı, genç hastalarda cerrahi tedavi sonuçlarını ve tümör evrelerini analiz etmek ve bunları yaşlı bireylerle karşılaştırmaktır.

Yöntem: Bu derlemede, 2015-2020 yılları arasında tek bir kurumda kolorektal adenokarsinom ameliyatı geçiren hastaların retrospektif bir analizi yapıldı. Hastalar iki kategoriye ayrılarak hastalık evresine ve ameliyat sonrası sonuçlara odaklanıldı: Elli yaşından genç hastalardaki erken başlangıçlı kolorektal kanserler (EOCRC) ve kolorektal kanser taramasının yapıldığı yaştaki hastalarda ortaya çıkan ortalama başlangıçlı kolorektal kanserler (AOCRC).

Bulgular: Otuz ikisi EOCRC grubunda olmak üzere 207 hasta dahil edildi. Ortanca yaş sırasıyla 42,10 [standart sapma (SS) =5,74] ve 65,38 (SS =7,19) idi. AOCRC grubunda dislipidemi daha yaygındı. EOCRC grubunda daha fazla üst rektum (%28,13'e karşı %8, p=0,001) ve transvers kolon (%21,88'e karşı %10,29, p=0,06) tümörleri vardı, komplikasyon oranları (%43,75'e karşı %28, p=0,07) ve yeniden operasyon oranları (18,75'e karşı %7,43, p=0,04) daha yüksekti. Ayrıca, majör komplikasyonlar genç hastalarda daha sıktı. EOCRC grubu önemli ölçüde daha fazla evre IV tümör ile ilişkili idi (%18,75'e karşı %5,13, p=0,01) ve bu hastaların %46,86'sında ameliyat sırasında ilerlemiş hastalık mevcuttu.

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Received/Geliş Tarihi: 07.03.2021 **Accepted/Kabul Tarihi:** 04.05.2021

Sonuç: Erken başlangıçlı kolorektal kanserler hastalığın daha ileri evrelerinde teşhis edilir ve tümör yerleşiminde farklılıklar gösterir. Bu grupta tekrar ameliyat gereksinimi gibi komplikasyonlar daha sık görülmektedir.
Anahtar Kelimeler: Kolorektal adenokarsinom, erken başlangıç, tarama stratejileri, kolonoskopi, ileri evre

Introduction

Worldwide, colorectal cancer (CRC) is the third most common cancer in both males and females, preceded by breast and lung tumors. It is also the second cause of cancer-related deaths.[1]

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

However, the increase in CRC among younger patients, a trend formerly addressed as "early-onset CRC" (EOCRC), has caused a rising concern.[6] Screening in patients aged 45 to 49 years is considered 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 excluded from the screening strategies. Consequently, they may consult at an advanced stage, usually when they are overtly symptomatic. It has been estimated that, by 2030, in patients younger than 34 years old, the CRC incidence rate will rise by 90% to 124%.[7,8] Although some guidelines recommend early CRC screening[9], the impact of this new tendency and the way to prevent tumor development in this population remain unclear.

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

Materials and Methods

Study Design and Population

We undertook a cross-sectional study at an academic hospital in 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 tumors and malignant tumors other than colorectal adenocarcinoma and those diagnosed with colorectal adenocarcinoma beyond 75 years of age.

Data Extraction

Patients who fulfilled the inclusion criteria were further classified into two groups according to the age of CRC diagnosis: the EOCRC group included patients younger than 50 years, and the AOCRC group included patients aged between 50 and 75 years. The medical history of each patient was reviewed, and the following clinical comorbidity data were collected: hypertension, dyslipidemia, diabetes mellitus, smoking, chronic obstructive pulmonary disease, chronic kidney disease, and history of abdominal surgeries. The tumor's location and stage were recorded according to the American Joint Committee on Cancer guidelines.[10] Surgery charts were also reviewed, and information on whether the surgery was urgent was retrieved for further analysis. 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 tumor complications: intestinal obstruction, hemorrhage, or tumor perforation.

