Prognostic Impact of Primary Tumor Location on Clinical Outcomes of Metastatic Colorectal Cancer Treated With Cetuximab Plus Oxaliplatin-Based Chemotherapy: A Subgroup Analysis of the JACCRO CC-05/06 Trials

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Abstract

Primary tumor location is a prognostic factor in metastatic colorectal cancer (mCRC). We assessed the prognostic impact of tumor location on survival and the association between *BRAF* mutation and tumor sidedness in mCRC patients treated with cetuximab. Tumor location is a prognostic marker for first-line cetuximab plus oxaliplatin-based chemotherapy, irrespective of *BRAF* status.

Introduction: Primary tumor location is a critical prognostic factor in metastatic colorectal cancer (mCRC); however, it remains unclear whether tumor location is a predictor of the response to cetuximab treatment. It is also uncertain if *BRAF* mutation contributes to the impact of tumor location on survival. We assessed the prognostic impact of tumor location on clinical outcomes in mCRC patients treated with first-line cetuximab chemotherapy. **Patients and Methods:** The associations of tumor location with overall survival and progression-free survival were evaluated in mCRC patients with *KRAS* exon 2 wild-type tumors who were enrolled onto 2 clinical trials: JACCRO CC-05 of cetuximab plus FOLFOX (n = 57, UMIN000004197) and CC-06 of cetuximab plus SOX (n = 61, UMIN000007022). Tumors proximal or from splenic flexure to rectum were defined as right-sided or left-sided, respectively. In addition, exploratory *RAS* and *BRAF* mutation analyses were performed. **Results:** A total of 110 patients were assessable for tumor location; 90 had left-sided tumors. Left-sided tumors were significantly associated with longer overall survival (36.2 vs. 12.6 months, hazard ratio = 0.28, $P < .0001$) and progression-free survival (11.1 vs. 5.6 months, hazard ratio = 0.47, $P = .0041$) than right-sided tumors; similar results were obtained in multivariate analysis. A subanalysis showed that the association was evident in the FOLFOX group and that tumor location was an independent prognostic

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factor irrespective of *BRAF* status in *RAS* wild-type patients. **Conclusion:** Primary tumor location might be a predictor of survival independent of *BRAF* status in mCRC patients who receive first-line cetuximab combined with oxaliplatin-based chemotherapy.

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Introduction

Several factors have been identified as prognostic biomarkers in colorectal cancer (CRC), including germ-line mutations in DNA mismatch repair genes in stage II/III disease and $BRAF^{V600E}$ mutations in stage IV disease.[1,2] Moreover, mortality has been shown to be higher in proximal than in distal colon cancer.[3-7] The proximal, right-sided colon originates from the embryonic midgut and is served by the superior mesenteric artery, whereas the distal, left-sided colon arises from the hind gut and is perfused by the inferior mesenteric artery.[8] There are differences in epidemiologic, clinical, and histologic features between right-sided and left-sided CRCs.[3] Such differences probably lead to the disparity in outcomes according to the primary tumor site.

Right-sided and left-sided CRCs differ with respect to their molecular pathways of carcinogenesis, biological characteristics, and genomic patterns. Right-sided tumors express the CIMP phenotype and are more likely to be characterized by microsatellite instability—high, CpG island methylation, and *BRAF* mutations.[9-12] In contrast, left-sided tumors have a phenotype that involves chromosomal instability and are characterized by loss of heterozygosity and *TP53* mutations.[9] Several microarray studies have found over 1000 genes that show different expression patterns between right- and left-sided tumors, potentially leading to distinct embryonic origins and postnatal regulation.[13-15]

Subanalyses of randomized clinical trials performed in the United States and Europe have demonstrated that primary tumor location is a critical prognostic factor in metastatic CRC (mCRC) treated by first-line chemotherapy combined with biological agents.[16-19] In the FIRE-3 trial, which compared FOLFIRI plus cetuximab with FOLFIRI plus bevacizumab as first-line therapy in mCRC patients with *KRAS* exon 2 wild-type tumors, a subanalysis indicated that left-sided tumors were associated with significantly longer overall survival (OS) and progression-free survival (PFS) than right-sided tumors among patients with *RAS* wild-type tumors who received cetuximab.[18] The impact of tumor sidedness on clinical outcomes in cetuximab-treated patients was also demonstrated in a subanalysis of the CALGB/SWOG 80405 trial; however, other *RAS* mutations were not taken into account and potential effects of treatment-related differences between the oxaliplatin-treated patients and irinotecan-treated patients could not be excluded.[19] In addition, it remains unclear if *BRAF* mutations contribute to the impact of tumor location on survival. To our knowledge, the impact of primary tumor location on outcomes has not been assessed in Asian patients enrolled onto prospective clinical trials.

