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**Original Research Article**

# Correlation between KRAS mutation status and clinical outcomes in colorectal cancer patients: a retrospective cohort study

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## ABSTRACT

**Background:** Kirsten rat sarcoma (KRAS) mutations are key drivers in colorectal cancer (CRC), but their prognostic impact in stage III disease remains debated. This study evaluated the correlation between KRAS mutations and clinical outcomes in stage III CRC patients.
**Methods:** A retrospective cohort study was conducted on 48 patients at Dr. Moewardi General Hospital. KRAS status was determined via immunohistochemistry (IHC) (G12D), and outcomes were analyzed using Fisher's Exact test.
**Results**: KRAS mutations were prevalent in 66.7% of patients. Distant metastasis occurred in 45.8% of cases, primarily in the liver and lungs. No significant correlation was found between KRAS mutation status and distant metastasis (p=0.735) or mortality (p=0.648).
**Conclusions:** While KRAS mutations are frequent in stage III CRC patients in this setting, they did not significantly predict metastasis or survival. Prognostic assessments should incorporate broader molecular profiling and clinicopathological factors.

**Keywords:** Colorectal cancer, KRAS mutation, Metastasis, Survival, Indonesia

## INTRODUCTION

Colorectal cancer (CRC) is defined as a malignancy originating from the glandular or epithelial cells of the large intestine.[1] This malignancy arises from a complex interaction between genetic and environmental factors, where a gradual accumulation of genetic and epigenetic alterations triggers the transformation of normal colonic mucosa into invasive cancer.[2] Global statistics report approximately 1.9 million new cases of CRC annually, making it the third most common cancer worldwide.[3,4] The mortality rate remains high, with around 935,000 deaths recorded in 2020.[4] Notably, the burden of CRC is shifting toward younger individuals; the average age at diagnosis decreased to 66 years by 2016.[5] In developing countries, the incidence in men is reported to be 3-4 times higher than in women.[1]

Genetic mutations, which can be sporadic (70%), hereditary (10%), or familial (20%), drive this disease progression by affecting oncogenes, tumor suppressor genes, and DNA repair mechanisms.[6] The Kirsten rat sarcoma (KRAS) gene is a frequently mutated oncogene in CRC, found in approximately 35-45% of patients.[7] Mutations in KRAS stimulate cell proliferation and survival, thereby driving tumorigenesis. The most prevalent mutations occur at glycine codon 12 (G12), followed by glycine 13 (G13) and glutamine 61 (Q61).[7,8]

These mutations, particularly G12D which accounts for 41% of G12 alterations, result in a constitutively active KRAS protein.[7,8] This persistent activation promotes tumor growth, transformation, and metastasis, while also increasing resistance to standard therapies.[9,10]

Patients harboring KRAS mutations often face a poorer prognosis. The aberrant activation of the KRAS pathway leads to resistance against epidermal growth factor receptor (EGFR) inhibitors, such as cetuximab and panitumumab.[9] While many studies identify KRAS as a negative prognostic marker associated with shorter survival and higher recurrence rates, others have observed no significant prognostic correlation.[8,11,12] Despite the established role of KRAS in treatment response, its definitive impact on the clinical outcomes of CRC patients remains a subject of academic debate. Therefore, this study aims to evaluate the prevalence of KRAS mutations and their specific impact on clinical outcomes-including distant metastasis and survival-at Dr. Moewardi General Hospital, Surakarta, serving as a primary tertiary referral center in Indonesia.

## METHODS

### *Study design and setting*

This study employed an analytical observational design with a retrospective cohort approach. The research was conducted at Dr. Moewardi General Hospital, Surakarta, Indonesia, from July to December 2024. Ethical clearance was obtained from the health research ethics committee of Dr. Moewardi General Hospital.

### *Participants*

The study population consisted of patients diagnosed with stage III CRC. A total of 48 patients were selected using a total sampling technique based on specific inclusion criteria: patients who had undergone curative surgery, received complete adjuvant chemotherapy (5-fluorouracil/oxaliplatin-based), and had available paraffin-embedded tissue blocks for IHC testing. Patients with incomplete medical records or inadequate tissue samples were excluded.

### *Data collection and KRAS mutation analysis*

Clinical data, including demographic characteristics (age, gender), histopathological features, distant metastasis, and mortality, were extracted from medical records. KRAS mutation status was determined via IHC staining at the anatomical pathology laboratory. The analysis utilized the G12D specific antibody to identify the presence of KRAS protein mutations in the tumor tissue.

### *Statistical analysis*

Data were analyzed using SPSS software. Descriptive statistics were used to summarize patient demographics and the distribution of KRAS mutations. The correlation between KRAS mutation status and clinical outcomes (metastasis and mortality) was analyzed using Fisher's exact test. A $p<0.05$ was considered statistically significant.

## RESULTS

### *Patient characteristics*

The study included 48 patients with stage III CRC. The majority of the subjects were male (56.3%), and the mean age of the participants was 54.2 years. All patients had undergone curative surgery followed by a complete 5-FU/oxaliplatin-based adjuvant chemotherapy regimen.

### *Distribution of KRAS mutation status*

The KRAS mutation status was assessed via IHC. The prevalence of KRAS mutations among the study subjects was 66.7% (32 patients), while 33.3% (16 patients) were identified as KRAS wild-type.

