

CLINICAL RESEARCH

Is primary tumor location an independent prognostic factor in stage IV colon cancer?

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Abstract:

Objectives: To determine whether primary tumor location is an independent prognostic factor in stage IV colon cancer, focusing on its relationship with chemotherapy and/or sex. **Methods:** We retrospectively analyzed clinicopathological data from 255 patients with stage IV colon cancer from two treatment eras according to the year of starting multidrug combination chemotherapy: period A was from 1985 to 2005 and period B from 2006 to 2013. Propensity score matching (1:1) was performed to assess overall survival(OS). **Results:** Right-sided colon cancer tended to be more common in elderly females with large-sized tumors, exhibiting mucinous histology or peritoneal dissemination. After propensity score matching, 130 patients were identified. There was no difference in OS between left-sided and right-sided tumors in either period A or B. The prognosis of patients receiving chemotherapy in either period was superior to that of those without chemotherapy. Better outcome of chemotherapy was seen only in female left-sided patients from both periods ($p < 0.05$). By multivariate analysis, liver metastasis, peritoneal dissemination, and chemotherapy were found to be independent risk factors in period A, whereas only liver metastasis and chemotherapy were the independent factors in period B. **Conclusions:** Primary tumor location is not an independent prognostic factor, but seems to be a chemotherapy effect modifier.

Keywords:

primary tumor location, chemotherapy, sex, independent prognostic factor, propensity score

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Introduction

A relationship between primary tumor location and prognosis of colon cancer was previously reported¹⁾, but this may vary at different tumor stages²⁾ owing to different underlying gene mutations³⁻⁸⁾. According to the latest ESMO guidelines, anti-EGFR antibody treatment is recommended for left-sided unresectable advanced recurrent colorectal cancer⁹⁾. However, the importance of primary tumor location relative to other prognostic factors for the outcome of chemotherapy for unresectable advanced recurrent colorectal cancer is not established.

Clearly, age is a strong risk factor for colorectal can-

cer^{10,11)}, and sex differences due to the hormonal background associated with aging are also present^{12,13)}. Moreover, Tsai et al. reported that BRAF mutations, MSI-high status, and N-RAS differ according to sex in colorectal cancer¹³⁾. In the present study, we investigated whether primary tumor location is an independent prognostic factor for survival, focusing on relationships with chemotherapy and/or sex.

Methods

Patients

A retrospective study of a single-center cohort was per-

Table 1. Patients' Background before Propensity Score Matching.

	period A (n=173)			period B (n=82)		
	left-sided (112)	right-sided (61)	p	left-sided (48)	right-sided (34)	p
age \geq 75y/o	21% (23/112)	28% (17/61)	0.345	29% (14/48)	47% (16/34)	0.110
Percentage of women	46% (51/112)	57% (35/61)	0.154	54% (26/48)	68% (23/34)	0.258
Intestinal obstruction	21% (19/89)	21% (9/43)	1	19% (9/48)	41% (14/34)	0.045
Tumor diameter \geq 55 mm	42% (39/92)	57% (31/54)	0.089	44% (21/48)	59% (20/34)	0.364
Histological type Well, Mod	95% (100/105)	85% (51/60)	0.090	89% (40/45)	87% (28/32)	1
Poorly, Muc	5% (5/105)	15% (9/60)		11% (5/45)	13% (4/32)	
H3	28% (31/109)	17% (10/60)	0.095	27% (13/48)	24% (8/34)	0.801
P2-3	18% (19/107)	30% (18/61)	0.085	21% (10/48)	21% (7/34)	1
M1b	32% (36/111)	31% (19/61)	1	45% (21/47)	38% (13/34)	0.795
Curability B	9% (10/112)	7% (4/61)	0.356	21% (10/48)	24% (8/34)	0.897
C	91% (102/112)	93% (57/61)		79% (38/48)	76% (26/34)	
Chemotherapy	72% (81/112)	62% (38/61)	0.229	70% (33/47)	44% (15/34)	0.023

Well: well-differentiated adenocarcinoma; Mod: moderately-differentiated adenocarcinoma; Poorly: poorly-differentiated adenocarcinoma; M1b: multi-organ metastasis (M1a, single organ metastasis)

