Original Article

Effect of *KRAS* mutational status on disease behavior and treatment outcome in patients with metastatic colorectal cancer: intratumor heterogeneity and mutational status

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Background: Nowadays, the outcomes of metastatic colorectal cancer (mCRC) have considerably improved. Genetic studies evaluating *KRAS* mutational status are important in the personalized therapy era to understand disease heterogeneity, disease behaviors, and treatment outcomes.

Methods: This multicenter retrospective study evaluated 360 patients with mCRC treated at three oncology centers in Saudi Arabia and Egypt between February 2011 and December 2015. Patients were treated with bevacizumab and cetuximab according to guidelines. Therapy outcome, time to progression, and disease-associated death were assessed. *KRAS* mutational status was evaluated by testing exons 12 and 13.

Results: Approximately 220 (61.1%) cases were of wild-type *KRAS*, whereas *KRAS* mutation was noted in 38.9%. *KRAS* mutation was common in the descending colon, whereas a low incidence of the *KRAS* mutation was observed in the ascending colon (P<0.001). Among patients with *KRAS* mutation, 64.3% initially presented as emergency cases with obstruction/perforation (P=0.002), and 62.9% had hepatic or pulmonary metastasis. The progression-free survival (PFS) was 10.7 months. Cases without *KRAS* mutation showed a higher PFS than did those with *KRAS* mutation (mean PFS: 11.5 *vs.* 9.6 months, P=0.001). The overall survival was 23.2 months. The survival varied considerably according to *KRAS* type: patients without mutation survived for 25.0 months and those with mutation survived for 19.6 months (P<0.001). Disease-related death occurred in 132 (36.7%) cases, approximately 57.1% of them (80 cases) had *KRAS* mutations (P=0.001).

Conclusions: A major association between *KRAS* mutational status and both disease behavior and treatment outcomes was found in this study. Patients with *KRAS* mutation show advanced disease presentation, with lower PFS and overall survival.

Keywords: Colorectal cancer (CRC); molecular study; KRAS; prognostic and predictive factors chemotherapy/target therapy; progression-free survival (PFS); overall survival (OS)

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Introduction

According to the American Cancer Society, colorectal cancer (CRC) is the 3rd most common malignancy identified in men and women. In 2017, approximately 95,520 new cases of colon cancer and 39,910 new cases of rectal cancer were diagnosed in the United States. Although the incidence of CRC was equal between male [47,700] and female [47,820] patients, rectal cancer was diagnosed in a larger proportion of men [23,720] than women [16,190]. An estimated 27,150 men and 23,110 women were expected to die of CRC in 2017 (1).

Genetic alterations through a multistep process have an essential part in the development of CRC. Therefore, characterizing the genetic origin of the cancer pathway is an ongoing exploration necessary in the development of a standardized treatment guideline based on molecular studies (2).

Early diagnosis of CRC, identification of standard prognostic factors, and proper management with multimodality treatments (surgery, chemotherapy, and targeted therapy +/– radiotherapy) have contributed to the improved outcomes in these patients.

Although the TNM (tumor-node-metastasis) classification is useful for staging cancers and facilitating treatment decisions, it is not sufficient because some patients with the same disease stage may have different disease behaviors and outcomes. Hence, other prognostic factors, based on either clinical factors (obstruction or perforation) or laboratory tests (tumor grade, venous invasion, perineural invasion, 18q deletion), have to be considered to select the optimal therapy for patients with CRC. In the era of molecular-based interventions, more effort is needed to understand the underlying causes of different disease behaviors in patients with CRC, especially those with metastatic CRC (mCRC).

In 1975, Arrington *et al.* (3) recognized *HRAS* and *KRAS* as the first 2 *RAS* genes from the revisions of 2 viruses initiating malignancy (Harvey sarcoma virus and Kirsten sarcoma virus). The human isoform was then identified in 1982, leading to the establishment of the three recognized subtypes: *NRAS*, *HRAS*, and *KRAS*. In all human cancers, *KRAS* mutations had the highest incidence (21.6%), whereas *NRAS* and *HRAS* mutations had a much lower incidence at 8.0% and 3.3%, respectively (4).

