Better survival of right-sided than left-sided stage II colon cancer: a propensity scores matching analysis based on SEER database

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ABSTRACT

Background/Aims: Most studies have found that right-sided colon cancer (RCC) has worse prognosis than left-sided colon cancer (LCC), especially in stage III, but the reported prognosis of stage II colon cancer is variable. This study aimed to evaluate the impact of tumor location on survival outcomes in stage II colon cancer.

Materials and Methods: Patients with stage II colon cancer were identified in the Surveillance, Epidemiology, and End Results database from 2004 to 2009. The effect of tumor location on overall survival and cancer-specific survival was analyzed using Cox proportional hazards regression models and propensity score matching.

Results: Of 16,519 patients, 69.6% had RCC and30.4% had LCC. In unadjusted analyses, RCC had a 13% increased overall mortality risk (hazards ratio [HR], 1.13; 95% confidence interval [CI], 1.07-1.19; p<0.001) but an18% reduction in cancer-specific mortality risk compared with LCC (HR, 0.82; 95% CI, 0.76-0.89; p<0.001). After propensity scores matching analyses, RCC had a 21% reduced overall mortality risk (HR, 0.79; 95% CI, 0.72-0.87; p<0.001) and a 49% reduction in cancer-specific mortality risk compared with LCC (HR, 0.51; 95% CI, 0.44-0.60; p<0.001).

Conclusion: When adjusted for multiple clinicopathological features, stage II RCC showed better prognosis than stage II LCC.

Keywords: Right colon cancer, left colon cancer, survival colonic neoplasms, SEER program, survival analysis

INTRODUCTION

Colorectal cancer is the third most common cancer in terms of incidence and mortality worldwide (1). Survival rates in colon cancer are influenced by many factors, including stage and histological type. Some investigators have found that right-sided colon cancer (RCC) was more common than left-sided colon cancer (LCC) in older patients and female patients and in tumors with worse histological grade (2-4). The concept that there are 2 colons (proximal and distal to the splenic flexure) is familiar to embryologists and physiologists (5), but tumor location as an independent prognostic factor in colon cancer is not common.

Information about the relationship between colon tumor location and survival is conflicting. Most studies have found that RCC, especially stage III, has a worse prognosis than LCC (6-8) but the prognosis of stage II colon cancer is variable. Some studies have found no difference in survival between stage II RCC and stage II LCC (9, 10); some have found that stage II RCC has a worse prognosis than stage II LCC (11, 12); and another has reported that stage II RCC has a better survival rate than stage II LCC (13). Insufficient correction of confounding factors and inaccurate staging may be responsible for these disparate results, but most cases of both RCC and LCC were American Joint Committee on Cancer (AJCC) stage II (11). To resolve the issue of correlation, or lack of it, between tumor location and survival in stage II colon cancer, we conducted a propensityscore matching analysis using the Surveillance, Epidemiology, and End Results (SEER) database on survival in stage II colon cancer.

MATERIALS AND METHODS

Because all the data used in this study were publicly available, this study did not require ethical approval.

Data Sources and Patient Selection

This is a retrospective cohort study. SEER is a population-based database that covers 18 geographic areas

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in the United States and involves approximately 28% of the population of United States (based on the 2010 census) (14). SEER*Stat 8.3.5 was performed to identify all the patients diagnosed with primary AJCC stage II colon adenocarcinoma. Diagnosis dates were limited from January 1, 2004 to December 31, 2009 because of the AJCC staging (AJCC tumor staging 6th edition) homogeneity of the encoded data during that period. All patients were 18 years or older and had undergone surgery with curative intent. Primary treatment codes 30 to 90 were defined as surgery. The primary cancer site codes C18.0, C18.2, C18.3, C18.4, C18.5, C18.6, and C18.7 were used to identify the tumor location. The splenic flexure of the colon is regarded as the dividing point between the right and left colon (11). Therefore, RCC includes C18.0 (cecum), C18.2 (ascending colon), C18.3 (hepatic flexure of the colon), and C18.4 (transverse colon). LCC includes C18.5 (splenic flexure of the colon), C18.6 (descending colon), and C18.7 (sigmoid colon). The International classification of diseases for oncology 3rd edition (ICD-O-3) histological types 8140-8147, 8210-8211, 8220-8221, 8260-8263, 8480-8481, and 8490 were defined as adenocarcinoma. The exclusion criteria were unknown grade of tumor, no curative surgery performed, intraoperative radiation or radiation given before or after surgery, other malignancies preceding the colon cancer, less than 12 lymph nodes examined, chemotherapy administered, and death within 30 days of surgery. The sample size was 16,519 patients.