Curability B: no evidence of residual tumor but not evaluable

Curability C: definite residual tumor

formed. Patients were stratified into different treatment eras, before and after the introduction of multidrug combination chemotherapy in 2006 at our hospital. Patients were designated as having been treated during period A (1985-2005) and period B (2006-2013). Of 1035 patients with colon cancer, data on 173 stage IV patients were extracted for inclusion in the period A group; of 412 patients, 82 stage IV patients were included in period B. The left-sided group was defined as the presence of the tumor in the colon between the splenic flexure and the rectosigmoid colon, and right-sided was defined as the presence of the tumor in the colon between the cecum and the transverse colon.

This study was approved by the ethics review board of Kumamoto City Hospital (Ethical Committee Approval No. 519).

Clinical data collection

Clinical information, including age, sex, tumor location, clinicopathological prognostic features, and follow-up, were retrieved from the database of the Department of Surgery, Kumamoto City Hospital.

Definitions

Curability refers to the degree of residual tumor (B, no evidence of residual tumor but not evaluable; C, definite residual tumor). M1 indicates distant metastasis (M1a, single organ metastasis; M1b, multi-organ metastasis). The extent of distant metastasis in the period A group was quantified according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus, 6th edition¹⁴⁾, and in period B group according to the 7th edition¹⁵⁾.

Statistics

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Chi-square or Fisher exact tests were used, when appropriate, to compare clinicopathological features. Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards test was used for univariate and multivariate analyses. In all analyses, statistical significance was set as $p < 0.05$.

We also performed a 1:1 propensity score analyses using a logistic regression model with potential variables, including age, sex, tumor size, histological type and peritoneal dissemination, according to clinical data.

Using nearest-neighbor matching without replacement, propensity scores were matched using a caliper of 0.001.

Results

Patient characteristics

Mean age was lower in the group of patients treated during period A than those treated during period B (65 years vs. 72 years, $p < 0.05$). The proportion of women was 0.5 and 0.6 in patients from periods A and B respectively. The clinicopathological characteristics of the patients are summarized in Table 1. Data from 61 right-sided and 112 left-sided patients from period A and 34 right-sided and 48 left-sided patients from period B were available for analysis. In patients from period B, the frequency of intestinal obstruction

Table 2. Patients' Background after Propensity Score Matching.

	period A (n=78)			period B (n=52)		
	left-sided (39)	right-sided (39)	p	left-sided (26)	right-sided (26)	p
age ≥75y/o	26% (10/39)	26% (10/39)	1	35% (9/26)	35% (9/26)	1
Percentage of women	49% (19/39)	51% (20/39)	1	62% (16/26)	62% (16/26)	1
Intestinal obstruction	27% (8/30)	19% (5/27)	0.677	23% (6/26)	38% (10/26)	0.368
Tumor diameter ≥55 mm	56% (22/39)	54% (21/39)	1	62% (16/26)	62% (16/26)	1
Histological type Well, Mod	95% (37/39)	95% (37/39)	1	96% (25/26)	92% (24/26)	1
	Poorly, Muc	5% (2/39)	5% (2/39)	4% (1/26)	8% (2/26)	
H3	36% (14/39)	18% (7/39)	0.125	35% (9/26)	23% (6/26)	0.541
P2-3	21% (8/39)	21% (8/39)	1	19% (5/26)	19% (5/26)	1
M1b	33% (13/39)	33% (13/39)	1	42% (11/26)	42% (11/26)	1
Curability B	10% (4/39)	5% (2/39)	0.675	19% (5/26)	23% (6/26)	1
	C	90% (35/39)	95% (37/39)	81% (21/26)	77% (20/26)	
Chemotherapy	79% (31/39)	72% (28/39)	0.599	69% (18/26)	50% (13/26)	0.258

Well: well-differentiated adenocarcinoma; Mod: moderately-differentiated adenocarcinoma; Poorly: poorly-differentiated adenocarcinoma; M1b: multi-organ metastasis (M1a, single organ metastasis)