We therefore investigated the prognostic impact of primary tumor location on the clinical outcomes of Japanese patients with *KRAS* exon 2 wild-type mCRC who were enrolled onto the JACCRO CC-05 (UMIN000004197) or CC-06 (UMIN000007022) trial, which evaluated the efficacy of cetuximab combined with either FOLFOX or SOX as first-line treatment. Moreover, we attempted to assess the effect according to *RAS* and *BRAF* status in preparation for forthcoming molecular analyses.

Patients and Methods

Patient Population

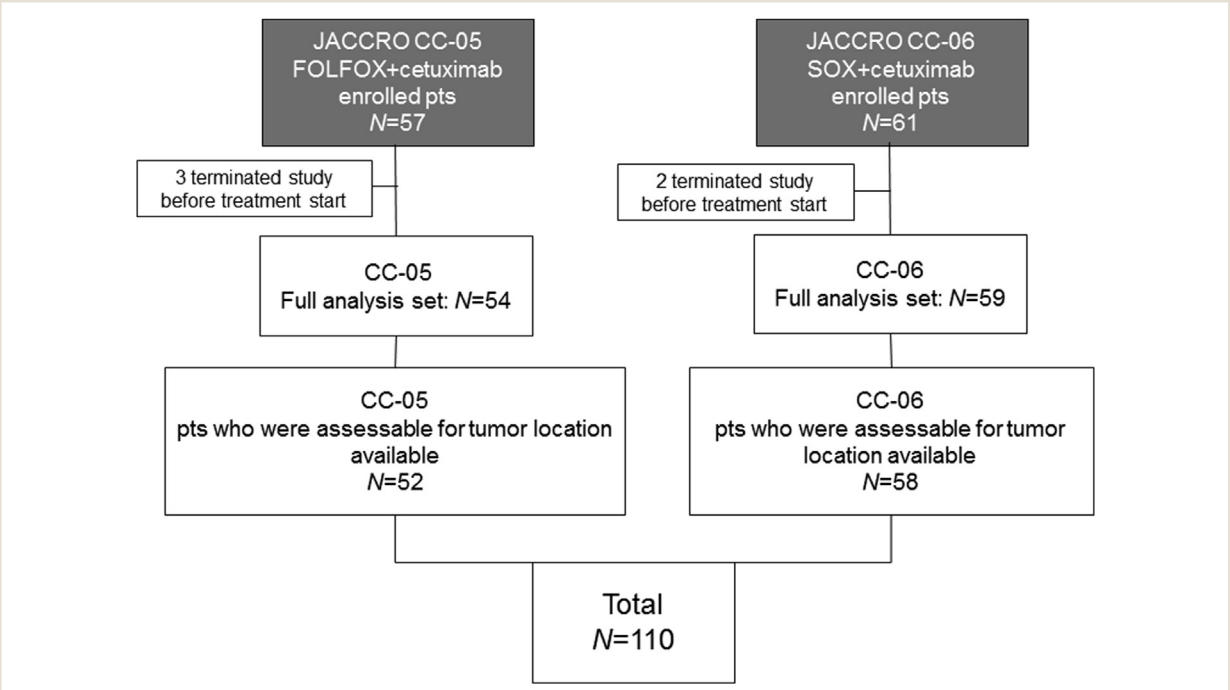
We studied mCRC patients who were enrolled onto the phase 2 JACCRO CC-05 or CC-06 trial, evaluating first-line cetuximab treatment combined with FOLFOX or SOX, respectively, and were assessable for primary tumor location (Figure 1). The identical eligibility criteria of the 2 trials was as follows: adenocarcinoma of the colon or rectum with immunohistologic expression of *EGFR*; *KRAS* exon 2 wild-type tumor with unresectable metastases; at least one measurable lesion of 10 mm or a residual nonmeasurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; adequate bone marrow function (hemoglobin $>$ 9.0 g/dL, neutrophil count $>$ 1500/mm^3;, platelet count $>$ 100,000/mm^3;), hepatic function, and renal function; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; and an age of 20 to 79 years. Patients with uncontrolled infection, massive ascites or pleural effusion, symptomatic brain metastases or other malignancies within 5 years before enrollment (with the exception of early carcinoma that had been treated with curative intent), a history of systemic chemotherapy for mCRC, or previous treatment with oxaliplatin or cetuximab were excluded. The studies were conducted in accordance with the Declaration of Helsinki and were approved by the ethical committee of each participating institute. Written informed consent was obtained from all patients before enrollment.