RAS gene mutations have been identified in different malignancies, such as pancreatic cancer (90%), thyroid cancer (55%), lung cancer (35%), and rhabdomyosarcoma (35%). The *KRAS* mutant type has been recognized in 30–50% of CRC cases, and it is associated with aggressive behavior, rapid disease progression, and poor survival.

Polymerase chain reaction (PCR) is a real-time investigation used to quantitatively detect the mutational status of exon 2 (codons 12/13) and exon 3 (codon 61) of the *KRAS* gene. Although point alterations in codon 12 are the furthermost *KRAS* mutations in CRC, this test can detect up to 19 *KRAS* mutations (5).

Aim of the study

This study is a retrospective, multicenter chart review carried out to compare the disease behavior, therapy outcomes, as well as progression-free survival (PFS) and overall survival (OS), according to *KRAS* mutational status (wild or mutant) in patients with mCRC.

Methods

This multicenter retrospective study analyzed the diagnostic and monitoring workup of 360 patients with mCRC treated at three oncology hospitals (King Fahad Specialist Hospital in Saudi Arabia in collaboration with King Faisal Specialist Hospital in Riyadh and Zagazig University Hospitals in Egypt) from February 2011 to December 2015. Data were collected from the following assessments:

- Initial clinical examination: this was performed at the time of diagnosis with assessment for the presence or absence of comorbidities.
- Radiologic assessment: this included standard radiologic workup comprising chest, abdominal, and pelvic computed tomography (CT) for all patients. Magnetic resonance imaging and positron emission tomography-CT were performed for some cases, if needed.
- Laboratory assessment: This consisted of recording of pathologic characteristics and baseline carcinoembryonic antigen (CEA) levels, as well as a review of routine laboratory test results, such as complete blood counts and liver/kidney functions test, which were requested before chemotherapy.
- Staging: all cases were assessed on the basis of the 7th edition of the American Joint Committee on Cancer staging system.
- Treatment history: according to the chart review, all patients received oxaliplatin-based or irinotecan-based chemotherapy either alone or in combination

with targeted therapy. Bevacizumab was administered regardless of *KRAS* type (wild or mutant) and to patients who did not have contraindications, whereas cetuximab was administered to wild-type *KRAS* cases. Only four patients in this study received regorafenib after failure of the above therapy; unfortunately, all of them showed poor tolerance even with dose reduction. Palliative surgical intervention was performed in patients with emergency obstruction or perforation, whereas palliative radiotherapy was indicated for a few patients.

- Response status: this was assessed on the basis of the RECIST (Response Evaluation Criteria in Solid Tumors) 1.0 criteria.

Interpretation of KRAS mutation assay

KRAS mutational status was recorded in this study to determine the effects of mutation on patient outcomes. *KRAS* mutation analysis with real-time PCR detects the wild-type sequence and seven known mutations associated with two codons (codons 12 and 13) of the *KRAS* oncogene.

Real-time PCR with eight primer sets was used to amplify the region of the *KRAS* gene containing codons 12 and 13. A set of eight probes was used to detect the *KRAS* type (wild type or mutant) and had the ability to identify mutations up to 1% in a wild-type background.

For statistical analysis, patients in this study were categorized into two groups on the basis of the *KRAS* mutational status: *KRAS* wild type and *KRAS* mutant type.

Ethical and regulatory considerations

The study protocol was approved by the Institutional Review Board of King Fahad Hospital, Saudi Arabia (ONC0310) and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). Due to the retrospective nature of this study, the need for informed consent was waived.

