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Original Article

Long-term outcomes and genetic mutation patterns in early-onset colorectal cancer

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ABSTRACT

Objective: This study aimed to evaluate long-term outcomes and mutation patterns in early-onset colorectal cancer (EOCRC) patients.
Methods: A retrospective study was conducted on 67 colorectal cancer (CRC) patients under 40 years old. Patients were stratified by tumor location, disease stage, and genetic mutation status. Comparative analysis assessed their characteristics and clinical outcomes.
Results: Among EOCRC cases, 94 % were sporadic. The male-to-female distribution was nearly equal, with tumors predominantly localized in the left colon. The mean interval from symptom onset to diagnosis was 2.5 months. A majority (68.7 %) were diagnosed at an advanced stage (III–IV). Notably, left-sided colorectal cancer (LCC) had a significantly higher prevalence of advanced-stage disease than right-sided colorectal cancer (RCC) ($p = 0.012$). However, prognosis did not significantly differ by tumor location. Overall survival (OS) and disease-free survival (DFS) were 49 months (95 % CI, 45–54) and 48 months (95 % CI, 43–53), respectively. Germline mutations were identified in 17.9 % of cases, with over half occurring in Lynch syndrome (LS)-associated genes. Somatic mutations were found in 94 % of cases, with TP53, APC, and KRAS being the most frequently mutated genes (65.7 %, 38.8 %, and 35.8 %, respectively). No significant association was observed between these mutations and OS, and disease stage remained the only independent prognostic factor.
Conclusion: The majority of EOCRC cases are sporadic, with prognosis appearing independent of tumor location. The mean OS and DFS were 49 months and 48 months, respectively. No significant prognostic impact was observed for individual somatic mutations in TP53, APC, or KRAS.

1. Introduction

The incidence of CRC in individuals under 50 years old, commonly referred to as EOCRC, has been rising. By 2030, CRC is projected to become the most prevalent cancer among individuals aged 20–49 in the United States.[1] In Vietnam, the incidence of CRC in younger individuals ranges from 11.7 % to 30 %, depending on the research methodology and the age criteria used to define EOCRC.[2–4]

EOCRC patients are frequently diagnosed at advanced stages (III/IV), often with tumors localized on the left side of the colon and exhibiting less favorable pathological characteristics.[5–8] Additionally, hereditary cancer syndromes have been identified in 5 %–35 % of EOCRC cases.[6–11]

Despite the growing recognition of EOCRC and its association with multiple poor prognostic factors, studies focusing on this patient population and its genetic mutations remain limited, particularly in Vietnam and Southeast Asia. Therefore, this study aims to characterize the baseline clinical features, long-term outcomes, mutation patterns, and prognostic factors in EOCRC patients.

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2. Materials and methods

2.1. Study design and patient selection

This retrospective study included CRC patients younger than 40 years old who were diagnosed and treated at the University Medical Center Ho Chi Minh City (HCMC) from January 2017 to December 2020. Eligible patients had a confirmed pathological diagnosis of carcinoma and underwent genetic sequencing of both tumor and blood samples. Exclusion criteria included recurrent CRC, prior malignancies, or synchronous tumors (diagnosed within six months of the primary CRC). 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 family members in a clinical setting.

2.2. Protocol for managing patients

All patients underwent a comprehensive clinical assessment, including physical examination, laboratory tests, and imaging (colonoscopy, CT, MRI, or PET-CT when necessary) for tumor staging according to the 8th Edition of the American Joint Committee on Cancer (AJCC).[12] A multidisciplinary tumor board, comprising surgeons, radiologists, oncologists, and pathologists, determined treatment strategies following Vietnam's Ministry of Health guidelines. Follow-up visits were conducted at regular intervals for up to 60 months post-treatment or until patient death, whichever occurred first.

2.3. Molecular analysis

DNA extraction was performed from paired tumor tissues and blood samples of all patients. A 21-gene panel (including *PIK3CA, KRAS, NRAS, BRAF, APC, TP53, STK11, PTEN, BMPR1A, SMAD4, CHEK2, POLD1, POLE, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, ATM, and CDH1*) sequencing protocol was applied to identify both somatic and germline mutations. The detailed protocols and results of next-generation sequencing and direct sequencing have been described previously.[13,14]

2.4. Clinical data collection and statistical analysis

Data were collected from the center's databases, with missing information supplemented through patient follow-up when possible. Baseline variables included demographics (age, sex, BMI), comorbidities, bowel disease history, clinical presentation, complete blood count (CBC), CEA levels, serum albumin, tumor characteristics, initial treatment, TNM staging, follow-up duration, recurrence details, and CRC-related genetic mutations.

