Correlation of Tumor Location to Clinical Outcomes in Colorectal Cancer: A Single-institution Retrospective Analysis

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Abstract. *Background/Aim:* Recent data highlighted that location of metastatic colorectal cancer (mCRC) may have a prognostic impact and also a predictive value of the outcomes of first-line therapy. *Materials and Methods:* The records of mCRC patients who underwent first-line therapy from 2011 to April 2018 at our Institute were retrospectively reviewed. Progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) according to the primary tumor location were investigated. *Results:* Overall, 130 patients were eligible. Two-year OS was 82.9% in left-sided colon cancers (LCC) and 67.5% in right-sided (RCC) ($p=0.32$). One-year mPFS was statistically longer in LCC (46.8% vs. 24.2%, $p=0.0005$). mPFS was longer in LCC treated with anti-VEGF vs. anti-EGFR ($p=0.06$). ORR was 51.1% in LCC, 25% in RCC ($p=0.008$). Overall, 11 complete responses all in LCC were observed ($p=0.03$). *Conclusion:* Tumor location has a prognostic impact and might influence the outcomes of mCRC patients.

In the era of personalized management of metastatic colorectal cancer, there is a general consensus that anatomical location may have a prognostic impact and also a predictive value on the outcomes of first-line therapy with monoclonal antibodies (mAbs) and cytotoxic agents in patients (pts) with metastatic colorectal cancer (mCRC). A significant amount of data from advances in the treatment of mCRC help us better understand the biology of this disease

and individualize regimen planning. mCRC is a heterogeneous disease that appears to be responsible for the third highest incidence rate, with about 1,849,518 (10.2%) new cases in 2018, in both sexes and all ages and for the second highest mortality rate, with about 880,792 (9.2%) deaths in 2018, in both sexes and all ages (1). About 50-60% of patients diagnosed with colorectal cancer develop metastases, most commonly at the liver. LCC patients tend to have hepatic and pulmonary metastases while RCC patients have peritoneal secondary metastases that determine the worst outcome (2, 3). Several studies have consistently reported that left-side is associated with better prognosis with an overall survival strictly depended on the stage of cancer and the presence of metastases (4, 5). The clinical management of this disease with first-line doublets plus tailored biological agents that takes into account mutational characterization, has further improved survival to more than 32 months (6, 7). The pathogenesis of colorectal cancer depends on the anatomical position of the tumor and differs between the right and left sides of the colon. Tumors arising from different sides of the colon are clinically and molecularly distinct, exhibit different features, such as epidemiological incidence, physiological characteristics, molecular alterations, and even survival outcome and are more and more considered as separate tumor types (8, 9). Bufill has first proposed in 1990, that right and left colon tumors may arise from different biological pathways and represent distinct genetic entities (10). In particular, carcinomas of the left colon (those originating from splenic flexure, descending colon, sigmoid colon, rectum or one-third of the transverse colon) derive from the embryonic hindgut; on the contrary, carcinomas of the right colon (those originating from the appendix, the blind, the ascending colon, hepatic flexion or two-thirds of the transverse colon) derive from the embryonic midgut. Clinically, this

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heterogeneity is very useful in therapeutic decision-making and in helping to predict and prognosticate the results. The molecular factors that predict the effectiveness of CRC treatment are largely unknown; the mutational state of *RAS* and perhaps *BRAF* are currently the only references in the decision-making process of systemic therapy. The principal differences between right- and left-sided primary colon cancers are listed in Figure 1 (11-15). The objective of this current investigation was principally to evaluate the prognostic and predictive effect of primary tumor location on clinical outcomes of first-line therapy in previously untreated patients with mCRC, using retrospectively collected data from 2011 to April 2018 at our institute.

