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Original Article

Molecular Markers and Survival Outcomes in Patients with Metastatic Colorectal Cancer at the Hospital de Especialidades Eugenio Espejo

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Abstract

Background and objectives: Colorectal cancer (CRC) ranks third in incidence and second in mortality worldwide. In Ecuador, there are 2,481 new CRC cases per year and 2,366 cancer deaths yearly. CRC presents in stages III-IV in more than 50% of patients. The standard treatment for CRC is chemotherapy, with an overall survival (OS) of 29–31 months. The status of biomarkers KRAS, NRAS, BRAF, and MSI provides prognostic and predictive value. This study aimed to determine OS and progression-free survival (PFS) for metastatic CRC based on these molecular markers with a minimum follow-up of one year.

Methods: This was an observational longitudinal analytical study at the Hospital de Especialidades Eugenio Espejo (HEEE). We obtained demographic, anatomopathological-molecular, and clinical data from the medical records of patients with metastatic CRC from July 1, 2018 until December 31, 2020.

Results: Data were collected from a total of 177 patients. The median follow-up was 21.6 months. The median PFS was 15 months (11.6–18.3) in those with mutated (MT) markers, 18 months (15.7–20.2) for wild type (WT), and 9 months (4.1–13.8) for not performed markers (NR), with a hazard ratio (HR) for PFS in MT versus WT of 0.76; the 95% confidence interval (CI) (0.4–1.4) with $p = 0.4$. for OS was 21 months (17.1–24.8) for MT markers, 22 months (17.7–26.2) for WT markers, and 19 months (17.7–20.2) for NR. There were no significant differences in OS for MT vs. WT: HR = 1.38, 95% CI (0.8–2.3) $p = 0.6$. There was no significant association between OS or PSF and KRAS, NRAS, BRAF, and MSI mutations. KRAS was the most mutated marker, with a frequency of 40.2%.

Conclusions: In the first monocentric study of mutations in metastatic CRC patients from Ecuador, patients with WT molecular markers reached the most prolonged OS and PFS, and KRAS had the highest mutation frequency. However, further studies with larger sample sizes are required to corroborate our findings.

Keywords: Colon cancer; Rectal cancer; KRAS; NRAS; BRAF; MSI.

Abbreviations: BRAF, v-Raf murine sarcoma viral oncogene homolog B; CI, confidence interval; CRC, colorectal cancer; HEEE, Hospital de Especialidades Eugenio Espejo; KRAS, Kirsten rat sarcoma virus; MSI, microsatellite instability; MT, mutated; NR, not performed molecular markers; NRAS, neuroblastoma RAS viral oncogene homolog; OS, overall survival; PFS, progression free survival; WT, wild type.

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Introduction

Colorectal cancer (CRC) is the third leading cause of cancer worldwide.[1] Ecuador has 2,481 new CRC cases every year and

2,366 cancer deaths per year.[2] In developing countries, mortality is influenced by factors commonly associated with metastatic disease presentation, including race and ethnicity (i.e. African American, Hispanic, and American Indian), low education and socioeconomic status, and people living in rural areas.[3] Importantly, the Ecuadorian population shares these risk factors.

Currently, CRC in Quito predominantly presents in stage IV in 36% of patients.[4] However, with advances in CRC molecular profiling using KRAS, NRAS, BRAF, and microsatellite instability (MSI) markers, prognostic and predictive results are now being integrated into clinical practice guidelines.[5]

Since 2008, it has been possible to prescribe vascular endothelial growth factor inhibitors such as bevacizumab. In combination with chemotherapy, such as oxaliplatin and irinotecan, CRC treatment can achieve an OS of 21.3 months and 25.8 months, respectively.[6,7] As of 2011, epithelial growth factor receptor inhibitors such as cetuximab, combined with oxaliplatin and irinotecan-based chemotherapy, have achieved OS of 22.8 and 28.7 months, respectively.[8,9] With these precedents, it is necessary to determine the OS and PFS using the molecular markers KRAS, NRAS, BRAF, and MSI in the Ecuadorian population. In this study, we are the first to determine OS and progression-free survival (PFS) in Ecuadorian patients with metastatic CRC based on these molecular markers at the Hospital de Especialidades Eugenio Espejo (HEEE).

