DOI: 10.14744/ejmi.269385
EJMI 2026;10(3):385–391

Research Article

Prognostic Impact of RAS Mutation and Biologic Therapy in Second-Line Treatment of De-Novo Metastatic Colorectal Cancer: A Real-World Retrospective Analysis

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Abstract

Objectives: For patients with de novo metastatic disease who progress after first-line therapy, optimal second-line treatment selection remains challenging, particularly regarding the choice between anti-EGFR and anti-VEGF biologic agents and the impact of molecular markers such as RAS mutation status and metastatic site.

Methods: This retrospective analysis included 62 patients with de novo mCRC who received second-line chemotherapy at a single center. Demographic, clinicopathological, and treatment data were collected. Overall survival (OS) and progression-free survival (PFS) were estimated using Kaplan–Meier methods. Univariate and multivariate Cox proportional hazards models were employed to identify independent predictors of survival. Subgroup analyses were performed to compare outcomes by biologic type and RAS status.

Results: The cohort had a balanced sex distribution (50% male, 50% female), with a mean age of 57.7±10.4 years. Tumor localization was evenly distributed (left colon, 33.9%; right colon, 32.3%; rectum, 33.9%). RAS mutation status was nearly balanced (mutant, 48.4%; wild-type, 51.6%). At diagnosis, the most common metastatic site was liver-only (53.2%). Second-line biologic use was 74%. Median OS from second-line initiation was 19.2 months (95% CI: 15.8–22.6), with 1-year and 2-year survival rates of 68% and 42%, respectively. Median PFS was 7.8 months (95% CI: 6.5–9.1). RAS wild-type patients demonstrated significantly longer OS than mutant patients (21.8 vs. 16.4 months, p=0.04). Peritoneal metastases showed a trend toward worse outcomes (median OS, 14.2 months; p=0.09). In multivariate analysis, RAS mutation remained the only significant independent predictor of mortality (HR=1.74, 95% CI: 1.08–2.80; p=0.02). Comparison of biologic types revealed that anti-VEGF therapy was associated with a trend toward improved overall survival compared with no biologic therapy (HR=0.55, 95% CI: 0.30–1.01; p=0.05), with a nonsignificant trend favoring anti-VEGF over anti-EGFR therapy.

Conclusion: This real-world analysis confirms the prognostic significance of RAS mutation in de novo mCRC patients receiving second-line therapy and suggests a potential survival benefit associated with biologic use, though this did not reach statistical significance in multivariate analysis. The findings align with recent large-scale registry data and network meta-analyses, supporting current treatment paradigms while highlighting the need for larger studies to refine biologic selection based on molecular and clinical subtypes.

Keywords: Anti-EGFR, Anti-VEGF, Metastatic Colorectal Cancer, RAS Mutation, Second-Line Chemotherapy

Cite This Article: *Ağdaş G, Demir MS. Prognostic impact of RAS mutation and biologic therapy in second-line treatment of de-novo metastatic colorectal cancer: A real-world retrospective analysis. EJMI 2026;10(3):385–391.*

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Submitted Date: June 16, 2026 **Revised:** August 11, 2026 **Accepted Date:** August 14, 2026

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-related death globally, with approximately 20–25% of patients presenting with de novo metastatic disease (mCRC) at diagnosis.[1] Prognosis remains poor, with 5-year survival below 15%.[2] Over the past two decades, management has evolved with the introduction of targeted biologic agents and an improved understanding of tumor biology.[3]

First-line treatment typically combines chemotherapy (FOLFOX, FOLFIRI, or XELOX) with a biologic agent: anti-VEGF (bevacizumab) for all patients or anti-EGFR (cetuximab or panitumumab) for patients with RAS wild-type tumors.[4] Despite initial responses, most patients experience disease progression, making second-line therapy a critical decision point for extending survival.[5]

RAS mutations occur in 45–55% of mCRC cases, predict poor responses to anti-EGFR therapy, and are associated with aggressive disease and worse outcomes.[6] The CAIRO2 trial update showed that patients with extended RAS/BRAF wild-type left-sided tumors achieved a median overall survival of 28.6 months, underscoring the importance of molecular profiling.[7]

Metastatic patterns also influence prognosis. Liver-only metastases have relatively favorable outcomes, whereas peritoneal metastases confer a poor prognosis.[8] The JSCCR project identified factors independently associated with worse survival in patients with synchronous peritoneal metastases, including age ≥75 years, rectal primary tumors, liver metastases, a higher peritoneal cancer index, noncurative resection, and lack of systemic chemotherapy.[9]