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

Statistical Analysis

Analyses were conducted using STATA (v11.1, StataCorp, College Station, Texas USA). The categorical variables are described as percentages, whereas numerical variables are described as median with 25%-75% interquartile range. Chi-square and Mann-Whitney U tests were used for comparing the categorical variables and continuous numerical variables, respectively. Odds ratio with 95% confidence intervals were calculated. A multivariable analysis using a logistic regression model was performed including all the variables compared with a p value less than 0.1. A p value less than 0.05 was considered statistically significant. Our primary outcome variable was overall complication prevalence. Other variables comparing between EOCRC and AOCRC groups (p value <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, of which 207 patients were included in the analysis (Figure 1).

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

Moreover, symptomatic presentation varied in both groups (Table 2). In the EOCRC group, 6% of the patients (2/32) were diagnosed using screening methods, whereas 94% were diagnosed based on symptomatic presentations. Five patients (15.6%) had an acute complication, which required urgent surgery. However, in the AOCRC group, 36.5% of the patients were diagnosed using screening methods, and only 6.8% underwent urgent surgery for acute complications.

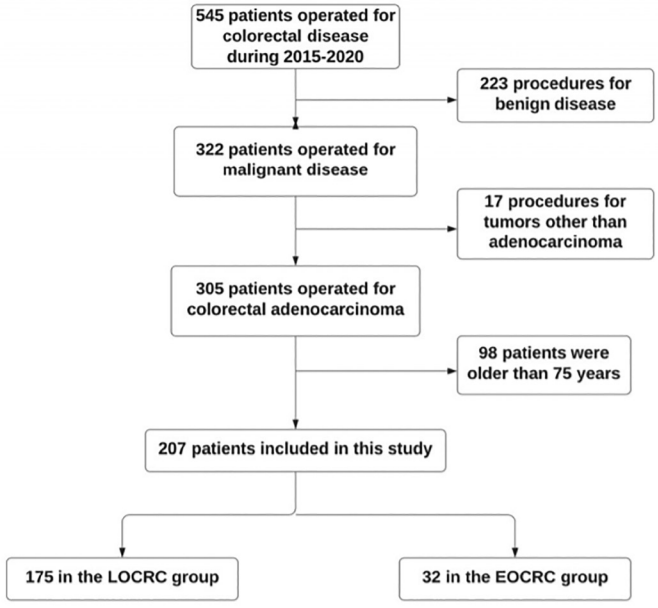

Figure 1. Patient selection

Table 1. Patient characteristics

	EOCRC (N=32) (%, n)	AOCRC (N=175) (%, n)	OR (CI 95%)	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

EOCRC: Early-onset colorectal cancer, AOCRC: Average-onset colorectal cancer, OR: Odds ratio

Overall, 6.25% of the patients (2/32) in the EOCRC cohort had a history of a first-degree family member with CRC. The two patients were diagnosed at an early stage following 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 reintervention 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 reoperation for surgery-related complications: two patients due to hemoperitoneum, one due to evisceration, one due to bowel obstruction, and two patients due to major anastomotic leaks. 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 had postoperative myocardial infarction; two had pneumonia; two had a metastatic disease a month after surgery.

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

Table 4 describes the comparison of tumor 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

Table 2. Presenting symptoms

	EOCRC (%, n/N)	AOCRC (%, n/N)
Screening (n, %)	6 (2/32)	36.5 (64/175)
Nonspecific 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 and weight loss)	9.3 (3/32)	11.4 (20/175)
Acute complications (hemorrhage, bowel obstruction, and perforated tumor)	15.6 (5/32)	6.8 (12/175)

EOCRC: Early-onset colorectal cancer, AOCRC: Average-onset colorectal cancer

Table 3. Operative data

	EOCRC (%, n/N)	AOCRC (%, n/N)	OR (CI 95%)	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
Reoperation rate	18.75 (6/32)	7.43 (13/175)	2.87 (1-8.34)	0.04

EOCRC: Early-onset colorectal cancer, AOCRC: Average-onset colorectal cancer, OR: Odds ratio

the AOCRC group were operated for early-onset tumors (stage 0, I, or IIA of the AJCC classification), whereas 46.86% of the EOCRC group had advanced diseases (stages IIB or more of the AJCC classification) at the time of the operation.

