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ORIGINAL ARTICLE

Systemic treatment and primary tumor location in patients with metastatic colorectal cancer

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Summary

Purpose: *Tumor location (right-sided vs. left-sided) is known to exert a significant influence on the prognosis of primary colorectal cancer (CRC). Given the genetic continuity between primary and metastatic lesions, we aimed to summarize the existing literature on the prognostic implications of primary tumor site as well as to examine the response to chemotherapy by primary tumor location in patients with metastatic CRC (mCRC).*

Methods: *A structured review of the literature was performed between 6/1/2016-7/1/2016 using the Pubmed database. Original research articles published between 1/1/2000-07/01/2016 were considered eligible. The primary endpoints were overall survival (OS)/ progression free survival (PFS) and response to systemic treatment in patients with mCRC.*

Results: *Eleven studies were included. Tumor site was a strong independent predictor of worse OS/PFS in 9 studies, with right-sided tumors having worse prognosis in all cases. Furthermore, 6 studies demonstrated an inferior response to systemic treatment or worse prognosis following the administration of specific regimens among patients with right-sided cancers. As such, there is significant evidence that right-sided lesions are associated with poor outcomes and resistance to systemic treatment.*

Conclusion: *Consequently, primary tumor location should be a consideration, when the administration of systemic therapy is contemplated in mCRC.*

Key words: *bevacizumab, cetuximab, chemotherapy, colorectal cancer, metastasis*

Introduction

Colorectal cancer (CRC) is currently the third most common malignancy worldwide [1]. Furthermore, its incidence is expected to increase according to recent population-based studies [2,3]. Unfortunately, up to one-fifth of CRC patients may initially present with metastatic disease while a similar percentage of patients eventually develops metachronous metastases [4]. In turn, systemic chemotherapy with or without biological agents is indispensable in the management of metastatic colorectal cancer (mCRC) and plays a leading role in improving survival [5,6]. Nonetheless, CRC is known to be a heterogeneous disease with considerable variation in molecular background and biologic behavior [7,8]. As such, the identification of prognostic markers that will 'bridge the gap' between underlying disease biology and observed treatment response is of paramount importance [8-10].

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One such factor, with potential prognostic significance, is primary CRC tumor location. Specifically, the right and left colonic segments develop from the midgut and hindgut respectively and are known to be physiologically distinct [11]. In turn, there is significant evidence that right and left-sided colon tumors differ in terms of genetic background and immunopathologic characteristics [12,13]. To this end, it has been previously reported that primary tumor location is also associated with prognosis, as right-sided tumors have been shown to result in decreased OS in patients with primary CRC, as well as in the setting of metastatic disease [14-16]. The reasons for this prognostic disparity are largely unknown; however, right and left-sided tumors are known to differ in the frequency of mutations, such as KRAS and BRAF that are recognized predictors of response to biologic agents, such as cetuximab [13,17-23]. As such, it is possible that differential response to treatment with chemotherapy and/or biologic agents by primary tumor location may underlie at least some of the prognostic variability observed in patients with right and left-sided tumors [12].

Unlike molecular parameters such as KRAS and BRAF mutational status, primary tumor location is an easily identifiable clinical factor that can be immediately taken into account during clinical decision making without the need for expensive laboratory tests. As such, a deeper understanding of its association with prognosis and response to treatment would be of immense value in everyday clinical practice. Consequently, the aim of this study was to summarize the existing literature regarding long-term prognosis and response to chemotherapy by primary tumor location, among patients receiving systemic therapy with or without biological agents in the setting of mCRC.

