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RESEARCH ARTICLE

Clinical characteristics and prognosis of different primary tumor location in colorectal cancer: a population-based cohort study

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Abstract

Purpose Emerging data have shown that patients with left-sided cancers have better survival than patients with right-sided cancers in terms of metastatic colorectal cancer. However, the available information and findings remain limited and contradictory in localized colorectal cancer. This study aimed to evaluate the clinical characteristics and prognosis of primary tumor location (PTL) in colorectal cancer.

Methods Patients' diagnoses were identified using the Surveillance, Epidemiology, and End Result database between 2006 and 2015. The analyses were further stipulated to patients with primary cancer site, histology, and stage information. The correlations between PTL and overall survival (OS) were assessed.

Results Compared with left-sided tumors, right-sided tumors were more likely to develop into T3 cancers (50.0% vs. 44.8%), T4 cancers (15.8% vs. 12.3%), mucinous or mucin-producing adenocarcinoma (10.8% vs. 5.0%), and signet ring cell carcinoma (1.4% vs. 0.7%), $P < 0.01$, respectively. Patients with right-sided tumors showed inferior OS (56.1% vs. 60.2%), and the hazard ratio was 1.224 (95% CI, 1.208–1.241, $P < 0.001$) in all stages. Stage-specific Cox regression analysis revealed that patients with right-sided tumors also showed inferior OS in every stage (respectively, $P < 0.05$) than left-sided tumors.

Conclusions This study demonstrated that the prognoses of patients with left-sided cancers were better than those of patients with right-sided cancers regardless of stage. PTL can be a prognosis factor in colorectal cancer. We encourage developing clinical and translational studies to elucidate the causative relationship between PTL and prognosis.

Keywords Primary tumor location · Colorectal cancer · Prognosis · Overall survival

Introduction

Colorectal cancer (CRC) is an important public health problem; it is the third commonly diagnosed cancer and the second leading cause of death worldwide [1]. CRC is a significantly heterogeneous cancer on the basis of its histological type, grade, stage, and treatment response. Different genetic, etiological, environmental, microbiotic, and lifestyle factors lead to the heterogeneity of CRC [2] and influence its prognosis. Advancements in medical therapy have gradually improved the survival of patients. These advancements include the exploitation and utilization of new drugs, improved treatment, and discovery of predictive factors. Emerging studies have demonstrated that primary tumor location can serve as an important predictive factor, which might predict curative effects in metastatic CRC [3, 4]. The outcomes of patients with left-sided cancers are better than those of right-sided cancers in metastatic CRC [5–8]. However, the available information and findings remain limited and contradictory in localized CRC [9, 10]. Thus, we aimed to evaluate the clinical characteristics and prognosis of PTL in CRC.

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Materials and methods

Study design and patient selection

This population-based cohort study analyzed the correlation between PTL and outcomes in CRC. The study data were extracted from the Surveillance, Epidemiology, and End Results (SEER), which covered 27.8% patients with cancer in the USA [11]. SEER*Stat version 8.3.5 was employed. We examined data from Incidence—SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000–2015). The data were extracted and described according to data items and codes as documented by the North American Association of Central Cancer Registries (NAACCR) [12]. We extracted data for all cases of CRC between 2006 and 2015, which were coded according to THE year of diagnosis (NAACCR Item390). Primary cancer site and histology were coded using the criteria in the third edition of the International Classification of Diseases for Oncology (ICDO-3) [13]. The patients who were diagnosed at autopsy or only by death certificate and without histologically confirmed cancer (NAACCR Items 490 and 2180) and with occurrence of another malignancy preceding CRC (NAACCR Item 380) were excluded. These analyses were further stipulated to patients with adenocarcinoma identified by the ICDO-3 histology codes 8140, 8144, 8210,8211, 8220, 8221,8255, 8260, 8261, 8262, and 8263; mucinous 8480; mucin-producing adenocarcinoma 8481; and signet ring cell carcinoma 8490 (NAACCR Item 522). These analyses were also stipulated to patients with clear stage (0, I, IIA, IIB, IIIA, IIIB, IIIC, and IV) identified by the DERIVED AJCC-6 STAGE GRP (NAACCR Item 3000). Right-sided colon cancers included C18.0-cecum, C18.2-ascending colon, C18.3-hepatic flexure of colon, and C18.4-transverse colon. Left-sided CRCs included C18.5-splenic flexure of colon, C18.6-descending colon, C18.7-sigmoid colon, C19.9-rectosigmoid junction, and C20.9-rectum (NAACCR Items 522 and 523).