Statistical analysis

SPSS version 17.0 was used for statistical analysis. Quantitative data are presented as means and standard deviations. Parametric and non-parametric *t*-tests were used for comparison of two independent groups. The Kaplan-Meier analysis was performed to assess OS. Log-rank assessment was performed to compare survival between groups and was used to calculate P values for the differences between groups.

Results

In the current study, the median patient age was 51 years (range, 35–76 years), and approximately 19.4% of patients were aged <40 years. The age of the majority of patients (55.0%) ranged from 40 to 60 years (*Table 1*).

Only 34.4% of patients were women. The most frequent presenting complaints were obstruction (30.6%), followed by constipation (25.0%), perforation (19.4%), and rectal bleeding (10.0%).

Among our patients, 50.0% had descending colon lesions, whereas 15.0% patients had ascending colon lesions. Lesions in the transverse colon were noted in 14.4% of patients, and rectal lesions were diagnosed in 20.6% of patients.

Isolated hepatic metastasis was observed in 45.0% of patients, and isolated pulmonary metastasis was observed in 20.0% of patients. Hepatic and pulmonary metastases, in addition to metastasis in other areas, occurred in 30.0% of patients. Single metastatic lesions occurred in 10.0% of patients.

With regard to TNM stage, 80.0% of patients were classified as T4 and 59.4% were classified as N2. All patients were confirmed to have M1 disease at the time of this study. The pathologic assessment of the patients showed well-differentiated adenocarcinoma in 40.0% and isolated mucinous features in 21.7%. The majority of the patients did not exhibit perineural (69.4%) or vascular invasion (78.9%).

Wild-type *KRAS* was confirmed in 61.1% of patients and mutant *KRAS* in 38.9%. The pre-treatment evaluation showed that the serum CEA level was high in 85.0% of patients and normal in 15.0% of patients (*Table 2*).

About 55.7% of *KRAS* mutations were observed in male patients in our study (P=0.027). For statistical analysis, the cases were categorized into three groups according to age, as follows: <40 years, 40–60 years, and >60 years (*Table 3*). We found that 47.1% of patients within the 40–60-year-old category had mutant *KRAS*, compared with 44.3% in the >60-year-old category and only 8.6% (P<0.001) in the <40-year-old category.

Although the initial symptoms varied among patients, the majority of critical presentations was observed in cases with *KRAS* mutation, which included intestinal obstruction (38.6% for mutant *KRAS vs.* 25.5% for wild type) and

Table 1 Patient characteristics

Variable	Number	%
Age (years)		
<40	70	19.4
40–60	198	55.0
>60	92	25.6
Sex		
Male	236	65.6
Female	124	34.4
Initial complaint		
Perforation	70	19.4
Obstruction	110	30.6
Constipation	90	25.0
Bleeding	36	10.0
Others	54	15.0
Co-morbid diseases		
None	135	37.5
HTN	88	24.4
DM	110	30.6
Cardiac	8	2.2
Thrombosis	19	5.3
Site of disease		
Ascending colon (Rt. side)	54	15.0
Transverse colon	52	14.4
Descending colon (Lt. side)	180	50.0
Rectal	74	20.6
Site of metastatic lesion		
Liver	162	45.0
Lung	72	20.0
Liver and lung	108	30.0
Others	18	5.0
Number of metastatic lesions		
Single	36	10.0
Multiple	324	90.0
Tumor marker		
Normal	54	15.0
High	306	85.0
Mortality		
Alive	228	63.3
Died	132	36.7

HTN, hypertension; DM, diabetes mellitus; Rt., right; Lt., left.

