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Clinicopathological Characteristics of Metastatic Colorectal Cancer Patients with Prolonged Survival

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ABSTRACT

Objective: The median overall survival (OS) of metastatic colorectal cancer (mCRC) has reached 30 months in recent trials; however, data on the the clinicopathological features of long-term survivors remain limited.

Material and Methods: This is a single-center retrospective analysis of the clinical, pathological, and genetic characteristics of patients who survived more than 30 months after diagnosis of mCRC.

Results: Fifty-eight patients were included; mean age was 59.7±10.0 years. At diagnosis, 63.8% of patients had stage 4 disease and 84.5% had left-sided tumors. All underwent primary tumor surgery; a KRAS mutation was present in 48.3% of patients. Of the patients, 84.5% received local treatment, with metastasectomy being the most common (70.7%). The identified mutations were PIK3A (3 patients), SMAD4 (2), ERBB3 (1), MAP2K and FGFR (1), and germline POL (1) mutations. The most common metastatic sites were the liver (65.5%), the lungs (56.9%), and the peritoneum (15.5%). The Fluoropyrimidine-oxaliplatin combination was the most commonly used first-line treatment (59.6%). The median OS was not reached (range: 31.5-217.03 months). Univariate analysis identified female gender (p=0.019), KRAS mutation (p=0.033), higher number of metastatic lesions (p=0.016), increased number of treatment lines (p=0.001), and liver metastases in segments 6 (p<0.001) and 8 (p=0.007) as poor prognostic factors. Multivariate analysis confirmed that female sex (p=0.036), KRAS mutation (p=0.02), liver metastasis in segment 6 (p=0.018), and an increased number of treatment lines (p=0.007) were associated with poorer survival.

Conclusion: Patients with mCRC and above-average survival constituted a heterogeneous group. However, female sex, KRAS mutation, and segment 6 liver metastasis were associated with poor prognosis. Primary tumor surgery may have contributed to prolonged survival, warranting further comparative studies to guide clinical decisions.

Keywords: Prolonged; survival; colorectal; cancer

INTRODUCTION

According to the Global Cancer Statistics 2022, colorectal cancer (CRC) is the third most commonly diagnosed cancer, with approximately 2 million cases, and the second leading cause of cancer-related deaths.[1] Although the overall burden of CRC has decreased in recent years, the disease's presentation has shifted to a less favorable clinical pattern. Compared to the 1990s, CRC patients are now typically younger, more likely to have right-sided tumors, and present at more advanced stages.[2] Although the five-year survival rate for metastatic colorectal cancer (mCRC) remains 10-15%, advances in understanding disease biology and targeted therapies are improving median survival rates for mCRC patients in phase 3 trials.[3] Recent trials indicate that the median overall survival (OS) in patients with mCRC has reached approximately 30 months, thanks to ongoing treatment developments.[4,5] However, there remains a subset of patients who experience prolonged survival despite metastatic disease. Identifying the key characteristics of these patients is crucial for a better understanding of disease biology and for determining which patients are most likely to benefit from treatment.

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In this study, we evaluated the clinicopathological characteristics of patients who survived more than 30 months following diagnosis of metastatic colorectal carcinoma.

MATERIAL AND METHODS

Study Design and Patient Population

This study is a single-center, retrospective cohort analysis. Patients diagnosed with mCRC in the past 10 years were evaluated retrospectively. The cohort included patients who either initially presented with metastatic disease or progressed to metastatic disease after initial surgery, with or without adjuvant therapy. Only patients who survived more than 30 months after the initial diagnosis of mCRC were included in the study. The Exclusion criteria were non-metastatic disease and missing survival data. This study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the Gazi University Rectorate Institutional ethics Committee (approval number: 2025-436, date: 17.03.2025).

Data Collection and Endpoints

Demographic characteristics of the patients, including gender and age at diagnosis, were recorded. Data on the primary tumor's localization, histological subtype, and molecular markers (KRAS, NRAS, BRAF, and microsatellite status, if available) were collected. Additionally, information on metastasis type (synchronous or metachronous) and location was documented. Patients' treatment histories, including details on surgical interventions, systemic therapies, and local treatments, were retrieved from electronic health records and patient files. Beyond KRAS, NRAS, BRAF, and microsatellite status, germline mutations and next-generation sequencing (NGS) results were recorded when available. The primary endpoint of the study was OS.

