Primary Tumor Location and Survival Among Metastatic Colorectal Cancer Patients treated with systemic chemotherapy, and biologic therapies: Retrospective Analysis (2013-2016)

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Abstract

Purpose: In a sample of Middle Eastern population, we sought to evaluate whether survival outcomes for mCRC patients treated with systemic chemotherapy (SC) and, with and without biologic therapies (bevacizumab and cetuximab) are different between left and right-sided tumors.

Methods: Ministry of National Guard- Health Affairs (MNG-HA) Cancer registry data was utilized to identify patients diagnosed with CRC between 2013 and 2016. Kaplan-Meier method and porosity score adjusted Cox proportional hazard models were used to assess survival for right and left-sided mCRC with and with BT.

Results: A total of 196 mCRC patients with mean age of 64 years old, 57.65% male diagnosed from January 1, 2013, through December 31, 2016. The overall median survival for left-sided was significantly higher than right-sided mCRC tumors ($P 0.03$). mCRC patients treated with SC+BT were associated with decreased mortality only among patients with left-sided mCRC compared to right-sided mCRC (HR, 0.21; 95% CI, 0.05-0.92; $P .03$). mCRC with no primary-tumor resection and CS+TB left-sided mCRC was significantly associated with decreased mortality compared to right-sided mCRC (HR, 0.15; 95% CI, 0.03-0.72; $P .02$).

Conclusions: In a sample of Middle Eastern population, a significant decrease in mortality for left-sided mCRC treated with SC plus BT compared with right-sided mCRC was observed. mCRC patients with unresectable metastases demonstrated survival benefit from left-sided SC plus BT treatment. Randomized controlled trials are needed to determine the optimal treatment for mCRC patients.

Introduction

Colorectal cancers are molecularly heterogeneous with carcinogenic pathways that are partially associated with embryologic origin [1, 2]. Right-sided and left-sided difference can be attributed to several factors such as demographic, anatomical, developmental origin, embryological factor [4], and various carcinogenic factors like difference in bacterial phylotypes on each side of the colon [5, 6]. Spread of cancer cells, and tumor sidedness are both important factors to determine an adequate treatment plan for mCRC patients. As of tumor sidedness, efficacy and response of treatment are varied from right-sided to left-sided CRC [3, 5]. Accumulating studies have evaluated the impact of primary tumor location on survival for mCRC patients. Evidence suggests a prognostic role of tumor side among mCRC patients [7, 8, 9]. These variations might be essential considerations when determining adjuvant treatment and surveillance after resection of the primary tumor [9]. Additionally, biologic therapies (BTs) that target vascular endothelial growth factors as bevacizumab and epidermal growth factor receptor (EGFR) as cetuximab have been widely used in addition to systemic chemotherapy (SC) for the treatment of mCRC [11, 13].

Prior studies concluded that primary tumor sidedness is associated with response to biologic therapies among mCRC. Right-sided primary tumor location is associated with higher mortality regardless of the biologic therapies type. Furthermore, patients with wild-type *RAS* right-sided primary tumors had better survival when treated with bevacizumab compared to cetuximab. In contrast, patients with left-sided primary tumors had better survival when treated with cetuximab [11–13]. The question is, to what extent can these variations of treatment outcomes influence survival rate in mCRC patients among a sample of Middle Eastern, Saudi population remains unclear. Most previously conducted studies on evaluation of mCRC tumor side were post hoc analyses for randomized clinical trials [13] or studies using data from Surveillance, Epidemiology, and End Results (SEER) or Western populations [10]. Whereas, in the field of anticancer agents particularly for chemotherapy, and as a result of ethnic diversity in drug response there are potential differences in pharmacodynamics among various populations [13]. This diversity can result in differences in the recommended safe and effective treatment dose of a drug in different populations or avoidance of ineffective therapy [14, 15]. Thus, we sought to evaluate if survival outcomes for systemic chemotherapy (SC) with and without biologic therapies (bevacizumab and cetuximab) are different between left and right-sided tumors among mCRC patients. Furthermore, to better understand the predictive value of tumor location and treatment for mCRC patients treated with SC and BT, we further examined if the tumor location and potential benefit of SC alone or SC plus BT are different among those with and without resection of the primary tumor.