Table 2 Clinicopathologic characteristics

Variable	Number	%
Tumor size		
T3	72	20.0
T4	288	80.0
Nodal status		
N1	36	10.0
N2	214	59.4
N3	110	30.6
Pathologic type		
Well differentiated	144	40.0
Moderately differentiated	180	50.0
Undifferentiated	36	10.0
Mucinous		
No	282	78.3
Yes	78	21.7
Vascular invasion		
No	284	78.9
Yes	76	21.1
Perineural invasion		
No	250	69.4
Yes	110	30.6
KRAS mutational status		
Wild	220	61.1
Mutant	140	38.9

perforation (25.7% for mutant *KRAS vs.* 15.5% for wild type), whereas constipation occurred mainly in cases without *KRAS* mutations (26.4% for wild type *vs.* 22.9% for mutant *KRAS*) and bleeding per rectum was seen only in wild-type *KRAS* cases. A statistically significant relationship was established between initial presentation and both *KRAS* types (P=0.002) (*Figure 1*).

A statistically significant relationship (P<0.001) was seen between disease site and *KRAS* mutational status. Ascending colon lesions were mainly found in wild-type *KRAS* cases (16.4% wild type *vs.* 12.9% mutant *KRAS*), and descending colon lesions were found mainly in mutant *KRAS* cases (34.3% mutant *KRAS vs.* 19.1% wild type). The majority of sigmoid lesions in our study were in wild-type *KRAS* cases

Table 3 Correlation between *KRAS* mutational status and clinical characteristics

Variable	*KRAS*, n (%)		Total, n (%)	P value
	Mutant (n=140)	Wild (n=220)		
Sex				0.027
Male	78 (55.7)	158 (71.8)	236 (65.6)	
Female	62 (44.3)	62 (28.2)	124 (34.4)	
Age at diagnosis (years)				<0.001
<40	12 (8.6)	58 (26.4)	70 (19.4)	
40–60	66 (47.1)	132 (60.0)	198 (55.0)	
>60	62 (44.3)	30 (13.6)	92 (25.6)	
Initial complaint				0.002
Perforation	36 (25.7)	34 (15.5)	70 (19.4)	
Obstruction	54 (38.6)	56 (25.5)	110 (30.6)	
Constipation	32 (22.9)	58 (26.4)	90 (25.0)	
Bleeding	0 (0.0)	36 (16.4)	36 (10.0)	
Others	18 (12.9)	36 (16.4)	54 (15.0)	
Site of disease				<0.001
Rt. side	18 (12.9)	36 (16.4)	54 (15.0)	
Transverse	30 (21.4)	22 (10.0)	52 (14.4)	
Lt. side	48 (34.3)	42 (19.1)	90 (25.0)	
Sigmoid	10 (7.1)	80 (36.4)	90 (25.0)	
Rectal	34 (24.3)	40 (18.2)	74 (20.6)	
No. of mets				<0.001
Single	0 (0.0)	36 (16.4)	36 (10.0)	
Multiple	140 (100.0)	184 (83.6)	324 (90.0)	
Site of mets				<0.001
Liver	18 (12.9)	144 (65.5)	162 (45.0)	
Lung	34 (24.3)	38 (17.3)	72 (20.0)	
Liver + lung	88 (62.9)	20 (9.1)	108 (30.0)	
Others	0 (0.0)	18 (8.2)	18 (5.0)	

Rt., right; Lt., left; mets, metastasis.

(36.4% wild type *vs.* 7.1% mutant *KRAS*). Seventy-four patients had rectal lesions; 40 of them had wild-type *KRAS* and 34 had mutant *KRAS* (*Figure 1*).

The liver and lung were the most common sites of metastases in mutant *KRAS* patients, compared with wild-type *KRAS* patients (62.9% mutant *KRAS vs.* 9.1% wild type). Only 12.9% of patients with liver metastases showed evidence of a *KRAS* mutation, in contrast to 65.5% for patients without a *KRAS* mutation. Lung metastasis was observed in 24.3% of patients with mutant *KRAS*, but in only 17.3% of patients with wild-type *KRAS*. A codon 12 mutation was found mostly in patients with liver metastases, whereas a codon 13 mutation was found in those with lung metastases (P<0.001). A statistically significant

