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Research Paper

Primary Tumor Location as a Predictive Factor for First-line Bevacizumab Effectiveness in Metastatic Colorectal Cancer Patients

Wen-Zhuo He*, Fang-Xin Liao*, Chang Jiang, Peng-Fei Kong, Chen-Xi Yin, Qiong Yang, Hui-Juan Qiu, Bei Zhang and Liang-Ping Xia✉

VIP Region, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong 510060, P. R. China.

*Wen-Zhuo He and Fang-Xin Liao contributed equally to this paper.

✉ Corresponding author: Liang-Ping Xia. Email: xialiangping@163.com; Fax: +8620-87343392; Tel: +8620-87343107; Mobile: 13926410608. Addresses: Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong 510060, P. R. China.

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Abstract

Background: Published papers reported contradictory results about the correlation between bevacizumab effectiveness and primary tumor location of metastatic colorectal cancer (mCRC).

Methods: 740 mCRC patients treated with chemotherapy (CT group) and 244 patients treated with bevacizumab plus chemotherapy as first-line setting (CT + B group) were included. Propensity score analyses were used for patients' stratification and matching. Kaplan-Meier curves with log-rank tests were used to detect different overall survival (OS).

Results: Patients in CT + B group had similar OS comparing with CT group only when the primary tumor located at right-side colon (20.2 for CT + B versus 19.7 months for CT group, $p = 0.269$). For left-side colon and rectal cancer patients, significantly longer OS were observed in CT + B than CT group.

Conclusion: Our data suggested only patients with left-side colon or rectal cancer could get survival benefit from the addition of bevacizumab to first-line chemotherapy.

Key words: Colorectal cancer, metastasis, prognosis, bevacizumab, and location.

Introduction

Colorectal cancer is a group of distinct diseases rather than a homogeneous one[1]. The colon can be divided into left and right sides with the splenic flexure as the boundary[2]. Various evidences suggest that left-side colon cancer differs significantly from right-side colon cancer in terms of risk factors, histological grade, tumor size and metastatic features[3, 4]. Indeed, different molecular characteristics exist between right-side colon and left-side colon, as well as rectum[5]. What's more, clinical evidence supports that right-side and left-side colon cancers response differently to palliative chemotherapy, as well as cetuximab[4, 6-8]. When it comes to anti-angiogenic therapy, Boisen et al. reported that patients with tumors originating from sigmoid colon or rectum had better survival than those from cecum to descending colon when treated with capecitabine and oxaliplatin (CAPEOX) plus bevacizumab (median OS were 23.5 versus 13.0 months), and the survival advantage disappeared when patients were treated with CAPEOX without bevacizumab[9]. However, Fotios et al. reported a study which failed to validate the correlation since both primary tumor location and bevacizumab use were independent factors in multivariable analyses[10, 11]. Venook et al. reported that

bevacizumab was superior to cetuximab in right-side colon cancer patients[12]. Given all of these inconsistent results, in this study we evaluated the prognostic impact of primary tumor location on survival of mCRC patients, as well as the predictive value of primary tumor location on bevacizumab effectiveness. We also performed propensity score analyses to reduce the impact of clinical and pathological features which distributed differently between right-side and left-side colon.

Materials and Methods

Data source and patient selection

From January 2005 to December 2013, we retrospectively recruited consecutive patients with histologically proven mCRC at Sun Yat-sen University Cancer Center. The study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center, and informed consent was obtained from every patient. Patients who accepted at least three cycles palliative chemotherapy were included. Exclusion criteria were as follows: 1) case history not available; 2) without follow up information; 3) with cetuximab as first-line treatment; 4) with other coexisting malignancy.

Date analyses and statistics

Right-sided colon cancers included those occurring in cecum, ascending colon or transverse colon. Left sided colon cancers included those occurring in descending or sigmoid colon. All patients were grouped into chemotherapy group (CT group) or chemotherapy + bevacizumab group (CT + B group) according to the first-line treatment. We also performed propensity score analyses to adjust for heterogeneity since several clinical and pathological features were not balanced when patients were grouped by primary tumor location. As previously reported[13], we performed a 1:1 propensity score analyses by modeling logistic regression with balanceable variables, including gender, mucinous histology, stage at diagnosis and LDH levels. The matching tolerance for propensity score analyses was 0.001. The primary endpoint of this study was overall survival (OS), defined as the time from the establishment of metastatic or recurrent disease to the date of death or the last follow-up. Follow-up information was updated in 30th December 2015. We called all the patients or their family members through the phone numbers they left at our hospital. All statistical analyses were performed with the SPSS software version 22. The differences in survival were compared by Kaplan-Meier analyses and log-rank test. Multivariate analysis using a Cox proportional hazards model was used to test independent significance by backward elimination of insignificant explanatory variables. A two-tailed p value less than 0.05 was considered statistically significant.