Statistical analysis

Statistical analyses were carried out using SAS statistical software (SAS, version 9.4; SAS Institute Inc.). Chi-square test was used to evaluate proportions. Multivariable logistic analysis was conducted to analyze the correlation between every factor with overall survival (OS).The Cox regression model and Kaplan–Meier method were employed to analyze the correlation between PTL and OS. A two-sided p value < 0.05 was considered as statistically significant.

Results

Study population

We identified a population-based sample of 311,239 patients diagnosed with CRC between 2006 and 2015. We excluded living patients without survival time information from OS analysis. Thus, 248,861 patients were retained in this cohort. The selection process for patients in the study is listed in Fig. 1.

Population characteristics

The stage distribution was 3.8, 25.1, 25.8, 26.8, and 18.6% for stages 0, I, II, III, and IV, respectively. The characteristics of patients are listed in Table 1. This study comprised more patients with left-sided cancers than those with right-sided cancers [57.0% (177,444 of 311,239) vs. 43.0% (133,795 of 311,239)]. Females were more likely to present with right-sided cancers (53.3% [71,330 of 133,795] vs. 42.9% [76,182 of 177,444], $P < 0.001$) than left-sided cancers. Patients with right-sided tumors were older [≥ 75 years, 43.4% (58,027 of 133,795) vs. 25.9% (45,916 of 177,444), $P < 0.001$] than those with left-sided tumors. Compared with left-sided tumors, right-sided tumors were more likely to develop into T3 cancers [50.0% (66,877 of 133,795) vs. 44.8% (79,545 of 177,444), $P < 0.001$], T4 cancers [15.8% (21,084 of 133,795) vs. 12.3% (21,753 of 177,444), $P < 0.001$], mucinous or mucin-producing adenocarcinoma [10.8% (14,413 of 133,795) vs. 5.0% (8869 of 177,444), $P < 0.001$], and signet ring cell carcinoma [1.4% (1918 of 133,795) vs. 0.7% (1314 of 177,444), $P < 0.001$].

Factors correlated with survival

The factors correlated with 5-year survival are listed in Table 2. Multivariable analysis indicated that the following factors were correlated with inferior prognosis (OS): male, old age (≥ 75 years), unmarried status, histopathology grades 3 and 4, mucinous adenocarcinoma, mucin-producing adenocarcinoma, signet ring cell carcinoma, stages III and IV, and right-sided tumor.

Exploratory analyses of the associations between PTL and survival

We performed exploratory analyses to identify the association between PTL and the OS of the patients with CRC. The patients of all stages (stages 0–IV) were merged in analysis to identify the prognostic relevance of PTL. The PTL was correlated with prognosis. Cox regression analysis revealed