Patients were categorized based on tumor location (right-sided and left-sided colon cancer), disease stage (early-stage: I–II; advanced-stage: III–IV), and genetic mutation status for comparative analysis. Right-sided colon cancer (RCC) included tumors in the cecum, appendix, ascending colon, hepatic flexure, and transverse colon, whereas left-sided colon cancer (LCC) comprised tumors in the splenic flexure, descending colon, sigmoid colon, and rectum.

Sporadic CRC was defined as cases lacking pathogenic germline mutations associated with CRC, clinical features suggestive of hereditary syndromes, or a family history of CRC in first-degree relatives (FDR).

Categorical variables were analyzed using the Chi-square test or Fisher's exact test, while continuous variables were analyzed using the independent samples *t*-test. OS and DFS were calculated from the date of surgery to the last follow-up or until death. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test, with results presented as means and 95 % confidence intervals (CI). A p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

From 2017 to 2020, our study enrolled 67 EOCRC patients younger than 40 years who met the inclusion criteria (Table 1). The age at diagnosis ranged from 18 to 39 years, with an approximately equal male-to-female ratio. The majority of primary tumors were located in the left colon, accounting for 69 % of cases. Reported comorbidities included mitral valve dysfunction, type 1 diabetes, and one case of concurrent four-month pregnancy. A family history of colorectal cancer in a first-degree relative was reported in 4.5 % of patients. Notably, three cases (4.5 %) were diagnosed with EOCRC following surgeries performed for other indications: one for ovarian cancer, another for a liver tumor, and a third for appendicitis. Postoperative histopathological examinations in these cases revealed colorectal carcinoma in the first two and appendiceal cancer in the latter. The overall curative treatment rate was 83.6 %, with all stage I–III patients (100 %) receiving curative treatment. In contrast, only one stage IV patient (8.3 %) underwent curative treatment.

A higher proportion of LCC patients were diagnosed at advanced stages (III–IV) than RCC patients. Although this trend suggested a poorer prognosis for LCC, the difference was not statistically significant. Stage-stratified analysis revealed a significantly worse prognosis for patients with advanced-stage cancer (OS: 46 months; 95 % CI: 40–51) than for those diagnosed at an early stage (OS: 58 months; 95 % CI: 54–61) ($p = 0.003$) (Fig. 1). Regarding histological type and grade, the prognostic impact analysis demonstrated that patients with mucinous or signet ring cell carcinoma, as well as those with poorly differentiated or undifferentiated tumors, exhibited worse outcomes than their respective reference groups. However, these differences were not statistically significant (OS: 45 vs. 50 months, $p = 0.300$; OS: 41 vs. 51 months, $p = 0.095$, respectively).

Germline mutations were detected in 12 patients (17.9 %). Of these, four (6 %) were classified as pathogenic variants linked to hereditary cancer syndromes, while eight (11.9 %) were variants of uncertain significance (VUS), potentially pathogenic based on SIFT (<0.05) and/or PolyPhen-2 (>0.95) scores. The APC gene was the most frequently affected, accounting for 25 % of all detected variants. Germline mutations linked to LS accounted for 58 % of all detected germline mutations ($n = 7$), with pathogenic variants identified exclusively in the PMS2 gene ($n = 2$), while VUS were detected in MLH1, MSH2, and PMS2 ($n = 5$).

For somatic mutations, we observed a mutation rate of 94 % ($n = 63$) in tumor tissue samples, with a total of 274 recorded mutations. These mutations were classified into oncogenic, tumor suppressor, and DNA repair gene categories, accounting for 58.2 %, 86.6 %, and 32.8 % of cases, respectively. The three most frequently mutated genes were TP53 (65.7 %), APC (38.8 %), and KRAS (38 %) (Fig. 2). No mutations were detected in NRAS, STK11, or EPCAM. The majority of cases (71.6 %) harbored two or more somatic mutations, with a maximum of nine mutations identified in a single patient ($n = 1$). Additionally, somatic mutations in the four LS-associated genes (MLH1, MSH2, MSH6, PMS2) were identified in 23.9 % of cases, with a prevalence of 33.3 % in the RCC group and 19.6 % in the LCC group ($p = 0.220$).

