Survival outcomes and prognostic factors in early-onset colorectal cancer

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Abstract

Introduction: Despite the increasing incidence of early-onset colorectal cancer (EOCRC) worldwide, data from Vietnam remain limited, especially concerning long-term treatment outcomes. This study aimed to evaluate the clinical characteristics, long-term outcomes, and prognostic factors in patients with EOCRC.

Patients and Methods: This retrospective study included patients diagnosed with colorectal cancer (CRC) before the age of 50. Clinical and paraclinical data were collected, and patients were followed up to evaluate long-term treatment outcomes. The primary endpoints were overall survival and the identification of prognostic factors.

Results: EOCRC cases were evenly distributed between genders and were predominantly localized on the left side of the colon. The median interval from symptom onset to diagnosis was 2 months. A total of 96% of patients reported no first-degree family history of colorectal cancer. Abdominal pain was a characteristic symptom of right-sided tumors, whereas lower gastrointestinal bleeding was more frequently observed in left-sided tumors. The mean overall survival (OS) was 50.0 months (95% CI, 46.7–53.4), and the mean disease-free survival (DFS) was 49.9 months (95% CI, 46.1–53.8). The 5-year survival rate was 68.4%. Poor prognostic factors associated with reduced OS included a serum CEA level > 4.7 ng/mL at diagnosis (HR: 3.1; 95% CI, 1.5–6.4; p = 0.003), poorly differentiated tumors (HR: 3.2; 95% CI, 1.4–7.3; p = 0.005), and advanced stage at diagnosis (HR: 16.8; 95% CI, 2.3–123.6; p = 0.006).

Conclusions: The majority of EOCRC cases occurred sporadically, with a short interval from symptom onset to diagnosis. Tumors were more commonly located in the left side of the colon. Additionally, left-sided tumors were associated with lower gastrointestinal bleeding as a prominent symptom and were linked to higher serum CEA levels compared to right-sided tumors. In contrast, right-sided tumors more commonly presented with abdominal pain and showed a higher proportion of mucinous or signet

ring cell histology. The mean overall survival (OS) was 50.0 months. Serum CEA level at diagnosis, tumor differentiation grade, and disease stage were identified as key prognostic factors.

Keywords: Long-term outcomes, prognostic factor, early-onset colorectal cancer

Introduction

Colorectal cancer (CRC) ranked as the third most common cancer (9.6%) and the second leading cause of cancer-related mortality (9.3%) worldwide in both sexes in 2022 [1]. Since the 1990s, the incidence and mortality of CRC have gradually declined due to improved screening programs and advances in treatment. However, an increasing trend in CRC incidence has been observed among individuals under 50 years of age, a group commonly referred to as EOCRC. According to projections, by 2030, CRC is expected to become the most common cancer among individuals aged 20–49 in the United States[2]. In Vietnam, GLOBOCAN 2022 reported 16,835 new CRC cases and 8,454 CRC-related deaths, ranking fourth (9.3%) and fifth (7.0%), respectively, among all cancers. CRC is currently the third most common cancer in females and the fourth in males in the country [1]. The reported incidence of CRC in younger individuals in Vietnam ranges from 11.7% to 30%, depending on the study methodology and the age criteria used to define EOCRC [3-5].

Young-onset CRC patients tend to exhibit distinct clinical and pathological characteristics compared to those with typical, late-onset CRC. These patients are more frequently diagnosed at advanced stages (stage III/IV), with a predominance of left-sided tumors and more unfavorable histopathological features[6, 7]. In addition, EOCRC is also characterized by a higher prevalence of hereditary cancer syndromes, reported to range from 5% to 35%, compared to only 2–5% in late-onset CRC (LOCRC)[7].

Despite the increasing recognition of EOCRC as a distinct clinical entity, studies focusing on this patient population in Vietnam remain limited. Therefore, this study was conducted to investigate the clinical features, treatment outcomes, and prognostic factors in patients with EOCRC.

Patients and Methods

This retrospective study included EOCRC patients who were diagnosed before the age of 50 who received treatment at the University Medical Center Ho Chi Minh City (HCMC) between January 2017 and December 2020. All included patients had a histologically confirmed diagnosis of carcinoma. Patients with recurrent CRC, a history of other malignancies, or synchronous tumors (defined as a second primary tumor diagnosed within six months of the index CRC) were excluded. The study protocol was approved by the Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (approval number 291/ĐHYD-HDDD). Informed consent was obtained from all patients or their legal guardians in a clinical setting.

