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Clinical Impact of Primary Tumor Site in Stage IV Colorectal Cancer: A Statewide Cohort Study

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Abstract. *Background/Aim: We investigated the clinical impact of the primary tumor site in stage IV colorectal cancer (CRC). Patients and Methods: In this statewide multicenter retrospective cohort, patients with stage IV CRC from nine hospital-based cancer registries across the Fukushima Prefecture (2008-2015) were categorized based on three primary tumor sites: right colon cancer (RCC), left colon cancer (LCC), and rectal cancer. Overall survival was assessed using Cox regression analysis. Results: A total of 1,211 patients were included. The most common clinical symptom was obstruction in LCC and bleeding in rectal cancer. Liver metastases were multiple and larger in LCC, while lung metastases were multiple in rectal cancer. Compared to LCC, the adjusted hazard ratio (HR) for overall survival was 1.19 [95% confidence interval (CI)=1.01-1.39, p=0.032] in RCC and 1.03 (95% CI=0.86-1.23, p=0.77) in rectal cancer. Conclusion: RCC was independently associated with a worse prognosis in stage IV CRC.*

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Key Words: Primary tumor site, colorectal neoplasms, population-based study, observational study, survival analysis.

Colorectal cancer (CRC) is one of the most common cancers worldwide (1, 2). Twenty percent of CRC patients have metastatic lesions at initial diagnosis (3) and one-third will eventually develop metastasis (4). Although metastatic CRC remains lethal, the prognosis of patients with metastatic CRC has been improving due to recent advances in multidisciplinary therapy (5). Since treatment strategies are based on their expected survival time in individuals, the identification of prognostic factors is relevant. The primary tumor site is considered one of the most important prognostic factors.

Some previous reports have shown that patient or tumor characteristics depend on the primary tumor site. Epidemiological and histological differences between primary tumor sites have been observed, including age, gender, and degree of differentiation (6). Secondly, many biological differences exist between primary tumor sites, including differing embryological origins, distinct site-associated microbiota, and differential gene expression and methylation statuses (7, 8). Thirdly, recent studies have reported that patients with right colon cancer (RCC) show a worse prognosis than those with left colon cancer (LCC) in systemic chemotherapy (9, 10).

However, previous studies that included many patients with metachronous metastatic CRC lack the perspectives of

patient clinical symptoms from the primary tumor and the metastatic pattern, including severity (11, 12). Treatment of synchronous metastatic CRC, stage IV CRC, is more complex than metachronous metastatic CRC, because clinicians have to consider the impact of not only metastatic site but also the primary tumor and metastatic pattern for their treatment strategy. Furthermore, patients who have severe metastases and clinical symptoms from the primary tumor, such as obstruction, bleeding, or perforation, could be excluded from previous studies. Herein, we focused on patients with stage IV CRC and conducted this study to investigate the impact of the primary tumor site for survival outcomes, metastatic pattern, and clinical symptoms from the primary tumor in a statewide multicenter cohort study.

Patients and Methods

Study design and cohort development. All nine designated cancer hospitals across the Fukushima Prefecture participated in this statewide multicenter retrospective cohort study. First, we extracted data on patients with stage IV CRC, defined based on the International Classification of Diseases for Oncology, Third Edition (ICD-O3) topographical codes: C18.0, C18.2-C18.9, C19.9, C20.9, from each hospital-based cancer registry. Second, we extracted data on patient clinical and demographic characteristics, including Charlson comorbidity index (CCI), clinical symptoms from the primary tumor, clinical Tumor-Node-Metastases (cTNM) stage, Barthel index [as a measure of activities of daily life (ADL)], and treatment type from medical records and administrative data. Two gastrointestinal surgeons (MH and HK) who were blinded to the survival outcome reviewed medical records and computed tomography images before initial treatment in this cohort and diagnosed cTNM, metastatic pattern, and clinical symptoms from the primary tumor. Anonymized datasets acquired from individual hospitals were merged into a single dataset. At this stage, eligible patients were selected for participation.

The inclusion criteria were as follows: consecutive adult patients (≥18 years old) with histologically confirmed colorectal adenocarcinoma, clinically or intraoperatively diagnosed with stage IV CRC between 2008 and 2015. Patients were excluded if they lacked data on the primary tumor site or treatment type.

Primary tumor site. Three investigators reviewed medical records of all included patients and identified the primary tumor site. The primary tumor site in CRC was classified as follows: RCC (tumor located in the cecum, ascending colon, hepatic flexure, or transverse colon), LCC (tumor located within the splenic flexure, descending colon, sigmoid colon, or rectosigmoid junction), or rectal cancer.

