Right or Left Primary Site of Colorectal Cancer: Outcomes From the Molecular Analysis of the AGITG MAX Trial

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Abstract

For metastatic colorectal cancer, previous reports have described differences in biology and outcomes, including response to biological therapies, based on the sidedness (left vs. right) of the primary lesion. We explored the molecular markers from the AGITG MAX trial and found that right-sided cancer patients had poorer outcomes. We also found that the effectiveness of bevacizumab was independent of the site of the primary lesion.

Background: For metastatic colorectal cancer, previous reports have described differences in biology and outcome, including response to biologic agents, based on whether the primary tumor is right- or left-sided. We explored the molecular markers from the AGITG MAX trial. **Patients and Methods:** The AGITG MAX trial was a randomized study comparing capecitabine versus capecitabine + bevacizumab versus capecitabine + bevacizumab + mitomycin C as first-line therapy in advanced colorectal cancer. Patients were classified as having right-sided (caecum to transverse colon) or left-sided (descending colon to rectum) disease according to anatomic location. Baseline characteristics and previously described molecular profiles were compared by side of primary tumor. Survival outcomes were analyzed by the Kaplan-Meier approach and proportional hazards regression modeling. **Results:** Among the 471 patients, the location of primary tumor was known in 440 patients (93%). Molecular profile was known in 298 patients (63%). Twenty-eight percent had right-sided primary tumors. Major differences between right and left are as follows: female 49% versus 33% ($P < .01$), *BRAF* mutant 16% versus 3.5% ($P \leq .001$), and phosphatase and tensin homolog (PTEN) loss 27.6% versus 53% ($P = .01$). There were no differences in *RAS* mutation, *PIK3CA* mutation, or high versus low expression of assessed angiogenic markers. Right-sided primary lesion predicted a poor outcome for median overall survival: right-sided disease 13.2 months versus left-sided disease 20 months ($P = .001$; hazard ratio [HR] = 0.67; 95% confidence interval [CI], 0.53-0.85), but not for progression-free survival (HR 0.96; 95% CI, 0.78-1.20). The relative treatment effect did not differ significantly according to location of primary tumor: right primary tumor HR (bevacizumab containing arm vs. capecitabine monotherapy arm) was 0.82 (95% CI, 0.54-1.22), and left primary HR (bevacizumab containing arm vs. capecitabine monotherapy arm) was 0.51 (95% CI, 0.4-0.63) (interaction $P = .10$). **Conclusion:** There are more negative prognostic factors in patients with right-sided primary tumors, in particular high *BRAF* mutations, and these patients have inferior overall survival compared to those with a left-sided primary tumor. There was no suggestion that side of primary site had any impact on bevacizumab effect on progression-free survival.

Clinical Colorectal Cancer, Vol. 18, No. 2, 141-8
Keywords: Angiogenesis, Biomarkers, Molecular profile, Predictive, Survival

Presented in part at ESMO Madrid, September 2014.

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Submitted: Nov 1, 2018; Revised: Dec 2, 2018; Accepted: Dec 11, 2018; Epub: Jan 3, 2019

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1533-0028/$ - see frontmatter
https://doi.org/10.1016/j.clcc.2018.12.002

Introduction

Colorectal cancer (CRC) is a major health problem, with an estimated 1.2 million new cases and over 600,000 deaths occurring each year worldwide.[1] There are differences in reported population rates, with higher rates of CRC in New Zealand and Australia compared to other countries.[2] Hereditary familial conditions also define separate subgroups based on potentially differing biologic behavior and molecular profiles.

