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Clinical and pathological characteristics of early-onset colorectal cancer in South Korea

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Abstract

Background: Early-onset colorectal cancer (EOCRC) may differ by race and ethnicity, and recently South Korea has witnessed a surge in cases. We aimed to evaluate the clinical and pathological features of patients with EOCRC, and to determine the predictors of overall survival.

Methods: In this retrospective study, EOCRC was defined as CRC diagnosed in patients aged < 50 years, and late-onset CRC was defined as CRC diagnosed in those over 75 years of age. The clinical and pathological characteristics of patients with EOCRC were compared with late-onset CRC. We also used multivariable Cox proportional hazard models to find predictors of overall survival in patients with EOCRC.

Results: The proportion of early-onset CRC was 9.1% of 518 patients with CRC, and the clinical and pathological characteristics were similar between early-onset (n = 47) and late-onset CRC (n = 134). However, EOCRC had a preponderance for distal tumor location (70.2% vs. 50.7%, P = 0.02) and T1-2 stage disease (23.4% vs. 11.2%, P = 0.04), compared with those of late-onset CRC. Using multivariable Cox proportional hazard models, only vascular invasion (hazard ratio = 8.75, 95% confidence interval 1.139–67.197) was found to be a risk factor for overall survival (P = 0.04) for patients with CRC.

Conclusion: EOCRC had preponderance for distal tumor location and early T-stage disease, compared with late-onset CRC. Considering the increasing incidence of EOCRC, more studies on clinical and pathological characteristics of EOCRC may be warranted.

Keywords: Age, early-onset colorectal cancer, pathology, risk factor, survival

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INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and the leading cause of cancer-related deaths worldwide.[1] The Centers for Disease Control and Prevention of the United States (US) reported statistically significant decreases in the CRC incidence rate and mortality from 1999 through 2008, for all racial and ethnic groups.[2] An increase in the proportion of population undergoing screening colonoscopies and the removal of benign precancerous polyps is thought to partly account for this decrease.[3] In contrast, the incidence rate of CRC among the population under

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50 years of age, i.e., early-onset CRC (EOCRC), has increased.[4,5]

Patients with EOCRC and no known predisposing genetic risk factors are often diagnosed with late-stage disease and have poor outcomes,[4,5] which may result from the clinicians' failure to consider the possibility of CRC in the differential diagnosis in young individuals. As EOCRC is one of the hallmarks of familial CRC syndromes and is also often associated with inflammatory bowel disease (IBD), previous studies focusing on EOCRC have included these patients.[6,7] In addition, the clinical and pathological characteristics of EOCRC may be diverse by different race and ethnicity.[8]

Recently, South Korea has witnessed a notable surge in EOCRC cases,[9] causing a shift in the age distribution of diagnosed CRC. However, little is known about the clinicopathological characteristics of EOCRC in the country. In many previous studies,[10] the clinicopathological characteristics of EOCRC were compared with those of late-onset CRC, which is defined as CRC in patients older than 50 years. However, the clinicopathological characteristics of EOCRC may not be differentiated from those of late-onset CRC according to a previous definition,[10] as they may share similar features among patients with CRCs around the age of 50. In this context, late-onset CRC, as a relative concept of EOCRC, may be defined as CRCs in patients older than 75 years rather than 50 years.

The aim of this study was to characterize the clinical and pathological features of EOCRC, compared with those of late-onset CRC, in South Korea. We also sought to determine the predictable risk factors for overall survival in patients with EOCRC.

PATIENTS AND METHODS

Patients

We collected data retrospectively from consecutive patients with primary CRC who underwent surgery at the hospital, where this study was conducted between June 2006 and March 2015. "EOCRC" was defined as CRC diagnosed in patients aged less than 50 years, as that age is recommended by most medical societies as the appropriate time to begin screening for sporadic CRC.[11-13] "Late-onset CRC" was defined as CRC diagnosed in those over 75 years of age, because the US Preventative Services Task Force advises against routine CRC screening in patients over this age.[14] Patients were excluded from the analysis, if they had familial adenomatous polyposis, Lynch syndrome, IBD, non-epithelial neoplasms such as a gastrointestinal stromal tumor or neuroendocrine tumor, or if they had a strong positive family history of CRC. "Strong family history" was defined as a family history with multiple cases of CRC or a family history of CRC in a first-degree relative less than 60 years of age. Patients with a simple positive family history for sporadic CRC over 60 years were not excluded from the analysis. Patients were also excluded from this analysis if they underwent surgery outside of the hospital or had inadequate electronic medical records.