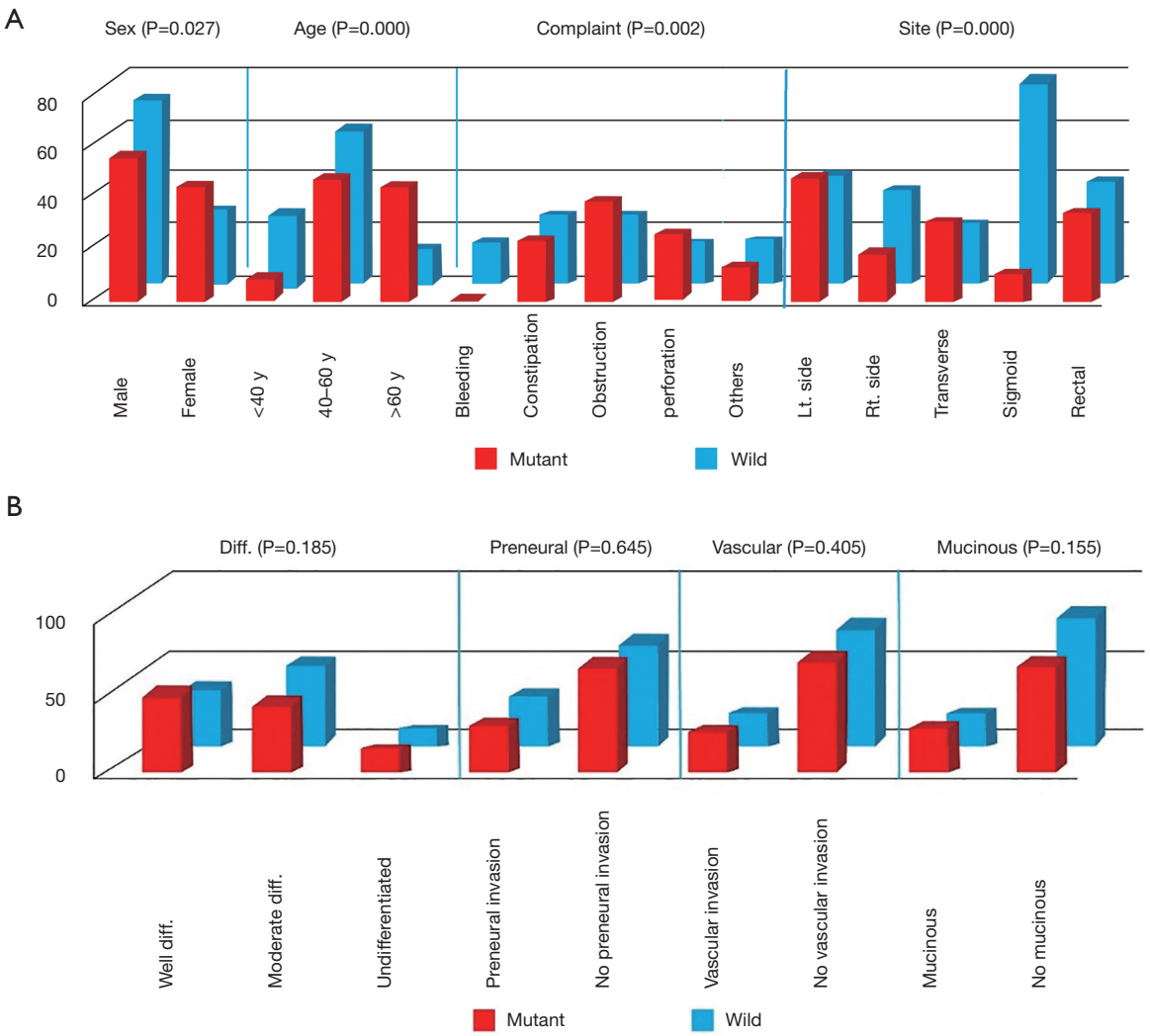

Figure 1 Patient (A) and pathologic (B) characteristics. Lt, left; Rt., right; Diff., differentiation.

association was observed between the number of metastatic lesions and *KRAS* mutational status (P<0.001) (*Table 3*).

