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Prognostic Effect of Tumor Sidedness in Colorectal Cancer: A SEER-Based Analysis

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Abstract

A retrospective population-based study was conducted based on the SEER database stratified by colorectal cancer (CRC) histologic subtype and differentiation. Unlike adenocarcinoma (AC), stage III right-sided poorly differentiated mucinous and signet-ring cell AC showed significantly better survival than left-sided disease. Combining histologic subtype and sidedness may help to more precisely predict prognosis and help guide personalized treatment for patients with CRC.

Background: The prognostic value of tumor sidedness in metastatic colorectal cancer (CRC) has been established, but its impact on nonmetastatic disease remains unclear. Our study aimed to explore the prognostic effect of tumor sidedness by subgroup survival analyses, according to histology and tumor grade in stage I-IV CRCs. **Methods:** A retrospective population-based study was conducted based on Surveillance, Epidemiology and End Results (SEER) data. Population data in the SEER 9 registry (1975-2014) were used to determine survival trends of CRCs, and associated population data in the SEER 18 registry (2000 to 2014) were used to assess the prognostic impact of tumor sidedness on CRCs. **Results:** The 5-year cause-specific survival for all subgroups of CRCs improved from 1975 to 2014. Of 238,826 patients, 44.2% had right-sided cancer. Patients with right-sided cancer were more likely to be older, to be women, to have disease of mucinous or signet-ring cell histology, to have more poorly differentiated tumors, and to be diagnosed with a more advanced disease stage. Multivariate Cox regression showed stage I-II right-sided cancers had better cause-specific survival than the left-sided cancers (left colon: hazard ratio [HR] = 1.091, 95% confidence interval [CI], 1.052-1.132; rectum: HR = 1.363; 95% CI, 1.304-1.425; $P < .001$), while stage III and IV right-sided cancers had worse cause-specific survival. In subgroup analyses by histology and tumor grade within stage III CRCs, right-sided poorly differentiated mucinous adenocarcinoma showed significantly better survival (left colon: HR = 1.352; 95% CI, 1.145-1.596; rectum: HR = 1.125; 95% CI, 0.916-1.381; $P = .002$). **Conclusion:** The relationship between sidedness and prognosis in CRCs depends on stage and histopathologic characteristics, especially for stage III disease.

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy among both men and women in the United States.[1] Sidedness has become a hot spot of clinical and basic research to help predict prognosis and to guide personalized treatment for CRC patients. As early as 1990, Bulfill[2] first proposed that the primary tumors with various locations (proximal or distal to the splenic flexure of the colon) may present distinct genetic profiles of the disease. Right-sided tumors are more likely to occur in women, to occur in older patients, to be undifferentiated, to have mucinous or signet-ring cell histology, to have more CIMP (CpG island methylator phenotype)-high, microsatellite instability (MSI)-high disease, and to have more *BRAF* mutation.[2-7] The physical basis for the

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discrepancies may lie in the fact that the right and left colon have different embryologic beginnings and vascular supplies; they are also exposed to different toxins and microbiota.

These distinct biologic characteristics of right- and left-sided CRCs may contribute to the different prognosis and treatment response. Metastatic right-sided CRCs have inferior overall survival and treatment response to anti-EGFR therapy.[8-11] However, the prognostic impact of tumor sidedness for nonmetastatic (stage I-III) CRC remains controversial.[3,12,13]

Our study was designed to explore the prognostic effect of tumor sidedness by subgroup survival analyses according to histology and tumor grade in stage I-IV CRCs based on the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

Data Source

The SEER Program emerged in 1973 (SEER 9 registry) and has gradually become a comprehensive system of population-based state registries collecting cancer incidence and survival data based on cases reported from different geographic areas of the United States. The program had expanded 2 times to include additional areas (SEER 13 in 1992 and SEER 18 in 2000), and it currently includes 20 geographic areas covering approximately 28% of the US population. The November 2016 submissions of the SEER database were used for the present study,[14] and data from both SEER 9 and SEER 18 registries were adopted. We obtained permission to access the research data file (reference 10359-Nov2016). Per policy of Fudan University Shanghai Cancer Center, no institutional review board was required for this database study of deidentified data.

Patient Selection

Two cohorts of patients with pathologically confirmed colorectal neoplasms as their first malignancy were created and analyzed. One cohort, including colorectal neoplasms diagnosed in SEER 9 registries from 1975 to 2014, was created to estimate the long-term survival trend. Patients with unknown age at time of diagnosis, and those with data reported from autopsies or death certificates were excluded. We used the SEER historic stage A definition for extent of disease at diagnosis for the analyses in this cohort, which is the only staging variable that has been recorded consistently over the study period. Localized disease refers to disease confined to the colon or rectum; regional disease refers to contiguous and adjacent organ spread (eg, lymph nodes, kidney, pelvic wall); and distant disease refers to remote metastases.

A second cohort was created to analyze survival by clinicopathologic variables by adopting the SEER 18 registries from 2000 to 2014. Patients who had surgically treated, pathologically confirmed histologic subtype and tumor grade, clear classification of tumor location, and definite diagnoses of stage I to IV from the 6th edition of American Joint Committee on Cancer were included. Age at diagnosis was classified as age $<$ 50 years and age $\geq$ 50 years. Patients with adenocarcinoma (AC) defined by histologic codes 8140, 8210, 8261, and 8263; mucinous adenocarcinoma (MAC) by codes 8480 and 8481; and signet-ring cell carcinoma (SRCC) by code 8490, based on International Classification of Diseases for Oncology, Third Edition (ICD-O-3),[15] were included. Site of CRCs were divided as previously described.[13] Right-sided colon cancers were identified by ICD-O-3 site codes: 18.0—Cecum, 18.2—Asceding colon, 18.3—Hepatic flexure of colon, and 18.4—Transverse colon. Left-sided colon cancers were identified by codes 18.5—Splenic flexure of colon, 18.6—Descending colon, 18.7—Sigmoid colon, and 18.9—Rectosigmoid. Rectum cancers were noted with code 20.9.