Ethical approvals

This study was approved by the institutional review board of the Kyung Hee University Hospital at Gang Dong. Since the study is based on the retrospective analysis of existing administrative and clinical data, the requirement of obtaining informed patient consent was waived by the board.

Data abstraction

One author extracted the clinical and pathological data from the patient records. The main study variables included were the following: demographics; body mass index (BMI); family history of CRC; duration of survival and mortality; pathologies, such as location, size, and differentiation; tumor-node-metastasis (TNM) staging; number of lymph nodes harvested; lymphatic or vascular invasion; and epidermal growth factor receptor (EGFR) or p53 expression. The location of tumors in the colon was defined as right-sided (cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure), left-sided (descending colon, sigmoid colon), or rectal. CRCs in the left-sided colon and rectum were defined as distal CRCs, whereas CRCs in the right-sided colon were defined as proximal CRCs. Aggressive pathologic features were defined as "poorly differentiated adenocarcinoma", "signet ring cell carcinoma", and "mucinous adenocarcinoma".[4]

Statistical analysis

The Student's *t*-test or non-parametric Mann–Whitney U-test was used to compare means, and the X^2 test or the Fisher's exact test was used to compare proportions. The hazard ratio (HR) and 95% confidence intervals (95% CI) were calculated using multivariable Cox proportional hazard analysis. All *P* values were 2-tailed. A *P* value <0.05 indicated statistical significance, and a *P* value <0.1 was considered a statistical trend. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

Patient characteristics

A total of 527 patients who underwent surgery during the study period were initially eligible. Of these patients, nine patients were excluded for the following reasons: inadequacy of electronic medical records (n = 1), gastrointestinal stromal tumor (n = 2), and operation outside of the hospital (n = 6). After filtering, 518 patients with CRC were enrolled in the study cohort. The mean age was 66.2 ± 11.8 years, and the mean BMI was 23.3 ± 3.6 kg/m^2. In the study population, 58.5% of the participants were male and 2.5% had a family history of CRC in a first-degree relative. The study group was classified as EOCRC patients (n = 47, 9.1%), late-onset CRC patients (n = 134, 25.9%), and patients with disease diagnosis at 50–74 years (n = 337, 65.1%).

EOCRC versus late-onset CRC

Table 1 shows the clinical and pathologic characteristics of the patients with EOCRC and late-onset CRC. In the EOCRC group, the mean age was 44.9 ± 4.0 years and 25 patients were male (53.2%). In the late-onset CRC group, the mean age was 80.1 ± 4.6 years and 67 patients were male (50.0%). Generally, the clinical characteristics were similar between the two groups. For the pathological characteristics, the EOCRC group had a preponderance for distal tumor locations (70.2% vs. 50.7%, P = 0.02) and T1-2 stage disease (23.4% vs. 11.2%, P = 0.04), compared with late-onset CRC patients [Figure 1]. Other pathologic characteristics were similar between the two groups.

Clinical and pathological characteristics of EOCRC

The clinical and pathological characteristics of patients with EOCRC are shown in [Supplementary Table 1], and Table 2 according to sex and tumor location, respectively there was no statistically significant difference in the clinical and pathological characteristics of patients with EOCRC according to sex or tumor location.