Methods

This was an observational longitudinal analytical study conducted at the HEEE. This study followed the methodology of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE).[10] The inclusion criteria were as follows: patients over 18 years with a diagnosis of stage IV CRC or any stage plus progression or relapse of disease, and locally advanced unresectable disease. The exclusion criteria were as follows: the presence of a second primary tumor, and comorbidities (uncontrolled chronic kidney disease, uncontrolled type 2 diabetes mellitus, cardiac failure NYHA functional class III-IV, exacerbated COPD, Child-Pugh B, and C liver failure) that contraindicate oncologic treatment.

Demographic, anatomopathological, molecular (MSI, KRAS, NRAS, BRAF), and clinical data were collected from detailed medical records of patients with metastatic CRC, with a minimum follow-up of one year, death, or palliative care.

This study aimed to identify OS and PFS in patients with metastatic CRC based on molecular markers with a minimum follow-up of one year. OS was determined from the date of CRC diagnosis to the date of confirmation of death, loss to follow-up, or palliative care. PFS was determined from the date of diagnosis to the date of disease progression (identification of CRC during adjuvant treatment or first six months of follow-up) or relapse (identification of CRC during follow-up beyond six months).

The secondary objectives of this study were to determine the prevalence of mutated and non-mutated molecular markers, to verify a potential association between the anatomical primary tumor location to molecular markers, to verify a potential association between the anatomical location of metastases to molecular markers, and to compare OS according to the type of treatment given.

Data were recorded in a Microsoft Excel spreadsheet and analyzed with IBM SPSS Statistics for Windows (Version 25.0). After one year of follow-up, the Kaplan-Meier statistic and Log-Rank tests were used to determine the mean difference in PFS and OS. For the secondary objective, we specified the mutation frequencies in molecular markers. To verify the association, we used Cox regression adjusted for the status of molecular markers (MSI, KRAS, NRAS, and BRAF), treatment scheme, primary tumor location, and sites of metastasis. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Ethical statement

The teaching unit of the HEEE, the Research Committee of the Faculty of Medical Sciences of the Universidad Central del Ecuador (COIF) protocol number CM-COIF-CPONC-22- 005, and the Committee for Research on Human Beings of the Universidad Técnica Equinoccial (CEISH - UTE) protocol number CEISH-2022-034 granted the authorization. The study was carried out according to the ethical guide of the Helsinki Declaration. The individual consent for this study was waived according to the national regulations of Ecuador to obtain anonymized data provided by the institution. In this case Hospital de Especialidades Eugenio Espejo. Authorization was given by the teaching department and the CEISH (Ethics and Human Research Committee of the Universidad Técnica Equinoccial).

Results

Initially, 263 patients were identified from July 1, 2018 until December 31, 2020, but 86 patients were excluded based on the study criteria. Thus, 177 patients were included in the final analysis (Fig. 1). The mean follow-up of patients was 21.6 months (1–54).

Regarding patient characteristics, the patient population was predominantly female (109 females 61.6%; 68 males, 38.4%), and the mean age was 56.4 years. The rectum was the most frequent primary tumor location (87 patients, 49.2%). There were 35 patients (15.7%) with primary tumors in the right colon (ascending colon and transverse colon) and 142 patients (84.3%) with primary tumor in the left colon (descending colon, sigma, and rectum). The most common tumor stage was stage IVA (50 patients, 28.2%). Metastatic sites were most frequently distributed in non-regional lymph nodes (111 patients, 29.6%), followed by the liver, lung, and peritoneum. With regard to disease progression or relapse, the site most involved was at the local level (Table 1). The results of follow-up outcomes were 61 patients (34.0%) with progression and 30 patients (16.9%) with relapse of the disease. The median time to progression was 15.9 months (1–53). The median time to relapse was 17.5 months (3–50). The mean time to OS was 20 months (17.9–22.0), and 50.4% of patients were still alive. Furthermore, at the close of this investigation 39 patients (22%) remained alive (Table 2).

