Clinicopathological Features of KRAS-Mutated Colon Cancer: An Analytical Cross-Sectional Study

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Abstract

Background: Colon cancer is a leading neoplasm worldwide, with 35% to 45% of colorectal cancer (CRC) patients exhibiting mutations in the Kirsten rat sarcoma oncogene (*KRAS*). This mutation affects disease development and serves as a biomarker for early detection, prognosis, and treatment. The objective of the present study was to identify the clinicopathological characteristics of colon cancer patients with *KRAS* mutations.

Methods: An analytical cross-sectional study involving patients with CRC was conducted. The study variables included sex, age, tumor location, *KRAS* and B-Raf proto-oncogene (*BRAF*) mutations, and the presence of metastases.

Results: The study involved 51 patients, with a mean (standard deviation) age of 61.4 ± 11.0 years. The most common tumor location was the sigmoid colon (35.3%), and 45.1% of patients were classified as tumor, node, metastasis (TNM) stage III with lymph node dissemination. Genetic analysis revealed that 35% of patients had *KRAS* mutations, while 32% had *BRAF* mutations. Notably, 61.1% of KRAS-positive patients also had *BRAF* mutations compared to 15.1% of KRAS-negative patients (P = 0.02).

Conclusions: KRAS-positive patients predominantly had tumors in the sigmoid colon. The coexistence of *KRAS* and *BRAF* mutations suggests a potential molecular interaction influencing disease progression. These findings highlight a distinct genomic pattern and the need for further research into its clinical implications.

Keywords: *KRAS* mutation; Colon cancer; Clinicopathological features; Staging

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Introduction

Colorectal cancer (CRC) is one of the central neoplasms worldwide, becoming a focus of attention due to its high prevalence and mortality [1]. The World Health Organization has reported that it accounted for 10.4% of all cancer diagnoses in the last 5 years until 2020, with an age-adjusted incidence of 28.3 cases per 100,000 inhabitants annually [2]. This disease, which originates mainly in the epithelium of the colon and rectum, has shown an alarming increase in incidence, making it the second most diagnosed cancer globally [3].

The lifetime risk of CRC is similar in women and men, at 4.1% and 4.4%, respectively, although age-specific increases in incidence and mortality occur later in women than in men. The average age of diagnosis is 68 years in men and 72 years in women; however, in recent years, an increase in incidence has been observed in people younger than 50 years [4, 5].

About 80% of patients with colon cancer are sporadic; however, 20% have hereditary syndromes, which play a significant role in susceptibility to this disease. Syndromes such as Lynch syndrome or familial adenomatous polyposis follow an autosomal dominant inheritance pattern, where significant alterations occur in the genes associated with proteins responsible for repairing mismatch errors [2-4].

Certain diseases influence the site where this neoplasm appears; the behavior on the right side (cecum, ascending colon, hepatic angle, and transverse colon) is related to diseases not associated with polyps, such as Lynch syndrome and diabetes mellitus, since they share signaling pathway to cause damage to target organ [6]; on the left side (splenic angle, descending

colon, and sigmoid colon), it is more frequent in patients with a history of polyp-related diseases [7].

CRC is a disease of significant genetic heterogeneity from different genetic and epigenetic pathways. The progression from adenoma to adenocarcinoma involves inactivation of tumor suppressor genes such as adenomatous polyposis coli (*APC*), tumor suppressor gene TP53 (*TP53*), and deleted in colorectal cancer (*DCC*) and mutations in Kirsten rat sarcoma oncogene (*KRAS*), suppressor of mothers against decapentaplegic (*SMAD*), and B-Raf proto-oncogene (*BRAF*), which lead to genomic instability. As CRC increases in size, the adenoma portion may disappear or remain part of the tumor [8].

Kirsten rat sarcoma is a commonly mutated oncogene in CRC in 40% of all cases; its mutations result in constitutive activation of the KRAS protein, which acts as a molecular switch to persistently stimulate downstream signaling pathways, including cell proliferation and survival, leading to tumorigenesis [9].

KRAS mutations are more associated with right colon cancer than left colon cancer; they are also less likely to have a first-degree relative with CRC or to be smokers [10].

Codons 12 (G12), 13 (G13), and 61 (Q61) are the most frequent sites by up to 85%; among them, codon 12 mutation is dominant and accounts for 65%; the remaining represent mutations affected at codons, 146, 51, and 117 low-grade tumors and have a less poor mismatch repair status [9].