Outcomes. The primary endpoint for each primary site was overall survival (OS), calculated as the number of days from the date of stage IV CRC diagnosis until death, loss to follow-up, or alive by December 31, 2017. Patients who had not experienced any events of interest were censored at the last follow-up date. Secondary outcomes included clinical symptoms from the primary tumor and metastatic pattern. Clinical symptoms from the primary tumor were classified into three categories (bleeding, obstruction, or perforation). Bleeding was defined as anemia requiring a transfusion or bleeding requiring medical intervention. Obstruction was defined as cases in which the colonoscope did not pass through the primary lesion and obstruction symptoms (fullness, nausea, or vomiting) were present. Based on the Japanese Classification of Colorectal Carcinoma, we distinguished the following types of metastases: liver metastases [H1, ≤5 hepatic tumors (HT) and HT size ≤5 cm; H2, ≥5 HT or HT size ≥5 cm; and H3, ≥5 HT and HT size ≥5 cm], and pulmonary metastases [PUL1, <3 lung tumors (LT) in one lung or two LTs in both lungs; PUL2, ≥3 LTs in both lungs, carcinomatous pleurisy, or mediastinum lymph node metastasis] (13). Additionally, we described the remaining metastatic patterns as follows: peritoneal dissemination (presence or absence), non-regional lymph node metastasis (presence or absence), other organ metastasis: bone, brain, ovary, and other (presence or absence); and number of metastatic organs (1, 2, or ≥3).

Covariates. Several demographic and clinical variables were included in the analysis, such as sex, age at diagnosis (<75 and ≥75 years), and degree of tumor differentiation (high and low). The CCI was used to measure patients' comorbidities at first admission for CRC-related hospitalization; the results were classified into binary variables based on CCI scores (0-2 and ≥3) (14). The Barthel index was used to measure patient ADL on admission and discharge from the first hospitalization. This index uses a scale from 0 to 100 points; the scores were categorized into binary variables (100-61 and 60-0) for analysis (15). Depth of tumor invasion (T-factor) was classified into binary variables (T1/T2/T3 and T4), as was regional lymph node metastasis (N-factor; N0, and N1, N2).

Statistical analyses. Patient characteristics were reported as descriptive statistics, with continuous variables expressed as median and range or interquartile range (IQR), and categorical variables expressed as counts and percentages. Univariate analyses were used to compare patient characteristics among the three primary site groups. Binary variables were compared using the Chi-squared test. Categorical variables with multiple outcomes and continuous variables were compared using the Kruskal–Wallis test.

We described the missing values and applied multiple imputation by a chained equation, which created 20 multiple imputed datasets. The estimates were based on combined results from multiple imputed datasets using Rubin's rule to compensate for missing values (16). In the same way with sensitivity analysis, we applied a complete case analysis.

Survival analysis was performed using the Kaplan–Meier method, and survival estimates were compared using the log-rank test. The association between the primary site and OS was analyzed using Cox proportional hazards regression models for all-cause mortality, adjusted for confounding and prognostic factors (age at diagnosis, sex, CCI, Barthel index, obstruction, bleeding, perforation, degree of tumor differentiation, T-stage, N-stage, liver metastases, lung metastases, peritoneal dissemination, non-regional lymph node metastases, other organ metastases, and number of metastatic organs). Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. All significance tests were 2-sided, and *p*-values <0.05 were considered statistically significant. Statistical analyses were performed using STATA version 16.0 software (STATA Corporation, College Station, TX, USA).

Ethics statements. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of all participating hospitals (UMIN000033718). Informed

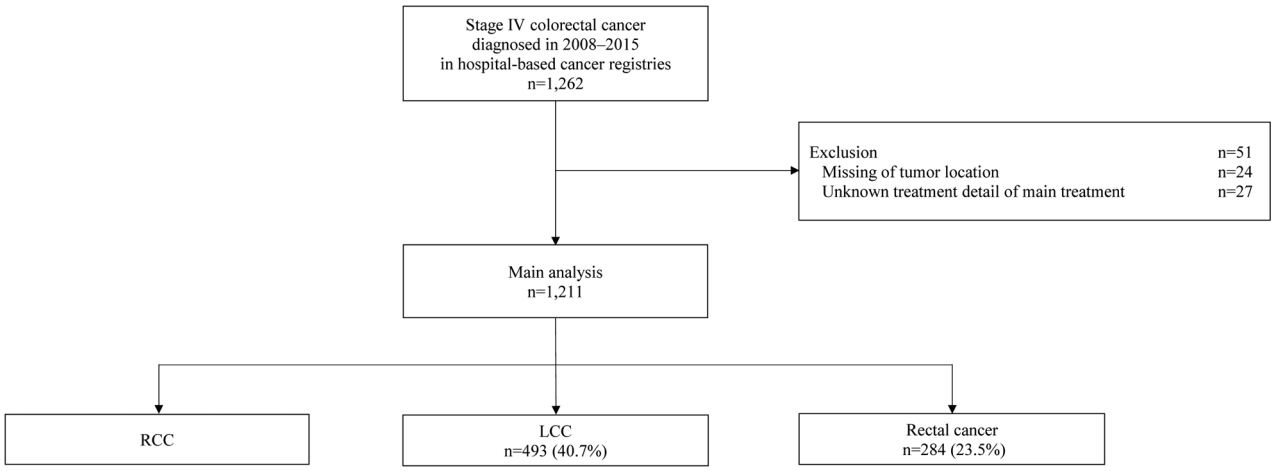

Figure 1. *Overview of patient selection. RCC, Right colon cancer; LCC, left colon cancer.*