Curability B: no evidence of residual tumor but not evaluable

Curability C: definite residual tumor

was higher in the right-sided than in the left-sided group (41% vs. 19%, $p < 0.05$). Although not reaching significance, the proportion of older female patients (≥ 75 y/o), those with maximal tumor size exceeding 55 mm and histological types such as mucinous adenocarcinoma and poorly differentiated adenocarcinoma tended to be higher in the right-sided group in both period A and B groups. A high degree of peritoneal dissemination (P2-3) in period A tended to be more frequent in the right-sided than in the left-sided group, whereas there was a higher degree of liver metastasis (H3) in period A in the left-sided than in the right-sided group (Table 1).

After propensity score matching, all variables were balanced (Table 2).

K-RAS-screening was performed in 11 of 52 patients in period B. K-RAS wild-type was found in 2 of 4 right-sided patients, and 2 of 7 left-sided patients.

Treatment

There were no differences in the rates of curability between the right- and left-sided patients from either treatment period before or after propensity score-matching (Table 1, 2). In the post-matching data, chemotherapy was administered to 76% of period A patients and 60% of period B patients. Chemotherapy during period A included hepatic arterial infusion and chemoembolization for liver metastasis, fluorouracil-based oral medication, or intravenous fluorouracil plus leukovorin (Table 2). In contrast, mFOL-FOX/CAPOX and bevacizumab were the main chemotherapeutic agents used during period B. Anti-EGFR antibody was administered to 44% of right-sided patients and 29% of left-sided patients. After multidrug combination chemother-

apy, hepatic resection for liver metastasis was performed in 38% of the 8 left-sided M1a patients, and in 33% of the 6 right-sided M1a patients.

Prognosis

The prognostic superiority of left-sided group in the pre-matching data was not recognized in the post-matching data [Figure 1-A(a), B(a), n.s.]. The prognoses of patients receiving chemotherapy in either period were superior to those of patients without chemotherapy [Figure 1-A(b), $p < 0.01$; Figure 1-B(b), $p < 0.01$]. In the left-sided patients, the prognoses of patients receiving chemotherapy in either period were superior to those of patients without chemotherapy [Figure 1-A(c), $p < 0.05$; Figure 1-B(c), $p < 0.01$]. In contrast, this tendency was not seen in the right-sided patients. In patients without chemotherapy, there were no differences between period A or B for either left-sided or right-sided tumors (data not shown). In patients receiving chemotherapy in either period, the prognoses were similar between the left- and the right-sided groups, especially in males [Figure 2-A(e-f), B(e-f), n.s.]. Additionally, superiority of chemotherapy vs. no chemotherapy was seen in women with left-sided tumors in both periods [Figure 2-A(g), $p < 0.01$; B(g), $p < 0.05$], but not in those with right-sided tumors [Figure 2-A(h), B(h), n.s.].

Univariate Cox regression analyses revealed that the following factors were significantly associated with prognoses of patients from period A: liver metastasis, peritoneal dissemination, chemotherapy, and sex. These were limited to M1ab, liver metastasis, peritoneal dissemination and chemotherapy but not sex in period B. Multivariate Cox regression analyses for patients from period A identified liver metastasis