Data were obtained from the medical records databases of both participating centers. All available data points for each variable were considered, and when feasible, patients were contacted to supplement missing information. Extracted baseline data included demographic characteristics (age at diagnosis, sex, BMI), history of comorbidities, bowel disease, and toxic exposures; presenting signs and/or symptoms; serum markers including carcinoembryonic antigen (CEA), complete blood count (CBC), and serum albumin; tumor location,

histological subtype, tumor grade, CRC staging according to the 8th edition of the American Joint Committee on Cancer (AJCC)[8], initial treatment modality; TNM classification; follow-up duration (up to 60 months); time and site of recurrence; and cancer-related mortality. Patients with stage I and low-risk stage II tumors underwent curative surgery alone. In contrast, high-risk stage II and stage III tumors were managed with multidisciplinary treatment including curative surgery combined with chemotherapy and/or radiotherapy, depending on tumor location and disease stage. For stage IV disease, one of the following three treatment strategies was selected: curative-intent multidisciplinary treatment (if feasible), systemic therapy, or palliative care.

Patients were classified based on tumor location: right-sided colon cancer (RCC) included tumors in the right colon, whereas left-sided colon cancer (LCC) included tumors in the left colon and rectum. Early-stage CRC was defined as stage I–II disease, while advanced-stage disease included stage III–IV.

Baseline characteristics among EOCRC subgroups were compared using Chi-square and Fisher's exact tests for categorical variables. Continuous variables were analyzed using the independent t-test, Welch's t-test, Mann–Whitney U test, one-way ANOVA, Welch's ANOVA, or Kruskal–Wallis test as appropriate. The Kolmogorov–Smirnov test was applied to assess the normality of data distribution.

Overall survival (OS) was the primary endpoint of this study, defined as the interval from initial CRC diagnosis to death from any cause. OS was estimated using Kaplan–Meier survival curves and compared using the log-rank test. Cox proportional hazards regression was used to calculate hazard ratios. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA).

Results

From 2017 to 2020, a total of 100 CRC patients younger than 50 years met the inclusion criteria and were enrolled in our study. The mean age at diagnosis was 37.4 ± 7.5 years, ranging from 18 to 49 years. The male-to-female distribution was nearly equal, with 52% males and 48% females. At the time of diagnosis, 6% of patients had underlying comorbidities, including hypertension, mitral valve dysfunction, and type 1 diabetes. A family history of colorectal cancer in a first-degree relative was reported in 4% of cases.

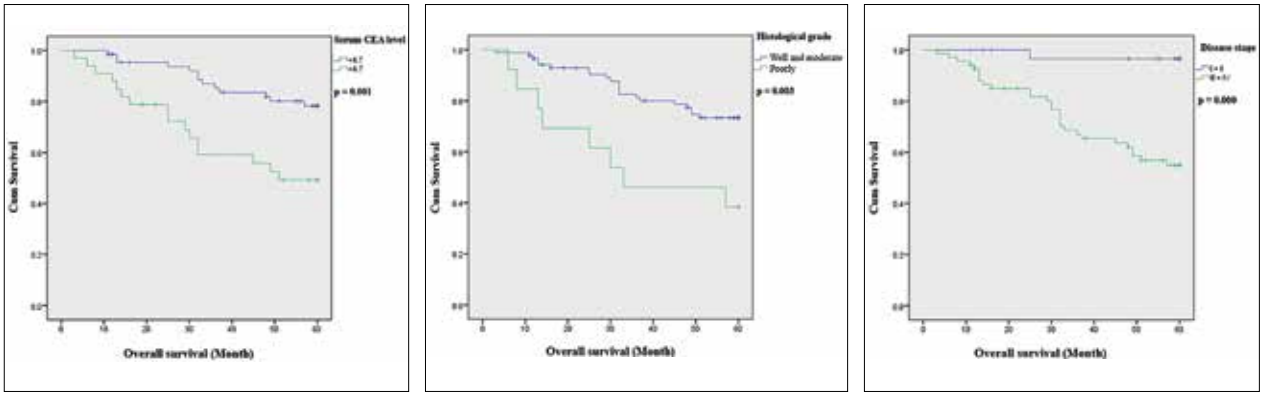
The median interval from symptom onset to diagnosis was 60 days, with most patients (range: 15 to 90 days) receiving a diagnosis within three months of symptom onset. The shortest diagnostic interval was same-day diagnosis (0 days), and the longest was two years. Overall, 65% of patients were diagnosed within three months of symptom onset. Tumor location was reported in the right colon (31%), left colon (26%), and rectum (43%). Abdominal pain, lower gastrointestinal bleeding, and changes in bowel habits were the three most commonly observed presenting symptoms in this study. Among these, abdominal pain was the predominant symptom in patients with right-sided colon cancer, whereas lower gastrointestinal bleeding was more frequently associated with left-sided tumors.

