Distinctive features of early onset colorectal cancer.

A tertiary hospital experience

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Yusuf Sevim*, Yunus Donder*, Mehmet Patmano**

**Department of General Surgery, Kayseri Faculty of Medicine, University of Health Sciences, Kayseri City Health Practice and Research Center, Kayseri, Turkey.*
****Kayseri City Training and Research Hospital, General Surgery, Kayseri, Turkey.*

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PURPOSE: *The colorectal cancer rate under the age 50 years tends to increase, and we aimed to identify the general features of early-onset colorectal cancer and the differences between cancer in younger and older patients.*
METHODS: *The patients with colorectal cancer who underwent surgery between 2016 and 2021 were included. The subjects were divided into two groups by age under and over 50. Demographic, clinical, and pathological features of early-onset colorectal cancer were identified retrospectively.*
RESULTS: *226 patients were included in our study, and 36 (15.9%) of them were under 50 years old. The mean age of the patients in the early-onset colorectal cancer group was 43.1±5.9 years. Most of the young patients were male, similar to the elderly CRC group. The tumors in the EOCRC group were significantly located left site (86.1% vs. 66.8%) compared to elderly CRC. Most of the tumors were medium or poorly differentiated (80.6%). The numbers of removed lymph nodes were significantly higher in the EOCRC group compared to the elderly CRC group (p<0.05), and postoperative complications were detected lower in EOCRC.*
CONCLUSIONS: *The incidence of EOCRC continues to increase. There is no information about the exact reason for this increase. Comprehensive studies are needed to reveal general characteristics, genetic background, and predisposing factors in cancer formation and figure out the increase in the incidence.*

KEY WORDS: Colorectal Cancer, Hereditary Colorectal Cancer, Early Onset, Young Adults

Introduction

Colorectal cancer (CRC) is the third most commonly occurring cancer in men and the second most commonly occurring cancer in women and accounts for approximately 10% of all cancers [1]. Interestingly, the frequency of CRC, predominantly rectal cancer, increases in young people (age <50 years) while decreases in older people over 50 years. Although the incidence of CRC under 50 years of age increased by an average of 2.1% annually from 1992 to 2012 in both genders, this increase continues today. The SEER database shows 9.2 and 8.2 per 100000 by the year of 2019 for men and women respectively [2]. Therefore, we aimed to identify general features of early-onset colorectal cancer (EOCRC) and differences between cancer in younger and older patients.

Materials and Methods

The patients with colorectal cancer who underwent surgery between 2016 and 2021 with available data were included in the study. Patients with missing data and who had known hereditary cancer syndrome and other organs tumors were excluded from the study. The subjects were divided into two groups by age under and over 50 years as EOCRC (36 patients, 15.93%) and

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Correspondence to: Yusuf Sevim, M.D., University of Health Sciences, Kayseri Faculty of Medicine, Kayseri City Health Research Center, Department of General Surgery, Seker Mah. Muhsin YAZICIOGLU Bulvari, No:77 38080 Kocasinan, Kayseri, Turkey (E-mail: yusufsevim@gmail.com)

late-onset CRC (LOCRC) (190 patients, 84.07%). Demographic, clinical, and pathological features of the patients were recorded retrospectively by using the hospital's automated database. Also, we compared the groups in terms of that features such as tumor localization, complication rates, and mismatch repair genes.

Statistical analysis of data was performed by using IBM SPSS Statistics for Windows, version XX (IBM Corp., Armonk, N.Y., USA). Categorical variables were summarized as numbers and percentages, and continuous measurements as mean, deviation, and minimum-maximum. The Chi-square test and Fischer's Precision Test were used to compare categorical variables. Shapiro-Wilk test was used to determine whether the parameters in the study showed a normal distribution. Mann Whitney U test was used for the parameters that did not show normal distribution. Statistical significance level was taken as 0.05 in all tests.