The G12C mutation occurs at position 12 of the *KRAS* gene, where an amino acid cysteine (C) replaces glycine (G). This mutation produces a mutated KRAS protein with altered function, which remains constitutively active; it causes short responses to standard chemotherapy and worse overall survival than non-G12C mutations. Several KRAS G12C inhibitors have demonstrated clinical activity in recent years, although all patients eventually progressed [11].

Identifying negative feedback through the epidermal growth factor receptor (EGFR) has led to the development of KRAS inhibitors plus an anti-EGFR combination, which enhances antitumor activity [12].

Among the genetic changes found in CRC is the p. V600E pathogenic variant of the *BRAF* gene, which encodes a serine/threonine kinase involved in the EGFR-mitogen-activated protein kinase (MAPK) signaling pathway. This variant is vital to this cancer, as it causes constitutive activation of the protein, resulting in inhibition of apoptosis and uncontrolled cell proliferation [13].

EGFR is an important therapeutic target in CRCs. The essential nature of *KRAS* mutation testing in clinical practice to predict resistance to EGFR inhibitors during the treatment of metastatic CRC offers a promising outlook in the battle against this disease.

Although the mutation of the *KRAS* gene is one of the most studied genetic alterations in CRC, several uncertainties persist, such as regional differences in the frequency of *KRAS* mutations, the influence of comorbidities on its clinical impact, and its coexistence with other mutations that may modify the response to targeted therapies and the overall prognosis of the patient. Furthermore, the role of *KRAS* in the early stages of CRC, its function in metastasis, and how it influences resistance to treatments such as EGFR inhibitors remain subjects of ongoing research. This study aimed to describe these uncertainties regarding the clinicopathological characteristics and potential prognostic implications of *KRAS* mutations in a regional cohort of colon cancer patients in western Mexico.

Materials and Methods

An analytical cross-sectional study, which involved 51 patients over 18 years of age with a diagnosis of colon cancer who underwent *KRAS* mutation testing, was conducted at the Hospital de Especialidades de Centro Medico Nacional de Occidente by the microsurgery service from January 2022 to January 2023. The key study variables were sex, age, tumor location, cell differentiation, staging, and *KRAS* and *BRAF* mutation.

The present study adhered to the ethical principles for research on human beings of the World Medical Assembly established in the Declaration of Helsinki of 1989 and to the General Health Law of the United Mexican States, which establishes in article 17, and to the regulations for health research in Mexico. The protocols for carrying out the project were approved by the local research and ethics committee of the Mexican Social Security Institute under registration number R-2023-1301-191.

KRAS detection

Representative areas of tissue with an adequate sample of neoplastic cells were selected. Histopathology confirmed the diagnosis of adenocarcinoma of the colon or rectum.

After tissue acquisition, we performed genomic DNA extraction with the highly precise commercial QIAamp DNA Mini Kit (QIAGEN). The qualitative detection of mutations in codons 12, 13, 61, 117, and 146 of the *KRAS* oncogene and codon 600 of the *BRAF* oncogene was carried out with the KRAS Mutation Analysis Kit and BRAF codon 600 Mutation Analysis Kit II (EntroGen) on the Cobas Z 480 kit (Roche), which has a reported detection limit of 1% mutant DNA on a 99% base of normal DNA (KRAS-BRAF).

Statistical analysis

The data collected from the anatomic pathology service were meticulously emptied into an Excel database and subsequently into the SPSS v26 statistical program for univariate descriptive and bivariate comparative analysis.

Our study findings, which we will discuss in detail, hold significant implications for the understanding and treatment of colon cancer with *KRAS* mutation. We will present the results of our univariate descriptive and bivariate comparative analysis, which were conducted using the SPSS v26 statistical program. Qualitative variables were expressed as frequency and percentages, while quantitative variables were expressed as mean ± standard deviation (SD). For the bivariate analysis, qualitative variables were compared using the Chi-square test, and quantitative variables were compared using the Student's