Patients and Methods

For this analysis, 153 patients diagnosed with stage IV colorectal cancer who received first-line chemotherapy with palliative intent were identified and collected from an electronic database pertaining to patient and disease characteristics, treatment and outcomes from January 2011 to April 2018 at our Institute. The enrolled patients met the following inclusion criteria: 1) histologically confirmed adenocarcinoma; 2) stage IV colorectal cancer at diagnosis or in the postoperative follow-up; 3) previous administration of adjuvant or neoadjuvant therapies for colorectal cancer stages II-III; 4) first-line therapy with monoclonal antibodies (mAbs) and cytotoxic agents; 5) synchronous or metachronous metastases; 6) known *RAS* mutational status. Patients with multiple primary tumors, those with primary tumors in both left- and right-site and those treated with curative intent were excluded from the analysis. For the overall study population, primary tumors originating into the appendix, cecum, ascending colon, hepatic flexure and transverse colon were classified as right-sided. Primary tumors originating in the splenic flexure, descending colon, sigmoid colon and rectum were classified as left-sided. The endpoints investigated were OS, PFS, ORR and DFS post-adjuvant treatment. OS (overall survival) was defined as the time from first-line treatment initiation until death from any cause. PFS (progression-free survival) was defined as the time from commencement of first-line therapy until the date of objective disease progression or death from any cause. ORR (objective response rate) including complete and partial responses, was assessed according to RECIST criteria. DFS (disease-free survival or recurrence-free survival) following curative-intent primary therapy, has been defined as the time spent free of signs and symptoms of cancer, from the ending of adjuvant treatment until the first of either recurrence or relapse, second cancer, or death or last follow-up; we divided this interval of time into 3 groups: <6 months, 6-12 months, >12 months after the completion of adjuvant chemotherapy. Informed consent was waived because of the nature of retrospective study, and confidentiality was maintained for patient data. Patients were followed until 30th of April 2018. The study was approved by the Lazio 1 Ethics Committee (approval no. 937/CE Lazio 1).

Statistical analysis. Descriptive statistics were used to summarize pertinent study information. PFS and OS were calculated by the Kaplan-Meier product limit method from the date of therapy until progression, death due to cancer and/or death from any cause. The

Table I. Baseline patient characteristics and treatment.

	Primary tumor location			
	RCC		LCC	
	N	% total	N	% total
Total	37	28.4	93	71.5
Median age (years)	66.5		62.3	
Gender				
Female	16	12.3	32	24.6
Male	22	16.9	60	46.1
RAS status				
Wild type	15	11.5	49	37.6
Mutant type	21	16.1	40	30.7
Not tested	1	0.7	4	3.07
Right side				
Appendix	1	0.7		
Cecum	10	7.6		
Ascending colon	7	5.3		
Hepatic flexure colon	3	2.3		
Transverse colon	8	6.1		
Right colon NOS	9	6.9		
Left side				
Splenic flexure colon			1	0.7
Descending colon			9	6.9
Sigmoid colon			22	16.9
Rectum-sigmoid junction			16	12.3
Rectum			29	22.3
Left colon NOS			15	11.5
Prior adjuvant therapy	13	10.0	45	34.6
Metastatic patients at diagnosis	24	18.4	48	36.9
Metastatic disease sites				
Liver only	12	9.2	19	14.6
Liver + other	15	11.5	30	23.0
Other	11	8.4	43	33.0
Chemotherapy regimen				
Fluoropyrimidine alone	6	4.6	6	4.6
Doublet chemotherapy	31	23.8	82	63.0
Triplet chemotherapy	1	0.7	4	3.0
Monoclonal Abs				
Cetuximab use	9	6.9	30	23.0
Panitumumab use	1	0.7	4	3.0
Bevacizumab use	21	16.1	46	35.3

N: Number; LCC: left-sided colon carcinoma; RCC: right-sided colon carcinoma; NOS: not otherwise specified; DFS: disease-free survival; Monoclonal Abs: monoclonal antibodies.

log-rank test was used to assess differences between subgroups. Significance was defined at the p less than 0.05 level. The SPSS (version 21.0) was used for statistical analyses.

Results

The baseline patients' characteristics and treatment data regarding all eligible patients are summarized in Table I. Of the 130 patients considered eligible, 82 (63.0%) were males and 48 (36.9%) were female, with a median age of 63 years

Figure 1. Differences between right- and left-sided primary colon cancers.

