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ARTÍCULO ORIGINAL

Survival Outcomes of Metastatic Colorectal Cancer (mCRC) in A Single Practice Cohort in Medellín, Colombia

Resultados de supervivencia del cáncer colorrectal metastásico (CCRm) en una cohorte de una práctica en Medellín, Colombia

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Abstract

Therapy for mCRC is based on surgery, cytotoxic chemotherapy, and biologic agents. In randomized clinical trials, median progression-free survival (PFS) and overall survival (OS) hover around 10mo and 29mo, respectively. There are no published results on survival outcomes of patients with mCRC in Colombia. **Objective:** Describe the survival outcomes of patients with mCRC treated by Mauricio Lema in Medellín, Colombia. **Methods:** This is a retrospective, case series (2008-2020) of mCRC, ≥18 years old, treated with systemic therapy for metastatic disease, and ≥3-month follow-up. Stratification factors included: use of biologic (anti-VEGF or anti-EGFR) plus chemotherapy in 1st-Line (yes/no) and metastasectomy (yes/no). Survival analyses were evaluated using Kaplan-Meier curves. Results from the general population are described, and they are also discriminated against by the use of a biological agent in the first-line of systemic therapy. **Results:** 89 patients with mCRC were included. The Median follow-up was 35 months (IQR: 21-57). Median PFS and OS were 12.1mo (95%CI: 10.4-13.8) and 29.3mo (95%CI: 23.2-34.4), respectively. Median OS in patients receiving biologics was 28.8mo (95%CI: 22.1 – 35.6) vs 33.7mo (95%CI: 16.4 – 51.0) in the chemo-only group (p=0.01). Median OS in the metastasectomy and non-metastasectomy groups were 36.1 (95% CI: 26.5 - 45.7) and 25.0 months (95% CI: 15.4 - 34.5), respectively (NS). **Conclusion:** In this case series

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of patients' survival outcomes were similar to thosereported in large phase III trials. A small sample size precludes any conclusion as to the impact of biologic agents on survival in this study.

Keywords: Colonic neoplasms; neoplasm metastasis; biological therapy; bevacizumab; survival analysis.

Resumen

La terapia para CCRm consiste en cirugía, quimioterapia citotóxica y agentes biológicos. En los ensayos clínicos aleatorizados, la mediana de supervivencia libre de progresión (SLP) y supervivencia global (SG) ronda los 10 y 29 meses, respectivamente. No existen publicaciones sobre los resultados de supervivencia en CCRM en Colombia. **Objetivo:** Describir los resultados de supervivencia de pacientes con CCRm tratados por Mauricio Lema, Medellín, Colombia. **Métodos:** Serie de casos retrospectiva (2008-2020) de CCRm, ≥18 años, tratados con terapia sistémica para la enfermedad metastásica y seguimiento ≥3 meses. Los factores de estratificación incluyeron: uso de biológico (anti VEGF/anti EGFR) más quimioterapia en 1ª línea (sí/no) y metastasectomía (sí/no). Se realizó análisis de supervivencia con Kaplan-Meier. Se describen los resultados discriminados por el uso de un agente biológico en la primera línea de tratamiento. **Resultados:** Se incluyeron 89 pacientes con CCRm. Mediana de seguimiento: 35 meses (RIQ: 21-57). Mediana de SLP fue 12,1 meses (IC95%: 10,4-13,8) y SG fue 29,3 meses (IC95%: 23,2-34,4). La mediana de SG en quienes recibieron biológicos fue 28,8 meses (IC95%: 22,1-35,6) frente a 33,7 meses (IC95%: 16,4-51,0) en el grupo de quimioterapia sola (p = 0,01). La mediana de SG en los grupos con metastasectomía, y sin metastasectomía fue de 36,1 (IC95%: 26,5-45,7), y 25,0 meses (IC95%: 15,4-34,5) respectivamente (NS). **Conclusión:** Los resultados de supervivencia fueron similares a los informados en grandes ensayos de fase III. El tamaño de la muestra excluye cualquier conclusión sobre el impacto de los agentes biológicos en la supervivencia en este estudio.

