Original Article

The association of *KRAS* mutation with primary tumor location and survival in patients undergoing resection of colorectal cancers and synchronous liver metastases

Niccolo Allievi[1], Paolo Goffredo[2], Alan F. Utria[2], Michele Pisano[1], Elia Poiasina[1], Alessandro Lucianetti[1], Paige Zhou[2], Imran Hassan[2]

[1]Department of Surgery, Papa Giovanni XXIII Hospital, Piazza OMS 1, Bergamo, Italy; [2]Department of Surgery, University of Iowa Hospitals & Clinics, 200 Hawkins Dr, Iowa City, IA, USA

Contributions: (I) Conception and design: N Allievi, P Goffredo, I Hassan; (II) Administrative support: N Allievi, P Goffredo, P Zhou, I Hassan; (III) Provision of study materials or patients: N Allievi, P Goffredo; (IV) Collection and assembly of data: N Allievi, P Goffredo, M Pisano; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Imran Hassan, MD, FACS, FASCRS. Department of Surgery, University of Iowa, 200 Hawkins Drive, 1516 JCP, Iowa City, IA 52242, USA. Email: ihassan@mercycare.org.

Background: Recent evidence suggests that a mutation in the *KRAS* gene has a significant impact on the clinical behavior and prognosis of patients with metastatic colorectal cancer. The *KRAS* mutation (*m-KRAS*) has been associated with decreased survival among patient undergoing treatment with a curative and palliative intent. This is believed to be secondary to a reduced response to anti-EGFR chemotherapy agents and a more intrinsically aggressive biology. The aims of this study were to identify risk factors for *m-KRAS* in patients with curatively resected colorectal cancer and synchronous liver metastases and to assess its association with disease-specific survival (DSS).

Methods: The Surveillance, Epidemiology and End Results (SEER) Database was surveyed for patients undergoing resection of colorectal cancer and synchronous liver metastases from 2010 to 2015.

Results: A total of 806 patients were included, of which 40% had *m-KRAS*. Right-sided primary lesions (OR 2.56, 95% CI: 1.90–3.44, P<0.001) and African-American ethnicity (OR 1.58, 95% CI: 1.05–2.40, P=0.03) were independently associated with *m-KRAS* on multivariable analysis. Compared to wild-type *KRAS* (*wt-KRAS*), *m-KRAS* was associated with decreased 3- and 5-year DSS (59% *vs.* 50% and 29% *vs.* 21%, respectively, P=0.024). After adjusting for confounders, a decreased DSS was observed in patients with right-sided lesions (HR 1.68, 95% CI: 1.32–2.12, P<0.001), while *m-KRAS* was associated with a trend toward decreased DSS (HR 1.15, 95% CI: 0.91–1.46, P=0.24).

Conclusions: In patients undergoing surgical resection of colorectal cancer and synchronous liver metastases, *m-KRAS* was associated with right-sided lesions and African-American ethnicity. Compared to *wt-KRAS*, *m-KRAS* was associated with a reduced DSS. Additionally, right-sided lesions were an independent negative prognostic factor for DSS.

Keywords: Colorectal cancer; *KRAS*; liver metastases

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Introduction

Colorectal cancer has an annual global incidence of 1.65 million cases (1). At the time of diagnosis, up to 25% of patients already have liver metastases and an additional 25% will develop hepatic metastases during the course of their disease (2). The median overall survival (OS) for patients with metastatic colorectal cancer that is treated with a palliative intent with multi-agent chemotherapy is approximately 30 months (3). Although surgical indications and timing of resections in colorectal cancer and liver metastases are still a matter of debate, hepatic metastasectomy with resection of the primary tumor remains the only potentially curative treatment (3-5). Mutations of the Kirsten Rat Sarcoma viral antigen homolog (*KRAS*) gene are found in about 40% of patients (6) with metastatic colorectal cancer. The determination of *KRAS* status is a relevant prognostic characteristic in these patients, as mutated *KRAS* (*m-KRAS*) reflects a poor response to anti-EGFR immunotherapy (3) and is associated with an increased cumulative incidence of metastatic disease as well as an adverse prognosis (6-8).

In recent years, the molecular pathways of oncogenesis in colorectal cancer and the intrinsic differences between right-sided and left-sided lesions have been investigated. Two meta-analyses (6,9) of institutional studies evaluating the prognostic significance of *m-KRAS* in patients treated with surgical resection of primary colorectal cancer and synchronous hepatic metastases, observed that *m-KRAS* was associated with decreased OS and disease-free survival (DFS). More recently, a study (10) using the National Cancer Database (NCDB) confirmed the negative prognostic impact of *m-KRAS* in colorectal cancer with synchronous liver metastases and demonstrated that *m-KRAS* was associated with right-sided lesions and African-American ethnicity. Two main limitations of the NCDB are the lack of data on disease-specific survival (DSS) and the limited generalizability to the United States (U.S.) population as this database only collects data from the Commission on Cancer (CoC) affiliated Hospitals.