The optimal second-line biologic agent remains controversial, especially for patients with RAS wild-type tumors. The Onco-colon Türkiye registry found no significant efficacy difference between anti-EGFR and anti-VEGF combinations in second-line treatment among 588 patients with RAS wild-type tumors (median OS, 15.7, 14.3, and 14.7 months for panitumumab, cetuximab, and bevacizumab/aflibercept, respectively; p=0.764).[10] A Bayesian network meta-analysis of 47 trials concluded that FOLFOX plus bevacizumab may be optimal for most patients, although subgroup differences exist: for patients with RAS-mutant tumors, FOLFIRI plus bevacizumab plus panitumumab ranked highest; for patients with RAS wild-type tumors, FOLFIRI plus bevacizumab significantly improved survival.[11]

Tumor laterality adds complexity. A recent analysis of right-sided RAS/RAF wild-type mCRC suggested a non-significant survival advantage with continued anti-VEGF versus switching to anti-EGFR in second line (median OS 15.3 vs. 12.0 months; HR=1.24, p=0.10), indicating that sidedness may influence biologic class benefit.[12]

Given these complexities and the need for real-world evidence, we conducted a retrospective analysis of patients with de-novo mCRC who received second-line chemotherapy at our institution. The primary aim of this study was to evaluate the prognostic impact of RAS mutation status on overall survival in patients receiving second-line therapy for de-novo metastatic colorectal cancer. The secondary aim was to compare the effectiveness of anti-VEGF versus anti-EGFR biologic agents in this setting, with the hypothesis that biologic therapy, particularly anti-VEGF, is associated with improved survival outcomes compared to chemotherapy alone.

Methods

Study Design and Patient Population

This retrospective analysis included 62 patients with de novo metastatic colorectal cancer who received second-line chemotherapy at a single center between [dates]. Patients were identified through the institutional oncology database. The inclusion criteria were as follows: (1) histologically confirmed colorectal adenocarcinoma, (2) de novo metastatic disease at initial diagnosis, (3) receipt of second-line chemotherapy after progression on first-line therapy, and (4) availability of RAS mutation status. Patients with incomplete medical records were excluded. The study was approved by the Institutional Review Board of Van Training and Research Hospital (approval number: GOKAEK/2026-03-19, date: March 6, 2026). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

Demographic, clinicopathological, and treatment data were collected from electronic medical records. Variables included age, sex, tumor localization (left colon, right colon, or rectum), RAS mutation status (mutant vs. wild-type), metastatic sites (liver only, liver plus other sites, lung only, peritoneum only, or other), and type of second-line biologic therapy (anti-VEGF, anti-EGFR, or no biologic therapy). First-line treatment history and subsequent therapies were also recorded when available.

Outcomes

The primary outcome was overall survival (OS), defined as the time from the initiation of second-line chemotherapy to death from any cause or the last follow-up. Secondary outcomes included progression-free survival (PFS), defined as the time from the initiation of second-line chemotherapy to disease progression or death. Survival data were censored for patients who were alive at the last follow-up.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Continuous variables were expressed as mean±standard deviation or median with range. Categorical variables were presented as frequencies and percentages.

OS and PFS were estimated using the Kaplan–Meier method, with comparisons between groups performed using the log-rank test. Univariable and multivariable Cox proportional hazards models were employed to identify independent predictors of survival. Variables with $p<0.10$ in univariable analysis were included in the multivariable model. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

Subgroup analyses were performed to compare outcomes by biologic type and RAS status. All statistical tests were two-sided, and $p<0.05$ was considered statistically significant. Analyses were performed using SPSS version [version] or R software [version].

Results

Patient Characteristics

A total of 62 patients with de novo metastatic colorectal cancer who received second-line chemotherapy were included in this analysis. The patient selection process is shown in Figure 1. The cohort had a balanced sex distribution (50% male, 50% female), with a mean age of 57.7±10.4 years (range: 41–77 years). Tumor localization was evenly distributed: left colon in 21 patients (33.9%), right colon in 20 patients (32.3%), and rectum in 21 patients (33.9%). RAS mutation status was nearly balanced, with 30 patients (48.4%) having mutant tumors and 32 patients (51.6%) having wild-type tumors.

At diagnosis, the most common metastatic site was liver only (33 patients, 53.2%), followed by liver with other sites (12 patients, 19.4%), lung only (7 patients, 11.3%), peritoneum only (5 patients, 8.1%), and other combinations (5 patients, 8.1%). Baseline demographic and clinicopathological characteristics are summarized in Table 1.

