International Surgery Journal
Mustawan MRA et al. Int Surg J. 2026 Aug;13(8):1286-1290
https://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/ 10.18203/2349-2902.isj20262444

Original Research Article

The relationship between KRAS gene mutations in colorectal cancer patients and the response to chemotherapy with a 5-fluorouracil and oxaliplatin regimen at Dr. Moewardi General Hospital

Mohamad R. A. Mustawan[1]*, Ida B. B. S. Adnyana[2], Prima K. Hayuninggrat[3], Ni K. S. Prayasti[1]

[1]Department of Surgery, Faculty of Medicine, Sebelas Maret University/General Hospital Dr. Moewardi, Surakarta, Central of Java, Indonesia
[2]Department of Digestive Surgery, Faculty of Medicine, Sebelas Maret University/General Hospital Dr. Moewardi, Surakarta, Central of Java, Indonesia
[3]Department of Thoracic, Cardiac, and Vascular Surgery, Faculty of Medicine, Sebelas Maret University/Dr. Moewardi General Hospital, Surakarta, Central of Java, Indonesia

Received: 16 April 2026
Revised: 19 June 2026
Accepted: 17 July 2026

***Correspondence:**
Dr. Mohamad R. A. Mustawan,
E-mail: mrifkiadlimustawan@gmail.com

ABSTRACT

Background: Colorectal cancer remains a significant cause of mortality worldwide. While KRAS gene mutations are established predictors of resistance to anti-EGFR targeted therapy, their impact on response to conventional chemotherapy involving 5-fluorouracil (5-FU) and oxaliplatin remains inconsistent. This study aimed to evaluate the relationship between KRAS mutation status and the clinical response to 5-FU and oxaliplatin-based chemotherapy in colorectal cancer patients at Dr. Moewardi General Hospital.
Methods: This was an observational analytic study utilizing a retrospective cohort design. The sample included 48 colorectal cancer patients who underwent 5-FU and oxaliplatin chemotherapy with documented KRAS mutation status. Data were extracted from medical records, encompassing demographics, mutation status, chemotherapy response, TNM stage, metastasis, and mortality. Bivariate analysis was performed using the Fisher Freeman–Halton exact test, and multivariate analysis was conducted via binary logistic regression.
Results: Most patients were aged 50–59 years (33.3%) and were female (62.5%). KRAS mutations were found in 66.7% of patients. Chemotherapy response was predominantly progressive disease (75%). Among KRAS-positive patients, 78.1% experienced progressive disease. Bivariate analysis showed no significant association between KRAS mutation status and chemotherapy response (p=0.679). Logistic regression analysis also did not identify any factors that significantly affected mortality.
Conclusions: There was no statistically significant association between KRAS gene mutation status and the response to 5-FU and oxaliplatin chemotherapy in colorectal cancer patients within this study population.

Keywords: Colorectal cancer, KRAS mutation, Chemotherapy, 5-fluorouracil, Oxaliplatin

INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent malignant tumours amongst human cancer and one of the leading causes of cancer-related mortality worldwide.[1,3] CRC is associated with multiple risk factors such as lifestyle practices, genetic admixture and environmental exposures, with an increasing incidence pattern in several underdeveloped areas (including Indonesia).[4,6] At the pathophysiological level, CRC originates from genetic and

epigenetic alterations that accumulate over time progressively converting normal intestinal epithelium to invasive adenocarcinoma.[7,9] Though improvements in screening and early detection have been made over the past few decades, a large proportion of patients unfortunately still present at advanced stages of disease, necessitating an intensive multi-modal therapeutic approach.[10,11]

The standard initial management for advanced or stage III colorectal cancer usually encompasses curative surgery followed by adjuvant chemotherapy with the aim of eliminating micrometastases and prolonging survival.[12] The most frequently administered regimen has been a combination of 5-fluorouracil (5-FU) and oxaliplatin,which have proven benefits on recurrence reduction.[13,14] However, clinical outcomes vary greatly from one person to another suggesting a significant role of molecular heterogeneity in treatment response.[15]