Statistical Analysis

Statistical analyses were performed with IBM SPSS software version 25.0 (S.P.S.S. Inc., Chicago, IL, USA). Categorical variables are presented as counts and percentages. The mean and standard deviation for normally distributed variables and the median and interquartile range (25^{th}–75^{th} percentiles) for non-normally distributed variables were reported. Normality was assessed using the Kolmogorov-Smirnov test. Survival estimates were calculated using the log-rank test and presented as Kaplan-Meier curves. Survival data were expressed as hazard ratios with 95% confidence intervals (CIs). Cox regression models using the enter method were used to perform univariate and multivariate analyses of OS. When performing multivariate analysis, variables that were statistically significant in univariate analysis and those that were clinically significant were selected. Statistical significance was determined by two-tailed p-values ≤0.05.

RESULTS

Demographics and Baseline Tumor Characteristics

A total of 58 patients were included in this study. The mean age was 59.7±10 years, and 72.4% of the patients were male. Among them, 36 (62.1%) had colon cancer, while 22 (37.9%) had rectal cancer. The primary tumor was located in the right colon in only 9 patients (15.5%). At initial presentation, 63.8% of the patients had stage 4 disease. The most common sites of metastasis were the liver (65.5%), lungs (56.9%), and peritoneum (15.5%). KRAS mutations were detected in 48.3% of patients, whereas microsatellite instability was observed in only one patient (Table 1).

TABLE 1: Clinicopathological features of patients.

Variable	Cohort (n=58)
Age (years)	59.7±10
Gender (n, %)	
Male	42 (72.4%)
Female	16 (27.6%)
Tumor localisation (n, %)	
Colon	36 (62.1%)
Rectum	22 (37.9%)
Sidedness (n, %)	
Right colon	9 (15.5%)
Left colon	49 (84.5%)
Stage at diagnosis (n, %)	
Stage 1	3 (5.2%)
Stage 2	5 (8.6%)
Stage 3	13 (22.4%)
Stage 4	37 (63.8%)
Pathology (n, %)	
Adenocarcinoma	54 (93.1%)
Mucinous carcinoma	3 (5.2%)
Signet-cell carcinoma	1 (1.7%)
Differentiation (n, %)	
Well	19 (32.8%)
Moderate	27 (46.6%)
Poor	2 (3.4%)
Unknown	10 (17.2%)
KRAS (n, %)	
Mutant	28 (48.3%)
Wild	26 (44.8%)
Unknown	4 (6.9%)

TABLE 1: Continued	
Variable	**Cohort (n=58)**
NRAS (n, %)	
Mutant	0 (0%)
Wild	42 (72.4%)
Unknown	16 (27.6%)
BRAF (n, %)	
Mutant	2 (3.4%)
Wild	40 (69.4%)
Unknown	16 (27.6%)
Microsatellite status (n, %)	
Microsatellite stable	45 (77.6%)
Microsatellite instable	1 (1.7%)
Unknown	12 (20.7%)
Metastasis site (n, %)	
Liver	38 (65.5%)
Lung	33 (56.9%)
Peritoneum	9 (15.5%)
Soft tissue	5 (8.6%)
Bone	4 (6.9%)
Surrenal gland	1 (1.7%)
Spleen	1 (1.7%)
Metastatic liver segment (n, %)	
Segment 2	8 (14.5%)
Segment 3	5 (9.1%)
Segment 4a	14 (25.5%)
Segment 5	8 (14.5%)
Segment 6	16 (29.1%)
Segment 7	16 (29.1%)
Segment 8	14 (25.5)
Number of metastatic organ site at first presentation (n, %)	
Single organ	55 (94.8%)
Multiple organs	3 (5.2%)
Number of metastases at first presentation (n, %)	
Single lesion	25 (43.1%)
Multiple lesions	25 (43.1%)
Unknown	8 (13.8%)

Twelve patients underwent NGS, and one underwent germline genetic testing. The germline test revealed a POLH mutation. Among the patients who underwent NGS, one had a PIK3A+SMAD4 mutation; one had an ERBB3 mutation; one had an SMAD4 mutation; one had a MAP2K1+FGFR1 mutation; and two had a PIK3A mutation. No identifiable mutations were detected by NGS in the remaining six patients.