Survival Outcomes

Median OS from second-line initiation was 19.2 months (95% CI: 15.8–22.6), with 1-year and 2-year survival rates of 68% and 42%, respectively (Fig. 2). Median PFS was 7.8 months (95% CI: 6.5–9.1).

Prognostic Factors

Patients with RAS wild-type tumors demonstrated significantly longer OS than patients with mutant tumors (21.8 vs. 16.4 months, p=0.04) (Fig. 3). Peritoneal metastases showed a trend toward worse outcomes (median OS, 14.2 months; p=0.09).

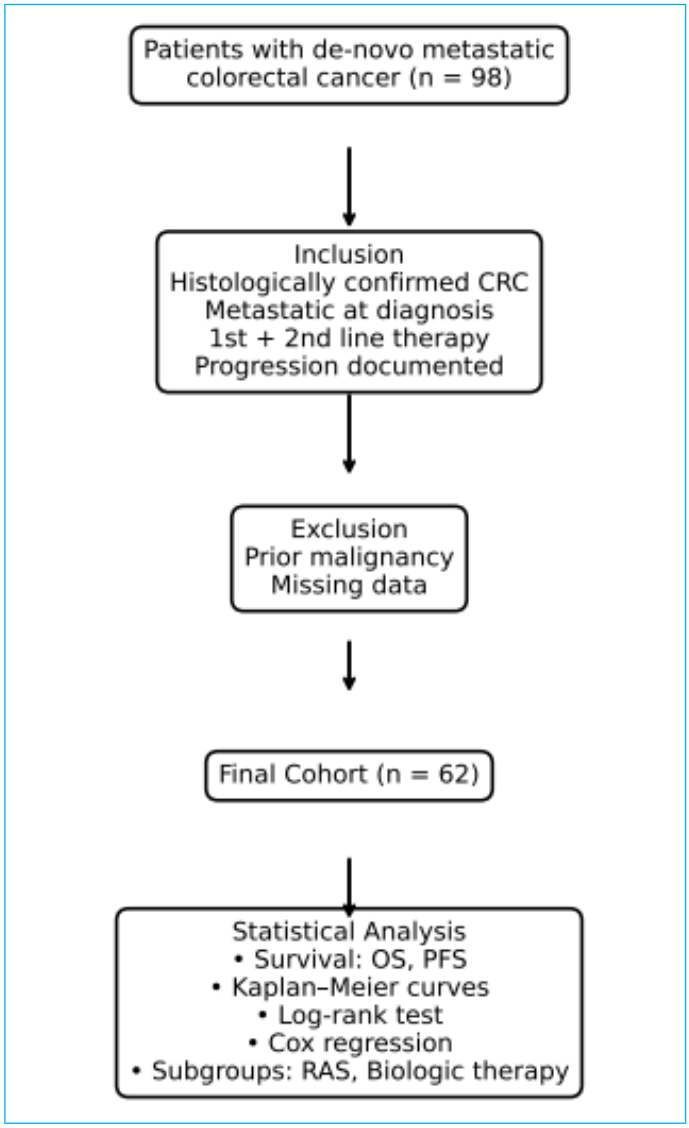

Figure 1. Flowchart of patient selection and study design.

Multivariate Analysis

Univariate Cox regression analysis for overall survival by RAS status and biologic type is presented in Table 4**.** In multivariate Cox analysis, RAS mutation remained the only significant independent predictor of mortality (HR=1.74, 95% CI: 1.08–2.80; p=0.02) (Table 3). Peritoneal metastases showed a trend toward worse outcomes (HR=1.68; p=0.06), and biologic use showed a trend toward a protective effect (HR=0.65; p=0.08). Right-sided tumors had a numerically increased hazard (HR=1.42; p=0.14), while age and sex were not significant (Table 3).