Although a significant correlation was observed between T-stage and *KRAS* mutational status (P=0.056), other pathologic parameters including pathologic type, nodal status, presence of mucinous changes, perineural invasion, and vascular invasion showed no statistically significant correlations (*Table 4*, *Figure 1*).

Cancer-related death occurred in 132 cases, and most of these cases had a *KRAS* mutation (P=0.001). A statistically significant relationship was seen between the *KRAS* mutation type and PFS and OS, with a P value of 0.001 and 0.002, respectively (*Table 5*).

The overall PFS was 10.730±0.275 months (range, 10.19–11.27 months). Patients without a *KRAS* mutation showed a significantly longer PFS (11.450±0.238 months; range, 10.98–11.92 months) than those with mutant *KRAS* (9.600±0.574 months; range, 8.476–10.724 months; P=0.001). Since there was many censored participants and many events were there, different statistical tests were carried out, all indicated P values ≤0.05 (*Figure 2*).

The OS was about 23 months (23.160±0.408 months; range, 22.368–23.967 months). Patients with wild-type *KRAS* had an OS of 25 months (25.04±0.38 months; range, 24.29–25.80 months), which was significantly longer (P=0.002) than that of patients with mutant *KRAS*, which was 19 months (19.57±0.70 months; range, 18.19–20.95 months) (*Figure 2*).

Table 4 Correlation between *KRAS* mutational status and pathologic characteristics

Variable	*KRAS*, n (%)		Total, n (%)	P value
	Mutant (n=140)	Wild (n=220)		
Pathology type				0.185
Well differentiated	66 (47.1)	78 (35.5)	144 (40.0)	
Moderately differentiated	58 (41.4)	122 (55.5)	180 (50.0)	
Undifferentiated	16 (11.4)	20 (9.1)	36 (10.0)	
T stage				0.056
T3	18 (12.9)	54 (24.5)	72 (20.0)	
T4	122 (87.1)	166 (75.5)	288 (80.0)	
N stage				0.090
N1	18 (12.9)	18 (8.2)	36 (10.0)	
N2	92 (65.7)	122 (55.5)	214 (59.4)	
N3	30 (21.4)	80 (36.4)	110 (30.6)	
Mucinous				0.155
No	102 (72.9)	180 (81.8)	282 (78.3)	
Yes	38 (27.1)	40 (18.2)	78 (21.7)	
Perineural invasion				0.645
No	100 (71.4)	150 (68.2)	250 (69.4)	
Yes	40 (28.6)	70 (31.8)	110 (30.6)	
Vascular invasion				0.405
No	106 (75.7)	178 (80.9)	284 (78.9)	
Yes	34 (24.3)	42 (19.1)	76 (21.1)	
Tumor marker				0.521
Normal	18 (12.9)	36 (16.4)	54 (15.0)	
High	122 (87.1)	184 (83.6)	306 (85.0)	

Discussion

Colorectal malignancies account for most of the malignancy-related mortality worldwide among male and female patients. In 2016, 1,344,900 new CRC cases were detected in the United States, and an estimated 491,900 persons died of CRC (6).

Since 2000, a decrease in the incidence and mortality rates of CRC was noted. This decrease is attributable to lifestyle changes including reduction in red meat consumption, increase in the use of aspirin, and decrease in smoking, as well as increased utilization of screening tests and improvements in treatment, especially targeted therapy.

A *KRAS* mutation is detected in approximately 40% of sporadic CRC cases. Approximately 90% of activating mutations of the *KRAS* gene are observed in codons 12 and 13, but very few are observed in codons 61 and 63 (7).

An interesting international study by Andreyev *et al.* (8) evaluated 2,721 patients with CRC from 22 research groups in 13 different countries. This study, known as the RASCAL study, clarified the relationship between *KRAS* mutational status and outcomes. The authors concluded that the presence of a *KRAS* mutation was significantly associated with a poorer prognosis.