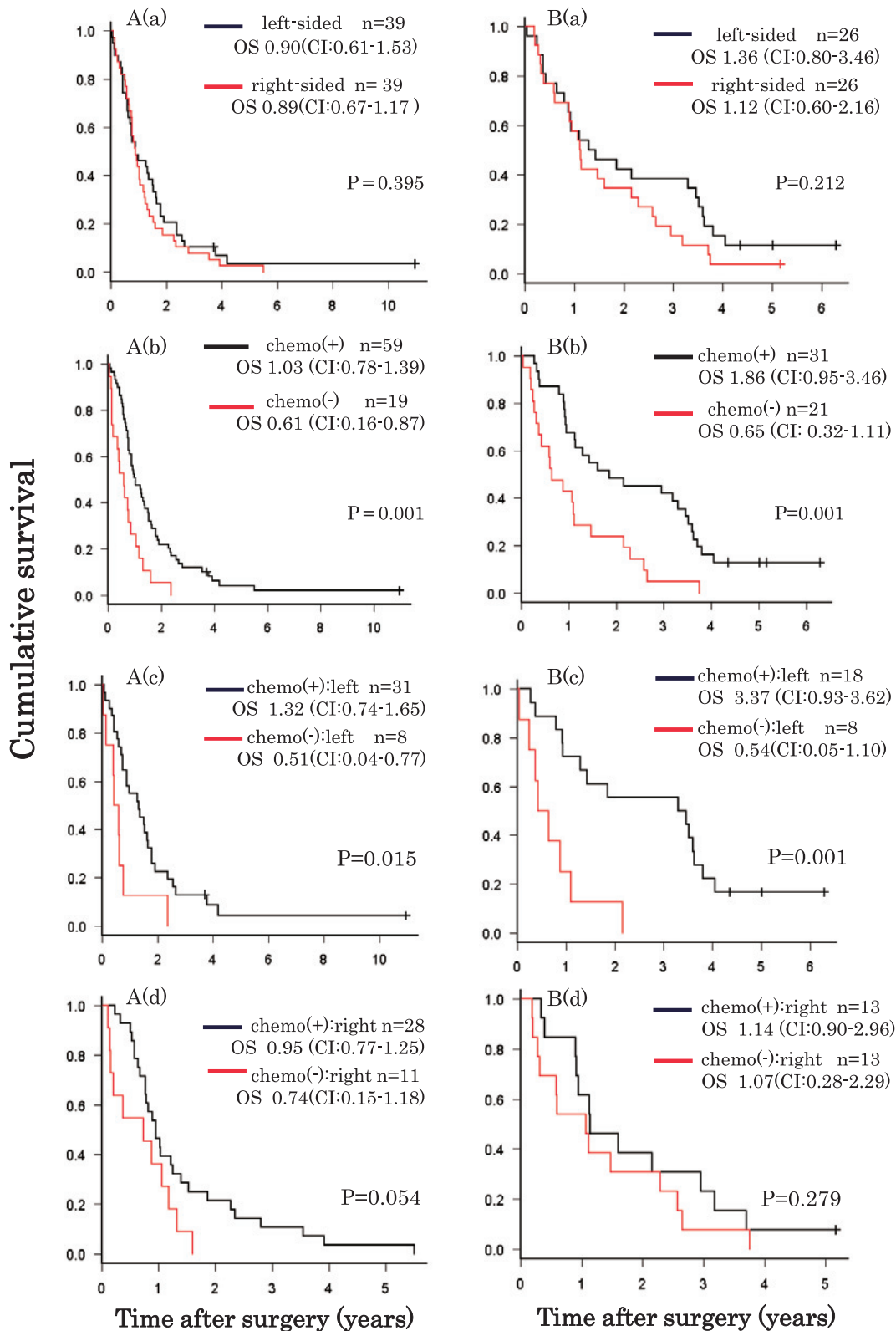


Figure 1. Overall survival of patients dichotomized according to tumor location (left-sided vs. right-sided; a), chemotherapy (+ vs. -; b), chemotherapy for left-sided cases (+ vs. -; c) and chemotherapy for right-sided cases (+ vs. -; d).

sis, peritoneal dissemination and chemotherapy as independent factors, whereas in period B these factors were liver me-

tastasis and chemotherapy only (Table 3).