Results

Colorectal cancer (CRC) diagnosed 226 patients who were operated on between 2016 and 2021 were included in our study. The mean age of the subjects was 65±14.06, and 142 (62.8%) of them were male. There were 36 patients with EOCRC (15.9%). The mean age of the patients in the EOCRC group was 43.1±5.9 years. Similarly to LOCRC, most of the subjects were male (n:21, 58.3%). Nine patients (25%) had a concomitant disease, and the most co-morbidity was hypertension (3 patients [8.3%] in EOCRC group vs 43 patients [22.6%] in LOCRC). Concomitant diseases were found significantly higher in the elderly CRC group (p<0.001). Also, the number of patients in the LOCRC group evaluated as ASA III and above was greater than the EOCRC group (p<0.001). There were no significant differences in terms of tumor markers between the groups (p>0.05). Significant lower albumin (p=0.245) and elevated BUN levels (p=0.008) were identified in the elderly CRC group compared to the EOCRC group. No other blood biochemical parameters were causing a significant difference. The tumors in the EOCRC group were located left site primarily (n:31, 86.1%), and this was significantly higher compared to elderly CRC (p=0.021). Stage IV CRC was diagnosed in 7 patients (19.4%). Emergency surgery was performed higher in the elderly CRC group than EOCRC (n=84, 44.2 % vs. n=10, 27.8%), but this difference was not statistically significant (p=0.067). Most of the tumors were medium or poorly differentiated (n:29, 80.6%) (Table I). The number of removed lymph nodes was 23±14.1 in the EOCRC group, and it was significantly higher than LOCRC (18.6±11.3, p=0.019). However, there was no significant difference regarding metastatic lymph nodes between the groups. Among the mismatch repair genes, MLH1 was found negative more in LOCRC group (14.6% vs 9.1%, p=0.032). Postoperative complications were not developed in 24 (66.7%) and 79 (41.6%) patients in groups EOCRC and LOCRC, respectively, and this difference was statistically significant (p=0.006).

Discussion

Colorectal cancer is the third most common cancer worldwide and is a disease that can progress mortally [3]. Besides the mortality, colorectal cancer and surgery can

TABLE I - *Some properties of the study groups.*

	EOCRC Group		LOCRC Group		
	n	%	n	%	p
Age (mean±SD)	43.1±5.9	69.7±10.8			
Gender F	15	41.7%	69	36.3%	
M	21	58.3%	121	63.7%	0.542
Localization Left sided*	31	86.1%	127	66.8%	0.028
Concomitant disease	9	25.0%	132	69.5%	<0.001
ASA 3	10	27.8%	129	67.9%	<0.001
Metastatic disease	7	19.4%	22	11.6%	0.273
Neoadjuvant therapy	10	27.8%	30	15.8%	0.084
Postoperative intensive care	13	36.1%	157	82.6%	<0.001
Histopathological diagnosis					0.438
Adenocarcinoma	29	80.6%	163	85.8%	
Mucinous cell carcinoma	6	16.7%	21	1.1%	
Others	1	2.7%	6	13.1%	
Differentiation					0.019
Medium and poor	29	80.6%	121	63.7%	

*Splenic flexure and its distal. EOCRC: Early-onset colorectal cancer, LOCRC: Late-onset colorectal cancer, CRC: colorectal cancer, SD: standard deviation. Fischer's Precision Test was used to compare the groups in terms of localization and metastatic disease, and chi-square test was used for the other parameters.

cause some major morbidities related with age and additional diseases [4]. Colorectal The incidence rate under 50 years of age has been increasing in recent years [5]. The incidence of EOCRC increased steadily at a rate of 2.1% per year from 1992 to 2012 and continues to increase. In terms of localization, it is seen that this increase is mostly caused by left-sided colon cancer and rectum cancer, as in our study (86.1%) [6].

When EOCRC and advanced age CRC are compared, it is seen that right-sided colon cancer is significantly higher in advanced age [7]. The underlying causes of this increase are multifactorial, such as genetic factors, environmental, and lifestyle changes.

The EOCRC, USA data, constitutes 11% of CRC in men and 10% in women. It is the second most common cancer seen under the age of 50 and is the third leading cause of cancer-related deaths [8]. Considering that the number of patients was limited and it was single-center, this rate was 15.9% in our study, and most of the patients were male. Although the course of CRC observed at an early age has fluctuated over the years, it has continued to increase. When the updated data in SEER is examined, the annual increase in EOCRC from 2000 to 2013 was 1.5%, but no significant increase was observed in the data between 2015 and 2018. When examined in terms of gender-dependent, it is seen that the increase in the male gender continues, but it decreases somewhat in females [9]. 75.2% of EOCRC is seen between the ages of 40 and 49, and similar to our study, the median age is 44 in CRCs below the age of 50 [10]. CRC at a young age is diagnosed when patients are more symptomatic; incidental diagnosis or diagnosis after screening programs are less common. In the literature, the rate of symptomatic patients is 86.4%, and the most common symptom is rectal bleeding with 50.8%. This is followed by abdominal pain (32.5%) and changes in bowel habits (18.0%) [11]. Mucinous cell carcinoma is detected between 11-14% for EOCRC [11-13]. In our study, mostly adenocarcinoma was detected in the histopathological examination of the specimens, and mucinous cell carcinoma was diagnosed in 16.7% of the cases. This rate may have been high in our study since the number of patients in our study was limited, and data from a localized center were used. Mucinous type cancer consequently is detected more frequently at an early age, but it can be said that this frequency is not significant.

