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Original Article

Impact of primary tumor location on the overall survival of patients with stage IV colorectal cancer: a propensity score analysis of data from the surveillance epidemiology and end results program data

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Abstract: There is an ongoing debate as to whether right-sided versus left-sided tumor location itself represents an independent prognostic factor for patients with stage IV colorectal cancer. Patients with stage IV colorectal cancer were identified from the Surveillance, Epidemiology, and End Results (SEER) database (2004-2013). Both univariate and multivariate Cox regression analyses as well as propensity score matching were used. Overall, 45,471 patients 15,239 (33.5%) with right-sided, 27,314 (60.1%) with left-sided colorectal cancer, and 2918 (6.4%) with cancer of the transverse colon; median follow-up of 17 (months) were eligible. Multivariate analysis showed that patients with right-sided colorectal cancer had worse overall and cancer-specific survival compared to patients with left-sided colorectal cancer. According to results from propensity score matching, prognosis for patients with right-sided carcinomas was showed worse overall and cancer-specific survival. In a population-based series of patients with stage IV colorectal cancer, patients with right-sided tumors exhibited inferior survival.

Keywords: Colorectal cancer, right-sided, left-sided, survival, SEER

Introduction

Colorectal cancer is the 4th most common cancer and the second leading cause of cancer-related death worldwide, creating a serious threat to public health. Approximately 20% of patients are diagnosed with metastatic colorectal cancer (mCRC, or stage IV CRC), and more than 1/3 of those initially diagnosed with localized disease will develop mCRC [1, 2]. Over the past several years, the distinction between right-sided and left-sided colorectal cancer has been emphasized for the following reasons: right-sided colorectal cancers (RCC) and left-sided colorectal cancers (LCC) are of different embryological origins, and thus various differences exist between them. Recent studies have revealed an increased frequency of right-sided colorectal cancer over the last decade [3, 4], which has prompted the investigation of potential variations within different anatomic sites. Data regarding the prognosis of patients with right-sided versus left-sided colorectal cancers are conflicting, and it remains a matter of great debate whether the tumor location itself has a significant prognostic impact. The majority of studies have demonstrated a poorer survival of patients with right-sided colorectal cancer compared to those with left-sided colorectal cancer [5-8]. In contrast to those data, Weiss found no overall difference in the 5-year mortality rate between patients with right-sided and left-sided colorectal cancer after adjusting for multiple variables [9]. Apopulation-based analysis of stage I-III colon cancer has provided evidence that the prognosis of localized right-sided colon cancer is better than that of left-sided colon cancer according to propensity score matching [10]. Recently, several clinical trials including CALGB/SWOG80405 have revealed differences in the overall survival of patients with metastatic colorectal cancer based on the location of the primary tumor, but this information is not rou-

Table 1. The characteristics of 45471 patients with metastatic colorectal cancer

Risk factor	N (N%) Total N = 45471	Median (months) 17	3-year OS % 16
Age, year, mean ± SD	64.40±13.89		
Gender			
Female	20773 (45.7)	15	16
Male	24698 (54.3)	17	15
Race			
White	34937 (76.8)	16	16
Black	6542 (14.4)	15	12
Other*	3887 (8.5)	18	17
Unknown	105 (0.3)	17	14
Year of diagnosis			
2004-2005	9157 (20.1)	14	15
2006-2007	9062 (19.9)	15	16
2008-2009	9140 (20.1)	16	16
2010-2011	9266 (20.4)	15	16
2012-2013	8846 (19.5)	17	0
Location of primary tumor			
Right-sided colorectal	15239 (33.5)	12	11
Left–sided colorectal	27314 (60.1)	18	18
Transverse colon	2918 (6.4)	12	14
Histological type			
Adenocarcinoma	40831 (89.8)	16	16
Mucinous adenocarcinoma	3596 (7.9)	15	14
Signet ring cell carcinoma	1044 (2.3)	9	5
Differentiated grade			
Well	1807 (4.0)	18	19
Moderate	25473 (56.0)	19	19
Poor	10215 (22.5)	12	12
Undifferentiated	1040 (2.3)	11	12
Unknown	6936 (15.2)	10	8
The level of CEA			
Positive	25228 (55.5)	14	13
Negative	5631 (12.4)	22	27
Unknown	14612 (32.1)	15	15
Radiation performed			
Performed	3222 (7.1)	30	32
Not performed	42249 (92.9)	16	14
Operation performed			
Performed	29035 (63.9)	20	21
Not performed	16020 (35.2)	9	5
Unknown	416 (0.9)	15	11