Palabras clave: Neoplasias del colon; metástasis de la neoplasia; terapia biológica; bevacizumab; análisis de supervivencia.

Introduction

Colorectal cancer is the third most common cancer worldwide, with approximately 1.9 million cases diagnosed annually worldwide. [1] In addition, it represents the second cause of death from cancer with 935 thousand deaths per year. Colorectal cancer incidence rates have steadily increased in many countries in Eastern Europe, South-East and Central Asia, and South America. [2,3] The incidence and mortality of colorectal cancer in Colombia is 16.9 / 100,000 inhabitants-years and 8.2 / 100,000 inhabitants-years, respectively. [4] Colorectal cancer ranks third and fifth in cancer incidence and mortality in Colombia, respectively. Approximately 20% of colorectal cancer patients will experience metastatic disease. [5] In a study from a center in Medellín, de-Novo metastatic involvement was found in 22.1%, and development of metastasis in an additional 15.2%[6] The survival of patients with metastatic colorectal cancer (mCRC) has improved markedly in recent decades due to advances in surgery for metastatic disease, as well as in systemic therapies. Current therapeutic options for mCRC are diverse and consist of chemotherapeutic drugs such as 5-fluorouracil, capecitabine, oxaliplatin, irinotecan, TAS-102; targeted therapies such as cetuximab, panitumumab, bevacizumab, regorafenib. [7] Immune checkpoint inhibitors have improved survival in patients with mCRC and microsatellite instability. [8,9] With these advances, median survival has gone from 6

months with supportive therapy to 30 months. [7] In the small subset of patients with operable mCRC, median survival exceeds 5 years. [10]

In Colombia, the survival outcomes of patients with mCRC is not known, so this research aims to describe the demographic, clinical characteristics, progression-free survival (PFS) and overall survival (OS) of patients with mCRC treated in the practice of an oncologist (ML) in two centers, in Medellín, Colombia, between 2008 and 2020.

Methods

This is an observational retrospective study aimed to describe survival outcomes of patients with mCRC undergoing systemic therapy for metastatic disease in a solo oncology practice in a real world setting in Medellín, Colombia. Eligibility criteria included: 1. Patients older than 18 years, 2. Histological diagnosis of metastatic colorectal carcinoma, 3. Treated by an oncologist (ML) at either the Clínica SOMA, or the Clínica de Oncología Astorga, both in Medellín, between 2008 and 2020, 4. Subjects must have received systemic therapy for metastatic disease, with a minimum follow-up of 3 months. Patients with histology other than carcinoma and those who started systemic treatment for metastatic disease at another institution were excluded.

Data was extracted from medical records. Sociodemographic variables were collected, such as age at diagnosis, sex, type of health insurance (contributory, subsidized) and site of residence. Clinical variables, such as the location of the primary tumor (right colon, left colon, rectum); histological type (adenocarcinoma, squamous cell carcinoma); degree of histological differentiation; stage at initial diagnosis; the presence of a KRAS mutation, if available. Information on the treatment received by patients, such as chemotherapy and biological therapies used; the performance, or not of, metastasectomy; and response to treatment. Survival outcomes such as progression-free survival (PFS, defined as the time elapsed between the start of treatment for metastatic disease, and progression after first line of systemic therapy for metastatic disease) and overall survival (OS, defined as the time elapsed between the start of treatment for metastatic disease, and death) were established. Patients were stratified according to administration of chemotherapy with or without a biological agent (bevacizumab or anti-EGFR monoclonal antibody) in first line for metastatic disease. These will be referred from now on as: biol-1L, and non-biol-1L, respectively. Patients were also stratified according to the performance of cytoreductive surgery for metastatic disease (metastasectomy), or not (non-metastasectomy).

The date of death was obtained from any reliable source such as: medical records, from the database of the Sectional Secretary of Health and Social Protection of Antioquia, the ADRES (Administrator of the Resources of the General System of Social Security in Health) database, or the Registrar's Office National Civil Status (another governmental institution). August 31, 2020 was defined as the closing date for obtaining the information for PFS and the OS. Patients in whom their vital status could not be known from the mentioned sources were censored on the date of the last clinical contact.