Statistical Analysis

Survival trend analyses were performed by SEER*Stat software. Baseline characteristics stratified by tumor location were compared by chi-square tests. Survival and prognostic factors were analyzed by Kaplan-Meier analysis and Cox proportional hazard regression model. These analyses were conducted in R 2.15.0 software (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/). Patients who were alive or dead of other disease at last follow-up were censored for analysis. All confidence intervals (CIs) were stated at the 95% confidence level. Statistical significance was defined as $P < .05$ (2 sided).

Results

Long-Term Survival Change in SEER 9 Registry Cohort, 1975-2014

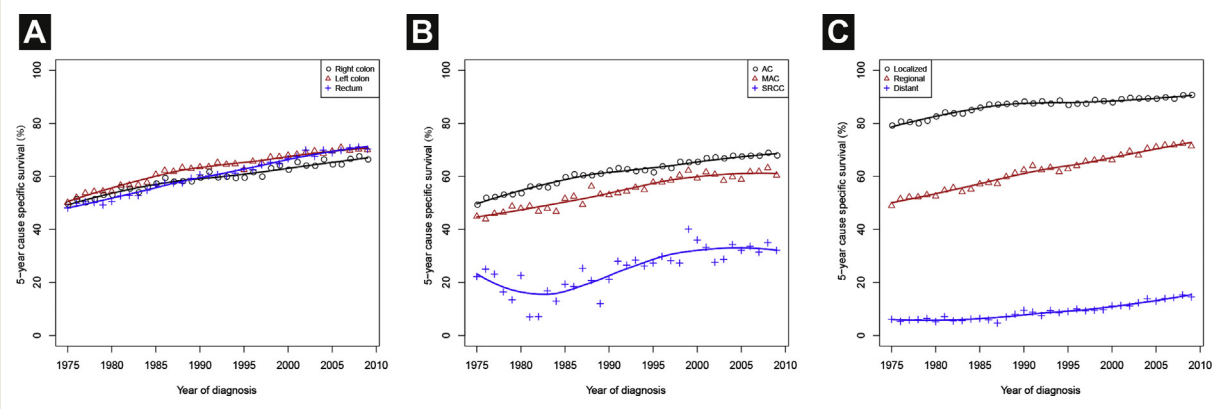
As indicated in Figure 1, 5-year cause-specific survival (CSS) of CRCs with any tumor location, histologic subtype, and historic stage was increasing during the years 1975 to 2009. By tumor location, the 5-year CSS of the right-sided colon cancer increased from 49.5% to 66.3% in 2009, with an annual percentage increase of 0.82%; and the 5-year CSS of left-sided disease also increased, from 50.1% and 48.1% in 1975 to 70.0% and 70.3% in 2009, with annual percentage increases of 0.93% and 1.19%, respectively. By histologic type, the 5-year CSS of AC and MAC increased, from 49.2% and 44.9% in 1975 to 67.8% and 60.4% in 2009, with an annual percentage increase of 0.88 and 1.03, respectively; and for SRCC, the 5-year CSS rose from 22.2% in 1975 to 32.1% in 2009, with an annual percentage increase of 2.80%. By historic stage, the 5-year CSS was increased by 11.5% (from 79.1% to 90.6%) and 22.5% (from 48.9% to 71.4%) for localized and regional tumors, respectively. For metastatic CRCs, the 5-year CSS was increased by 8.4% (from 6.1% to 14.5%), and the annual percentage improvement of survival was 3.36% between 1998 and 2009, compared to 2.71% between 1975 and 1997.

Baseline Characteristics of Patients in SEER 18 Registry Cohort, 2000-2014

Of 238,826 patients, 88.6% were $\geq$ 50 years old, 48.4% were female, and 79.4% were white (Table 1). The frequency of disease-related characteristics showed that the majority were diagnosed with stage III disease (30.4%), followed by stage II disease (28.8), stage 0-I disease (27.3), and stage IV disease (13.4%). Only about a fifth of all tumors were poorly or undifferentiated (grade 3-4). AC accounted for more than 90% of tumors, MAC for 8.4%, and SRCC only for 0.9%.

About 44.2% of patients had right-sided colon cancer, 38.7% had left-sided colon cancer, and 17.1% had rectal cancer. Patients with right-sided colon cancer were significantly older, were more likely to be women, were more likely to have poorly or undifferentiated tumors, and were more likely to have MAC and SRCC

Figure 1 Trend of 5-Year Cause-Specific Survival of Colorectal Cancer in SEER 9 Registries, 1975-2009. By (A) Tumor Location, (B) Histologic Type, and (C) Tumor Stage



Abbreviation: SEER = Surveillance, Epidemiology, and End Results.

histology, but were less likely to have stage 0-I disease. Patients' characteristics for those with metastatic and nonmetastatic tumors are listed in Table 1.

Prognostic Factors for CSS in CRCs of Different Stages and Subgroup Analyses by Histologic Subtype and Tumor Grade

Kaplan-Meier survival curves demonstrated significant differences in CSS of CRC patients stratified by tumor location (Supplemental Figure 1 in the online version). For stage I-II disease, 5-year CSS of right-sided colon cancer was 88.9%, better than that of 87.0% for left-sided colon cancer and 83.3% for rectal cancer. For stage III and IV disease, 5-year CSSs of right-sided colon cancer were the worst.

The prognostic impact of different disease-related factors were evaluated by multivariate Cox regression (Supplemental Table 1 in the online version). In the stage I-II subgroup, right-sided disease had a significantly lower risk of mortality (left colon: hazard ratio [HR] = 1.091; 95% CI, 1.052-1.132; rectum: HR = 1.363; 95% CI, 1.304-1.425; $P < .001$), while right-sided colon cancer presented a significantly higher risk of mortality in the stage III and IV subgroups ($P < .001$).

