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ORIGINAL ARTICLE – COLORECTAL CANCER

Prognostic Value of Primary Tumor Sidedness for Unresectable Stage IV Colorectal Cancer: A Retrospective Study

Dai Shida, MD, PhD[1], Taro Tanabe, MD[1], Narikazu Boku, MD, PhD[2], Atsuo Takashima, MD[2], Takefumi Yoshida, MD, PhD[1], Shunsuke Tsukamoto, MD, PhD[1], and Yukihide Kanemitsu, MD[1]

[1]Department of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan; [2]Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan

ABSTRACT

Background. When treated with molecular targeted agents, patients with unresectable colorectal cancer with right-sided tumors have poorer prognoses than those with left-sided tumors. While primary tumor sidedness may have prognostic value, the prognostic value of tumor sidedness in chemotherapy regimens without targeted therapy is unclear.

Methods. Our study population comprised 678 consecutive patients with unresectable stage IV colorectal cancer who received systemic chemotherapy at the National Cancer Center Hospital in Japan from 1999 to 2015. Patients were stratified by treatment subgroup (with or without molecular targeted agents and with or without palliative primary tumor resection), and relationships between overall survival (OS) and primary tumor sidedness were evaluated. Multivariate analyses were also performed.

Results. Overall, 193 (28%) tumors were right-sided (cecum to transverse colon) and 485 (72%) were left-sided (splenic flexure to rectum). In the overall population, median survival time was 16.4 months for those with right-sided tumors and 23.4 months for those with left-sided tumors ($p < 0.01$). Regardless of the use or non-use of targeted agents and performance or non-performance of palliative resection of the primary tumor, those with right-sided tumors showed significantly poorer prognosis than those with left-sided tumors, in all categories. Multivariate analyses showed right-sided tumors to be associated with shorter OS compared with left-sided tumors (hazard ratio 1.26, 95% confidence interval 1.03–1.53; p =0.024).

Conclusion. Unresectable stage IV right-sided colorectal tumors were associated with shorter OS compared with left-sided tumors, regardless of treatment strategy. Primary tumor sidedness may be an independent prognostic factor.

In the interests of precision medicine and individualized patient care, the TNM classification (8th edition)[1] newly described several prognostic factors for survival in patients with colorectal cancer. In addition to anatomic extent of disease (TNM categories), age, race, screening program, vascular/lymphatic invasion, perineural invasion, grade, tumor budding, KRAS, and BRAF were indicated as prognostic factors of colorectal cancer. For example, activation of the KRAS gene is a modestly poor prognostic factor in stage III and IV disease[2,3] and the BRAF V600E mutation is associated with a significantly poor prognosis.[4] Prognostic models play an important role in clinical care since treatment strategies can be optimized based on outcome risks in individual patients. Moreover, due to disease heterogeneity, prognostic models play a critical role in the design, conduct, and analysis of clinical trials in oncology; thus, there is great interest in identifying prognostic factors.

Many biological differences exist between the right- and left-sided colons, including differing embryologic origins, distinct site-associated microbiota, and differential gene expression and methylation.[5] Recent studies have reported on the prognostic value of primary tumor sidedness. For instance, pooled analyses of several randomized trials that

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D. Shida, MD, PhD
e-mail: dshida-tky@umin.ac.jp

assessed the prognostic influence of primary tumor location in patients with unresectable colorectal cancer treated with molecular targeted agents (e.g. vascular endothelial growth factor-targeted antibody [bevacizumab] and epidermal growth factor receptor (EGFR)-targeted antibodies [cetuximab, panitumumab]) revealed a significantly poorer prognosis in those with right-sided tumors compared with those with left-sided tumors.[6–8] However, it remains unclear whether tumor sidedness also has prognostic value in chemotherapy regimens that do not involve molecular targeted agents.

The present study aimed to evaluate the prognostic value of tumor sidedness, specifically with respect to overall survival (OS), in patients with unresectable stage IV colorectal cancer regardless of treatment strategy.