Univariate analysis identified KRAS mutations as the only significant factor among the three most frequently mutated genes

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

Factors	Total (n = 67)	Right colon cancer (n = 21)	Left colon cancer (n = 46)	p-value
Age, mean (±SD)	33 ± 4.7	33.2 ± 4.4	32.9 ± 4.9	0.741
Sex, n (%)				
Male	32 (47 %)	13	19	0.117
Female	35 (53 %)	8	27	
Comorbidities, n (%)	3 (4.5 %)			
CRC family history, n (%)	3 (4.5 %)			
Time (days) from onset of clinical signs and/or symptoms to diagnosis				
mean (range)	71 (2–360)	44 (2–180)	83 (3–360)	0.058
≤3 Months	55 (82.1 %)	19 (90.5 %)	36 (78.3 %)	0.314
Abdominal pain, n (%)	43 (64.2 %)	19 (90.5 %)	24 (52.2 %)	**0.002**
Lower gastrointestinal tract bleeding, n (%)	33 (49.3 %)	2 (9.5 %)	31 (67.4 %)	**0.000**
Bowel habits changes, n (%)	34 (50.7 %)	9 (42.9 %)	25 (54.3 %)	0.383
Weight loss, n (%)	13 (19.4 %)	6 (28.6 %)	7 (15.2 %)	0.317
Anemia, n (%)	8 (11.9 %)	4 (19 %)	4 (8.7 %)	0.419
Emergency surgery, n (%)	13 (19.4 %)	5 (23.8 %)	8 (17.4 %)	0.740
Bowel obstruction	10	5	5	
Bowel perforation	2		2	
Rectal prolapse	1		1	
Stage, n (%)				
I + II	21 (31.3 %)	11	10	**0.012**
III + IV	46 (68.7 %)	10	36	
Histological type, n (%)				
Adenocarcinoma	58 (86.6 %)	15	43	**0.022**
Mucinous or signet ring cell carcinoma	9 (13.4 %)	6	3	
Histological grade, n (%)				
Well and moderately differentiated	58 (86.6 %)	18	40	1.000
Poorly differentiated and undifferentiated	9 (13.4 %)	3	6	
Curative treatment, n (%)	56 (83.6 %)	19 (90.5 %)	37 (80.4 %)	0.481
Death rates, n (%)	20 (29.9 %)	4 (19 %)	16 (34.8 %)	0.192
Recurrence rates, n (%)	17/56 (30.4 %)	3 (15.8 %)	14 (37.8 %)	0.089
Germline mutations, n (%)	12 (17.9 %)	6 (28.6 %)	6 (13 %)	0.171
Number of somatic mutations per patient, mean (±SD)	2.6 ± 1.6	3.1 ± 2	2.4 ± 1.3	0.094
OS, mean (95 % CI)	49 (45–54)	53 46–60)	48 (43–53)	0.380
3 and 5-year survival rates	77.1 %–66.2 %	81.6 %–74.8 %	75.3 %–63.4 %	
DFS, mean (95 % CI)	48 (43–53)	55 (49–61)	46 (39–52)	0.208

(TP53, APC, and KRAS), with KRAS-mutant patients exhibiting longer OS (55 vs. 47 months, p = 0.047) (Fig. 3). However, multivariate analysis using the Cox proportional hazards model, adjusted for primary tumor location, disease stage, histology type, and histology grade, revealed no significant impact of KRAS mutations on OS. Disease stage remained the sole independent prognostic factor (Table 2).