Treatment History of the Patients

Sixteen patients (27.6%) received neoadjuvant treatment. All patients had undergone surgery for the primary tumor, including those who initially presented with metastatic disease. Among the 20 patients, the primary tumor was resected at diagnosis, when the disease was non-metastatic. Of the 37 patients who presented with metastatic disease, 14 underwent emergency surgery due to ileus or subileus; 5 underwent surgery after an excellent response to first-line therapy; and 7 underwent palliative surgery for severe symptoms (3 for bleeding, 2 for severe constipation, and 2 for pain). The remaining 11 patients were referred to our clinic postoperatively, and the exact indication for their initial surgery was unknown. A Fluoropyrimidine combined with oxaliplatin was the most commonly used first-line treatment regimen (61.4%). The median number of treatment lines received by patients was 2 (range: 1-8). Among the patients, 70.7% underwent metastasectomy, 24.1% underwent radiofrequency ablation, 15.5% underwent radiotherapy, and 6.9% underwent transarterial chemoembolization or radioembolization (TACE/TARE) as local treatments (Table 2). Among the patients who underwent local treatment, 27 underwent only metastasectomy; 6 underwent metastasectomy plus radiofrequency ablation (RF); 1 underwent metastasectomy plus TACE/TARE; 4 underwent metastasectomy plus radiotherapy (RT); 1 underwent metastasectomy plus RF plus TACE/TARE; 2 underwent metastasectomy plus RF plus TACE/TARE plus RT; 5 underwent only RF; and 3 underwent only RT.

TABLE 2: Treatment modalities received by patients.	
Variable	**Cohort (n=58)**
Neoadjuvant treatment (n, %)	
No	42 (72.4%)
Yes	16 (27.6%)
Surgical resection of the primary tumour (n, %)	58 (100%)
First-line treatment* (n, %)	
XELOX	24 (42.1%)
FOLFOX	11 (19.3%)
FOLFOX+panitumumab/cetuximab	8 (14%)
FOLFOX+bevacizumab	4 (7%)
FOLFIRINOX	4 (7%)
Capecitabine	1 (1.8%)
FOLFIRI+bevacizumab	3 (5.3%)
FOLFIRI+panitumumab/cetuximab	1 (1.8%)
FOLFIRINOX+bevacizumab	1 (1.8%)

TABLE 2: Continued

Variable	Cohort (n=58)
Number of the treatment lines (median; minimum-maximum)	2 (1-8)
Chemotherapeutics* (n, %)	
Fluoropyrimidine	57 (100%)
Oxaliplatin	51 (89.5%)
Irinotecan	37 (64.9%)
Bevacizumab	29 (50.9%)
Anti-EGFR	16 (28.1%)
Regorafenib	19 (33.3%)
Aflibercept	5 (8.8%)
Trifluridine/tipiracil	1 (1.8%)
Temozolamide	5 (8.8%)
Local treatments (n, %)	
Metastasectomy	41 (70.7%)
RF ablation	14 (24.1%)
TARE/TACE	4 (6.9%)
RT	9 (15.5%)

*: Since the treatment information for one patient was missing, the calculation was performed on 57 patients; EGFR: Epidermal growth factor receptor; FOLFOX: 5-FU+leucovorin+oxaliplatin, FOLFIRI: 5-FU+leucovorin+irinotecan; FOLFIRINOX: 5-FU+leucovorin+oxaliplatin+irinotecan; RF ablation: Radiofrequency ablation; RT: Radiotherapy; TARE/TACE: Transarterial radioembolization/transarterial chemoembolization; XELOX: Capecitabine+oxaliplatin.