METHODS

Study Population

Our study cohort comprised 678 consecutive patients with initially unresectable (non-recurrent) stage IV colorectal cancer who underwent systemic chemotherapy (multiple cytotoxic agent therapy with or without molecular targeted agents) at the National Cancer Center Hospital from January 1999 to December 2015. During the study period, molecular targeted agents (bevacizumab, cetuximab, and panitumumab) were introduced as systemic chemotherapy for stage IV colorectal cancer after 2007, in Japan; half of our study subjects received chemotherapy using multiple cytotoxic agents without molecular targeted agents. Patients who received R0 resection (primary tumor resection and metastasectomy, including dissection of the diseased portion of the peritoneum such that no macroscopic tumors remained[9,10]) and patients who received only best supportive care were excluded. Patients who did not receive irinotecan and/or oxaliplatin, but did receive 5-fluorouracil, were also excluded because this treatment strategy is outdated and does not reflect current medical practice. Initial treatment with palliative resection, as well as the chemotherapy regimen, were typically decided during a multidisciplinary team meeting attended by colorectal surgeons, medical oncologists, hepatobiliary surgeons, thoracic surgeons, and radiologists, taking into consideration disease severity, comorbidities, and patient condition.

This retrospective study was approved by the Institutional Review Board (IRB) of the National Cancer Center Hospital (IRB code: 2015-320).

Data Collection

For primary tumor sidedness, right-sided was defined as tumors of the cecum, ascending colon, hepatic flexure, and transverse colon, and left-sided was defined as tumors of the splenic flexure, descending colon, sigmoid, rectosigmoid junction, and rectum. The following parameters were retrospectively assessed using medical records: treatment year, sex, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), M subcategories (M1a, M1b, M1c) according to the TNM classification (8th edition),[1] tumor differentiation, preoperative carcinoembryonic antigen (CEA) levels, chemotherapy regimens (5-fluorouracil, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab), the use of bevacizumab beyond first progression,[11] type of systemic chemotherapy regimen (multiple cytotoxic agent therapy without molecular targeted agents, and a combination of cytotoxic agents with at least one molecular targeted agent (i.e. bevacizumab, cetuximab, or panitumumab), and type of surgery (i.e. palliative primary tumor resection; primary tumor resection without metastasectomy; and unresected cases, including diverting stoma construction without primary tumor resection, bypass surgery, or probe laparotomy).

Stratification by Treatment Subgroup

Patients were stratified by chemotherapy regimen (i.e. with or without molecular targeted agents) and the presence or absence of palliative primary tumor resection, based on our previous finding that palliative primary tumor resection may be associated with longer OS in patients with unresectable stage IV colorectal cancer.[12]

Statistical Analysis

Pearson's Chi square test for categorical variables and the Wilcoxon rank-sum test for continuous variables were performed to compare various factors in both groups (right-sided and left-sided tumors). OS was defined as the interval between the date of stage IV colorectal cancer diagnosis and the date of death from all causes; survivors at the date of data cut-off (June 2018) were censored. The Kaplan–Meier method was used to estimate OS; differences in survival were assessed using the log-rank test; and multivariate Cox proportional hazards regression models were used to evaluate the prognostic impact of tumor sidedness on OS by adjusting for several key clinical factors.

In order to balance the distribution of the covariates in the two groups (right-sided and left-sided), propensity score matching analysis was conducted as described previously.[12, 13] Multivariable logistic regression was used to

generate propensity score-predicting sidedness based on confounding covariates, including age (≥ 65 vs. < 65 years), ECOG performance status (PS0 vs. PS1, PS2), M subcategories (M1a, M1b vs. M1c) according to the TNM classification (8th edition), and tumor differentiation (differentiated vs. not differentiated). A Propensity scores were then used for matching, which pair patients with right-sided tumors and patients with left-sided tumors according to similarities in his/her observed baseline characteristics. Each patient with right-sided cancer was matched 1:1 with a patient with left-sided cancer using the closest estimated propensity on the logit scale within a specified range (smaller than 0.05 of estimated logits as the caliper width) to reduce differences between the two groups.