consent was waived in accordance with the Japanese government's Ethical Guidelines for Medical and Health Research Involving Human Subjects, which allow an opt-out approach.

Results

We identified 1,211 patients diagnosed with stage IV CRC between 2008 and 2015 (Figure 1). Among them, there were 434 (35.8%) patients with RCC, 493 (40.7%) with LCC, and 284 (23.5%) with rectal cancer. The median follow-up time was 17.8 (0-116.1) months; 900 (74.3%) patients died during the study period. Patient demographics and clinical characteristics are summarized in Table I. Regarding the primary tumor treatment, 839 patients (69.3%) underwent primary tumor resection, 159 (13.1%) underwent palliative surgery, and 213 (17.6%) did not receive any treatment. Regarding treatment of metastatic organs, 697 patients (57.6%) received systemic chemotherapy, 218 (18.0%) underwent metastasectomy, and 296 (24.4%) received systemic chemotherapy as main treatment for the metastatic organs.

Clinical symptoms from primary tumor. Table II shows symptoms from the primary tumor. The percentage of patients with obstruction in the LCC group [n=299 (60.6%), $p<0.001$] was higher than in the RCC group [n=210 (48.4%)] or rectal cancer group [n=144 (50.7%)]. A higher percentage of patients had bleeding in the rectal cancer group [n=50 (17.6%), $p<0.001$] than in the RCC group [n=37 (8.5%)] or LCC group [n=44 (8.9%)]. The frequency of perforation was not significantly different [RCC: n=14 (3.2%), LCC: n=19 (3.9%), and rectal cancer: n=10 (3.5%), $p=0.88$].

Metastatic pattern and severity. Table III shows the metastatic pattern and severity. The severity in liver metastases was significantly different ($p<0.001$) between the primary tumor sites. Patients with LCC [n=121 (24.5%)] had more frequent and severe liver metastases (H3) than patients with RCC [n=75 (17.3%)] and patients with rectal cancer [n=60 (21.1%), $p<0.001$]. Regarding lung metastases, patients with rectal cancer [n=75 (26.4%)] had more frequent and severe metastases (PUL2) than patients with RCC [n=66 (15.2%)] and LCC [n=82 (16.6%)]. The highest percentage of patients had peritoneal dissemination in RCC group ($p<0.001$).

Adjusted HRs and OS curves. OS analysis for all patients was performed using the Kaplan–Meier method (Figure 2a). The median OS for RCC, LCC, and rectal cancer was 17.1 (IQR=6.3-36.6), 22.7 (IQR=9.6-42.3), and 23.6 (IQR=10.1-48.1) months, respectively ($p=0.011$). Additionally, OS analysis for each treatment was performed similarly (Figure 2b, c, and d). However, there were no statistically significant differences.

Compared to LCC, the adjusted HR for OS was 1.19 (95% CI=1.01-1.39, $p=0.032$) in RCC and 1.03 (95% CI=0.86-1.23, $p=0.77$) in rectal cancer, indicating a significant poorer OS for RCC than LCC (Table IV). Regarding clinical symptoms from the primary tumor, only obstruction was a statistically poorer prognostic factor on univariate analysis, but no clinical symptoms from the primary tumor were statistically significant in the multivariate analysis. However, regarding metastatic pattern and severity, liver metastasis, peritoneal dissemination, and other organ metastases were independent poorer prognostic factors. Sensitivity analysis with complete data revealed similar results for the comparison between LCC and RCC (HR=1.20, 95% CI=1.01-1.43, $p=0.042$) and between LCC and rectal cancer (HR=1.04, 95% CI=0.84-1.28, $p=0.75$).

Figure 3 shows adjusted HRs for OS from the subgroup analysis performed on treatment for metastatic organs. Compared to LCC, the adjusted HR for OS was 1.24 (95%

Table I. *Patients characteristics*.