Risk factors for overall survival

To determine the independent predictors of overall survival, we performed multivariable Cox proportional hazard analysis adjusted for age group (early-onset *vs.* late-onset), sex, BMI, tumor location, differentiation, T stage, N stage, and lymphatic and vascular invasion [Table 3]. In this analysis, only vascular invasion (OR = 8.75, 95% CI = 1.139–67.197) was found to be a possible risk factor for overall survival (P = 0.04) in patients with CRC. Kaplan-Meier survival analysis showed significantly lower overall cumulative survival in patients with vascular invasion (P = 0.04, Figure 2). The overall cumulative survival was lower in patients with vascular invasion in the late-onset CRC group (P = 0.05). However, the impact of vascular invasion in EOCRC was not analyzed, as no mortality was identified in this subgroup.

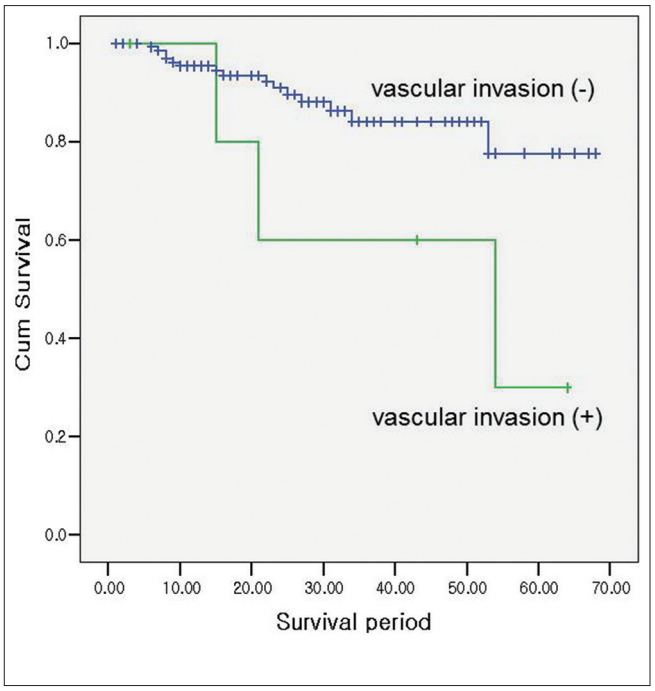

Figure 1: Pathological characteristics of early-onset colorectal cancer (EOCRC). The EOCRC group had a preponderance for distal tumor locations (70.2% vs. 50.7%, P = 0.02) and T1-2 stage disease (23.4% vs. 11.2%, P = 0.040), compared with late-onset colorectal cancer patients

DISCUSSION

This is the first study to characterize the clinical and pathological features of EOCRC compared with those

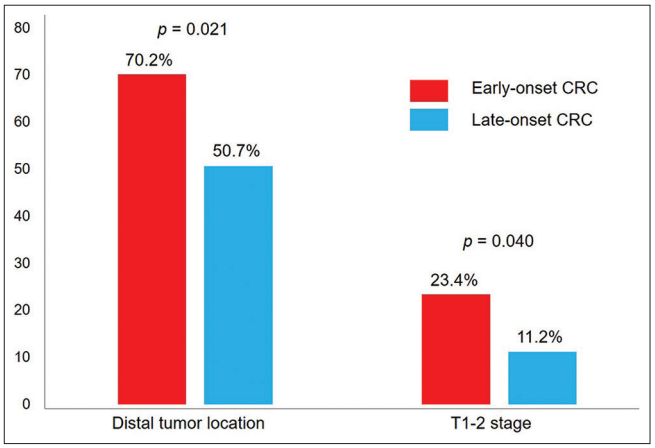

Figure 2: Overall cumulative survival of patients with colorectal cancer according to vascular invasion. Kaplan–Meier survival analysis showed significantly lower overall survival (P = 0.04) in colorectal patients with vascular invasion

Table 1: Clinical and pathological characteristics of the patients in early-onset and late-onset colorectal cancer

