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Original article

Prognostic Value of KRAS Mutation Status in Libyan Patients with Colorectal Cancer

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Abstract
Colorectal cancer (CRC) remains a major public health issue. The identification of markers that affect CRC prognosis is of great importance. KRAS mutations play a crucial role in carcinogenesis with a powerful predictive value. The present study investigated the associations of KRAS mutation status with clinicopathological variables and survival outcomes in Libyan patients with CRC. The clinicopathological variables of 168 patients with CRC diagnosed at the National Cancer Institute in Misurata, Libya, between 2010 and 2018 were retrospectively investigated. Tumour tissue samples were analyzed at Biomnis, Lyon, France (LCD-Array kit). The results were categorized into two groups: KRAS wild-type (KRAS WT) and KRAS mutant-type (KRAS MT). The relationships between KRAS mutation status and clinicopathologic variables and survival outcomes were analyzed using the Kaplan-Meier method, log-rank test, and Cox regression test. KRAS wild-type (WT) was detected in 52.4% of patients, while KRAS mutant-type (MT) was found in 47.6. KRAS MT was significantly associated with more indicators of a malignant phenotype, including high-grade tumour, large tumour size, positive lymph nodes, advanced stage, distant metastasis, surgically unresectable tumour, and high carcinoembryonic antigen (CEA) expression. Regarding survival, patients with KRAS MT had shorter overall survival rates ($P < 0.0001$, log-rank) and lower disease-free survival rates ($p=0.001$, log-rank). Multivariate analysis showed that KRAS MT ($P<0.0001$), advanced stage ($P<0.0001$), and high CEA expression ($P=0.018$) were independent predictors of poor prognosis. Tumours with KRAS MT were found in 47.6% of primary CRC in Libyans. Patients with KRAS MT were significantly associated with a high grade of malignancy, with poorer prognosis, and with an increased rate of recurrence.
Keywords. *Colorectal Cancer, KRAS, Mutations, Prognosis.*

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Introduction

Worldwide, Colorectal cancer (CRC) is the third most frequent cancer and the second in mortality rate [1]. In 2020, two million new cases and one million deaths were attributed to CRC, according to the International Agency for Research on Cancer (IARC). Standard treatments for CRC may include a combination of surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy [2]. The outcomes varied significantly between the patients, and survival rates ranged from 5% to 90% depending on disease stage and other variables [3]. In a metastasis setting, cancer is usually not curable, with management being directed towards improving quality of life and symptoms [2]. However, several oncological guidelines suggest advanced treatment strategies such as cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) as a valuable option for improving disease control in selected patients [4]. Nevertheless, the risk of recurrence remains high, and further therapeutic strategies are needed [5]. CRC is a group of heterogeneous diseases with different genetic and biological behaviours that explain diverse tumour characteristics and prognosis [6].

Recently, biological molecular markers (KRAS, BRAF, microsatellite instability markers) have been evaluated to improve prognostic stratification and personalized therapy of metastatic CRC [7]. The Kristen rat Sarcoma (KRAS) gene is the most common proto-oncogene mutated in human cancers [8]. KRAS is an effector molecule that makes the signal transduction from ligand-bound epidermal growth factor receptor (EGFR) to the nucleus [9]. KRAS has intrinsic GTPase activity, and it binds to GTP to activate downstream pathways, such as RAS/RAF/MAPK and PI3K/AKT pathways, to promote cell proliferation [10]. In healthy cells, the GTPase-activating proteins would enhance the GTPase activity of

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KRAS and transform the status of GTP-bound KRAS into a status of GDP-bound KRAS, terminating the downstream signaling. However, KRAS mutation impairs the GAP binding to KRAS and leads to a continuous GTP-bound KRAS status to promote the proliferation-related pathways and carcinogenesis [11]. The mutation of KRAS impaired the efficacy of EGFR-targeted therapy [9]. KRAS mutations have been found in 30-40% of CRC patients, with most cases in codons 12 and 13 [12]. So, the KRAS testing is recommended for CRC patients who would receive anti-EGFR therapy. The anti-EGFR therapy is limited to KRAS wild-type (WT) CRC patients [13]. Although KRAS mutation status is an important predictive marker, its prognostic significance remains controversial. Some studies showed that KRAS mutant type (MT) patients had worse progression-free survival and/or overall survival than KRAS WT patients [14-15 and 16]. Moreover, Tanaka et al. observed that KRAS mutation was an independent factor associated with prognosis in a multivariate analysis [17]. While other studies found no association between KRAS mutation status and survival outcomes [18 and 19]. The aims of the study were to evaluate the association between KRAS mutation status and survival outcomes of Libyan patients with CRC.