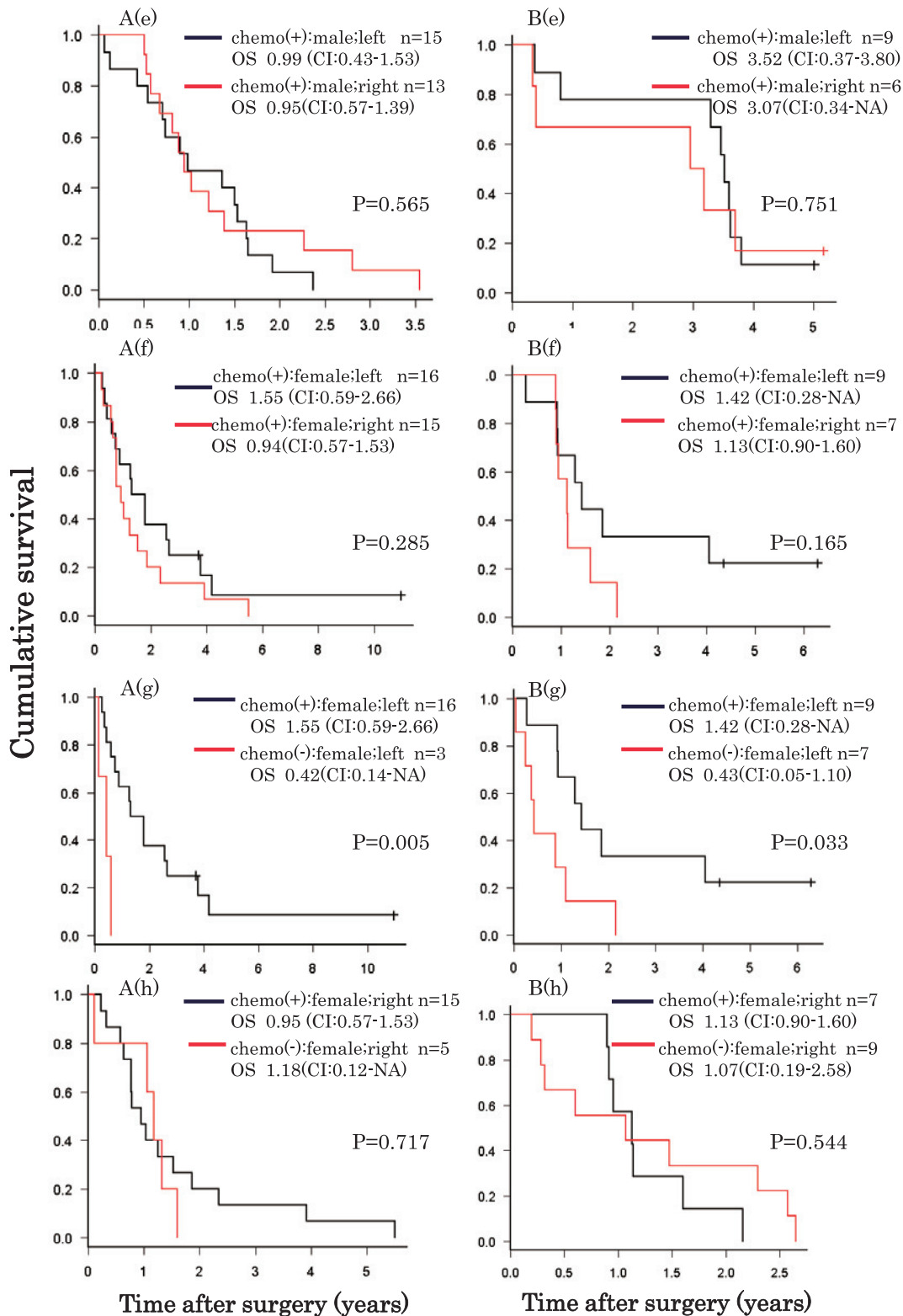


Figure 2. Overall survival of patients dichotomized according to tumor location in males receiving chemotherapy (left-sided vs. right-sided; e), tumor location in females receiving chemotherapy (left-sided vs. right-sided; f), chemotherapy in women with left-sided colon cancer (+ vs. -; g), and chemotherapy in women with right-sided colon cancer (+ vs. -; h). A, period A; B, period B.