Data are presented as numbers of patients, percentages (%), or hazard ratios (HRs) and 95% confidence intervals (CI), as indicated. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using the JMP14 software program (SAS Institute Japan Ltd, Tokyo, Japan).

RESULTS

Characteristics of the Study Cohort

The consort diagram for this study is shown in Fig. 1. Between January 1999 and December 2015, 801 patients with unresectable stage IV colorectal cancer were referred to the National Cancer Center to receive systemic therapy. Of these, 114 patients who received 5-fluorouracil monotherapy and 9 patients who received 5-fluorouracil plus molecular targeted agents were excluded, resulting in a final study population of 678 patients, among whom 44% received chemotherapy using multiple cytotoxic agents without molecular targeted agents. Of the final study population, 193 (28%) had right-sided (cecum to transverse colon) tumors and 485 (72%) had left-sided (splenic flexure to rectum) tumors. Overall, 93 (48%) of the 193 patients with right-sided tumors and 216 (45%) of the 485 patients with left-sided tumors underwent palliative primary tumor resection.

Patient characteristics are summarized in Table 1. Treatment year, sex, and preoperative CEA levels did not differ between the two groups (p =0.881, p =0.457, and p =0.909, respectively); however, there were significant differences in age (< 65 vs. ≥ 65 years; p =0.022), performance status (PS0/PS1, 2, 3; p =0.016), M subcategories ($p < 0.001$), and tumor differentiation (p =0.006) between the two groups. Significant group-dependent differences were also observed in the type of systemic chemotherapy regimen (multiple cytotoxic agent therapy without molecular targeted agents, versus a combination of cytotoxic agents with at least one molecular targeted agent; p =0.036); however, type of surgery (palliative primary tumor resection vs. unresected) did not differ between the two groups (p =0.389).