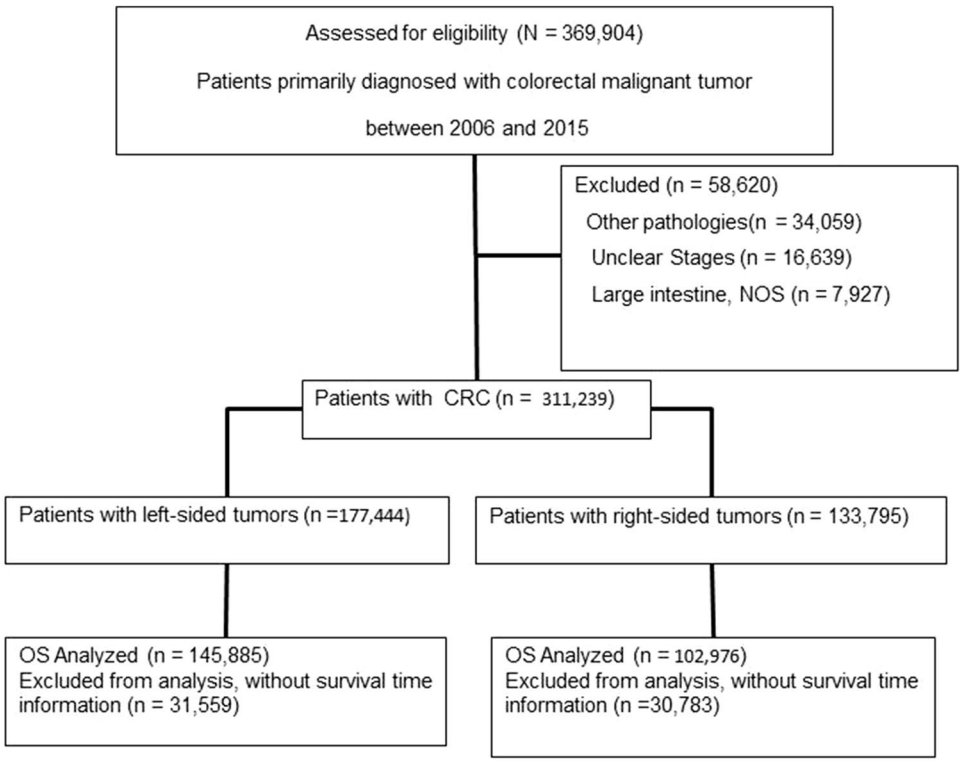

Fig. 1 Selection process for patients in the cohort study

that patients with right-sided tumors showed inferior OS (56.1% vs. 60.2%), and the hazard ratio was 1.224 (95% CI, 1.208–1.241, $P < 0.001$) in stages 0–IV. The Kaplan–Meier analysis results listed in Fig. 2 also indicated that the patients with right-sided tumors had inferior OS. We further analyzed the correlation between PTL and the OS in every stage. Stage-specific Cox regression analysis revealed that patients with right-sided cancers had inferior OS in every stage (Table 3). Patients with stage III showed the greatest difference between the left-sided and right-sided cancers in OS (64.4% vs. 54.0%, $P < 0.001$) than patients with other stages.

Discussion

In this study, we evaluated the clinical characteristics and prognostic relevance of PTL in CRC. We further confirmed through historical data that patients with right-sided cancers were more likely to be old, female and mucinous adenocarcinoma or signet ring cell histology than those with left-sided cancers [14–16]. Our data were consistent with the growing body of evidence showing that those with left-sided cancers have better prognosis than patients with right-sided cancers among patients with metastatic CRC (stage IV) [5–8]. Our analysis further showed that patients with left-sided cancers exhibited better prognosis than patients with right-sided cancers in all stages (including localized CRC). When grouped based on tumor stage, all patients with left-sided cancers showed significantly better prognosis than those with right-sided cancers regardless of stage. This difference was not apparent between patients with metastatic CRC and those with localized CRC. However, the reason for the different survival rates of patients with different PTL in CRC remains unclear. We speculate that differences in embryological origin and detection time may contribute to this discrepancy. The embryological junction between the midgut and hindgut leads to a potential watershed area in the area of the splenic flexure, and it is supplied by the superior and inferior mesenteric arteries. The rectum also arises from the hindgut and the blood supply from the inferior mesenteric artery. So, we included it in the left half colon analysis. Due to the larger diameter of the right-sided colon tube, all patients with right-sided cancers had later onset of clinical symptoms, such as abdominal pain and intestinal obstruction. Right-sided tumors were more likely to develop into advanced cancers (stage III and IV). After controlling for tumor stage and histology, the patients' prognosis in left-sided cancers remained better than those of right-sided cancers. This result also suggested that the difference in prognosis between the two groups may be related to genetic and environmental factors. Right-sided cancers are more likely to involve genome-wide hypermethylation and hypermutations than left-sided cancers [17–20]. Gene analyses elucidated four biological consensus molecular subtypes (CMSs) in CRC [21]. Notably, the differential CMSs were distributed between