Therefore, aim of this study was to analyze the impact of *m-KRAS* on DSS as well as its associated risk factors in patients undergoing resection of colorectal cancer and synchronous liver metastases in a U.S. population-based cohort utilizing the Surveillance, Epidemiology and End Results (SEER) database.

Methods

The SEER Program (11) provides information on cancer statistics within the U.S. It is supported by the Surveillance Research Program (SRP) within the National Cancer Institute (NCI). Data were available for a total of 18 registries representing approximately 30% of the U.S. population. The population covered by SEER is representative of the general U.S. population with regards to measures of income and education level. However, the SEER population presents a higher proportion of foreign-born patients as compared to the general U.S. population. SEER employs the International Classification of Diseases for Oncology, third edition (ICD-O-3) for histology classification (12).

In order to select patients diagnosed with colorectal cancer and synchronous liver metastases between 2010 and 2015, the Incidence—SEER 18 Regs Custom Data Colon and Rectum Database was queried (13). The selection of patients was conducted as follows: age older than 18 years, Stage IV colorectal adenocarcinoma with isolated liver metastases, resection of the primary tumor, nonprimary surgical procedure to distant site (i.e., patients undergoing liver resection) and known mutational status of *KRAS*.

Demographic variables included in the analyses were gender, age at diagnosis, year of diagnosis, ethnicity and insurance status. Clinicopathologic variables included administration of chemotherapy and radiation therapy, surgical treatment of the primary tumor and metastatic lesions, location and size of the primary tumor, involvement of the lymph nodes and *KRAS* status of the primary colorectal cancer. Primary tumor location was classified as 'right-sided' for lesions located from the cecum to the transverse colon and as 'left-sided' for lesions located from the splenic flexure to the rectum.

Statistical analyses

Descriptive statistics of demographic and clinicopathologic variables were performed. Student's *t*-test and Chi-square test were performed to compare continuous and discrete variables, respectively. Univariate and multivariate binary logistic regression was used to recognize factors associated with *m-KRAS* and odds ratios (OR) and 95% CI were calculated. DSS was estimated with the Kaplan-Meier method and the log-rank test was used to evaluate statistical significance of the differences in survival. Cox proportional hazard regression was used for the multivariable survival model. Hazard ratios (HR) and 95% confidence intervals were computed for the power of association between each variable and survival.

Table 1 Characteristics of patients based on *KRAS* mutational status

Patient variable	*KRAS* status		P
	Wild-type (n=485)	Mutated (n=321)	
Sex (female), %	42.7	46.7	0.257
Age at diagnosis (years), mean (SD)	57.3 (13.7)	59.4 (13.1)	0.038
Ethnicity, %			0.01
Caucasian	78.4	71.7	
African-American	11.3	19.0	
Other	10.3	9.3	
Year of diagnosis, %			0.424
2011	58	42	
2012	59.5	40.5	
2013	66.4	33.6	
2014	61.8	38.2	
2015	57	43	
Insurance status, %			0.368
Uninsured	5.4	4.7	
Medicaid	11.5	11.8	
Insured	82.1	72.5	
Unknown	1	11	
Radiotherapy (received), %	9.9	11.8	0.639
Chemotherapy (received), %	90.3	91.6	0.619
Primary tumor size (mm), mean (SD)	51.6 (21.44)	54 (31.6)	0.218
Location of primary tumor (right), %	31.3	54.7	<0.001
Lymph node involvement (pN+), %	81.3	81.2	0.9

Data analyses were performed using SEER*Stat software (14) and Statistical Package for the Social Sciences (SPSS) software (version 20.0; SPSS Inc., Chicago, IL, USA). P values were considered significant if <0.05 and all tests were two-sided. Considering that data included in the SEER Database is publicly available and de-identified, approval by an institutional review board was not considered necessary for the current study.