Over the last few years, considerable research analyzing the molecular differences within the colon itself has been a focus culminating in the 2012 report from the Cancer Genome Atlas project.[3] Furthermore, there is renewed interest in clinical markers as predictors of cancer behavior. Side of primary site (right vs. left) for CRC is an example of this. The study of Bufill[4] in 1990 was one of the first to propose differences in biology and outcome based on whether the primary lesion for metastatic CRC (mCRC) was right- or left-sided. There are a number of differences between the sides of the bowel—for example, embryologic beginnings, with the right bowel arising from the midgut and the left side from the hind gut. The vascular supply is therefore divided on this basis, and there are also capillary network[5] and crypt length variations.[6] Subsequent reports support the division of right- and left-sided CRCs.[7,8]

As regards presentation and symptomatology in relation to the primary site, the differences between right- and left-sided primary colon cancers appear to be as follows: right-sided colon tumors are more likely to be seen in older female patients who usually present with subtle signs and symptoms such as microcytic anemia and weight loss. These are therefore generally diagnosed at a more advanced tumor stage. From the pathology perspective, right-sided colon tumors have a higher tumor grade and are more frequently associated with mucinous histology and exophytic growth patterns. By contrast, left-sided CRCs are seen more commonly in younger patients who present with obstructive symptoms or rectal bleeding at diagnosis, with often infiltrating lesions. Further support for molecular differences based on the primary site in the bowel comes from a recent analysis of *KRAS, BRAF,* and microsatellite instability (MSI).[9] Thus, right-sided tumors are usually more likely to be associated with MSI, diploidy, epidermal growth factor receptor (EGFR) expression, *BRAF* mutation, and possibly *KRAS* mutation. In contrast, it has been postulated that left-sided CRC is associated with higher chromosomal instability, *p53* mutation, COX2 expression, and aneuploidy.[10] All these factors may contribute to the difference observed in patient prognosis, with increasing pooled data demonstrating a shorter overall survival (OS) for patients with right-sided colon tumors; a clear prognostic value of sidedness has therefore been proposed.

Differences in response to biologic agents have also been reported based on the side of the primary lesion. The effect of the primary tumor is more pronounced in patients treated with anti-EGFR therapy. In patients with left-sided tumors, treatment with anti-EGFR therapy in the first-line setting leads to a significantly longer median OS compared to patients treated with bevacizumab.[11] Left-sided primary tumors also tend to respond better to chemotherapy + bevacizumab compared to right-sided colon tumors.[12,13]

The phase 3 MAX trial (capecitabine vs. capecitabine + bevacizumab [± mitomycin C]) has confirmed improved progression-free survival (PFS) with the addition of bevacizumab to capecitabine.[14] The availability of a control arm without bevacizumab treatment makes this an ideal data set for examining predictive factors for bevacizumab. We have previously published molecular markers from the MAX trial: extended *RAS*, *BRAF*, phosphatase and tensin homolog (PTEN), phosphatidylinositol 3-kinase (*PIK3CA*), vascular endothelial growth factor (VEGF), interleukin (IL)-6 and IL-8, basic fibroblast growth factor (BFGF), and platelet-derived growth factor (PDGF-BB).[15-19]

We assessed the panel of markers based on right or left primary lesion site to assess if the primary site affects outcome with bevacizumab when combined with capecitabine, and to assess differences in biomarker patterns based on side.

Patients and Methods

Patients and Treatment

The Australasian Gastro-Intestinal Cancer Trials Group (AGITG) MAX study design and eligibility criteria have been reported previously.[14] The primary objective of this phase 3 study was to evaluate the effect of adding bevacizumab with or without mitomycin C to capecitabine on PFS among patients receiving first-line chemotherapy for unresectable mCRC. Enrollment of patients onto the original trial occurred between July 2005 and June 2007. Patients were randomly assigned to receive capecitabine, capecitabine + bevacizumab, or capecitabine + bevacizumab + mitomycin C in a 1:1:1 ratio. All patients who participated in the MAX translational studies provided written informed consent at the time of study enrollment. Ethics approval for translational studies was obtained centrally.

Right- Versus Left-Sided Colon Cancer

To examine the difference in outcomes between patients with right- and left-sided CRC, the primary tumor site of all MAX study patients was coded. Tumors originating in the splenic flexure, descending colon, sigmoid colon, or rectum were classified as left-sided; tumors originating in the appendix, cecum, ascending colon, hepatic flexure, or transverse colon were classified as right-sided.