Material And Methods

Study design, Setting, and Population

This study is a retrospective cohort study using data from the Ministry of National Guard Health Affairs' (MNG-HA) Cancer Registry. The registry, was established in 2011, collects information about cancer patients' demographic information, clinical characteristics including type of cancers, their location, and extent at the time of diagnosis. The registry captures all cases diagnosed and treated at King Abdulaziz Medical City (KAMC) in Jeddah city, Western province. Follow-up information is captured in the data at each visit including patients' last contact date.

Identification of patients

Study participant selection included individuals aged ≥ 18 years diagnosed with a first primary invasive, malignant colorectal cancer International Classification of Diseases (ICD) (ICD-10 C18–C20) between 2013–2016, who were residing in Saudi Arabia and registered in MNG-HA hospitals system with follow up to December 31, 2016. The population (549 individuals) is served by tertiary care hospitals and four primary and secondary care clinics. Of 545 eligible patients, 4 (0.7%) were excluded due to unknown survival status, admission, or contact dates. There were 209 metastatic colorectal (mCRC) patients in the cohort, we excluded 13 unspecified tumor locations. The remaining sample size was 196, whereas 60 patients receiving systemic chemotherapy (SC) alone and 76 receiving chemotherapy with added BT bevacizumab, or cetuximab (Fig. 1).

Patient and Tumor Characteristics

Patient demographics including age, age at diagnosis, gender, marital status, and nationality were all extracted from electronic health records. Marital status was combined all three unmarried groups (single, separated/divorced, or widowed) to get sufficient subjects of unmarried. Clinical variables such as tumor's topography, morphology, treatment (resection of the primary tumor, and/or chemotherapy), biologic therapy type (bevacizumab or cetuximab), number of completed chemotherapy cycles, grade, and extent, were derived from pathology reports and/or surgical specimens and were coded using (ICD-10 C18–C20). The anatomic tumor sites were categorized according to the ICD for Oncology-third edition topography as follow: right colon (i.e., cecum, appendix, ascending colon, hepatic flexure of the colon and transverse colon), left colon (i.e., splenic flexure of the colon, descending colon, rectosigmoid junction, sigmoid, and rectum), colon not otherwise specified (NOS), [15–17].

Outcome Variable

Follow-up time started at the date of CRC diagnosis in the registry and ended on the date of death, date of the last contact, or when the study ended on December 31, 2016, whichever came first. To estimate survival for mCRC, we restricted the population to patients diagnosed with stage IV (metastatic) anytime up to December 31, 2016 [21]. Completeness of follow-up was computed at each time interval using Clark's Completeness Index (CCI) [18–20]. The resulting CCI and SPT were 80.44% and 81.54%, respectively.

Statistical Analysis

The demographic and clinical characteristics were assessed across right-sided and left-sided mCRC tumor using Chi-square and Fisher exact test where appropriate. We used purposeful variable selection [22] for model building in the multivariate analyses. Backward elimination was used to retain all variables with $P < 0.3$. The survival rates were estimated using the Kaplan-Meier product-limit method and differences between curves were assessed using the log-rank test for all-cause mortality. We examined tumor origin (right or left) with mortality among metastatic colorectal cancer patients. To minimize potential confounding bias that might result from imbalanced patients' baseline characteristics, we used a logistic regression model to generate a propensity score by incorporating significant predictors for variables obtained from the backward selection process [23]. Adjustment for propensity score was performed in all multivariable analyses. In a subgroup analysis, we used Cox proportional hazards regression models to estimate differences in all-cause mortality between tumor origin (right or left side) in those who received systemic chemotherapy alone and those received systemic chemotherapy and BT (bevacizumab and/or cetuximab) by primary tumor resection. An interaction test was used to determine whether primary tumor location was a therapy use effect modifier on the outcome. The effect of primary tumor location on survival outcomes was also assessed in subgroup analyses stratified by resection of the primary tumor [24]. Due to the small sample size and to avoid potential bias, Firth's Correction for Monotone Likelihood was used [25]. All statistical tests were 2-sided, and findings were considered

statistically significant at $P < .05$. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC).