Subgroup analyses were then performed, first stratified by stage and histologic type (Figure 2). The survival of tumors of various location for stage I-II disease seems similar. Five-year CSS for right-sided colon cancer was 88.0%, compared to 88.6% for left-sided colon cancer and 87.0% for rectal cancer ($P < .001$, Supplemental Table 2 in the online version). It should be noted that when the observational end point extended to 10 years, the CSS for right-sided colon cancer became better than for left-sided colon cancer, with 10-year CSS of 82.5%, compared to 82.1% for left-sided colon cancer and 78.2% for rectal cancer ($P < .001$, Supplemental Table 2 in the online version). Multivariate Cox regression analysis indicated that stage I-II right-sided colon cancer had better CSS than left-sided colon cancer and rectal cancer (left colon: HR, 1.061, 95% CI, 1.021-1.103; rectum: HR, 1.316, 95% CI, 1.256-1.378), while stage III and IV right-sided colon cancer had worse CSS (Table 2).

For MAC, better 5-year CSS was found for right-sided colon cancer for stage I-II (86.4%) and stage III (63.1%) groups, compared to left-sided colon cancer (stage I-II, 82.1%; stage III, 58.5%) and rectal cancer (stage I-II, 76.1%; stage III, 61.9%) (Figure 2). Five-year CSS of right-sided colon cancer remained the worst for stage IV disease. Multivariate Cox regression analysis indicated stage I-II right-sided colon cancer had better CSS than left-sided colon cancer and rectal cancer (left colon: HR = 1.380; 95% CI, 1.225-1.554; rectum: HR = 1.951; 95% CI, 1.670-2.280 $P < .001$), while stage IV right-sided colon cancer had worse CSS (left colon: HR = 0.840; 95% CI, 0.768-0.919; rectum: HR = 0.750; 95% CI, 0.646-0.870; $P < .001$). Tumor location was not an independent prognostic factor for CSS for MAC in stage III disease.

Next, subgroup analyses were further performed, stratified by tumor grade. For AC, tumor location remained an independent prognostic factor in all subgroups of tumor grades across stage groups (Table 2). However, for MAC, tumor location was found to be an independent prognostic factor for CSS in the poorly differentiated or undifferentiated subgroups of stage III disease (left colon: HR = 1.352; 95% CI, 1.145-1.596; rectum: HR = 1.125; 95% CI, 0.916-1.381; $P = .002$). In this subgroup, right-sided tumors had much better 5-year CSS (57.1%) than the left-sided tumors (45.1%) (Figure 3, Supplemental Table 2 in the online version). In addition, tumor location lost its significance in the poorly differentiated or undifferentiated subgroups of stage IV disease.

Survival Analyses for SRCC by Tumor Location and Stage

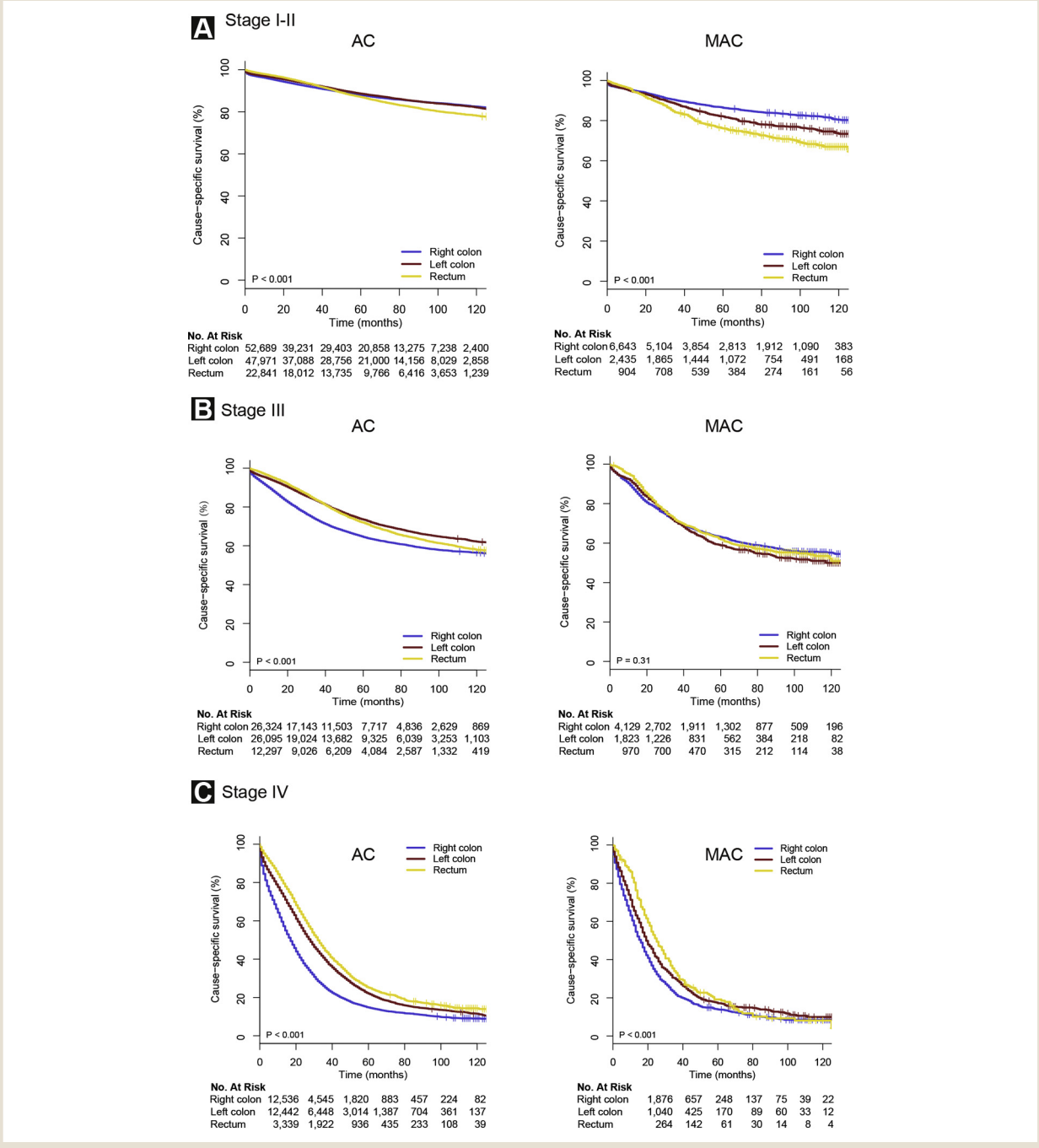
Kaplan-Meier survival analysis indicated significant differences between different tumor locations of SRCC only for stage I-II diseases ($P = .013$, Supplemental Figure 2 in the online version). Right-sided stage I-II colon SRCC had the best 5-year CSS of