Table 3. Univariate and Multivariate Analyses of Clinicopathological Parameters in Relation to Overall Survival.

	period A				period B			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	p	HR (95% CI)	p	HR (95%CI)	p	HR (95% CI)	p
M1ab	1.58 (0.97-2.56)	0.064			3.77 (1.97-7.22)	0.000		
1a vs 1b								
Liver metastasis	1.93 (1.15-3.26)	0.013	1.86 (1.05-3.28)	0.034	2.88 (1.51-5.50)	0.001	4.53 (2.22-9.23)	0.000
H0-2 vs H3								
Peritoneal dissemination	2.29 (1.29-4.04)	0.005	2.31 (1.26-4.24)	0.007	2.14 (1.02-4.46)	0.043		
P0-1 vs P2-3								
Chemotherapy	0.41 (0.24-0.70)	0.001	0.47 (0.27-0.81)	0.007	0.37 (0.20-0.68)	0.001	0.25 (0.13-0.49)	0.000
no vs yes								
Curability	1.76 (0.76-4.08)	0.187			1.48 (0.73-2.97)	0.274		
B vs C								
Tumor location	1.22 (0.77-1.91)	0.396			1.44 (0.81-2.57)	0.214		
lt vs rt								
Age	1.28 (0.76-2.15)	0.362			1.57 (0.86-2.86)	0.141		
<75 vs ≥75								
Sex	1.61 (1.01-2.57)	0.047			0.56 (0.31-1.04)	0.065		
female vs male								

CI: confidence interval; HR: Hazard ratio

Discussion

A relationship between primary tumor location and prognosis has been suggested in colorectal cancer¹. Schrag et al. reported that patients with right-sided stage III and IV colorectal cancer have poorer survival than those with left-sided². Further, Arnold et al. reported that prognosis and chemosensitivity was worse for patients with right-sided RAS wild-type metastatic colorectal cancer³.

According to the latest ESMO guidelines, anti-EGFR antibody treatment is recommended for left-sided, unresectable advanced recurrent colorectal cancer^{5,9}. However, the underlying pathophysiology regarding the significance of primary tumor location in the treatment of colorectal cancer is not clear. It remains necessary to build an evidence base to reveal the relationship between primary tumor sites and prognostic values for clinical outcome. Here we investigated prognostic factors by focusing on tumor site and patient sex over two treatment periods before and after strong multidrug combination chemotherapy became available.

In the present study, we used propensity score matching to minimize potential bias. We found that the left-sided group did not experience better survival than the right-sided group in either period [Figure 1-A(a), B(a), n.s.]. Although the intensity of chemotherapy markedly differed between period A and B, the prognoses of patients receiving chemotherapy vs. no chemotherapy was better for patients in either period [Figure 1-A(b), p < 0.01; Figure 1-B(b), p < 0.01]. In the left-sided patients, the prognoses of patients receiving chemotherapy in either period was superior to those of pa-

tients without chemotherapy [Figure 1-A(c), p < 0.05; Figure 1-B(c), p < 0.01], but the same tendency was not found in the right-sided patients. Similarly, an advantage of chemotherapy was seen in women with left-sided tumors in either of the two periods [Figure 2-A(g), p < 0.01; B(g), p < 0.05], but not in women with right-sided tumors from either period [Figure 2-A(h), B(h), n.s.]. The difference in chemosensitivity depending on tumor site seems to be more pronounced in women than in men in all the analyses [Figure 2-A(e-f), B(e-f)].

Multivariate analysis identified three independent prognostic factors (liver metastasis, peritoneal dissemination, and chemotherapy) in patients from period A and just two of these (liver metastasis and chemotherapy) from period B. Thus, it can be concluded that the location of the primary tumor is not an independent prognostic factor related to chemotherapy and sex.

Salem et al. reported that estrogen receptor positivity is predominant in the right-sided colon, and decreases with age¹⁶. Reduced mismatch repair and the increased microsatellite instability caused by this decrease leads to reduced fluorouracil sensitivity and a reduction in anti-EGFR antibody sensitivity through mutant BRAF^{7,16,17}. It is speculated that in metastatic lesions from the right-sided colon, fluorouracil-based chemotherapy plus anti-EGFR antibody is affected by estrogen, whereas, lesions from the left colon are probably not affected by female sex hormones.

The present study has some limitations, not only due to its retrospective nature and single-center data but also the small number of patients, thereby not allowing a comparison

before and after menopause and not being able to consider K-RAS status.

In conclusion, primary tumor location does not seem to be an independent prognostic factor in patients with stage IV colon cancer, but does seem to be a modifier of chemotherapeutic efficacy.

Conflicts of Interest

There are no conflicts of interest.

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