Patients And Methods

Study population

The study group consisted of 168 patients with CRC diagnosed between 2010 and 2018 at the National Cancer Institute in Misurata, Libya. Tumour samples were obtained during surgery or biopsies. Tumour tissue samples were embedded in paraffin and analyzed at Biomnis, Lyon, France (LCD-Array kit) [20]. The LCD-Array kit was used for the detection of p.G12S, p.G12R, p.G12C, p.G12D, p.G12A, p.G12V, p.G13D, p.G13R, and p.G13C mutations within codons 12 and 13 of KRAS exon 2. The results of KRAS mutation status were categorized into two groups: KRAS wild-type (KRAS WT) and KRAS mutant-type (KRAS MT). Complete demographic and clinicopathological data included age, gender, family history, Tumour location and size, lymph node status, stage, histological type and grade, serum levels of carcinoembryonic antigen (CEA), type of treatment, and follow-up data. These data were obtained from the patients' records and are summarized in (Table I). The mean age of the patients was 49.31 years (range, 22–74 years). (Figure 1). Tumour staging of CRC was evaluated according to the American Joint Committee on Cancer (AJCC), TNM classification [21]. Pan-colonoscopy and radiological staging by Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) was performed in all patients to assess tumour extension. The extent of the tumour (local and distant) at the time of diagnosis and/or follow-up was confirmed by imaging [CT, MRI, or Positron Emission Tomography (PET)]. Blood samples from the patients were analyzed for CEA levels before treatment by electrochemiluminescence immunoassay (double antibody sandwich ELISA). A CEA level equal to or more than 5 ng/ml was considered high expression [22].

Treatment and follow-up

Nearly 71 patients were treated by radical surgery, while palliative surgery was performed in fifty-seven patients, and no surgery was performed in 36 patients who had metastases at the time of diagnosis. However, Colonoscopy and/or sigmoidoscopy with biopsy were performed in these patients for histopathological diagnosis. In the National Cancer Institute in Misurata, the following guidelines were established: Adjuvant combined chemotherapy based on FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and/or XELOX (oxaliplatin and capecitabine) was given to 72 patients, while 81 patients received palliative combined chemotherapy based on FOLFIRI (folinic acid, fluorouracil, and irinotecan) with or without bevacizumab. In addition, 11 patients were not eligible for chemotherapy, so these patients did not receive chemotherapy. Concurrent chemoradiotherapy was given to rectal cancer patients (n=19). Anti- epidermal growth factor receptor therapy (cetuximab and/or panitumumab) was given to 37 KRAS WT CRC patients. Follow-up of patients was carried out every 3 months for 2 years, 6 months for 5 years, and thereafter every 1 year. Disease recurrence (local and distant) was confirmed by colonoscopy and imaging (CT, MRI, or PET) performed when clinical symptoms suggestive of disease recurrence were present. Patient outcomes were considered as follows: overall survival (OS), duration between the date of pathological diagnosis and the date of death and/or to the date of the end follow up period; disease-free survival (DFS), duration between the date of pathological diagnosis and the date of diagnosis of recurrence (local and/or distant) or death. Patients were followed up until death or to the end of the observation period (until December 2023). The median follow-up duration was 36 months (range, 20-115 months). At the end of follow up period, 129 patients (78.7%) had died of CRC.

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Table 1. Association of sociodemographic and clinicopathological variables with KRAS mutation status (KRAS WT vs. KRAS MT)