Methods

Literature review and study selection

From June to July 2016, a structured review of the literature was performed using the PubMed database to identify original research articles assessing the impact of primary tumor location on OS, PFS and objective response rate (ORR) or their equivalents, among patients with mCRC that were treated with systemic chemotherapy and/or biologic agents. Articles were identified using the following search strings:1) (Advanced OR Metastatic) AND ((Colorectal AND Cancer) OR CRC) AND ((Primary AND Tumor AND Location) OR hindgut OR midgut OR left OR right) AND Prognos* AND (Chemotherapy OR Cetuximab OR Bevacizumab); 2) (Primary AND Tumor AND Location) OR (midgut OR hindgut) OR (Left-sided OR right-sided) AND Colorectal AND CANCER AND (Chemotherapy OR Cetuximab OR Bevacizumab OR FOLFOX OR FOLFIRI OR OR CAPEOX OR 5-fluorouracil); 3) (Colorectal AND Cancer) OR (CRC)) AND Chemotherapy OR Cetuximab OR Bevacizumab OR FOLFOX OR FOLFIRI OR CAPEOX OR 5-fluouracil) AND Predic*. Furthermore, the references of all selected articles were reviewed to identify any additional, potentially eligible studies. Only studies published in English were considered. The results were cross-checked to exclude overlapping series or double entries. Conference abstracts that did not proceed to publication in peer-reviewed journals, studies with insufficient details with respect to patient selection and treatment indications and studies limited to cell lines or animal models were also excluded from this review.

All relevant studies in humans with publication dates from 2000 to 2016 were considered for analysis. Ultimately, 11 eligible publications were identified (Table 1). Information regarding the number of included patients, the treatment setting, the time period of treatment and the chemotherapeutic regimens and/or biologic agents administered was collected and reported for each original research article. Due to the considerable heterogeneity in definitions with respect to what constitutes a right vs a left-sided primary tumor, the individual definition employed by each study was also noted. When available, data were extracted for ORR, as well as for indicators of long-term prognosis such as median OS and PFS for each primary tumor location. Secondary outcomes of the included studies were also discussed depending on their clinical relevance.

Results

One of the first studies to associate primary tumor location with survival and response to chemotherapy among patients with mCRC, was published by Massacesi et al. in 2002. The study cohort consisted of 321 patients from multiple institutions with either metastatic disease (n=287, 89.4%) or locally advanced disease (n=34, 10.6%). Patients underwent treatment with 5-FU (5-fluorouracil) based regimens in the period between 1988 and 1999. No biologic agents were administered. Right-sided tumors were defined as tumors originating from the cecum to the transverse colon; on the other hand, tumors of the descending colon, sigmoid colon and rectum were defined as left-sided. The authors then proceeded to investigate factors associated with short survival (defined as survival ≤ 6 months) as well as disease progression with the aid of multivariate analysis. Interestingly, primary right-sided tumor location was shown to be a strong independent predictor of short survival in multivariate analysis [hazard ratio (HR) 3.04, 95% confidence interval (CI) 1.71-5.41, p=0.020)]. Similarly, right-sided tumors were shown to be associated with disease progression in univariate analysis (p=0.016). This association was not statistically significant in multivariate

Table 1. Included studies and prognosis by primary tumor location

Authors	*Inclusion period*	*Patient number*	*Chemotherapy regimen*	*Biologic agent*	*Median PFS** (RS vs. LS)*	*p (PFS)*	*Median OS** (RS vs. LS)*	*p (OS)*
Massacesi et al.	1988-1999	321	5-FU +/- multiple agents	0	n/r	n/r	n/r	n/r
Negri et al.	1992-1998	135	5-FU +/- mitomycin C/ interferon	0	n/r	n/r	n/r	n/r
Boisen et al.*	2006-2011	667	CAPEOX	Bevacizumab	7.2 *vs.* 9.3	**<0.001**	13.0 *vs.* 23.5	**<0.001**
Modest et al.	2000-2004	423	FuFIRI/mIROX	0	6.0 *vs.* 8.2	**0.024**	13.6 *vs.* 21.8	**0.001**
Von Einem et al.	2004-2006	146	CAPIRI/CAPOX	Cetuximab	5.2 *vs.* 7.8	**0.020**	14.8 *vs.* 26.3	**0.016**
Loupakis et al.*	2009-2014	200	FOLFIRI	Bevacizumab	9.9 *vs.* 12.1	**0.010**	24.8 *vs.* 42.0	**0.010**
Brule et al.	2003-2005	399	0	Cetuximab	n/r	0.670	n/r	0.780
Wang et al.*,***	2006-2013	206	mFOLFOX-6/ XELOX/modified FOLFIRI	Cetuximab	1) 5.6 *vs.* 9.1 2) 3.3 *vs.* 4.9	1) 0.244 2) 0.723	1) 25.1 *vs.* 28.9 2) 13.4 *vs.* 17.1	1) 0.512 2) 0.120
Lu et al.	2007-2013	121	FOLFOX/FOLFIRI	Cetuximab Bevacizumab	5.8 *vs.* 11.8	**<0.001**	15.7 *vs.* 27.7	**0.008**
Wong et al.	2009-2014	926	Fluoropyrimidine-based/Doublet chemotherapy	Bevacizumab	7.6 *vs.* 10.2	**0.031**	18.2 *vs.* 23.6	**<0.001**
Chen et al.	2004-2011	969	Multiple regimens	Cetuximab	n/r	n/r	8.1 *vs.* 12.6	<0.001