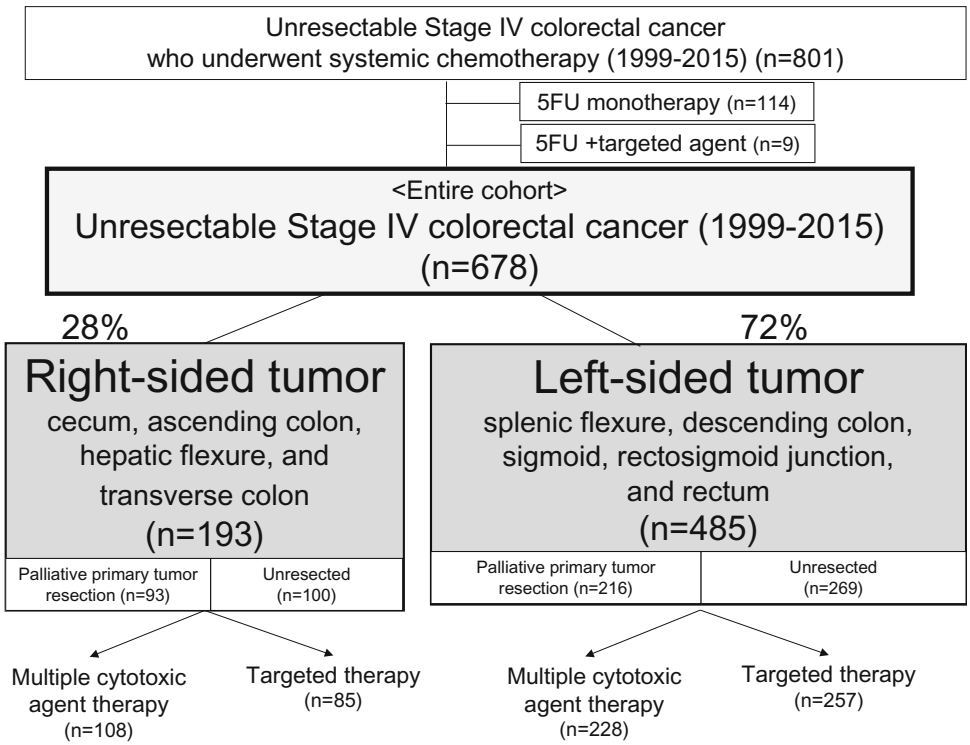

FIG. 1 Study cohort selection process. Of a total of 678 patients with unresectable stage IV colorectal cancer who underwent systemic therapy at the National Cancer Center, 193 (28%) had right-sided tumors (cecum to transverse colon) and 485 (72%) had left-sided tumors (splenic flexure to rectum); 114 patients who received chemotherapy without irinotecan or oxaliplatin were excluded. *5FU* 5-fluorouracil

TABLE 1 Clinical characteristics of patients

Variable	Category	Entire cohort (n =678)		
		Right-sided (n =193)	Left-sided (n =485)	p value
Treatment year	1999–2007	82 (42)	203 (42)	0.881
	2008–2015	111 (58)	282 (58)	
Sex	Male	111 (58)	294 (61)	0.457
	Female	82 (42)	191 (39)	
Age, years	< 65	113 (59)	329 (68)	0.022
	≥ 65	80 (41)	156 (32)	
ECOG PS	PS0	80 (401)	251 (52)	0.016
	PS1, PS2	113 (59)	234 (48)	
M category	M1a	61 (32)	218 (45)	<0.001
	M1b	57 (29)	163 (34)	
	M1c	75 (39)	104 (21)	
Tumor differentiation	Differentiated	162 (84)	438 (90)	0.006
	Poorly differentiated	21 (11)	36 (7)	
	Mucinous	9 (5)	4 (1)	
	Signet ring cell/undifferentiated	1 (1)	7 (1)	
Preoperative CEA levels, ng/ml	< 30	84 (44)	213 (44)	0.909
	≥ 30	109 (56)	271 (56)	
Type of chemotherapy	Multiple cytotoxic agent therapy without targeted agents	108 (56)	228 (47)	0.036
	Targeted therapy	85 (44)	257 (53)	
Type of surgery	Palliative primary tumor resection	93 (48)	216 (45)	0.389
	Unresected	100 (52)	269 (55)	
Chemotherapy regimens	5-fluorouracil			
	Yes	193 (100)	485 (100)	–
	No	0 (0)	0 (0)	
	Irinotecan			
	Yes	112 (58)	319 (66)	0.059
	No	81 (42)	166 (34)	
	Oxaliplatin			
	Yes	152 (79)	398 (82)	0.321
	No	41 (21)	87 (18)	
	Bevacizumab			
	Yes	77 (40)	225 (46)	0.125
	No	116 (60)	260 (54)	
	Cetuximab/panitumumab			
	Yes	27 (14)	104 (21)	0.027
	No	166 (86)	381 (79)	
	Bevacizumab beyond first progression			
	Yes	24 (57)	94 (61)	0.681
	No	18 (43)	61 (39)	

Data are expressed as n (%)

ECOG PS Eastern Cooperative Oncology Group performance status, *CEA* carcinoembryonic antigen

Chemotherapy regimens are summarized in Table 1. The use of 5-fluorouracil, irinotecan, oxaliplatin, and bevacizumab did not differ between the two groups, and the use of bevacizumab beyond first progression also did not differ between the two groups (p =0.681). On the other hand, cetuximab/panitumumab were used more for left-sided tumors compared with right-sided tumors (p =0.027).

Long-Term Outcomes

Figure 2a shows OS curves for patients with unresectable stage IV colorectal cancer. The median survival time (MST) was 16.4 and 23.4 months for those with right-sided and left-sided tumors, respectively, indicating a significantly poorer OS for right-sided tumors compared with left-sided tumors ($p < 0.01$).

