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Original Research Article

Association between KRAS, NRAS, and BRAF mutations and tumor localization in colorectal cancer patients in BSMMU

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ABSTRACT

Background: Colorectal cancer (CRC) is a common malignancy with significant genetic heterogeneity. Mutations in proto-oncogenes such as KRAS, NRAS, and BRAF play a pivotal role in CRC development, impacting prognosis and treatment. This study aims to correlate mutations in these genes with tumor localization in both primary and metastatic CRC in the Bangabandhu Sheikh Mujib medical university (BSMMU) cohort.
Methods: This prospective cross-sectional study was conducted between July 2023 and June 2024 at BSMMU. A total of 30 CRC patients, confirmed via histopathology, were included. Purposive sampling was used to select patients. Tumor tissue samples were collected and analyzed for KRAS, NRAS, and BRAF mutations using DNA isolation, PCR amplification, and sequencing techniques.
Results: Among the 30 patients, the majority were male (66.7%) with a mean age of 50.4 years. KRAS mutations were found in 5 patients (16.7%), while no mutations in NRAS or BRAF were detected. Rectal cancer was the most frequent tumor location (36.7%), followed by hepatic and splenic flexure (16.7% each). No significant correlation was observed between KRAS mutations and tumor localization.
Conclusions: There was no statistically significant correlation between KRAS, NRAS, and BRAF mutations and tumor localization in the BSMMU CRC patient cohort. The study highlights the need for larger sample sizes to better understand the genetic landscape of CRC in Bangladesh. Small sample size may limit the ability to detect significant associations. Further large-scale studies could offer more conclusive insights.

Keywords: Colorectal cancer, KRAS, NRAS, BRAF, DNA isolation, PCR amplification

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies worldwide, accounting for over 10% of cancer cases, and ranks as the second leading cause of cancer-related mortality globally.[1] Early-stage CRC has favorable outcomes with high survival rates when detected and treated promptly. However, approximately 10% of early-stage CRC patients experience poor outcomes, highlighting the complexity of the disease.[2] The understanding of CRC pathogenesis has evolved considerably, and it is now known that genetic alterations play a pivotal role in the development and progression of this disease.

KRAS, NRAS, and BRAF are key oncogenes involved in colorectal carcinogenesis. Mutations in these genes can disrupt cell growth and survival pathways, notably the RAS-RAF-MEK-ERK pathway, contributing to tumor development and progression.[3] KRAS mutations are found in approximately 40% of CRC cases, particularly affecting codons 12 and 13, and are often associated with poor prognosis and resistance to therapies targeting the epidermal growth factor receptor (EGFR), such as

cetuximab and panitumumab.[4,5] Similarly, BRAF mutations, which occur in about 10% of CRC cases, especially in the V600E codon, are linked to more aggressive tumor behavior and poor survival rates.[6,7]

While the genetic landscape of CRC has been extensively studied in Western populations, there is limited data on the prevalence of KRAS, NRAS, and BRAF mutations and their relationship with tumor localization in Bangladeshi patients. Understanding these mutations in the Bangladeshi population is critical for optimizing treatment strategies, particularly in light of the increasing use of targeted therapies. This study aims to investigate the correlation between KRAS, NRAS, and BRAF mutations and the anatomical location of primary and metastatic colorectal tumors in a cohort of Bangladeshi patients treated at Bangabandhu Sheikh Mujib medical university (BSMMU).

METHODS

This prospective cross-sectional study was conducted at the department of colorectal surgery, BSMMU, between July 2023 and June 2024. A total of 30 patients with histopathologically confirmed CRC were recruited. Inclusion criteria encompassed patients over the age of 18, diagnosed with adenocarcinoma of the colon or rectum, and those who provided informed consent. Patients with obstructed or perforated CRC or those with recurrent disease were excluded.

Tissue samples were collected from surgical specimens and processed for genetic analysis. DNA was extracted using the GeneJET™ DNA extraction kit and subjected to polymerase chain reaction (PCR) amplification. Specific primers were used to amplify regions of the KRAS, NRAS, and BRAF genes. Following amplification, PCR products were sequenced, and the presence of mutations was confirmed using sequence analysis software. The frequency of mutations was analyzed, and their correlation with tumor localization was assessed.

RESULTS

Out of the 30 patients, 20 were male (66.7%) and 10 were female (33.3%). The mean age of the cohort was 50.4±10.9 years, with most patients (70%) falling in the 41-60 age group. Rectal cancer was the most common tumor site (36.7%), followed by the hepatic and splenic flexures (16.7% each). KRAS mutations were detected in 5 patients (16.7%), while no mutations were observed in NRAS or BRAF genes. The mutations in KRAS did not show any significant correlation with tumor localization.