Table 1. Characteristics of Patients With Colon Cancer With *KRAS* Mutation

Variable	KRAS+ (n = 18)	KRAS- (n = 33)	P value	OR	95% CI
Male, n (%)	11 (61.1%)	22 (66.7%)	0.69[a]	0.78	0.2 - 2.5
Age, mean ± SD	66.5 ± 10.9	58.3 ± 10.1	0.01[b]		
≥ 60 years	16 (88.9%)	18 (54.5%)	0.01[a]	6.6	1.3 - 33
< 60 years	2 (11.1%)	15 (45.4%)	0.01[a]	0.15	0.03 - 0.7
Comorbilities, n (%)	18 (100%)	15 (45.4%)	0.001[a]	0	0
heart disease, n (%)	9 (50%)	9 (27.2%)	0.132[c]	2.6	0.8 - 8.8
Diabetes, n (%)	9 (50%)	5 (15.1%)	0.008[a]	5.6	1.4 - 21
Others (PCa, thyroid cancer, COPD, bladder cancer), n (%)	5 (27.7%)	2 (6.0%)	0.044[c]	5.9	1.0 - 34.7
Anatomical region					
Sigmoid	11 (61.1%)	10 (30.3%)	0.03	3.6	1.0 - 12
Rectum	3 (16.6%)	9 (27.2%)	0.393	0.53	0.1 - 2.2
Ascending colon	2 (11.1%)	7 (21.2%)	0.366	0.46	0.08 - 2.5
Descending colon	1 (5.6%)	6 (18.2%)	0.210	0.26	0.02 - 2.3
Transverse colon	1 (5.6%)	1 (3%)	0.657	1.88	0.1 - 32

[a]Chi-square test. [b]Student *t*-test. [c]Fisher exact test. CI: confidence interval; COPD: chronic obstructive pulmonary disease; *KRAS*: Kirsten rat sarcoma oncogene; OR: odds ratio; PCa: prostate cancer.

t-test for small samples. Differences were considered significant with a P-value < 0.05.

Results

General characteristics

Fifty-one patients with confirmed diagnoses of colon cancer were included, with a predominance of male sex in 31 (60.8%) and a mean age of 61 years (SD 11), hypertension in 13 (25.5%), diabetes in 11 (21.6%), cardiovascular in five (9.8%), prostate cancer in two (3.9%), thyroid cancer, bladder cancer, and chronic obstructive pulmonary disease (COPD) in one (2%).

Anatomical site

Regarding the location of the tumor, 18 (35.3%) of the patients presented a tumor mass identified in the sigmoid colon, 13 (25.5%) in the rectum, 11 (21.6%) in the ascending colon, seven (13.7%) in the descending colon, and two (3.9%) in the transverse colon.

Histological characteristics

As for the histological grade concerning the colon tumor, 37 (72.5%) of the lesions evaluated were moderately differentiated tumors, eight (15.7%) reported well-differentiated lesions, and only six (11.8%) were poorly differentiated. The most frequent histological type was tubular adenocarcinoma, present in 48 (94.1%) of the colon tumors identified in this population.

Staging

These lesions presented a staging by the tumor, node, metastasis (TNM) system, predominantly in stage III, accounting for 23 (45.1%) of all lesions observed. In comparison, stage IV was present in 18 (35.3%), stage II corresponded to seven (13.7%), and three (5.9%) presented a stage I. However, in the evaluation of tumor size for TNM stage determination, it was perceived that 23 (45.1%) presented T3 lesions, 10 (19.6%) T2 lesions, and seven (13.7%) T4 lesions. Invasion of lymph node tissue was observed in 19 (37.3%) of the patients presenting N1, 16 (33.3%) N2, and 14 (29.4%) N0. In this sample of patients, 34 (66.7%) presented distant metastases at the time of evaluation.

Identification of the *KRAS* gene

Of the 51 patients tested, genetic characteristics were found in 18 (35.7%) with *KRAS* mutation; among these, 10 mutations (55.6%) occurred in codon 12, five (27.8%) in codon 13, two (11%) in codon 61, and one (5.6%) in codon 146. No mutations were observed in codon 117. In contrast, 33 patients (64.7%) did not exhibit *KRAS* mutations. In contrast, *BRAF* gene mutations were detected in 16 patients (31.4%), while 35 patients (68.6%) tested negative for *BRAF* alterations.