Results were analyzed using the SPSS V 22 statistical software. The data obtained from nominal qualitative variables were summarized with absolute and relative frequencies. Quantitative variables were expressed with median and interquartile range (IQR), according to the symmetry of the variable. Survival was estimated with the Kaplan-Meier method.

Results

Between 2008 and 2020, 380 medical charts of patients with colorectal cancer were found, of which 291 were excluded (Figure 1). For analysis, 89 patients were included. These were divided into two groups according to the systemic treatment administered in first line for mCRC: 62 (69.6%) in the biol-1L, and 27 (30.3%) in the non-biol-1L groups, respectively *(Figure 1)*.

Median age at diagnosis was 59 years (IQR 54-69). 56.2% were men and 86.5% belonged to the regimen contributivo (government-regulated health insurance for workers and

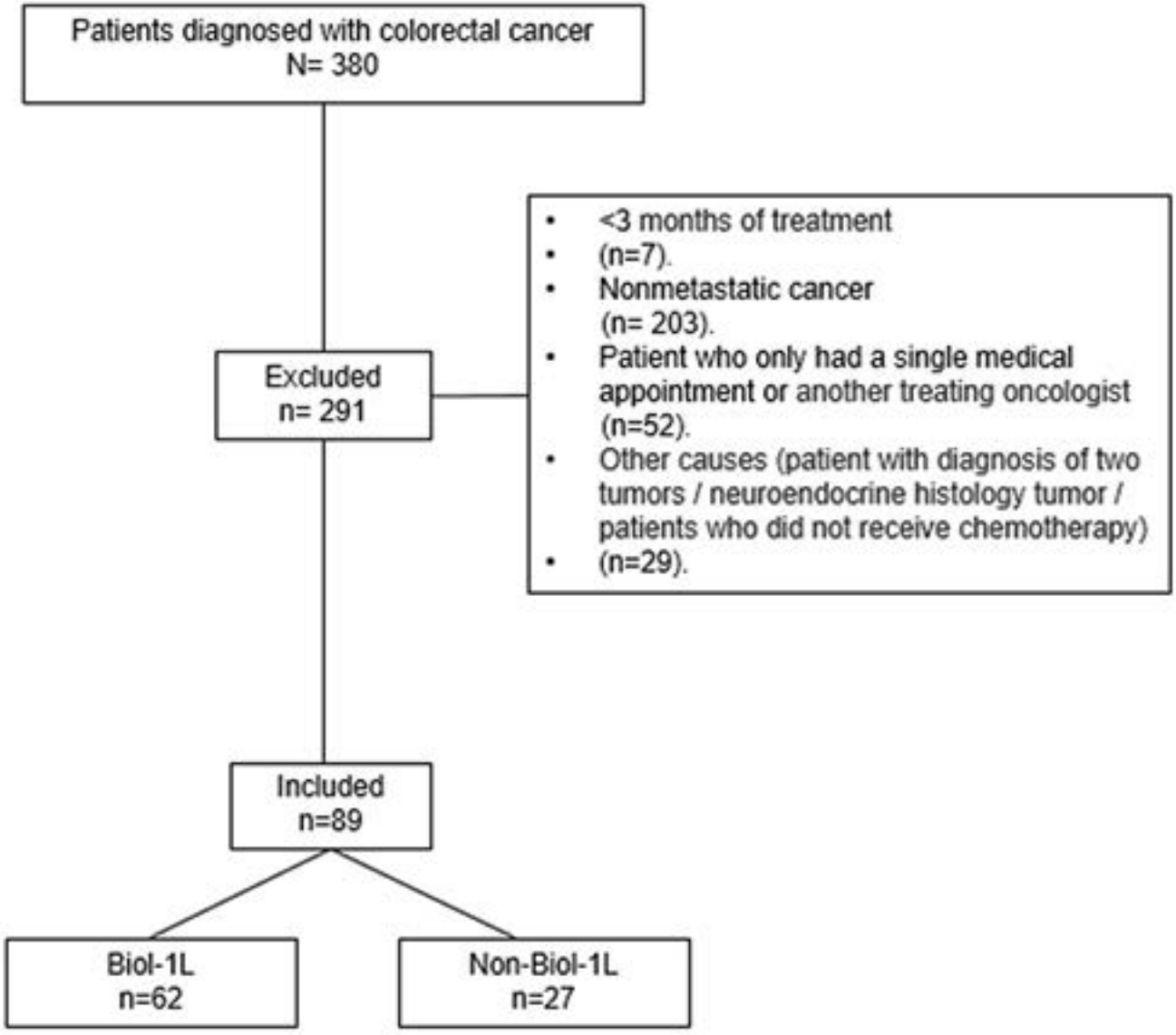

Figure 1. Patient´s flowchart.

their families). The distribution by location of the primary tumor was left colon in 37 (41.6%), right colon 22 (24.7%), and rectum in 29 (32.6%). Adenocarcinoma was the histology in 98.9%. The initial presentation was stage IV in 42 (47.2%), and stage III in 31 (34.8%) *(Table 1)*. Performance status was not recorded in 41.6%. RAS mutation status was also unavailable in 43.8%. Therefore, both variables were excluded from the analysis.

Table 2 summarizes the description of the surgical and pharmacological treatment and outcomes of the study population. A total of 69 (77.5%) of the patients required surgical management of the primary tumor. Of the 27 (30.3%) underwent metastasectomy. Of these, 17 (63.0%) and 10 (37.0%) in the biol-1L and non-biol-1L, respectively. Local