Results

The study flowchart is shown in Figure 1. 984 patients were included in the study. The median follow-up period was 22 months; during this follow-up period, 624 deaths (63.4%) were documented. The median OS of all patients was 21.8 months. The study comprised 740 patients in CT group and 244 patients in CT + B group. The distributions of primary tumor location as well as other characteristics were shown in the Table 1. The distributions of most characteristics were similar, except gender, mucinous histology, stage at diagnosis, and lactate dehydrogenase (LDH) levels. In all patients, bevacizumab was associated with longer OS (p=0.001, Figure 2a).

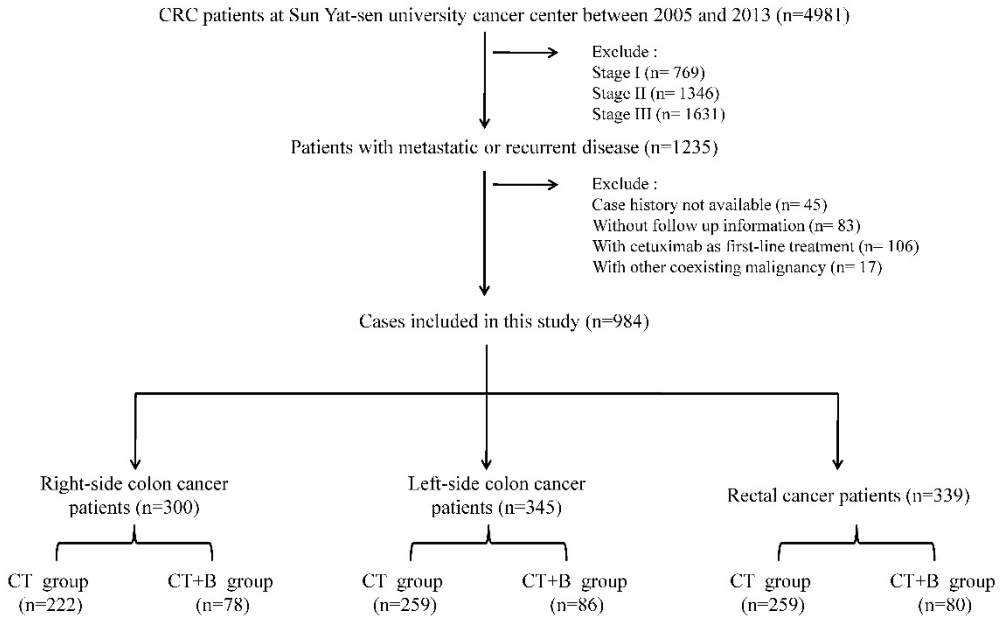

Figure 1: The flow chart of this study.