(range=40-82 years). Regarding tumor location, 37 (28.4%) patients had RCC, including 1 (0.7%) appendix cancer, 10 (7.6%) cecal cancers, 7 (5.3%) ascending colon cancers, 3 (2.3%) hepatic flexure colon cancers, 8 (6.1%) transverse colon cancers and 9 (6.9%) NOS (not otherwise specified) right colon cancers, whereas 93 (71.5%) patients had LCC, including 1 (0.7%) splenic flexure colon cancer, 9 (6.9%) descending colon cancers, 22 (16.9%) sigmoid colon cancers, 16 (12.3%) rectum-sigmoid junction cancers, 29 (22.3%) rectum cancers and 15 (11.5%) NOS left colon cancers. As far as the mutational analysis of the RAS gene is concerned, 64 patients were wild-type (49.2%) (11.5% right-sided and 37.6% left-sided colon cancers) and 61 mutant (46.9%) (16.1% right-sided and 30.7% left-sided colon cancer) and 5 not tested (3.8%). Metastatic disease sites included: liver only 23.8%, liver + other 34.6% and the others 41.5%. A total of 102 patients (78.4%) had visceral metastases *vs.* 28 patients (21.5%) without visceral metastases; 67 patients (51.5%) had one metastatic site and 63 (48.4%) had more than one metastatic site. The median duration of follow-up was 17.9 months (range=1-101 months). Nine patients (6.9%) underwent neoadjuvant treatment and 47 (36.1%) a post-operative adjuvant therapy. At the time of diagnosis, 72 patients (55.3%) had already metastases, 10 patients (7.6%) developed metastases within 6 months, 14 patients (10.7%) between 6 and 12 months and 34 patients (26.1%) after 12 months from surgery. A total of

33.6% of patients were treated with anti-EGFR antibodies *vs.* 51.4% of patients treated with anti-VEGF antibody. In terms of responses to first-line treatment, disease progression was observed in 30 cases (23.1%), partial responses in 43 (33.1%) and stable diseases in 40 (30.8%). The 2-yr OS for all pts was 80.7% (Figure 2A), 82.9% for LCC and 67.5% for RCC regardless of the treatment performed ($p=0.32$) (Figure 2B). OS of LCC treated with anti-VEGF (90.3%) was longer than LCC treated with anti-EGFR (68.1%) ($p=0.18$) (Figure 2C) while in RCC treated was 74.2% with anti-VEGF and 64.3% with anti-EGFR ($p=0.25$) (Figure 2D). The 1-yr mPFS for all patients was 40% (11 months, 95%CI=9-12) (Figure 3A); it was longer in pts treated with anti-VEGF *vs.* anti-EGFR in LCC: 14 (95%CI=10-17) *vs.* 8 months (95%CI=5-11) ($p=0.06$) (Figure 3B) and longer than just 2 months in RCC treated with anti-EGFR: 9 (95%CI=1-17) *vs.* 7 months (95%CI=3-12) ($p=0.92$) (Figure 3C). However, the 1-yr mPFS was statistically longer in LCC *vs.* RCC (46.8% *vs.* 24.2%, $p=0.0005$) (Figure 3D), regardless of the therapy performed. The ORR (complete + partial responses) was 51.1% for left-sided and 25% in right-sided tumors ($p=0.008$). We found a trend towards a higher ORR in RCC treated with anti-EGFR based therapy compared to anti-VEGF based therapy (50% *vs.* 17.9%, $p=0.09$). The ORR was about the same in LCC treated with anti-EGFR *vs.* anti-VEGF based therapy (48.3% *vs.* 52.5%, $p=0.71$). A total of 11 complete responses (CRs) (12.5%) were observed, all

Figure 2. Overall survival (OS). (A) OS in all patients. (B) OS stratified by primary tumor site, regardless of the therapy performed. (C) OS stratified by primary tumor site (LCC) and therapy performed. (D) OS stratified by primary tumor site (RCC) and therapy performed.

in the left-sided ($p=0.03$): 8 (13.6%) with anti-VEGF and 3 (10.3%) with anti-EGFR. The <6 months and >12 months DFS post-adjuvant therapy were found better in RCC than LCC (respectively 33.3% vs. 13.3% and 66.7% vs. 57.8%) whereas 6-12 months DFS was observed only in 28.9% of LCC, $p=0.056$). The efficacy outcomes are summarized in Table II.