Physicians offered patients first-, second-, and third-line treatment in the metastatic setting. The most frequent surgery was discharging colostomy (25 patients, 14.1%), and radiotherapy was received by 64 patients (36.2%). Monoclonal antibodies were received by 52 patients (29.4%). The distribution of the most used chemotherapy regimens in the first line was FOLFOX (55 patients, 31%), in the second line were FOLFIRI and FOLFIRI plus bevacizumab (9 patients, 5%), and in the third line was FOLFIRI plus bevacizumab (3 patients, 1,6%). Eighty-seven patients carried mutations in the KRAS gene, which was the most frequent (71 patients, 40.2%) mutation located at codon 12/13 in (68 patients, 38.4%) (Table 3).

There was no significant association between KRAS ($p = 0.7$), NRAS ($p = 0.1$), and BRAF ($p = 0.1$) with the primary tumor location. Finally, there was a statistically significant association between primary tumor location and the MSI molecular marker ($p = 0.002$). When multiple linear regression was performed to determine the correlation with any possible sites in the right versus left colon, a negative association was identified. However, this association was not statistically significant. When multinomial logistic

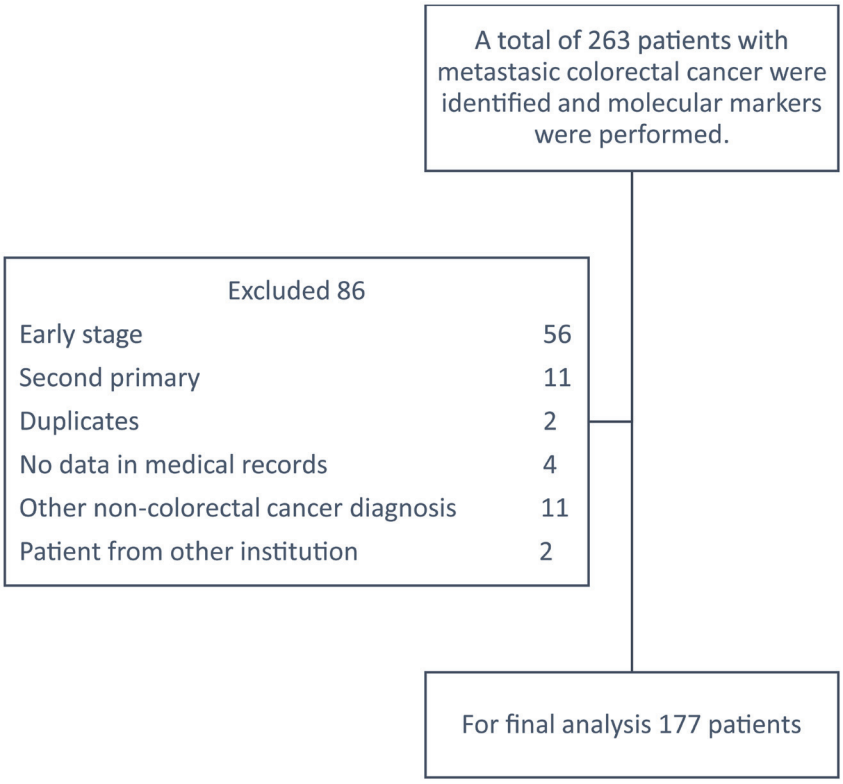

Fig. 1. Detailed selection of patients with metastatic CRC at the HEEE. CRC, colorectal cancer; HEEE, Hospital de Especialidades Eugenio Espejo.

regression was applied, mutated KRAS was positively associated with liver metastasis ($p = 0.002$), but not with lung, lymph nodes, peritoneum, or bone. There were no associations with metastasis location for NRAS, BRAF, and MSI.

The mean PFS was 15 months in the MT group, 18 months in the WT group, and 9 months in the NR groups with a hazard ratio (HR) for PFS in MT versus WT of 0.76 with a 95% confidence interval (CI) (0.4–1.4) ($p = 0.4$). The overall mean PFS was 15 months (12.3–17.6) (Fig. 2).