n/r: not reported, RS: Right-sided primary colorectal tumor, LS: Left-sided primary colorectal tumor, PFS: Progression-free survival, OS: Overall survival, * Data from the primary cohort. Data from the validation/control cohorts are discussed in the text, ** time in months, *** 1) and 2) denote survival and p figures for the group that received first and second line chemotherapy plus cetuximab treatment, respectively. Bold numbers denote statistical significance

analysis; nonetheless, a trend towards more frequent disease progression among patients with right-sided tumors was detected (p=0.076) [24].

The prognostic implications of primary tumor location for patients receiving chemotherapy for mCRC were further demonstrated by Negri et al. The original purpose of the study was to compare response to chemotherapy among patients with mucinous and non-mucinous CRC; as such, the study population consisted of 45 patients with mucinous CRC and 90 appropriately selected controls for a total study population of 135 patients. Of note, a small minority of patients had locally advanced, rather than metastatic disease (n=14;10.4%). All patients were treated at a single-institution with either 5-FU alone (31.0%) or 5-FU with either mitomcyin-C or interferon-a (69.0%). The treatment period was from 1992 to 1998 and the entire patient population was derived from the databases of 3 previously conducted randomized clinical trials [25-27]. Right-sided tumors were defined as tumors originating in the cecum, ascending colon or hepatic flexure; tumors of the descending colon and sigmoid colon were defined as left-sided. Tumors of the transverse colon, rectosigmoid junction and rectum were treated as left-sided for the purpose of the analysis. The primary outcomes of the study were OS and response to chemotherapy. Although no association between primary tumor location and response to chemotherapy was reported by the authors, OS was strongly associated with tumor site. Specifically, patients with right-sided tumors had an almost 1.6 fold increased risk of death in multivariate analysis (HR 1.59, 95% CI 1.07-2.37, p=0.022). This finding was independent of other prognostic factors such as mucinous histology [28].

In a later study, Boisen et al. directly compared OS and PFS following chemotherapy administration after stratifying by primary tumor location. The study cohort consisted of 667 patients with mCRC and was derived from 10 different institutions during the time period between 2006 and 2011. Patients were treated with CAPEOX (capecitabine and oxaliplatin) and also received bevacizumab. Right-sided tumors were defined as tumors originating in the cecum, ascending colon, transverse colon or descending colon, while tumors of the sigmoid colon and rectum were grouped together as left-sided. After analyzing long-term outcomes by primary tumor location, the authors reported a significantly decreased risk of progression (HR 0.69, 95% CI 0.57-0.84, p<0.001) and death (HR 0.51, 95% CI 0.42-0.61, p <0.001) among patients with left-sided tumors. Interestingly, no association between primary tumor

location and prognosis was noted among a similarly selected control group of 213 patients treated with CAPEOX, but without bevacizumab [29].