Tumor location was reported in the right colon (31%), left colon (26%), and rectum (43%). The overall curative surgery rate was 83%, including all patients with stage I and II disease, 98% of those with stage III disease (with one case not eligible for curative resection), and 15.8% (n = 3) of stage IV patients. The proportion of patients undergoing curative surgery was significantly higher in early-stage CRC than in advanced-stage disease ($p = 0.002$).

The mean overall survival (OS) observed in our cohort was 50.0 months (95% CI, 46.7–53.4), while the mean disease-free survival (DFS) was 49.9 months (95% CI, 46.1–53.8). Factors significantly associated with reduced overall survival (OS) included elevated serum CEA levels at diagnosis ($\geq$ 4.7 ng/mL), poor tumor differentiation, and advanced disease stage.

Table 1. Characteristics and long-term outcomes of the patients

Factors	Total (n = 100)	Right colon cancer (n=31)	Left colon cancer (n=26)	Rectal cancer (n=43)	p value
Age, mean	37.4	37.9	34.7	38.7	0.074
< 35 year old	37	11 (35.5%)	14 (53.8%)	12 (27.9%)	0.094
35 – 49	63	20 (64.5%)	12 (46.2%)	31 (72.1%)	
Sex, n (%)					0.442
Male	52	19 (61.3%)	13 (50%)	20 (46.5%)	
Female	48	12 (38.7%)	13 (50%)	23 (53.5%)	
Abdominal pain	n = 61	29 (93.5%)	17 (65.4%)	15 (34.9%)	0.000
Bowel habits changes	n = 53	13 (41.9%)	10 (38.5%)	30 (69.8%)	0.014
Lower gastrointestinal bleeding	n = 48	2 (6.5%)	9 (34.6%)	37 (86%)	0.000
Weight loss	n = 21	11 (35.5%)	4 (15.4%)	6 (14%)	0.058
Emergency surgery, n (%)	n = 15	6 (19.4%)	6 (23.1%)	3 (7%)	0.172
Bowel obstruction	11	5	3	3	
Bowel perforation	3	1	2	0	
Rectal prolapse	1	0	1	0	
CEA					0.116
< 4.7 ng/mL	67	23 (74.2%)	20 (76.9%)	24 (55.8%)	
≥ 4.7 ng/mL	33	8 (25.8%)	6 (23.1%)	19 (44.2%)	
Mean value (ng/mL)	47.6	3.8	121.3	34.6	0.023
Histological grade, n (%)					0.265
Well and moderately differentiated	87	25 (80.6)	22 (84.6)	40 (93)	
Poorly differentiated	13	6 (19.4)	4 (15.4)	3 (7)	
Histological type, n (%)					0.001
Adenocarcinoma	88	22 (71)	24 (92.3)	42 (97.7)	
Mucinous or signet ring cell carcinoma	12	9 (29)	2 (7.7)	1 (2.3)	
Disease stage, n (%)					0.223
I + II	32	13 (41.9)	9 (34.6)	10 (23.3)	
III +IV	68	18 (58.1)	17 (65.4)	33 (76.7)	
OS mean (month)	50.0	48.5	46.5	52.9	0.510
5-year survival rates (%)	68.4	63.8	64.1	73.4	
DFS mean (month)	49.9	53	44.9	51	0.621



(a) (b) (c)

Figure 1. Kaplan–Meier curves illustrating OS in patients with EOCRC, stratified by (a) Serum CEA level, (b) Histological grade and (c) Disease stage

Table 2. Univariate analysis of overall survival in relation to serum CEA level, tumor differentiation grade, and disease stage

Factors	HR	95% CI	p
Serum CEA level			0.003
< 4.7 ng/mL	[Reference]		
≥ 4.7 ng/mL	3.1	1.5 – 6.4	
Histological grade			0.005
Well and moderately differentiated	[Reference]		
Poorly differentiated	3.2	1.4 – 7.3	
Disease stage			0.006
I + II	[Reference]		
III + IV	16.8	2.3 – 123.6	