4. Discussion

Consistent with previous studies, our findings indicate a nearly equal gender distribution in EOCRC, with tumors primarily localized in the distal colon and rectum. The most frequently reported clinical symptoms include abdominal pain, lower gastrointestinal bleeding, and altered bowel habits.[6,15–19] Our study also found that abdominal pain was the predominant symptom in RCC cases, whereas LCC was primarily associated with lower gastrointestinal bleeding. The time from symptom onset to diagnosis in EOCRC is often prolonged, with an average delay of six months. Several studies have reported that this delay is significantly longer in late-onset colorectal cancer (LOCRC), approximately 1.4 times that observed in EOCRC.[8,15,20–22] A study by Ruiz-Grajales ÁE on CRC in patients under 50 years of age reported that 52 % experienced a diagnostic delay of over four months. In contrast, this proportion was below 15 % in our study.[6] Delayed diagnosis in EOCRC may be attributed to a low index of suspicion for malignancy, lack of awareness, or failure to recognize relevant symptoms, underscoring the need for improved early detection strategies. A family history of CRC or hereditary cancer syndromes associated with CRC is a prominent characteristic of EOCRC, with most studies reporting a higher prevalence in EOCRC than in LOCRC.[6,8,21,23,24] The estimated prevalence of a family history of CRC among EOCRC patients ranges from 11 % to 30 %, depending on the criteria used to define the degree of relatedness.[6,25,26] In our study, only 4.5 % of cases had a FDR with CRC. Similarly, a Vietnamese study reported an FDR prevalence of 7.7 %.[27] EOCRC cases associated with hereditary cancer syndromes account for approximately 5–35 %, with an average prevalence of 13 %, compared to 2–5 % in LOCRC. The association is stronger at younger ages, with prevalence reaching up to 35 % in patients younger than 35 years.[7–11,15,25,26,28,29]

Multigene germline testing has demonstrated that the prevalence of pathogenic germline variants in EOCRC (16–25 %) is nearly twice that observed in LOCRC, with half of these mutations involving LS-associated genes.[9,10,21,25,26,28] A study of 125 patients found that germline mutations, including both pathogenic and likely pathogenic variants, were detected in 16 % of cases, with APC being the most frequently mutated gene (21 %).[30] Our findings were consistent, with 17.9 % of the study population carrying germline variants (either pathogenic or likely pathogenic) associated with CRC. APC was the most frequently mutated gene, accounting for 25 % of all detected variants, while LS-related variants comprised 58 % of them. Regarding somatic mutations in EOCRC, Zhaoran Su (2024) analyzed 4477 samples from 4255 CRC patients and identified seven genes with a somatic mutation prevalence of ≥10 %, including TP53 (67 %), APC (66 %), KRAS (43 %), PIK3CA (18 %), FBXW7 (14 %), SMAD4 (14 %), and BRAF (10 %), with 95.5 %