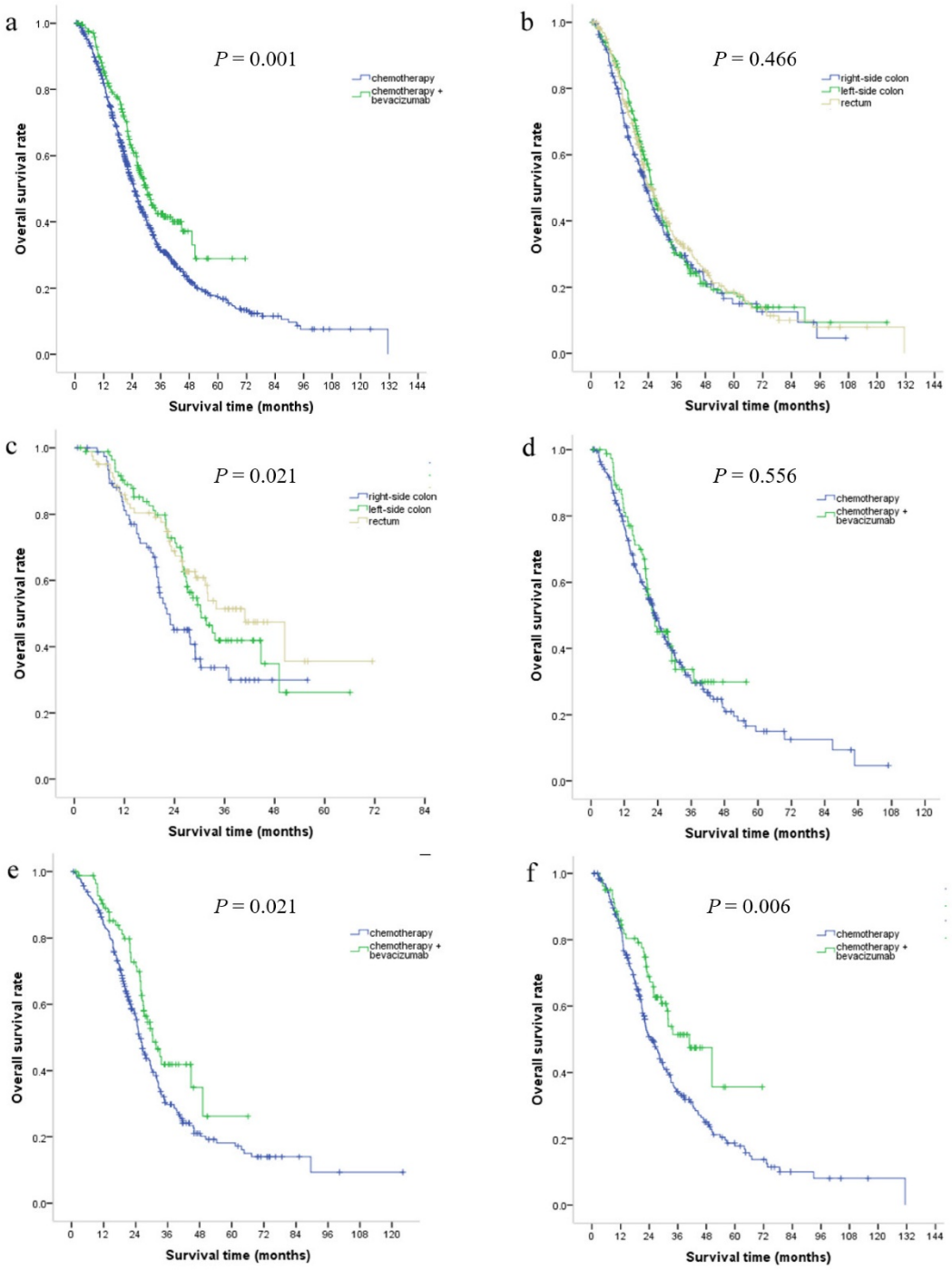

Figure 2: Overall survival (OS) of all patients treated with and without bevacizumab (a); OS of patients grouped by primary tumor location in chemotherapy (CT) group (b); OS of patients grouped by primary tumor location in chemotherapy plus bevacizumab (CT + B) group (c); OS of patients in CT group and CT + B in patients with right-side colon cancer (d), left-side colon cancer (e) and rectal cancer (f).

No evidence of difference was found in survival outcome for different primary tumor location in CT group. Median OS for right-side colon, left-side colon and rectal cancer patients were 19.7, 22.3 and 21.1 months, respectively (p=0.466, Figure 2b). However, significant differences were detected in OS according to primary tumor location in CT + B group. Median OS for patients with right-side colon, left-side colon and rectal cancer patients were 20.2, 26.3 and 26.4 months, respectively (p=0.021, Figure 2c). The detailed differences of CT + B group in left and right side colon were shown in Table 2. Multivariate analysis including primary tumor location, primary tumor resection, number of metastatic organ, LDH and CEA levels confirmed that primary tumor location was an independent factor (hazard ratio 0.765, 95 % confidence interval 0.607-0.966, p =0.024) in CT + B group.

Table 1: The characteristics of patients.