Discussion

Our study population seemed to be younger than those reported in previous studies. For instance, Ruiz-Grajales[6] reported a mean age of 40 years, while Hoang Dinh Kinh[9] noted a mean age of 43 years in a 2023 Vietnamese study. In a 2024 study by Liao[10], the median age of EOCRC patients was 44 years, with 75% of cases occurring in individuals aged 40–49. Notably, all of these studies focused on CRC diagnosed before the age of 50. Regarding sex distribution, our findings demonstrated a nearly equal male-to-female ratio,

consistent with known characteristics of EOCRC, which tends to affect both sexes equally. This contrasts with LOCRC or CRC in the general population, where a higher incidence in males is typically observed. According to GLOBOCAN 2022, the male-to-female ratio in CRC generally ranges from 1.1 to 2[1]. A report by Tran Dinh Phuong Tran (2025) from Cho Ray Hospital indicated a male-to-female ratio as high as 2.7[11], while a study at the 108 Military Central Hospital reported a ratio of 1.97:1 in 110 CRC cases [12]. Internationally, Gandini et al. (2024) reported a male-to-female ratio of 1.2 in EOCRC, compared to 1.45 in LOCRC[13]. Similarly, Chun-Kai Liao observed a nearly equal sex distribution in EOCRC (ratio ~1.0), which was significantly different from the 1.4 ratio reported in LOCRC ($p < 0.001$)[10]. Several domestic studies also reported comparable findings. Hoang Dinh Kinh[9], Hoang Manh Duc[14], Pham Hung Cuong[15], and Quach Trong Duc [16] all found male-to-female ratios ranging from 1.2 to 1.3, despite differences in the age groups analyzed across studies.

There is general consistency among studies regarding the primary tumor location in EOCRC, with most authors reporting a predominance of tumors in the distal colon (descending and sigmoid colon) and the rectum, collectively referred to as left-sided colon cancer. In Vietnam, two reports by Hoang Dinh Kinh[9] and Hoang Manh Duc[14] documented right-sided tumor rates of 40% and 28%, respectively, while left-sided colon cancer accounted for 60% and 72% of cases. Similarly, Pham Hung Cuong[15] reported that, 81% of EOCRC cases in his study were located in the left colon, compared to 75% in LOCRC, a statistically significant difference ($p = 0.013$). Our findings also demonstrated a predominance of tumors in the distal colon and rectum, with a combined proportion of 69%. These results are consistent with those of Chun-Kai Liao[10] who reported a similar rate of 77% for left-sided colon cancer, including 39% located in the rectum. Notably, Liao's study found no significant difference in tumor location between EOCRC and LOCRC patients.

Regarding clinical presentation, in this study abdominal pain was the predominant symptom in patients with right-sided colon cancer, whereas lower gastrointestinal bleeding was more frequently recorded in those with left-sided tumors. This difference was statistically significant. Similarly, in a meta-analysis, Chun-Kai Liao[10] concluded that symptom profiles differ between right- and left-sided colon cancer in EOCRC patients. As for the interval between symptom onset and diagnosis, previous studies have reported an average delay of 4 to 6 months in EOCRC, with some cases extending up to two years[7, 17]. A recent review indicated that diagnostic delays in EOCRC are often longer than in LOCRC —on average 1.4 times longer[17]. This diagnostic delay has been attributed to several factors, including a lower index of suspicion for malignancy in younger patients, lack of awareness, and failure to recognize relevant symptoms. In contrast to these reports, our study showed a more favorable diagnostic timeline, with a median time to diagnosis of only 60 days. Most patients were diagnosed within 15 to 90 days of symptom onset, and 65% were diagnosed within three months. By comparison, Ruiz-Grajales[6] reported that 52% of EOCRC patients in his study experienced a diagnostic delay of more than four months. A domestic study by Quach Trong Duc[16] also reported that 58% of CRC patients were diagnosed within three months of initial symptom presentation.