Tumors located from the cecum to the hepatic flexure were classified as right-sided, while tumors that included the splenic flexure, descending colon, sigmoid colon, and rectum were classified as left-sided. Patients with tumors in the transverse colon or synchronous right-sided and left-sided tumors were excluded from analysis.

Chemotherapy

In the FOLFOX regimen (JACCRO CC-05), on day 1 of each 14-day treatment cycle, patients received cetuximab (a 120-minute infusion of 400 mg/m^2 of body surface area [BSA] followed by a 60-minute infusion of 250 mg/m^2 of BSA provided weekly thereafter) plus modified FOLFOX6 (a 120-minute infusion of oxaliplatin at a dose of 85 mg/m^2 of BSA; a 120-minute infusion of leucovorin at a dose of 200 mg/m^2 of BSA; and an intravenous bolus of fluorouracil at a dose of 400 mg/m^2 of BSA followed by a continuous 46-hour infusion of 2400 mg/m^2 of BSA). In the SOX regimen (JACCRO CC-06), on day 1 of each 21-day treatment cycle, patients received cetuximab (a 120-minute infusion of 400 mg/m^2 of BSA followed by a 60-minute infusion of 250 mg/m^2 of BSA provided weekly thereafter) plus SOX (a 120-minute infusion

Figure 1 Flowchart of Patient Allocation to Treatment Group



of oxaliplatin at a dose of 130 mg/m^2 of BSA on day 1; and oral S-1 at a dose of 80 mg/m^2 of BSA on days 1-15). Pretreatment with dexamethasone and a histamine-1 blocker was strongly recommended to prevent allergic or hypersensitivity reactions to cetuximab. Treatment was continued until disease progression, unacceptable toxic effects developed, a complete response was achieved, surgical resection became possible, or the patient requested or the physician decided that therapy should be withdrawn. Dose modifications of chemotherapy and cetuximab were permitted according to protocol-defined criteria. In the event of grade 3 or 4 allergic or hypersensitivity reaction, cetuximab or oxaliplatin was permanently discontinued.

Assessment of Efficacy

The primary end point of these two phase 2 trials was the proportion of patients who had an objective response (complete or partial response). Secondary end points included early tumor shrinkage (ETS) (percentage change in the size of target lesions compared to baseline value), evaluated every 8 weeks until progression, PFS based on disease progression detected by external review or death from any cause, OS, secondary resection of metastases with curative intent, and safety. Responses were evaluated according to RECIST, version 1.1, by the investigators and were then validated by an external review board. ETS was defined as a minimal tumor reduction of 20% at 8 weeks.

DNA Isolation and RAS/BRAF *Mutation Analysis*

Formalin-fixed, paraffin-embedded (FFPE) tumor specimens were cut into sections with a thickness of 3 or 10 μm. In a preparation for macrodissection, one 3 μm slide was stained with hematoxylin and eosin and was then evaluated for tumor content and marked for areas with dominant tumor foci by a pathologist. Macrodissection was performed by scratching the marked areas with a blade to ensure that as many tumor cells as possible were dissected. The dissected particles of tissue were transferred to reaction tubes for isolation of genomic DNA. Genomic DNA was extracted from the FFPE tissue derived from the tumor samples with the use of a QIAamp DNA FFPE Tissue Kit (Qiagen, Germantown, MD) according to the manufacturer's protocol.

RASKET KIT (MBL, Nagoya, Japan) was used in accordance with the manufacturer's protocol to detect *KRAS/NRAS* exon 2 mutations (G12S, G12C, G12R, G12D, G12V, G12A, G13S, G13C, G13R, G13D, G13V, and G13A), 8 types of *KRAS/NRAS* exon 3 mutations (A59T, A59G, Q61K, Q61E, Q61L, Q61P, Q61R, and Q61H), and 4 types of *KRAS/NRAS* exon 4 mutations (K117N, A146T, A146P, and A146V). $BRAF^{V600E}$ mutations were detected by dye terminator sequencing. Exon 15 of the *BRAF* gene was amplified by polymerase chain reaction (PCR), and the PCR products were then visualized using agarose gel electrophoresis with ethidium bromide staining. The products were directly sequenced with the use of an ABI 3130xl Genetic Analyzer (Thermo Fisher Scientific, Yokohama, Japan) according to the manufacturer's instructions.