Biologic Therapy Outcomes

Second-line biologic use was 74%. Comparing biologic types, anti-VEGF therapy was associated with a trend toward improved overall survival compared with no biologic therapy (HR=0.55, 95% CI: 0.30–1.01; p=0.05), cor-

Table 1. Baseline demographic and tumor characteristics

Characteristic	n	%
Sex		
Male	31	50.0
Female	31	50.0
Age (years)		
Mean±SD	57.7±10.4	–
Range	41–77	–
Tumor localization		
Left colon	21	33.9
Right colon	20	32.3
Rectum	21	33.9
RAS status		
Mutant	30	48.4
Wild-type	32	51.6
Metastatic sites		
Liver only	33	53.2
Liver + other	12	19.4
Lung only	7	11.3
Peritoneum only	5	8.1
Other combinations	5	8.1

SD: Standard deviation; RAS: Rat sarcoma viral oncogene homolog.

responding to a 45% reduction in mortality. Anti-EGFR therapy showed a nonsignificant 32% reduction (HR=0.68; p=0.25). Direct comparison of anti-VEGF vs. anti-EGFR therapy numerically favored anti-VEGF but was not significant (HR=0.81; p=0.48). The pooled biologic group had better OS than the no-biologic group (19.8 vs. 14.5 months; p=0.03). These results are summarized in Table 2.

Among patients with RAS wild-type tumors (n=32), those receiving anti-VEGF therapy (n=14) had a median OS of 23.5 months, those receiving anti-EGFR therapy (n=10) had a median OS of 20.1 months, and those receiving no biologic therapy (n=8) had a median OS of 14.2 months (global p=0.08) (Table 2). Pairwise comparison of anti-VEGF vs. anti-EGFR therapy approached significance (p=0.08).

Discussion

This retrospective analysis of 62 patients with de novo metastatic colorectal cancer receiving second-line chemotherapy provides several clinically relevant insights. First, we confirm that RAS mutation status is a powerful independent prognostic factor. Patients with RAS-mutant tumors experienced significantly shorter overall survival (median, 16.4 months) than patients with RAS wild-type tumors (median, 21.8 months), with a hazard ratio of 1.74 (p=0.02). Second, biologic therapy in the second-line setting, particularly anti-VEGF therapy, was associated with a survival benefit. Anti-VEGF use was associated with a trend toward reduced mortality compared with chemotherapy alone (HR=0.55; p=0.05). Third, peritoneal metastases were associated with particularly poor outcomes (median OS, 14.2 months) and approached independent prognostic significance (HR=1.68; p=0.06). Fourth, although anti-VEGF therapy showed numerically longer survival than anti-EGFR therapy in the overall population (20.8 vs. 18.3 months) and in the RAS wild-type subgroup (23.5 vs. 20.1 months; p=0.08), these differences were not statistically significant, indicating that both biologic classes remain viable options.

Our findings align with the Onco-colon Türkiye registry, which reported no significant efficacy difference between anti-EGFR and anti-VEGF therapy in second-line treatment of patients with RAS wild-type tumors.[10] Similarly, the

Table 2. Overall survival according to RAS status and biologic type

Group	Subgroup	n	Events	Median OS (months)	95% CI	p
RAS Status (Overall Cohort)	Mutant	30	24	16.4	13.0–19.8	**0.04**
	Wild-type	32	20	21.8	17.5–26.1	
Biologic Type (Overall Cohort)	Anti-VEGF	32	21	20.8	17.1–24.5	0.06
	Anti-EGFR	14	9	18.3	13.4–23.2	
	No biologic	16	14	14.5	10.2–18.8	
RAS Mutant Subgroup	Anti-VEGF	18	14	17.2	13.5–20.9	0.42
	No biologic	12	10	14.4	10.0–18.8	
RAS Wild-Type Subgroup	Anti-VEGF	14	7	23.5	18.9–28.1	0.08
	Anti-EGFR	10	6	20.1	15.0–25.2	
	No biologic	8	7	14.2	9.8–18.6	

OS: Overall survival; CI: Confidence interval; RAS: Rat sarcoma viral oncogene homolog; VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor.

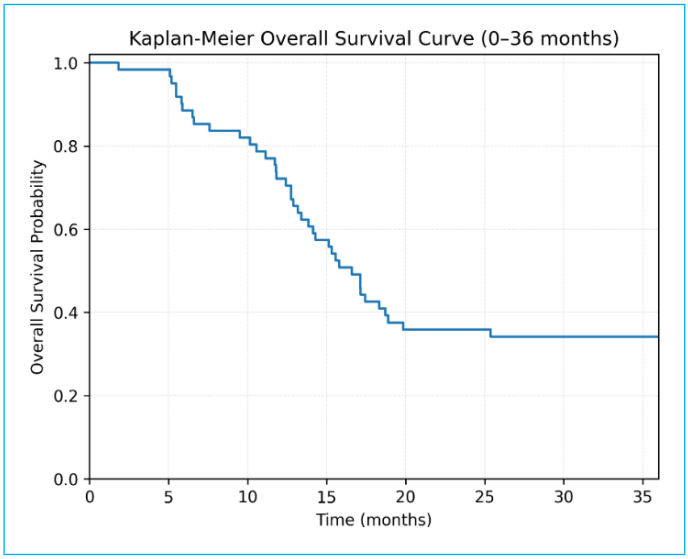

Figure 2. Kaplan–Meier overall survival (OS) curve for the entire study cohort from the initiation of second-line treatment.