Similarly, a study by Modest et al. investigated the impact of primary tumor location on OS, PFS and ORR following chemotherapy administration for mCRC. A total of 423 patients were included in the study. The patient population consisted of participants in the FIRE1 trial, a randomized multi-institutional trial that took place between 2000-2004 [30]. Patients were initially treated with either FuFIRI (irinotecan, infusional 5-FU and leucovorin) or mIROX (irinotecan and oxaliplatin), but treatment cross-over was common (69.0% of the cohort). Of note, the participants did not receive biological agents. Right-sided tumors were defined as tumors originating from the cecum to the distal part of the transverse colon; on the other hand, tumors of the splenic flexure, descending colon, sigmoid colon and rectum were defined as left-sided. The authors assessed objective response to chemotherapy by primary tumor location, but were unable to demonstrate a statistically significant difference in the overall cohort (37.0% in right-sided tumors vs 43.0% in left-sided tumors respectively, p=0.340). Interestingly, however, this finding was not consistent among different chemotherapy regimens. Specifically, patients with right-sided tumors had significantly worse response to FuFIRI when compared to patients with left-sided tumors (33.0% in right-sided tumors vs 46.0% in left-sided tumors, p=0.030). This was not the case with mIROX (p=0.940). As for long-term outcomes, patients with left-sided tumors fared better in terms of both PFS (HR 0.75 95% CI 0.59-0.87, p=0.024) and OS (HR 0.65, 95% CI 0.50-0.84, p=0.001). Interestingly, after performing separate subanalyses by chemotherapy regimen, the authors reported that left-sided primary tumor location was associated with PFS and OS only among patients treated with first-line FuFIRI (HR 0.66, 95% CI 0.46-0.94, p=0.020; HR 0.55, 95% CI 0.39-0.79, p=0.001 for PFS and OS respectively) [31].

Subsequently, a study by von Einem et al. investigated the effect of tumor site on prognosis and response to chemotherapy among 146 patients with mCRC, enrolled in the AIO KRK-0104 trial [32]. The trial was conducted between 2004 and 2006 and patients were treated with either CAPOX (capecitabine and oxaliplatin) plus cetuximab or CAPIRI (capecitabine and irinotecan) plus cetuximab. Tumors located from the cecum to the distal part of the transverse colon were defined as right-sided, whereas tumors of the splenic flexure, descending colon, sigmoid and rectum were defined as left-sided. The authors demonstrated that, in the overall cohort, left-sided tumors were associated with both improved OS (HR 0.63, 95% CI 0.43-0.92, p=0.016) and PFS (HR 0.67, 95% CI 0.47-0.95, p=0.020). Interestingly, however, after further stratifying patients by KRAS mutational status, it was demonstrated that primary tumor location had no bearing on outcome among patients with mutant KRAS tumors. (p=0.460 and p=0.960 for OS and PFS, respectively). On the contrary, among patients with wild-type KRAS tumors left-sided tumor location was associated with both improved OS (HR 0.42, 95% CI 0.25-0.67, p<0.001) and PFS (HR 0.54, 95% CI 0.34-0.85, p=0.007). With respect to ORR, no statistically significant difference by primary tumor location was detected in the overall cohort (p=0.700). Nonetheless, a trend towards inferior ORR for right-sided tumors was detected in the wild-type KRAS subgroup, although it did not reach statistical significance (p=0.120) [33].

More recently, a study by Loupakis et al. reexamined the prognostic implications of primary tumor location in three separate study cohorts derived from an equal number of clinical trials. Specifically, the primary study cohort consisted of 200 patients with mCRC from the PROVETTA trial that were treated with FOLFIRI (leucovorin, 5-FU and irinotecan) and bevacizumab [34]. Two additional cohorts derived from the AVF2107g (n=559) and NO16966 (n=1268) trials were used for validation [35-37]. The latter two cohorts were also comprised of patients with mCRC, but received substantially different treatment regimens, namely IFL (irinotecan, 5-FU and leucovorin) with or without bevacizumab (AVF2107g) and XELOX (capecitabine and oxaliplatin) or FOLFOX4 (oxaliplatin, 5-FU and leucovorin) with or without bevacizumab (NO16966). Tumors located from the cecum to the distal part of the transverse colon were defined as right-sided, whereas tumors of the descending colon, sigmoid and rectum were defined as left-sided. OS, PFS and ORR stratified by primary tumor location were then examined. Specifically, in the PROVETTA cohort, left-sided tumors were independently associated with less frequent progression (HR 0.55, 95% CI: 0.37-0.83, p=0.010) and a lower risk of death (HR 0.47, 95% CI 0.28-0.80, p=0.010) in multivariate analysis. On the contrary, no association was detected between primary tumor location and ORR (p=0.590). In the two validation cohorts, left-sided tumor location was again shown to be an independent predictor of OS (HR 0.52, 95% CI 0.40-0.67, p<0.001; HR 0.72, 95% CI 0.63-0.83, p<0.001 for the AVF2016g and NO16966 cohorts, respectively). As for PFS, left-sided tumors had lower progression risk in