Discussion

In our monocentric retrospective study, the possible prognostic and predictive impact of primary tumor location in patients with mCRC treated with first-line chemotherapy alone or in combination with anti-EGFR or anti-VEGF agents were assessed. So, we decided to examine, in our small clinical reality, the impact of the primary tumor location on prognosis and prediction of outcomes as well as its significance in guiding the choice of the most appropriate therapy for patients with mCRC in order to offer them the most beneficial, current, and novel therapies. To develop effective therapeutic regimens and improve therapeutic options, we also evaluated left and right-sided tumors as separate entities taking into account the

differences between these tumors. First of all, regarding the relevance of the predictive value, the findings of the present analysis concur with previous reports and showed that treatment outcomes were better in patients with left-sided tumors than in those with right-sided tumors, indicating that the primary tumor location has a strong prognostic effect on survival irrespective of the chemotherapy and targeted agents used in first-line treatment. Our observations suggest that there is still a clinical need of novel treatment strategies for patients with right-sided mCRC. The literature data clearly indicate that RCC is associated with an inferior prognosis compared to LCC and that the prognostic value is evident both for first-line chemotherapy alone and chemotherapy plus targeted agents. Patients with RCC do not respond well to conventional chemotherapy, but show more promising results with immunotherapy because these cancers have high antigenic load. Longer survival is exhibited in LCC than RCC after palliative chemotherapies regardless of the treatment performed. Patients with LCC benefit more from adjuvant chemotherapy, such as 5-fluorouracil (5-FU) regimens, and from targeted therapies such as anti-EGFR therapy, and have a better prognosis. Our work confirms and emphasizes

Figure 3. Progression-free survival (PFS). (A) PFS in all patients. (B) PFS stratified by primary tumor site (LCC) and therapy performed. (C) PFS stratified by primary tumor site (RCC) and therapy performed. (D) PFS stratified by primary tumor site, regardless of the therapy performed.

Table II. Efficacy outcomes.

	OS		PFS				ORR		DFS post-adjuvant therapy			
	2-yr (%)	p-Value	mPFS (months)	95%CI	1-yr (%)	p-Value	PR + CR (%)	p-Value	<6 months	6-12 months	>12 months	p-Value
All patients	80.7		11	9-12	40		43.5	0.008	17.5	22.8	59.6	0.056
RCC	67.5	0.32	7	2-13	24.2	0.0005	25.0		33.3	-	66.7	
LCC	82.9		11	9-13	46.8		51.1		13.3	28.9	57.8	
RCC												
Anti-EGFR Abs	64.3	0.25	9	1-17	15.6	0.92	17.9	0.09				
Anti-VEGF Ab	74.2		7	3-12	26.4		50.0					
LCC												
Anti-EGFR Abs	68.1	0.18	8	5-11	29.7	0.06	52.5	0.71				
Anti-VEGF Ab	90.3		14	10-17	55.2		48.3					

RCC: Right-sided colon cancer; LCC: left-sided colon cancer; CI: confidence interval; OS: overall survival; PFS: progression-free survival; RR: response rates; Anti-EGFR Abs: anti-EGFR antibodies; Anti-VEGF Abs: anti-VEGF antibody; DFS: disease-free survival; PD: progressive disease; PR: partial response; CR: complete response.

previous reports indicating an increasing importance of primary tumor location in daily clinical decision-making processes. We also confirmed that the provision of anti-VEGF alongside first-line chemotherapy is associated with improved

PFS outcomes in mCRC, as demonstrated in multiple clinical trials. Importantly for routine clinical practice, our small analysis with 130 patients with mCRC who received first line palliative chemotherapy with or without concurrent