After propensity score matching, 188 matched pairs of patients were selected. Patient distributions were balanced between the right-sided and left-sided groups (electronic supplementary table). Figure 2b shows OS curves for patients with unresectable stage IV colorectal cancer in the cohort of matched patients (n =376). The MST was 16.4 and 21.5 months for those with right-sided and left-sided tumors, respectively, indicating a significantly poorer OS for right-sided tumors compared with left-sided tumors ($p < 0.01$).

Figures 3a and b show OS curves for patients with unresectable stage IV colorectal cancer stratified into two groups by type of systemic chemotherapy regimen. Since the use of cetuximab/panitumumab differed between the two groups, the patient cohort excluding the patients who received anti-EGFR antibody was also analyzed. Among patients who did not receive an anti-EGFR antibody (n =547), right-sided tumors (n =166; MST 15.6 months) were also associated with a significantly poorer prognosis compared with left-sided tumors (n =381; MST 21.2 months) [data not shown]. Figure 3c and d show OS curves for patients with unresectable stage IV colorectal cancer stratified into two groups by type of surgery. Regardless of not only the type of chemotherapy regimen but also the type of surgery, all of these analyses showed that right-sided tumors were associated with a significantly poorer prognosis compared with left-sided tumors.

Factors Affecting Prognosis

According to univariate analysis, good performance status (PS0; $p < 0.001$), M1a subcategory of the TNM classification (p =0.027, 0.005), differentiated tumors ($p < 0.001$), and preoperative CEA levels lower than 30 ng/ml ($p < 0.001$) were significantly associated with better OS, whereas sex and age were not associated with prognosis (Table 2). As for type of chemotherapy regimen, compared with patients who received multiple cytotoxic agent therapy without molecular targeted agents (MST 16.1 months), patients who received targeted therapy (MST 27.7 months) showed better OS ($p < 0.001$). As for type of surgery, compared with unresected patients (MST 17.9 months), patients who underwent palliative primary tumor resection (MST 24.3 months) showed better OS ($p < 0.0001$). Right-sided tumors also showed a significantly stronger association with shorter OS compared with left-sided tumors ($p < 0.001$).

To investigate the prognostic impact of primary tumor sidedness, multivariate analyses were performed using Cox proportional hazards regression models adjusted for the above-mentioned six key clinical factors (i.e. performance status, M subcategories of the TNM classification, tumor differentiation, preoperative CEA levels, type of surgery, and type of chemotherapy regimen). Right-sided tumors were associated with significantly shorter OS compared