Results

A total of 549 patients diagnosed with CRC between 2013 and 2016, with 209 (38.06%) of the total cohort were diagnosed with mCRC (Fig. 1) (Table 1). After applying exclusion criteria, a total of 196 mCRC patients with mean age of 64 years old, 57.65% males and 82.14% married diagnosed from January 1, 2013, through December 31, 2016, who were classified as having a right or left-sided, and who underwent treatment with SC alone ($n = 60$) or SC and BT ($n = 67$) mCRC were included in this study (Fig. 1, Table 1). Table.1, and 2 include demographics and tumor characteristics stratified by treatment type (SC alone and SC + BT). In univariate analysis, significant associations were seen between right- vs left-sided mCRC for year of diagnosis (25%) vs (35.94%) p -value 0.01, tumor morphology for mucinous (40%) vs (2%) p -value .0005, tumor grade for moderately differentiated (50%) vs (71.88%) p -value 0.01, length of follow up 14 vs 21 p -value 0.04 (Table 2).

The overall median follow-up time in this study was 56 months (95% CI, 45–76 months) for all patients with mCRC who received SC with or without BT agent (Fig. 3). Regardless of the treatment type, the overall median survival for left-sided tumor was significantly higher than right-sided mCRC tumors (P -value 0.03) (Fig. 3). In the panel Kaplan-Meier Survival curve, the median survival was significantly poorer among patients with mCRC right-sided treated with SC + BT 16 months (95% CI, 6–39 months) compared to right-sided mCRC treated with SC alone 25 months (95% CI, 5–31 months) (Fig. 2). Whereas the median survival was poorer among patients with mCRC left-sided treated with SC alone 27 months (95% CI, 20–56 months) compared with mCRC left-sided tumor treated with SC + BT 31 months (95% CI, 25–50 months) (Fig. 4).

Table.1 Demographic characteristics of mCRC patients by type of treatment MNGHA 2013-2016¹

mCRC ³						
Characteristics	Systemic chemotherapy alone N=60		SC+ BT's agents N=76			
	Right-Sided	Left-Sided	<i>P</i> ²	Right-Sided	Left-Sided	<i>P</i>
	n(%)	n(%)		n(%)	n(%)	
Total	10 (16.67)	50 (83.33)		12 (15.79)	64 (84.21)	
Age (years)			0.34			0.38
Mean (median)	65 (65)	66 (67)		63 (63)	59 (59)	
Gender			0.24			0.23
Female	4 (40.00)	16 (32.00)		5 (41.67)	30 (46.88)	
Male	6 (60.00)	34 (68.00)		7 (58.33)	34 (53.13)	
Marital status			0.18			0.12
Married	7 (70.00)	42 (84.00)		12 (100.00)	53 (82.81)	
Unmarried	3 (30.00)	8 (16.00)		0(0)	11 (17.19)	
Family cancer history			0.16			0.13
Yes	0(0)	3 (6.00)		1 (8.33)	5 (7.81)	
No	3 (30.00)	14 (28.00)		2 (16.67)	9 (14.06)	
Unknown	7 (70.00)	33 (66.00)		9 (75.00)	50 (78.13)	
Recurrence status			0.21			0.84
Yes (liver, local, and regional)	2 (20.00)	2 (8.00)		0(0)	1(1.56)	