recurrence resection was performed in 8 (9.0%) patients. Of these, 6 (75.0%) belonged to the non-biol-1L. No statistically significant differences between biol-1L and non-biol-1L groups for the surgically treated for metastatic disease group was found *(Table 2)*.

Pelvic radiotherapy was restricted to patients with rectal cancer. Pelvic radiotherapy was administered to 5/29 (17.2%) patients. Of these, 80.0% (4/5) received a biological agent combined with chemotherapy in the first-line.

Table 1. Sociodemographic and clinical characteristics of the patient population.

Variable	Total N=89		Biol -1L (n=62)		Non -Biol -1L (n=27)		P
Sociodemographic							
Age	59 (RIQ 54-69)		60 (RIQ 55-70)		57 (RIQ 47-65)		0.048
Sex - n (%)							
Female	39	(43.8)	25	(40.3)	14	(51.9)	0.219
Male	50	(56.2)	37	(59.7)	13	(48.1)	
Type of insurance - n (%)							
Contributivo	77	(86.5)	52	(83.9)	25	(92.6)	0.226*
Subsidiado	12	(13.5)	10	(16.1)	2	(7.4)	
Clinical variables							
Primary tumor site – n (%)							
Left colon	37	(41.6)	29	(46.8)	8	(29.6)	0.402
Right colon	22	(24.7)	14	(22.6)	8	(29.6)	
Rectum	29	(32.6)	18	(29.0)	11	(40.7)	
Unknown	1	(1.1)	1	(1.6)	0		
Pathology - n (%)							
Adenocarcinoma	88	(98.9)	61	(98.4)	27	100	1
Squamous	1	(1.1)	1	(1.6)			
Grade differentiation - n (%)							
Well-	58	(65.2)	41	(66.1)	17	(63.0)	0.51*
Moderate-	16	(18.0)	12	(19.4)	4	(14.8)	
Poor-	6	(6.7)	3	(4.8)	3	(11.1)	
Unknown	9	(10.1)	6	(9.7)	3	(11.1)	
Stage at presentation - n (%)							
I	1	(1.1)	1	(1.6)	0		0.389*
II	11	(12.4)	7	(11.3)	4	(14.8)	
III	31	(34.8)	21	(33.9)	10	(37.0)	
IV	42	(47.2)	31	(50.0)	11	(40.7)	
Unknown	4	(4.5)	2	(3.2)	2	(7.4)	

+Median (Interquartile range)
*Fisher Exact Test

Table 2. Surgical and systemic treatment of the patient population.