Gene Expression Analysis

DNA was extracted from archival formalin-fixed, paraffin-embedded tumor tissue samples. A histopathologist reviewed cases, and if deemed to have < 50% malignant crypts in the section, the tissue was macrodissected to ensure a high proportion (90%) of tumor cells. Mutation status for extended *RAS* was determined using pyrosequencing and confirmed by Sanger sequencing. *BRAF* V600E mutations were determined by high-resolution melt analysis and confirmed by Sanger sequencing. Expression of proangiogenic markers was assessed by the BioPlex platform (Bio-Rad, Hercules, CA) using a 5-plex panel (IL-6, IL-8, basic fibroblast growth factor, PDGF-BB, VEGF-A). Protein was extracted in 2% w/v lysis buffer (2% sodium dodecyl sulfate, 200 mM dithiothreitol, 20 mM Tris-HCl, pH 8.8) at 100°C for 20 minutes, then at 80°C for 2 hours with agitation. Protein was solubilized in BioPlex lysis buffer via 2D

Table 1 Patient Characteristics

Characteristic	Variable	Primary Tumor Location		Missing[a]	*P* (Fisher Exact Test)
		Right (N = 124, 28%)	Left (N = 316, 72%)		
Treatment arm	Capecitabine (n)	39	108	0	.660
	Capecitabine + bevacizumab (n)	40	108		
	Capecitabine + bevacizumab + mitomycin C (n)	45	100		
Gender	Male	51%	67%	0	.002
	Female	49%	33%		
Age (years) (mean)		67.26	65.41	0	
Diabetes	Yes	9%	18%	0	.019
ECOG PS	0	50%	59%	0	.115
	1	40%	36%		.012
	2	10%	5%		.109
Metastasis resected	Yes	8%	10%	0	.069
Primary tumor resected	Yes	81%	79%	0	.600
Prior adjuvant chemotherapy	Yes	13%	26%	0	.003
Prior adjuvant radiotherapy	Yes	2.4%	17%	0	< .0001

Abbreviation: ECOG PS = Eastern Cooperative Oncology Group performance status.
[a]Total number considered in this analysis was 440. There were another 31 patients with tumor location unknown.

Cleanup kit (Bio-Rad).[16] PTEN status was assessed by TaqMan copy-number PCR.[17]

Statistical Analysis

Survival estimates were calculated by the Kaplan-Meier method with the log-rank test for survival comparisons. Variables were compared by the chi-square method or *t* test. Two-tailed $P < .01$ were considered significant. Univariate and multivariate Cox regression analyses were undertaken for PFS and OS to determine whether variables including chemotherapy combination treatment group, primary tumor resected, Eastern Cooperative Oncology Group performance status, number of metastatic sites, primary tumor resection, serum alkaline phosphatase and bilirubin, and prior radiotherapy (applicable to rectal cancers only) were independent factors. These variables were chosen for multivariate analyses because they were found to be statistically significant predictors in the intention-to-treat population in the original MAX publication.[14] Biologic/molecular marker status was correlated with efficacy outcomes (response rate, PFS, OS). Predictive analyses were undertaken using a test for interaction involving both capecitabine versus capecitabine + bevacizumab and capecitabine + bevacizumab + mitomycin C.

Results

Patients

Four hundred forty patients had primary site documented and were analyzed for baseline characteristics. Of these, 298 patients had molecular results available for analysis. Twenty-eight percent of patients in the tissue population had a right-sided primary tumor. The baseline patient, disease characteristics, and molecular profile are shown in Tables 1 and 2. Major differences between right- versus left-sided tumors, respectively, are as follows: female 49% versus 33% ($P < .01$), history of diabetes 13% versus 27% ($P = .02$), and metastatic lung involvement 28% versus 44% ($P < .01$). There was no significant difference between patients with right- and left-sided cancers in terms of age, Eastern Cooperative Oncology Group performance status, or resection of the primary tumor and/or metastases.