CEA = Carcinoembryonic antigen, OS = Overall survival. *American Indian/AK Native, Asian/Pacific Islander.

tinely included in study design, reporting or patient counseling [11].

The objective of the present population analysis of 45,471 patients with stage IV colorectal cancer from the Surveillance, Epidemiology, and End Results (SEER) database was to compare the overall and cancer-specific survival between two large, virtually identical groups of patients with right-sided and left-sided colorectal cancer using propensity-score matching.

Materials and methods

Origins of materials

The SEER registry, which was sponsored by the National Cancer Institute, collects information on cancer incidence and survival. The current SEER database (from 2004-2013) consists of 18 population-based cancer registries that represent approximately 28% of the population of the United States. The SEER data contain no identifiers and are publicly available for studies of cancer-based epidemiology and health policy. We obtained permission to access the research data (Reference Number: 12061-Nov 2015).

Inclusion and exclusion criteria

The specific inclusion criteria were as follows: year of diagnosis ranged from 2004 to 2013; site record ICD-0-3 was limited to the colon and rectum; histological type ICD-0-3 was limited to 8140 (adenocarcinoma), 8480 (mucinous adenocarcinoma), and 8490 (signet

Table 2. Imbalances of baseline characteristics between right-sided and left-sided metastatic colorectal cancer patients

Factor	Right-sided colorectal cancer (n = 15239, %)	Left-sided colorectal cancer (n = 27314, %)	*P*[a]
Age, year	67.64±13.31	62.38±13.81	0.000
≤ 64	6158 (40.4)	15389 (56.3)	0.000
> 64	9081 (59.6)	11925 (43.7)	
Race			0.000
White	11712 (76.8)	20984 (76.8)	
Black	2557 (16.8)	3519 (12.9)	
Other*	942 (6.2)	2737 (10.0)	
Unknown	28 (0.2)	74 (0.3)	
Radiation			0.000
Performed	370 (2.4)	2776 (10.2)	
No performed	14869 (97.6)	24538 (89.8)	
Grade			0.000
Well	549 (3.6)	1150 (4.2)	
Moderate	7793 (51.2)	16110 (59.0)	
Poor	4340 (28.5)	5079 (18.6)	
Undifferentiated	478 (3.1)	471 (1.7)	
Unknown	2079 (13.6)	4504 (16.5)	
Surgery			0.000
Performed	10955 (71.9)	15910 (58.3)	
No performed	4208 (27.6)	11074 (40.5)	
Unknown	76 (0.5)	330 (1.2)	
CEA			0.000
Positive	8087 (53.1)	15543 (56.9)	
Negative	2094 (13.7)	3146 (11.5)	
Unknown	5058 (33.2)	8625 (31.6)	
Histology			0.000
Adenocarcinoma	13064 (85.8)	25236 (92.3)	
Mucinous adenocarcinoma	1683 (11.0)	1600 (5.9)	
Signet ring cell carcinoma	492 (3.2)	478 (1.8)	
Sex			0.000
Female	7959 (52.2)	11367 (41.6)	
Male	7280 (47.8)	15947 (58.4)	
Diagnosis year			0.000
2004-2005	3139 (20.6)	5402 (19.8)	
2006-2007	3047 (20.0)	5446 (19.9)	
2008-2009	3090 (20.3)	5433 (19.9)	
2010-2011	3076 (20.2)	5642 (20.7)	
2012-2013	2887 (18.9)	5391 (19.7)	