Treatment	Total N=89		Biol-1L (n=62)		Non-biol-1L (n=27)		P
Surgery							
Surgery at initial presentation - n (%)							
Yes	69	(77.5)	45	(72.6)	24	(88.9)	0.105
No	20	(22.5)	17	(27.4)	3	(11.1)	
Metastasectomy – n (%)							
No information	1	(1.1)	1	(1.6)	0		0.455
No	61	(68.5)	44	(71.0)	17	(63.0)	
Yes	27	(30.3)	17	(27.4)	10	(37.0)	
Resection of local recurrence – n (%)							
No information	1	(1.1)	0		1	(3.7)	0.003*
No	80	(89.9)	60	(96.8)	20	(74.1)	
Yes	8	(9.0)	2	(3.2)	6	(22.2)	
Systemic therapy							
First-line systemic therapy (1L)							
FOLFIRI plus Bevacizumab	34	(38.2)	34	(54.8)			<0.001*
FOLFOX plus Bevacizumab	18	(20.2)	18	(29.0)			
FOLFIRI	3	(3.4)			3	(11.1)	
FOLFOX	12	(13.5)			12	(44.4)	
FOLFOXIRI	2	(2.2)			2	(7.4)	
FOLFOXIRI plus Bevacizumab	1	(1.1)	1	(1.6)			
FULV	6	(6.7)			6	(22.2)	
FULV plus Bevacizumab	2	(2.2)	2	(3.2)			
XELOX	3	(3.4)			3	(11.1)	
XELOX plus Bevacizumab	4	(4.5)	4	(6.5)			
IFL plus Bevacizumab	1	(1.1)	1	(1.6)			
Carboplatino + paclitaxel	1	(1.1)			1	(3.7)	
Cetuximab + carboplatino + fluoruracilo	1	(1.1)	1	(1.6)			
FLOX plus Bevacizumab	1	(1.1)	1	(1.6)			
Best response to 1L therapy - n (%)							
Complete	30	(33.7)	15	(24.2)	15	(55.6)	0.024*
Partial	12	(13.5)	10	(16.1)	2	(7.4)	
Stable	15	(16.9)	13	(21.0)	2	(7.4)	

Progression	23	(25.8)	18	(29.0)	5	(18.5)	
Not specified	9	(10.1)	6	(9.7)	3	(11.1)	
Disease progression after 1L – n (%)							
Yes	75	(84.3)	54	(87.1)	21	(77.8)	0.211
No	14	(15.7)	8	(12.9)	6	(22.2)	
Survival status - n (%)							
Alive	22	(24.7)	14	(22.6)	8	(29.6)	
Lost to follow-up	3	(3.4)	1	(1.6)	2	(7.4)	
Dead	64	(71.9)	47	(75.8)	17	(63.0)	
Disease-related	56	(87.5)	44	(93.6)	12	(70.6)	0.261
Not disease-related	1	(1.5)	1	(2.1)	0		
Unknown	7	(11.0)	2	(4.3)	5	(29.4)	
* P value <0,05							

In regard to first-line systemic therapy, FOLFIRI plus bevacizumab was administered to 34 (54.8%) of the patients who received first-line biologic. While the combination of fluoropyrimidine plus oxaliplatin was used as the first-line in 15 (55.6%) of the patients who did not receive a biologic agent in first-line.

When evaluating the best response to the first line, a complete response was achieved in 30 (33.7%). There were statistically significant differences between the groups (P = 0.024) *(Table 2)*.

Biological agent was administered at some point during their illness in 70 of 89 (78.7%). The most widely used biologic agent in all lines of treatment was bevacizumab. Biological agent was used in both the first-line and in subsequent lines in 34/89 (38.2%) patients. The same biological agent was used beyond first-line of treatment in 28/89 (31.5%) and a different biological agent was used beyond the first-line in 14/89 (15.7%). Eight patients received the same biological and a different one in subsequent lines.