Variable	Early-onset CRC (*n*=47)	Late-onset CRC (*n*=134)	*P*
Clinical characteristics			
Age (years)	44.9 ± 4.0	80.1 ± 4.6	0.000
Sex (men)	25 (53.2)	67 (50.0)	0.71
BMI (kg/m²)	23.5 ± 3.8	22.3 ± 3.6	0.06
Family history of CRC	3 (6.4)	2 (1.5)	0.11
Survival duration (months)	24.4 ± 15.1	26.5 ± 17.2	0.47
*Mortality	4/40 (10.0)	16/107 (14.9)	0.59
Pathologic characteristics			
Location (distal)	33 (70.2)	68 (50.7)	0.02
Size of tumor (cm)	5.2 ± 2.5	5.4 ± 2.0	0.53
†Aggressive histology	3 (6.4)	21 (15.7)	0.14
Early stage (pTNM I-II)	24 (51.1)	66 (49.3)	0.83
Early T stage (T1-2)	11 (23.4)	15 (11.2)	0.04
LN metastasis	23 (48.9)	68 (50.7)	0.83
No. of LN harvested	26.3 ± 12.2	28.2 ± 14.2	0.42
Lymphatic invasion (yes)	13 (27.7)	43 (32.1)	0.57
Vascular invasion (yes)	0 (0.0)	8 (6.0)	0.11
‡EGFR expression (positive)	26/45 (57.8)	76/131 (58.0)	0.98
§p53 expression (positive)	27/45 (60.0)	95/132 (72.5)	0.13

Data presented as n (%), or mean ± standard deviation. CRC, Colorectal cancer; BMI, Body mass index; LN, Lymph node; EGFR, Epidermal growth factor receptor. *Data from 13 patients were not available for mortality due to follow-up loss. †Aggressive histology included "poorly differentiated adenocarcinoma", "signet ring cell carcinoma" and "mucinous adenocarcinoma". ‡,§Data from five and four patients were not available for EGFR and p53 expression, respectively.

of late-onset CRC, which was defined as CRCs in patients older than 75 years. In this study, 9.1% of 518 patients with CRC were EOCRC, which was consistent with the results of previous studies.[4,15-17] The overall prevalence of EOCRC in the United States and European Union ranges from 3.0% to 8.6%.[16] In a recent review from the United States, the proportion of EOCRC has increased up to 10.9% - 12.0%.[4,15,16,18] The underlying cause of the increasing EOCRC incidence is not well understood; however, an increasing incidence of risk factors of CRC, such as a sedentary lifestyle, obesity, and diabetes mellitus, in the young population might be a possible mechanism.[19-21]

Screening for CRC in average-risk individuals may be the largest single driver of the decreasing CRC incidence and mortality. However, CRC screening is generally recommended for average-risk individuals after 50 years of age, according to guidelines.[14] Therefore, the young population is not undergoing regular CRC screening, which might partially explain the increase in the EOCRC incidence and mortality. In this regard, Myers *et al*.[15] suggested that young, symptomatic patients merit a timely colonic evaluation to avoid presentation with late-stage CRC. Recently, Bailey *et al*.[5] predicted that the incidence rates for colon and rectal cancers will increase by 90.0%

Table 2: Clinical and pathological characteristics of the patients with early-onset colorectal cancer according to tumor location

Variable	Proximal cancer (*n*=14)	Distal cancer (*n*=33)	*P*
Clinical characteristics			
Age (years)	44.5 ± 3.8	45.1 ± 4.0	0.64
Sex (men)	7 (50.0)	18 (54.5)	0.78
BMI (kg/m²)	23.1 ± 4.6	23.6 ± 3.5	0.64
Family history of CRC	1 (7.1)	2 (60.6)	1.00
Survival duration (months)	22.7 ± 13.5	25.1 ± 16.0	0.63
*Mortality (death)	0/13 (0.0)	4/27 (14.8)	0.28
Pathologic characteristics			
Size of tumor (cm)	5.6 ± 2.5	5.0 ± 2.5	0.47
†Aggressive histology	1 (7.1)	2 (6.1)	1.00
Early stage (pTNM I-II)	8 (57.1)	16 (48.5)	0.59
Early T stage (T1-2)	4 (29.6)	7 (21.2)	0.71
LN metastasis	6 (42.9)	17 (51.5)	0.59
No. of LN harvested	30.1 ± 12.7	24.7 ± 11.8	0.17
Lymphatic invasion (yes)	4 (28.6)	9 (27.3)	1.00
Vascular invasion (yes)	0 (0.0)	0 (0.0)	-
‡EGFR expression (positive)	9/14 (64.3)	17/31 (54.8)	0.55
§p53 expression (positive)	9/14 (64.3)	18/31 (58.1)	0.69