Variables		KRAS WT group (n=86).		KRAS MT group (n=78)		p value
		Number	%	Number	%	
Age/years	< 50	39	52.0	36	48.0	0.521
	≥ 50	47	52.8	42	47.2	
Gender	Male	52	62.7	31	37.3	0.006
	Female	34	42.0	47	58.0	
Family history	Positive	3	75.0	1	25.0	0.348
	Negative	83	51.9	77	48.1	
Site of tumour	Right	24	42.1	33	57.9	0.153
	Left	29	58.0	21	42.0	
	Rectum	33	57.9	24	42.1	
Histology type	Adenocarcinoma	74	51.4	70	48.6	0.316
	Other types	12	60.0	8	40.0	
Histology grade	1	10	83.3	2	16.7	0.022
	2	48	55.2	39	44.8	
	3	28	43.1	37	56.9	
T	T1	1	100.0	0	0.0	0.008
	T2	4	80.0	1	20.0	
	T3	45	66.2	23	33.8	
	T4	11	37.9	18	62.1	
	Tx	25	41.0	36	59.0	
N	N0	21	84.0	4	16.0	0.002
	N1	15	60.0	10	40.0	
	N2	24	46.2	28	53.8	
	Nx	26	41.9	36	58.1	
M	M0	46	64.8	25	35.2	0.004
	M1	40	43.0	53	57.0	
Stage	Early (stage 1 and 2)	17	85.0	3	15.0	0.001
	Late (stage 3 and 4)	69	47.9	75	52.1	
CEA	< 5	25	71.4	10	28.6	0.009
	≥ 5	61	47.3	68	52.7	
Surgical treatment	Radical	46	64.8	25	35.2	0.012
	Palliative	22	38.6	35	61.4	
	No	18	50.0	18	50.0	
Systemic therapy	Adjuvant	47	65.3	25	34.7	0.012
	Palliative	35	43.2	46	56.8	
	No	4	36.4	7	63.6	
Concurrent chemoradiotherapy	Yes	11	57.9	8	42.1	0.398
	No	75	51.7	70	48.3	
Anti-EGFR therapy	Yes	37	100.0	0	0.0%	<0.0001
	No	49	38.6	78	61.4	

CEA: carcinoembryonic antigen, EGFR: epidermal growth factor receptor

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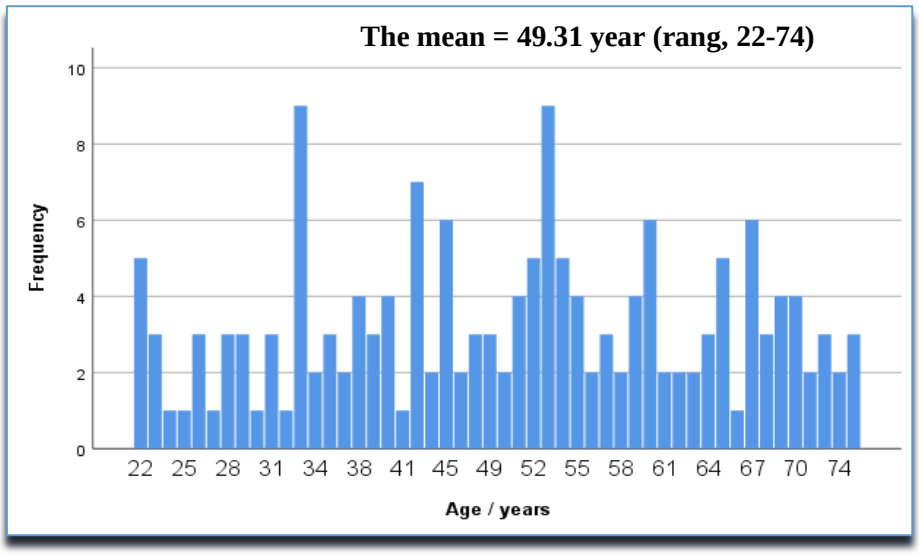

Figure 1. Age distribution of 168 patients with colorectal cancer in Libya (2010-2018)

Statistical analysis

The variables of the material were grouped into logical classes, and descriptive statistics were calculated for the continuous variables using SPSS 26.0 for Windows (SPSS, Inc., Chicago, USA). Frequency tables were analysed using the Chi-square test, with likelihood ratio (LR), to assess the significance of the correlation between the categorical variables. For survival analysis, Kaplan- Meier curves were plotted, and differences between the curves were analyzed using the log-rank test. Multivariate survival analysis for the outcome measure [overall survival (OS) and disease-free survival (DFS)] was carried out using Cox's proportional hazards model in a backward stepwise manner with the log-likelihood ratio (L-R) significance test, using the default values for enter and exclusion criteria. The assumption of proportional hazards was controlled by log-minus-log (LML) survival plots. In all tests, the values $P < 0.05$ were regarded as statistically significant.

Results

Study information

As shown in (Figure 2), A total of 168 CRC patients were included in this study; KRAS MT occurred in 78 patients (47.6%) out of the 168 analyzed. The mean age in all the patients was 49.31 years (range, 22-77 years), (Figure 1). There was no statistically significant difference in terms of age distribution between the two groups ($p > 0.05$), (Table 1). Significant differences were found between KRAS WT and KRAS MT patients among variables of gender, histology grade, tumour size, lymph nodes involvement, tumour stage, CEA expression, and surgical resectability ($p < 0.05$), (Table 1). Moreover, compared with KRAS WT, the KRAS MT was significantly associated with female patients (p=0.006), with poorly differentiated tumours (P=0.022), with large tumour size (P=0.008), with positive lymph nodes (P=0.002), with advanced stage (P=0.001), with distant metastasis (P=0.004), with surgically unresectable tumour (P=0.012) and with high expression of CEA (P=0.009) (Table 1).