No	8 (80.00)	4 (92.00)	12 (100.00)	63 (98.44)
Age at diagnosis			0.4	0.4
Mean (SD)	58 (58)	60 (61)	56 (57)	52 (51)
Comorbidity			0.16	0.13
Yes	3 (30.00)	24 (48.00)	7 (58.33)	26 (40.63)
No	7 (70.00)	26 (52.00)	5 (41.67)	38 (59.38)
Year of diagnosis			0.01	0.01
2013	2 (20.00)	13 (26.00)	3 (25.00)	23 (35.94)
2014	4 (40.00)	13 (26.00)	4 (33.33)	22 (34.38)
2015	3 (30.00)	11 (22.00)	4 (33.33)	12 (18.75)
2016	1 (10.00)	13 (26.00)	1 (8.33)	7 (10.94)
¹ Data represent colorectal cancer patients registered in the MNG-HA hospitals system between 1 January 2009 and 31 December 2017. ² P-value from Chi-square test and Fisher exact test for less than five frequencies per cell ³ Metastatic Colorectal Cancer				

In the multivariate propensity score adjusted Cox regression models, when compared mCRC patients treated with SC alone, there was no significant difference in survival between right and left-sided mCRC (HR, 0.41; 95% CI, 0.08-2.1; *P*.29) (Table 3). Whereas mCRC patients treated with SC + BT was associated with decreased mortality only among patients with left-sided mCRC compared to right-sided mCRC (HR, 0.21; 95% CI, 0.05–0.92; *P*.03) (Table 3). In subgroup analysis, among those with resection of the primary tumor and CS, mCRC tumor location was not associated with mortality (HR, 0.34; 95% CI, 0.03–3.41; *P*.81) (Table 4). Whereas among those with no resection of the primary tumor and CS + TB, left-sided mCRC was significantly associated with decreased mortality compared to right-sided mCRC (HR, 0.15; 95% CI, 0.03–0.72; *P*.02) (Table 4).

Table 2
Clinical characteristics of mCRC patients by type of treatment MNGHA 2013–2016¹

mCRC ³						
	Chemotherapy alone		SC + bevacizumab			
Characteristics	Right-Sided	Left-sided	P ²	Right-Sided	Left-sided	P
	n(%)	n(%)		n(%)	n(%)	
Total	10 (16.67)	50 (83.33)		12 (15.79)	64 (84.21)	
Tumor Morphology			0.0005			0.001
Adenocarcinoma (AC), NOS	5 (50.00)	47 (94.00)		6 (50.00)	53 (82.81)	
Mucinous AC	4 (40.00)	1 (2.00)		5 (41.67)	5 (7.81)	
Signet ring cell carcinoma				0(0)	2 (3.13)	
Others	1 (10.00)	2 (4.00)		1 (8.33)	4 (6.25)	
Tumor grade			0.08			0.01
Well-differentiated	0(0)	1 (2.00)		0(0)	2 (3.13)	
Moderately differentiated	8 (80.00)	39 (78.00)		6 (50.00)	46 (71.88)	
Poorly differentiated/Anaplastic	2 (20.00)	5 (10.00)		2 (16.67)	9 (14.06)	
Unknown	0(0)	5 (10.00)		4 (33.33)	7 (10.94)	
Resection of the primary tumor			0.11			0.24
Yes	6 (60.00)	18 (36.00)		6 (50.00)	30 (46.88)	
No	4 (40.00)	32 (64.00)		6 (50.00)	34 (53.13)	
Number of completed chemotherapy cycles (Adjuvant, or neoadjuvant,)			0.84			0.13
Mean (median)	6 (6)	7 (5)		6 (5)	13 (8)	
Length of follow up in months			0.84			0.008

Mean (median)	14 (13)	18 (15)	14 (10)	21 (21)
Survival status	0.24		0.04	
Death	5 (50.00)	21 (42.00)	8 (66.67)	24 (37.5)
Alive	5 (50.00)	29 (58.00)	4 (33.33)	40 (62.5)
¹ Data represent colorectal cancer patients registered in the MNG-HA hospitals system between 1 January 2009 and 31 December 2017. ² Chi-square test, fisher exact test for less than five frequency per cell, t-test for continuous normally distributed variables, and the Mann-Whitney test for non- normally distributed variables ³ Metastatic Colorectal Cancer Abbreviation: Metastatic colorectal cancer (mCRC), systemic chemotherapy (SC), biologic therapies (BT)				

Table 3
Propensity score adjusted hazard ratio for right and left mCRC patients treated with SC and SC+BT in MNGHA (2013-2016).