	All patients				
Variable	Total	Right-side colon	Left-side colon	Rectum	*P*-value, chi-square
Number of patients	984	300	345	339	
Age					
≤50 y	387	120	138	129	0.934
51-65 y	387	120	131	136	
>65 y	210	60	76	74	
Gender					
Male	637	177	228	203	*0.036*
Female	347	123	117	107	
Mucinous histology					
Yes	158	69	49	40	*<0.001*
No	826	231	296	299	
Stage at diagnosis					
I	8	1	2	5	*<0.001*
II	70	20	20	30	
III	206	48	56	102	
IV	700	231	267	202	
First line therapy					
Chemotherapy	740	222	259	259	0.685
Bevacizumab + chemotherapy	244	78	86	80	
Metastatic organ					
1	714	221	251	242	0.808
>1	270	79	94	97	
CEA					
≤5 ng/ml	275	81	92	102	0.563
>5 ng/ml	702	217	250	235	
unknown	7	2	3	2	
LDH					
≤245 U/ml	702	228	230	244	*0.035*
>245 U/ml	279	71	113	95	
unknown	3	1	2		
Backbone chemotherapy					
Oxaliplatin-based	682	213	244	225	0.685
Irinotecan-based	257	73	87	97	
5-fluorouracil only	45	14	14	17	
Bevacizumab beyond first line					
Yes	83	26	31	26	0.813
No	901	274	314	313	
Cetuximab treated					
Yes	104	29	40	35	0.637
No	880	271	304	304	
Primary tumor resection					
Yes	606	186	220	200	0.432
No	378	114	125	139	

To further evaluate the predictive value of primary tumor location in regards to bevacizumab effectiveness, we studied whether the treatment benefit of bevacizumab differed among three primary tumor locations. Patients with right-side colon cancer had similar OS (19.7 months vs 20.2 months, p=0.556, Figure 2d) comparing CT group with CT + B group. However, patients with left-side colon cancer could derive benefit from bevacizumab (median OS was 26.3 months for CT+B group and 22.3 months for CT group, p=0.021, Figure 2e). Significant longer OS were also detected in rectal cancer patients when bevacizumab were added (median OS was 26.4 months for CT+B group and 21.1 months for CT group, p=0.006, Figure 2f). The routinely clinical-pathological factors were comparable in those comparisons.

Since gender, mucinous histology, stage at diagnosis and LDH levels were not balanceable, we performed propensity score analyses to adjust for those heterogeneities, as shown in the Table 3. Similar results were observed after matching. 58 right-side colon, 86 left-side colon and 99 rectal cancer patients were included in CT group (total: 243) while 78 right-side colon, 86 left-side colon and 80 rectal cancer patients were included in CT + B group (total: 244). For patients in CT group, median OS for right-side colon, left-side colon and rectal cancer patients were

20.4, 23.1 and 21.2 months, respectively (p=0.800). Patients in CT + B group had a similar OS in comparison with CT group only when the primary tumor located at right-side colon (median OS were 20.2 months for CT + B group versus 20.5 for CT group, p = 0.851). For left-side colon cancer patients, those in CT + B group had longer OS than CT group (26.3 versus 23.1 months, P = 0.021). For rectal cancer patients, significantly longer OS were also observed in CT + B than CT group (26.3 versus 21.1 months, p = 0.014).

Table 2: Patient characteristics in the chemotherapy + bevacizumab group.

Variable	Right-side colon	Left-side colon	*P*-value, chi-square
Number of patients	78	86	
Age			
≤50 y	41	41	0.598
51-65 y	25	34	
>65 y	12	11	
Sex			
Male	44	56	0.266
Female	34	30	
Mucinous histology			
Yes	15	14	0.684
No	63	72	
Stage at diagnosis			
I	1	9	0.207
II	6	24	
III	26	53	
IV	45	86	
Metastatic organ			
1	59	61	0.597
>1	19	25	
CEA			
≤5 ng/ml	15	28	0.051
>5 ng/ml	63	56	
unknown	0	2	
LDH			
≤245 U/ml	57	57	0.494
>245 U/ml	21	28	
unknown	0	1	
Backbone chemotherapy			
Oxaliplatin-based	41	49	0.304
Irinotecan-based	37	35	
5-fluorouracil only	0	2	
Bevacizumab beyond first line			
Yes	16	15	0.691
No	62	71	
Cetuximab treated			
Yes	7	13	0.245
No	71	73	
Primary tumor resection			
Yes	57	67	0.585
No	21	19	

Discussion

In this study, we observed that survival was inferior for right-side as compare to left-side colon or rectal cancer patients when they were treated with chemotherapy plus bevacizumab. Since right-side colon cancer has prevalence toward being mucinous type and more advanced disease, we also performed propensity score analyses to reduce the impact of its nature. What's more, in patients treated with chemotherapy plus bevacizumab, we conducted multivariate analysis to confirm that primary tumor location was an independent factor. At last, we compared the survival between patients who accepted chemotherapy alone and chemotherapy plus bevacizumab in patients with right-side colon cancer, as well as left-side colon and rectal cancer.