This study was conducted in accordance with the REporting recommendations for tumor MARKer prognostic studies (REMARK).[20,21] Tissue analyses were performed at SRL Inc (Tokyo, Japan) and G&G Science Co Ltd (Fukushima, Japan) after obtaining approval from the institutional review board of each

institution that participated in the JACCRO CC-05/06AR trials (UMIN000010635).

Statistical Analysis

The prognostic impact of primary tumor location on outcomes was investigated in all subgroups of enrolled patients in addition to the cohort of patients with *RAS* wild-type tumors. The primary end point of the present study was OS. Objective response rate (ORR), ETS (yes, no), and PFS were the secondary end points. The associations of primary tumor location with tumor response or ETS were examined by Fisher's exact test. The associations between tumor location and OS or PFS were assessed by Kaplan-Meir curves and log-rank tests in univariate analyses. A multivariable Cox regression model was used to evaluate the independent effects of a marker on OS or PFS and to adjust for ECOG PS (0 vs. 1), the number of organs involved (1 vs. $\geq$ 2), and primary tumor site (right vs. left), all of which were significantly associated with outcomes ($P < .05$).

SAS 9.0.3 software (SAS Institute, Cary, NC) was used to perform all analyses. All tests were 2 sided with a significance level of .05.

Results

Patient Characteristics

A total of 110 patients were enrolled. Ninety patients (82%) had left-sided tumors, and 20 (18%) had right-sided tumors. The patient characteristics are summarized in Table 1. Primary tumor was resected among 75% of patients in each side of tumor location. There were no statistically significant differences in characteristics between patients with left-sided tumors and those with right-sided tumors (see Supplemental Table 1 in the online version). In the enrolled patients, the ORR was 65% (95% confidence interval [CI], 57-74). The median PFS and OS were 9.4 months (95% CI, 8.1-11.3) and 33.9 months (95% CI, 26.5-43.6), respectively.

Table 1 Characteristics of 110 Patients

Characteristic	N (%)
Gender	
Male	63 (57)
Female	47 (43)
Age (Years)	
Median (range)	61.5 (34-83)
<65	66 (60)
≥65	44 (40)
Performance Status	
ECOG 0	98 (89)
ECOG 1	12 (11)
Diagnosis	
Metachronous	26 (24)
Synchronous	84 (76)
Primary Lesion	
Yes	27 (25)
No	83 (75)
No. of Metastatic Sites	
1	49 (45)
≥2	61 (55)
Previous Adjuvant Chemotherapy	
Yes	8 (7)
No	102 (93)
Regimen	
FOLFOX	52 (47)
SOX	58 (53)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Clinical Outcomes According to Primary Tumor Location

The ORR was 69% (95% CI, 59-78) in patients with left-sided tumors and 50% (95% CI, 28-72) in those with right-sided tumors. There was no significant difference in the ORR between the left-tumor cohort and right-tumor cohort ($P = .12$). ETS also did not differ significantly between the 2 cohorts (78% vs. 74%, $P = .76$). The median PFS and OS were significantly longer in the left-sided tumor cohort than the right-sided tumor cohort (11.1 vs. 5.6 months, hazard ratio [HR] = 0.47, $P = .0041$; 36.2 vs. 12.6 months, HR = 0.28, $P < .0001$, respectively) (Table 2, Figure 2).

Multivariate analysis adjusted for ECOG PS, number of organs involved, and tumor location revealed that primary tumor location was an independent prognostic factor for both PFS and OS (HR = 0.48, $P = .0041$; HR = 0.31, $P < .0001$, respectively) (Table 3).

Subgroup Analysis According to Backbone Chemotherapeutic Regimen and RAS/BRAF *Status*

We performed a subgroup analysis stratified according to regimen (modified FOLFOX6 or SOX). An association of tumor location with clinical outcomes was evident in the FOLFOX group ($P = .0002$ for PFS and $P < .0001$ for OS) but was not significant in the SOX group ($P = .30$ for PFS and $P = .079$ for OS). In patients with right-sided tumors, median PFS and OS were numerically longer in the SOX group than in the FOLFOX group (6.7 vs. 3.0 months, and 18.3 vs. 5.7 months, respectively) (see Supplemental Figure 1 in the online version).

