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Clinicopathological features of early-onset colorectal cancer in Japanese patients: a single-center retrospective study

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Abstract

Background The incidence of early-onset colorectal cancer (EoCRC), defined as CRC diagnosed at < 50 years of age, is increasing globally. However, only a few studies are reported from Japan, and the clinicopathological features of EoCRC in Japanese patients remain unknown.

Methods We retrospectively investigated consecutive Japanese patients who were pathologically diagnosed with invasive CRC at our hospital from January 2015 to December 2021. Patients were categorized into those who were diagnosed with CRC at < 50 years (early-onset group) and ≥ 50 years (late-onset group) of age. We compared the clinicopathological findings between the two groups.

Results The analysis included 731 patients. EoCRC was diagnosed in 46 patients (6.3% of all patients). Of them, 41.3% demonstrated a positive fecal immunochemical test (FIT) for CRC screening as a diagnostic opportunity, which was significantly higher than that in the late-onset group ($p = 0.032$). Rectal cancer was significantly more prevalent in the early-onset group compared to the late-onset group (45.7% vs. 26.4%, $p < 001$). No significant difference in the rate of clinical stage at presentation was found between the two groups. Furthermore, patients with positive FIT were more likely diagnosed at an earlier stage.

Conclusions EoCRC among Japanese patients tends to occur on the rectum and is more frequently diagnosed with FIT screening compared to late-onset CRC. Patients with advanced stage were diagnosed by symptoms, indicating the usefulness of FIT screening in diagnosing EoCRC at an early stage.

Keywords Colorectal cancer, Early-onset, Japanese

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Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second leading cause of cancer-related death globally [1]. In Japan, the prevalence and mortality rates of CRC have been reportedly high [2]. In recent years, the incidence of early-onset CRC (EoCRC), a CRC diagnosed at < 50 years of age, has been increasing globally, especially among high-income countries [3–5]. EoCRC accounts for approximately 10% of all patients with CRC, and > 10% of all colon cancers and 25% of all rectal cancers are estimated to be diagnosed in young patients by 2030 [6, 7]. Various risk factors, such as genetics, westernized diet, obesity, alcohol consumption, gut microbiome, and racial disparities, have been involved in developing of EoCRC [5, 8–12]. However, the exact underlying mechanisms remain unclear. The majority of EoCRC appear to arise sporadically, and approximately 25% of EoCRC exhibited a family history of CRC [13, 14]. EoCRC has been more predominantly located in the left-sided colon, especially the rectum, and has a higher proportion of poorer cell differentiation, including signet-ring cell carcinoma or mucinous carcinoma [15–17]. Furthermore, EoCRC is frequently diagnosed at an advanced stage compared with late-onset CRC (diagnosed at ≥ 50 years of age) [15].

EoCRC is a global concern and an important topic of investigation because of the significant loss to young people when diagnosed with CRC. However, only a few studies are reported from Japan [18, 19], and the clinicopathological features of EoCRC in Japanese patients remain unknown.

In Japan, population-based CRC screening using a 2-day fecal immunochemical test (FIT) begins at the age of 40 years [20]. This differs from the United States, most European countries, and Asia-Pacific countries, except Japan, which has a starting age of 45–50 years [21–23]. Additionally, the rate of obesity, which is one of the risk factors of CRC, is lower in Japan than in Western countries [24]. The characteristics of EoCRC in the Japanese population may vary from previous reports due to various background differences from other countries. Additionally, investigating the clinicopathological features of EoCRC in the Japanese population is important to detect and treat patients who are expected to increase in number. This study aimed to analyze patients diagnosed with CRC at our hospital and investigate the clinicopathological findings of EoCRC among Japanese patients.

Methods

Study design and patients

This single-center, retrospective study was conducted at Tonan Hospital, Sapporo, Japan. The institutional review board of Tonan Hospital approved study protocol (approved number 1-21-1), conducted under the World Medical Association Declaration of Helsinki. All participants were given opportunities to decline participation in this study using the opt-out method on the hospital's website although written informed consent was waved because of the retrospective study design.