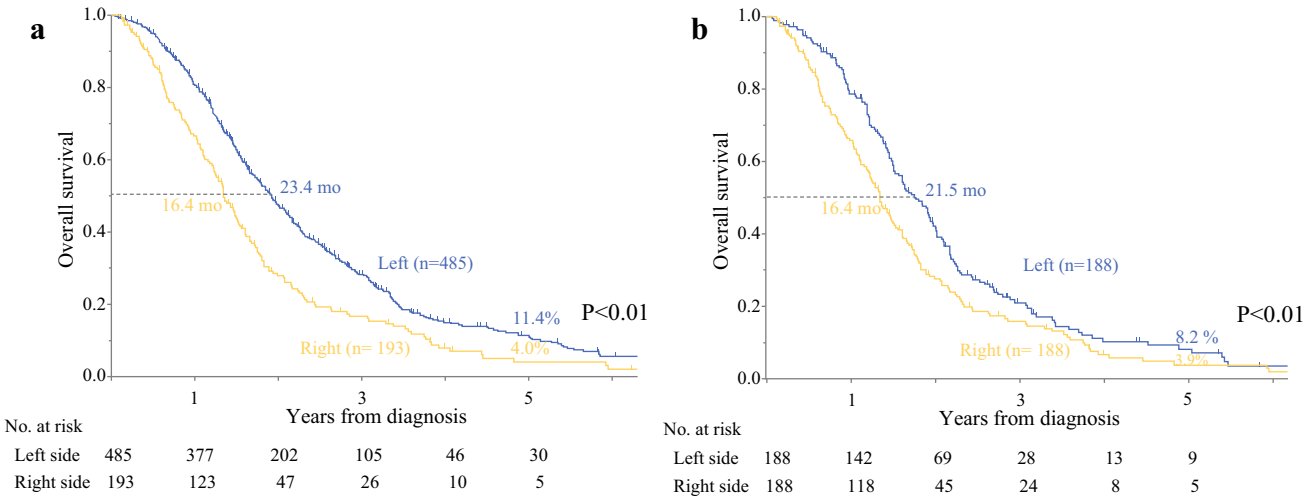

FIG. 2 **a** Overall survival curve for unresectable stage IV colorectal cancer in the entire cohort (n =678), stratified by tumor sidedness: right-sided tumors (n =193) and left-sided tumors (n =485). **b** Overall survival curve for unresectable stage IV colorectal cancer in the propensity score-matching pairs (n =376), stratified by tumor sidedness: right-sided tumors (n =188) and left-sided tumors (n =188)