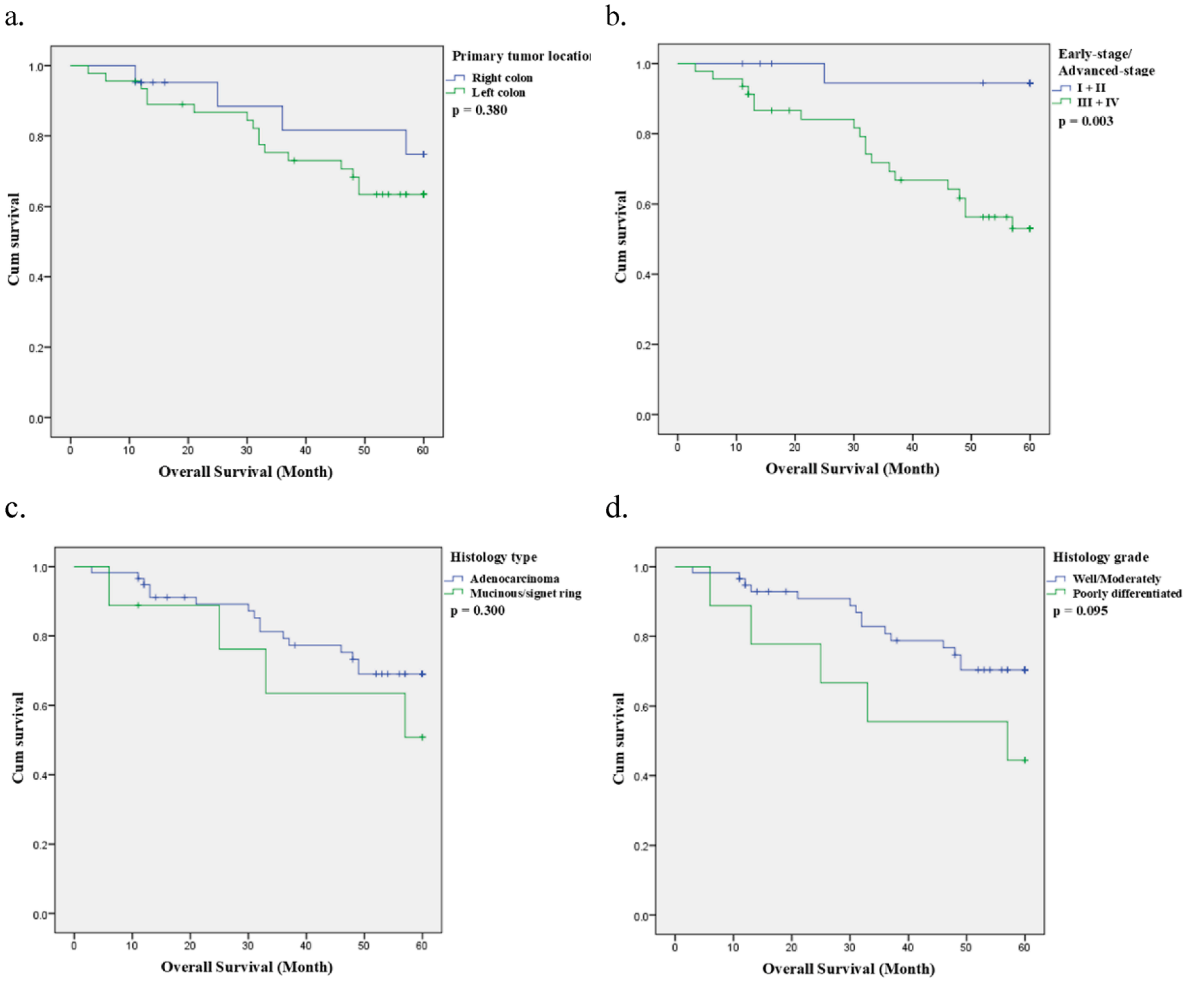

Fig. 1. Kaplan–Meier curves illustrating OS in patients with EOCRC, stratified by (a) Primary tumor location, (b) Disease stage, (c) Histological type and (d) Histological grade. A trend toward worse OS was observed in patients with left-sided tumors, advanced-stage disease, mucinous or signet ring cell carcinoma, and poorly differentiated tumors. Of these factors, only disease stage showed a statistically significant association with OS (p = 0.003).

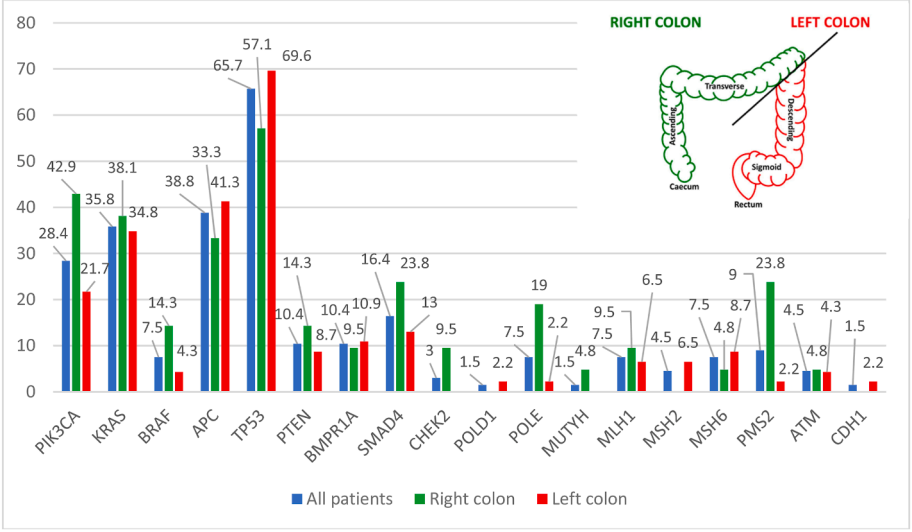

Fig. 2. Proportion of somatic mutations by gene (%). On average, patients with RCC harbored 3.1 mutations per case, compared to 2.4 mutations in the LCC group (p = 0.094). In addition, RCC exhibited a trend toward higher mutation frequencies in several genes compared to LCC, including PIK3CA (42.9 % vs. 21.7 %, p = 0.075), BRAF (14.3 % vs. 4.3 %, p = 0.315), SMAD4 (23.8 % vs. 13.0 %, p = 0.301), CHEK2 (9.5 % vs. 0 %, p = 0.095), POLE (19.0 % vs. 2.2 %, p = 0.031), and PMS2 (23.8 % vs. 2.2 %, p = 0.010).

