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Higher prevalence of KRAS mutations in colorectal cancer in Saudi Arabia: Propensity for lung metastasis

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Abstract KRAS mutation is widely accepted as a key factor in colorectal tumorigenesis. Although KRAS mutation is widely studied in CRC limited data are available about mutation rates and spectrum in CRC from developing countries like Saudi Arabia where epidemiological features of the disease are different. We studied retrospectively tumor samples of 83 Saudi metastatic CRC patients for KRAS mutations in codon 12 and codon 13, to evaluate the relevance of KRAS mutation positive colorectal cancers with metastatic sites. KRAS mutation was observed in 42.2% (35/83) patients with CRC. The most common mutations were in codon 12 (p.G12D, 46%; 16/35, $P < 0.0001$), codon 12 (pG12V, 31%; 11/35, $P < 0.0001$), and codon 13 (p.G13D, 11%; 4/35, $P < 0.016$). Of these 51% and 23% of the tumors are from the left hemicolon and rectum respectively, 83% were moderately differentiated and 86% were invasive adenocarcinoma. Observed mutations are 74% in patients with advanced stage CRC ($P = 0.006$). Among patients with KRAS mutated CRC (CRC) isolated lung and liver metastases were 32% and 23% whereas in WT KRAS was 3% and 53.1% ($P < 0.005$) respectively. The study revealed 69% and 81% of colorectal patients that responded to treatment with complete response (CR)/partial response (PR)/stable disease (SD) were KRAS mutated and WT KRAS respectively ($P = 0.182$). In the mutated KRAS cohort 31% had disease progression compared to 19% in WT KRAS ($P = 0.182$). Multivariate logistic regression analysis showed WT CRC associated with 3-fold increase in positive response to first-line treatment with an odds ratio of 2.83; 95% CI 0.910–8.832. The frequency of KRAS

Abbreviations: 5FU, Fluorouracil; AJCC, American Joint Committee on Cancer; BRAF, v-rafmurine sarcoma viral oncogene homolog B1; CR, complete response; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; GDP, guanosinediphosphate; GTP, guanosine triphosphate; *KRAS* WSC, KRAS wild-type suppressor compound; *KRAS*, Kristen Rat Sarcoma; *MAPKs*, mitogen-activated protein kinases; mCRC, metastatic colorectal cancer; MSI, microstellate instability; OS, overallsurvival; PD, progressive disease; PR, partial response; RAF, serine/threonine kinase; RECIST, response evaluation criteria in solid tumors; RR, relative risk; SD, stable disease; WT, wild-type.

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mutations appears higher in the Saudi population. KRAS mutated CRC patients had a higher propensity for lung metastases by passing liver metastases indicating the need for more extensive chest imaging for effective staging. KRAS WT responds better to treatment compared to KRAS mutated colorectal cancers.

1. Introduction

Colorectal cancer (CRC) is the second most common cancer in developed countries, only surpassed by prostate cancer in men and breast cancer in women, and accounts for about 1 million new cases in 2002 and 530,000 deaths every year.[1] In Saudi Arabia it is the commonest cancer among males (11.8%) and third among females (8.8%) superseded only by breast and thyroid cancers.[2] Surgery is still the only curative treatment for patients with colorectal cancer, but chemotherapy plays an important role in prolonging disease free and overall survival of patients with CRC.[3]

The Kristen Rat Sarcoma (*KRAS*) gene encodes a signal transduction protein, which in its active state forms a complex with a guanosine triphosphate (GTP) group. This complex is inactivated by the hydrolysis of GTP to guanosinediphosphate (GDP). The frequency of mutations in the *KRAS* gene in sporadic CRC is 30–50%.[4,5] It can be as high as 90% in pancreatic cancer mostly in codon 12.[6] The most common mutations found in CRC are in exon 2 and to a lesser magnitude in exon 3.[5] If *KRAS* is mutated, the resulting complex is less sensitive to hydrolysis, remaining in a constitutively active state, leading to cell proliferation by a variety of signaling pathways, including the mitogen-activated protein kinases (*MAPKs*) pathway.[6,7] A high frequency of mutations in this gene in benign lesions suggests that, although providing a selective growth advantage to cells, it is not sufficient by itself to trigger tumor genesis. The accumulation of mutations in this gene and others, including the *APC* gene, will presumably give a selective advantage to the mutated cells, resulting in their clonal proliferation.[8] When *KRAS* is activated, it induces the *MAPK* signal transduction cascade, transferring signals from the cell membrane to the nucleus. The proteins encoded by the *RAS* gene activate *RAF* family proteins of transcription factors. The activation of these transcription factors leads to the expression of proteins that control the cell cycle.[9–11]