On multivariable analysis, the location of the tumor at the upper rectum and its stage were significantly different between patients with EOCRC and AOCRC (Table 5).

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 patients. We did not find significant differences in terms of comorbidities among the two groups, except for dyslipidemia, which was more frequent in the AOCRC group (33.71% vs. 9.38%; p=0.006). The need for neoadjuvant therapy was significantly higher in the EOCRC group (15.63% vs. 4.57%; p=0.01), which is consistent with the fact that this group presented with more advanced tumors.

Discussion

Despite the current efforts to understand the causes underlying EOCRC, most reasons for this new presentation remain unclear.[12] Many of these patients do not show the traditional risk factors for CRC (e.g., smoking).[13,14] Although familial predisposition is detected in up to 25% of these patients, most of the tumors seem 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, this new tendency of CRC affecting younger individuals represents a major concern for the medical community, because, lately, the incidence of colon and rectum tumors has significantly decreased in older patients, whereas it has been rising in patients younger than 50 years old.[17]

This study found some interesting results related to the differences between the EOCRC and AOCRC groups. First,

Table 4. Tumor stage

Stage	EOCRC (%, n/N)	AOCRC (%, n/N)	OR (CI 95%)	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

EOCRC: Early-onset colorectal cancer, AOCRC: Average-onset colorectal cancer, OR: Odds ratio, N/A: Not applicable, CI: Confidence interval

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)

AJCC: The American Joint Committee on Cancer

young patients 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] This finding led to suggesting sigmoidoscopy as a screening strategy for these patients. However, such a diagnostic method 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], although other studies found a significantly lower incidence of EOCRC compared with elder patients.[21]

Our EOCRC group showed a higher proportion of postoperative complications, and consequently, a higher proportion of patients required reoperation. Publications on comparing CRC surgery-associated morbidities in young and older patients are scarce, and the results are controversial. The study by Hanna et al.[22] including 15,957 patients (10% were classified as EOCRC, which is similar to our group) compared the surgical results. They found that although young patients had a more advanced disease, this group had better surgical outcomes, including less short-term complications, shorter hospital length of stay, and lower 30-day mortality.

Another study, including 7,538 patients, compared between the differences in young and elderly patients operated for rectal cancer.[23] Although 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 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.

The 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 in young patients presenting with symptoms that could suggest colorectal neoplasia (e.g., rectal bleeding and weight loss).[27] It has also stated the importance of handling certain aspects in these young patients differently than the elderly (e.g., the necessity of preserving fertility in young women subjected to neoadjuvant therapy for advanced rectal cancer). However, we believe that studying the symptomatic patients only might prove insufficient because symptoms usually appear when the disease is advanced, and therefore, these patients have a worse prognosis, with an overall five-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 the 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 study, two 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 on analyzing the molecular features of tumors in young patients. A recent publication by Willauer et al.[30] found that tumors in patients with EOCRC seem molecularly different from those found in the elderly population, and even more, differences might be found between different age ranges in the younger population. Similar findings were published by other authors as well.[31,32] Putting these tumor characteristics into consideration, in addition to our results regarding the surgery, might help us better understand the behavior of the disease and, consequently, find answers to the current questions.

Study Limitations

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

Conclusion

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

Ethics

Ethics Committee Approval: This paper was approved by the ethics committee of the institution, and written consent was provided by all patients.

Informed Consent: Obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: N.L.A., M.S., P.O.S., Concept: N.L.A., M.S., P.O.S., Design: N.L.A., R.O., A.C., M.S., P.O.S., Data Collection or Processing: N.L.A., R.O., A.C., J.L., F.V., A.H., Analysis or Interpretation: N.L.A., R.O., A.C., J.L., F.V., A.H., Literature Search: N.L.A., J.L., F.V., A.H., Writing: N.L.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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