	RCC (n=434)	LCC (n=493)	Rectal cancer (n=284)
Age in years, median (range)	72 (28-97)	67 (23-95)	66 (34-89)
Gender, n (%)			
Male	204 (47.0)	345 (70.0)	194 (68.3)
Female	230 (53.0)	148 (30.0)	90 (31.7)
CCI, n (%)			
0	221 (50.9)	256 (51.9)	165 (58.1)
1, 2	164 (37.8)	191 (38.7)	93 (32.7)
≥3	49 (11.3)	46 (9.3)	26 (9.2)
Barthel index, n (%)			
100	298 (68.7)	320 (64.9)	175 (61.6)
99-91	0 (0.0)	8 (1.6)	4 (1.4)
90-61	32 (7.4)	35 (7.1)	17 (6.0)
60-21	29 (6.7)	36 (7.3)	14 (4.9)
20-0	27 (6.2)	31 (6.3)	21 (7.4)
Unknown	48 (11.1)	63 (12.8)	53 (18.7)
Differentiation, n (%)			
High	340 (78.3)	435 (88.2)	242 (85.2)
Low	67 (15.4)	29 (5.9)	21 (7.4)
Unknown	27 (6.2)	29 (5.9)	21 (7.4)
T-stage, n (%)			
T1-T2	11 (2.5)	13 (2.6)	13 (4.6)
T3	114 (26.3)	131 (26.6)	124 (43.7)
T4a	226 (52.1)	252 (51.1)	83 (29.2)
T4b	83 (19.1)	97 (19.7)	64 (22.5)
N-stage, n (%)			
N0	64 (14.7)	89 (18.1)	30 (10.6)
N1	153 (35.3)	170 (34.5)	85 (29.9)
N2	217 (50.0)	234 (47.5)	169 (59.5)
Main treatment for metastatic organs, n (%)			
Metastasectomy	67(15.4)	103 (20.9)	48 (16.9)
Systemic chemotherapy	247 (56.9)	273 (55.4)	177 (62.3)
No treatment	120 (27.6)	117 (23.7)	59 (20.8)
Treatment for primary tumor, n (%)			
No treatmment	95 (21.9)	74 (15.0)	44 (15.5)
Palliative surgery	37 (8.5)	54 (11.0)	68 (23.9)
Primary tumor resection	302 (69.6)	365 (74.0)	172 (60.6)

RCC, Right colon cancer; LCC, left colon cancer; CCI, Charlson comorbidity index.

CI=0.89-1.73, p=0.21) in RCC and 0.98 (95% CI=0.66-1.45, p=0.93) in rectal cancer, in best supportive care. The adjusted HR was 1.21 (95% CI=0.98-1.49, p=0.077) in RCC and 1.10 (95% CI=0.87-1.38, p=0.43) in rectal cancer in systemic chemotherapy. The adjusted HR was 1.08 (95% CI=0.66-1.77, p=0.75) in RCC and 1.10 (95% CI, 0.50-1.62, p=0.72) in rectal in metastasectomy.

Discussion

This study showed that the OS of patients with RCC was poorer than that of patients with LCC when adjusted for

Table II. *Clinical symptoms from primary tumor.*

	RCC (n=434)	LCC (n=493)	Rectal cancer (n=284)	*p*-Value
Obstruction, n (%)				
Presence	210 (48.4)	299 (60.6)	144 (50.7)	<0.001
Absence	224 (51.6)	194 (39.4)	140 (49.3)	
Bleeding, n (%)				
Presence	37 (8.5)	44 (8.9)	50 (17.6)	<0.001
Absence	397 (91.5)	449 (91.1)	234 (82.4)	
Perforation, n (%)				
Presence	14 (3.2)	19 (3.9)	10 (3.5)	0.88
Absence	420 (96.8)	474 (96.1)	274 (96.5)	

RCC, Right colon cancer; LCC, left colon cancer.

Table III. *Metastatic pattern and severity.*

	RCC (n=434)	LCC (n=493)	Rectal cancer (n=284)	*p*-Value
Liver metastasis, n (%)				
H0	156 (35.9)	117 (23.7)	94 (33.1)	<0.001
H1	113 (26.0)	130 (26.4)	72 (25.4)	
H2	90 (20.7)	125 (25.4)	58 (20.4)	
H3	75 (17.3)	121 (24.5)	60 (21.1)	
Lung metastasis, n (%)				
PUL0	343 (79.0)	378 (76.7)	168 (59.2)	<0.001
PUL1	25 (5.8)	33 (6.7)	41 (14.4)	
PUL2	66 (15.2)	82 (16.6)	75 (26.4)	
Peritoneal dissemination, n (%)				
Absence	271 (62.4)	355 (72.0)	240 (84.5)	<0.001
Presence	163 (37.6)	138 (28.0)	44 (15.5)	
Non-regional lymph node metasitasis, n (%)				
Absence	326 (75.1)	375 (76.1)	209 (73.6)	0.74
Presence	108 (24.9)	118 (23.9)	75 (26.4)	
Other organ metasitasis, n (%)				
Absence	407 (93.8)	451 (91.5)	260 (91.5)	0.36
Presence	27 (6.2)	42 (8.5)	24 (8.5)	
Number of metastatic organ, n (%)				
1	272 (62.7)	297 (60.2)	166 (58.5)	0.36
2	112 (25.8)	124 (25.2)	74 (26.1)	
≥3	50 (11.5)	72 (14.6)	44 (15.5)	