Table 1 Demographics and clinical characteristics of patients with colorectal cancer between 2006 and 2015

Variable	All patients ($N=311,239$)	Tumor location		
		Left ($N=177,444$)	Right ($N=133,795$)	P value
Sex, no. (%)				< 0.001
Male	163,727 (52.6)	101,262 (57.1)	62,465 (46.7)	
Female	147,512 (47.4)	76,182 (42.9)	71,330 (53.3)	
Age, years, no. (%)				< 0.001
≤ 44 years	16,432 (5.3)	11,995 (6.8)	4437 (3.3)	
45–59 years	75,976 (24.4)	53,512 (30.2)	22,464 (16.8)	
60–74 years	114,888 (36.9)	66,021 (37.2)	48,867 (36.5)	
≥ 75 years	103,943 (33.4)	45,916 (25.9)	58,027 (43.4)	
Marital status, no. (%)				< 0.001
Unmarried	164,833 (53.0)	96,583 (54.4)	68,250 (51.0)	
Married	129,553 (41.6)	70,651 (39.8)	58,902 (44.0)	
Unknown	16,853 (5.4)	10,210 (5.8)	6643 (5.0)	
Race, no. (%)				< 0.001
White	246,763 (79.3)	139,135 (78.4)	107,628 (80.4)	
Black	36,141 (11.6)	18,935 (10.7)	17,206 (12.9)	
AI/A	2195 (0.7)	1369 (0.8)	826 (0.6)	
A/PI	24,495 (7.9)	16,809 (9.5)	7686 (5.7)	
Unknown	1645 (0.5)	1196 (0.7)	449 (0.3)	
T, no. (%)				< 0.001
T0	98 (0.0)	80 (0.0)	18 (0.0)	
Tis	11,890 (3.8)	7983 (4.5)	3827 (2.9)	
T1	55,876 (18.0)	37,179 (21.0)	18,697 (14.0)	
T2	41,049 (13.2)	22,469 (12.7)	18,580 (13.9)	
T3	146,422 (47.0)	79,545 (44.8)	66,877 (50.0)	
T4	42,837 (13.8)	21,753 (12.3)	21,084 (15.8)	
Tx	13,147 (4.2)	8435 (4.8)	4712 (3.5)	
N, no. (%)				< 0.001
N0	186,803 (60.0)	106,617 (60.1)	80,186 (59.9)	
N1	73,582 (23.6)	43,341 (24.4)	30,241 (22.6)	
N2	43,440 (14.0)	22,609 (12.7)	20,831 (15.6)	
NX	7414 (2.4)	4877 (2.7)	2537 (1.9)	
M, no. (%)				< 0.001
M0	253,131 (81.3)	143,087 (80.6)	110,044 (82.2)	
M1	57,843 (18.6)	34,167 (19.3)	23,676 (17.7)	
MX	265 (0.1)	190 (0.1)	75 (0.1)	
Stage, no. (%)				< 0.001
0	11,810 (3.8)	7983 (4.5)	3827 (2.9)	
I	78,036 (25.1)	47,234 (26.6)	30,802 (23.0)	
II	80,267 (25.8)	40,434 (22.8)	39,833 (29.8)	
III	83,283 (26.8)	47,626 (26.8)	35,657 (26.7)	
IV	57,843 (18.6)	34,167 (19.3)	23,676 (17.7)	
Histology, no. (%)				< 0.001
Adenocarcinoma	284,725 (91.5)	167,261 (94.3)	117,464 (87.8)	
AM/MPA	23,282 (7.5)	8869 (5.0)	14,413 (10.8)	
SRCC	3232 (1.0)	1314 (0.7)	1918 (1.4)	
Grade, no. (%)				< 0.001
I	25,611 (8.2)	14,955 (8.4)	10,656 (8.0)	
II	201,082 (64.6)	117,591 (66.3)	83,491 (62.4)	
III	46,222 (14.9)	20,411 (11.5)	25,811 (19.3)	
IV	6550 (2.1)	2539 (1.4)	4011 (3.0)	
Unknown	31,774 (10.2)	21,948 (12.4)	9826 (7.3)	