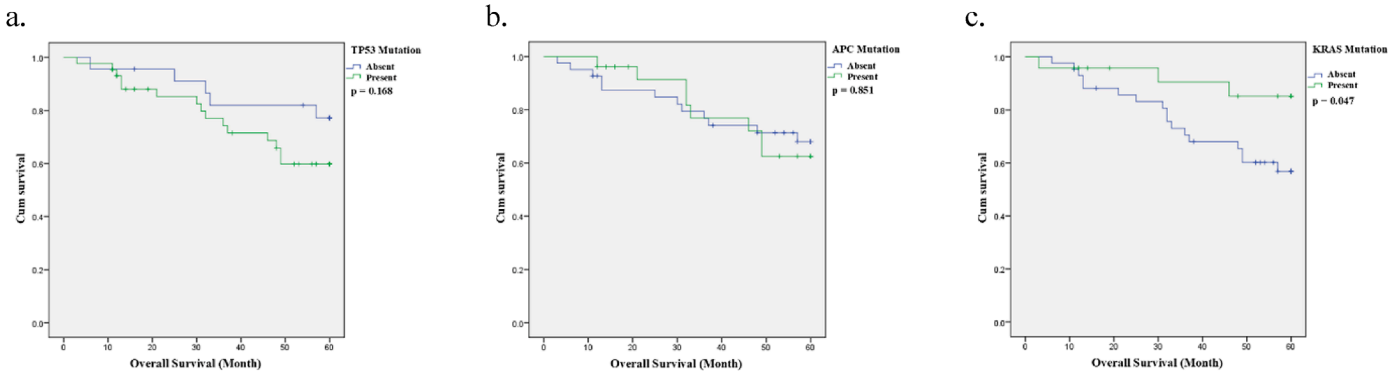

Fig. 3. Kaplan–Meier curves illustrating overall survival (OS) in patients with early-onset colorectal cancer (EOCRC), stratified by mutation status in (a) TP53, (b) APC, and (c) KRAS. Patients with TP53 mutations showed a trend toward worse OS compared to those without mutations ($p = 0.165$), while KRAS mutations were significantly associated with improved OS compared to the wild-type group ($p = 0.047$).

Table 2
Multivariate analysis of KRAS mutations for OS, adjusted for primary tumor location, disease stage, histological type and grade.

Factors	HR	95 % CI	p-value
KRAS mutation	0.564	0.155–2.053	0.385
Advanced stage	12.129	1.249–117.8	0.031

of patients carrying at least one mutation.[31] Our findings were consistent with the five most frequently mutated genes identified in this study, except that FBXW7 was not analyzed in our cohort. Compared to CRC in general or LOCRC, EOCRC exhibits lower mutation rates in APC, KRAS, BRAF V600, and NRAS, whereas TP53 mutation rates remain stable.[7,18,21,28,32,33] Another characteristic of EOCRC that has been reported – and also observed in our study – is the higher prevalence of LS-related gene mutations on the right side of the colon compared to the left[25,28,34,35]

EOCRC is often characterized by aggressive histopathological features, including poor differentiation, perineural and vascular invasion, mucinous and/or signet-ring cell histology, and a higher likelihood of advanced-stage diagnosis, with increased recurrence and metastasis rates.[7,8,15,21,36–39] A study based on the North American National Cancer Database reported that CRC patients younger than 50 years old had a significantly higher prevalence of poorly differentiated and undifferentiated tumors, mucinous and signet-ring cell histology, and advanced-stage disease than those aged 50 years or older.[40] Our study, which focused on EOCRC, showed that advanced-stage disease (Stage III + IV) was more prevalent than early-stage disease, accounting for 68.7 % of cases. The high prevalence of advanced-stage disease in EOCRC is likely due to the absence of routine screening programs, diagnostic delays, aggressive histopathological characteristics, and underlying genetic mutations that may accelerate tumor progression. However, some studies have yielded conflicting results. For instance, Hoang D.K. reported that the prevalence of advanced-stage disease was comparable to that of early-stage disease, while Ruiz-Grajales ÁE observed a predominance of well-differentiated tumors.[6,27]