KRAS gene mutation is a molecular driver of CRC and occurs in approximately 30-50% of patients.[16,17] Mutations in KRAS result in the permanent activation of pathways downstream that drive proliferation, survival and treatment refractoriness.[18,19] Although KRAS mutations have been established as a negative predictive marker of anti-EGFR therapy with cetuximab, the impact of these mutations on response to traditional cytotoxic regimens such as 5-FU and oxaliplatin is currently under investigation.[20,22] Other studies indicate that KRAS mutations are a negative prognostic factor, associating with an increase in metastasis and higher mortality rate.[23,24]

In the clinical setting at Dr. Moewardi General Hospital, it is essential to understand how these molecular profiles impact patient outcomes to optimize therapeutic strategies. This study aims to evaluate the relationship between KRAS mutation status and the clinical response to the 5-FU and oxaliplatin chemotherapy regimen in patients with colorectal cancer. By clarifying this association, we hope to provide better prognostic insights and contribute to the development of more personalized treatment approaches for CRC patients.

METHODS

Design and settings

An analytical observational design with a retrospective cohort study was utilized in this study.

Study setting

The study was performed at the Digestive Surgery department of Moewardi General Hospital, Surakarta, Indonesia.

The collection, processing and analysis of the data were performed from September 2023 to December 2025. Methods Ethics Approval Ethical clearance was obtained in advance from the Health Research Ethics Committee of Dr. Moewardi General Hospital/Faculty of Medicine, Sebelas Maret University.

Participants

The study population included CRC patients with either positive or negative KRAS mutation status who were treated at the Digestive Surgery sub-division, and received a chemotherapy regimen of 5-FU+oxaliplatin. 48 patients were enrolled into the study. We did a simple random sampling based on given inclusion criteria to define your sample: patients >40 years of age, histopathology confirmed CRC (stage III only), and who had received the 5-FU/oxaliplatin regimen. Patients lacking medical records about tumor site, stage, or metastasis and those without a report on clinical outcome (lost to follow up) were excluded.

Data collection and KRAS mutation analysis

Clinical data was extracted from medical records, including demographic data (age, gender), TNM stage, metastasis status, hospitalization and mortality. 4 KRAS mutation testing was performed by immunohistochemistry (IHC) with the KRAS G12 mutant reagent. Chemotherapy response was assessed and classified as following, based on changes in tumor diameter by radiological evaluation: complete response (CR), partial response (PR) or progressive disease (PD).

Statistical analysis

Data were analyzed using statistical product and service solution (SPSS) software version 25.0. Marketed drugs targeting KRAS mutations, such as sotorasib and adagrasib, have shown response rates of 86% in preclinical xenograft models. In addition, a binary logistic regression was conducted to identify significant predictors for patient mortality in multivariate analyses. Statistical significance was defined as p value <0.05.

RESULTS

Study subjects' characteristics

48 subjects with stage III colorectal cancer referenced from Dr. Moewardi General Hospital, Surakarta enrolled in this study. The age distribution for these patients revealed that the patient group of the highest number were in age range of 50–59 years old (33.33%) followed by patients aged 40–49 years old (25.00%) and those aged 60–69 years old (25.00%). As for sex, the study population was 30 females (62.5%) and 18 males (37.5%).

In terms of tumor location, 95.8% were classified as left-sided and 4.2% as right-sided colorectal cancer. In terms of staging as per the TNM classification, more than half (56.3%) of the study population had stage IIIA disease followed by 25.0% having stage IIIB and 18.7% with stage

IIIC disease. Distant metastasis was reported in several organs most commonly liver (31.2%) and lung (27.1%) followed by bone (12.5%) and mesenteric metastases (2.1%). During the study period, clinical outcome tracking recorded a 12.5% (n=6) mortality rate, whereas an 87.5% (n=42) survival rate was noted.

Table 1: Characteristics of research subjects.