This study included consecutive patients diagnosed with CRC at Tonan Hospital in Japan from January 2015 to December 2021. The inclusion criteria were Asian Japanese patients who were pathologically diagnosed with CRC in our hospital. The exclusion criteria were patients with hereditary diseases, including familial adenomatous polyposis, inflammatory bowel disease, a CRC history, and stage 0 diagnosis (high-grade dysplasia). This study excluded metachronous CRC detected within the enrollment period and adopted a more advanced lesion when synchronous CRC was diagnosed. Synchronous CRC was defined as CRC diagnosed within 1 year.

Outcome measures

The patients were categorized into those diagnosed with CRC at < 50 years (early-onset group) and ≥ 50 years (late-onset group) of age. We compared the patient's background, CRC location, pathological findings, clinical stage at presentation, and prognosis between the two groups. Obesity was defined as individuals with a body mass index (BMI) of ≥ 25 kg/m2 according to the guidelines of the Japan Society for the Study of Obesity [24], and a family history of CRC was defined as the presence of CRC diagnosis in a first-degree relative. Alcohol consumption was defined as individuals who drink alcohol at least thrice weekly and smoking was defined as current or former regular use. This study defines CRC location as a right-sided colon, including the cecum, ascending colon, and transverse colon, and a left-sided colon, including the descending colon, sigmoid colon, and rectum. Histopathological results were classified into the differentiated-type (well differentiated, moderately differentiated, and papillary adenocarcinoma) and undifferentiated-type (poorly differentiated, mucinous adenocarcinoma, and signet-ring cell carcinoma) based on the predominant histology. Clinical stages were followed under the Japanese guidelines [25]. This study defines stage I and II as non-advanced stages and III and IV as advanced stages [26]. Concerning the prognosis, we analyzed the overall survival and disease-specific survival of patients in the advanced and non-advanced stages. Overall survival and disease-specific survival were defined as the time from clinical stage confirmation to death. For prognostic analysis, patients who received treatment according to the Japanese guidelines [27] were analyzed, and those who did not receive treatment were excluded from the study. For patients with Stage I, endoscopic resection was indicated for slightly invasive T1 CRC and surgical resection was performed for deep invasive T1 and T2 CRC. Surgical

resection was performed for Stages II and III patients. Furthermore, postoperative adjuvant chemotherapy was performed for patients with Stages III and II with a high risk of recurrence. Systemic chemotherapy was performed for unresectable Stage IV patients, while those with resectable metastasis underwent surgical resection combined with systemic chemotherapy. Additionally, we analyzed clinicopathological findings in the early-onset group between patients aged < 40 years for whom CRC screening is not recommended and ≥ 40 years for whom it is recommended in Japan.

Statistical analysis

EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria), was used for all statistical analysis [28]. Quantitative variables were expressed as the median, whereas categorical variables were presented as total numbers and percentages. Pearson's chi-squared test and Mann–Whitney U-test were applied as appropriate. Survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test. A p-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 1,207 patients with CRC were reviewed from January 2015 to December 2021. Of these patients, 476 were excluded for the following reasons: familial adenomatous polyposis ($n = 2$), inflammatory bowel diseases ($n = 2$), CRC history ($n = 35$), and stage 0 diagnosis ($n = 437$). Therefore, we analyzed 731 patients. A total of 46 patients (6.3%) were diagnosed at < 50 years of age and 685 (93.7%) at ≥ 50 years of age (Fig. 1). Table 1 shows baseline patient characteristics. Median age was 45 and 72 years in the early- and late-onset groups, respectively. The proportion of males was not significantly different between the two groups ($p = 0.779$). The rates of obesity were 30.4% and 23.8% in the early- and late-onset groups, respectively, with no significant difference ($p = 0.309$). The prevalence of hypertension, dyslipidemia, and diabetes mellitus was significantly higher in the late-onset than in the early-onset group ($p < 0.01$). Additionally, the percentage of patients with a medical history of malignancy, excluding CRC, was significantly higher in the late-onset group ($p < 0.01$). Regarding the diagnostic opportunity, FIT for CRC screening triggered CRC detection in 41.3% of the patients in the early-onset group, which was significantly higher than that in the late-onset group ($p = 0.032$). Conversely, significantly more patients were diagnosed due to screening or surveillance in the late-onset group