The PFS of those with KRAS in the WT group was 19 months, but this was not significantly different from the MT group (14 months) ($p = 0.2$). The PFS of those with NRAS in the WT group was 17 months, but this was not significantly different from the NR group (10 months) ($p = 0.1$). The PFS of those with BRAF in the MT group was 31 months, but this was not significantly different from the WT group (17 months) ($p = 0.1$). The PFS of those with MSI in the MSS group was 17 months, but this was not significantly different from the MSI-H group (15 months) ($p = 0.8$).

In the group of patients with MT molecular markers, the mean OS was 21 months; in the WT group, the mean OS was 22 months; and in the NR group, the mean OS was 19 months. Overall, the mean OS was 20 months (17.9–22.0). There were no significant differences in OS for MT vs. WT [HR = 1.38, 95% CI (0.8–2.3)] ($p = 0.6$) (Fig. 3).

OS in those with KRAS in the WT group was 22 months, but this was not significantly different than the MT group (20 months) ($p = 0.7$). The OS in those with NRAS in the WT group was 21 months, but this was not significantly different than the WT group (17 months) ($p = 0.6$). The OS in those with BRAF in the MT group was 29 months, but this was not significantly different than the WT group (21 months) ($p = 0.1$). Finally, the OS in those with MSI in the MSS group was 32 months, but this was not significantly different than the MSI-H group (20 months) ($p = 0.2$).

In the case of patients who received first-line treatment, there was no significant predilection for any of the schemes in better OS after applying the Cox proportional regression model. The treatment scheme that showed the best results in OS was FOLFIRINOX (36 months) ($p = 0.4$), followed by FOLFIRI plus bevacizumab (27 months) ($p = 0.2$), and FOLFOX plus cetuximab (27 months) ($p = 0.3$).

Discussion

This study reports OS as a function of molecular markers in CRC patients diagnosed at late stages in a specialist hospital in Ecuador. After a mean follow-up of 21.6 months, 50.4% of patients were still alive. There is a convergence in the survival curves at 20 months of follow-up between the groups evaluated. This may be due to periods of drug shortage, increased mortality associated with the SARS-COV-2 pandemic, and lack of response to the first-line treatment given the natural course of the disease. The OS in our study was higher compared to the OS (24 months, 35.9%) based on the SEER data for a similar follow-up period in the United States.[11] On the other hand, when comparing data from Latin America, 195 patients with metastatic CRC from Colombia reported an OS of 27% at 24 months.[12] As can be seen from these data, there is a marked difference between developed and developing countries. Thus, it is crucial to clarify why the OS presented in this study is higher than the data presented in the reference studies. This could be done by better characterizing the patients and including a more homogeneous

Table 1. Tumor characteristics of 177 patients with metastatic CRC at the HEEE

Variable	Value
Carcinoembryonic antigen	1,119.3 ng / ml (21–11,036)
Location of the primary tumor	
Ascending colon	30 (16.9%)
Descending colon	9 (5.1%)
Transverse colon	5 (2.8%)
Sigma	46 (26%)
Rectum	87 (49.2%)
Initial Stage	
I	6 (3.4%)
IIA	15 (8.5%)
IIB	3 (1.7%)
IIC	1 (0.6%)
IIIA	3 (1.7%)
IIIB	22 (12.4%)
IIIC	24 (13.6%)
IVA	50 (28.2%)
IVB	23 (13%)
IVC	30 (16.9%)
Histological type adenocarcinoma	
Tubular type	38 (21.5%)
Papillary type	5 (2.8%)
Mucinous type	32 (18.1%)
No special type	102 (57.6%)
Margins	
Not realized	107 (60.5%)
Free	43 (24.3%)
Committed	27 (15.3%)
Number of involved nodes	2.29 (0–27)
Number of resected nodes	11.79 (0–67)
Lymphovascular invasion	
Yes	40 (22.6%)
No	58 (32.8%)
Not performed	79 (44.6%)
Perineural invasion	
Yes	17 (9.6%)
No	79 (44.6%)
Not performed	81 (45.8%)
Obstruction or perforation	
None	94 (53.1%)
Obstruction	70 (39.5%)
Perforation	10 (5.6%)
Both	3 (1.7%)
Metastatic sites	
Liver	82 (21.9%)
Lung	79 (21.1%)
Nodes	111 (29.6%)
Peritoneum	45 (12%)
Bone	5 (1.3%)
Brain	1 (0.3%)
Others*	14 (3.7%)
Local	38 (10.1%)