Regarding long-term treatment outcomes, Hoang Dinh Kinh[9] conducted a study on 78 EOCRC patients diagnosed before the age of 50 in Vietnam and reported a 5-year overall survival (OS) rate of 73%, which is comparable to the findings of our study. Notably, Hoang Manh Duc[14] reported

on a subset of EOCRC patients without distant metastases but with very early onset (diagnosed before age 35). In this group, the estimated 5-year OS rate was only 56.6%, despite a mean OS of 59 months. The study also found that the 5-year OS rate decreased significantly with advancing stage (83%, 73%, and 18% for stages I, II, and III, respectively; p = 0.05). In an even younger cohort, Nguyen Thi Mai[18] investigated EOCRC patients diagnosed before age 30 and reported poorer outcomes, with a median OS of only 28 months and a 5-year OS rate of 37%. The recurrence rate following curative treatment in this group was 20.4%. The study also confirmed that disease stage significantly influenced prognosis, with more advanced stages associated with lower 5-year OS (p = 0.0001). These two studies highlight two important points. First, prognosis in very early-onset CRC (before age 35) appears to be significantly worse. This observation is supported by other studies, which have also identified younger age at diagnosis as an independent poor prognostic factor in CRC[19]. Second, both authors consistently emphasized the negative impact of advanced disease stage on overall survival, which is consistent with the findings of our study.

A study of 1,240 EOCRC patients under 50 years old in Taiwan reported a 5-year overall survival (OS) rate of 75% across all stages, and 87% among those who underwent curative treatment[10]. Interestingly, the same study found that compared to LOCRC patients (with 5-year OS rates of 83% overall and 91% in curatively treated cases), the EOCRC group had significantly lower survival outcomes. However, when stratified by disease stage, this difference was observed only in stage IV disease: the 5-year OS rate for EOCRC patients was 29%, compared to 45% in the LOCRC group (p = 0.012). No significant differences were noted between the two groups in stages I, II, or III. In contrast, Ren et al. (2024)[2] conducted a large-scale study including 10,036 metastatic EOCRC patients and 56,225 metastatic LOCRC patients from 2010 to 2019. Their findings indicated that EOCRC was associated with significantly better survival compared to LOCRC. The median OS in the EOCRC group was 18 months (95% CI, 8–33 months), compared to 10 months in the LOCRC group. Overall, when survival outcomes are compared by disease stage, younger patients with early-stage disease tend to have more favorable prognoses than older patients at the same stage. Conversely, in advanced-stage disease, the prognosis in EOCRC appears to be similar or even worse than that in LOCRC patients [17].

In addition to disease stage, our study identified serum CEA level at diagnosis and tumor differentiation grade as significant prognostic factors. This observation aligns with several previous reports highlighting the prognostic value of CEA levels in CRC. For instance, Nguyen Thi Mai [18] concluded that elevated pre-treatment CEA levels were associated with poorer outcomes in patients with early-onset colon cancer diagnosed before the age of 30. In her study, patients with pre-treatment CEA levels above 5 ng/mL had a significantly higher recurrence rate than those with normal levels (62.5% vs. 14.7%, p = 0.012). In 2021, Leilani Lakemeyer conducted a study involving 1,487 CRC patients, which showed that the 5-year OS rate significantly declined with increasing CEA levels: 69% in patients with normal CEA, 44% in those with elevated CEA <200 ng/mL, and only 7% in patients with CEA ≥200 ng/mL[20]. Another study of 1,027 stage I–III CRC patients demonstrated that those with CEA levels >5 ng/mL at diagnosis had significantly lower 3-year disease-free survival compared to those with normal levels[21]. Regarding tumor differentiation, a study of 237 CRC patients reported that poorly differentiated tumors were associated with worse clinical

outcomes[22]. Similarly, an analysis based on SEER data identified poor tumor differentiation as an independent prognostic factor for decreased OS in both EOCRC and LOCRC cohorts[2].

This study has certain limitations. Notably, the absence of a LOCRC control group, which would have strengthened the contextual interpretation of the findings. Future research should aim to incorporate a well-defined control cohort and adopt a more robust, prospective design to enhance the validity and generalizability of the results.

Conclusion

The majority of EOCRC cases occurred sporadically, diagnosed within a short interval from symptom onset to diagnosis. Tumors were more commonly located in the left side of the colon. Additionally, left-sided tumors were characterized by lower gastrointestinal bleeding as a prominent symptom and exhibited higher serum CEA levels compared to right-sided tumors. In contrast, right-sided tumors predominantly presented with abdominal pain and showed a higher proportion of mucinous or signet ring cell histology. The mean OS was 50.0 months. Serum CEA level at diagnosis, tumor differentiation grade, and disease stage were identified as key prognostic factors.

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