Disease progression after first-line occurred in 75 (84.3%) patients. Progression was documented in 54 out of 62 patients in biol-1L group (87.1%). Progression was documented in 21 out of 27 patients in the non-biol-1L group (77.8%). There were no statistically significant differences between groups *(Table 2)*.

At the time of study cut-off, with a median follow-up of 35 months (IQR: 21-57), 64 patients (71.9%) had died. Death was disease-related in 56 (87.5%). Three patients were lost to follow-up. No statistically significant difference on the risk of death between biol-1L and non-biol-1L groups was found *(Table 2)*.

The median overall survival (OS) in the total population was 29.3 months (95% CI: 23.2 - 34.4) (Figure 2A). The median progression-free survival (PFS) was 12.1 months (95% CI: 10.4-13.8) (Figure 2B). The median OS was 28.8 months (95% CI: 22.1 - 35.6) in the biol-1L group. Median OS was 33.7 months (95% CI: 16.4 - 51.0) in the non-biol-1L group. These differences were statistically significant, in favor of the group that did not receive biologic agents in first line (Log-Rank test = 5.99; P = 0.014) *(Figure 3A)*.

Median PFS was 12.1 months (95% CI: 10.4-13.8) in the biol-1L group, and 12.0 months (95% CI: 5.5 - 18.5) for non-biol-1L group. These differences were not statistically significant (log-Rank test = 1.85; P = 0.174) *(Figure 3B)*.

Median OS in the metastasectomy group was 36.1 months (95% CI: 26.5 - 45.7). In the non-

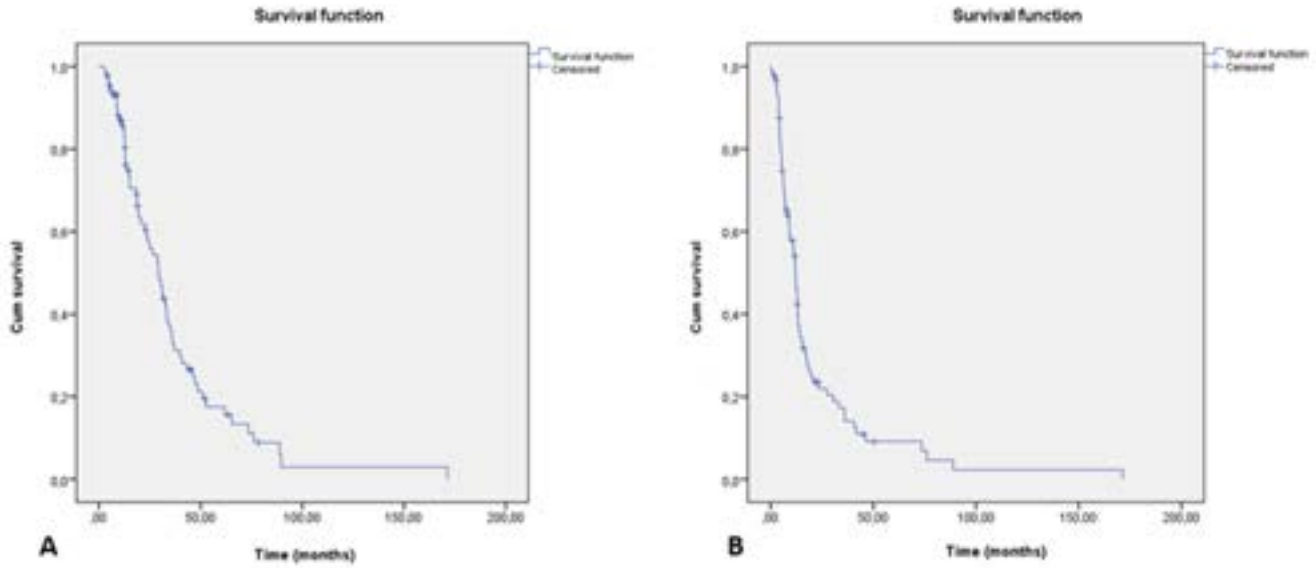

Figure 2. Kaplan-Meier survival curves in patients with metastatic colorectal cancer. A. Overall survival. B. Progression-free survival.