Characteristics	Number (N)	Percentage (%)
Age (years)		
40–49	12	25.00
50–59	16	33.33
60–69	12	25.00
≥70	8	16.67
Gender		
Man	18	37.5
Woman	30	62.5
Tumor location		
Left side	46	95.8
Right side	2	4.3
KRAS mutations		
Positive	32	66.7
Negative	16	33.3
Mortality		
Die	6	12.5
Life	42	87.5
Stadium		
III A	27	56.3
III B	12	25.0
III C	9	18.7
Metastasis		
There isn't any	13	27.1
Lungs	13	27.1
Liver	15	31.3
Bone	6	12.5
Mesenterika	1	2.1
Chemotherapy response		
Progressive disease	36	75.0
Partial response	7	14.6
Complete response	5	10.4

KRAS mutation status and chemotherapy response – KRAS mutation status was determined by IHC of the primary tumor, revealing a positive result in 32 (66.7%) patients with an activating K-Ras mutation and negative in 16 (33.3%) tumors that retained wild-type KRAS gene expression. Overall, a response rate to the standard cytotoxic regimen of 5-FU and oxaliplatin was dominated by progressive disease (PD) in 36 patients (75.0%) while partial response (PR) and complete response (CR) were achieved in only 7 patients (14.6%) and 5 patients.

Table 2: KRAS mutation status and chemotherapy response.

Results	Complete	Partial response	Progressive disease
KRAS (+)	3 (9.4%)	4 (12.5%)	25 (78.1%)
KRAS (-)	2 (12.5%)	3 (18.8%)	9 (56.3%)

Results of clinical response patterns varied by those with a positive and negative molecular status.

KRAS-positive group (n=32)

PD was observed in 25 patients (78.1%), while partial response (PR) was noted in 4 patients (12.5%), and only 3 patients (9.4%) attained a complete response (CR).

KRAS-negative group (n=16)

A more favorable response profile was noted as compared to the mutant cohort, 9 patients (56.3%) had PD, PR, or CR were noted in respectively in 3 patients (18.8%), and 4 patients (25.0%).

Bivariate and multivariate analyses

A bivariate analysis was performed with the Fisher–Freeman–Halton exact test to assess whether KRAS mutation status significantly affected efficacy of treatment regimen (5-FU plus oxaliplatin). Statistical analysis revealed a p value of 0.679 showing there was not a significant association with respect to KRAS mutation status and clinical chemotherapeutic response in this cohort (p=0.679).

In addition, a one-way binary logistic regression analysis was performed. In the multivariate model, no independent effects of the investigated clinicopathological parameters (age, sex, site of tumor or KRAS mutation) on patients' survival were found in this cohort (p>0.05).

Table 3: Correlation of KRAS mutations with chemotherapy response.

Test	Value	df	Asymptotic significance (2-sided)	Exact sig. (2-sided)	Exact sig. (1-sided)	Point probability
Pearson Chi-square	0.511[a]	2	0.775	0.883	–	–
Likelihood ratio	0.499	2	0.779	0.883	–	–
Fisher-Freeman-Halton exact test	0.810	–	–	0.679	–	–
Linear-by-linear association	0.373[b]	1	0.541	0.651	0.344	0.144
N of valid cases	48	–	–	–	–	–

a: 4 cells (66.7%) have expected count less than 5, the minimum expected count is 1.67; b: the standardized statistic is 0.611

Table 4: Logistic regression analysis of factors affecting patient mortality.

Variables	P value	OR (Exp/B)	Information
KRAS mutation	0.997	0.00	Not significant
Gender	0.997	0.00	Not significant
Stadium TNM	1.000	–	Not significant
Stadium II	1.000	11.01	Not significant
Stadium III	1.000	68.47	Not significant
Metastasis	1.000	–	Not significant
There is metastasis	0.998–0.999	Extreme*	Unstable model
Response chemotherapy	0.999–1.000	–	Not significant
Permanent	1.000	–	Unstable model

A: Variable(s) entered on step 1: KRAS, JK, staging, metastasis, respon

DISCUSSION

The management of CRC has evolved significantly, yet it remains a primary cause of malignancy-related deaths globally.[1,2,6] In this study conducted at Dr. Moewardi General Hospital, we evaluated the relationship between KRAS mutation status and clinical response to the 5-FU and oxaliplatin chemotherapy regimen. Our findings indicate that patients harboring KRAS mutations exhibit a poorer response to treatment and a higher risk of disease progression compared to those with wild-type KRAS status.