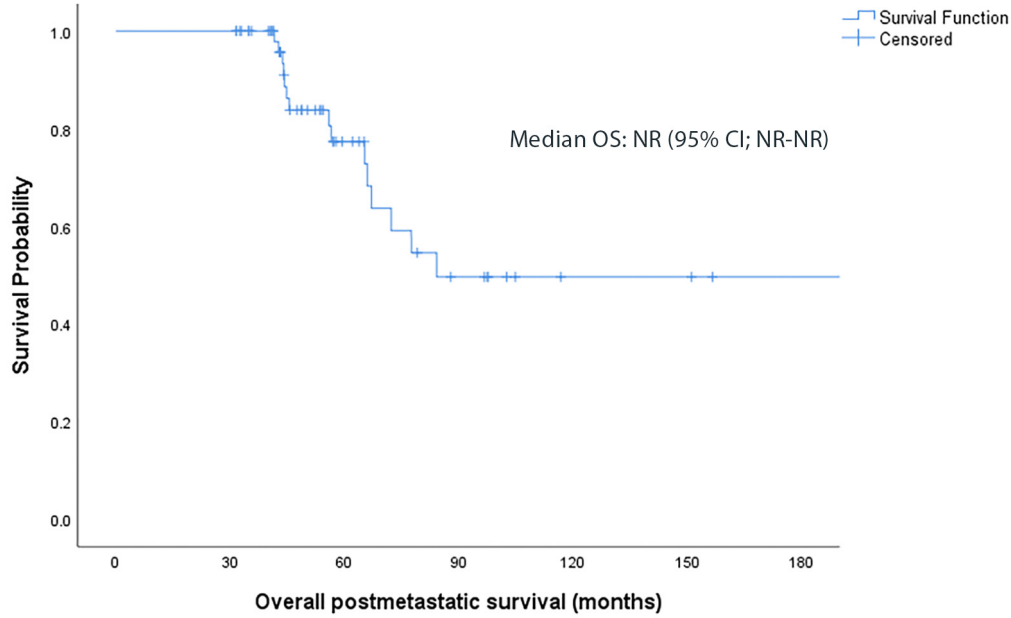
Survival Analysis

The median follow-up of the cohort was 57.2 months (95% CI: 50.2-64.1 months). The median survival of the patients was not reached (95% CI: NR-NR; range, 31.5-217.03 months) (Figure 1). In univariate Cox regression analysis, female gender (p=0.019), presence of a KRAS mutation (p=0.033), a higher number of metastases at diagnosis (p=0.016), an increased number of treatment lines (p=0.01), and metastases in liver segments 6 (p<0.001) and 8 (p=0.007) were associated with worse OS. In the multivariate analysis, only female gender (p=0.036), the presence of a KRAS mutation (p=0.02), an increased number of treatment lines (p=0.007), and metastases in liver segment 6 (p=0.018) remained significantly associated with poorer OS (Table 3). OS stratified by gender and KRAS mutation is shown in Figures 2A, B.

DISCUSSION

In this study, we evaluated the clinicopathological characteristics of patients with mCRC who exhibited extended survival. All patients had a history of surgery for the primary tumor, and a significant proportion underwent local treatments. Female sex, presence of a KRAS mutation, and metastases in liver segment 6 were associated with poorer OS.

CRC was the second leading cause of cancer-related mortality in 2022.[1] Over the past decade, significant advancements have been made in its treatment. Available treatment options



Number at risk	58	20	9	3	3	1

FIGURE 1: Overall survival of the patients after diagnosed with metastatic colorectal cancer.

CI: Confidence interval; NR: Not reached; OS: Overall survival.

include surgical resection, liver-directed therapies, targeted therapies, immunotherapy, and systemic chemotherapy.[6-8] Despite these advances, the long-term survival rates for patients with mCRC remain poor.[3] However, a subset of patients exhibits exceptional responses to treatment and achieves extended survival. Identifying the clinical, pathological, and genomic characteristics of this patient group is crucial for determining which patients may benefit most from treatment.