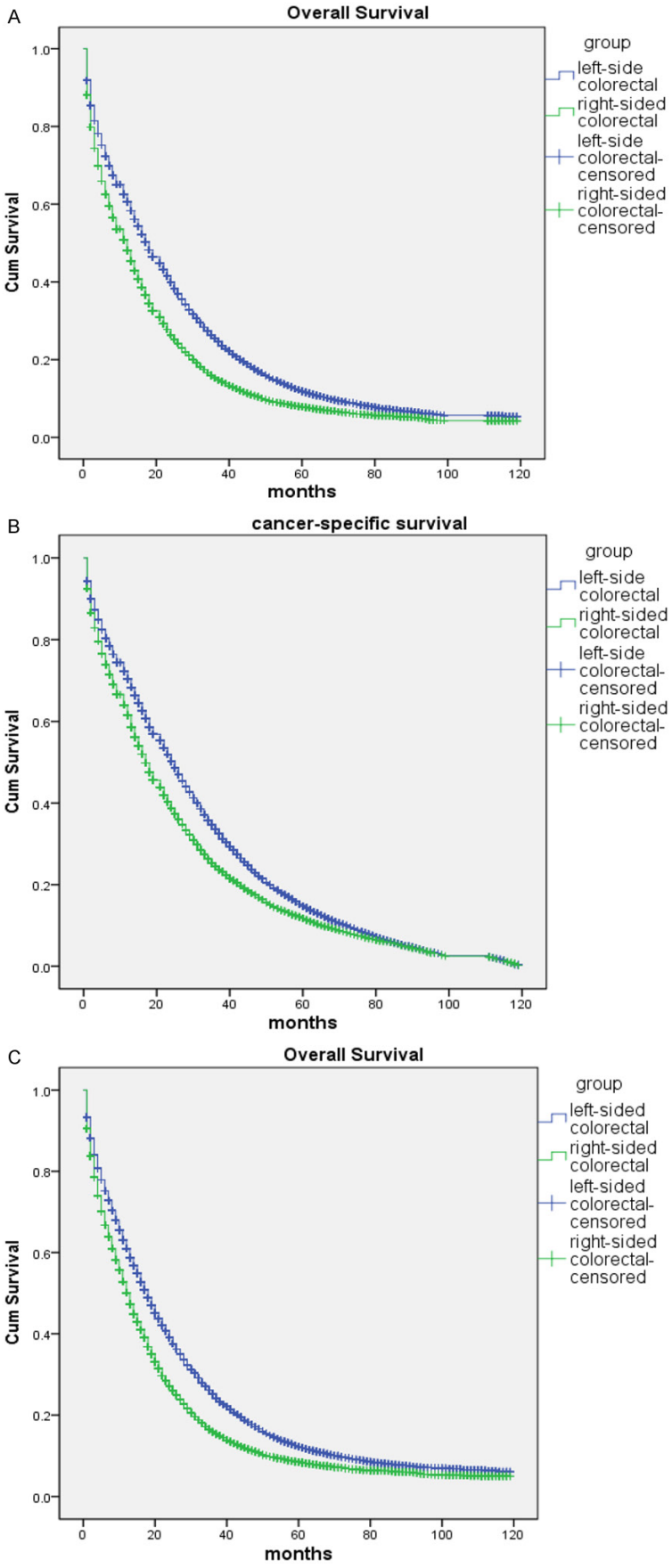
CEA = Carcinoembryonic antigen, OS = Overall survival. *American Indian/AK Native, Asian/Pacific Islander. [a]Chi-square test, student's t test or the nonparametric Mann-Whitney test.

ring cell cancer); the stage was confirmed to be stage IV, including stage IVa and stage IVb, according to the 7th AJCC TNM staging system. The exclusion criteria were as follows: patients without documentation of race and age at diagnosis; and patients younger than 18 years. In addition, patients with multiple primary tumors were excluded so that the analyses of cancer-specific survival were more accessible, and patients who survived less than 1 month were excluded because such patients may die from surgical complications or they may experience rapid progression after palliative resection. We characterized the primary tumor site according to the SEER data as Right-sided (cecum to the hepatic flexure), Left-sided (splenic flexure to the rectum) or Transverse (T, hepatic to the splenic flexure).