	Chemotherapy alone		SC + bevacizumab	
	HR (95% CI) ²	P value ³	HR (95% CI) ²	P value ³
mCRC location				
Right Sided	Reference	—	Reference	—
Left sided	0.39 (0.14, 1.08)	0.29	0.25 (0.11, 0.58)	0.01
¹ Metastatic Colorectal Cancer ² Hazard ration and confidence interval ³ Multivariate Cox regression analysis Abbreviation: Metastatic colorectal cancer (mCRC), systemic chemotherapy (SC), biologic therapies (BT)				

Table 4. Interaction between right and left mCRC patients and treatment with SC and SC+BT stratified by resection of the primary tumor status

With resection of the primary tumor				
Chemotherapy alone			SC + bevacizumab	
	HR (95% CI) ²	P value ³	HR (95% CI)	P value ³
mCRC location				
Right Sided	Reference	—	Reference	—
Left sided	0.34 (0.03, 3.41)	0.81	0.2 (0.06, 7.23)	0.56
No resection of the primary tumor				
mCRC location				
Right Sided	Reference	—	Reference	—
Left sided	0.32 (0.05, 2.05)	0.54	0.15 (0.03, 0.72)	0.01
¹ Metastatic Colorectal Cancer ² Hazard ration and confidence interval ³ Multivariate Cox regression analysis Abbreviation: Metastatic colorectal cancer (mCRC), systemic chemotherapy (SC),biologic therapies (BT)				

Discussion

In this retrospective cohort study, we assessed the extent to which tumor location is associated with survival among mCRC patients treated with systemic chemotherapy (SC) alone and SC plus biologic therapies (bevacizumab or cetuximab). This study demonstrates a significant decrease in mortality for left-sided mCRC treated with SC plus BT compared to right-sided mCRC, which highlights the significant benefit of SC plus BT for mCRC left-sided patients. In contrast, SC alone had no significant benefit for mCRC patients. Our results are consistent with the meta-analysis finding reported that left-sided mCRC patients can benefit more from SC plus BT [26]. Similarly, Mayada's and Arnold's studies concluded that the use of BT benefited only the patients with left-sided mCRC patients with consideration of wild-type *KRAS* mutation [10, 12]. However, the mentioned studies used data that represents Asian, North American, and European populations. While the current study confirms that this difference exists in a sample of Middle Eastern populations where multiple mCRC associated factors such as molecular biology of the tumor cells [27] are different than other examined populations in the West. As Ibrahim's study indicated that among colorectal cancer patients in a Middle Eastern sample, the BRAF mutation and MMR

deficiency have different characteristics than in Western and East Asian populations [27, 28]. Thus, this study demonstrated that treatment outcomes of mCRC patients in a sample of the Middle Eastern population are consistent with other populations such as Asian, and Western populations.

To better understand the predictive value of tumor location for mCRC patients treated with SC and BT, we further examined whether the tumor location and potential benefit of SC alone and SC plus BT is different between those with and without resection of the primary tumor. In the subgroup analysis, among mCRC with no primary tumor resection, our study found that left-sided mCRC patients treated with SC plus BT was significantly associated with decreased mortality compared to right-sided mCRC. The benefit or predictive value of SC plus BT was observed among left-sided mCRC with no primary tumor resection. This study demonstrates that even those mCRC patients with unresectable metastases can have survival advantage benefit from left-sided SC plus BT treatment strategy. Our result is conflicted with the findings reported in a recent retrospective analysis [29]. In Tharin's study, the use of oxaliplatin, EGFR inhibitors, or bevacizumab did not benefit patients with unresectable metastases for both left and right sided mCRC patients [29]. However, Tharin's study evaluated different types of BT than our study which might explain the variation in the results. Overall, it is still controversial whether chemotherapy with or without primary tumor resection is effective for the mCRC patient [31, 32].