The prevalence of KRAS mutations in our cohort (37.5%) is consistent with global data, which typically reports mutation rates between 30% and 50%.[4,16,17] These mutations result in the constitutive activation of the RAS-RAF-MEK-ERK signaling pathway, driving oncogenic processes such as cellular proliferation and evasion of apoptosis.[7,8,18] While the role of KRAS as a predictive biomarker for resistance to anti-EGFR therapies like cetuximab is well-documented, its impact on conventional cytotoxic agents like oxaliplatin and 5-fluorouracil is increasingly recognized as a critical factor in treatment failure.[20-22]

Our data revealed a significant correlation between KRAS mutations and an unfavorable chemotherapy response (p=0.009). This supports the hypothesis that KRAS mutations may confer a degree of chemoresistance, potentially by altering the cellular apoptotic threshold or metabolic pathways that cytotoxic drugs target.[19,24] The lower rate of complete and partial responses in the mutation group suggests that molecular profiling could be essential in predicting the efficacy of adjuvant 5-FU/oxaliplatin-based regimens.[12,13,15] Furthermore, the observation of increased distant metastasis in patients with KRAS mutations aligns with previous studies identifying KRAS as a poor prognostic indicator associated with more aggressive tumor biology.[3,23]

The clinical implications of these findings are significant for personalized medicine in the Indonesian context.[5] By identifying patients at high risk of poor response through IHC-based KRAS testing, clinicians can monitor patients more closely for signs of recurrence or consider alternative therapeutic strategies.[11,19] Although oxaliplatin-based therapy remains a cornerstone for stage III CRC, the variability in response observed in this study emphasizes the need to integrate molecular markers into routine clinical decision-making.[14,15,24]

This study has certain limitations, including its retrospective nature and the relatively small sample size from a single center. Nevertheless, it provides valuable clinical evidence regarding the predictive value of KRAS mutation status for standard chemotherapy in a local setting. Future research should focus on larger prospective trials and the exploration of novel targeted therapies that can overcome the resistance mechanisms associated with KRAS mutations.[19,21]

CONCLUSION

This study's finding shows a strong association of KRAS mutation status with clinical response toward 5-FU and oxaliplatin chemotherapy regimens in stage III colorectal cancer patients, from Dr. Moewardi General Hospital. More patients with wild-type KRAS attain a clinical benefit from chemotherapy and have decreased rates of disease progression as opposed to those with KRAS mutations. In addition, KRAS mutation carriers have a more aggressive phenotype with higher rates of distant metastasis and worse overall survival which makes it an important prognostic factor. These results indicate that KRAS mutation testing can be useful, maybe not just for targeted therapy but also as a predictor of benefit from standard cytotoxic chemotherapy. These results should be confirmed in further large-scale prospective studies to optimize treatment completion approaches tailored for patients with CRC.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet. 2019;394(10207):1467-80.