Statistical analyses

The year and age at diagnosis, gender, race, site record, histological type, degree of differentiation (grade), the level of carcinoembryonic antigen (CEA), survival in months, and cause of death were retrieved from the SEER database. The outcomes of interest in this study included overall survival (OS) and colorectal cancer-specific survival (CCSS), which were determined according to specific codes provided by SEER. Death attributed to other causes was defined as a censored observation.

Categorical variables were analyzed by Pearson X^2 test or Fisher exact test, and the means ± standard deviations were compared using Student's t test or the nonparametric Mann-Whitney test, as appropriate. Survival curves were generated using the



Kaplan-Meier method, and the log-rank test was used to evaluate the differences in survival. Adjusted hazard ratios along with 95% confidence intervals (CI) were calculated using the Cox proportional hazards regression model. To further adjust for the differences in baseline characteristics, and therefore to further minimize bias, a propensity score-matched (PSM) analysis was performed as a further statistical method for adjustment. A 1:1 "nearest neighbor" match paradigm was used. After matching, the two groups were compared to control for the covariate balance and the similarity in the baseline covariates between groups. Then, the two matched groups were compared with respect to the goals of the study. All statistical analyses were two-sided, and $P < 0.05$ was indicative of statistical significance. All statistical analyses and PSM were performed with SPSS software (Statistical Package for the Social Sciences, IBM SPSS Statistics, version 22 for Macintosh; IBM, Armonk, NY).

Results

Patient characteristics

The cut-off date for follow-up was November 2015, and the median follow-up time was 17.0 months (range, 1 to 119 months). A total of 45,471 eligible patients were analyzed and showed a median survival of 17.0 months and a 3-year overall survival of 16%. The median age was 64 years of age (range, 18 to 108 years of age). At the end of the follow-up period, 10,138 (22.3%) patients were

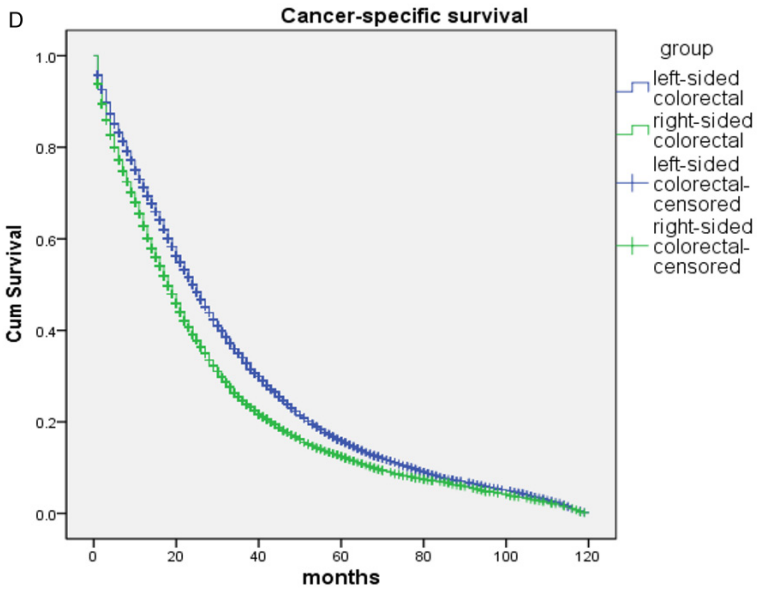


Figure 1. Kaplan-Meier curves for overall and cancer-specific survival. Panel (A and B) depict the overall and cancer-specific survival in the original data set and panel (C and D) depict the overall and cancer-specific survival after propensity score matching.