Table 1 Baseline Clinicopathologic Characteristics of Patients in SEER 18 Cohort, 2000-2014

Characteristic	All Stages (N = 238,826)					Stage I-III (N = 114,811)				Stage IV (N = 32,089)			
	Total (N = 238,826)	Right Colon (N = 105,571)	Left Colon (N = 92,354)	Rectum (N = 40,901)	*P*	Right Colon (N = 90,800)	Left Colon (N = 78,683)	Rectum (N = 37,254)	*P*	Right Colon (N = 14,771)	Left Colon (N = 13,671)	Rectum (N = 3647)	*P*
Age					< .001				< .001				< .001
< 50 years	27,298 (11.4)	7823 (7.4)	12,647 (13.7)	6828 (16.7)		6,18 5 (6.8)	9949 (12.6)	5972 (16.0)		1638 (11.1)	2698 (19.7)	856 (23.5)	
≥ 50 years	211,528 (88.6)	97,748 (92.6)	79,707 (86.3)	34,073 (83.3)		84,615 (93.2)	68,734 (87.4)	31,282 (84.0)		13,133 (88.9)	10,973 (80.3)	2791 (76.5)	
Sex					< .001				< .001				< .001
Male	123,169 (51.6)	48,528 (46.0)	50,347 (54.5)	24,294 (59.4)		41,485 (45.7)	42,736 (54.3)	22,037 (59.2)		7043 (47.7)	7611 (55.7)	2257 (61.9)	
Female	115,657 (48.4)	57,043 (54.0)	42,007 (45.5)	16,607 (40.6)		49,315 (54.3)	35,947 (45.7)	15,217 (40.8)		7728 (52.3)	6060 (44.3)	1390 (38.1)	
Race					< .001				< .001				< .001
White	189,527 (79.4)	84,786 (80.3)	71,342 (77.2)	33,399 (81.7)		73,464 (80.9)	60,948 (77.5)	30,471 (81.8)		11,322 (76.7)	10,394 (76.0)	2928 (80.3)	
Black	26,717 (11.2)	13,297 (12.6)	10,293 (11.1)	3217 (7.9)		10,880 (12.0)	8496 (10.8)	2893 (7.8)		2417 (16.4)	1797 (13.1)	324 (8.9)	
Other	21,351 (8.9)	7122 (6.7)	10,138 (11.0)	4091 (10.0)		6113 (6.7)	8687 (11.0)	3705 (9.9)		1009 (6.8)	1451 (10.6)	386 (10.6)	
Unknown	1142 (0.5)	366 (0.3)	581 (0.6)	194 (0.5)		343 (0.4)	552 (0.7)	185 (0.5)		23 (0.2)	29 (0.2)	9 (0.2)	
Tumor Grade					< .001				< .001				< .001
1-2	194,231 (81.3)	80,277 (76.0)	78,859 (85.4)	35,095 (85.8)		70,987 (78.2)	68,632 (87.2)	32,308 (86.7)		9290 (62.9)	10,227 (74.8)	2787 (76.4)	
3-4	44,615 (18.7)	25,294 (24.0)	13,495 (14.6)	5806 (14.2)		19,813 (21.8)	10,051 (12.8)	4946 (13.3)		5481 (37.1)	3444 (25.2)	860 (23.6)	
Histology					< .001				< .001				< .001
AC	216,534 (90.7)	91,549 (86.7)	86,508 (93.7)	38,477 (94.1)		79,013 (87.0)	74,066 (94.1)	35,138 (94.3)		12,536 (84.0)	12,442 (91.0)	3339 (91.6)	
MAC	20,084 (8.4)	12,648 (12.0)	5298 (5.7)	2138 (5.2)		10,772 (11.9)	4258 (5.4)	1874 (5.0)		1876 (12.7)	1040 (7.6)	264 (7.2)	
SRCC	2208 (0.9)	1374 (1.3)	548 (0.6)	286 (0.7)		1015 (1.1)	359 (0.5)	242 (0.6)		359 (2.4)	189 (1.4)	44 (1.2)	
Stage					< .001				< .001	NA			
0-I	65,139 (27.3)	25,245 (23.9)	25,694 (27.8)	14,200 (34.7)		25,245 (27.8)	25,694 (32.7)	14,200 (38.1)					
II	68,876 (28.8)	34,443 (32.6)	24,814 (26.9)	9619 (23.5)		34,443 (37.9)	24,814 (31.5)	9619 (25.8)					
III	72,722 (30.4)	31,112 (29.5)	28,175 (30.5)	13,435 (32.8)		31,112 (34.3)	28,175 (35.8)	13,435 (36.1)					
IV	32,089 (13.4)	14,771 (14.0)	13,671 (14.8)	3647 (8.9)		NA							

Data are presented as n (%).
Abbreviations: SEER = Surveillance, Epidemiology and End Results; AC = adenocarcinoma; MAC = mucinous adenocarcinoma; NA = not applicable; SRCC = signet-ring cell carcinoma.

Figure 2 Kaplan-Meier Survival Analysis for Patients With Colorectal AC and MAC of Different Tumor Locations. (A) Stage I-II Disease. (B) Stage III Disease. (C) Stage IV Disease



Abbreviations: AC = adenocarcinoma; MAC = mucinous adenocarcinoma.

82.2%, followed by left-sided colon SRCC of 73.6% and rectal SRCC of 62.3% (Supplemental Table 3 in the online version). Although not statistically significantly different, right-sided colon SRCC still had better CSS than left-sided disease for stage III, and, we note, rectal SRCC had the worst survival across all stages. After adjustment, tumor location was an independent prognostic factor for CSS only for stage I-II disease, and rectal SRCC had a significantly worse prognosis in this group (HR, 2.096;95% CI, 1.230-3.571).