Data presented as n (%), or mean ± standard deviation. CRC, Colorectal cancer; SD, Standard deviation; BMI, Body mass index; LN, Lymph node; EGFR, Epidermal growth factor receptor. *Data from seven patients were not available for mortality due to follow-up loss. †Aggressive histology included "poorly differentiated adenocarcinoma", "signet ring cell carcinoma" and "mucinous adenocarcinoma". ‡,§Data from two patients were not available for EGFR and p53 expression, respectively.

Table 3: Multivariable analysis of risk factors for cancer-specific survivals

Variables	Hazard ratio (95% CI)	*P*
Age group (early-onset *vs*. late-onset)	1.085 (0.312–3.323)	0.90
Sex (female *vs*. male)	1.215 (0.424–3.479)	0.72
BMI (<25 *vs*. ≥25 kg/m²)	0.763 (0.194–3.005)	0.70
Tumor location (distal *vs*. proximal)	0.762 (0.261–2.231)	0.62
T stage (T1-2 *vs*. T3-4)	4.638 (0.478–44.958)	0.19
N stage (N0 *vs*. N1-3)	1.919 (0.571–6.443)	0.29
Lymphatic invasion (no *vs*. yes)	1.432 (0.441–4.657)	0.55
Vascular invasion (no *vs*. yes)	8.750 (1.139–67.197)	0.04

CI, Confidence interval; BMI, Body mass index

and 124.2%, for patients aged 20 to 34 years, respectively, and by 27.7% and 46.0% for patients aged 35 to 49 years, respectively, by 2030, based on a steadily increasing current trend. Our findings show that the incidence of EOCRC is similar in South Korea.

In the present study, EOCRC had a preponderance for distal tumor locations compared with late-onset CRC, which is consistent with the results of previous studies.[4,16,18,22-26] According to the National Cancer Database of the US,[16] EOCRC more commonly arises from a distal location than a proximal location (69.0% *vs.* 57.7%, $P < 0.001$). Previous studies from the United States, Spain, Singapore, and Vietnam have also produced consistent findings of a preponderance of distal tumor locations in EOCRC.[22-26] The predisposition of distal cancers in EOCRC is mostly driven by the rising rate of rectal cancer.[4,18,26] As EOCRC occurs more often in the distal colon, especially in the rectum, screening sigmoidoscopy to detect EOCRC in young populations might confer a substantial benefit. Considering flexible sigmoidoscopy reduced CRC incidence and mortality by 23% and 31% in the 55–64 years age-group,[27] its role for the EOCRC might be evaluated in young populations.

This study had some inconsistent findings with those of previous studies for family history, aggressive pathologic features, and late-stage presentation. First, patients with EOCRC often had a positive familial history of CRC from 12% to 24% in previous studies.[15,22] In this study, the rate of positive family history was relatively low (6.4%). However, this result should be interpreted cautiously, as this study adopted a strict definition of family history and excluded cases with a "strong family history" to exclude a possible case of hereditary CRC syndrome. Second, many previous studies have reported the presence of aggressive pathological features in EOCRC.[16,18,23,24,26,28-31] In a recent Korean study comparing EOCRCs with CRCs >50 years also showed higher poor histological differentiation in EOCRC group.[32] In this study, however, the aggressive pathologic features were not more common in EOCRC than in late-onset CRC. However, it may be explained that the number of CRC cases with aggressive pathologic features were small in this study and definition of aggressive pathologic features was different in each study. Finally, an increase in the number of EOCRC patients with late-stage disease at presentation has also been commonly reported in previous studies.[28-33] In this study, however, the number of early-stage disease (pTNM stage I-II) was not different between EOCRC and late-onset CRC patients. In many previous studies,[10] EOCRC was compared with CRCs in patients older than 50 years, in whom colonoscopy screening was performed. However, in our study, late-onset CRC was defined as CRCs occurring in patients older than 75 years, in whom colonoscopy was not routinely performed similar to the younger population less than 50 years. Different definitions of late-onset CRC may have been the cause of inconsistent findings regarding the late-stage presentations. In addition, it may also be explained by our surgery-based data collection method, as inoperable CRC cases were not included in this study. As the clinical and pathologic characteristics of EOCRC may be influenced by the study methodology and compared population such as late-onset CRC, as well as genetic, environmental, or lifestyle factors, further investigations focusing on the clinical and pathological features of EOCRC may be necessary.