RCC, Right colon cancer; LCC, left colon cancer. H1: ≤5 hepatic tumours (HT) and HT size ≤5 cm; H2: ≥5 HT or HT size ≥5 cm; H3; ≥5 HT and HT size ≥5. PUL1: <3 lung tumours (LT) in one lung, or two LTs in both lungs; PUL2: ≥3 LTs in both lungs, carcinomatous pleurisy, or mediastinum lymph node metastasis.

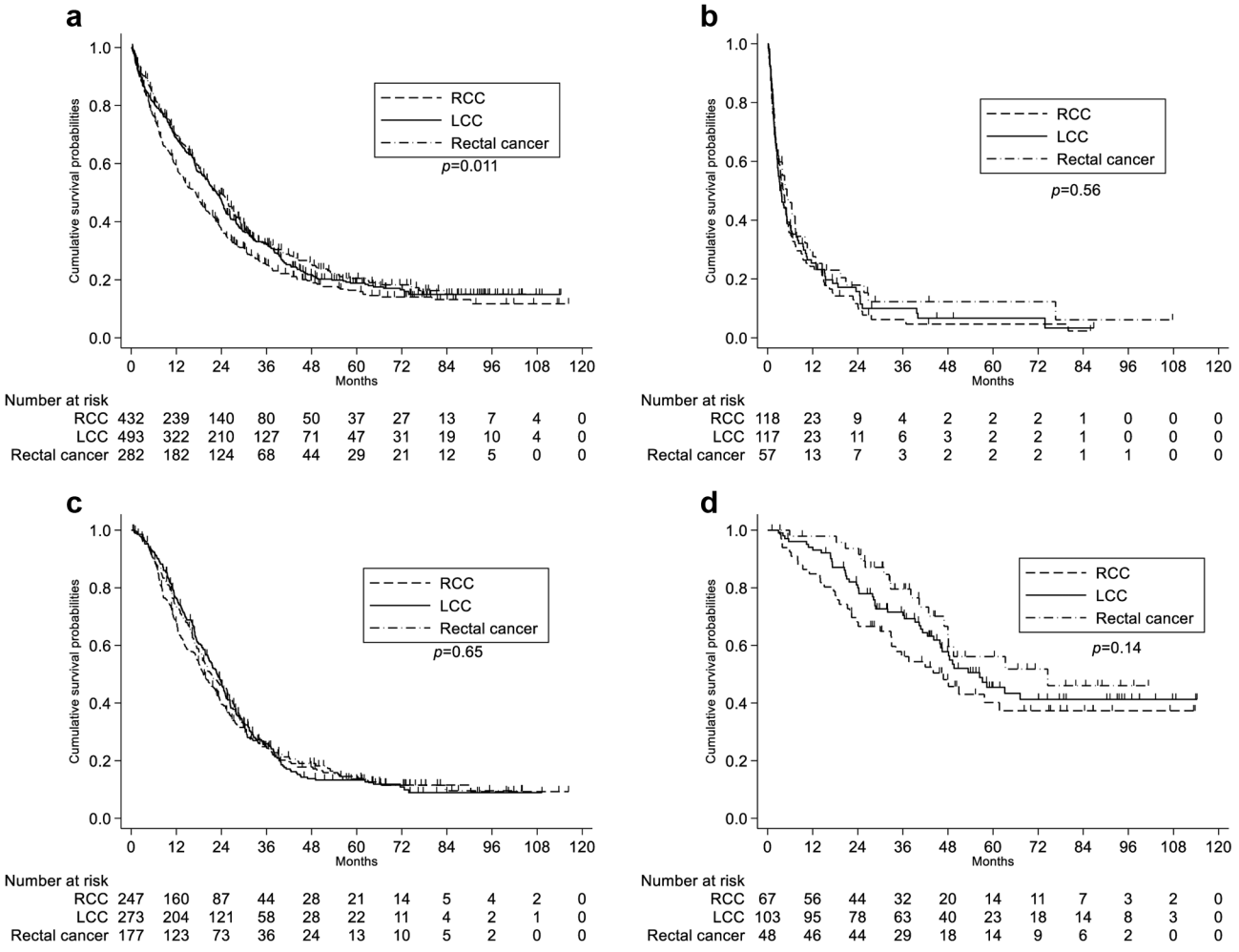

Figure 2. *Overall survival according to primary tumor site. (a) All patients. (b) Patients with best supportive care. (c) Patients with systemic chemotherapy. (d) Patients with metastasectomy. RCC, Right colon cancer; LCC, left colon cancer.*

clinical symptoms from the primary tumor and metastatic pattern in stage IV CRC. Moreover, the incidence of peritoneal dissemination was relatively higher in patients with RCC; in contrast, liver metastasis was common and multiple and larger in LCC, while lung metastasis was common and multiple in rectal cancer. Next, the most common clinical symptom from the primary tumor was obstruction in LCC and bleeding in rectal cancer. Finally, no clinical symptoms were statistically significant, but metastatic patterns were independently poorer prognostic factors for OS. These results demonstrate that RCC, LCC, and rectal cancer should be regarded as separate entities.