Discussion

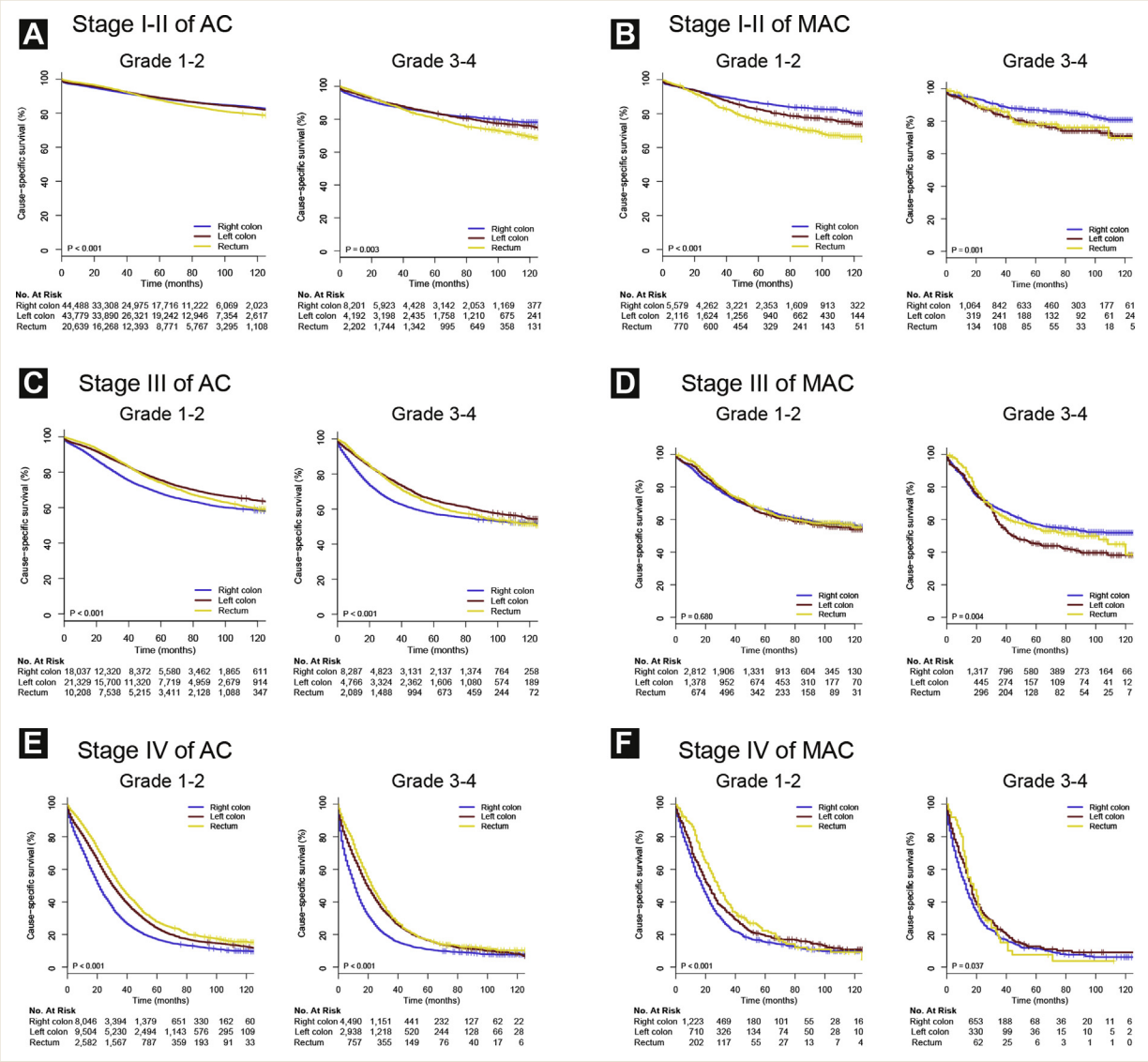
In current study, based on the SEER database, we reported what is to our knowledge the largest retrospective analysis of the survival trends and prognosis of patients with differently located CRCs by

Table 2 Multivariate Cox Regression Analysis for Cause-Specific Survival of AC and MAC by Stage and Tumor Grade

	Stage I-II (N = 134,015)			Stage III (N = 72,722)			Stage IV (N = 32,089)		
Characteristic	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
AC									
All grades									
Right colon	1 [Reference]		< .001	1 [Reference]		< .001	1 [Reference]		< .001
Left colon	1.061	1.021-1.103		0.761	0.736-0.788		0.742	0.720-0.764	
Rectum	1.316	1.256-1.378		0.808	0.774-0.844		0.645	0.615-0.677	
Grade 1-2									
Right colon	1 [Reference]		< .001	1 [Reference]		< .001	1 [Reference]		< .001
Left colon	1.045	1.002-1.089		0.764	0.733-0.795		0.756	0.728-0.783	
Rectum	1.276	1.213-1.343		0.808	0.768-0.850		0.640	0.605-0.677	
Grade 3-4									
Right colon	1 [Reference]		< .001	1 [Reference]		< .001	1 [Reference]		< .001
Left colon	1.129	1.024-1.246		0.760	0.714-0.810		0.715	0.677-0.755	
Rectum	1.523	1.358-1.709		0.821	0.755-0.894		0.661	0.603-0.723	
MAC									
All grades									
Right colon	1 [Reference]		< .001	1 [Reference]		.079	1 [Reference]		< .001
Left colon	1.380	1.225-1.554		1.116	1.014-1.228		0.840	0.768-0.919	
Rectum	1.951	1.670-2.280		1.021	0.903-1.155		0.750	0.646-0.870	
Grade 1-2									
Right colon	1 [Reference]		< .001	1 [Reference]		.811	1 [Reference]		< .001
Left colon	1.321	1.161-1.505		1.013	0.901-1.138		0.831	0.745-0.927	
Rectum	1.979	1.674-2.340		0.959	0.822-1.119		0.712	0.599-0.847	
Grade 3-4									
Right colon	1 [Reference]		< .001	1 [Reference]		.002	1 [Reference]		.089
Left colon	1.775	1.315-2.397		1.352	1.145-1.596		0.851	0.729-0.994	
Rectum	1.752	1.145-2.683		1.125	0.916-1.381		0.843	0.630-1.127	

Cox regression model controlling for age, sex, tumor grade, and disease stage according to 6th edition of American Joint Committee on Cancer.
Abbreviations: AC = adenocarcinoma; CI = confidence interval; HR = hazard ratio; MAC = mucinous adenocarcinoma.