Among the 110 patients, external analysis of *RAS* mutations was conducted in 71 patients from whom tumor samples were available for *RAS* and *BRAF* molecular analyses. *RAS* and *BRAF* mutations were successfully analyzed in 67 (94%) of the 71 patients. The analyses detected *RAS* mutations in 7 (10%) of the 67 patients and *BRAF* mutations in 9 patients (15%). In 60 patients with *RAS* wild-type tumors, left-sided tumors were significantly associated with longer PFS and OS than right-sided tumors (11.3 vs. 5.6 months, HR = 0.49, $P = .061$; 42.8 vs. 18.3 months, HR = 0.21, $P = .0001$, respectively). Moreover, in patients with *RAS/BRAF* wild-type tumors, left-sided tumors were associated with significantly longer OS than right-sided tumors ($P = .039$) (Table 4). Left-sided tumors were significantly associated with OS on multivariate analysis adjusted for factors including *BRAF* status in patients with *RAS* wild-type tumors (HR = 0.21, $P = .0018$), suggesting that tumor location can serve as a prognostic marker irrespective of *BRAF* status.

Discussion

Our study demonstrated that primary tumor location is a predictor of survival in mCRC patients who receive first-line cetuximab

Table 2 Clinical Outcomes According to Primary Tumor Location

Location	N	Tumor Response		Early Tumor Shrinkage		PFS		OS	
		CR, PR	SD, PD	Yes	No	Median (95% CI) Months	HR (95% CI)	Median (95% CI) Months	HR (95% CI)
Right-sided	20	10 (50%)	9	14 (74%)	5 (26%)	5.6 (1.9-7.3)	1	12.6 (4.9-23.5)	1
Left-sided	90	62 (69%)	23	67 (78%)	19 (22%)	11.1 (9.1-13.5)	0.47 (0.28-0.80)	36.2 (27.5-45.3)	0.28 (0.15-0.52)
P			.12		.76		.0041*		<.0001*

P values were based on Fisher's exact test for tumor response and early tumor shrinkage and log-rank test for PFS and OS in univariate analysis.
Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.
*Statistical significance.

plus oxaliplatin-based chemotherapy. Our results potentially confirm the prognostic impact of tumor location in mCRC. Moreover, our findings suggest that primary tumor location is an independent prognostic biomarker irrespective of *BRAF* status.

Several studies have revealed that left-sided tumors are present more often than right-sided tumors in early-stage disease.[4,22-25] A subanalysis of the database of the Surveillance, Epidemiology, and End Results program, a large epidemiologic study, reported that right-sided tumors are associated with poorer outcomes than left-sided tumors after adjustment for tumor stage,[4,5] indicating that primary tumor location can potentially be used as a prognostic marker in CRC. A subgroup analysis of the AIO KRK-0104 trial has shown favorable survival of mCRC patients with left-sided tumors who received first-line combination chemotherapy with cetuximab.[26] In addition, multivariate Cox regression analyses of PFS and OS in the FIRE-3 trial demonstrated that left-sided tumor location is a predictor of favorable outcomes in *RAS* wild-type mCRC patients who receive first-line FOLFIRI plus cetuximab.[18] However, there has been no report regarding the impact of tumor sidedness on survival in patients who receive only oxaliplatin-based chemotherapy as a platform regimen plus cetuximab. Our results support the findings of previous studies and further indicate that primary tumor location can serve as a predictor of survival in mCRC patients treated with first-line cetuximab combined with oxaliplatin-based chemotherapy. In our study, the primary tumor location was unrelated to tumor response as an outcome of treatment. A subanalysis of the FIRE-3 trial indicated a significant effect of primary tumor location on ORR (odds ratio 2.7, $P = .019$).[18] However, in the AIO KRK-0104 study, left-sided tumors were not significantly associated with a higher ORR compared to right-sided tumors (64% vs. 43%, $P = .12$) in patients with *KRAS* exon 2 wild-type tumors.[26] The relation between tumor location and ORR thus remains controversial.