KRAS WT, KRAS MT, and survival outcome

Univariate survival analysis (survival rates) with (*KRAS WT vs. KRAS MT)* is shown in (Table 2). The survival rate was 33.7% in patients with *KRAS WT* and 7.7% in patients with KRAS MT (p<0.0001). Kaplan-Meier survival curves showed that shorter survival was associated with KRAS MT (P<0.0001, long rank), (Figure 3). On the other hand, patients with KRAS WT were associated with a lower recurrence rate and therefore had longer disease-free survival (P=0.001, long rank), (Figure 4).

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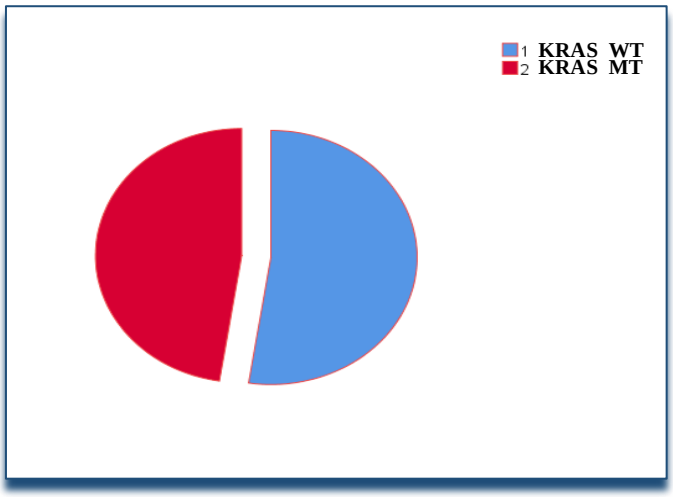

Figure 2. KRAS mutation status (KRAS WT vs. KRAS MT) in Libyan patients with colorectal cancer (n=168)

Table 2. Univariate survival according to analysis of KRAS mutation status (KRAS WT vs. KRAS MT) in Libyan patients with colorectal cancer (n= 168)

Variables	Survival analysis			p-value
	Median time (months)	Mean time (months)	Survival rate (present)	
Overall survival				
All patients	36.04	40.90	21.3	
KRAS WT group	41.67	47.86	33.7	< 0.0001
KRAS MT group	33.00	33.23	7.7	
Disease-free survival				
All patients	8.85	18.26	18.9	
KRAS WT group	12.89	26.22	26.7	0.001
KRAS MT group	5.09	9.49	10.3	

Multivariate Cox analysis

Multivariate survival analysis with KRAS WT and KRAS MT is shown in (Table 3). To assess the role of KRAS mutation status as an independent predictor of OS and DFS, a multivariate Cox regression model was used containing the following prognostic predictors: age, gender, tumour site, histological type, stage, and CEA expression. Multivariate analysis confirmed that KRAS MT was an independent factor for poor prognosis (p< 0.0001), which was also independently predicted by stage (p< 0.0001), and high expression of CEA (P= 0.018).

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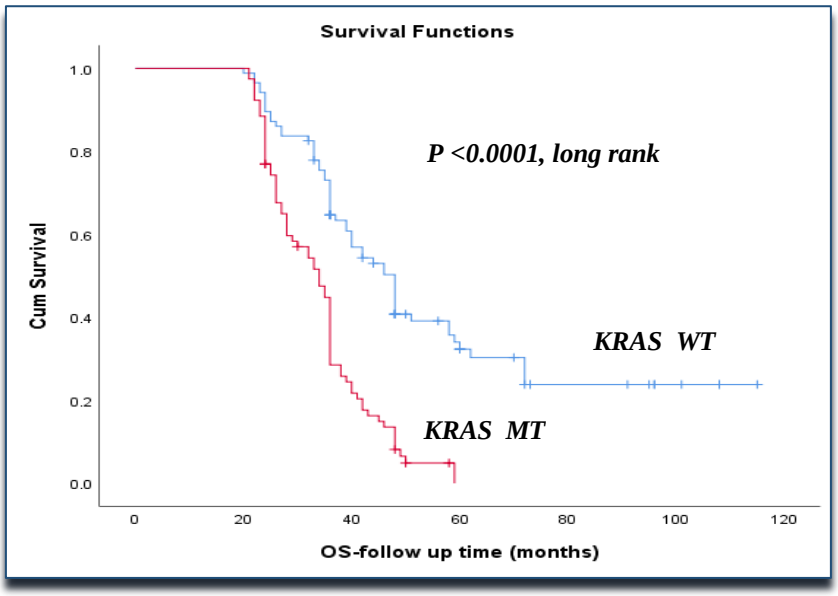