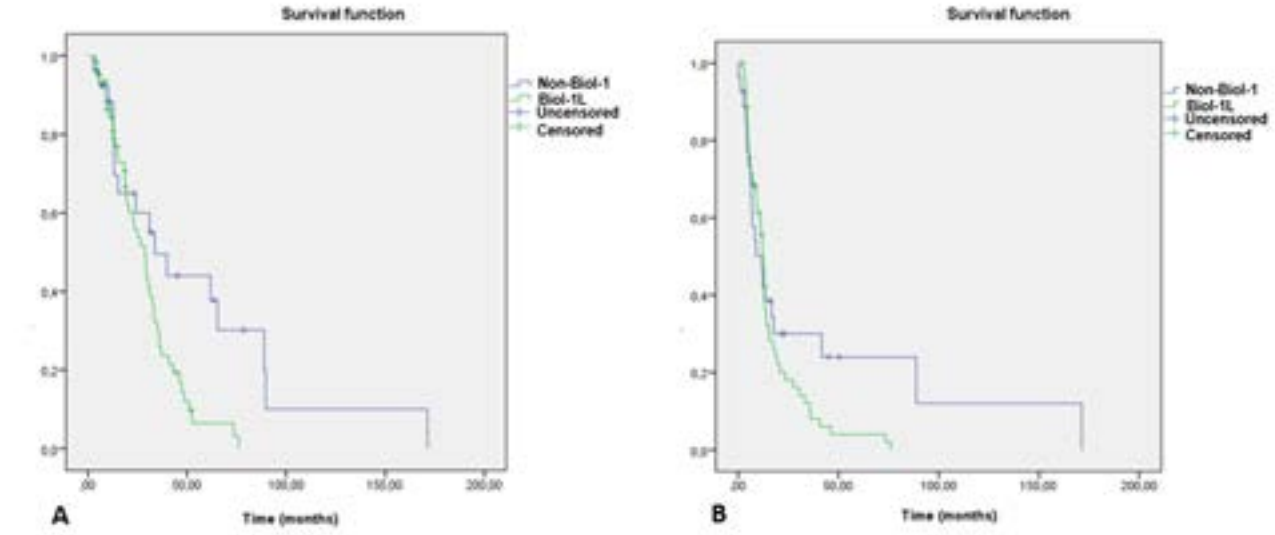

Figure 3. Kaplan-Meier survival curves in patients with metastatic colorectal cancer according to the use of a biologic agent in first-line. A. Overall survival B. Progression-free survival. Green: Biologic agent included in the first-line. Blue: No biologic included in the first-line.

metastasectomy group, median OS was 25.0 months (95% CI: 15.4 - 34.5). This difference did not reach statistical significance (Log-Rank test = 2.83; P = 0.92). Median OS was 36.0 months (95% CI: 32.0 - 40.0) for the metastasectomy/biol-1L group. Median OS was 61.9 months (95% CI: 0 - 154.6) in the metastasectomy/non-biol-1L group. There were no statistically significant differences between these groups (log-Rank test = 2.96; P = 0.085).

Median OS in the non-metastasectomy group were 23.3 months (95% CI: 15.4 - 31.2) and 33.7 months (95% CI: 2.8 - 64.6), in the biol-1L and non-biol-1L, respectively. There were no statistically significant differences between these groups (Log-Rank test = 2.49; P = 0.115).

Discussion

This real-life evidence study describes the survival outcomes of a cohort of patients with metastatic colorectal cancer in Medellín, Colombia. To our knowledge, the survival outcomes for mCRC in Colombia have not been published. Other colon cancer studies conducted in Colombia focus on epidemiological, clinical, or non-metastatic disease. [11–13] From these studies, it is highlighted that the 5-year survival of patients with colorectal cancer in Cali went from 29.7% in 1995-1999, to 39.8% in 2000-2004. [11] It should be noted that this study included patients at all stages. The Bucaramanga population registry focuses on the incidence and mortality rates of various types of cancers, including colorectal. [13] However, colorectal cancer specific PFS or OS is not reported in this study. A cohort of 1500 patients was reported by the Institudo de Cancerología de Medellín. [6] In this study, 66.7% and 63.9% for colon and rectal cancer patients were alive at the 27.3 months' follow-up, respectively. Overall survival inferred from the charts for stage IV was less than 20 months, [6] However, no explicit discussion is made about the survival of the cohort with mCRC in this study.