RAS *Status and Other Genetic Mutations, and Correlation With Site of CRC Primary Tumor*

In this patient population of 298 patients, extended *RAS* mutation was more frequent but not statistically higher in right-sided primary tumors compared to left-sided tumors, at 45% versus 37%, respectively ($P = .27$). Right- versus left-sided CRC tumor rates for *BRAF* and PTEN loss was as follows: *BRAF* V600E mutant 16% versus 3.5% ($P \leq .001$) and PTEN loss 27.6% versus 53% ($P = .01$). There was no difference in the rate of *PIK3CA* mutation by primary site. There were no differences in high versus low expression of assessed angiogenic markers (VEGF, IL-6, IL-8, BFGF, PDGF-BB) by side of primary tumor (Table 2).

Site of Primary Lesion and Prognosis

The OS was higher for the left-sided primary site compared to the right-sided site (Figure 1). When comparing right versus left sidedness, a right-sided primary tumor predicted for poor outcome in terms of OS (median right 13.2 vs. left 20 months; $P = .001$; hazard ratio [HR] = 0.67; 95% confidence interval [CI], 0.53-0.85), but not for PFS (HR = 0.96; 95% CI, 0.78-1.20). Multivariate analysis confirmed side of primary tumor as an independent prognostic factor for the whole group (Table 3, n = 440) and when analyzed by availability of tissue (Table 4, n = 298).

Site of Primary Lesion as Predictive Marker of Benefit From Bevacizumab

The relative treatment effect did not differ significantly according to location of primary tumor. For right primary tumor, HR

Table 2 *RAS* Status and Other Genetic Mutations, and Correlation With Site of Colorectal Cancer Primary Tumor

Characteristic	Variable	Right (N = 124) (%)	Left (N = 316) (%)	No. Missing	*P*
Site of Disease at Baseline					
Liver	Yes	72.6	75.3	0	.546
Lymph node	Yes	46	46	0	1.00
Lung	Yes	28	44	0	.002
Bone	Yes	2.4	4.8	0	.422
Peritoneum	Yes	24	15	0	.024
Mutation Status					
*PIK3CA*Exon_9	Mut	6	8	176	.801
*PIK3CA*Exon_20	Mut	2.6	4.3	176	.728
KRASExon_2	Mut	36	26	140	.126
KRASExon_3	Mut	0	4.5	186	.110
KRASExon_4	Mut	4	1.7	185	.367
NRASExon_2	Mut	0	2.2	185	.321
NRASExon_3	Mut	1.3	0.6	197	.517
NRASExon_4	Mut	0	0	185	NA
BRAF	Mut	22	5.3	142	< .0001
All *RAS*	Mut	55	63	171	.275
BioPlex Analysis					
VEGF	> 5.73 pg/mL	53	48	255	.630
	≤ 5.73 pg/mL	47	52		
IL-6	> 0.91 pg/mL	55	48	254	.521
	≤ 0.91 pg/mL	45	52		
IL-8	> 1.21 pg/mL	65	56	291	.360
	≤ 1.21 pg/mL	35	44		
Basic FGF	> 5.12 pg/mL	57	45	260	.191
	≤ 5.12 pg/mL	43	55		
PDGF-BB	> 4.99 pg/mL	63	47	278	.062
	≤ 4.99 pg/mL	37	53		
PTEN CNV	No loss	28	44	153	.009
	Loss	72	56		

Abbreviations: FGF = fibroblast growth factor; Mut = mutation; NA = not applicable; PDGF-BB = platelet-derived growth factor BB; PTEN CNV = phosphatase and tensin homolog copy-number variation.