BRAF mutation is a strong negative prognostic determinant in mCRC, and patients with *BRAF*-mutated tumors have an extremely poor life expectancy.[27,28] The frequency of *BRAF* mutations in CRC significantly increases linearly along the bowel from the rectum to ascending colon rather than changing abruptly at the splenic flexure.[12] Right-sided tumors are therefore more likely to be characterized by *BRAF* mutations. The impact of sidedness on survival may reflect the contribution of *BRAF* mutation to poor outcomes; however, a subanalysis of a clinical trial showed that tumor sidedness has a prognostic effect on outcomes regardless of *BRAF* status.[16] We analyzed the association between tumor location and clinical outcomes according to *RAS* and *BRAF* status. In patients with *RAS* wild-type as well as those with *RAS/BRAF* wild-type tumors, left-sided tumors were significantly associated with longer OS. Moreover, a multivariate analysis adjusted for factors including *BRAF* status revealed that tumor location had a prognostic effect on survival in patients with *RAS* wild-type tumors, suggesting that primary tumor location is an independent prognostic biomarker irrespective of *BRAF* status. This finding needs to be confirmed in larger studies.

Figure 2 Kaplan-Meier Curves of Clinical Outcomes According to Primary Tumor Location for (A) Progression-Free Survival and (B) Overall Survival

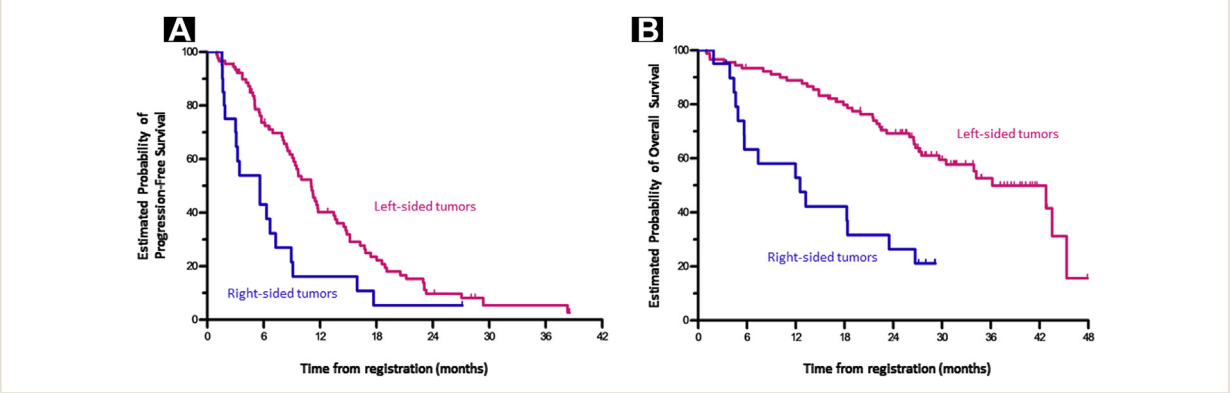


Table 3 Prognostic Factors in Multivariate Analysis

Characteristic	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Gender						
Male vs. female	1.22	0.78-1.89	.76	1.14	0.66-1.97	.96
ECOG PS						
0 vs. 1	0.69	0.37-1.30	.20	0.50	0.23-1.07	.12
No. of Organs Involved						
1 vs. ≥2	0.97	0.63-1.49	.98	0.41	0.22-0.76	.0025*
Tumor Location						
Left vs. right	0.48	0.28-0.81	.0041*	0.31	0.17-0.58	<.0001*

P values were based on Wald test for PFS and OS in multivariable Cox regression model adjusted for ECOG PS, number of organs involved, and tumor location.
Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.
*Statistical significance.

Our study group comprised patients who received FOLFOX or SOX as backbone chemotherapy. We therefore additionally analyzed the association of tumor location with clinical outcomes according to regimen (FOLFOX or SOX). The association was significant in the FOLFOX group ($P = .0002$ for PFS and $P < .0001$ for OS) but was not significant in the SOX group ($P = .30$ for PFS and $P = .079$ for OS). Interestingly, median PFS was numerically longer in the SOX group than in the FOLFOX group in patients with right-sided tumors (6.7 vs. 3.0 months). In contrast, in patients with left-sided tumors median PFS was numerically shorter in the SOX group than in the FOLFOX group (9.2 vs. 11.3 months). In the SOFT trial, which showed that SOX plus bevacizumab was noninferior to FOLFOX plus bevacizumab as first-line treatment for mCRC, the subgroup analysis of PFS indicated no significant interaction between the regimen and primary tumor location (colon vs. rectosigmoid vs. rectum).[29] Additional analyses according to tumor sidedness (left vs. right) may provide informative evidence on the relations between the effectiveness of S-1 and tumor location in trials evaluating S-1–based regimens.