*Others (bladder, pleura, ovary, skin, soft tissues, cervix, prostate, vulva, spleen). CRC, colorectal cancer; HEEE, Hospital de Especialidades Eugenio Espejo.

sample. Subsequent studies with a better design and sample selection should be done to validate our findings and substantiate the superiority of OS and PFS based on genetic, environmental, and demographic factors.

Patients with non-mutated molecular markers, such as the KRAS gene, have an average OS of 2 months difference compared to those with mutated KRAS (20 vs. 22 months). In a combined study of N-0147 and NSABP C-08 in patients with recurrent CRC and mutated KRAS, the OS was 23.8 months. In a subgroup of patients with a mutation in codon 13, the OS was 27.8 months, while in the group with unmutated KRAS the OS was 28 months.[13] Therefore, when analyzing OS according to molecular markers, there is a difference of 6 months in OS in cases of non-mutated KRAS. In the case of mutated KRAS, there was a difference of 3.8 months, which is in contrast to a study in Argentina, which reported no differences in OS based on KRAS gene mutation status.[14]

Concerning the BRAF molecular marker, those who presented with the V600E mutation had a better OS (29 months). However, this mutation was only observed in six patients, which contrasts with the 102 patients with BRAF mutations in the Sinicrope study who had a lower OS (14.5 months).[13] This finding is striking and suggests that this mutation has a poor prognostic value and is associated with high-risk features for metastasis.

KRAS had the highest mutation rate of 40.2% in this study. The College of American Pathology reports a KRAS mutation rate in 40–45% of patients.[15] Thus, compiling studies from Peru, Argentina, Mexico, and Colombia, the rate of KRAS mutations varies from 16.7% to 35%.[14,16–18] In this study, the BRAF mutation rate was 3.4%, which is comparable to data from Peru and Mexico, where BRAF mutations ranged from 4% to 9.9%[17,19] and to the global level of 7.8%.[20] As is evident, the observed data do not deviate from those reported.

With regard to the frequency of mutations in MMR genes, MSI-H status was the most frequently observed at 4%, which is considerably lower compared to 38.6% in Peruvian study of 90 patients[17] and 23% in a Colombian study of examined 575 cases.[21]

When determining the predilection of the primary tumor location with the molecular markers KRAS, NRAS, BRAF, and MSI, we found no association at any segment (ascending, transverse, descending colon, sigma, or rectum). There were also no significant differences when comparing the localization between the right and left sides. This is in contrast to a meta-analysis of 66 studies that included more than 1,000,000 patients, which found that tumors on the left side were associated with lower mortality.[22] It is essential to mention that the Cancer Genome Atlas showed that tumors on the left side have a better prognosis and are RAS WT, while those on the right side are RAS MT and BRAF WT, and some MSI-H with better prognosis.[23]

The limitations of this observational study were that the medical records were not homogeneous in the description of relevant data. Furthermore, not all patients had access to diagnosis or adequate follow-up. In addition, the physician ordered analysis based only on a subset of molecular markers, and there was a shortage of medicines. Finally, the SARS-COV-2 health emergency generated absenteeism, loss of follow-up, and irregularity in the treatment of patients.

Conclusions

In the first monocentric study of mutations in metastatic CRC patients from Ecuador, patients with wild-type molecular markers had the most prolonged OS and PFS compared to other studies in

Table 2. Distribution of follow-up outcomes of 177 patients with metastatic CRC at the HEEE

Variable	Value
Progression	
Yes	61 (34.5%)
No	116 (65.5%)
Relapse	
Yes	30 (16.9%)
No	147 (83.1%)
Unraveling	
Death	29 (16.4%)
Palliative	65 (36.4%)
Alive	39 (22%)
Loss of follow-up	44 (24.9%)
Number of months of follow-up	21.60 months (1–54)
The mean number of patients alive after a mean follow-up	90 patients (50.4%)

CRC, colorectal cancer; HEEE, Hospital de Especialidades Eugenio Espejo.