the AVF2017g cohort (HR 0.69, 95% CI 0.56-0.86, p=0.001). Interestingly, this was not the case in the NO16966 cohort (p=0.100), but a similar trend was, in fact, observed. In terms of ORR, both validation cohorts demonstrated a statistically significant association of left-sided tumor location with increased chemotherapy response (HR 2.48, 95% CI 1.66-3.69, p<0.001; HR 1.49, 95% CI 1.15-1.92, p=0.010 for the AVF2016g and NO16966 cohorts, respectively). Interestingly, in a separate analysis, the authors reported that the efficacy of bevacizumab was independent of tumor location [34].

A later study by Brule et al. assessed the impact of tumor site on prognosis among patients with chemotherapy refractory mCRC, randomized to cetuximab vs Best Supportive Care (BSC) as part of the NCIC CO.17 trial (2003-2005) [38]. From the original cohort of 572 patients, 161 patients with rectal tumors and 12 patients with indeterminate primary tumor site were excluded, for a final study population of 399 patients. Tumors of the cecum, ascending colon, hepatic flexure and transverse colon were defined as right-sided, while tumors of the splenic flexure, descending colon, sigmoid colon and rectosigmoid junction were classified as left-sided. Unlike previous reports, the authors noted no association between primary tumor location and either OS or RFS among patients that underwent BSC (p=0.780 and p=0.670, respectively). However, when comparing cetuximab treatment efficacy by primary tumor location an interesting pattern emerged. Specifically, cetuximab treatment was associated with superior OS (HR 0.60, 95% CI 0.46-0.80, p<0.001) and PFS (HR 0.53, 95% CI 0.41-0.69, p<0.001) among patients with left-sided tumors, but not among patients with right-sided tumors (p=1.000 and p=0.640 for OS and PFS, respectively). In a subanalysis restricted to KRAS wild-type patients, the authors noted similar results. In addition, among the KRAS wild-type subgroup, left-sided primary tumor location was associated with benefit from cetuximab treatment in terms of PFS (p=0.002), but not OS (p=0.250). Similar results were obtained after adding the initially excluded patients with rectal tumors to the left-sided group [39].