It remains controversial whether left-sidedness of primary tumors is a predictor of the response to cetuximab in patients with *KRAS*/*RAS* wild-type mCRC. A recent study that reanalyzed data from the NCIC CO.17 trial has reported that tumor location is a strong predictor of a beneficial effect of cetuximab therapy on PFS. Among patients with *KRAS* exon 2 wild-type colon cancer, cetuximab treatment was associated with significantly better PFS than best supportive care only in patients with left-sided tumors (median 5.4 vs. 1.8 months, HR = 0.28, $P < .0001$) and not in patients with right-sided tumors (median 1.9 vs. 1.9 months, HR = 0.73, $P = .26$) (interaction $P = .002$).[30] Retrospective analyses of the FIRE-3 and CALGB/SWOG 80405 trials showed that treatment effects in patients with left-sided tumors were more prominent in the cetuximab arm: chemotherapy plus cetuximab significantly improved OS compared to chemotherapy plus bevacizumab in patients with *KRAS*/*RAS* wild-type mCRC who had left-sided tumors, whereas the benefit of treatment with cetuximab appeared to be limited in patients who had right-sided tumors.[18,19] In our study, multivariate analysis showed that tumor location was significantly associated with PFS. Further studies are needed to assess the predictive relevance of primary tumor location in patients with *RAS* wild-type mCRC treated with first-line cetuximab-containing regimens.

Although the number of patients included in this pooled analysis of 2 prospective trials was relatively small, our results are consistent with the findings of previous studies. However, because *RAS* and *BRAF* tests were performed using samples that were retrospectively

Table 4 Primary Tumor Location and Clinical Outcomes According to *RAS/BRAF* Status

Characteristic	*KRAS* Exon 2 wt (N = 110)		*RAS* wt (N = 60)		*RAS/BRAF* wt (N = 51)	
	Left	Right	Left	Right	Left	Right
No.	90	20	51	9	47	4
ORR (%)	69	50	78	56	79	50
	$P = .12$		$P = .21$		$P = .23$	
Median PFS (months)	11.1	5.6	11.3	5.6	11.6	6.1
	HR = 0.47 (0.28-0.80)		HR = 0.49 (0.24-1.13)		HR = 1.02 (0.36-4.28)	
	$P = .0041$*		$P = .061$		$P = .97$	
Median OS (months)	36.2	12.6	42.8	18.3	NR	18.3
	HR = 0.28 (0.15-0.52)		HR = 0.21 (0.09-0.53)		HR = 0.29 (0.09-1.27)	
	$P < .0001$*		$P = .0001$*		$P = .039$*	

P values were based on Fisher's exact test for tumor response and early tumor shrinkage and log-rank test for PFS and OS in univariate analysis.
Abbreviations: HR = hazard ratio; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; wt = wild type.
*Statistical significance.

collected from patients for whom tumor-tissue specimens were available, a selection bias cannot be excluded. Therefore, the prognostic impact of primary tumor location on clinical outcomes should be confirmed in future studies of larger groups of patients.

Conclusion

Primary tumor location was significantly associated with survival in mCRC patients who received cetuximab plus oxaliplatin-based chemotherapy as first-line treatment. Patients with left-sided tumors had significantly better OS than those with right-sided tumors. Our results further indicate that the primary tumor location may be a viable prognostic marker regardless of *BRAF* status.

Clinical Practice Points

- Primary tumor location is a prognostic factor in mCRC; however, it remains unclear whether location of the primary tumor is a predictive marker of the response to cetuximab treatment. It is also unclear whether *BRAF* mutation contributes to the impact of tumor location on survival.
- In the present study, the prognostic impact of tumor location on survival and the association between *BRAF* mutation and tumor sidedness were investigated in mCRC patients who were enrolled onto clinical trials and received first-line cetuximab combined with oxaliplatin-based chemotherapy.
- Left-sided tumors were associated with significantly longer OS and PFS than right-sided tumors; moreover, this association remained statistically significant in multivariate analysis.
- Subanalyses showed that the association between tumor sidedness and outcomes was evident in the FOLFOX group rather than in the SOX group and that tumor location was an independent prognostic factor irrespective of *BRAF* status in patients with *RAS* wild-type tumors.
- Our study confirms the prognostic impact of tumor location on survival in mCRC patients treated with first-line cetuximab plus oxaliplatin-based chemotherapy. Moreover, our results suggest that tumor location might be a prognostic marker irrespective of *BRAF* status.

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Disclosure

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Supplemental Data

A supplemental figure and table accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clcc.2016.09.010.