When evaluated according to stages in EOCRC, it tends to present more in advanced stages. In a study conducted using the SEER database, it was observed that 43.9% of the patients were admitted with regional disease and 27.9% with distant metastasis [13]. In our study, although the metastatic disease was not found to be significant in the EOCRC group, it was at a higher rate than the patient group over 50 years of age. We predict that this frequency will be significant with our young age patient population increase. The high rate of symptomatic admission is compatible with the diagnosis at an advanced stage. In another study, it was observed that 66.2% of the patients were stage III and IV [12]. Also, the patients are more likely to present with synchronous and metachronous tumors [14].

Contrary to expectations, survival is better in patients aged 50 years with a later diagnosis. This may be because, as in our study, there were fewer comorbid diseases. In this patient group, the need for intensive care is also less. Another important issue in the EOCRC is the reason for the increase of cancer at an early age. The exact reason for this increase has not been revealed, but many factors that are thought to have an effect have been tried to be revealed. First of all, positive family history is more common in this age group. Young age, strong family history, and multiple primary tumors may be associated with hereditary colon cancer syndromes, especially Lynch Syndrome. These do not include all cases in the EOCRC. Cancer screening starts at an early age in those who have a family history or have a family member diagnosed with hereditary cancer. Since premalignant lesions are intervened in the screened cases, cancer formation is prevented. Besides, the number of diagnoses may be increasing with the increasing use of colonoscopic procedures at younger ages. So, hereditary and familial CRC cases are not alone in increasing EOCRC. Also, sedentary life and obesity affect the development of CRC cancer [15]. Weight gain, especially in the young middle age range, increases the risk.

On the contrary, the risk of CRC decreases with regular exercise. Like other risk factors, smoking and heavy-moderate alcohol consumption, increased consumption of processed foods, inflammatory diet, increased folate consumption, genetically modified foods, insecticide and radiation exposure, intra-uterine and childhood antibiotic exposure are also associated with the development of CRC [16]. Consequently, EOCRC development is multifactorial. In addition to these, carcinogenesis was tried to be studied at EOCRC. The microsatellite instability pathway was found to be prominent in young patients. We can associate this frequency with Lynch syndrome. We can also say low CpG island methylator phenotype for CRC was observed at a young age. When the microsatellite and chromosomally stable pathway is activated, more distal colon and rectal cancers are not observed, and this location is more dominant at younger ages [17]. As a result, a dominant cancer pathway could not be detected in EOCRC; it can be described as polygenic [15, 18].

Conclusion

CRC attracts attention as a disease that has begun to affect the younger population more than the elderly. With the increasing interest in this subject and the increase in research, the general framework of EOCRC

disease is tried to be drawn, and carcinogenesis and risk factors are tried to be revealed. If we can reveal the risk factors for young age more clearly with the increasing data and information, we can reveal the screening criteria for this patient group in which we have detected advanced stage and prevented the development of cancer with earlier screening.

Riassunto

L'incidenza del cancro del colon-retto al di sotto dei 50 anni tende, e ci siamo proposti di identificare le caratteristiche generali delle forme ad esordio precoce e le differenze nei pazienti più giovani e più anziani.
Sono stati inclusi nell'indagine retrospettiva 226 pazienti con carcinoma colorettale operati tra il 2016 e il 2021, dividendoli in due gruppi per età inferiore o superiore ai 50 anni. Sono state identificate le caratteristiche demografiche, cliniche e patologiche delle forme di carcinoma colorettale ad esordio precoce.
Dei 226 pazienti, 36 (15,9%) di loro avevano meno di 50 anni. L'età media dei pazienti nel gruppo con carcinoma colorettale ad esordio precoce era di 43,1 ± 5,9 anni. La maggior parte dei giovani pazienti era di sesso maschile, simile al gruppo CRC anziano. I tumori nel gruppo EOCRC erano prevalentemente localizzati nella sede di sinistra (86,1% vs. 66,8%) rispetto al CRC anziano. La maggior parte dei tumori era media o scarsamente differenziata (80,6%). Il numero di linfonodi rimossi era significativamente più alto nel gruppo EOCRC rispetto al gruppo CRC anziano ($p < 0,05$) e le complicanze postoperatorie sono state rilevate inferiori in EOCRC.
Conclusioni: L'incidenza di EOCRC continua ad aumentare. Non ci sono informazioni sul motivo esatto di questo aumento. Sono necessari studi completi per rivelare le caratteristiche generali, il background genetico e i fattori predisponenti nella formazione del cancro e capire l'aumento dell'incidenza.

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