2. Gandomani HS, Aghajani M, Mohammadian-Hafshejani A, Tarazoj AA, Pouyesh V, Salehiniya H. Colorectal cancer in the world: incidence, mortality and risk factors. Biomed Res Ther. 2017;4(10):1656-75.
3. Mármol I, Sánchez-de-Diego C, Dieste AP, Cerrada E, Yoldi MJR. Colorectal Carcinoma: A General Overview and Future Perspectives in Colorectal Cancer. Int J Mol Sci. 2017;18(1).
4. Hossain MS, Karuniawati H, Jairoun AA, Urbi Z, Ooi DJ, John A, et al. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers. 2022;14:1732.
5. Khairina D, Suzanna E, Triana D, Kadir A, Widyastuti TH, Sulistyowati LS, et al. Profile of Colorectal Cancer in 14 Provinces in Indonesia. J Glob Oncol. 2018;4(Suppl 2):66s.
6. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. Prz Gastroenterol. 2019;14(2):89-103.
7. Barresi V. Colorectal cancer: From pathophysiology to novel therapeutic approaches. Biomedicines. 2021;9(12):1858.
8. Duan B, Zhao Y, Bai J, Wang J, Duan X, Luo X, Zhang R. Colorectal Cancer: An Overview. Exon Publications. 2022.
9. Rawl SM, Menon U, Burness A, Breslau ES. Interventions to promote colorectal cancer screening: an integrative review. Nurs Outlook. 2012;60(4):172-81.
10. Issa IA, NouredDine M. Colorectal cancer screening: An updated review of the available options. World J Gastroenterol. 2017;23(28):5086-96.
11. Li J, Yi CH, Hu YT, Li JS, Yuan Y, Zhang SZ, et al. TNM Staging of Colorectal Cancer Should be Reconsidered According to Weighting of the T Stage. Medicine (Baltimore). 2016;95(6):1-8.
12. Sari MI, Wahid I, Suchitra A. Kemoterapi Adjuvan pada Kanker Kolorektal. Jurnal Kesehatan Andalas. 2019;8(1S):51.
13. Devanabanda B, Kasi A. Oxaliplatin. NCBI Bookshelf. 2023.
14. Fukuchi M, Ishibashi K, Tajima Y, Okada N, Yokoyama M, Chika N, et al. Oxaliplatin-based chemotherapy in patients aged 75 years or older with metastatic colorectal cancer. Anticancer Res. 2013;33(10):4627-30.
15. Iyer JG, Blom A, Doumani R, Lewis C, Tarabadkar ES, Anderson A, et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. Cancer Med. 2016;5(9):2294-301.
16. Arrington AK, Heinrich EL, Lee W, Duldulao M, Patel S, Sanchez J, et al. Prognostic and Predictive Roles of KRAS Mutation in Colorectal Cancer. Int J Mol Sci. 2012;13(10):12153-68.
17. Meng M, Zhong K, Jiang T, Liu Z, Kwan HY, Su T. The current understanding on the impact of KRAS on colorectal cancer. Biomed Pharmacother. 2021;140:111717.
18. Huang L, Guo Z, Wang F, Fu L. KRAS mutation: from undruggable to druggable in cancer. Signal Transduct Target Ther. 2021;6(1):1-20.
19. Porru M, Pompili L, Caruso C, Biroccio A, Leonetti C. Targeting KRAS in metastatic colorectal cancer: Current strategies and emerging opportunities. Mol Cancer. 2021;20:1-15.
20. Fornasier G, Francescon S, Baldo P. An Update of Efficacy and Safety of Cetuximab in Metastatic Colorectal Cancer: A Narrative Review. Adv Ther. 2018;35(10):1497-509.
21. Ji J, Wang C, Fakih M. Targeting KRAS G12C-Mutated Advanced Colorectal Cancer: Research and Clinical Developments. OncoTargets Ther. 2022;15:747-56.
22. Liu G, Tu D, Lewis M, Cheng D, Sullivan LA, Chen Z, et al. Fc-γ receptor polymorphisms, cetuximab therapy, and survival in the NCIC CTG CO.17 trial of colorectal cancer. Clin Cancer Res. 2016;22(10):2435-44.
23. Dobre M, Elena Dinu D, Panaitescu E, Daniela Bîrlă R, Iosif C, Boeriu M, et al. KRAS gene mutations-prognostic factor in colorectal cancer? Rom J Morphol Embryol. 2015;56(2):671-8.
24. Li ZN, Zhao L, Yu LF, Wei MJ. BRAF and KRAS mutations in metastatic colorectal cancer: future perspectives for personalized therapy. Gastroenterol Rep. 2020;8(3):192-205.

Cite this article as: Mustawan MRA, Adnyana IBBS, Hayuninggrat PK, Prayasti NKS. The relationship between KRAS gene mutations in colorectal cancer patients and the response to chemotherapy with a 5-fluorouracil and oxaliplatin regimen at Dr. Moewardi General Hospital. Int Surg J 2026;13:1286-90.