Our analysis of patients with colon cancer and *KRAS* mutation revealed a significant finding: those with KRAS+ were typically over 60 years of age, a stark contrast to patients without this mutation. The risk of comorbidities was also notably higher in patients with the mutation, particularly for diabetes mellitus and other diseases such as prostate cancer, thyroid cancer, bladder cancer, and COPD. However, the most striking revelation was the prevalence of the mutation in the sigmoid colon, as detailed in Table 1, underscoring the importance of

Table 2. Histological Characteristics of Patients With Colon Cancer

Variable	KRAS+ (n = 18)	KRAS- (n = 33)	P value[a]	OR	95% CI
Histological grading					
Well-differentiated, n (%)	2 (11.1%)	4 (12.1%)	0.91	0.90	0.14 - 5.5
Moderately differentiated, n (%)	14 (77.7%)	25 (75.7%)	0.87	1.12	0.28 - 4.3
Poorly differentiated, n (%)	2 (11.1%)	4 (12.1%)	0.91	0.90	0.14 - 5.5
Histological type					
Tubular adenocarcinoma, n (%)	16 (88.8%)	29 (87.8%)	0.91	1.10	0.18 - 6.7
Mucinous adenocarcinoma, n (%)	2 (11.1%)	2 (6.0%)	0.52	1.93	0.24 - 15
Serrated Adenocarcinoma, n (%)	0 (0%)	2 (6.0%)	0.28	0	0

[a]Chi-square test. CI: confidence interval; KRAS: Kirsten rat sarcoma oncogene; OR: odds ratio.

this location in the context of colon cancer research.

The results of histological grade and TNM staging are shown in Tables 2 and 3.

No lymph node invasion and distant metastasis were identified in patients with *KRAS* mutation, presenting a higher proportion of N0 stage (P = 0.001), in contrast to patients without mutation, in which lymph node invasion was observed with a predominance of N1 stage (P = 0.18) (Fig. 1).

All patients with *KRAS* mutations received standard chemotherapy; none received anti-EGFR, in accordance with clinical guidelines.

The patients with the presence of *KRAS* mutation and its association with *BRAF* mutation are shown in Table 4.

Discussion

The present study reveals a prevalence of 35.7% for *KRAS* and 32.1% for *BRAF* in our population. Similar data were mentioned by Lee et al [14] in a study conducted on the Korean

Table 3. Tumor Staging of Colon Cancer Patients in Relation to *KRAS* Mutation

TNM stage	KRAS+ (n = 18)	KRAS- (n = 33)
I, n (%)	0 (0%)	0 (0%)
II, n (%)	2 (11.1%)	2 (6.0%)
IIa, n (%)	0 (0%)	0 (0%)
IIb, n (%)	2 (11.1%)	0 (0%)
IIc, n (%)	0 (0%)	2 (6.0%)
III, n (%)	5 (27.7%)	13 (39.3%)
IIIa, n (%)	2 (11.1%)	0 (0%)
IIIb, n (%)	2 (11.1%)	7 (21.2%)
IIIc, n (%)	2 (11.1%)	5 (15.5%)
IV, n (%)	11 (61.1%)	18 (54.5%)
IVa, n (%)	2 (11.1%)	4 (12.1%)
IVb, n (%)	7 (38.8%)	15 (45.4%)
IVc, n (%)	2 (11.1%)	0 (0%)

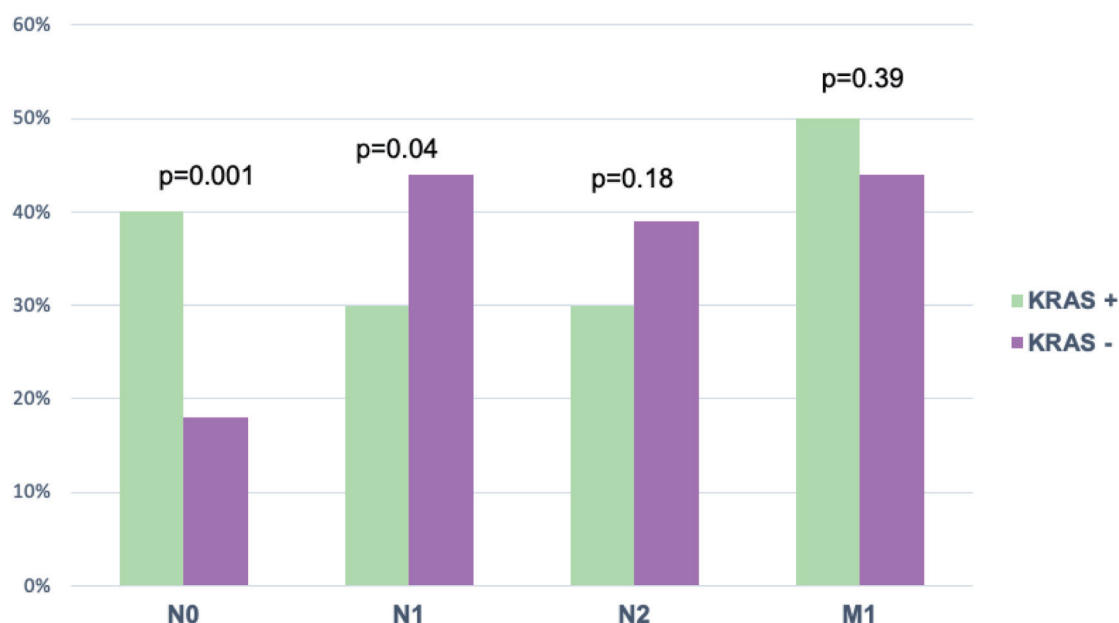*KRAS*: Kirsten rat sarcoma oncogene; TNM: tumor, node, metastasis.