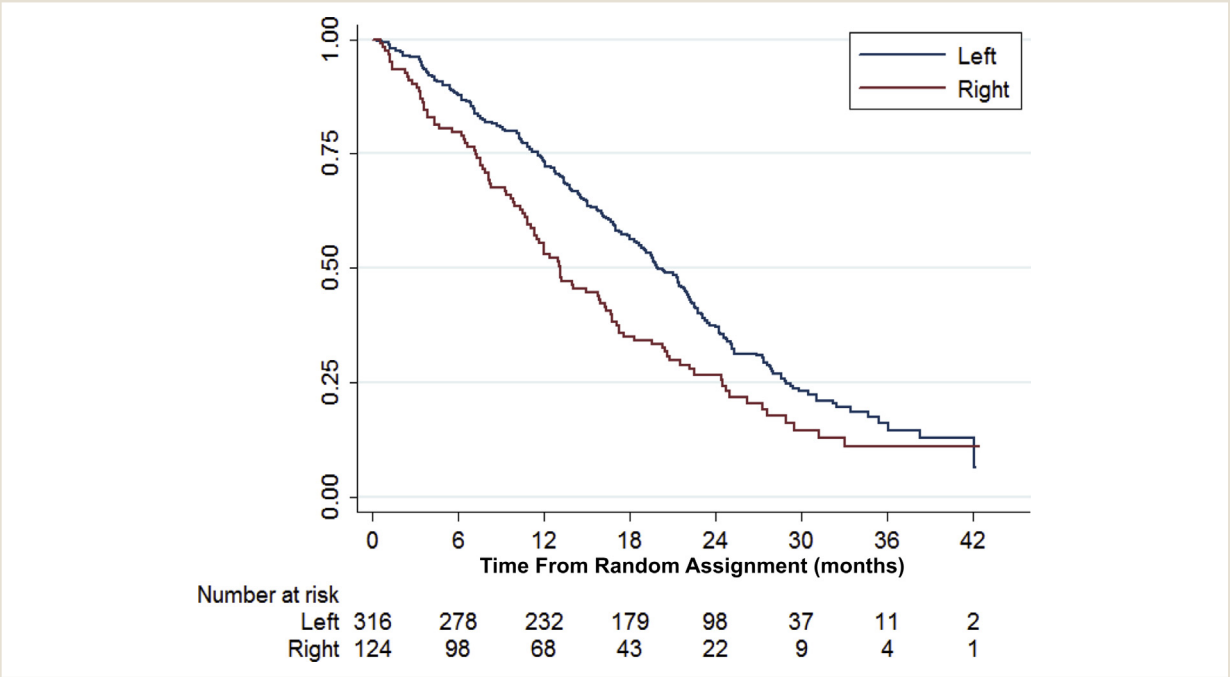
(bevacizumab-containing arm vs. capecitabine monotherapy arm) was 0.82 (95% CI, 0.54-1.22). For left primary tumor, HR (bevacizumab-containing arm vs. capecitabine monotherapy arm) was 0.51 (95% CI, 0.4-0.63). The test for interaction between relative treatment effect and primary tumor location was $P = .10$ (Figure 2).

Discussion

Prior reports and more recent retrospective analyses have shown that the site of primary tumor for mCRC is prognostic, with right-sided cancers correlated with a decreased life expectancy compared to left-sided cancers.[20-24] Our results from the MAX trial again confirm that patients with right-sided primary tumors have an inferior median OS compared to those with left-sided primary tumors. Multivariate analysis adjusting for known prognostic factors also confirmed that the side of the primary lesion was an independent prognostic factor. The insidious symptoms of right-sided tumors, leading to a delay in diagnosis, as well as the technical difficulty of imaging tumors arising from the ascending colon, either endoscopically or radiologically, were thought to be responsible (at least in part) for these survival differences.[25,26] However, there is growing evidence that this difference in prognosis and patterns of metastases is not solely dependent on the dichotomy of CRC tumor location. It is also dependent on the molecular profile of right- and left-sided CRC.

Different genetic alterations in neoplastic transformation have been found in CRC from different subsegments of the colon and rectum. However, neither *BRAF* nor *RAS* mutations are found exclusively in tumors from one specific section of the colon.[27] In a recent analysis of *BRAF*, *KRAS* mutation rates, and MSI-high,[9] the authors concluded that MSI-high status and *KRAS* and *BRAF* mutation rates were independent of tumor location. Other studies have suggested that the incidence of MSI and *BRAF* mutation is strongly associated with right-sided tumors.[28] Popovici et al[29] found that *BRAF* mutations seemed mainly prognostic in left-sided, but