Patients with RCC had a significantly worse OS than those with LCC. Additionally, the subgroup analysis for each treatment had shown the similar tendencies, though statistically significant. This result is consistent with previous reports, thus suggesting a prognostic impact of the primary tumor site in mCRC (11, 17, 18). Our study was limited to only stage IV CRC, because the characteristics of stage IV CRC were different from metachronous mCRC (19).

The reason for the differences in survival according to the primary tumor sites is due to several factors. Some reports have questioned if the delayed diagnosis for RCC could result in more extensive metastatic disease at diagnosis, which could explain the poorer survival in RCC in stage IV CRC (11, 20, 21). To date, few reports have considered clinical symptoms in patients with CRC. Saidai *et al*. reported that both obstruction and bleeding are common in rectal cancer (22). Chen *et al*. reported that 11% of patients with stage IV CRC present with either obstruction or perforation of the primary cancer and require urgent surgical treatment (23). Their report has certain limitations, including

Table IV. *Hazard ratios of all-cause mortality using Cox proportional hazards regression models with multiple imputation.*

	Unadjusted			Adjusted		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Primary site						
LCC	(Reference)			(Reference)		
RCC	1.20	(1.03-1.39)	0.016	1.19	(1.01-1.39)	0.032
Rectal cancer	0.95	(0.80-1.12)	0.53	1.03	(0.86-1.23)	0.77
Age						
<75	(Reference)			(Reference)		
≥75	1.55	(1.35-1.78)	<0.001	1.67	(1.44-1.94)	<0.001
Gender						
Male	(Reference)			(Reference)		
Female	1.12	(0.98-1.28)	0.094	1.01	(0.88-1.17)	0.87
CCI						
0. 1. 2	(Reference)			(Reference)		
≥3	1.13	(1.03-1.24)	0.009	1.07	(0.97-1.18)	0.18
Barthel index						
100-61	(Reference)			(Reference)		
60-0	1.79	(1.47-2.18)	<0.001	1.68	(1.37-2.07)	<0.001
Differentiation						
High	(Reference)			(Reference)		
Low	1.58	(1.28-1.97)	<0.001	1.46	(1.15-1.84)	0.002
T-stage						
1. 2, 3	(Reference)			(Reference)		
4	1.40	(1.21-1.61)	<0.001	1.20	(1.03-1.41)	0.019
N-stage						
0	(Reference)			(Reference)		
1. 2	1.49	(1.30-1.70)	<0.001	1.27	(1.09-1.47)	0.002
Obstruction						
Absence	(Reference)			(Reference)		
Presence	1.21	(1.06-1.38)	0.005	1.11	(0.97-1.28)	0.14
Bleeding						
Absence	(Reference)			(Reference)		
Presence	0.93	(0.75-1.15)	0.51	0.84	(0.67-1.05)	0.13
Perforation						
Absence	(Reference)			(Reference)		
Presence	1.28	(0.90-1.83)	0.17	1.04	(0.71-1.50)	0.85
Liver metastasis						
H0	(Reference)			(Reference)		
H1	0.76	(0.63-0.92)	0.004	0.87	(0.66-1.15)	0.32
H2	1.51	(1.26-1.81)	<0.001	1.76	(1.33-2.33)	<0.001
H3	2,08	(1.73-2.50)	<0.001	2,37	(1.79-3.14)	<0.001
Lung metastasis						
PUL0	(Reference)			(Reference)		
PUL1	0.87	(0.67-1.12)	0.27	0.85	(0.61-1.18)	0.33
PUL2	1.45	(1.23-1.71)	<0.001	1.22	(0.93-1.60)	0.15
Peritoneal dissemination						
Absence	(Reference)			(Reference)		
Presence	1.45	(1.26-1.68)	<0.001	1.34	(1.05-1.72)	0.021
Non-regional lymph node metastasis						
Absence	(Reference)			(Reference)		
Presence	1.38	(1.19-1.60)	<0.001	1.12	(0.88-1.43)	0.37
Other organ metastasis						
Absence	(Reference)			(Reference)		
Presence	1.57	(1.24-2.00)	<0.001	1.39	(1.01-1.91)	0.044
Number of metastatic organ						
1	(Reference)			(Reference)		
2	1.52	(1.31-1.77)	<0.001	1.15	(0.89-1.49)	0.29
≥3	2,55	(2.11-3.07)	<0.001	1.47	(0.88-2.47)	0.15

RCC, Right colon cancer; LCC, left colon cancer; CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio. H1: ≤5 hepatic tumours (HT) and HT size ≤5 cm; H2: ≥5 HT or HT size ≥5 cm; H3; ≥5 HT and HT size ≥5. PUL1: <3 lung tumours (LT) in one lung, or two LTs in both lungs; PUL2: ≥3 LTs in both lungs, carcinomatous pleurisy, or mediastinum lymph node metastasis.