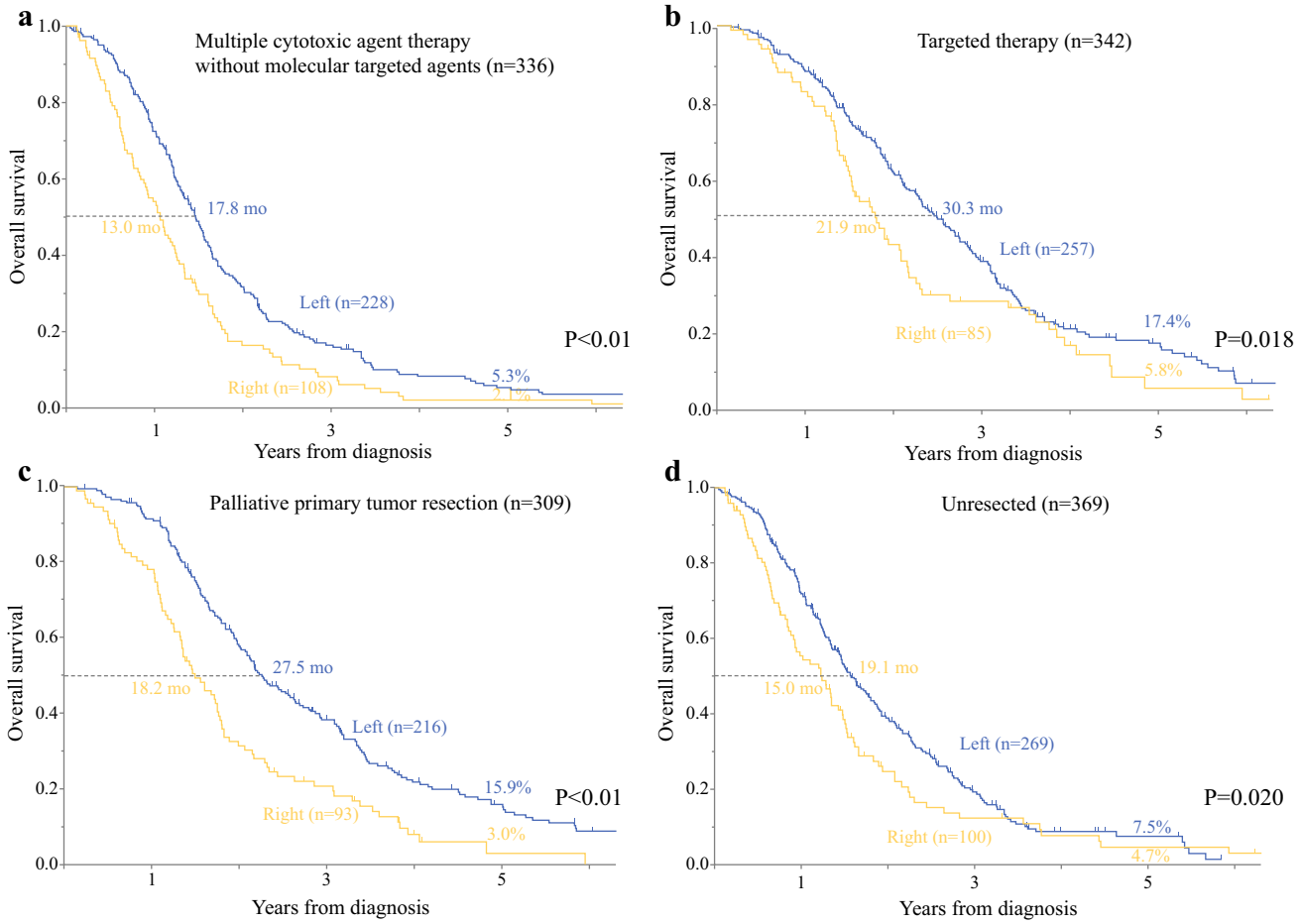

FIG. 3 **a**, **b** Overall survival curves for unresectable stage IV colorectal cancer stratified into two groups according to the type of chemotherapy regimen (multiple cytotoxic agent therapy with or without molecular target agents). **c**, **d** Overall survival curves for unresectable stage IV colorectal cancer stratified into two groups according to the type of surgery (palliative primary tumor resection or unresected)

with left-sided tumors (HR 1.26, 95% CI 1.03–1.53; p =0.024) and were found to be an independent factor associated with poorer prognosis (Table 2).

DISCUSSION

In the present study, we demonstrated that for unresectable stage IV colorectal cancer, right-sided tumors were associated with shorter OS compared with left-sided tumors, using several different measures. First, in an analysis of the entire cohort (n =678) and the propensity score-matched pairs (n =376), right-sided tumors were associated with shorter OS compared with left-sided tumors. Second, analyses with stratification by mode of treatment revealed that regardless of not only the type of chemotherapy regimen but also the type of surgery, right-sided tumors showed significantly poorer prognosis compared with left-sided tumors. Third, multivariate analyses revealed that, after adjusting for key clinical factors (e.g. performance status, M subcategories, tumor differentiation, type of chemotherapy regimen, and type of surgery), right-sided tumors were associated with shorter OS compared with left-sided tumors (HR 1.26). These results clearly suggest that primary tumor sidedness is an independent prognostic factor for unresectable stage IV colorectal cancer.

A prognostic factor is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy that patients are likely to receive, which can be thought of as a measure of the natural history of the disease.[14] A predictive factor is a measurement that is associated with response or lack of response to a particular therapy and is useful for treatment selection.[14] Although these terms are often used interchangeably, careful evaluation of whether a factor is prognostic or predictive is important. Our stratification-based results (i.e. by type of chemotherapy regimen and type of surgery) strongly suggest that tumor sidedness is at

TABLE 2 Univariate and multivariate analyses of factors affecting survival in patients with unresectable stage IV colorectal cancer