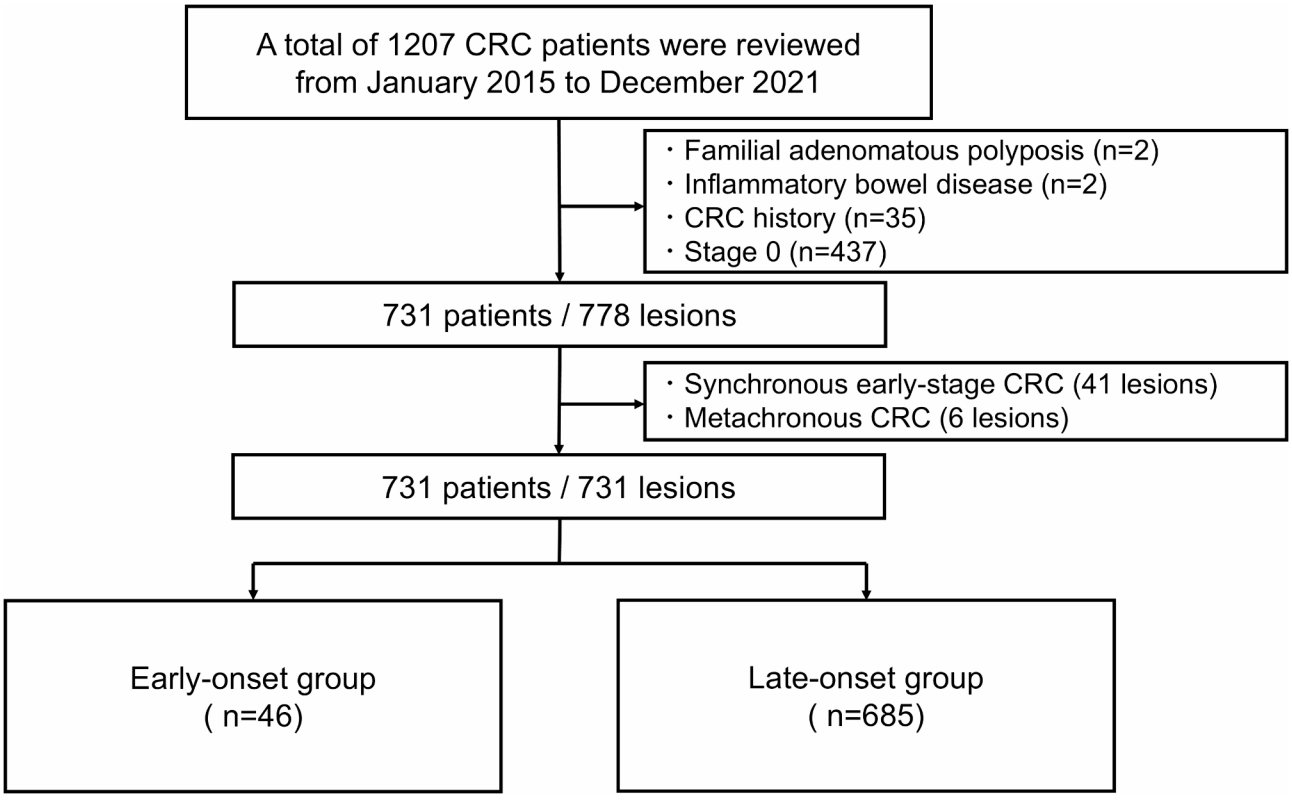

Fig. 1 Patient selection flow diagram for the study. Abbreviations: CRC: colorectal cancer