Figure 3. Overall survival curves between KRAS WT and KRAS MT. Kaplan-Meier survival analysis shows a significant statistical difference in 5-year survival between two group

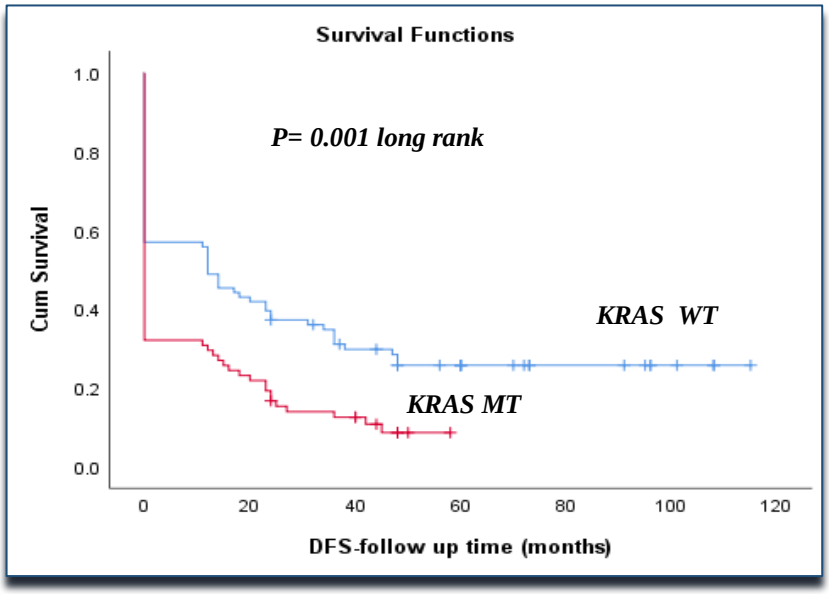

Figure 4. Disease free survival curves between KRAS WT and KRAS MT. Kaplan-Meier survival analysis shows KRAS WT group had the best DFS with statistically significant

Table 3. Multivariate analysis (Cox proportional hazard model) of prognostic factors for 168 patients with colorectal cancer

Variables	*Overall survival model*		*Disease-free survival model*	
	Hazard Ratio (95% CI)	*P value*	*Hazard Ratio (95% CI)*	*P value*
Age (<50 years / ≥50 years)	0.804 (0.564- 1.146)	0.227	0.842 (0.594-1.193)	0.333
Gender (male/female)	1.227 (0.852- 1.768)	0.275	1.064 (0.742- 1.526)	0.734
Tumour site (colon/rectum)	0.913 (0.621- 1.341)	0.641	0.945 (0.653-1.368)	0.765
Histology type (adenocarcinoma /others)	1.180 (0.677- 2.056)	0.559	0.962 (0.548-1.689)	0.892
Clinical Stage (I + II / III + IV)	6.118 (2.415- 15.493)	*<0.0001*	32.685 (4.498-237.499)	*0.001*
CEA (high expression / low expression)	1.796 (1.103- 2.925)	*0.018*	1.607 (0.990-2.608)	0.055
KRAS WT / KRAS MT	2.119 (1.450- 3.098)	*<0.0001*	1.185 (0.826-1.700)	0.357

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Discussion

The presence of KRAS mutations in CRC carries significant clinical implications. KRAS mutations are detected in about 40% of CRC patients; these mutations promote persistent activation of oncogenic pathways such as MAPK/ERK and PI3K/AKT, contributing to carcinogenesis, poor prognosis, and reduced responsiveness to anti-EGFR therapies [23 and 24]. KRAS mutations have been proven as important predictive markers, but their prognostic significance is under evaluation [25 and 26]. The worst prognosis of KRAS-mutated CRC has been shown in several studies [27-29]. In this study, we evaluate the association between KRAS mutation status and survival outcomes of Libyan patients with CRC. 168 patients with CRC diagnosed between 2010 and 2018 at the National Cancer Institute in Misurata, Libya were retrospectively analyzed. Out of 168, CRC KRAS MT was detected in 78 patients (47.6%). The frequency of KRAS MT in our study was higher than published Western data [30 and 31]. However, Libyan patients with CRC were associated with a high grade of malignancy and lower survival rates than Western patients with CRC [32]. These variations may be due to genetic and/or biological differences. Schneider et al suggested that CRC is a group of heterogeneous diseases with different genetic and biological behaviour that explain diverse tumour characteristics and outcomes [33]. CRC was considered a disease of the elderly. Anyhow, the incidence of early-onset CRC has markedly increased in several countries over the past decade, mainly in European and Western countries [34]. Age was observed as a risk and prognostic factor of CRC patients [35].