Statistical Analysis

The categorical descriptive statistics between RCC and LCC were performed using the chi-squared (c^2) test. Survival analysis was shown in Kaplan-Meier curves and analyzed using log-rank tests and multivariate Cox proportional hazards models. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 23.0. (IBM Corp.; Armonk, NY, USA). A 2-sided $p<0.05$ was considered statistically significant.

In observational studies, patients in the groups being compared often differ in crucial covariates. Thus, covariate imbalances can lead to biased estimates of the treatment effect. Propensity scores are used to create matched pairs that balance many observed covariates (15, 16). We performed a matched dataset using propensity score matching for sex, age, race, tumor grade, stage, and carcinoembryonic antigen (CEA) status. A 1:1 matched cohort that included RCC and LCC was created using SPSS propensity score matching calculator.

MAIN POINTS

- *The prognosis of colon cancer is related to a number of factors.*
- *After propensity scores matching analyses, stage II RCC has a better prognosis than stage II LCC.*

RESULTS

Patient Characteristics

Between January 2004 and December 2009, 39,338 patients with stage II colon cancer were identified, of which 22,819 were excluded. The flowchart of the patients' cohort from the SEER database is illustrated in Figure 1. Among the remaining (eligible) 16,519 patients, 11,495 (69.6%) were in the RCC group and 5,024 (30.4%) were in the LCC group. Using the propensity score, patients were matched into an RCC group of 3,719 and an LCC group of 3,719. Baseline characteristics and the grade and stage of the tumors are listed in Table 1. Moreover, 54% of the patients were women; median age was 73 years; 71% of patients were 65 years and older; and 82% of patients were white. The median follow-up time was 82 months (range, 0-143 months). RCC was more prevalent than LCC among female patients (56% vs. 48%, $p<0.05$), older patients (75% vs. 63% ≥65, $p<0.05$), and poorly differentiated or undifferentiated grade (20% vs. 11%, $p<0.05$). Of the tumors, 75% were moderately differentiated and 91% were stage IIA ($p<0.05$). The level of CEA was unbalanced between the 2 groups ($p<0.05$).

Impact of Tumor Location on Survival

At the end of the follow-up period, 7,178 (43.5%) patients were deceased; 2,458 (14.9%) from colon cancer and 4,720 (28.6%) from other causes. Unadjusted Cox proportional hazards models showed that the overall mortality risk in patients with RCC was increased by 13% (hazard ratio [HR], 1.13; 95% confidence interval [CI], 1.07-1.19; $p<0.001$), but the risk for cancer-specific mortality decreased by 18% compared with that of LCC (HR, 0.82; 95% CI, 0.76-0.89; $p<0.001$) (Tables 2 and 3). After multivariate risk adjustment, the overall and cancer-specific mortality did not change substantially using univariate analysis (Tables 2 and 3). The 5-year overall survival in patients with RCC was 71.9% (95%CI, 71.1%-72.7%) compared with 73.4% (95%CI, 72.2%-74.6%) for patients with LCC ($p<0.001$) (Figure 2). The 5-year cancer-specific survival in patients with RCC was 88.2% (95%CI, 87.6%-88.8%) compared with 86.5% (95%CI, 85.5%-87.5%) for patients with LCC ($p<0.001$) (Figure 3).

Table 1. Baseline characteristics of patients included in the study.

Characteristics	Total (16,519; n, %)	Right-sided cancer (11,495; 69.6%) (n, %)	Left-sided cancer (5024, 30.4%) (n, %)	p
Sex				<0.001[a]
Male	7,645 (46.3)	5,045 (43.9)	2,600 (51.8)	
Female	8,874 (53.7)	6,450 (56.1)	2,424 (48.2)	
Age (years)				<0.001[a]
<65	4,798 (29)	2,913 (25.3)	1,885 (37.5)	
≥65	11,721 (71)	8,582 (74.7)	3,139 (62.5)	
Race				<0.001[a]
White	13,459 (81.5)	9,516 (82.8)	3,943 (78.5)	
Black	1,773 (10.7)	1,231 (10.7)	542 (10.8)	
Other	1,287 (7.8)	748 (6.5)	539 (10.7)	
Tumor grade				<0.001[a]
Well differentiated	1,247 (7.5)	861 (7.5)	386 (7.7)	
Moderately differentiated	12,369 (74.9)	8,294 (72.2)	4,075 (81.1)	
Poorly differentiated	2,694 (16.3)	2,164 (18.8)	530 (10.5)	
Undifferentiated	209 (1.3)	176 (1.5)	33 (0.7)	
Stage (AJCC 6th edition)				0.044[a]
IIA	15,017 (90.9)	10,484 (91.2)	4,533 (90.2)	
IIB	1,502 (9.1)	1,011 (8.8)	491 (9.8)	
CEA				0.013[a]
Positive	3,380 (20.5)	2,287 (19.9)	1,093 (21.8)	
Negative	6,023 (36.5)	4,265 (37.1)	1,758 (35.0)	
Borderline	76 (0.5)	50 (0.4)	26 (0.5)	
Unknown	7,040 (42.6)	4,893 (42.6)	2,147 (42.7)	