Results

Patient characteristics

A total number of 806 patients with colorectal cancer and synchronous liver metastases and documented *KRAS* mutational status who underwent surgical treatment of their primary tumor and liver metastases were retrieved in the SEER Database. *m-KRAS* was present in 321 cases (39.8%). Overall *m-KRAS* was associated with older age (59.4 *vs.* 57.3 years, P=0.038; *Table 1*) and African-American ethnicity (19.0% *vs.* 11.3%, P=0.01), but was not related to gender, insurance status or year of diagnosis. Furthermore, *m-KRAS* was more commonly found in right-sided primary lesions, when compared to left-sided lesions (54.7% *vs.* 31.3%, P<0.001). Clinicopathologic variables, such as primary tumor size, lymph node involvement and radio-chemotherapy administration were not significantly associated with *m-KRAS*. On multivariable analysis, right-sided lesions (OR 2.56, 95% CI: 1.90–3.44, P<0001) and African-American ethnicity (OR 1.58, 95% CI: 1.05–2.40,

Table 2 Multivariable analysis for predictors of *m-KRAS* status

Patient variable	OR	95% CI	P
Ethnicity			
Caucasian	Reference	–	–
African-American	1.58	1.05–2.40	0.03
Other	1.08	0.66–1.77	0.77
Primary tumor location			
Left-sided	Reference	–	–
Right-sided	2.56	1.90–3.44	<0.001

Age and gender were not significantly associated with *m-KRAS*. OR, odds ratio; CI, confidence interval.

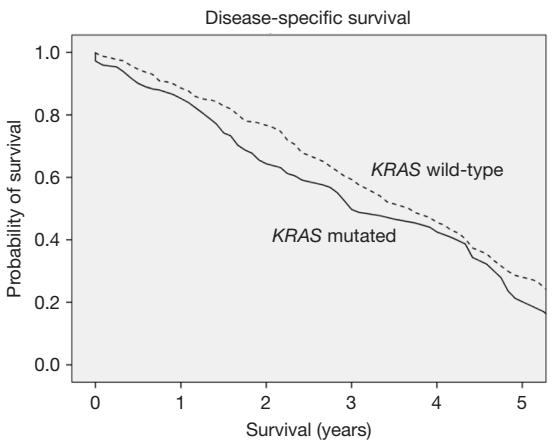

Figure 1 DSS by *KRAS* mutational status. Log-rank test: P=0.024. DSS, disease-specific survival.

Table 3 Multivariable analysis for prognostic factors

Patient variable	HR	95% CI	P
Right-sided primary lesion	1.68	1.32–2.12	<0.001
m-KRAS	1.15	0.91–1.46	0.24

Age, gender, ethnicity, lymph node involvement and primary tumor size were not significant. HR, hazard ratio; CI, confidence interval.

P=0.03) were significantly associated with *m-KRAS* status (*Table 2*).

Survival analyses

Compared to *wt-KRAS*, *m-KRAS* status was associated with decreased DSS; 3- and 5-year DSS were 59% *vs.* 50%, and 29% *vs.* 21%, respectively (P=0.024; *Figure 1*). Similarly, patients with right-sided lesions demonstrated an increase in disease-specific mortality, with a 5-year DSS of 19%, as compared to 29% for left-sided lesions (P<0.001).

After adjusting for the available confounders, patients with right-sided lesions had a decreased DSS (HR 1.68, 95% CI: 1.32–2.12, P<0.001; *Table 3*). Furthermore, *m-KRAS* demonstrated a trend toward decreased DSS (HR 1.15, 95% CI: 0.91–1.46, P=0.24).

Discussion

The present study investigated the associations between *KRAS* mutational status, primary tumor location and survival in a cohort of 806 patients from a population-based dataset. African-American ethnicity and right-sided lesions were independently associated with *m-KRAS*. Moreover, *m-KRAS* and the presence of a right-sided primary lesion were negative prognostic factors in patients with colorectal cancer and synchronous liver metastases undergoing surgical resection of both their primary colorectal cancer and liver metastases.

Given its relatively high incidence, the relative ease of detectability, and the various targeted therapeutic options available (3,4), *m-KRAS* is an important prognostic consideration in the management of metastatic colorectal cancer. In the context of multi-disciplinary strategies, the decision-making process is often driven by clinical and radiological features, rather than pathologic and biologic elements. However, the mutational status of *KRAS* may predict the responsiveness to upfront chemotherapy in presence colorectal cancer and synchronous liver metastases (15) and may also explain intrinsic aggressive tumor biology (16,17), resulting in increased risk of progression and relapse after resection. *m-KRAS* is acquired early in the mutational cascade, it remains stable over the course of the disease, and has a high concordance between primary tumor and liver metastases (18). Several preoperative clinical risk scores for patients presenting with resectable colorectal cancer and synchronous liver metastases were developed (19-22) based on institutional cohorts, although there have been concerns regarding the absence of external validation of these scores as well as the accuracy and applicability of the reported prognostic factors (23). Therefore, using current knowledge of the mutational profile of colorectal cancer to guide clinical practice could harbor the potential of improving oncologic

outcomes. This has led to the creation of the Genetic and Morphological Evaluation (GAME) Score (24), which is based on morphologic and biologic tumor information and represents the first clinical risk score including the genetic status (*KRAS*) of the primary tumor. The score was developed using a derivation cohort, including 502 patients, and an external validation cohort (747 patients) and its discriminatory capacity resulted to be superior to other institutionally derived scores. Integrating genetic, biologic and clinical information not only is likely to improve comparison of different cohorts, but may also guide treatment selection and provide relevant prognostic details (24).