AI/A American Indian/Alaska native, *AM/MPA* adenocarcinoma mucinous or mucin-producing adenocarcinoma, *A/PI* Asian or Pacific Islander; SRCC indicates signet ring cell carcinoma. *T, N, M* tumor, node, and

Table 1 (continued) metastasis classification according to AJCC 6th

Table 2 Factors correlated with five-year overall survival among 248,861 patients with colorectal cancer

Covariate	Total no.	OS rate (%)	Multivariable analysis	
			Hazard ratio (95% CI)	*P* value
Sex				
Male	130,934	57.5	1 [Reference]	
Female	117,927	58.7	0.952 (0.937–0.967)	< 0.001
Age, years				
≤ 44 years	15,306	65.8	1 [Reference]	
45–59 years	68,210	67.8	0.914 (0.881–0.948)	< 0.001
60–74 years	92,659	62.7	1.145 (1.104–1.186)	< 0.001
≥ 75 years	72,686	42.2	2.635 (2.541–2.733)	< 0.001
Marital status				
Married	132,569	63.7	1 [Reference]	
Unmarried	103,050	50.2	1.741 (1.712–1.770)	< 0.001
Unknown	13,242	62.9	1.035 (0.997–1.074)	.068
Stage				
0	8930	80.2	1 [Reference]	
I	59,442	77.9	1.149 (1.087–1.215)	< 0.001
II	63,647	68.9	1.828 (1.731–1.931)	< 0.001
III	68,555	60.2	2.678 (2.537–2.827)	< 0.001
IV	48,287	11.3	31.795 (29.968–33.733)	< 0.001
Histology				
Adenocarcinoma	228,381	58.9	1 [Reference]	
AM/MPA	17,989	52.1	1.318 (1.278–1.358)	< 0.001
SRCC	2491	27.7	3.740 (3.425–4.085)	< 0.001
Grade				
I	20,358	70.0	1 [Reference]	
II	161,834	61.3	1.473 (1.427–1.520)	< 0.001
III	36,654	44.8	2.875 (2.772–2.981)	< 0.001
IV	5107	45.0	2.852 (2.678–3.037)	< 0.001
Unknown	24,908	49.9	2.343 (2.253–2.436)	< 0.001
Site				
Left	145,885	60.2	1 [Reference]	
Right	102,976	55.1	1.233 (1.213–1.253)	< 0.001

AM/MPA adenocarcinoma mucinous or mucin-producing adenocarcinoma, *SRCC* signet ring cell carcinoma

the left-sided and right-sided cancers, and "microsatellite unstable/immune" CMS1 and "metabolic" CMS3 were more prevalent in right-sided cancers than in left-sided cancers [21]. The different PTLs also exhibited varied microbiota and histories of exposure to potential carcinogenic toxins [22, 23]. In stage IV, patients with left-sided cancers have a higher rate of liver metastases and lung metastases was found when compared with those of right-sided cancers, whereas patients with right-sided cancers were associated with a higher rate of peritoneal metastases and metastases at other sites [24]. In fact, several recent studies have exhibited that PTL may be prognostic and predictive of the response to antiepidermal growth factor receptor (EGFR) therapy in mCRC. Trials using cetuximab as an anti-EGFR therapy, including CRYSTAL and FIRE-3, showed that the prognosis of patients with left-sided cancers were superior to those of patients with right-sided cancers [25]. In terms of treatment, compared to right-sided cancers, some patients with rectal cancers received preoperative or postoperative radiotherapy. Some studies demonstrated that those treatments could improve local control [26–29]. However, those studies also demonstrated that OS were not improved [27–30]. It might not affect the results (OS) of our study that the rectum was incorporated into the left colon for analysis. In addition,