CRC patients under 50 years of age had a higher rate of recurrence and shorter survival time than older patients ≥50 years. [36]. Moreover, older KRAS MT patients might have better outcomes than younger patients [37]. In this study, the mean age in all the patients was 49.31 years, and there was no statistically significant difference in terms of age distribution between the two groups ($p < 0.05$). These results are in agreement with other published data [38]. The present study showed that the highly aggressive malignant phenotype of KRAS MT is manifested by poorly differentiated tumours, large tumour size, positive lymph nodes, advanced stage, distant metastasis, and unresectable tumour. This observation was in agreement with others. Dongjun et al. reported that compared with KRAS WT patients, the KRAS MT patients had more high-grade tumours, larger tumour size, more positive lymph nodes, more advanced stages, more distant metastasis, and less radical surgical intervention [38]. Significant differences were detected between the KRAS mutation status and the initial serum CEA levels. Patients with KRAS MT had higher initial CEA levels compared to patients with KRAS WT, as observed by Fatih et al. [39].

Our study confirms these results, and we showed that the KRAS MT was significantly associated with high expression of CEA ($P=0.009$). The most important finding of the present study was undoubtedly the significant correlation of KRAS mutation status and disease progression, especially overall survival and disease-free survival. The median follow-up time of the cohort study was 36 months, and ~79% of patients had died of CRC at the end of the follow-up period. Patients with KRAS WT had a lower recurrence rate and lived longer than their counterparts with KRAS MT. Analysis using Kaplan-Meier curves also showed that short survival was more common in the group with KRAS MT, while the group with KRAS WT had longer disease-free survival ($P<0.0001$ and $P=0.001$, respectively). This was a single-institution retrospective study, with a small sample size, and only a single source of previously used data was available for assessment. An extended multinational study with a larger cohort is needed to confirm these results. In conclusion, tumours with KRAS MT were found in 47.6% of primary CRC in Libyans. Significantly, patients with KRAS MT were associated with a high grade of malignancy, with poorer prognosis ($P<0.0001$), and with an increased rate of recurrence. On the other hand, patients who had tumours with KRAS WT had a favorable prognosis and a low risk of recurrence ($P=0.001$).

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Authors' contributions

KH conceived the present study, drafted the manuscript, and wrote the text. ER, RB, NR, ME, AJ, AR, MA, MR, and ME analyzed the data and performed the data interpretation and analysis, writing and proofreading, and discussions. EE performed the statistical analysis. prepared the figures and tables, reviewed the study, interpreted the data, and helped write and proofread the manuscript.

Ethical approval

The cohort study was done under research ethics approval by the ethical committee at the National Cancer Institute, Misurata. Written informed consent was obtained from all patients for surgical treatment, pathologic examinations, and investigations performed according to the institutional guidelines of the National Cancer Institute, Misurata, Libya.

Competing interests

The authors declare that they have no competing interests.