The proportion of patients with *m-KRAS* in the current study (39.8%) was consistent with previous reports in the literature (14–46%). In an analysis of all Stage IV colorectal cancers within the SEER database, Charlton *et al.* (25) reported an overall mutation rate of 44% among 6794 patients. Similarly, in their study utilizing the NCDB, Goffredo *et al.* (10) reported *m-KRAS* in 42% out of 2,655 patients who underwent surgical treatment of both their primary colorectal cancer and isolated liver metastases. Two meta-analyses of institutional studies by Brudvik *et al.*, that included 14 studies with 1,809 cases, and Tosi *et al.*, which included 11 studies with 1,369 patients, reported an overall *m-KRAS* incidence of 30.6% and 34.3%, respectively. While there was substantial overlap between these two studies, they differed in that Tosi *et al.* used a more stringent criteria for inclusion in their analysis and added three newer studies (6,9). Both these meta-analyses demonstrated that *m-KRAS* was negatively associated with OS and relapse free survival, irrespective of chemotherapy agent received.

In our cohort, the proportion of patients with a right-sided cancer within the *m-KRAS* subgroup was high at 54%, as compared to 31% within the *wt-KRAS* subgroup. In a meta-analysis including 66 studies and 1,437,846 patients, Petrelli *et al.* (26) reported that right-sided lesions were associated with worse OS. There have been several explanations in the literature for this difference in survival based on location. Firstly, surgical approaches to right-sided and left- sided colon/rectal cancer are different: while the standard of care is well defined for left-sided and rectal lesions, the optimal surgical resection for right-sided lesions remains debated, particularly in regards to the extent of mesocolic excision and lymphadenectomy (27,28). Secondly, benefits from anti-EGFR agents is less pronounced in right-sided lesions, as reported by two recent trials (29,30). Finally, right-sided colon cancer is associated with increased incidence of genetic mutations [microsatellite instability (MSI), BRAF and *KRAS* mutations] which may explain the survival difference in this subgroup of patients (31).

In the current study, right-sided tumors and African-American ethnicity were significantly associated with the presence of *m-KRAS* status. Right-sided lesions, but not African-American ethnicity, were associated with lower DSS on multivariable survival analysis. Using the NCDB, Goffredo *et al.* found comparable results in a U.S. based national cohort of patients (10), even though the NCDB and SEER databases are different in terms of quality and origin of data. The former collects data from Commission on Cancer-accredited cancer program registries, capturing around 70% of all newly diagnosed cases of cancer at an institutional level; the latter gathers data from population-based cancer registries and covers 34.6% of the U.S. population. Notwithstanding the possible overlapping between the two datasets, the reproducibility of results between these two studies underscores the validity of the association between *m-KRAS* and survival outcomes. Our findings appear to support the hypothesis that specific tumor biology and mutational status may be related to primary tumor location and could be the main driver for worse outcomes.

The present study has several limitations. Firstly, the retrospective nature of the analysis of the SEER database might be flawed by intrinsic biases of large databases. Secondly, the SEER is a population-based dataset and several potentially significant variables are not collected routinely. Thirdly, the vast range of therapeutic possibilities, including type of surgical resection, various lines of chemotherapy, radiotherapy and their temporal combination, could not be investigated in depth. Finally, the accuracy and extent of surgical treatment as well as other therapeutic maneuvers could not be evaluated.

Conclusions

In conclusion, the present study suggests a negative prognostic value of *m-KRAS* and right-sided lesions in a population-based cohort of patients undergoing resection of colorectal cancer and synchronous liver metastases. Our data show that African-American ethnicity and right-sided lesions were associated with *m-KRAS*. The mutational status of *KRAS* is likely to be associated with unfavorable tumor biology leading to decreased survival and should be discussed in the context of multi-disciplinary management

of patients with colorectal cancer and synchronous liver metastases.

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None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The data included in the SEER Database is publicly available and de-identified, approval by an institutional review board was not considered necessary for the current study.

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