population at Kangbuk Samsung Hospital in Seoul, South Korea. In this study, they evaluated 498 patients with colon cancer using *KRAS* sequencing. They identified a residual adenoma component, a precursor lesion of CRC [15], in 42 (8.4%) patients with CRC, which was associated with a high frequency of *KRAS* mutation (65%, P = 0.031). Among the 293 cases that received a *KRAS* mutation test, this mutation was identified in 37.9% of the population and located at codons 12 and 13 at a rate of 30.7% and 7.2%, respectively.

Yari et al [16] also supported these data in a study involving 100 consecutive patients with stage I to IV CRC who underwent surgical resection. They detected *KRAS* mutations in 29 patients (29%) at codons 12, 13, and 61 (72.4%, 20.7%, and 6.9%, respectively). However, unlike our findings, a study on the Mexican population conducted by Sanchez-Ibarra et al [17] in 2020 evaluated 500 patients with CRC from a hospital in northern Mexico and reported a *KRAS* mutation prevalence of 86%, with the most significant variant present in codon 12.

Patients with *KRAS* mutation were identified as older than 60 years in our population. They had a higher prevalence of comorbidities [18], specifically diabetes mellitus and other pathologies such as prostate, thyroid, bladder cancer, and COPD. Yari et al [16] reported similar findings, demonstrating that advanced age (> 60) was significantly associated with a higher rate of *KRAS* mutations. Regarding comorbidities, several studies have explored their association with *KRAS*, identifying an increased risk of mutation in the presence of metabolic, cardiovascular, and inflammatory diseases [19, 20]. These findings are consistent with our results and support the evidence linking *KRAS* mutations with advanced age and associated comorbidities.

The data showed that the sigmoid colon, as the anatomical site with the highest presence of *KRAS* mutation, is a crucial finding. Most cases did not show dissemination to lymph nodes, with stage N0 being more frequent in patients with the mutation and stage N1 in those without *KRAS*. These findings can guide treatment decisions and improve patient outcomes. However, this contrasts with Alharbi et al [21], who reported no significant differences between tumor location, clinical stage, or the presence of distant metastases. Kamphues [22], however, found that *KRAS* mutation in left-sided tumors decreases overall survival at 5 years due to the high risk of progression.

Figure 1. Nodal involvement and metastasis by TNM with *KRAS*. Values were expressed as percentages. Chi-square test was used for comparison. *KRAS*: Kirsten rat sarcoma oncogene; TNM: tumor, node, metastasis.

Study conclusions and contributions to disease understanding indicate that genetic variants vary substantially among different population groups. Therefore, it is relevant to contrast our data with that reported in the Mexican population by Sanchez-Ibarra et al [17]. Our study observed no differences between clinical stages, TNM categorization, or histological subtypes, contributing significantly to the understanding of the disease. However, we found greater involvement in the proximal colon for patients with *KRAS* mutation, whereas our study showed distal predominance in anatomical localization. The difference may be due to the sample size available in our study of patients with identified *KRAS* determination.

KRAS mutations were identified in 35.7% of patients, most frequently in codon 12 (55.6%), followed by codon 13 (27.8%), codon 61 (11%), and codon 146 (5.6%). These findings are consistent with those reported by Zhu et al who noted that mutations in codons 12 and 13 are the most common in CRC and are associated with resistance to anti-EGFR therapies and poor prognosis [9].