Table 1 Patients' characteristics

	Early-onset	Late-onset	*p*-value
	n **= 46 (%)**	***n*** **= 685 (%)**	
Median age (range)	45 (29–49)	72 (50–99)	< 0.01
Male / Female	24 / 22	372 / 313	0.779
Body mass index (≥ 25 kg/m2)	14 (30.4)	163 (23.8)	0.309
Comorbidity			
Hypertension	3 (6.5)	538 (49.3)	< 0.01
Dyslipidemia	6 (13.0)	402 (36.8)	< 0.01
Diabetes mellitus	4 (8.7)	266 (24.4)	< 0.01
Past history of malignancy (excluded CRC)	3 (6.5)	221 (20.3)	< 0.01
Diagnostic opportunity			
FIT positive	19 (41.3)	183 (26.7)	0.032
Screening / Surveillance	2 (4.3)	149 (21.8)	< 0.01
Symptoms	25 (54.3)	353 (51.5)	0.712
Family history of CRC	8 / 43 (18.6)	51 / 474 (10.8)	0.122
Alcohol consumption	19 / 43 (44.2)	294 / 656 (44.8)	0.936
Smoking	28 / 43 (65.1)	364 / 669 (54.4)	0.120

Abbreviation: CRC; colorectal cancer, FIT; fecal immunochemical test

Table 2 Clinicopathological features of all patients

	Early-onset	Late-onset	*p*-value
	n **= 46 (%)**	***n*** **= 685 (%)**	
Location			
Left-sided colon	33 (71.7)	416 (60.7)	0.138
Rectum	21 (45.7)	181 (26.4)	< 0.01
Pathology			
Predominantly differentiated-type	43 (93.5)	651 (95.0)	0.641
Stage			0.209
Non-advanced (I, II)	21 (45.7)	378 (55.2)	
Advanced (III, IV)	25 (54.3)	307 (44.8)	

Table 3 Clinical stage of patients with FIT and others as a diagnostic opportunity

	Early-onset		*p*-value	Late-onset		*p*-value
	FIT	Others		FIT	Others	
	n **= 19 (%)**	***n*** **= 27 (%)**		***n*** **= 183 (%)**	***n*** **= 502 (%)**	
Stage			0.048			< 0.01
Non-advanced	12 (63.2)	9 (33.3)		125 (68.3)	253 (50.4)	
Advanced	7 (36.8)	18 (66.7)		58 (31.7)	249 (49.6)	

Abbreviations: FIT; fecal immunochemical test

($p < 0.01$). The family history of CRC was 18.6% and 10.8% in the early- and late-onset groups, respectively, with no significant difference. No significant difference in alcohol consumption and smoking was found between the two groups.

Clinicopathological findings of CRC

In terms of CRC location, the rates of left-sided CRC were 71.7% and 60.7% in the early- and late-onset groups, respectively, with no significant differences (Table 2). However, the rate of rectal cancer in the early-onset was significantly higher than that in the late-onset group (45.7% vs. 26.4%, $p < 0.01$). Regarding the main histological type, the rates of predominantly differentiated-type were 93.5% and 95.0% in the early- and late-onset groups, respectively. No significant difference in the main component of CRC was found between the two groups ($p = 0.641$). Concerning the clinical stage, 45.7% and 55.2% in the early- and late-onset groups, respectively, were diagnosed at a non-advanced stage, with no significant difference ($p = 0.209$). In both groups, patients diagnosed at a non-advanced stage were more likely to have a positive FIT as a diagnostic opportunity (Table 3). Additionally, patients with advanced stage were more likely to be diagnosed by a cause other than positive FIT. In this study, 43 patients in the late-onset group were not treated due to various reasons, and these patients were excluded from the survival analysis. Endoscopic

resection was performed on 6 patients in the early-onset group and 74 patients in the late-onset group. Surgical resection was performed for 35 and 545 patients with Stages I to III CRC in the early- and late-onset group, respectively. Postoperative adjuvant chemotherapy was performed on 23 and 176 patients in the early- and late-onset group, respectively. Systemic chemotherapy was performed on 5 patients with unresectable Stage IV CRC and 6 recurrence patients with Stage I to III in the early-onset group. In the late-onset group, systemic chemotherapy was performed on 66 patients with unresectable Stage IV CRC and 63 recurrence patients with Stage I to III. Eleven patients with Stage IV with resectable metastasis in the late-onset group were treated by surgical resection and systemic chemotherapy. No significant difference in overall survival was found between the two groups (Fig. 2a, b). The median follow-up time was 1,327 days. Disease-specific survival rates were similar, with no significant difference between the two groups (Fig. 2c, d). Specific 3- and 5-years survival rates were examined. However, the results did not significantly differ. The prognosis was favorable in both groups when diagnosed at a non-advanced stage. The prognosis in patients with advanced stage appeared better in the early-onset group, although with no significant difference. Furthermore, for advanced-stage patients, the overall survival rates were analyzed separately for those who underwent surgery and those who received chemotherapy only. However, no significant difference was observed between the two groups (Supplementary Fig. 1). Regarding microsatellite instability (MSI), several patients were treated before the insurance coverage of MSI testing was approved in Japan. Only seven patients in the early-onset group were examined, one of whom had MSI-high. Moreover, 51 patients in the late-onset group were examined, one of whom had MSI-high.