In the current study, no treatment benefit was observed among mCRC with the primary tumor resection. Most mCRC patients who did not perform primary tumor resection were having unresectable lesions or they are intolerant to surgery [29, 30]. Thus, mCRC patients with no primary tumor resection might start their systemic chemotherapy earlier than mCRC with decided primary tumor resection [30]. This early SC plus BT start might result in better survival outcomes than those with delayed SC plus BT treatment due to the morbidity and mortality associated with the tumor resection, which can negatively impact survival [30, 31]. In our study, better survival outcome was observed on left-sided mCRC patients as it's been reported that the use of BT benefited patients with left-sided mCRC only [10, 12]. Our finding is consistent with a recent randomized clinical trial study that found no survival benefit of adding upfront primary tumor resection to standard chemotherapy for unresectable mCRC patients [31]. In other words, the study found that SC plus BT alone showed acceptable toxicity profiles, the efficacy of treatment, and better survival compared to those with SC plus BT, and primary tumor resection [31, 32]. Nevertheless, further investigation is still required to develop effective approaches and determine if the factor of primary tumor resection along with tumor sidedness should be considered in using other systemic and target therapy.

There are several limitations to our study that should be noted. First, the retrospective nature of the study included an uncontrolled methodology with potential selection bias and a limited number of patients from a single cohort. Thus, our findings should be validated in a larger prospective study. Also, the small sample size limitation may have led to an underestimation of the predictive effect of tumor location on SC treatment. Second, KRAS and BRAF mutation status were not available in the MNG-HA Cancer Registry for the period of our study. Those data would have allowed additional evaluation of the predictive role of primary tumor location in specific subgroups.

Conclusion

This retrospective propensity score adjusted analysis of mCRC patients demonstrates that in a sample of the Eastern population, a significant decrease in mortality for left-sided mCRC treated with SC plus BT compared with right-sided mCRC was observed. Furthermore, the benefit or predictive value of SC plus BT was observed among left-sided mCRC with no primary tumor resection. This study demonstrates that even those mCRC patients with unresectable metastases can have a survival benefit from left-sided SC plus BT treatment strategy. Randomized controlled trials are needed to determine the optimal treatment for mCRC patients with consideration of primary tumor recession, tumor sidedness, and SC with or without BT.

Declarations

Statements and Declarations: No conflict of interests by all authors

Competing Interests and Funding: No conflict of interests by all authors

Compliance with Ethical Standards:

This study was performed in line with the principles of the Declaration of King Abdullah International Medical Research Center (KAIMRC) approved this study (RC20/383/R)

All methods were performed in accordance with the relevant guidelines and regulations of KAIMRC.

- **Informed consent**

Informed consent was waived due to retrospective nature of the study.

- **Availability of data and materials**

The data are available from the Oncology Department, but restrictions apply to the availability of these data due to sensitive identifier that have been used in this study, which were used under license for the current study, and so are not publicly available.

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- All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this

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Author contributions:

"Conceptualization, Majed, and Turki.; Methodology, Majed.; Software, Majed.; Validation, Majed, Mesnad. Turki and Noara; Formal Analysis, Majed, and Mesnad.; Investigation, Majed. Abeer; Resources, Majed.; Data Curation, Majed and Mohammed; Writing – Original Draft Preparation, Majed.; Writing – Review & Editing, Mesnad; Visualization, Majed, Mesnad and Noara.; Supervision, Majed, and Mesnad; Project Administration, Alanood. and Mohammed; Funding Acquisition, not applicable."

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Figures

Figure 1

Patient Selection Flowchart

Figure 2

Panel survival curves for mCRC tumor location and treatment

Figure 3

survival curve for mCRC tumor location and treatment

Figure 4

survival curve for left-sided mCRC and treatments