Figure 1 Overall Survival by Lesion Side



not right-sided, tumors. Our results from the AGITG MAX trial showed more negative prognostic factors in patients with right-sided primary tumors, in particular a higher *BRAF* mutation rate (right vs. left, 16% vs. 3.5%; $P \leq .001$). We did not, however, demonstrate any additional significant molecular difference between left and right side of the colon primary lesion in this patient group. We also found clinical differences in metastatic lung involvement. These differences in the incidence of pulmonary metastases when comparing right- versus left-sided tumors may be explained by anatomic features of the venous drainage system of the rectum, a theory proposed over the years to explain why lung involvement is more frequently seen in patients with rectal cancers than those with colon cancers.[30,31]

Another important finding of our analysis is that there is no suggestion that the site of the primary tumor has any impact on bevacizumab's effect on PFS. Our results do not validate the hypothesis of an interaction of primary tumor location with bevacizumab efficacy. Similar conclusions were drawn by Loupakis et al,[13] who evaluated the association between tumor location and survival parameters in patients with previously untreated mCRC receiving first-line chemotherapy ± bevacizumab in 3 independent cohorts in a prospective pharmacogenetic study and 2 randomized phase 3 trials. In contrast, Boisen et al[12] selected 2 cohorts of mCRC patients treated with first-line chemotherapy. One was treated with capecitabine and oxaliplatin (n = 213), and the other was treated with capecitabine and oxaliplatin plus bevacizumab (n = 667). The authors suggested that

Table 3 Multivariate Analysis for Overall Survival of Whole Population of 440 Subjects

Characteristic	HR	95% CI		*P*
		Lower	Upper	
Capecitabine	1.00			
Capecitabine + bevacizumab	0.87	0.67	1.14	.319
Capecitabine + bevacizumab + mitomycin C	0.89	0.68	1.16	.389
ECOG PS ≥ 1	1.98	1.59	2.47	< .001
Neutrophils ≥ 8×10^9/L	1.56	1.14	2.13	.005
Alkaline phosphatase ≥ 140 U/L	1.70	1.35	2.14	< .001
Prior radiotherapy	1.63	1.17	2.25	.003
Primary tumor resected	0.67	0.52	0.87	.003
Left-sided tumor	0.60	0.47	0.77	< .001

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio.

Table 4 Multivariate Analysis for Overall Survival Stratified by *BRAF* Status for Patients With Molecular Results

Characteristic	%	HR	95% CI		*P*
			Lower	Upper	
Treatment Group					
Capecitabine	32				
Capecitabine + bevacizumab	35	0.9321	0.6715	1.2940	.675
Capecitabine + bevacizumab + mitomycin C	32	0.8735	0.6215	1.2279	.437
ECOG PS					
≥ 1	42	2.1800	1.6579	2.8665	.000
0	58	1			
Primary Tumor Resected					
Yes	87	0.5681	0.3838	0.84087	.005
No	13	1			
Alkaline Phosphatase					
≥ 140 U/L	33	1.6069	1.2035	2.1455	.001
< 140 U/L	67	1			
Neutrophils					
$\geq 8 \times 10^9$/L	15	1.5071	1.0181	2.2311	.040
$< 8 \times 10^9$/L	85	1			
Prior Radiotherapy					
Yes	10	1.5245	.9839	2.3622	.059
No	90	1			
Side					
Left	70	0.6832	.5062	0.9221	.013
Right	30	1			

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio.