Comparison between patients aged < 40 years and ≥ 40 years in the early-onset group

Patients in the early-onset groups were categorized into those aged < 40 years and patients ≥ 40 years for subgroup analysis, consisting of 14 and 32 patients, respectively (Table 4). The patients whose diagnostic opportunity was positive FIT were 1 (7.1%) and 18 (56.3%) among those aged < 40 years and ≥ 40 years, respectively, with significant differences ($p < 0.01$). Predominantly differentiated-type CRC demonstrated a significantly lower rate in patients aged < 40 years than in those aged ≥ 40 years ($p < 0.01$). The rates of non-advanced stage at presentation in patients aged < 40 and ≥ 40 years were 42.9% and 46.9%, respectively ($p = 0.803$).

Discussion

EoCRC was defined as CRC diagnosed before the age of 50 years, with this cutoff based on the general recommended age for CRC screening [29]. This study analyzed

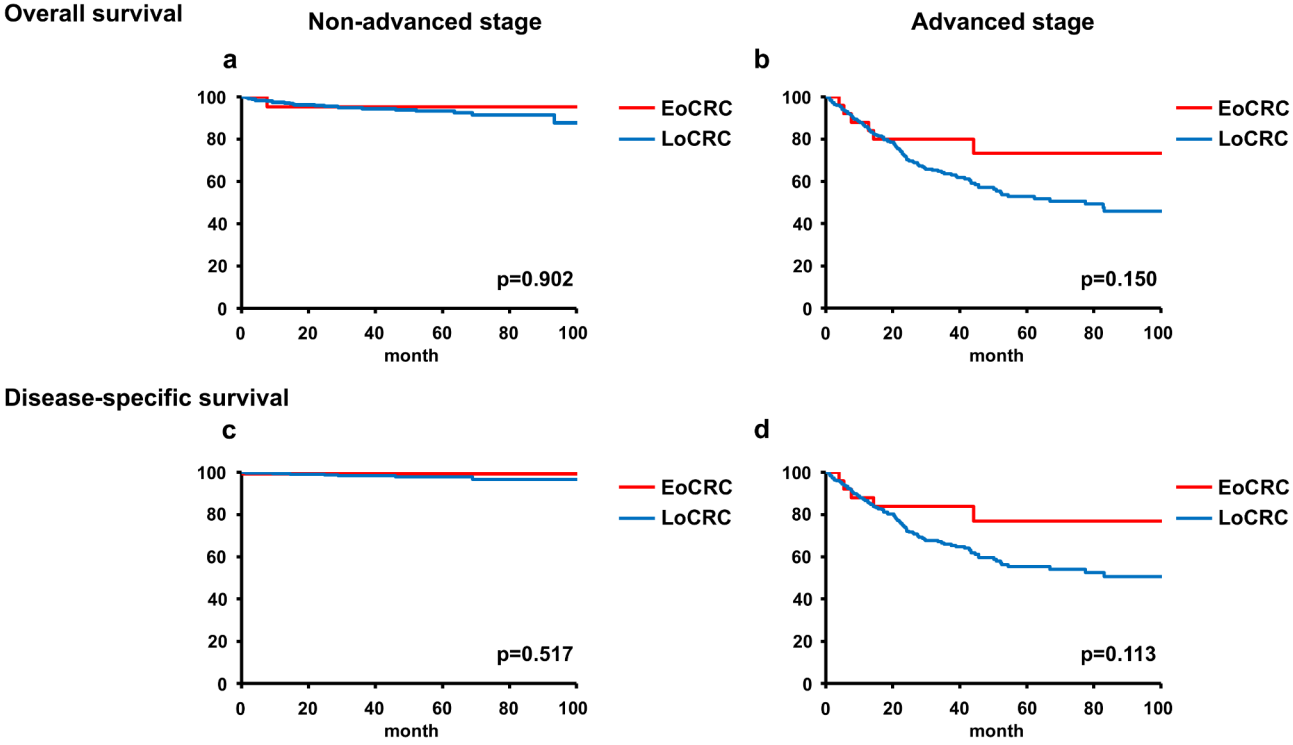

Fig. 2 Patient survival rate. The overall survival rate of non-advanced stage (**a**) and advanced stage (**b**). Disease-specific survival rate of non-advanced stage (**c**) and advanced stage (**d**)

Table 4 Comparison when divided at the age of 40 years in the early-onset group

	< 40 years	≥ 40 years	*p*-value
	n = 14 (%)	*n* = 32 (%)	
Diagnostic opportunity			
FIT positive	1 (7.1)	18 (56.3)	< 0.01
Screening / Surveillance	0 (0.0)	2 (6.3)	0.344
Symptoms	13 (92.9)	12 (37.5)	< 0.01
Location			
Left-sided colon	9 (70.6)	24 (81.7)	0.463
Rectum	6 (47.1)	15 (46.7)	0.803
Pathology			
Predominantly differentiated-type	11 (78.5)	32 (100)	< 0.01
Stage			0.803
Non-advanced	6 (42.9)	15 (46.9)	
Advanced	8 (57.1)	17 (53.1)	

Abbreviations: FIT; fecal immunochemical test