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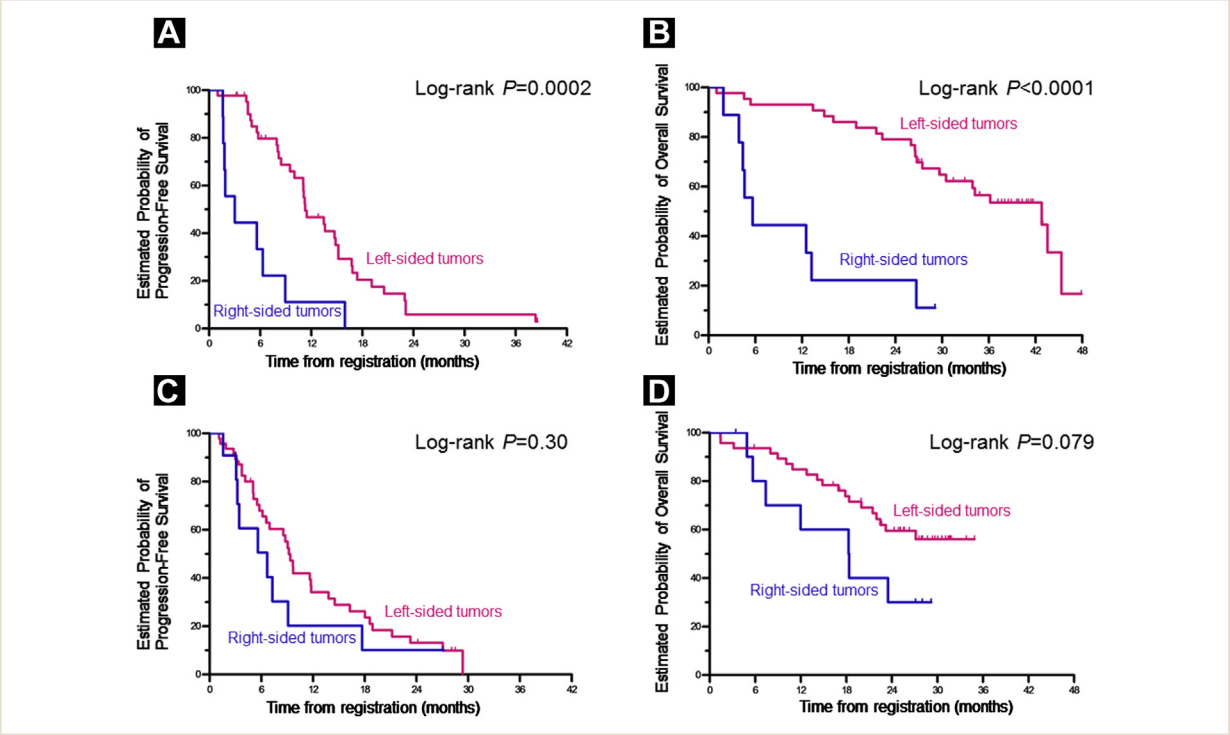
Supplemental Figure 1 Kaplan-Meier Curves of Clinical Outcomes According to Primary Tumor Location for (A) Progression-Free Survival and (B) Overall Survival in FOLFOX Plus Cetuximab Group, and (C) Progression-Free Survival and (D) Overall Survival in SOX Plus Cetuximab group



Supplemental Table 1 Patient Characteristics According to Primary Tumor Location

Characteristic	Left (N = 90), N (%)	Right (N = 20), N (%)	*P*
Gender			
Male	54 (60)	9 (45)	.32
Female	36 (40)	11 (55)	
Age (Years)			
Median (range)	61.5	61.5	.55
<65	53 (59)	13 (65)	.80
≥65	37 (41)	7 (35)	
ECOG Performance Status			
0	81 (90)	17 (85)	.45
1	9 (10)	3 (15)	
Diagnosis			
Metachronous	22 (24)	4 (20)	.78
Synchronous	68 (76)	16 (80)	
Primary Lesion			
Yes	22 (24)	5 (25)	1.00
No	68 (76)	15 (75)	
No. of Metastatic Sites			
1	43 (48)	6 (30)	.21
≥2	47 (52)	14 (70)	
Previous Adjuvant Chemotherapy			
Yes	7 (8)	1 (5)	1.00
No	83 (92)	19 (95)	
Regimen			
FOLFOX	43 (48)	9 (45)	1.00
SOX	47 (52)	11 (55)	

Differences in patients' baseline characteristics between locations were examined by Fisher's exact test.
Abbreviation: ECOG = Eastern Cooperative Oncology Group.