Table 1: Patient demographics, tumor location, and mutation distribution, (n=30).

Variables	Categories	N	Percentage (%)
Age (in years)	≤40	6	20.0
	41-60	21	70.0
	>60	3	10.0
	Mean±SD	50.4±10.9	
	Range (min-max)	25-72	
Sex	Male	20	66.7
	Female	10	33.3
Tumor location	Rectum	11	36.7
	Hepatic flexure	5	16.7
	Splenic flexure	5	16.7
	Ascending colon	4	13.3
	Sigmoid colon	2	6.7
	Descending colon	2	6.7
	Caecum	1	3.3
Gene mutation	KRAS	5	16.7
	BRAF	0	0.0
	NRAS	0	0.0
	No mutation	25	83.3

Table 2: Correlation between tumor location and mutation, (n=30).

Variables	Category	Metastatic, (n=5) (%)	Non-metastatic, (n=25) (%)	P value	KRAS mutated, (n=5) (%)	KRAS not mutated, (n=25) (%)	P value
Tumor location	Rectum	2 (40.0%)	9 (36.0%)	0.619	0 (0.0%)	11 (44.0%)	0.082
	Hepatic flexure	0 (0.0%)	5 (20.0%)	0.373	1 (20.0%)	4 (16.0%)	0.627
	Splenic flexure	0 (0.0%)	5 (20.0%)	0.373	1 (20.0%)	4 (16.0%)	0.627
	Ascending colon	1 (20.0%)	3 (12.0%)	0.538	0 (0.0%)	4 (16.0%)	0.462

Continued.

Variables	Category	Metastatic, (n=5) (%)	Non-metastatic, (n=25) (%)	P value	KRAS mutated, (n=5) (%)	KRAS not mutated, (n=25) (%)	P value
	Sigmoid colon	0 (0.0%)	2 (8.0%)	0.690	1 (20.0%)	1 (4.0%)	0.310
	Descending colon	1 (20.0%)	1 (4.0%)	0.310	1 (20.0%)	1 (4.0%)	0.310
	Caecum	1 (20.0%)	0 (0.0%)	0.167	1 (20.0%)	0 (0.0%)	0.167
KRAS mutation	Yes	2 (40.0%)	3 (12.0%)	0.183			
	No	3 (60.0%)	22 (88.0%)				

*P-values are calculated using chi-square tests. ns = not significant.

DISCUSSION

This study found that KRAS mutations were present in 16.7% of the CRC patients from BSMMU, with no mutations detected in NRAS or BRAF. These results align with the mutation rates reported in other studies, where KRAS mutations are found in 15-40% of CRC cases depending on the population and geographical location.[4,6] The absence of NRAS and BRAF mutations in this study may reflect the smaller sample size or unique population characteristics, but warrants further investigation in larger cohorts.

Tumor localization did not show a significant correlation with KRAS mutations in this study. Previous studies have suggested that KRAS mutations are more commonly associated with right-sided colon cancers, whereas BRAF mutations are predominantly found in tumors of the proximal colon.[7,8] Our study did not demonstrate this pattern, possibly due to the low frequency of mutations and the relatively small sample size. Nonetheless, studies such as those by Bożyk et al and Andreyev et al indicate that while KRAS and BRAF mutations are frequent in CRC, their exact distribution varies across populations and tumor sites.[9,10]

KRAS mutations are known to be key predictive markers for resistance to anti-EGFR therapies. Patients with CRC harboring these mutations typically do not respond to treatments like cetuximab or panitumumab, making molecular testing for these mutations crucial for personalized treatment strategies.[5,11] Interestingly, in this study, two of the five patients with KRAS mutations also had metastatic disease, emphasizing the importance of understanding these genetic alterations in guiding therapeutic decisions, especially in the metastatic setting.

The absence of BRAF mutations in our cohort contrasts with findings from Western populations, where BRAF mutations, particularly V600E, are found in 10-15% of cases and are associated with poor outcomes.[12] This difference might be attributed to population-specific genetic variations or the small sample size of our study. Future research with larger sample sizes and a broader genetic panel could provide a more comprehensive understanding of CRC mutations in the Bangladeshi population.

CONCLUSION

This study demonstrated that KRAS mutations were present in a subset of CRC patients treated at BSMMU, but no significant correlation was found between KRAS mutations and tumor localization. The absence of NRAS and BRAF mutations in this cohort highlights the need for larger studies to explore the genetic landscape of CRC in Bangladesh. Molecular testing for these mutations is crucial for guiding treatment decisions, particularly in the context of targeted therapies.

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