Despite EOCRC often being diagnosed at an advanced stage with poor prognostic factors, some studies have reported superior survival outcomes across all stages, including higher 5-year survival rates following curative treatment.[15,21,41–46] Overall, younger CRC patients tend to have better survival outcomes than their older counterparts in early-stage disease, whereas in advanced-stage disease, their survival rates are comparable to – or even worse than – those of older patients at the same stage.[21,38,47] A 2021 study utilizing data from the National Cancer Database reported that among EOCRC patients younger than 50 years old, the 3-year and 5-year overall survival (OS) rates were 72.8 % and 63.2 %, respectively.[47] The corresponding results from our study were 77.1 % and 66.2 % across all stages. With respect to CRC prognostic factors, reports indicate that histology and tumor location may influence prognosis. Specifically, tumor differentiation is an independent adverse prognostic factor in CRC, associated with reduced DFS, decreased disease-specific survival (DSS), and an increased risk of recurrence.[48] Regarding primary tumor location, studies have reported that RCC has a worse prognosis than LCC, irrespective of stage or age.[1,49] In our study, the LCC group did not show significantly poorer OS and DFS compared to the RCC group, despite a significantly higher proportion of advanced-stage disease in the LCC group. This outcome may be attributed to the fact that LCC is generally associated with several favorable prognostic factors compared to RCC, as demonstrated in our study and supported by previous reports. These include more favorable histological features, lower prevalence of BRAF mutations and microsatellite instability, as well as differences in embryological origin and gut microbiota composition, which may contribute to a better treatment response.[1,49]

When evaluating the impact of individual somatic mutations in TP53, APC, and KRAS on overall survival, our results did not reveal statistical significance. However, multiple studies have consistently reported the prognostic relevance of mutations in these three genes. For instance, univariate analysis in Zhaoran Su's study identified TP53 and APC mutations as poor prognostic factors, whereas KRAS mutations had no significant impact on survival.[31] Similarly, M. C. Liebl reported that TP53 mutations were associated with poor chemotherapy response and worsened survival outcomes.[50] Meanwhile, B. Li reported that APC mutations were linked to reduced immunotherapy response and decreased overall survival.[51] Multiple studies have indicated that KRAS mutations contribute to reduced survival and resistance to anti-EGFR therapy; however, the prognostic impact varies depending on the specific KRAS variant.[52,53] A key finding in Zhaoran Su's study was that mutational status significantly correlated with prognosis, but not in a uniform manner. For instance, while APC and TP53 mutations were individually associated with poor prognosis, their co-occurrence resulted in better survival outcomes compared to TP53 mutation alone. Therefore, the authors suggested that an accurate prognosis requires assessing the combined effects of somatic mutations rather than evaluating individual gene mutations in isolation.[31]

5. Conclusion

The majority of EOCRC patients in our study had sporadic tumors, with a mean diagnostic delay of 2.5 months from symptom onset. LCC was more frequently diagnosed at an advanced stage than RCC; however, prognosis appeared to be independent of tumor location. The mean OS was 49 months (95 % CI: 45–54). Germline APC mutations were the most frequently observed, while LS-associated genes remained the predominant hereditary alterations. At the somatic level, TP53, APC, and KRAS were the most frequently mutated genes. Univariate analysis suggested an association between KRAS mutations and OS; however, this relationship lost significance in multivariate analysis. The prognostic impact of individual somatic mutations on OS remains inconclusive. Therefore, analyzing multi-gene mutation models should be considered for a more comprehensive prognostic assessment. Overall, in our study, disease stage was the only independent prognostic factor. A major limitation of our study is the small sample size and the absence of an LOCRC control group, which may limit the generalizability of our findings. Nevertheless, these findings contribute valuable insights to the limited research on EOCRC in Vietnam and Southeast Asia, particularly in terms of genetic mutation profiles.

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