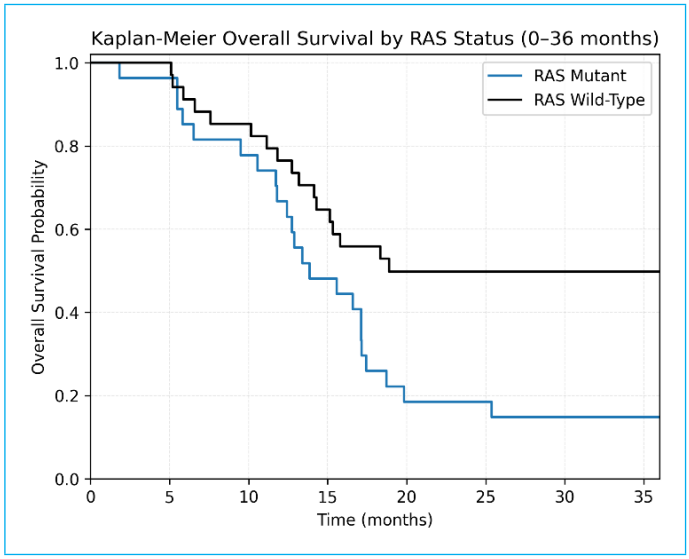

Figure 3. Kaplan–Meier overall survival (OS) curves according to RAS mutation status (mutant vs. wild-type).

Bayesian network meta-analysis by Sun et al.[11] suggested that FOLFOX plus bevacizumab may be optimal for most patients but also identified specific regimens that ranked highly for RAS-mutant and RAS wild-type subgroups. The consistent absence of clear superiority of one biologic class over the other in second-line treatment of patients with RAS wild-type tumors across multiple study designs and populations suggests that both options are reasonable and that treatment selection may be guided by other factors, such as toxicity profile, patient preference, prior treatment history, and tumor laterality.

The prognostic impact of peritoneal metastases observed in our study (median OS, 14.2 months; HR=1.68; p=0.06) is consistent with the literature. Franko et al.[8] reported that patients with peritoneal metastatic colorectal cancer have significantly worse outcomes than those with other metastatic sites, even when receiving systemic therapy. The JSCCR project further identified factors independently associated with worse survival in patients with synchronous peritoneal metastases, reinforcing the need for specialized clinical attention in this patient subset.[9] The genomic landscape of peritoneal metastasis in colorectal cancer has been increasingly characterized, with studies identifying specific molecular alterations that may drive this aggressive phenotype.[13]

Tumor sidedness also plays an important role in mCRC prognosis. Our study found that right-sided tumors had a numerically increased hazard (HR=1.42; p=0.14), consistent

Table 4. Univariate cox regression analysis for overall survival by RAS status and biologic type

Variable	HR	95% CI	p
RAS mutant (vs wild)	1.88	1.02–3.46	0.04
Biologic anti-VEGF (vs none)	0.55	0.30–1.01	0.05
Biologic anti-EGFR (vs none)	0.68	0.35–1.32	0.25

HR: Hazard ratio; CI: Confidence interval; VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor; RAS: Rat sarcoma viral oncogene

Table 3. Multivariate cox proportional hazards model for overall survival

Variable	HR	95% CI	p	Reference Category
Age (>65 vs ≤65)	1.32	0.81–2.15	0.260	≤65
Sex (Male vs Female)	0.98	0.62–1.55	0.930	Female
RAS (Mutant vs Wild-type)	**1.74**	**1.08–2.80**	**0.020**	**Wild-type**
Localization (Right vs Left/Rectum)	1.42	0.89–2.26	0.140	Left/Rectum
Peritoneal metastases (Present vs Absent)	1.68	0.98–2.88	0.060	Absent
Biologic use (Yes vs No)	0.65	0.40–1.06	0.080	No biologic

HR: Hazard ratio; CI: Confidence interval; RAS: Rat sarcoma viral oncogene.

with previous reports demonstrating that primary tumor sidedness affects prognosis and treatment outcomes.[14] Right-sided tumors are generally associated with a poorer prognosis and may respond differently to biologic agents than left-sided tumors.