Table 3. Distribution of mutations in molecular markers in patients with metastatic CRC

Molecular marker	Frequency	Percentage
KRAS		
MT 12/13	68	38,4
MT 61	3	1,7
Not mutated	61	34,5
Not performed	45	25,4
Total	177	100
NRAS		
MT 61	2	1.1
Not mutated	130	73.4
Not performed	45	25.4
Total	177	100
BRAF		
Mutated	6	3.4
Not mutated	129	72.9
Not performed	42	23.7
Total	177	100
MSI		
MSS	1	0.6
MSI-L	1	0.6
MSI-H	7	4
Not performed	168	94.6
Total	177	100
Total mutations identified	87	

BRAF, v-Raf murine sarcoma viral oncogene homolog B; CRC, colorectal cancer; HEEE, Hospital de Especialidades Eugenio Espejo; microsatellite instability; MSS, microsatellite stability; MSI, MSI–L, low microsatellite instability; MSI–H, high microsatellite instability; MT, mutated; NRAS, neuroblastoma RAS viral oncogene homolog.

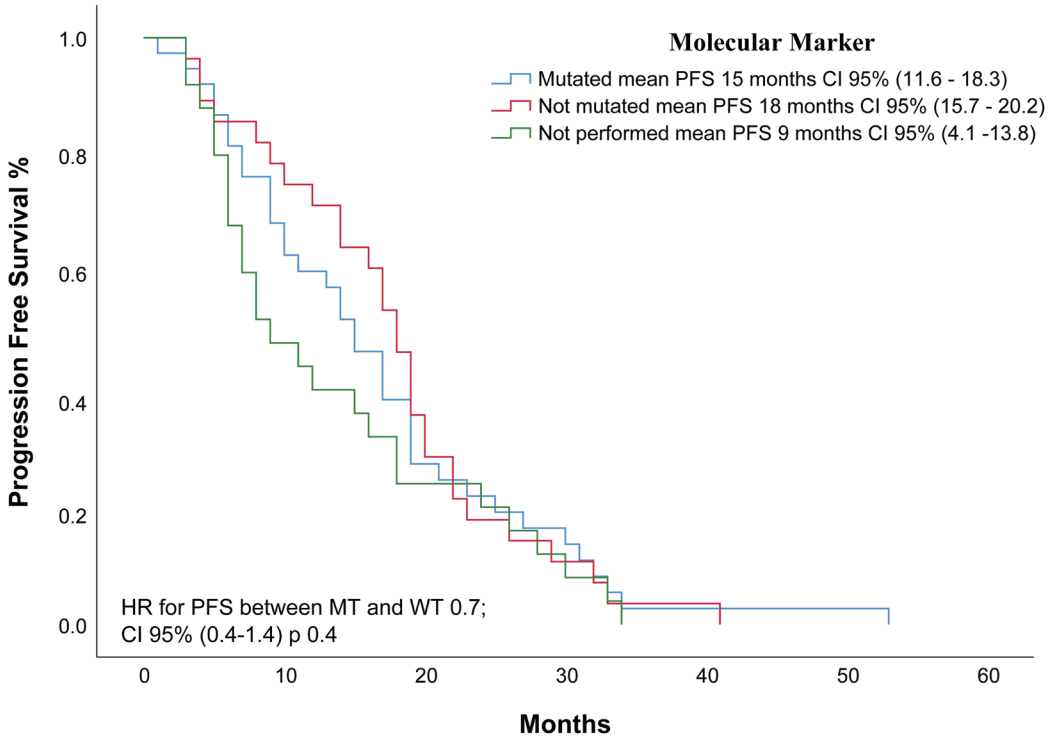

Fig. 2. Kaplan-Meier progression-free survival (PFS) in 177 patients with metastatic CRC at the HEEE according to molecular markers. Each treating physician evaluated and determined PFS by assessing control tomography. CI, confidence interval; CRC, colorectal cancer; HEEE, Hospital de Especialidades Eugenio Espejo; HR, hazard ratio; MT, mutated; PFS, progression-free survival; WT, wild type.