Building on the findings by Brule et al., a subsequent study by Wang et al. investigated the possibility of differential response to cetuximab by primary tumor location. The primary study cohort consisted of 206 patients with mCRC, treated with first (n=110) or second-line (n=96) chemotherapy plus cetuximab at two different institutions in the period from 2006 to 2013. A similarly selected cohort of 210 patients that received chemotherapy without cetuximab served as a control group. Multiple different chemotherapy regimens were administered (eg. mFOLFOX-6, XELOX, modified FOLFIRI). Right-sided and left-sided tumors were defined as tumors proximal and distal to the splenic flexure, respectively. The authors then proceeded to analyze ORR, PFS and OS by primary tumor location. It was demonstrated that the addition of cetuximab to first-line standard chemotherapy was associated with improved ORR among patients with left-sided tumors (49.4% vs 28.6% for cetuximab + chemotherapy vs chemotherapy alone, respectively, p=0.005), but not among patients with right-sided tumors (p=0.349). Interestingly, no difference in ORR by primary tumor location was detected in either the first-line cetuximab + chemotherapy (p=0.296) or chemotherapy alone groups (p=0.837). When the analysis was repeated for patients who received second-line chemotherapy, cetuximab exhibited a similar trend towards improving ORR when compared to chemotherapy alone only among patients with left-sided tumors (p=0.085 vs p=0.698, for left and right-sided tumors, respectively). After separately comparing the ORR rates by primary tumor location in the second-line cetuximab + chemotherapy and chemotherapy alone groups, no statistically significant difference was detected (p=0.085 and p=1.000 for the cetuximab + chemotherapy and chemotherapy alone groups, respectively). It was also demonstrated that the addition of cetuximab to chemotherapy was associated with improved median PFS (9.1 vs 6.2 months, p=0.002; 4.9 vs 3.5 months, p=0.064 for the first and second-line chemotherapy groups, respectively) only among patients with left-sided tumors. Similarly, the addition of cetuximab to standard chemotherapy was associated with improved median OS only among patients with left-sided tumors (28.9 vs 20.1 months, p=0.036; 17.1 vs 12.4 months, p=0.047 for the first and second-line chemotherapy groups, respectively). No significant difference in either OS or PFS by primary tumor location was detected among the cetuximab + chemotherapy and chemotherapy alone groups (all p>0.05) [40] .

A more recent study by Lu et al. simultaneously investigated the effect of primary tumor location on prognosis and ORR following administration of either cetuximab or bevacizumab in addition to standard FOLFOX/FOLFIRI treatment regimens. The study cohort included 121 patients with mCRC that received their treatment at a single institution between 2007 and 2013. All patients were KRAS wild-type. Tumors proximal to the splenic flexure were defined as right-sided, while tumors originating from the splenic flexure to the rectosigmoid junction were defined as left-

sided. Of note, no patients with rectal tumors were included in the cohort. In terms of survival, patients with left-sided tumors were shown to have superior median PFS (11.8 vs 5.8 months for left and right-sided tumors, respectively, p<0.001) and OS (27.7 vs 15.7 months for left and right-sided tumors respectively, p=0.008). However, when patients were separately analyzed according to the receipt of either cetuximab or bevacizumab, a different pattern emerged. Specifically, in the cetuximab group left-sided tumor location was shown to be independently associated with improved PFS (HR 0.24, 95% CI 0.11-0.51, p<0.001), but not OS (p=0.756) in multivariate analysis. On the contrary, in the bevacizumab group primary tumor location was neither prognostic of PFS nor OS (all p>0.05). Similar results were obtained when analyzing ORR. Specifically, in the cetuximab group, left-sided tumors were significantly more likely to respond favorably to chemotherapy (70.1 vs 33.3% for left and right-sided tumors respectively, p=0.024). On the contrary, among patients treated with bevacizumab, primary tumor location had no significant impact on ORR (41.4 vs 16.7% for left and right-sided tumors respectively, p=0.093) [41].

A subsequent publication by Wong et al. increased the controversy regarding the effects of bevacizumab by primary tumor location. The study cohort comprised 926 patients with mCRC treated with palliative intent, with either standard chemotherapy (fluoropyridine alone or doublet chemotherapy) or chemotherapy plus bevacizumab (n= 633, 68.3 %). Patients were derived from the TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) registry, a multi-institutional Australian cancer registry, during the period from 2009 to 2014 [42]. Tumors proximal to the splenic flexure were defined as right-sided, while tumors from the splenic flexure to the rectosigmoid junction were defined as left-sided. Rectal tumors were treated as a separate group in the analysis. In the overall study cohort, right-sided tumor location was associated with both inferior median PFS (7.6 vs 10.2 vs 10.3 months for patients with right-sided, left-sided and rectal tumors, respectively, p<0.001) and OS (18.2 vs 23.6 vs 26.2 for patients with right-sided, left-sided and rectal tumors, respectively, p<0.001). In fact, in multivariate analysis left-sided and rectal tumors were shown to be independently associated with improved PFS, when compared to right-sided tumors (HR 0.81, 95% CI 0.67-0.98, p=0.031; HR 0.66 95% CI 0.54-0.81, p<0.001 for left-sided and rectal tumors, respectively). In terms of treatment efficacy, the addition of bevacizumab to standard chemotherapy was shown to be an independent predictor of improved PFS, irrespective of primary tumor location (all p<0.05). Interestingly, this effect appeared to be greater among patients with right-sided tumors (HR 0.46, 95% CI 0.36-0.60, p<0.001). In a secondary analysis that replaced the study's original classification of right and left-sided tumors with the already discussed definitions used by Boisen et al., similar results were obtained [29,43].