the clinicopathological features of EoCRC in a Japanese population. The percentage of obesity appeared slightly higher in the early-onset group, but with no significant difference. This study defined obesity as individuals with a BMI of ≥ 25 kg/m2 under the Japanese guidelines [24], whereas the World Health Organization defines obesity as a BMI of ≥ 30 kg/m2 [30]. Obesity with a BMI of ≥ 30 kg/m2 has been a significant risk factor for EoCRC in women [31]; however, the proportion of obesity with a BMI of ≥ 30 kg/m2 is low among Japanese individuals, accounting for only 4.1% of all patients in the study. The prevalence of hypertension, dyslipidemia, and diabetes mellitus as well as the history of malignancy was significantly higher in the late-onset group than in the early-onset group. These results were influenced by the aging. The early-onset group consisted of significantly more patients with positive FIT as a diagnostic opportunity compared to those in the late-onset group. Conversely, more patients in the late-onset group were diagnosed due to screening or surveillance. These results are not surprising because total colonoscopy (TCS) is frequently performed as a screening in clinical practice in Japan, especially in older patients. However, such opportunities are rare in younger individuals, and the results of this study indicate that CRC screening using FIT is important for them. Previous meta-analysis indicated a family history of CRC in first-degree relatives as a stronger risk factor for EoCRC [32]. The American Cancer Society guidelines suggest that TCS should begin at the age of 40 years or 10 years younger than the earliest diagnosed relatives if there is a first-degree relative diagnosed CRC before the age of 60 years for the individuals without hereditary CRC [33]. A recent study from Japan revealed a family history of CRC as a risk for CRC and advanced adenoma in young patients [34]. In this study, no statistically significant difference in the family history of CRC was reported between the two groups. However, a bias in the number of patients available for analysis existed, and the accuracy of these results remains unclear; thus, more detailed and numerous case studies are warranted.