Several other studies were in line with the present study. Boisen reported the prognostic value of primary tumor location when mCRC patients were treated with CAPEOX plus bevacizumab, and the prognostic value of primary tumor location disappeared when patients were treated with CAPEOX only[9]. Brule et al. reported that tumor location within the colon is not prognostic in NCIC CO.17 trial, in which patients were treated with cetuximab versus best supportive care, [14]. In Brule's study, the the primary tumor location was not with prognostic values for OS (HR 0.96 [0.70–1.31], p = 0.78) or progression-free survival (HR 1.07 [0.79–1.44], p = 0.67). Together, these reports and our study make the interaction between bevacizumab effectiveness and primary tumor location less likely to be a coincidence.

One possible reason underlying the interaction between primary tumor location and bevacizumab effectiveness is that VEGF-A, the target of bevacizumab, is higher expressed in left-side colon and rectum than right-side colon[15]. Volz et al. also reported that germline polymorphisms related to pericyte maturation, which could predict treatment benefit of bevacizumab, was dependent on primary tumor location[16]. However, the exact mechanism underlying this interaction remains exclusive.

Our study has several implications. We suggest that investigators should consider the primary tumor location as a stratification factor in designing or reviewing clinical studies involving bevacizumab. In addition, primary tumor location of mCRC should be considered when cetuximab and bevacizumab are compared, since right-side and left-side mCRC patients also respond differently to cetuximab. Indeed, Venook et al. reported that bevacizumab might be superior to cetuximab for right-sided mCRC[12]. We think their results were not contradicted with our study since we compared chemotherapy plus bevacizumab with chemotherapy only, with first-line cetuximab excluded.

There are several limitations of this study. First,

the retrospective nature limited its power. Second, several molecular features were not available, such as kirsten rat sarcoma viral oncogene homolog (KRAS) status. Third, we did not compare progression free survival since we could not determine the precise time of tumor progression based on medical records. Those limitations should be considered when interpreting our study.

In conclusion, our data suggest that primary tumor location is a prognostic factor for mCRC patients when treated with bevacizumab, and patients with right-side colon cancer cannot get survival benefit from the addition of bevacizumab to first-line chemotherapy. Further data from randomized trials are needed to test our hypothesis.

Table 3: The characteristics of patients after propensity score analyses.

	Propensity score-matched patients				
Variable	Total	Right-side colon	Left-side colon	Rectum	*P*-value, chi-square
Number of patients	487	136	172	179	
Age					
≤50 y	230	67	85	78	0.787
51-65 y	176	46	61	69	
>65 y	81	23	26	32	
Gender					
Male	302	78	107	117	0.348
Female	185	58	65	62	
Mucinous histology					
Yes	81	27	30	24	0.295
No	406	109	142	155	
Stage at diagnosis					
I	6	1	1	4	*<0.001*
II	48	13	11	24	
III	163	39	47	77	
IV	270	83	113	74	
First line therapy					
Chemotherapy	243	58	86	99	0.084
Bevacizumab + chemotherapy	244	78	86	80	
Metastatic organ					
1	345	100	115	130	0.662
>1	142	36	57	49	
CEA					
≤5 ng/ml	138	31	53	54	0.216
>5 ng/ml	346	105	117	124	
unknown	3	0	2	1	
LDH					
≤245 U/ml	346	101	114	131	0.262
>245 U/ml	140	35	57	48	
unknown	1	0	1	0	
Backbone chemotherapy					
Oxaliplatin-based	190	52	72	66	0.903
Irinotecan-based	257	73	87	97	
5-fluorouracil only	40	11	13	16	
Bevacizumab beyond first line					
Yes	57	18	152	160	0.773
No	430	118	20	19	
Cetuximab treated					
Yes	55	13	21	21	0.655
No	432	123	151	158	
Primary tumor resection					
Yes	166	43	54	69	0.285
No	321	93	118	110	

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Competing Interests

The authors have declared that no competing interest exists.

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