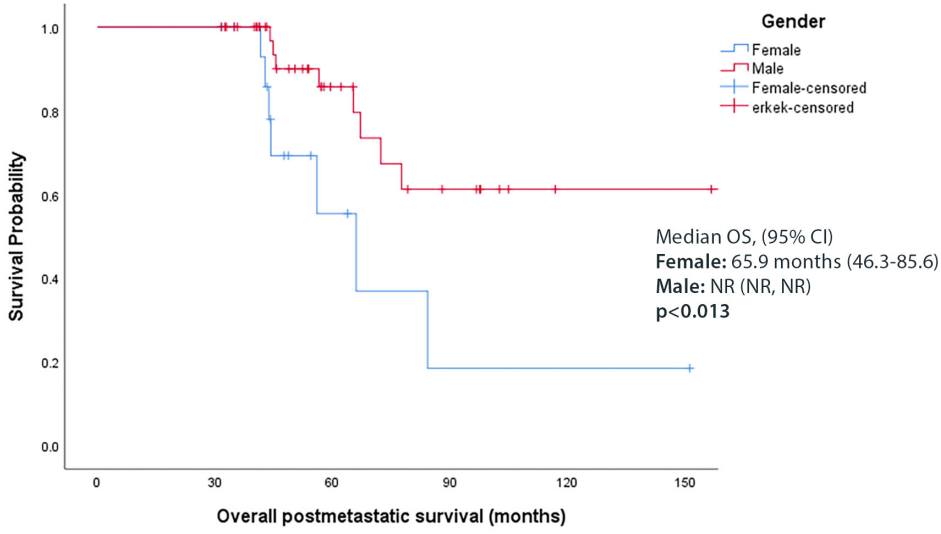
There is no universally accepted definition of long-term survival in mCRC. While some studies have used 36 months as a cut-off,[9] others have defined it as 5 years.[10] Since the median survival of patients with mCRC was approximately 30 months in recent phase 3 studies.[4,5] we defined long-term survival in this study as survival beyond 30 months.

One of the most notable findings of this study is that all patients underwent surgery for the primary tumor, even in the metastatic setting. Currently, there is no consensus regarding the resection of the primary tumor in mCRC. However, several studies support the idea that primary tumor resection may offer a survival advantage, even in the metastatic setting.

TABLE 3: Cox regression analysis of overall survival.

Variable	Univariate analysis		Multivariate analysis	
	HR [95% CI]	p-value	HR [95% CI]	p-value
Gender Female (ref.) Male	0.292 [0.105-0.815]	**0.019**	0.174 [0.034-0.891]	**0.036**
Number of metastatic lesions at first presentation	4.835 [1.337-17.481]	**0.016**	0.411 [0.27-6.257]	0.522
KRAS mutation Absent (ref.) Present	3.294 [1.098-9.877]	**0.033**	10.98 [1.45-83.18]	**0.02**
Liver segment 6 metastases	12.76 [3.479-46.788]	**<0.001**	31.37 [1.82-538.71]	**0.018**
Liver segment 8 metastases	4.171 [1.472-11.819]	**0.007**	4.29 [0.522-35.35]	0.175
Number of the treatment lines	1.424 [1.160-1.749]	**0.001**	1.590 [1.134-2.231]	**0.007**

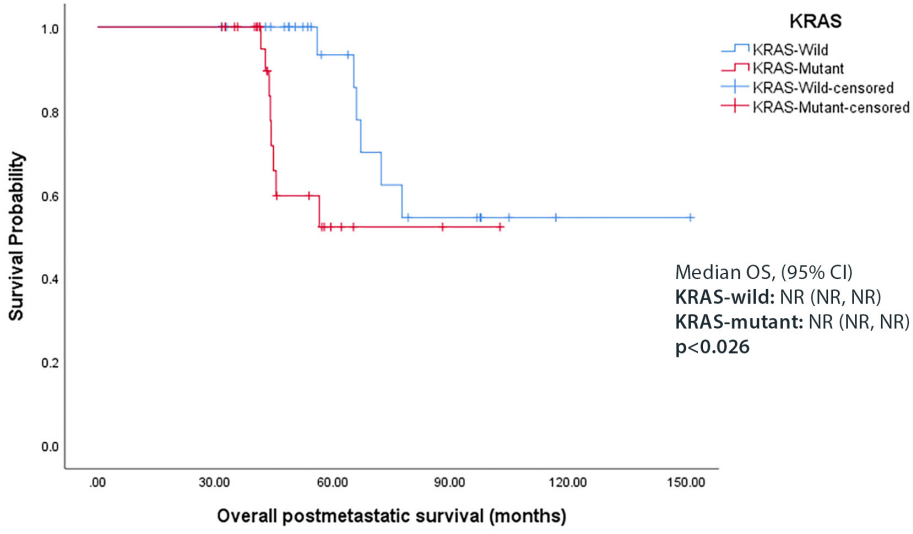
HR: Hazard ratio; CI: Confidence interval.