In this study, only vascular invasion was found to be a possible risk factor for poor overall survival, which was a consistent finding with previous European and Japanese studies.[34,35] Kaplan–Meier survival analysis also showed a significantly lower overall survival in CRC patients with vascular invasion [Figure 2]. In subgroup analysis, vascular invasion was also a strong prognostic predictor for CRC in the late-onset CRC group.

This study has some limitations. First, there is the possibility of selection bias, as our study was a retrospective single-center study based on patients undergoing surgery. Consequently, it was difficult to collect consistent data on the patients' personal information, such as smoking status, diet, and lifestyle. In addition, data that were difficult to objectify or quantify, such as clinical presentations, were also not collected. Second, there may be confounders that contribute to the prevalence of EOCRC, such as hereditary CRC syndromes. However, this bias may be minimal as we excluded patients with a strong family history. The lower rate of a positive family history in our EOCRC group may be influenced by this exclusion criterion. Finally, there is the possibility of a type 2 error when comparing rare endpoints, such as aggressive pathologic features, as the sample size was small. Therefore, further large-scale studies may be warranted on this issue.

In conclusion, the prevalence of EOCRC in Korea was similar to that of the West. EOCRC had preponderances for distal tumor location and early T-stage disease, compared with late-onset CRC. Considering the increasing incidence of EOCRC,[5,36] more studies on the clinical and pathological characteristics of EOCRC may be warranted.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Clinical and pathological characteristics of the patients with early-onset colorectal cancer according to sex

Variable	Men (*n*=25)	Women (*n*=22)	*P*
Clinical characteristics			
Age (years)	44.7 ± 4.0	45.2 ± 3.8	0.67
BMI (kg/m²)	23.4 ± 3.2	23.5 ± 4.5	0.91
Family history of CRC	2 (8.0)	1 (4.5)	1.00
Survival duration (months)	22.1 ± 14.1	26.9 ± 16.2	0.30
*Mortality (death)	4/21 (19.0)	0/19 (0.0)	0.11
Pathologic characteristics			
Location (distal)	18 (72.0)	15 (60.2)	0.78
Size of tumor (cm)	5.6 ± 2.5	4.6 ± 2.5	0.18
†Aggressive histology	1 (40.0)	2 (9.1)	0.59
Early stage (pTNM I-II)	4 (16.0)	7 (31.8)	0.30
Early T stage (T1-2)	12 (48.0)	12 (54.5)	0.65
LN metastasis	13 (52.0)	10 (45.5)	0.65
No. of LN harvested	25.0 ± 12.1	27.8 ± 12.4	0.44
Lymphatic invasion (yes)	6 (24.0)	7 (31.8)	0.55
Vascular invasion (yes)	0 (0.0)	0 (0.0)	-
‡EGFR expression (positive)	15/24 (62.5)	11/21 (52.4)	0.49
§p53 expression (positive)	15/24 (62.5)	12/21 (57.1)	0.71

Data presented as n (%), or mean ± standard deviation. CRC, Colorectal cancer; BMI, Body mass index; LN, Lymph node; EGFR, Epidermal growth factor receptor. *Data from seven patients were not available for mortality due to follow-up loss. †Aggressive histology included "poorly differentiated adenocarcinoma", "signet ring cell carcinoma" and "mucinous adenocarcinoma". ‡,§Data from two patients were not available for EGFR and p53 expression, respectively.