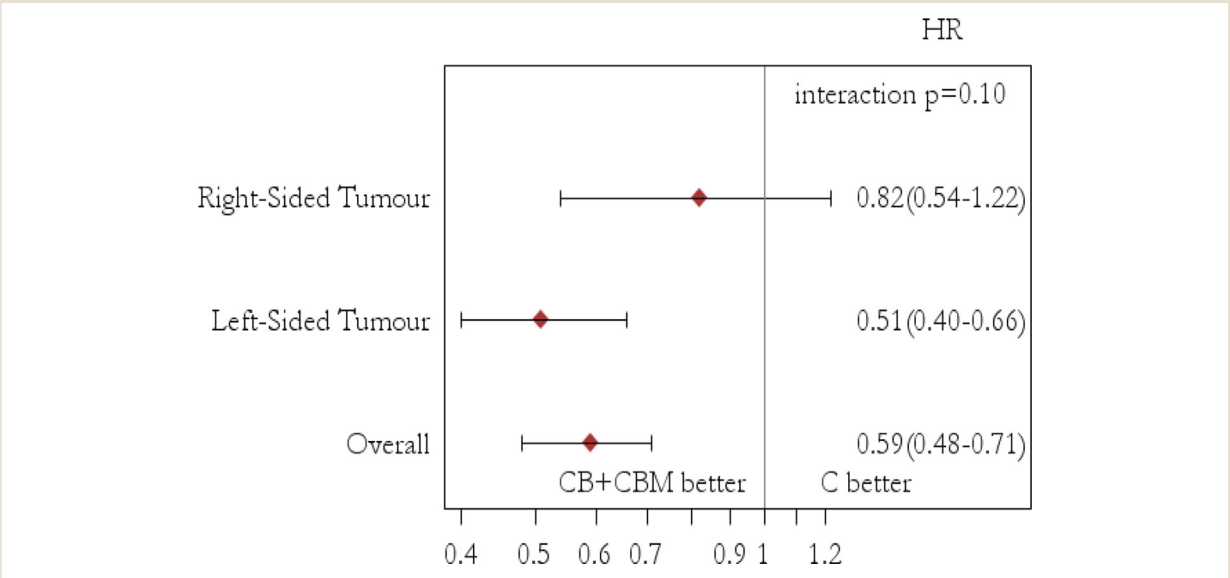
the addition of bevacizumab to chemotherapy in first-line treatment may predominantly benefit patients with primary tumors originating in the rectum and sigmoid colon. Conflicting conclusions were reached by Wong et al,[32] who analyzed the data of 926 patients from an Australian prospective multicenter mCRC registry treated with first-line chemotherapy ± bevacizumab. Patients who received anti-VEGF agent in addition to chemotherapy had superior outcomes, but the effect appeared greatest in patients with right-sided colon tumors. With regard to potential mechanisms, Bendardaf et al[33] demonstrated that left-sided colon and rectal cancers expressed higher levels of VEGF-A compared to right-sided colon cancers (61% vs. 45%, respectively), although this finding may not have any clinical relevance, given that there is no current evidence that the expression level of VEGF-A predicts the effectiveness of anti-VEGF therapies.[34] Here we found no difference in an antiangiogenic panel by side of primary tumor, including VEGF. Overall, the available data are inconsistent, and the potential predictive value of tumor location for bevacizumab therapy will only be answered by further randomized clinical trials.

In our population, all extended *RAS* mutations were more frequently seen (but not statistically higher) in right-sided primary tumors compared to left-sided CRC tumors (45% vs. 37%, respectively). Our results are consistent with some reports that have also found a higher rate of *KRAS* mutations in right-sided colon tumors compared to in left-sided CRC cancers.[35-37] However, other studies have reported different conclusions.[10,38]

Possible differences in response to anti-EGFR agents have also been reported on the basis of side of primary lesion. There is increasing (retrospective) data indicating that for *KRAS* wild-type cancers, the PFS benefit from cetuximab seems greater for left-sided tumors—a finding not only seen in chemotherapy-refractory *KRAS* wild-type mCRC patients[27,39] but also in first- or second-line chemotherapy for mCRC patients.[40,41] Some authors have hypothesized that this higher response rate to anti-EGFR therapies in patients with left-sided CRC might partly be explained by the fact that *BRAF* mutations are more frequently observed in right-sided than left-sided CRC.[37,38,42,43] In our study, right-sided tumors showed a far higher *BRAF* mutation rate compared to left-sided CRC, in keeping with the data reported in the literature. These data further confirm that right-sided and left-sided CRC have potentially important biologic differences that may affect prognosis and may have different benefits from chemotherapy and targeted therapies.