Number at risk					
Male	42	16	8	2	2
Female	16	4	1	1	1

FIGURE 2A: Overall postmetastatic survival of patients stratified by gender.

CI: Confidence interval; NR: Not reached; OS: Overall survival.



Number at risk					
KRAS-wild	26	13	6	1	1
KRAS-mutant	28	4	1	-	-

FIGURE 2B: Overall postmetastatic survival of patients stratified by KRAS mutation status.

CI: Confidence interval; NR: Not reached; OS: Overall survival.

The CAIRO study evaluated the combination of capecitabine, oxaliplatin, and irinotecan in patients with advanced CRC.[11] Similarly, the CAIRO2 study assessed adding cetuximab to the combination of capecitabine, oxaliplatin, and bevacizumab.[12] Retrospective analyses of both studies showed that patients who underwent primary tumor resection had a significant survival advantage in the trials: 16.7 vs. 11.4 months in CAIRO and 20.7 vs. 13.4 months in CAIRO2.[13] Several other retrospective studies favor primary tumor resection in mCRC.[14,15] However, a recent clinical trial found no survival benefit from primary tumor resection in patients with synchronous unresectable metastases in mCRC.[16] Among long-term survivors of mCRC, the results regarding primary tumor resection are conflicting. For example, in a Northern Italian cohort, 90.9% of the 33 patients with mCRC who survived more than 36 months had a history of primary tumor resection.[9] On the other hand, in an Indian cohort that evaluated long-term survival in mCRC, only 10 of 31 patients (7 before and 3 in the metastatic setting) underwent surgery.[10] In our cohort, 100% of patients underwent primary tumor resection: 63.8% in the metastatic setting and 36.2% before metastasis. Our results further support the potential benefit of primary tumor resection in mCRC. However, because only patients who survived beyond 30 months were included, we do not have information on their baseline performance status at the time of surgery. Consequently, we cannot determine whether these patients were inherently fitter or more likely to tolerate surgery than those who did not achieve prolonged survival. This limitation may introduce a selection bias, and the observed survival outcomes should be interpreted with caution. Additionally, a subset of surgeries was performed emergently due to complications such as ileus, subileus, or bleeding, while others were elective or palliative. Therefore, the potential benefit of primary tumor resection in this cohort may be influenced by these factors, and prospective studies are needed to better clarify the role of surgery in mCRC.

On the other hand, when comparing our findings with other cohorts, it is important to consider regional differences. Most published studies on long-term survival in mCRC originate from Western populations, where patient characteristics, tumor biology, and access to healthcare may differ. Non-Western studies, including those from India, China, and countries in the Eastern Mediterranean Region, show variable survival rates and treatment patterns. For example, 3-year survival rates in India were reported as 42.2%, whereas the 3-year survival rate in China was 74%. In the Eastern Mediterranean region, the 5-year survival rate was 57.3%, lower than in the US (65%) and in many European countries, but higher than in some Asian and African countries.[17-21] Although our study focused on the

characteristics of long-term survivors rather than OS rates, regional differences in survival may influence the distribution of factors that affect survival and should be considered when interpreting our findings. These comparisons underscore the influence of regional and socio-cultural factors on long-term outcomes in mCRC and highlight the need to contextualize our results within the specific characteristics of our patient population

In our extended survival cohort, female sex was associated with poorer survival. Historically, women have been largely excluded from clinical research outside of reproductive studies, leading to the extrapolation of data from male-centric studies to women.[22] While women diagnosed with CRC generally have better OS rates than men globally,[1,22] in some countries the 5-year survival rate for women has been reported to be lower than that for men, especially after the age of 70.[23] Biologically, distinct tumor molecular profiles in female patients, such as higher rates of right-sided tumors or a higher frequency of BRAF mutations, may contribute to differential tumor behavior and treatment response.[24] Treatment-related factors may also play a role: prior studies have suggested that women may experience more severe toxicity from fluoropyrimidine-based chemotherapy, potentially leading to dose reductions or treatment interruptions that could impact outcomes.[25,26] Beyond these factors, hormones may also contribute to differences in tumor behavior between men and women.[27] Supporting our findings, an Indian cohort of long-term mCRC survivors showed that female gender was associated with survival.[10] Additionally, sociocultural and healthcare access factors might further influence survival; for example, women may experience hesitation or embarrassment in reporting colorectal symptoms and delay seeking care, which could contribute to later-stage presentation or delayed treatment initiation.[28-30] Our findings are partially supported by other cohorts of long-term survivors of mCRC, in which female gender was similarly associated with worse survival; however, these reports are limited and often region-specific.[10] Overall, these observations underscore the need for further studies to elucidate the interplay between biological, treatment-related, and socio-cultural factors in determining gender-specific outcomes in mCRC.