PFS and OS observed in our study were similar to those reported in the literature. [14,15] Survival outcomes in modern, large phase III studies, show a median survival of 25-30 months. [14,15] Patients with resectable metastatic disease are excluded from these studies. Median survival in this cohort was 25 months. We find these results consistent with the literature.

The median survival of patients with metastasectomy in our cohort was 36.1 months. It was higher than that of unresected mCRC. However, OS in this subgroup was lower than reported in the literature. [16] No explanation can be glimpsed from our data. We speculate that difference in patient selection and surgical expertise could explain some of the differences.

Surprisingly, it was evidenced that OS of the group that received biological therapy in the study cohort was not superior to that of the group that only received chemotherapy. The reason for this finding cannot be stated with certainty. The possibility of imbalances between the groups is speculated (but not proven in formal statistical analysis). Specifically, the patients in the metastasectomy group, a good prognosis group, were more likely to belong to the non-biol-1L group. This difference did not reach statistical significance, presumably due to the low numbers involved.

The main strength of this study is that it shows survival outcomes in patients with metastatic colorectal cancer, in a real-life setting, in Colombia, which are close to those reported in the literature. As far as we know, this is the first study focused on survival outcomes of metastatic colorectal cancer in Colombia to be published.

We recognize several weaknesses to this study. First, this study is retrospective in nature. Second, there was considerable treatment heterogeneity, despite being prescribed by a single specialist. All administered treatments were within internationally accepted guidelines, but no treatment sequence algorithm was pre-specified. Third, another weakness of this study was the absence of some variables of potential importance such as universal genotyping for KRAS, and the unavailability of the report of the performance status at the beginning of treatment in a large proportion of patients. Fourth, this study included a low number of patients, which makes it difficult to explain some of the unexpected results. Finally, for some time it has been recognized that several molecular subtypes of the disease are grouped under the name colorectal cancer, with great divergence in their response and survival patterns. [17] It can be speculated that the relative contribution of each molecular subtype in a cohort could determine key survival outcomes. Molecular subtyping could not be ascertained in the study patient population.

Despite its weaknesses, this study contributes to the experience of oncology practice in Colombia. We conclude that modern systemic therapy for metastatic colorectal cancer is feasible, with survival outcomes similar to those reported in the literature.

The present study becomes a starting point that will be used as the historic baseline for

comparison for the ongoing prospective Clínica de Oncología Astorga's institutional cancer registry.

Ethical aspects

In accordance with the Resolution 8430 of 1993 that establishes the scientific, technical and administrative standards for health research in Colombia, this study is classified within the category of research without risk. The study was approved by the Ethics Committee for Clinical Research of the Fundación Centro de Investigación Clínica (CIC) de Medellín in full compliance with international standards of Good Clinical Practice.

Conflicts of interest

To carry out the study, an independent grant was received from Pfizer (Innovation for Evidence-I4E Call from the Pfizer Colombia Scientific Institute - ICPC). Within the last 10 years, Dr. Mauricio Lema has not received honoraria or fees for lectures or for an advisory role on the use of biological agents described in the study from the pharmaceutical industry (i.e., ROCHE, Merck). The other authors did not declare any conflict of interest.

Collaborations

Mauricio Lema Medina. Conception and study design, interpretation of results, manuscript writing and critical review.

Beatriz Elena Preciado Franco. Study design, review of medical records, data acquisition, critical review of intellectual content.

Camila Lema Calidonio. Study design, acquisition, analysis and interpretation of the results, manuscript writing and critical review.

Ana María Romero Millán, Sara Paulina Mora Vélez y Mónica Patricia Ríos Fergusson. Review of medical records, data acquisition.

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