alive, and 28,036 (61.7%) had died from colorectal cancer. Overall, 15,239 (33.5%) patients had right-sided colorectal cancer including 8,066 (17.7%) patients with cancer of the cecum, 5,535 (12.2%) patients with cancer of the ascending colon and 1,638 (3.6%) patients with cancer of the hepatic flexure. Left-sided colorectal cancer was diagnosed in 27,314 (60.1%) patients including 1,265 (2.8%) patients with cancer of the splenic flexure, 2,113 (4.6%) patients with cancer of the descending colon, 10,491 (23.1%) patients with cancer of the sigmoid colon, 4,550 (10.0%) patients with cancer of the rectosigmoid junction, and 8,895 (19.6%) patients with cancer of the rectum. Cancer of the transverse colon was diagnosed in 2,918 (6.4%) patients. The detailed characteristics of the patients are provided in (**Table 1**). (**Table 2**) compares the characteristics of the patients in the two groups and indicates relevant imbalances for all the characteristics (all $P < 0.001$).

Impact of cancer location on survival

The observed median overall survival of patients with right-sided colorectal cancer was 12 months (95% CI: 11.64 to 12.35) compared with 18 months (95% CI: 17.61 to 18.39) in patients with left-sided colorectal cancer. The median cancer-specific survival of patients with right-sided colorectal cancer was 17 months (95% CI: 16.47 to 17.52) compared with 25 months (95% CI: 24.57 to 25.43) in patients with left-sided colorectal cancer (**Figure 1A** and **1B**).

The Cox proportional hazards regression model was applied to investigate the effects of the cancer location and the other patient characteristics on OS and CCSS. In terms of prognosis, patients with right-sided colorectal cancer had a significantly worse overall survival than those with left-sided colorectal cancer (HR = 1.33, 95% CI: 1.30 to 1.36, $P < 0.001$); in addition, patients with right-sided colorectal cancer had a significantly worse cancer-specific survival (HR = 1.27, 95% CI: 1.24 to 1.30, $P < 0.001$) compared to patients with left-sided colorectal cancer. Moreover, the results also revealed that older age (64 years), the grade of tumor differentiation and the CEA level were independent risk factors for overall survival and cancer-specific survival in these patients. The detailed characteristics of the patients are provided in (**Table 3**).

Adjusting for patient characteristics with propensity score matching

Adjusting for the observed effects in non-randomized studies is a critical part of data analysis because confounding influences of covariates can bias effect estimates. Propensity score methods offer a principled approach to manage this type of confounding bias. Through efficient matching, covariate balance is created and their confounding effects can be minimized or entirely removed [12]. Before the matching procedure, the propensity score for patients with multivariate imbalance L1 was 0.368. After PSM, 12,303 of 15,239 patients with right-sided colorectal cancer could be matched with 12,303 of 27,314 patients with left-sided colorectal cancer at a 1:1 ratio. After matching, the propensity score for patients with multivariate imbalance L1 was 0.024, which

Table 3. Cox proportional hazards regression model for overall survival and colorectal cancer-specific survival in patients with right-sided and left-sided metastatic colorectal cancer