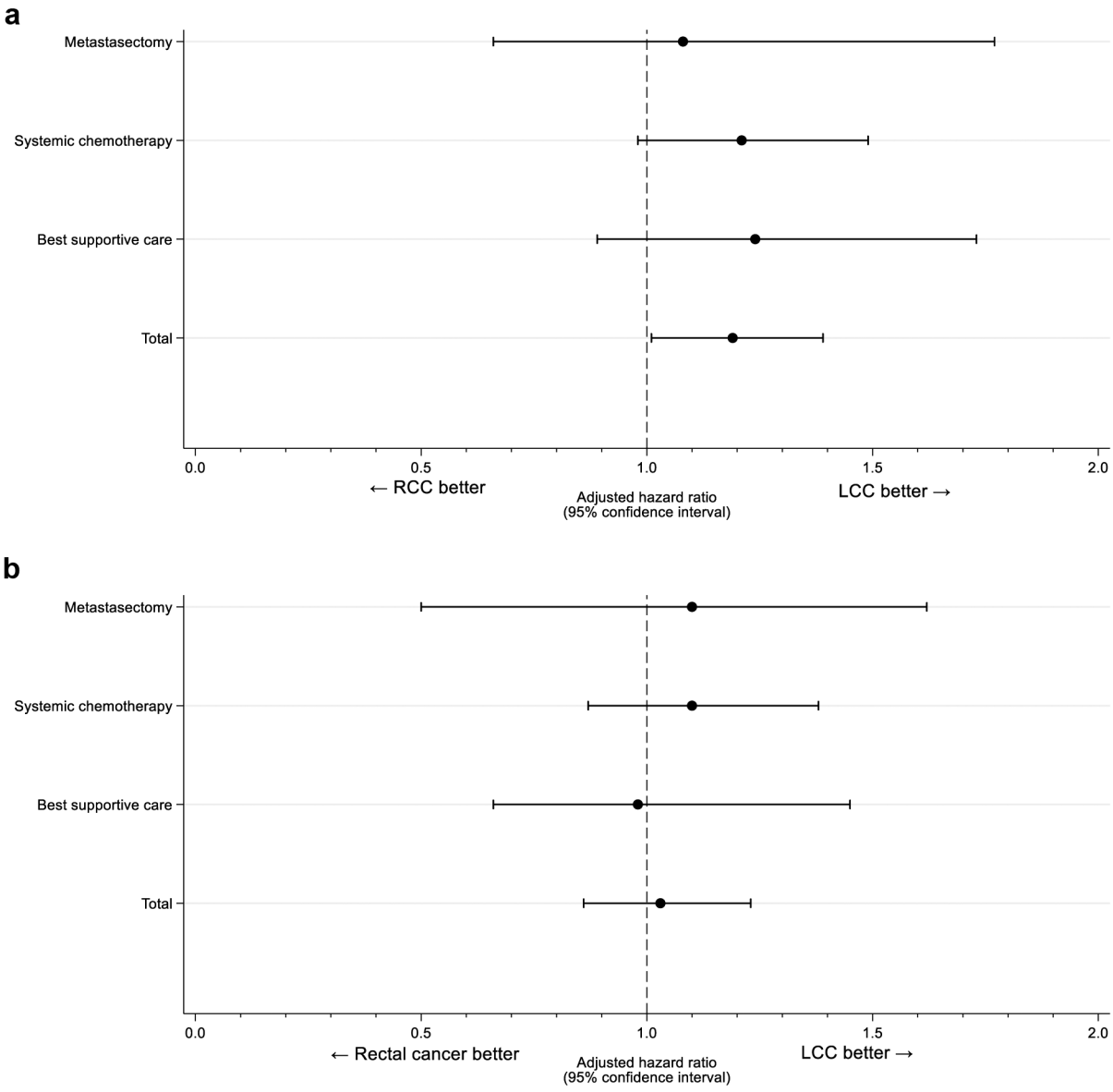

Figure 3. *Adjusted hazard ratio for treatment for metastatic lesions. (a) Right colon cancer vs. left colon cancer. (b) rectal cancer vs. left colon cancer. RCC, Right colon cancer; LCC, left colon cancer.*

that their data is more than 10 years old, resulting in no comprehensive overview of clinical symptoms associated with stage IV CRC. The current report shows the differences of clinical symptoms from the primary tumor between primary tumor sites, which could influence CRC detection. Obstruction was more common in LCC, and bleeding was more common in rectal cancer than RCC. This result is different from a previous report (22). Rectal cancer may present more with bleeding compared to RCC because the rectum is anatomically closer to the anus and has a wider lumen. Multivariate analysis revealed that RCC was independently associated with a relatively worse OS. However, no clinical symptoms from primary tumors were independent prognostic factors.