Real-world evidence from other settings has similarly supported the use of biologic agents in second-line treatment. Yamazaki et al. reported real-world data on second-line treatment using fluoropyrimidine, irinotecan, and angiogenesis inhibitors, demonstrating the feasibility and effectiveness of these approaches in clinical practice.[15] Maintenance strategies have also been explored, with studies such as the VALENTINO trial investigating panitumumab maintenance in patients with RAS wild-type tumors.[16]

Emerging treatment options continue to evolve. Regorafenib plus nivolumab has shown promise in mismatch repair-proficient/microsatellite-stable metastatic colorectal cancer.[17] Ongoing trials are also evaluating novel combinations that may further improve outcomes.[18] These developments underscore the importance of continued research in this area.

Strengths and Limitations

Strengths

This study has several notable strengths that enhance the validity and usefulness of its findings. Comprehensive data collection included detailed treatment histories, metastatic sites, and molecular status for all patients, allowing for thorough characterization of the cohort and robust subgroup analyses. The real-world patient population reflects actual clinical practice, enhancing the generalizability of our findings to similar patient populations in routine care settings. Rigorous statistical analysis included multivariate modeling, allowing us to identify independent predictors and explore complex relationships between variables. Contextualization of our findings within the current literature using recent large-scale studies and meta-analyses demonstrates the consistency of our results with the broader evidence base. Additionally, the balanced cohort, with equal sex distribution and even tumor localization across the three primary sites, facilitated meaningful subgroup comparisons without substantial imbalances.

Limitations

Despite these strengths, several important limitations must be acknowledged. The retrospective design carries an inherent potential for selection bias and unmeasured confounding, as treatment decisions were based on clinical judgment rather than randomization. The moderate sample size of 62 patients limits the statistical power for subgroup analyses, increasing the risk of type II errors and potentially obscuring clinically meaningful differences. The single-center setting may limit generalizability to other populations and practice settings with different patient characteristics or treatment patterns. Missing data, including an invalid date for one patient, may affect the precision of survival estimates, although the impact is likely minimal given the small proportion of affected data. The absence of data on performance status, a known prognostic factor and potential confounder, represents a significant limitation that may have affected our multivariate analysis. Additionally, data on BRAF mutation status and MSI/MMR status were not available for analysis. These biomarkers have established prognostic and therapeutic implications in metastatic colorectal cancer, and their absence represents a limitation that may affect the comprehensiveness of our prognostic evaluation. Limited follow-up duration for some patients may affect long-term survival estimates, particularly for patients censored early in the follow-up period. The heterogeneous treatment regimens within biologic classes, while reflecting real-world practice, may introduce variability that affects comparisons between classes. Finally, the absence of central radiology review, with progression dates based on clinical documentation, may introduce some variability in progression-free survival estimates.

Conclusion

In this retrospective analysis of 62 patients with de novo metastatic colorectal cancer receiving second-line chemotherapy, RAS mutation was confirmed as an independent prognostic factor, reinforcing the importance of molecular profiling. Biologic agents were associated with a potential survival benefit, with both anti-VEGF and anti-EGFR appearing to be viable options in patients with RAS wild-type tumors. Peritoneal metastases were associated with poor outcomes, warranting specialized clinical attention. While RAS mutation remains a dominant prognostic biomarker, metastatic pattern—particularly peritoneal involvement—also carries important prognostic information. Treatment selection should be individualized based on tumor characteristics, laterality, and emerging biomarkers. Larger prospective studies are needed to further refine treatment, especially for peritoneal metastases, right-sided tumors, and RAS-mutant disease.

Disclosure

Ethics Committee Approval: The study was approved by the Institutional Review Board of Van Training and Research Hospital (approval number: GOKAEK/2026-03-19, date: March 6, 2026).

Informed Consent: Informed consent was waived due to the retrospective design of the study.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: This study received no external funding.

Use of AI for Writing Assistance: ChatGPT (OpenAI, GPT-4) was used for language editing, grammar improvement, and translation support. The authors reviewed and approved all outputs and take full responsibility for the content of this manuscript.

Author Contributions: Concept – GA; Design – GA, MSD; Data Collection - GA; Analysis and Interpretation - GA, MSD; Writing – Original Draft - GA; Writing – Review & Editing - MSD; Final Approval: GA, MSD.

Peer-review: Externally peer-reviewed.

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