One of the most relevant findings in our population was identifying a significant association between *KRAS* and *BRAF* mutations, implying an interaction in the development and severity of the disease. Patients with positive *KRAS* reported a higher frequency of *BRAF* mutation [23] at 61.1%; in contrast, *BR*AF mutation was present in only 15.1% of patients without *KRAS* mutation. These data differ from Sanchez-Ibarra et al's [17] research, which identified a 6% prevalence of *BRAF* mutation. Hernandez-Sandoval et al [13] reported a prevalence of around 4% in the western Mexican population with CRC. In contrast, the Latin American population presents a higher prevalence, reaching 15%, still below the rate reported in our study. Although *KRAS* and *BRAF* mutations have traditionally been considered mutually exclusive in the literature due to their redundant roles in the MAPK signaling pathway, recent studies like Woolley et al have challenged this paradigm. In an analysis of 6,605 tumor samples, they identified co-occurrence of mutations in specific molecular subgroups, finding that class 2 and class 3 *BRAF* mutations (non-V600E) frequently co-occur with atypical mutations in the Ras pathway (including *KRAS*) in up to 45.7% of cases with class 3 *BRAF* mutations [24]. Therefore, although uncommon, the high co-mutation rate observed in our cohort does not contradict current literature; rather, it aligns with recent findings highlighting the molecular complexity of *BRAF* mutations and their interaction with *KRAS*, particularly in advanced clinical settings or in populations with distinct genetic profiles.

Table 4. *KRAS* and *BRAF* Mutation in Patients With Colon Cancer

BRAF mutation	KRAS+ (n = 18)	KRAS- (n = 33)	P value	OR	95% CI
Present, n (%)	11 (61.1%)	5 (15.1%)	0.001[a]	8.8	2.2 - 33
Absent, n (%)	7 (38.8%)	28 (84.8%)	0.056	3.5	0.9 - 13
CEA, mean ± SD	973.10 ± 162.53	132.15 ± 184.61	0.001[b]		

[a]Chi-square test. [b]Student's *t*-test. *BRAF*: B-Raf proto-oncogene; CEA: carcinoembryonic antigen; CI: confidence interval; *KRAS*: Kirsten rat sarcoma oncogene; OR: odds ratio.

The high prevalence of these variants in the present study suggests a possible interaction between oncogenes and a significant clinical role. However, it has been proposed that this interaction plays an essential role in treatment response [25]. A significant limitation of our study is the lack of long-term follow-up of patients, restricting our ability to understand the progression and prognosis of KRAS-mutated colon cancer fully. Long-term follow-up is crucial to assess survival, cancer recurrence, and response to different therapeutic modalities. Another significant area for improvement lies in the sample size; with only 51 patients, valuable and practice-relevant results can be obtained. However, due to the limited number of KRAS+ patients, the ability to generalize the findings to a broader population is limited.

Conclusion

In our study, we found that KRAS-positive patients predominantly presented with left-sided tumors, particularly in the sigmoid colon. The coexistence of *KRAS* and *BRAF* mutations suggests a potential molecular interaction that may influence disease progression. This finding could be attributed to a distinct genomic profile within the population studied, indicating a unique molecular pattern in CRCs. Further studies are warranted to elucidate the genetic interactions involved and their clinical implications.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Informed Consent

The authors confirm that all patients provided their written consent for participation in the study.

Author Contributions

HHG: design of the work, analysis, wrote the main manuscript text; EJCT: design of the work, wrote the main manuscript text; KDMM: design of the work, analysis, interpretation of data, wrote the main manuscript text; AG: analysis, interpretation of data, wrote the main manuscript text; XMA: interpretation of data, wrote the main manuscript text; VTHR: interpretation of data; CECT: interpretation of data, wrote the main manuscript text; JPGS: interpretation of data; ARVR: interpretation of data; SJVS: analysis; SEGM: analysis; AGO: analysis, interpretation of data; CFO: design of the work, analysis, interpretation of data. All authors reviewed the manuscript.

Data Availability

The data that support the findings of this study are available upon reasonable request from the corresponding author.

Abbreviations

APC: adenomatous polyposis coli; BRAF: B-Raf proto-oncogene; COPD: chronic obstructive pulmonary disease; CRC: colon cancer; DCC: deleted in colorectal cancer; EGFR: epidermal growth factor receptor; KRAS: Kirsten rat sarcoma oncogene; QIAGEN: QIAamp DNA Mini Kit; SMAD: suppressor of mothers against decapentaplegic; TNM: tumor, node, metastasis; TP53: tumor suppressor gene TP53

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