This study revealed not only the metastatic pattern, but also the severity of liver metastases and lung metastases from primary tumor sites. The incidence of peritoneal dissemination was relatively higher in patients with RCC; in contrast, liver metastasis was more common and severe in LCC, while lung metastasis was more common and severe in rectal cancer. Previous reports have shown that RCC is associated with a higher incidence of peritoneal dissemination

in contrast to LCC and rectal cancer, which have been associated with a higher incidence of liver and lung metastasis (24, 25). Our findings are consistent with these reports. The current study investigated not only dichotomized values (yes or no), but also severity of liver and lung metastases, following the Japanese Classification of Colorectal Carcinoma (13). LCC presented with more severe liver metastases (H3), and rectal cancer presented with more severe lung metastases (PUL2). Additionally, severity of liver metastases was an independent prognostic factor. This finding might occur because the severity of liver metastases differed between primary tumors and was an important prognostic factor. A previous study showed that RCC had a higher number of liver metastases and more liver segments at diagnosis (26); however, in the current study, LCC had more severe liver metastases than RCC. This result could support a particular type of biological aggressiveness. Severity of lung metastasis was not an independent prognostic factor. Lung metastases can grow slowly and have been associated with a better overall prognosis (27).

This study adds new information on the significance of the primary tumor site in stage IV CRC, adjusted for clinical symptoms from the primary tumor and metastatic severity, which are influenced by delayed diagnosis of stage IV CRC, and support the hypothesis that RCC might be associated with a particular type of biological aggressiveness. RCC is characterized by a high frequency of microsatellite instability (MSI) and *BRAF* mutation (8). *BRAF* mutation has been associated with a poor prognosis, and MSI has also been associated with a poorer prognosis in patients with mCRC and *BRAF* mutation (6, 7, 28).

To our knowledge, this is the first statewide multicenter cohort study to report clinical characteristics, symptoms, and metastatic patterns and severities in patients with RCC, LCC, and rectal cancer in stage IV CRC, and assess the impact of the primary tumor site on prognosis, adjusted for relevant covariates. Primary tumor site could be a prognostic factor, regardless of the delay in diagnosis which could result in more extensive metastatic disease at diagnosis. Previous studies based on cancer registries did not include data on comorbidities, ADL, clinical symptoms, T-factor, N-factor, or metastatic pattern (11, 25), whereas we were able to include these data and cross-validate them with imaging findings. Further, our dataset included all patients with stage IV CRC, regardless of treatment status, as we extracted relevant data from nine cancer hospitals across the Fukushima prefecture to minimize selection bias. Additionally, we stratified our sample by severity of liver and lung metastases, which are common metastatic sites (29), based on the Japanese Classification of Colorectal Carcinoma (13).

This study has certain limitations. Firstly, although patients were enrolled from 2008 to 2015, treatment strategies, including intensive chemotherapeutic regimens and molecular analysis (*RAS* and *BRAF* mutation and MSI), have changed significantly. Thus, our study may not be fully reflective of current medical practice. Secondly, some data on ADL (13.5%) and degree of differentiation (6.4%) were missing. We described the missing values and applied multiple imputation methods to compensate for them. We applied a complete case analysis for sensitivity analysis. Findings of the main and sensitivity analyses were similar. Finally, the sample size of the study could be insufficient. Therefore, subgroup analysis for each treatment may not have shown a statistical difference between tumor locations.

In conclusion, RCC is an independent factor associated with a relatively poor prognosis among patients with stage IV CRC, compared to LCC, after adjusting for clinical symptoms and metastatic pattern. Moreover, LCC was associated with higher risk of obstruction and multiple and larger lever metastases, and rectal cancer was associated with bleeding and multiple lung metastasis. These findings suggest that the primary tumor site may be useful for predicting the prognosis of patients with stage IV CRC in diagnosis.

Conflicts of Interest

The Authors declare that there are no conflicts of interest.

Authors' Contributions

H.K. analyzed and interpreted the data and was a major contributor in writing the manuscript. H.M., K.T., T.K., K. S., A.M, S.S., N.Y., T.I., S.S., K.K. Obtained and interpreted the data. S.K. interpreted the data. All Authors have read and approved the final manuscript.

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