In an attempt to correlate key biologic and molecular features with clinical behavior, and to potentially guide treatments with specific targeted therapies, the Colorectal Cancer Subtyping Consortium unified 6 independent molecular classification systems on the basis of gene expression data from more than 3000 pooled CRC tumors samples into a single consensus system with 4 distinct groups, known as the consensus molecular subtypes (CMS).[44] Importantly, these subtypes have been found to be differentially distributed between right- and left-sided CRCs, with greater proportions of the "microsatellite unstable/immune"

Figure 2 Primary Outcomes, Progression-Free Survival, and Side of Primary Colorectal Cancer Lesion (Hazard Ratio and 99% Confidence Interval)



CMS1 and the "metabolic" CMS3 subtypes found in right-sided colon cancers. However, in order for CMS classification to be a useful tool for guiding CRC patient management, further validation in additional cohorts is warranted. Mooi et al[45] reported the results of an exploratory study evaluating the role of CMS as a prognostic and predictive variable for bevacizumab benefit in mCRC using archived samples of primary tumors from patients on the MAX study. The authors found that CMS2 (and possibly CMS3 tumors) may preferentially benefit from the addition of bevacizumab to first-line capecitabine-based chemotherapy compared to other CMS groups. In this analysis we saw no difference in our panel of angiogenesis markers or outcomes with bevacizumab on the basis of side alone. Mooi et al highlight the fact that basing decisions on side alone may be too simplistic, and that the future may include CMS, or updated versions based on additional biologic markers.

There are some potential limitations of our study that should be considered when interpreting these results. First, this was a retrospective analysis from the MAX trial patients' cohort, in which only approximately 67% of patients had tissue available for molecular analysis. As a result, the sample size was limited (298 tissue samples in total). However, the outcomes seen in our results are comparable with what has been previously reported for left- and right-sided CRC in other scientific articles. For example, Price et al,[46] using the South Australian Metastatic Colorectal registry, evaluated almost 3000 patients looking for differences in outcomes according to site of primary tumor in mCRC. The median OS for that group of patients for right versus left was 9.7 versus 20.3 months ($P < .001$), comparable with our results. Another limitation is that a clear distinction is not made among left-sided tumors between sigmoid and rectal tumors, and the implications of primary tumor site in bevacizumab responses. While this study did not collect data on subsequent anti-EGFR therapy, potential differences in response to subsequent therapy based on side may account for the difference in OS observed, despite the lack of difference in PFS in this study. Additionally, although our analyses have been adjusted for known prognostic factors, the existence of other clinicopathologic elements may also have contributed to the difference in patients' outcomes, and these cannot be excluded.

In conclusion, our results indicate that primary tumor location has a prognostic effect, with poorer outcomes seen in patients with right-sided disease. These results further support stratification on the basis of site of primary tumor in upcoming and future randomized CRC clinical trials. In our cohort, we also found that the effectiveness of bevacizumab was independent of the primary site of CRC disease.

Clinical Practice Points

- Previous studies have reported the prognostic impact of primary tumor sidedness in metastatic colorectal cancer and its potential influence on targeted therapy efficacy.
- The present retrospective analysis of the previously reported phase 3 MAX trial (capecitabine vs. capecitabine/bevacizumab with or without mitomycin C) investigated differences in biology and outcomes for metastatic colorectal cancer, including response to bevacizumab, based on anatomic tumor location. The availability of a control arm without bevacizumab treatment makes this an ideal data set for examining predictive factors for bevacizumab.
- In this clinical study, we found that right-sided colon cancer patients had poorer outcomes compared to those with a left-sided primary tumor. More importantly, we also found that the effectiveness of bevacizumab was independent of the primary site of colorectal cancer.
- Our study focuses on the predictive value of sidedness for response to antiangiogenic therapy in metastatic colorectal

cancer—a topic for which the data currently available are inconsistent. We used a novel specific panel for this antiangiogenesis analysis by side.

- Stratification based on primary site in upcoming and future randomized clinical trials in colorectal cancers is supported.

Acknowledgments

Funding for the molecular testing was received from the Cancer Council South Australian. Additional untied funding was provided by Roche Australia. Statistical analysis was provided by NHMRC CTC.

Disclosure

T.P. declares advisory roles for Roche, Merck, and Amgen, and travel allowance for educational attendance from Amgen. N.T. declares advisory roles for Roche, Merck, Bristol-Myers Squibb, and Amgen, and travel allowance for educational attendance from Roche. The other authors have stated that they have no conflict of interest.

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