Variable	Overall survival		Cancer-specific survival	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age, year				
≤ 64	1.00 (reference)		1.00 (reference)	
> 64	1.521 (1.488-1.555)	0.000	1.292 (1.260-1.324)	0.000
Race				
White	1.00 (reference)		1.00 (reference)	
Black	1.149 (1.114-1.186)	0.000	1.120 (1.081-1.160)	0.000
Other*	0.998 (0.959-1.038)	0.925	1.030 (0.986-1.076)	0.180
Unknown	0.895 (0.699-1.146)	0.378	1.048 (0.810-1.356)	0.723
Radiation				
Performed	1.00 (reference)		1.00 (reference)	
No performed	1.251 (1.194-1.310)	0.000	1.149 (1.096-1.205)	0.000
Grade				
Well	1.00 (reference)		1.00 (reference)	
Moderate	1.082 (1.022-1.145)	0.007	1.088 (1.021-1.158)	0.009
Poor	1.515 (1.427-1.608)	0.000	1.411 (1.321-1.508)	0.000
Undifferentiated	1.724 (1.574-1.889)	0.000	1.572 (1.418-1.744)	0.000
Unknown	1.253 (1.178-1.333)	0.000	1.184 (1.105-1.269)	0.000
Surgery				
Performed	1.00 (reference)		1.00 (reference)	
No performed	2.033 (1.981-2.087)	0.000	1.840 (1.786-1.896)	0.000
Unknown	1.396 (1.244-1.566)	0.000	1.503 (1.330-1.699)	0.000
CEA				
Positive	1.00 (reference)		1.00 (reference)	
Negative	0.693 (0.668-0.718)	0.000	0.756 (0.727-0.786)	0.000
Unknown	0.947 (0.924-0.969)	0.000	0.953 (0.928-0.979)	0.000
Histology				
Adenocarcinoma	1.00 (reference)		1.00 (reference)	
Mucinous adenocarcinoma	1.084 (1.041-1.129)	0.000	1.042 (0.995-1.091)	0.082
Signet ring cell carcinoma	1.351 (1.260-1.448)	0.000	1.284 (1.181-1.396)	0.000
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	0.999 (0.977-1.021)	0.921	0.993 (0.969-1.018)	0.580
Diagnosis year				
2004-2005	1.00 (reference)		1.00 (reference)	
2006-2007	0.886 (0.858-0.914)	0.000	0.932 (0.899-0.966)	0.000
2008-2009	0.854 (0.827-0.882)	0.000	0.982 (0.9471-0.019)	0.334
2010-2011	0.834 (0.807-0.862)	0.000	1.062 (1.022-1.103)	0.002
2012-2013	0.765 (0.733-0.799)	0.000	1.145 (1.092-1.201)	0.000
Locationof primary tumor				
Left-side colorectal	1.00 (reference)		1.00 (reference)	
Right-side colorectal	1.330 (1.299-1.361)	0.000	1.269 (1.235-1.304)	0.000

CEA = Carcinoembryonic antigen, OS = Overall survival. *American Indian/AK Native, Asian/Pacific Islander.

indicates no persisting relevant bias regarding the observed characteristics in the two groups.

The baseline characteristics of the matched study population are summarized in (**Table 4**).

Table 4. Baseline characteristics of the propensity score-matched patients (1:1 matching)

Factor	Right-sided colorectal cancer (n = 12303, %)	Left-sided colorectal cancer (n = 12303, %)	*P*[a]
Age			
≤ 64	5382 (43.7)	5373 (43.7)	0.908
> 64	6921 (56.3)	6930 (56.3)	
Race			0.443
White	9686 (78.7)	9697 (78.8)	
Black	1882 (15.3)	1857 (15.1)	
Other*	731 (5.9)	748 (6.0)	
Unknown	4 (0.1)	1 (0.1)	
Radiation			0.641
Performed	280 (2.3)	291 (2.4)	
No performed	12023 (97.7)	12012 (97.6)	
Grade			0.989
Well	365 (3.0)	361 (2.9)	
Moderate	6992 (56.8)	7000 (56.9)	
Poor	2993 (24.3)	2979 (24.2)	
Undifferentiated	198 (1.6)	208 (1.7)	
Unknown	1755 (14.3)	1755 (14.3)	
Surgery			0.889
Performed	8462 (68.8)	8485 (69.0)	
No performed	3810 (31.0)	3790 (30.8)	
Unknown	31 (0.2)	28 (0.2)	
CEA			0.850
Positive	6856 (55.7)	6899 (56.1)	
Negative	1435 (11.7)	1430 (11.6)	
Unknown	4012 (32.6)	3974 (32.3)	
Histology			0.778
Adenocarcinoma	11331 (92.1)	11359 (92.3)	
Mucinous adenocarcinoma	797 (6.5)	778 (6.3)	
Signet ring cell carcinoma	175 (1.4)	166 (1.4)	
Sex			0.848
Female	6000 (48.8)	6015 (48.9)	
Male	6303 (51.2)	6288 (51.1)	
Diagnosis year			0.918
2004-2005	2585 (21.0)	2569 (20.9)	
2006-2007	2514 (20.4)	2483 (20.2)	
2008-2009	2480 (20.2)	2457 (20.0)	
2010-2011	2433 (19.8)	2455 (20.0)	
2012-2013	2291 (18.6)	2339 (18.9)	

CEA = Carcinoembryonic antigen, OS = Overall survival. *American Indian/AK Native, Asian/Pacific Islander. [a]Chi-squaretest, fisher exact test.