KRAS mutation is well-established as a poor prognostic factor for mCRC.[31] Although approximately half of the patients in our cohort had a KRAS mutation, its presence was also associated with poorer survival, including among long-term survivors. Additionally, the presence of metastases in liver segments 6 and 8 was associated with poorer OS in univariate analysis, and metastasis in segment 6 remained significant in multivariate analysis. Segments 6 and 8 are part of the right lobe of the liver.[32] Approximately 70% of liver metastases occur in the right hepatic lobe, with segment 8 being the most common site of metastasis.[33] Right-sided liver metastases have been associated with worse OS, disease-free survival, and higher recurrence rates.[34,35] There are virtually no published data directly comparing prognostic outcomes based on metastases to specific liver segments. Segment 6 is located in the posterior segment of the right lobe of the liver, which is less surgically accessible and may be associated with more complex vascular anatomy.[36] Moreover, surgical management of posterior liver segments is difficult because of the convex anatomy, restricted operative visibility, and the higher likelihood of bleeding and biliary complications.[37] These anatomical features could contribute to more challenging resections and potentially incomplete local treatment, which may partially explain the worse outcomes. On the other hand, segment 8, which is part of the central column of the liver, is considered topographically challenging. Such tumors are associated with increased surgical difficulty and a higher risk of severe postoperative complications, supporting the notion that segment 8 involvement may contribute to worse outcomes in patients with colorectal liver metastases.[38] These challenges may particularly reduce the feasibility and effectiveness of local treatments targeting these segments. Currently, there is limited evidence directly comparing the efficacy of local treatments (surgical resection, radiofrequency ablation, or TACE/TARE) across different liver segments. Future studies are needed to investigate whether segment-specific factors, including vascular supply, the tumor microenvironment, or treatment accessibility, contribute to the unfavorable prognosis of segments 6 and 8.

Study Limitations

This study has several limitations. First, it is a retrospective, single-center analysis, which may limit the generalizability of the findings and introduce potential selection biases. Second, the sample size is relatively small, and there is no control arm, limiting robust evaluation of the results. Third, only a small number of patients underwent germline testing or comprehensive next-generation sequencing, restricting the assessment of the full impact of genetic factors on survival. Finally, because our cohort included only patients who survived longer than 30 months, the observed features primarily describe this selected subgroup and should not be interpreted as causal determinants of prolonged survival. These limitations have been explicitly acknowledged to guide the interpretation of our findings.

CONCLUSION

In this study, all patients with mCRC who had prolonged survival underwent surgery for the primary tumor, underscoring the importance of evaluating the role of primary tumor resection in patients with metastatic disease. This further emphasizes the need to consider surgical intervention for every patient for whom it is feasible. The association of female gender and metastasis to the right lobe of the liver, particularly segment 6, with poorer outcomes in patients with prolonged survival may reflect underlying differences in tumor biology between genders and by the specific location of liver metastases. However, due to the highly selected nature of this cohort, these findings should not be interpreted as causal. Because the identification of basic features and genetic profiles of patients with mCRC who demonstrate extended survival may inform improved clinical decision-making, these findings should be validated in larger cohorts.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Gazi University Rectorate Institutional Ethics Committee (approval number: 2025-436, date: 17.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.S., G.S., F.G., U.C., A.Ü., O.Y., N.Ö., A.Ö., Concept: İ.E., N.Ö., A.Ö., Design: İ.E., A.Ö., Data Collection or Processing: İ.E., O.S., G.S., F.G., U.C., A.Ü., O.Y., A.Ö., Analysis or Interpretation: İ.E., N.Ö., Literature Search: İ.E., Writing: İ.E., N.Ö., A.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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