AJCC: American Joint Committee on Cancer; CEA: carcinoembryonic antigen.
[a]χ^2 test

Tumor Location as a Prognostic Factor for Survival after Propensity Score Matching

To further analyze the findings from univariate and multivariate Cox regression, propensity score matching was performed. In the remaining 7,438 patients, no afore mentioned listed bias between patients with RCC and LCC was observed (Table 4). When performing the Cox regression analysis after propensity score matching, the overall mortality risk in patients with RCC was decreased by 21% (HR=0.79; 95% CI, 0.72–0.87; p<0.001) and the risk for cancer-specific mortality decreased by 49% (HR, 0.51; 95% CI, 0.44-0.60; p<0.001). After propensity score matching, the 5-year overall survival in patients with RCC was 89.0%(95%CI, 88.0%-90.0%) compared with 79.3% (95%CI, 77.9%-80.7%) for patients with LCC (p<0.001) (Figure 4) and the 5-year cancer-specific survival in patients with RCC was 95.7%(95%CI, 95.1%-96.3%) compared with 89.6%(95%CI, 88.6%–90.6%) for patients with LCC (p<0.001) (Figure 5).

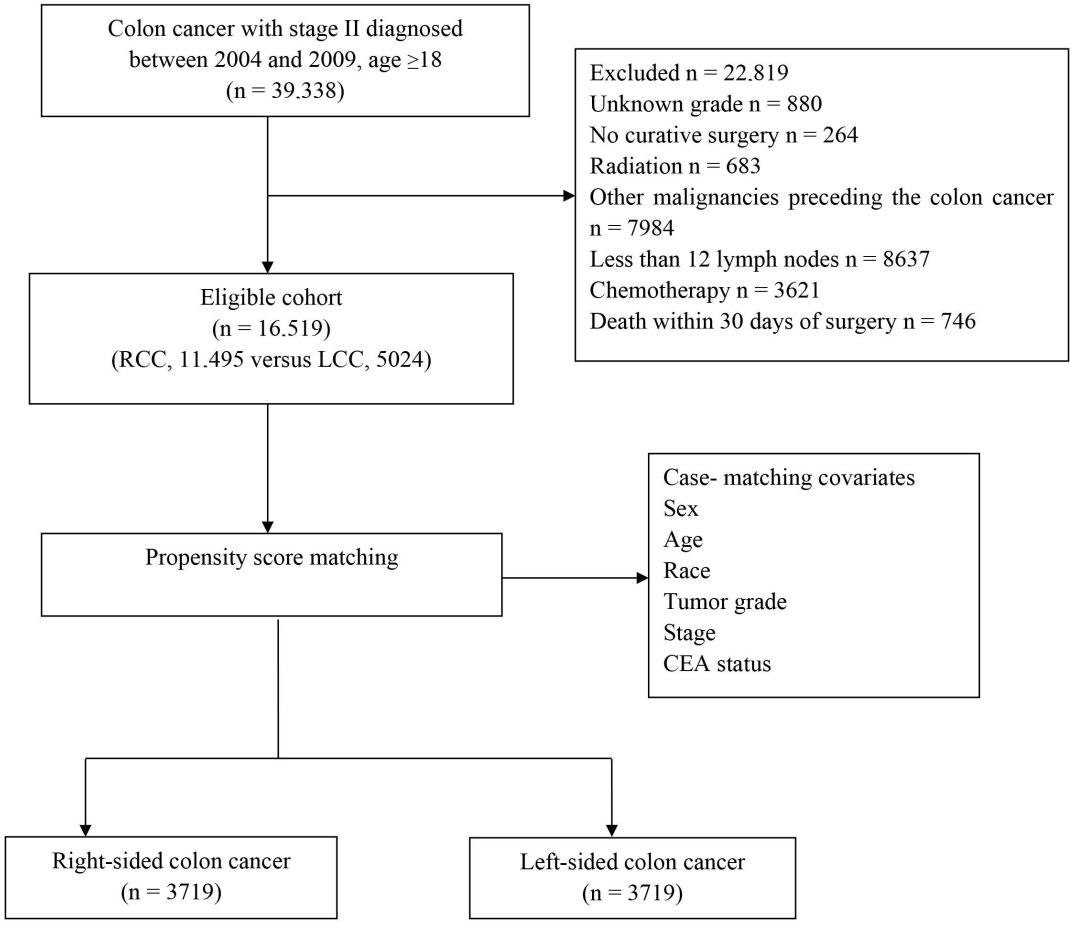

Figure 1. Flowchart of patients' cohort from the Surveillance, Epidemiology, and End Results database.

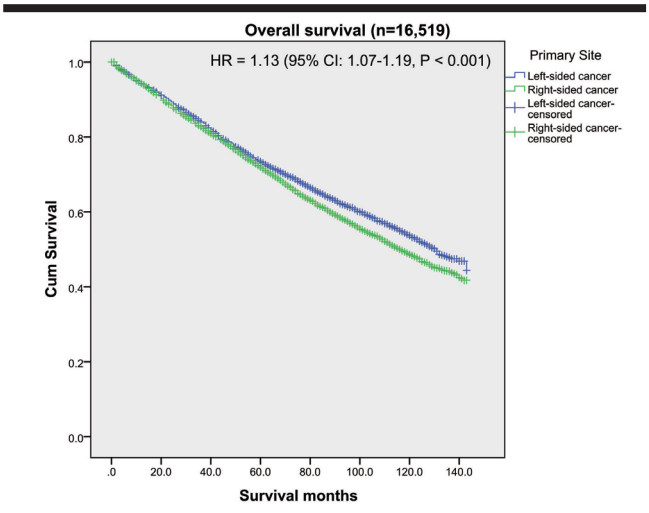

Figure 2. Kaplan-Meier plots of overall survival in patients with right-sided colon cancer and left-sided colon cancer.

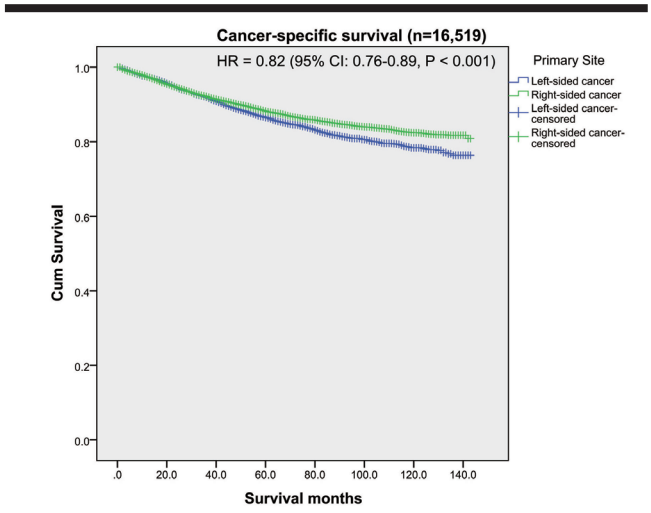

Figure 3. Kaplan-Meier plots of cancer-specific survival in patients with right-sided colon cancer and left-sided colon cancer.

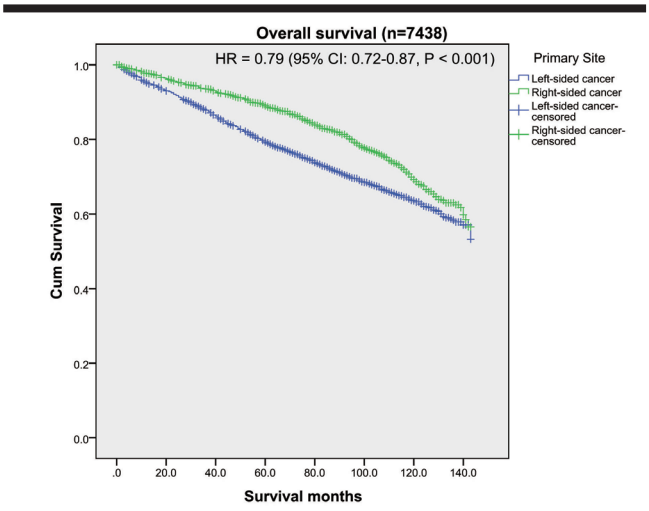

Figure 4. Kaplan-Meier plots of overall survival in patients with right-sided colon cancer and left-sided colon cancer after propensity score matching.