The addition of biologic agents that target specific signaling pathways involved in colon tumorgenesis significantly improved the response rate (RR) and overall survival (OS). However, 40–50% of mCRC patients neither show clinical benefit nor suffer from severe toxicity. Therefore, the quest for molecular markers that could predict the response to biological agent and improve clinical benefit began. The *KRAS* gene was one of the first studied due to its involvement in CRC carcinogenesis. The first retrospective studies that evaluated *KRAS* mutation status in patients treated with cetuximab or panitumumab revealed a significant association of favorable response in patients with *KRAS* WT, with RRs of 17–48%, but no response in patients with *KRAS* mutation.[12–18] The CRYSTAL and the OPUS clinical trials were the first to prospectively evaluate *KRAS* mutational status and clinical response to cetuximab.[19,20] CRYSTAL trial patients were treated with FOLFIRI alone or FOLFIRI + Cetuximab, whereas OPUS trial patients were treated with FOLFOX alone or FOLFOX + Cetuximab. Substantial association was observed between response to Cetuximab treatment and *KRAS* WT status in both studies, with no benefit seen in patients who had a *KRAS* mutation. This association was observed both in RR and progression-free survival. With this evidence, the American Society of Clinical Oncology recommended *KRAS* mutation testing in patients who are candidates of anti-EGFR therapy.[21]

In Venezuela Estrada et al.[22] reported mutations in codons 12 and 13 of the *KRAS* gene in 23.33% of patients. Of these, 28.57% were in codon 12, 57.14% were in codon 13 and 14.29% in both codons. They were more frequent in tumors located in the left hemicolon and most of them were well differentiated adenocarcinomas (58.70%) and mucinous (28.57%). The identified mutations were more frequent in Dukes C2 stage of CRC.

In Netherland, 37% (271/737) of CRC patients had *KRAS* mutation at exon 1. The predominant mutations are G > A transitions and G > T transversions, and codons 12 and 13 are the most frequently affected codons. Patients with a rectal tumor were found to have the highest frequency of G > T transversions as compared with patients with a colon or rectosigmoid tumor. This difference appeared to be confined to women with a rectal tumor harboring G > T transversions. The equal distribution of *KRAS* mutations among cases with or without a family history of colorectal cancer debates against an important role for this mutation in hereditary colorectal cancer, and could imply that *KRAS* mutations involving environmental mechanism rather than familial.[23]

In USA, Minoo et al.[24] suggested that colorectal cancer (CRC) should be viewed as heterogeneous disease, in his study 399 patients were evaluated for clinicopathological and molecular profile including *KRAS*, *BRAF* and *MSI* status. Proximal tumors showed significantly larger size, higher T-stage, more mucinous differentiation and high grade. There were high frequency of *BRAF* mutations and *MSI*-high phenotype in proximal colon cancers. Data were supporting the concept that proximal and distal CRCs are distinct pathological entities.

An Indian study[25] was done to find out *KRAS* gene mutation in CRC patients among the Kashmiri population. In a sample of 53 patients 12 had *KRAS* mutations (22.64%). *KRAS* mutation was significantly associated with advanced Duke stage ($P < 0.05$) and positive lymph node ($P < 0.05$). Moreover codon 12 *KRAS* mutations were associated with mucinous histotype ($P < 0.05$).

The aim of the current study is to evaluate the prevalence of *KRAS* mutation among the Saudi population treated at the King Fahad Medical City and try to correlate it with other clinicopathological factors and response to treatment.