Lastly, a study by Chen et al. assessed the prognostic implications of primary tumor site among a nationwide cohort of 969 patients with KRAS wild-type tumors that received salvage therapy with cetuximab for mCRC after previous treatment failure. Patient data were collected from two major nationwide databases, the Taiwan Cancer Registry (TCR) and National Health Insurance (NHI), respectively, and covered the time period from 2004 to 2011 [44,45]. Almost all patients also received chemotherapy along with cetuximab (n=961;99.2%), but details of the administered regimens were not reported. Tumors originating from the cecum to the hepatic flexure were defined as right-sided, while tumors originating from the splenic flexure to the rectum were defined as left-sided. Patients with tumors of the transverse colon (n=58;6.0%) and patients with unknown primary tumor location (n=10;1.0%) were excluded from subsequent analysis. The authors demonstrated that patients with left-sided primary tumors had significantly longer median OS (12.6 vs 8.1 months for left and right-sided tumors, respectively, p<0.001) as well as a longer median time to treatment discontinuation (TTD) (4.6 vs 2.8 months for left and right-sided tumors, respectively, p<0.001). Conversely, right-sided tumor location was demonstrated to be an independent predictor of both inferior OS (HR 1.45 95% CI 1.18-1.78, p<0.001) and treatment discontinuation (HR 1.32, 95% CI 1.08-1.61, p=0.007) in multivariate analysis [46].

Discussion

Tumor location is known to exert a significant influence on the molecular, clinical and pathologic characteristics of primary CRC [14,15]. For instance, right-sided primary CRC often occurs in patients of advanced age and presents more commonly with aggressive molecular and pathologic features, such as poor differentiation and BRAF activating mutations [15,16,47]. In turn, as may be expected, these differences in prognostic characteristics and tumor biology, result in worse long-term survival for patients with right-sided primary CRC compared to patients with left-sided CRC [15,48]. Given the genetic continuity between pri-

mary and metastatic lesions it may be that these "location-specific" primary tumor characteristics are "inherited" by metastatic lesions; however, to date only one study from our group has examined the implications of primary tumor location in the context of surgically treated patients with colorectal liver metastasis (CRLM) [49]. In addition, one might argue that the delayed diagnosis of right-sided CRC due to the paucity of symptoms might account for the worse prognosis of these patients in comparison with patients with left-sided tumors [13,15,16]. In contrast, when a patient population with metastatic CRC is examined, this confounder is no longer relevant, as TNM stage is by definition uniform. As such, the study of patients with mCRC greatly facilitates the identification of true biologic and prognostic disparities between right and left-sided primary tumors.

Of note, the studies that were included in the current review did not use a uniform definition of what constitutes a right and left primary tumor. The majority defined right-sided tumors as cancers proximal to the splenic flexure and left-sided tumors as tumors of the splenic flexure, descending colon, sigmoid and rectum. However, Lu et al. excluded rectal tumors from analysis [41]. Of note, Wong et al. performed two different analyses first using the former definition that excluded rectal tumors and subsequently performing a separate analysis for rectal cancers that used the same definitions as Boisen et al. [29,43]. Importantly, they obtained similar results with both analyses. This was also the case for Brule et al., a study that also initially excluded rectal tumors only to re-introduce them in a secondary analysis [39]. However, despite these different definitions of right vs left, most of the studies showed that right-sided tumors had a worse survival compared to left-sided tumors. Even when this was not the case, no study demonstrated that left-sided tumors had worse survival. These findings strongly underline the consistent association of right-sided primary tumor location with worse prognosis among patients with mCRC.