Variable	Category	Number	Median overall survival (months)	Univariate analysis *p* value	Multivariate analysis		
					HR	95% CI	*p* value
Sex	Male	405	22.2 (19.9–24.1)	0.193			
	Female	273	19.5 (17.7–21.3)				
Age, years	< 65	442	20.5 (18.5–22.4)	0.240			
	≥ 65	236	21.9 (19.5–25.4)				
ECOG PS	PS0	331	25.5 (23.4–28.2)	< 0.001	Reference		
	PS1, PS2	347	17.4 (16.1–18.6)		1.57	1.32–1.88	< 0.001
M category	M1a	279	23.5 (21.3–27.3)	Reference	Reference		
	M1b	220	19.9 (17.7–21.8)	0.027	1.16	0.95–1.42	0.147
	M1c	179	18.9 (16.8–21.3)	0.005	1.13	0.90–1.41	0.285
Tumor differentiation	Differentiated	600	22.2 (20.2–24.0)	< 0.001	Reference		
	Others	78	13.5 (10.0–15.5)		1.92	1.45–2.49	< 0.001
Preoperative CEA levels, ng/ml	< 30	297	23.6 (21.3–26.9)	< 0.001	Reference		
	≥ 30	380	18.7 (17.7–20.9)		1.31	1.10–1.56	0.002
Type of chemotherapy	Multiple cytotoxic agent therapy without targeted agents	336	16.1 (14.8–17.8)	< 0.001	Reference		
	Targeted therapy	342	27.7 (25.2–31.0)		0.48	0.40–0.57	< 0.001
Type of surgery	Palliative primary tumor resection	309	24.3 (21.9–26.6)	< 0.001	Reference		
	Unresected	369	17.9 (16.2–19.7)		1.51	1.27–1.81	< 0.001
Primary tumor site	Right side	193	16.4 (14.9–18.4)	< 0.001	1.26	1.03–1.53	0.024
	Left side	485	23.4 (21.3–25.5)		Reference		

Data are expressed as median (95% CI) or HR (95% CI)

HR hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *CEA* carcinoembryonic antigen

least a prognostic factor since right-sided tumors showed significantly poorer prognosis compared with left-sided tumors, regardless of the type of treatment.

Several studies have reported racial differences in survival among patients with stage IV colorectal cancer. For example, OS for African Americans was reported to be poorer compared with that for European Americans.[15] Similarly, OS for Hispanics was reported to be poorer compared with that for non-Hispanic White patients.[16] Japanese adolescent and young adult patients with stage IV colorectal cancer were shown to have shorter survival compared with adult patients,[17] which is not the case for patients in the US.[18] These reports suggest that racial differences may affect survival in patients with unresectable stage IV colorectal cancer. The present study found that, consistent with Western populations, tumor sidedness is also a prognostic factor for the Japanese population.[6–8]

Why can primary tumor location be a prognostic factor? One explanation may lie in the embryological origin of normal tissue. Briefly, the proximal colon from the cecum to approximately half to two-thirds of the oral portion of the transverse colon (right-sided) is derived from the embryonic mid-gut, while the distal third of the transverse colon to the rectum (left-sided) is derived from the embryonic hind-gut.[6] Consistent with this difference in embryological origin, the genetic carcinogenic pathways of proximal and distal colorectal cancers also differ, which could result in diverse clinical, pathological, and biological features.[19] For example, right-sided colon tumors are likely to be diploid and more commonly associated with poor prognostic indicators such as BRAF mutations.[20]

This study has some limitations. First, although consecutive patients were enrolled, the study period was from 1999 to 2015. During this long period, treatment strategies, including intensive chemotherapeutic regimens, have changed significantly. Thus, our study may not be fully reflective of current medical practice. Second is the skew in study population. Since 72% of patients had left-sided tumors and only 28% had right-sided tumors (although these distributions were typical in Japan according to the national registration of colorectal cancer in Japan[21]), this might affect the analysis. Third, no data were available regarding the genetic phenotypes of the lesions, which could potentially explain the prognostic differences between right-sided and left-sided tumors. Nonetheless, the present study is the first to demonstrate that tumor

sidedness is an independent prognostic factor for unresectable stage IV colorectal cancer, regardless of treatment strategy.

CONCLUSIONS

Our results demonstrated that, regardless of treatment strategy, right-sided tumors were associated with shorter OS compared with left-sided tumors. Thus, tumor sidedness should be considered a stratification parameter in future randomized trials for unresectable stage IV colorectal cancer.

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COMMERCIAL INTERESTS The authors have no commercial interests to report.

CONFLICT OF INTEREST Dai Shida, Taro Tanabe, Narikazu Boku, Atsuo Takashima, Takefumi Yoshida, Shunsuke Tsukamoto, and Yukihide Kanemitsu have no conflict of interest to report.

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