In oncology, any improvement in survival is considered an appropriate measurement of the clinical outcome and is considered the most important endpoint. On the basis of

Table 5 Correlation between *KRAS* mutational status and survival

Variable	*KRAS*		P value
	Mutant (n=140)	Wild (n=220)	
Survival (mo)			–
Mean	23.168±0.408 (range, 22.368–23.967)		
Median	26.000±0.306 (range, 25.400–26.600)		
Mortality, n (%)			0.001
No (total n=228, 63.3% within *KRAS*)	60 (42.9)	168 (76.4)	
Yes (total n=132, 36.7% within *KRAS*)	80 (57.1)	52 (23.6)	
PFS (mo)			0.001
Mean	9.600±0.574 (range, 8.476–10.724)	11.450±0.238 (range, 10.98–11.92)	
Overall	10.730±0.275 (10.19–11.27)		
OS (mo)			0.002
Mean	19.57±0.70 (range, 18.19–20.95)	25.04±0.38 (range, 24.29–25.80)	
Overall	23.160±0.408 (range, 22.368–23.967)		

PFS, progression-free survival; OS, overall survival; mo, months.

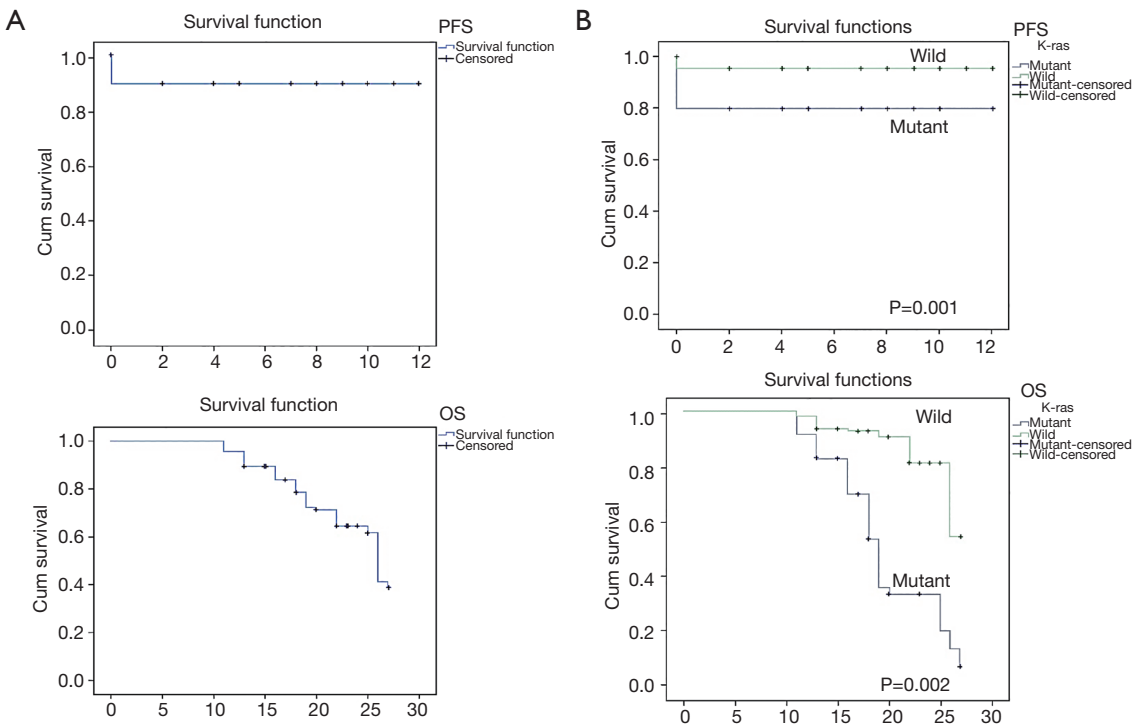

Figure 2 Kaplan-Meier survival curves for (A) all patients and, (B) according to *KRAS* mutational status. Cum, cumulative; PFS, progression-free survival; OS, overall survival.

the Food and Drug Association guidelines, OS was defined as "*the time from randomization until death from any cause*", and it was measured in the intention-to-treat population, whereas PFS was identified as "*the time from randomization until objective tumor progression or death*".