In this cohort, the prognosis of left-sided colorectal cancer was better than that of right-sided colorectal cancer with respect to OS (HR = 1.34 95% CI: 1.31 to 1.38, P < 0.001) and CCSS (HR = 1.29, 95% CI: 1.25 to 1.33, P < 0.001). The median overall survival time of patients with right-sided colorectal cancer was 13 months (95% CI: 12.66 to 13.34) compared with 18 months (95% CI: 17.50 to 18.49) in patients with left-sided colorectal cancer. The median cancer-specific survival time of patients with right-sided colorectal cancer was 18 months (95% CI: 17.49 to 18.51) compared with 25 months (95% CI: 24.34 to 25.66) in patients with left-sided colorectal cancer (**Figure 1C** and **1D**).

Discussion

We examined over 45,471 subjects with stage IV colorectal cancer from the SEER database. Upon analysis of the whole population and after PSM, the results from the present study confirm that subjects with right-sided colorectal cancer have a decreased overall survival and cancer-specific survival compared with those with left-sided colorectal cancer.

To the best of our knowledge, this is the first population-based, propensity score-adjusted analysis that has investigated the prognostic impact of tumor location in patients with metastatic colorectal cancer. We have generated awareness of the conflicting data and of the challenges in the management of relevant bias due to substantial imbalances regarding baseline characteristics between patients with right-sided and left-sided colorectal cancer. We also intentionally selected propensity score matching as a useful statistical method, in addition to common multivariate analysis, so that

confounding factors were minimized. A 1:1 "nearest neighbor" match paradigm was used. After matching, the two groups were compared to control the covariate balance and the similarity in the baseline covariates between groups. Then, the two matched groups were compared with respect to the goals of the study. The disadvantages of our study are its retrospective nature and the lack of randomization. Therefore, we performed the propensity score matching to improve the comparability of the two groups.

The majority of studies demonstrated a poorer survival of patients with right-sided colorectal cancer compared to those with left-sided colorectal cancer [5-8] and the results differ from the findings published by Warschkow. This population-based analysis of stage I-III colon cancer provides evidence that the prognosis of localized right-sided colon cancer is better than that of left-sided colon cancer after propensity score matching [10]. Differences between our present analysis and the study by Warschkow and colleagues may have arisen for several reasons. First, in our study, patients had stage IV colorectal cancer, but the study by Warschkow and colleagues was a population-based analysis of patients with stage I-III colon cancer. Second, we characterized the primary tumor site using SEER data, which is different than the method used by Warschkow. We also define right-sided as indicative of the cecum to the hepatic flexure and left-sided as indicative of the splenic flexure to the rectum. Transverse (T) was defined as the area between the hepatic flexure and the splenic flexure, which was similar to the definition used in clinical trials CALGB/SWOG 80405 [11].

We would like to acknowledge the limitations of the present study. One limitation of the present study is the lack of information regarding microsatellite instability (MSI) in the SEER database. According to the literature, colorectal cancer with MSI has a better prognosis [13, 14]. Second, whether or not subjects received chemotherapy is not recorded in the SEER database. Third, the models that were applied are simplified and used available and accepted measures; they clearly do not adequately account for all variables associated with subject outcomes. Fourth, while we performed a risk adjustment for known confounders, potential bias due to unknown confounding factors cannot be excluded. Finally, although propensity score-matched adjustment represents an additional, valuable statistical tool used in the present analyses, the results must be interpreted with some caution due to the fraction of unmatched patients.

However, due to the population-based nature of this analysis, which mirrors the actual US population with colorectal cancer, the absence of this information does not impact our results, but it does limit the extent of the interpretation of our data.

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Disclosure of conflict of interest

None.

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