References

1. Ucar G, Ergun Y, Akturk Esen S, Acikgoz Y, Dirikoc M, Esen I, et al. Prognostic and predictive value of KRAS mutation number in metastatic colorectal cancer. Medicine (Baltimore). 2020 Oct 2;99(40):e22407. doi: 10.1097/MD.0000000000022407.
2. National Cancer Institute. Colon Cancer Treatment (PDQ®)–Health Professional Version [Internet]. Bethesda (MD): National Cancer Institute; [updated 2014 May 12; cited 2014 Jun 29]. Available from: https://www.cancer.gov/types/colorectal/hp/colon-treatment-pdq
3. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst. 2004 Oct 6;96(19):1420-5. doi: 10.1093/jnci/djh275.
4. Quénet F, Elias D, Roca L, Goéré D, Ghouti L, Pocard M, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021 Feb;22(2):256-66. doi: 10.1016/S1470-2045(20)30599-4.
5. Feferman Y, Solomon D, Bhagwandin S, Gushchin V, Turaga KK, Sittig M, et al. Sites of recurrence after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for patients with peritoneal carcinomatosis from colorectal and appendiceal adenocarcinoma: a tertiary center experience. Ann Surg Oncol. 2019 Feb;26(2):482-9. doi: 10.1245/s10434-018-7068-3.
6. Schneider NI, Langner C. Prognostic stratification of colorectal cancer patients: current perspectives. Cancer Manag Res. 2014 Sep 5;6:291-300. doi: 10.2147/CMAR.S38827.
7. Hallam S, Tyler R, Price M, Beggs A, Youssef H. Meta-analysis of prognostic factors for patients with colorectal peritoneal metastasis undergoing cytoreductive surgery and heated intraperitoneal chemotherapy. BJS Open. 2019 Aug;3(4):585-94. doi: 10.1002/bjs5.50179.
8. Johnson CW, Burkhart DL, Haigis KM. Classification of KRAS-activating mutations and the implications for therapeutic intervention. Cancer Discov. 2022 Apr 1;12(4):913-23. doi: 10.1158/2159-8290.CD-21-1362.
9. Liu P, Wang Y, Li X. Targeting the untargetable KRAS in cancer therapy. Acta Pharm Sin B. 2019 Sep;9(5):871-9. doi: 10.1016/j.apsb.2019.03.002.
10. Rajagopalan H, Bardelli A, Lengauer C, Kinzler KW, Vogelstein B, Velculescu VE. Tumorigenesis: RAF/RAS oncogenes and mismatch-repair status. Nature. 2002 Aug 22;418(6901):934. doi: 10.1038/418934a.
11. Cox AD, Der CJ. Ras history: the saga continues. Small GTPases. 2010 Jul;1(1):2-27. doi: 10.4161/sgtp.1.1.12178.
12. Patelli G, Tosi F, Amatu A, Mauri G, Curaba A, Patane DA, et al. Strategies to tackle RAS-mutated metastatic colorectal cancer. ESMO Open. 2021 Oct;6(5):100156. doi: 10.1016/j.esmoop.2021.100156.
13. Markman B, Javier Ramos F, Capdevila J, Tabernero J. EGFR and KRAS in colorectal cancer. Adv Clin Chem. 2010;51:71-119. doi: 10.1016/s0065-2423(10)51004-7.
14. Modest DP, Ricard I, Heinemann V, Hegewisch-Becker S, Schmiegel W, Porschen R, et al. Outcome according to KRAS-, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group. Ann Oncol. 2016 Aug;27(9):1746-53. doi: 10.1093/annonc/mdw261.
15. Souglakos J, Philips J, Wang R, Marwah S, Silver M, Tzardi M, et al. Prognostic and predictive value of common mutations for treatment response and survival in patients with metastatic colorectal cancer. Br J Cancer. 2009 Oct 6;101(7):1094-6. doi: 10.1038/sj.bjc.6605296.
16. Taieb J, Shi Q, Pederson L, Alberts S, Wolmark N, Van Cutsem E, et al. Prognosis of microsatellite instability and/or mismatch repair deficiency stage III colon cancer patients after disease recurrence following adjuvant treatment: results of an ACCENT pooled analysis of seven studies. Ann Oncol. 2019 Mar 1;30(3):452-8. doi: 10.1093/annonc/mdz016.
17. Tanaka M, Omura K, Watanabe Y, Oda Y, Nakanishi I. Prognostic factors of colorectal cancer: K-ras mutation, overexpression of the p53 protein, and cell proliferative activity. J Surg Oncol. 1994 Sep;57(1):57-64. doi: 10.1002/jso.2930570113.
18. Kim HS, Heo JS, Lee J, Lee JY, Lee MY, Lim SH, et al. Prognostic impact of KRAS mutation in patients with colorectal cancer: a large retrospective study in a single institution. J Cancer. 2016;7(10):1322-9. doi: 10.7150/jca.15973.
19. Roth AD, Tejpar S, Delorenzi M, Yan P, Fiocca R, Klingbiel D, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol. 2010 Jan 20;28(3):466-74. doi: 10.1200/JCO.2009.23.3452.