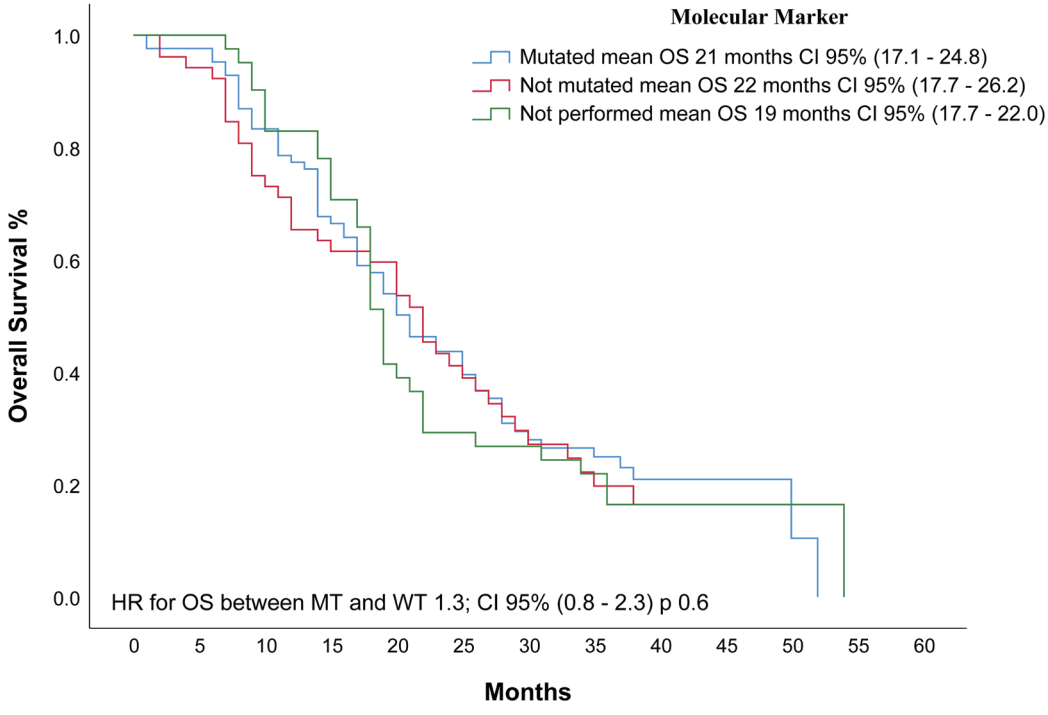

Fig. 3. Kaplan-Meier OS in 177 patients with metastatic CRC from the HEEE according to molecular markers. OS was determined based on medical records and their last follow-up date. CI, confidence interval; CRC, colorectal cancer; HEEE, Hospital de Especialidades Eugenio Espejo; HR, hazard ratio; MT, mutated; WT, wild type.

the region. However, given the heterogeneity of the sample and the non-standardized follow-up, caution should be exercised when interpreting these findings.

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Conflict of interest

None of the authors have any conflict of interest.

Author contributions

MF was responsible for data collection, medical records review, data analysis, and discussion; GG helped review and write the methodology; AM and AF helped in the final review of the paper; EP provided the final English translation; VZ, MB, and LG helped in data collection and medical records review.

Ethical statement

The teaching unit of the HEEE, the Research Committee of the Faculty of Medical Sciences of the Universidad Central del Ecuador (COIF) protocol number CM-COIF-CPONC-22- 005, and the Committee for Research on Human Beings of the Universidad Técnica Equinoccial (CEISH - UTE) protocol number CEISH-2022-034 granted the authorization. The study was carried out according to the ethical guide of the Helsinki Declaration. The individual consent for this study was waived according to the national regulations of Ecuador to obtain anonymized data provided by the institution. In this case Hospital de Especialidades Eugenio Espejo. Authorization was given by the teaching department and the CEISH (Ethics and Human Research Committee of the Universidad Técnica Equinoccial).

Data sharing statement

Technical appendix, statistical code, and datasets are available from the corresponding author upon request.

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