Figure 3 Subgroup Kaplan-Meier Survival Analysis for Patients With Colorectal AC and MAC of Different Tumor Locations by Tumor Grade. (A) Stage I-II Disease of AC. (B) Stage I-II Disease of MAC. (C) Stage III Disease of AC. (D) Stage III Disease of MAC. (E) Stage IV Disease of AC. (F) Stage IV Disease of MAC



Abbreviations: AC = adenocarcinoma; MAC = mucinous adenocarcinoma.

stage, histologic subtype, and tumor grade. The survival trend was studied for disease treated from 1975 to 2009, spanning the old and modern treatment modalities for CRCs. Survival and prognostic analyses were conducted from disease treated from 2000 to 2014, when the modern treatment modalities were widely used nationwide in the United States.

Our analysis the SEER database spanning a period of 35 years permits us to provide an overview of treatment outcomes of CRCs in United States. A clear improvement of 5-year CSS was observed. Specifically, the most remarkable survival improvement was obtained in regional tumors, which reflected the value of advances in neoadjuvant and adjuvant treatment. For metastatic CRCs, the 5-year CSS was also increased, from 6.1 % in 1975 to 14.5 % in 2009, and a distinct increase of 5-year CSS was observed since 1998, the year that the first modern chemotherapeutic medicine, irinotecan, was approved by the US Food and Drug Administration. However, according to 2 highly specialized cancer centers, MD Anderson Cancer Center and the Mayo Clinic,[16] a 35% of 5-year overall survival was obtained in patients with metastatic CRCs, which illustrates the space for great improvement for metastatic CRCs nationwide.

Our study demonstrated that right-sided colon cancers manifested varied outcomes for tumors of different stage, histopathology, and grade, although a meta-analysis of 1,437,846 colon cancer patients by Petrelli et al[17] showed left-sided primary tumor location was associated with significantly reduced risk of death independent

of stage. For metastatic tumors, right-sided tumors had a worse prognosis than left-sided tumors for both AC and MAC of CRCs.[9-11,18] However, the prognostic impact of sidedness for nonmetastatic (stage I-III) CRCs remains unclear. In stage I-II CRCs, we found a better survival of right-sided tumors regardless of histology and tumor grade, which was consistent with SEER-based studies by Meguid et al,[13] Benedix et al,[3] and Weiss et al.[12] One possible explanation for the inconsistency between survival and location in tumors with early and advanced stage may be the different distribution of MSI. MSI predominantly exists in right-sided colon cancers,[19] and less than 5% of left-sided colon and rectal cancers presented MSI.[20] Phipps et al[21] showed that unlike distal colon and rectal cancer, proximal colon cancer survival is especially dependent on MSI status. In addition, MSI-high tumors also have a more favorable stage distribution. Jernvall et al[22] estimated that 20% to 25% of stage II right-sided cancers are MSI-high, and that fewer than 15% of stage III right-sided cancers have the same attribute, with even fewer in stage IV CRC.

In patients with stage III CRCs, we found that patients with right-sided tumors had significantly worse survival than those with left-sided tumors in all histologic subtypes combined, which is also consistent with previous studies.[3,12,13] Compared to the survival of tumor sidedness in metastatic CRCs, similar outcome features were observed in patients with stage III colon cancer who had locally metastatic disease. The intrinsic causes for these features need to be further explored. However, when stratified by histology, right-sided stage III MAC resulted in better survival than left-sided colon MAC; the difference was mainly reflected in poorly differentiated MAC. Gao et al[23] found that MAC was an independent protective survival indicator in right-sided colon cancer, which can be explained by the predominant distribution of MSI-high tumors in right-sided colon[19] and MAC histology.[24] Yoshioka et al[25] studied clinicopathologic and genetic differences of colorectal MAC by grade; they found that high grade was an independent prognostic factor for disease-free survival and overall survival, while low grade was not. They also revealed that low-grade MAC had a considerably larger number of mutations. Poorly differentiated tumors were reported to have more MSI-high distribution and *BRAF* mutations,[26,27] which are also characteristics for right-sided cancers. These may explain the survival disparity by tumor location in poorly differentiated stage III MAC.

In our study, patients with colorectal SRCC showed distinctly lower 5-year CSS than AC and MAC, which may due to its lower R0 resection rate,[28] as well as resistance to chemotherapy and radiotherapy.[29] We also found that right-sided tumors of stage I-II disease resulted in a lower mortality than left-sided tumors. Similar to MAC, more MSI-high tumors were found in SRCC than in AC.[30] Together with the fact that more MSI-high tumors can be found in early-stage tumors, the survival difference of different locations in stage I-II SRCC may be explained.

Our study has several limitations. First, the SEER database does not record detailed pathologic parameters, such as neural or vascular invasion, or treatment information regarding quality of surgery and receipt of chemotherapy or radiotherapy, which may be closely related to survival outcomes. Second, molecular profiles of cancers, such as MSI, *KRAS*, and *BRAF* mutations, are missing, which does not permit us to study the intrinsic mechanisms of survival differences in various subgroups. Finally, the cohort of the SEER 9 registry covers patients diagnosed across 4 decades, and the termination and diagnosis criteria of MAC and SRCC may differ over time, which may cause bias regarding the incidence of these 2 rare histologic subtypes. However, the size of the present study, which we believe to be the largest to date, and the long duration of follow-up compensate for these drawbacks to a great extent and provide a comprehensive epidemiologic picture of CRC.