Subsequently, the question that arises is why patients with a right-sided CRC fare worse than patients with left-sided tumors. A possible explanation might be that, alongside the previously described clinicopathologic and molecular disparities among right and left-sided tumors, response to chemotherapy might also vary according to primary tumor site. To this end, Modest and coworkers, while unable to demonstrate a statistically significant difference with regard to objective response to chemotherapy by primary tumor location in the overall cohort, found location-specific differences in response after stratifying by chemotherapy regimen. Specifically, when they stratified by the receipt of either FuFIRI or mIROX, they found that patients with right-sided tumors had significantly worse response to FuFIRI when compared to patients with left-sided tumors. This was not the case with mIROX. Moreover, left-sided primary tumor location was associated with improved PFS and OS only among patients treated with first-line FuFIRI [31]. Of note, Loupakis et al. did not detect a different objective response to FOLFIRI and bevacizumab by primary tumor location in their primary cohort; however, a statistically significant association of left-sided tumor location with increased chemotherapy response was evident when they examined two validation cohorts, treated with IFL with or without bevacizumab (AVF2107g) and XELOX or FOLFOX4 with or without bevacizumab (NO16966) [34].

Studies that examined the effect of biological agents by primary tumor location also demonstrated interesting findings. For example, Brule et al. showed that cetuximab treatment alone was a predictor of superior OS and PFS among patients with left-sided tumors, but not among patients with right-sided tumors [39]. In line with their findings, Wang and colleagues reported that the addition of cetuximab to first-line standard chemotherapy significantly improved ORR among patients with left-sided tumors (49.4 vs 28.6% for cetuximab vs chemotherapy alone), but not among patients with right-sided tumors. Interestingly, no difference in ORR by primary tumor location was detected in the first-line cetuximab setting [40]. Similarly, Von Einem et al. when examining a cohort of patients treated with either CAPOX plus cetuximab or CAPIRI plus cetuximab found a trend towards inferior ORR for right-sided tumors in the wild-type KRAS subgroup [33]. Interestingly, Lu et al. also compared the impact of biologic treatments relative to primary tumor site. The authors found that among patients treated with cetuximab, left-sided tumors were significantly more likely to respond favorably to chemotherapy [41].

On the contrary, among patients treated with bevacizumab, primary tumor location appeared to have no significant impact on ORR, although the included studies were not unanimous in their respective findings. For example, Wong et al. demonstrated that the addition of bevacizumab to standard chemotherapy was an independent predictor of improved PFS, irrespective of primary tumor location. Interestingly, this effect appeared to be greater among patients with right-sided tumors [43]. Similarly, Loupakis et al. reported that the efficacy of bevacizumab was independent of tumor loca-

tion [34]. In contrast, Boisen et al. reported a significantly decreased risk of progression and death among patients with left-sided tumors treated with CAPEOX and concomitant bevacizumab. Interestingly, no association between primary tumor location and prognosis was noted among a similarly selected control group of 213 patients treated with CAPEOX, but without bevacizumab [29].

As such, it appears that the primary tumor site may have an impact on the response to certain chemotherapeutic agents; in fact, even stronger evidence suggests this to be the case for biologic agents. In particular, a greater therapeutic effect of cetuximab in contrast with bevacizumab seems to be exerted on left-sided cancers that, in turn, might explain the better survival of patients with mCRC and a left-sided primary tumor. Although the considerable heterogeneity of the included studies in terms of chemotherapy regimens employed, left/right CRC definitions and treatment indications certainly hampers any possible comparisons, it appears that primary tumor location may be an important factor to consider when selecting chemotherapy regimens for patients with mCRC. As suggested by Loupakis et al., future randomized control trials should routinely be stratified by primary tumor location, so as to determine the optimal therapeutic approach in each case [34]. Until the molecular underpinnings of the prognostic and therapeutic disparities associated with primary tumor location are fully elucidated, a simplified dichotomous classification of patients in left vs right-sided mCRC groups may prove a cost-effective way to administer individualized cancer care.

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Conflict of interests

The authors declare no conflict of interests.

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