Concerning the lesion location, rectal cancer was significantly more prevalent in the early-onset group than in the late-onset group. The mechanism that EoCRC tends to occur in the left-sided colon and rectum is unknown, but these findings were consistent with those previously reported [15–18]. Previous reports revealed that EoCRC tends to have poorer cell differentiation [15–17]. However, in this study, the majority of patients in both groups had predominantly differentiated-type CRC, with no significant difference between them. A significant difference in the rate of predominantly differentiated-type CRC was found in the early-onset group when compared patients aged < 40 years and ≥ 40 years, but the number of patients was too small to draw a definitive statement. A previous report from Japan has reported no difference in histology [18], indicating that differentiated-type CRC is the main histology in Japanese patients with EoCRC. However, only a few reports have been published; thus, further study with a large number of patients with EoCRC is desirable. Previous reports indicate that EoCRC is frequently diagnosed at an advanced stage [15, 35]; however, no significant difference in clinical stage was found between the early- and late-onset groups in this study. This difference from the previously reported results may be because the age for CRC screening using FIT begins at 40 of age in Japan. The early-onset group consisted of more patients diagnosed due to positive FIT, who were more likely to be diagnosed at a non-advanced stage. The difference in the starting age of CRC screening from other countries may have caused these results. The early-onset group demonstrated a significant difference in the rate of diagnostic opportunity between patients aged ≥ 40 years and < 40 years. The positive FIT was more predominant among those aged ≥ 40 years for whom CRC

screening is recommended, whereas the proportion was significantly lower among those aged < 40 years for whom CRC screening was not recommended. These results indicate that FIT screening is useful in detecting EoCRC and more education on current CRC screening for those ≥ 40 years of age may contribute to diagnosis in the non-advanced stage. Conversely, developing risk-based strategies by surveying and stratifying the risk of EoCRC may be necessary in the future for those under 40 years of age. TCS may need to be considered, especially among patients with a family history of early-onset CRC because of the possibility of Lynch syndrome as well as EoCRC. This study revealed no significant difference in the prognosis between the two groups, and a favorable prognosis was shown in patients with non-advanced stage at presentation. The prognosis of EoCRC is controversial, with some reports indicating a better prognosis compared to late-onset CRC and others exhibiting a poor prognosis in male patients at stage III [36, 37]. The prognosis appeared better in patients with advanced stage of the early-onset group. This may be due to the small number of patients in the early-onset group or because younger patients receive more aggressive treatments [38].

This study has several limitations. First, this was a single-center retrospective study with a small number, especially in the early-onset group. The present results may differ in a multicenter study with a large number. Due to the small number of patients in the early-onset group, appropriate multivariate analysis could not be performed. Second, the patient's background has not been fully analyzed due to a medical record-based analysis. The family history of CRC could be confirmed in approximately 90% of the early-onset group and only in approximately 70% of the late-onset group. Third, the median follow-up time was short at 43.6 months, and 48.0 months when patients at stage IV were excluded; therefore, prognosis may change with longer observation periods.

This study revealed that EoCRC among Japanese patients tends to occur on the rectum and be more diagnosed by a positive FIT compared to those with late-onset CRC. Patients with advanced stage were diagnosed by symptoms, indicating importance of striving for early EoCRC detection by educating the public about FIT screening. In Japan, 40 years of age is the considered starting age for CRC screening, and individuals aged ≥ 40 years must be educated to ensure that they undergo FIT screening to detect EoCRC. Furthermore, risk-based strategies by surveying and stratifying the risk of EoCRC may be necessary in the future for individuals aged < 40 years. Thus, this study can have potential clinical value and may guide public health policies and screening strategies. Future multicenter studies with a large number of patients should be conducted to determine a more appropriate approach for EoCRC.

Abbreviations

CRC	Colorectal cancer
EoCRC	Early-onset colorectal cancer
FIT	Fecal immunochemical test
BMI	Body mass index
TCS	Total colonoscopy

Supplementary Information

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Supplementary Material 1

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Author contributions
Conception and design: Y.O. Material preparation and data collection: K.S., K.Y., K.H., S.H., Y.T., K.T., T.M. Writing-original draft: Y.O. Writing-review and editing: Y.O., K.M., K.Y., M.H., H.K., T.S. All authors have read and approved the final manuscript.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective cohort study was conducted at Tonan hospital in Japan, in compliance with the principles of the Declaration of Helsinki of 1964 and later versions. The study protocol was approved by the institutional review board of Tonan Hospital (approval number 1-21-1). Written informed consent for TCS was obtained from all the patients. All participants were given opportunities to decline participation in this study using the opt-out method on each participating hospital's website.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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