A statistically significant relationship was seen among patient characteristics (age and sex), cancer site, and an initial presentation with *KRAS* mutation status. Our findings are comparable to those of previously reported studies. Imamura *et al.* (9) evaluated *KRAS* mutation in codons 12/13 in 1,261 patients. Similar to that in our study, these mutations were detected in 36% of patients and a high mortality was noted in this group. Kim *et al.* (10) reported on 143 patients in whom the incidence of liver metastases was higher than that of metastases at other sites (P<0.001); however, the incidence of *KRAS* mutation was higher in patients with lung metastasis (P=0.003). Finally, Huang *et al.* (11) studied *KRAS* mutation in 205 patients and found the mutation in 42% of the patients. Higher OS and PFS were observed in patients with wild-type *KRAS* than in those with mutant *KRAS* (OS: 23 *vs.* 18.7 months; PFS: 10.2 *vs.* 7.9 months).

The results of our study are in contrast to those of the study by Karapetis *et al.* (12) which was performed in 393 patients. In this study, *KRAS* mutation was found in about 41% of patients, with these patients being treated with either cetuximab or best supportive care only. Zocche *et al.* (13) also reported similar findings in a study analyzing 149 patients with stage IV disease treated with FOLFOX-4 or a modified FOLFOX-6 regimen as a first-line treatment. The main difference between our study and these two studies was the way in which the data were analyzed. In our study, the patients' age was analyzed in three groups, rather than in only two groups. Another contributing factor may be that we analyzed the data based on four anatomical locations (proximal colon, transverse colon, distal colon, and rectum), as opposed to only the colon and rectum. Furthermore, in our study, we classified the metastatic sites as either single or multiple sites; however, in the other studies, more metastatic subgroups were analyzed.

On the contrary, we found that *KRAS* mutation had no significant association with different pathologic findings except for T stage (with a strong tendency toward statistical significance, P=0.056). Birgisson *et al.* (14) and Huang *et al.* (11) also reported similar findings, except for T stage and vascular invasion. A possible explanation for this finding could be that most of the patients in these trials had stage T3 (71.7%) cancer, whereas most of the patients in the current study had stage T4 (80.0%) disease.

The main cause of mortality in cases with CRC is related to distant metastasis. In approximately 33% of the cases, the metastatic site was the liver (15,16) and the metastases may be present as synchronous metastases in about 25% of patients at the time of primary presentation. Nearly 50% of patients who underwent major dissection of CRC developed distant disease later. Santini *et al.* (17) revealed that *KRAS* C12V mutations were more frequently associated with hepatic metastasis.

Furthermore, a new trial on 143 Korean patients with metastatic or recurrent CRC showed that the lungs are the primary locations of distant metastasis in mutant *KRAS* cases. In this study, the metastatic site was significantly correlated with the *KRAS* mutational status, similar to the findings reported by Kim *et al.* (10).

A statistically significant relationship was found between *KRAS* mutational status and survival. This finding has been previously reported in the landmark RASCAL study on CRC (18), which found that cross mutations may indicate an unfavorable prognosis in CRC, especially in the advanced stages, which might lead to disease recurrence and mortality.

In conclusion, in patients with mCRC, KRAS molecular testing is a good prognostic and predictive tool. Additional molecular studies are needed to further explain the heterogeneity of the disease, in order to select the optimal treatment on the basis of molecular evaluation.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was approved by the Institutional Review Board of King Fahad Hospital, Saudi Arabia (ONC0310) and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). Due to the retrospective nature of this study, the need for informed consent was waived.

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