20. Weichert W, Schewe C, Lehmann A, Sers C, Denkert C, Budczies J, et al. KRAS genotyping of paraffin-embedded colorectal cancer tissue in routine diagnostics: comparison of methods and impact of histology. J Mol Diagn. 2010 Jan;12(1):35-42. doi: 10.2353/jmoldx.2010.090079.
21. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al., editors. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.
22. Zhao L, Bao F, Yan J, Liu H, Li T, Chen H, et al. Poor prognosis of young patients with colorectal cancer: a retrospective study. Int J Colorectal Dis. 2017 Aug;32(8):1147-56. doi: 10.1007/s00384-017-2828-2.
23. Andreyev HJ, Norman AR, Cunningham D, Oates J, Dix BR, Iacopetta BJ, et al. Kirsten ras mutations in patients with colorectal cancer: the 'RASCAL II' study. Br J Cancer. 2001 Sep 1;85(5):692-6. doi: 10.1054/bjoc.2001.1964.
24. De Roock W, Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilas G, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol. 2010 Aug;11(8):753-62. doi: 10.1016/S1470-2045(10)70130-3.
25. Lin YL, Liau JY, Yu SC, Ou DL, Lin LI, Tseng LH, et al. KRAS mutation is a predictor of oxaliplatin sensitivity in colon cancer cells. PLoS One. 2012;7(11):e50701. doi: 10.1371/journal.pone.0050701.
26. Siddiqui AD, Piperdi B. KRAS mutation in colon cancer: a marker of resistance to EGFR-I therapy. Ann Surg Oncol. 2010 Apr;17(4):1168-76. doi: 10.1245/s10434-009-0811-z.
27. Nieder C, Hintz M, Grosu AL. Colorectal cancer metastatic to the brain: analysis of prognostic factors and impact of KRAS mutations on presentation and outcome. Clin Transl Oncol. 2016 Jan;18(1):88-92. doi: 10.1007/s12094-015-1342-7.
28. Garcia-Carbonero N, Martinez-Useros J, Li W, Orta A, Perez N, Carames C, et al. KRAS and BRAF mutations as prognostic and predictive biomarkers for standard chemotherapy response in metastatic colorectal cancer: a single institutional study. Cells. 2020 Jan 17;9(1):219. doi: 10.3390/cells9010219.
29. Liang L, Tian J, Yu Y, Wang Z, Peng K, Liu R, et al. An analysis of relationship between RAS mutations and prognosis of primary tumour resection for metastatic colorectal cancer patients. Cell Physiol Biochem. 2018;50(2):768-82. doi: 10.1159/000494242.
30. De Roock W, Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilas G, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol. 2010 Aug;11(8):753-62. doi: 10.1016/S1470-2045(10)70130-3.
31. Shen Y, Wang J, Han X, Yang H, Wang S, Lin D, et al. Effectors of epidermal growth factor receptor pathway: the genetic profiling of KRAS, BRAF, PIK3CA, NRAS mutations in colorectal cancer characteristics and personalized medicine. PLoS One. 2013 Dec 2;8(12):e81628. doi: 10.1371/journal.pone.0081628.
32. Elamyal R, Kamoka H, Hashmi H. Clinico-demographic profile of colorectal cancer patients in National Cancer Institute of Sabratha - Libya. J Med Sci Clin Res. 2017;5(12):31123-6.
33. Schneider NI, Langner C. Prognostic stratification of colorectal cancer patients: current perspectives. Cancer Manag Res. 2014 Sep 5;6:291-300. doi: 10.2147/CMAR.S38827.
34. Kasi PM, Shahjehan F, Cochuyt J, Li Z, Colibaseanu D, Merchea A. Rising proportion of young individuals with rectal and colon cancer. Clin Colorectal Cancer. 2019 Mar;18(1):e87-95. doi: 10.1016/j.clcc.2018.10.002.
35. Charlton ME, Kahl AR, Greenbaum AA, Karlitz JJ, Lin C, Lynch CF, et al. KRAS testing, tumor location, and survival in patients with stage IV colorectal cancer: SEER 2010-2013. J Natl Compr Canc Netw. 2017 Dec;15(12):1484-93. doi: 10.6004/jnccn.2017.7007.
36. Zhao L, Bao F, Yan J, Liu H, Li T, Chen H, et al. Poor prognosis of young patients with colorectal cancer: a retrospective study. Int J Colorectal Dis. 2017 Aug;32(8):1147-56. doi: 10.1007/s00384-017-2828-2.
37. Van Eeghen EE, Bakker SD, Van Bochove A, Loffeld RJ. Impact of age and comorbidity on survival in colorectal cancer. J Gastrointest Oncol. 2015 Oct;6(5):605-12. doi: 10.3978/j.issn.2078-6891.2015.070.
38. Dai D, Wang Y, Zhu L, Jin H, Wang X. Prognostic value of KRAS mutation status in colorectal cancer patients: a population-based competing risk analysis. PeerJ. 2020 Jun 4;8:e9149. doi: 10.7717/peerj.9149.
39. Selcukbiricik F, Bilici A, Tural D, Erdamar S, Soyluk O, Buyukunal E, et al. Are high initial CEA and CA 19-9 levels associated with the presence of K-ras mutation in patients with metastatic colorectal cancer? Tumour Biol. 2014 Feb;35(2):1567-72. doi: 10.1007/s13277-013-1209-x.