Conclusion

The relationship between location and prognosis in CRC is not straightforward. For stage I-II CRCs, patients with right-sided colon cancer have better survival than those with left-sided tumors, regardless of histology and tumor grade. For CRCs with metastases—be they regional lymph node metastases or distant metastases—right-sided colon cancer resulted in distinctly worse survival than left-sided disease. It would be better to stratify CRC into 2 subgroups, tumors without any metastases and tumors with lymph node or distant metastases, to investigate their prognostic difference by tumor location; this may be of great importance to explore the intrinsic mechanisms of tumors.

Clinical Practice Points

- Sidedness has become a hot spot of clinical and basic research to help predict prognosis and to guide personalized treatment for patients with CRCs. It is known that patients with metastatic right-sided CRCs have inferior overall survival and treatment response to anti-EGFR therapy. However, the prognostic impact of tumor sidedness for nonmetastatic (stage I-III) CRC remains controversial.
- Though previous studies have initially showed that patients with stage II right-sided CRC have better survival than those with left-sided disease, no further subgroup analyses were conducted. The prognostic effect of tumor sidedness may depend on histopathologic factors other than disease stage.
- Our study was designed to explore the prognostic effect of tumor sidedness by subgroup survival analyses according to histology and tumor grade in stage I-IV CRCs based on the SEER database.
- We found that patients with right-sided tumors had better survival within stage I-II disease, regardless of tumor grade and histology. Within stage III disease, right-sided AC resulted in worse survival, while right-sided poorly differentiated mucinous and SRCC resulted in significantly better survival.
- We found that right-sided colon cancer had distinctly worse survival than left-sided disease for CRCs with metastases, regardless of whether the metastases were regional lymph node metastases or distant metastases.
- It would be better to stratify CRC into 2 subgroups, tumors without any metastases and tumors with lymph node or distant metastases, to investigate their prognostic difference by tumor location.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2018.10.005.

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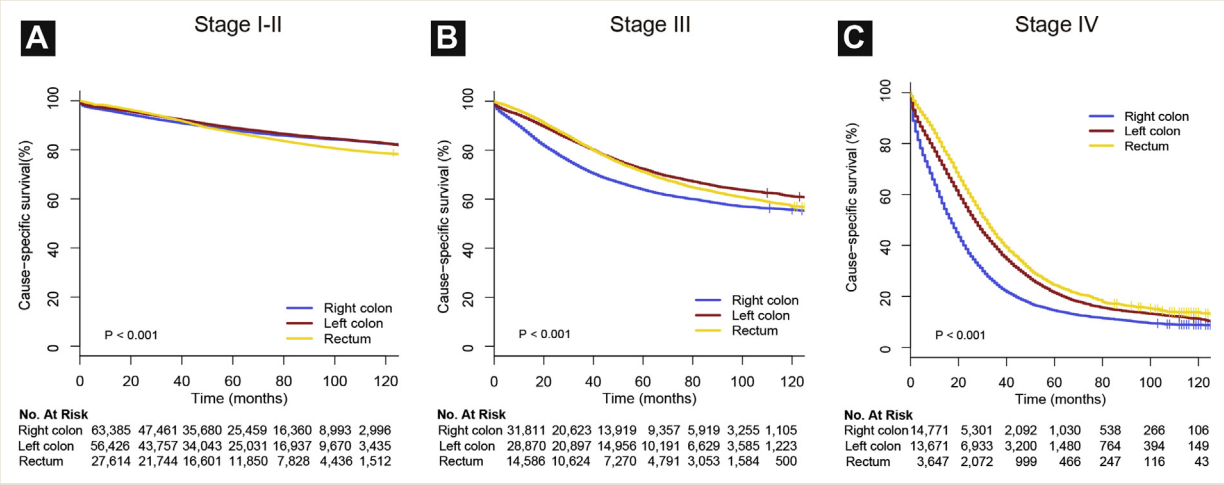
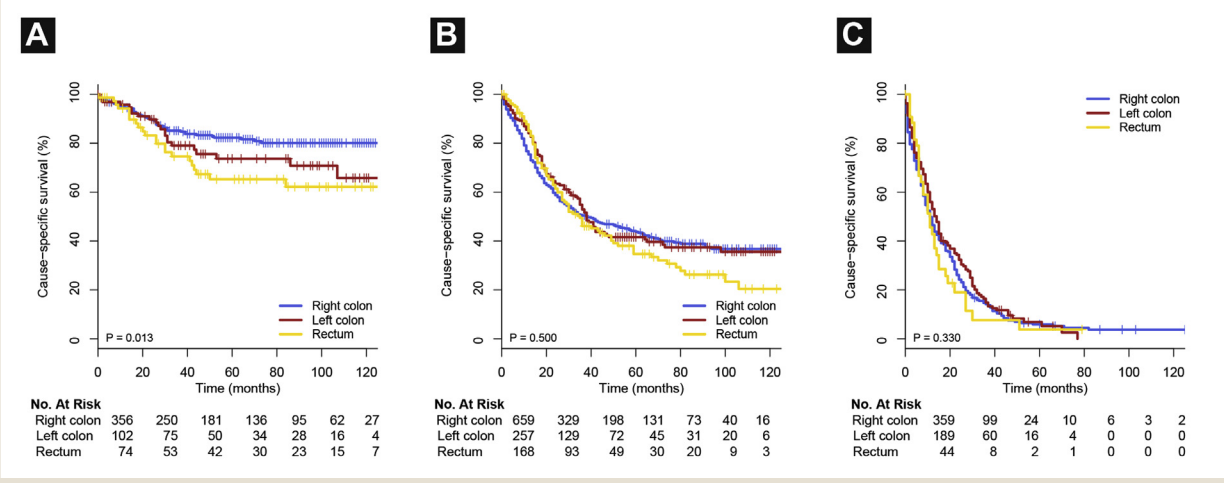
Supplemental Figure 1 Kaplan-Meier Survival Analysis by Disease Site and Stage. Survival of Patients With Right Colon (n = 105,571), Left Colon (n = 92,354), and Rectum Cancer (n = 40,901). (A) Stage I-II Disease. (B) Stage III Disease. (C) Stage IV Disease



Supplemental Figure 2 Kaplan-Meier Survival Analysis of Patients With Colorectal SRCC by Tumor Location. (A) Stage I-II Disease. (B) Stage III Disease. (C) Stage IV Disease



Abbreviation: SRCC = signet-ring cell carcinoma.