monoclonal antibodies, indicates an anti-VEGF efficacy regardless of primary tumor location. Based on current knowledge, reviewing the literature data, targeted therapies for mCRC have been developed and used in combination with conventional chemotherapy leading to improved overall survival. Some agents like bevacizumab, aflibercept, ramucirumab and regorafenib, specifically target the angiogenic pathways, others like cetuximab and panitumumab, target the EGFR pathway (16, 17). In the CALGB/SWOG 80405 study, patients who received cetuximab reached a median overall survival of 36 months for LCC and 16.7 months for RCC ($p < 0.0001$) (18). In addition, in the Canadian NCIC CO.17 study, LCC patients benefited more from cetuximab therapy than RCC patients (19). Similar results were obtained in the CRYSTAL and FIRE studies (20). In the PRIME study, panitumumab associated to FOLFOX regimen increased overall survival among LCC patients, but it was not effective in RCC patients (respectively, 32.5 months *versus* 23.6 months in LCC *vs.* 22.5 months *versus* 21.5 months in RCC) (21). Another commonly used targeted agent is bevacizumab that acts on the vascular endothelial growth factor (VEGFR) receptor. After treatment with bevacizumab, median overall survival was 31.4 months for LCC patients and 24.2 months for RCC patients. In the CALGB/SWOG 80405 study, patients with RCC benefited more from treatment with bevacizumab than from treatment with cetuximab (18). The association of bevacizumab and chemotherapy reduced mortality in both LCC and RCC patients, while the combination of cetuximab and chemotherapy was effective only in LCC patients (22). In addition, RCC patients with wild-type KRAS seem to benefit more from initial anti-VEGF-based therapy and those with LCC benefit more from anti-EGFR treatment in association with chemotherapy (23, 24). Do not underestimate that the tumor location may also be an important variable that can optimize therapy strategies in the adjuvant setting (25). The primary tumor location is so important that influences the current NCCN and ESMO guidelines. Regarding first-line treatment of mCRC, NCCN guidelines recommend both EGFR and VEGF antibodies in LCC with wild-type RAS, whereas ESMO guidelines recommend EGFR antibodies in combination with chemotherapy in LCC with wild-type RAS. Both guidelines for RCC with mutant RAS, recommend chemotherapeutic combinations with VEGF antibodies (26, 27). Actually, available data do not support tumor location as a predictor of first-line anti-VEGF treatment efficacy. The tumor site is not an independent prognostic factor for OS and DFS rate after surgical treatment in colon carcinoma, whereas advanced T stage, node positivity, and poor histological grade are independent prognostic factors in oncologic outcomes. In summary, RCC tends to have more node positivity, poor histological grade and advanced T stage than the LCC. Thus, the prognosis of RCC is expected to be worse than LCC.

Summarizing and taking inspiration from our little experience, we conclude that colorectal cancer is not one disease but many. We also confirm that LCC seems to be a predictive factor for survival benefit from anti-EGFR therapy in patients with wild-type RAS tumors. On the other hand, RCC presents a poor response to the standard chemotherapy alone or in association with targeted agents. Anti-VEGF-based therapy is associated with a more favorable outcome in terms of PFS and OS. As in the literature, it was very interesting to find a trend towards a higher ORR in RCC treated with anti-EGFR therapy compared to anti-VEGF therapy; the data are, however, to be taken with caution due to the limited size of our sample and the retrospective nature of this study. Therefore, further investigations are surely needed.

Conclusion

Our observations underscore and confirm some of the previous studies on the sidedness of colorectal cancer patients; mCRC is a heterogeneous disease and primary tumor location has prognostic and predictive significance. Based on the results of our analysis, limited by heterogeneity of treatments and by the small sample size, we suggest a location-based therapy, with a benefit from the addition of anti-EGFR for wild-type RAS left-sided tumors; complete responses and significantly better mPFS reached only in left-sided tumors regardless of the therapy performed. Anti-VEGF therapy prolongs OS in patients with left-sided tumors and more aggressive treatments are needed for patients with right-sided tumors especially in advanced disease. Thus, we suppose that the primary tumor site of colon cancer should be considered in the clinical practice decision-making including treatment intensity in metastatic and locoregional settings. It should also represent an important stratification factor for future studies in the adjuvant therapy setting but should not impact on clinical decision making when considering the use of anti-VEGF. Anyway, larger studies and proper specialized treatment related to the location of colon cancer are needed to define if the type of chemotherapy backbone adopted and tumor location could be associated in order to improve treatment efficacy.

Conflicts of Interest

The Authors declare that they have no competing interests regarding this study.

Authors' Contributions

Conceptualization: CS MGC. Data Curation: CS. Formal Analysis: IS CS. Investigation: CS MGC SG PMA RMP TVR VVG MER FN EMR. Resources: CS MGC. Validation: CS. Visualization: CS. Writing – Original Draft Preparation: CS. Writing – Review & Editing: EMR CS. All Authors have read and approved the final manuscript.

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