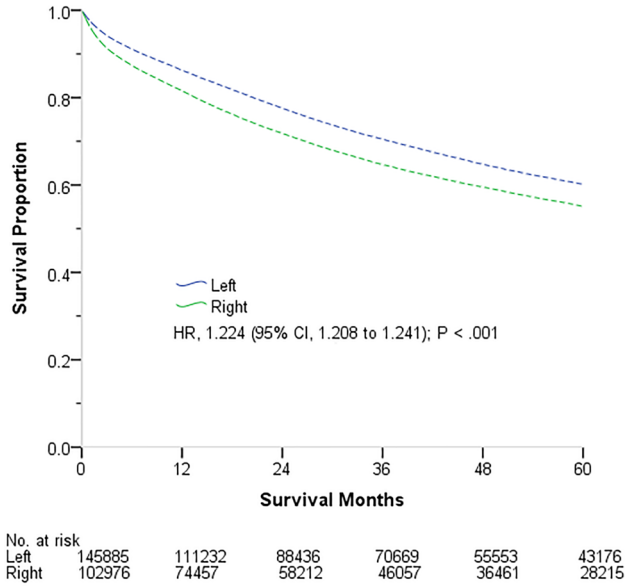

Fig. 2 Patients with left-sided tumors had better 5-year overall survival (60.2% vs. 55.2%, $P < 0.001$) compared with right-sided tumors in stage 0–IV

it might affect the OS that patients with right-sided tumors were older than those with left-sided tumors. Therefore, the clinical characteristics and prognostic mechanisms of different sites of colorectal cancer require further study, especially on locational cancers. Our results also differed from other study [10]. Such different results might be due to the different definitions for right- and left-sided cancers. Cancers located from the rectum to the splenic flexure colon are commonly defined as left-sided cancers, whereas those from the splenic flexure colon to the cecum are defined as right-sided cancers [8, 17, 31, 32]. By contrast, others employed different definitions of left-sided cancers, which only included the descending and sigmoid colon cancers, and right-sided cancers, which only included the cecum and ascending colon cancers; moreover, they excluded patients with cancers in other colorectal locations [10]. Our study was based on the former definition. Such different definitions may explain the inconsistency between the results of the two studies.

Limitations and strengths

To our knowledge, our study is the largest work to analyze the influence of PTL on the prognoses of patients with CRC in all stage. However, the study had some limitations. Data on treatments, family history, performance status, and molecular features were unavailable in the SEER database. Despite these limitations, the present study had some strengths. First, the population-based nature of the registry is associated with a high degree of generalizability. Second, our study reported data over a 10-year period and included over 311,000 patients with CRC. The large sample size was also associated with a high degree of power. Third, we used different analysis measures to prove the results of this study.

Conclusions

This study revealed the clinical characteristics and prognostic value of PTL in patients with CRC. The OS of patients with left-sided cancers was better than that of patients with right-sided cancers regardless of stage. We strongly recommend regarding PTL as a stratification factor in future studies. We encourage developing clinical and translational studies to elucidate the causative relationship between PTL and prognosis, and developing strategies for the prevention measures and clinical management of CRC by stratifying on the basis of PTL.

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Author contributions SL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the study design; collection, analysis, and interpretation of data; final approval of the version to be published. CZ performed acquisition,

Table 3 Primary tumor location correlated with 5-year overall survival among 248,861 patients with colorectal cancer

Stage	Primary tumor location					
	Left		Right		Cox regression	
	Total no.	OS (%)	Total no.	OS (%)	Right vs. left, HR (95) CI %	*P* value
0–IV	145,885	60.2	102,976	55.1	1.224 (1.208–1.241)	< 0.001
0	6220	81.7	2710	76.7	1.306 (1.171–1.457)	< 0.001
I	37,166	79.6	22,276	75.2	1.269 (1.220–1.319)	< 0.001
II	32,899	69.3	30,748	68.5	1.042 (1.009–1.075)	.011
III	40,592	64.4	27,963	54.0	1.501 (1.461–1.542)	< 0.001
IV	29,008	13.0	19,279	8.7	1.356 (1.328–1.385)	< 0.001

analysis, or interpretation of data and obtained funding. FJ offered technical and material support. HL performed statistical analysis.

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Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate As the data used was from SEER dataset (public), Ethics approval and consent to participate could be checked in SEER.

Patient consent for publication Not applicable.

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