### *Distant metastasis outcomes*

During the follow-up period, distant metastasis was observed in 22 patients (45.8%). The most frequent sites of metastasis were the liver (31.3%) and the lungs (27.1%). The correlation between KRAS mutation and the incidence of metastasis is summarized (Table 1). Statistical analysis using Fisher's Exact Test yielded a $p=0.735$, indicating that there was no significant correlation between KRAS mutation status and the occurrence of distant metastasis in stage III CRC patients.

### *Survival and mortality outcomes*

Mortality was recorded in 6 patients (12.5%) during the study period. The relationship between KRAS mutation status and mortality is presented (Table 2). The analysis showed no statistically significant correlation between KRAS mutation status and mortality ($p=0.648$). Furthermore, Cox Regression analysis was performed to evaluate the hazard ratio, confirming that KRAS status was not a significant independent predictor of survival in this cohort.

**Table 1: Correlation between KRAS mutation status and distant metastasis.**

| KRAS status | Metastasis (+) | Metastasis (-) | Total | P value |
|---|---|---|---|---|
| **Mutation** | 14 (43.8%) | 18 (56.2%) | 32 (100%) | |
| **Wild-type** | 8 (50.0%) | 8 (50.0%) | 16 (100%) | 0.735* |
| **Total** | 22 (45.8%) | 26 (54.2%) | 48 (100%) | |

**Table 2: Correlation between KRAS mutation status and patient mortality.**

| KRAS status | Deceased | Alive | Total | P value |
|---|---|---|---|---|
| **Mutation** | 3 (9.4%) | 29 (90.6%) | 32 (100%) | |
| **Wild-type** | 3 (18.8%) | 13 (81.2%) | 16 (100%) | 0.648 |
| **Total** | 6 (12.5%) | 42 (87.5%) | 48 (100%) | |

## DISCUSSION

The prevalence of KRAS mutations in this study was 66.7%, which is notably higher than the global average of 35-45% reported in previous literature.[7,9] This discrepancy might be attributed to the specific genetic landscape of patients at Dr. Moewardi General Hospital or the focus on Stage III patients. High KRAS mutation rates in local cohorts often suggest a distinct genetic profile that may be influenced by regional environmental factors, lifestyle, and dietary habits common in Central Java, Indonesia.

### *KRAS mutation and distant metastasis*

A critical finding in this study is the lack of a statistically significant correlation between KRAS mutation and distant metastasis (p=0.735). Theoretically, KRAS mutations cause permanent activation of the RAS-RAF-MEK-ERK pathway, leading to increased cell migration and invasion.[11] However, our data showed that metastasis occurred almost equally in both groups (43.8% in the mutant group vs. 50.0% in the wild-type group). This result suggests that in stage III CRC, KRAS status alone might not be the sole driver of progression. Other molecular pathways, such as the PI3K/AKT pathway or the presence of BRAF and TP53 mutations, could be bypassing the KRAS signaling to trigger metastasis.[14] Furthermore, all subjects in this study received 5-FU/Oxaliplatin-based adjuvant chemotherapy. Adjuvant therapy is designed to eliminate micrometastases; therefore, the clinical outcome of these patients may have been more significantly influenced by their sensitivity to chemotherapy rather than their initial mutation status.

### *Prognostic value and survival analysis*

The mortality rate in this study (12.5%) also showed no significant association with KRAS status (p=0.648). While KRAS is well-known predictive marker for resistance to anti-EGFR therapy in metastatic settings (Stage IV), its role as pure prognostic marker for overall survival in stage III remains controversial.[12,15] Our findings align with studies suggesting that in non-metastatic stages, other clinicopathological factors-such as lymph node ratio/tumor budding-might be stronger prognostic indicators than KRAS mutation alone.

### *Analysis of metastasis sites and organotropism*

We observed that the liver (31.3%) and lungs (27.1%) were the primary sites of distant metastasis. This organotropic distribution is consistent with the hematogenous spread pattern of CRC. Some literature suggests that KRAS-mutant tumors have a higher affinity for lung metastasis compared to wild-type tumors.[16] Although the statistical significance was low in this cohort, the trend of lung involvement in the mutant group warrants longer observation to see if a distinct pattern emerges over a 5-year follow-up.

### *Methodological considerations*

The use of IHC with the G12D-specific antibody in this study is a practical and cost-effective approach for clinical settings in Indonesia. However, we must acknowledge that IHC only detects specific protein expressions. Since KRAS mutations are heterogeneous, focusing on the G12D variant might miss other mutation subtypes (e.g., G12V or G13D) that would be captured by DNA sequencing methods like PCR or next-generation sequencing (NGS). This potential underestimation of the full mutational landscape could be a factor in the lack of statistical significance observed.

### *Limitations*

This study has several limitations, including its retrospective nature and the relatively small sample size of 48 patients, which may lack the power to detect small effect sizes in survival outcomes. Furthermore, the follow-up period may not be long enough to capture late recurrence or long-term mortality events typical of CRC.

## CONCLUSION

Based on the results of this study, it can be concluded that KRAS gene mutations are highly prevalent among stage III CRC patients at Dr. Moewardi General Hospital, occurring in 66.7% of the subjects. However, despite this high frequency, the status of KRAS mutation does not serve as a statistically significant predictor for distant metastasis (p=0.735) or mortality (p=0.648) in this specific cohort. These findings suggest that in the context of operable stage III CRC, the clinical outcome may be influenced by a more complex interplay of other molecular pathways and the efficacy of adjuvant chemotherapy, rather than being driven solely by KRAS mutation status.

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