Supplemental Table 1 Multivariate Cox Regression Analyses for Cause-Specific Survival in SEER 18 Cohort, 2000-2014

	Stage I-II (N = 134,015)			Stage III (N = 72,722)			Stage IV (N = 32,089)		
Characteristic	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age at Diagnosis			< .001			< .001			< .001
< 50 years	1 [Reference]			1 [Reference]			1 [Reference]		
≥ 50 years	1.805	1.687-1.931		1.519	1.451-1.591		1.318	1.270-1.368	
Sex			.197			.373			.047
Male	1 [Reference]			1 [Reference]			1 [Reference]		
Female	0.979	0.948-1.011		0.987	0.960-1.016		1.027	1.000-1.055	
Tumor Location			< .001			< .001			< .001
Right colon	1 [Reference]			1 [Reference]			1 [Reference]		
Left colon	1.091	1.052-1.132		0.799	0.774-0.825		0.755	0.734-0.777	
Rectum	1.363	1.304-1.425		0.841	0.807-0.875		0.661	0.632-0.692	
Histologic Subtype			< .001			< .001			< .001
AC	1 [Reference]			1 [Reference]			1 [Reference]		
MAC	1.135	1.074-1.200		1.216	1.164-1.271		1.129	1.082-1.179	
SRCC	1.231	1.005-1.507		1.864	1.704-2.038		1.311	1.194-1.438	
Tumor Grade			< .001			< .001			< .001
1-2	1 [Reference]			1 [Reference]			1 [Reference]		
3-4	1.341	1.284-1.401		1.527	1.480-1.575		1.498	1.456-1.541	
Stage			< .001						
0-I	1 [Reference]								
II	2.338	2.256-2.422							

Abbreviations: AC = adenocarcinoma; CI = confidence interval; HR = hazard ratio; MAC = mucinous adenocarcinoma; SEER = Surveillance, Epidemiology, and End Results; SRCC = signet-ring cell carcinoma.

Supplemental Table 2 Five- and 10-Year CSS of AC and MAC by Stage, Tumor Location, and Tumor Grade

Characteristic	Stage I-II (N = 134,015)				Stage III (N = 72,722)				Stage IV (N = 32,089)			
	5-Year CSS (%)	*P*	10-Year CSS (%)	*P*	5-Year CSS (%)	*P*	10-Year CSS (%)	*P*	5-Year CSS (%)	*P*	10-Year CSS (%)	*P*
AC												
All grades												
Right colon	88.0	< .001	82.5	< .001	64.5	< .001	56.5	< .001	14.8	< .001	9.1	< .001
Left colon	88.6		82.1		73.5		62.1		22.0		11.5	
Rectum	87.0		78.2		71.9		57.9		25.1		14.4	
Grade 1-2												
Right colon	88.8	.019	83.3	< .001	67.9	< .001	58.5	< .001	17.0	< .001	9.8	< .001
Left colon	89.0		82.7		75.4		63.9		23.8		12.5	
Rectum	87.7		79.2		74.0		59.2		27.7		15.6	
Grade 3-4												
Right colon	83.6	.149	78.2	.003	57.2	< .001	51.9	< .001	10.8	< .001	7.6	< .001
Left colon	83.6		75.5		65.2		54.6		16.4		8.4	
Rectum	80.6		69.4		62.2		51.6		16.5		10.2	
MAC												
All grades												
Right colon	86.4	< .001	80.5	< .001	63.1	.276	55.2	.308	13.9	< .001	8.5	< .001
Left colon	82.1		73.8		58.8		49.9		17.2		9.9	
Rectum	76.1		66.9		61.9		50.9		19.1		8.1	
Grade 1-2												
Right colon	86.3	< .001	80.4	< .001	65.9	.589	56.6	.690	15.3	< .001	9.7	< .001
Left colon	82.7		74.3		63.2		53.8		19.1		10.7	
Rectum	75.7		66.4		65.4		55.3		22.3		NA	
Grade 3-4												
Right colon	86.8	.002	80.8	.001	57.1	.009	51.9	.005	11.4	.045	6.1	.037
Left colon	78.2		70.8		45.1		38.1		12.6		9.3	
Rectum	78.1		69.8		54.3		38.4		7.5		NA	

Abbreviations: AC = adenocarcinoma; CSS = cause-specific survival; MAC = mucinous adenocarcinoma.

Supplemental Table 3 Kaplan-Meier Analysis and Multivariate Cox Regression Analysis for Cause-Specific Survival of SRCC by Stage

Characteristic	Kaplan-Meier Analysis				Multivariate Analysis*		
	5-Year CSS (%)	*P*	10-Year CSS (%)	*P*	HR	95% CI	*P*
Stage I-II							
Right colon	82.2	.022	80.1	.018	1 [Reference]		.017
Left colon	73.6		65.7		1.586	0.952-2.643	
Rectum	62.3		62.1		2.096	1.230-3.571	
Stage III							
Right colon	43.8	.711	36.7	.502	1 [Reference]		.555
Left colon	41.6		35.6		0.944	0.759-1.175	
Rectum	34.7		20.4		1.097	0.863-1.395	
Stage IV							
Right colon	5.8	.230	3.7	.325	1 [Reference]		.592
Left colon	6.8		NA		0.949	0.774-1.163	
Rectum	3.8		NA		1.147	0.803-1.638	

Abbreviations: CI = confidence interval; CSS = cause-specific survival; HR = hazard ratio; SRCC = signet-ring cell carcinoma.
*Cox regression model controlling for age, sex, tumor grade, and stage according to 6th edition of American Joint Committee on Cancer.