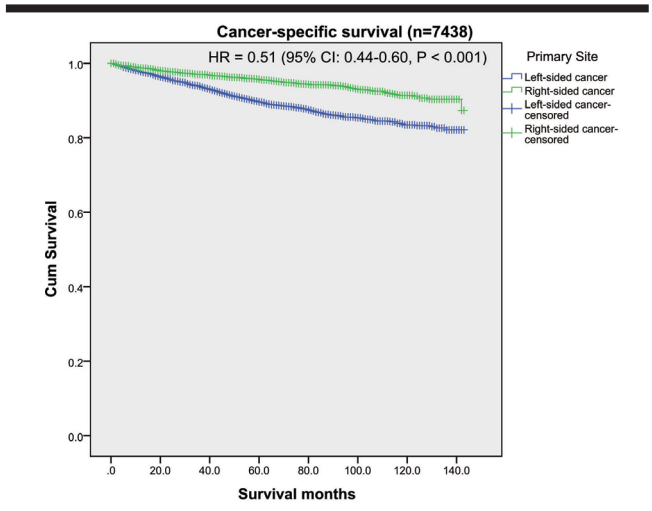

Figure 5. Kaplan-Meier plots of cancer-specific survival in patients with right-sided colon cancer and left-sided colon cancer after propensity score matching.

Table 2. Univariate and multivariate analyses of overall survival in patients with stage II colon cancer.

	Univariate analysis		Multivariate analysis	
Variable	HR (95%CI)	p	HR (95%CI)	p
Sex				
Male	Reference		Reference	
Female	1.28 (1.22,1.34)	<0.001	1.22 (1.16,1.27)	<0.001
Age(years)				
<65	Reference		Reference	
≥65	2.88 (2.71,3.07)	<0.001	3.24 (3.04,3.46)	<0.001
Race				
White	Reference		Reference	
Black	0.11 (0.09,0.13)	<0.001	0.10 (0.09,0.11)	<0.001
Other	0.40 (0.36,0.45)	<0.001	0.35 (0.31,0.38)	<0.001
Tumor grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.15 (1.05,1.26)	0.004	1.01 (0.92,1.11)	0.804
Poorly differentiated	1.43 (1.29,1.58)	<0.001	1.26 (1.13,1.40)	<0.001
Undifferentiated	1.36 (1.10,1.69)	0.005	1.19 (0.96,1.47)	0.122
Stage (AJCC 6th edition)				
IIA	Reference		Reference	
IIB	1.66 (1.55,1.78)	<0.001	1.52 (1.41,1.63)	<0.001
CEA				
Positive	Reference		Reference	
Negative	0.63 (0.59,0.67)	<0.001	0.51 (0.47,0.54)	<0.001
Borderline	0.93 (0.68,1.28)	0.659	0.60 (0.44,0.83)	0.002
Unknown	0.81 (0.77,0.86)	<0.001	0.73 (0.69,0.78)	<0.001
Primary site				
Left	Reference		Reference	
Right	1.13 (1.07,1.19)	<0.001	1.28 (1.21,1.35)	<0.001

AJCC: American Joint Committee on Cancer; CEA: carcinoembryonic antigen; HR: hazard ratio; CI: confidence interval.

Table 3. Univariate and multivariate analysis of cancer-specific survival in patients with stage II colon cancer.

	Univariate analysis		Multivariate analysis	
Variable	HR (95%CI)	p	HR (95%CI)	p
Sex				
Male	Reference		Reference	
Female	1.23(1.13,1.33)	<0.001	1.15(1.06,1.25)	<0.001
Age(years)				
<65	Reference		Reference	
≥65	2.87 (2.57,3.20)	<0.001	3.35 (2.99,3.76)	<0.001
Race				
White	Reference		Reference	
Black	0.10 (0.08,0.14)	<0.001	0.11 (0.09,0.15)	<0.001
Other	0.47 (0.39,0.55)	<0.001	0.47 (0.40,0.56)	<0.001
Tumor grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.23 (1.05,1.46)	0.012	1.08 (0.91,1.27)	0.391
Poorly differentiated	1.47 (1.22,1.76)	<0.001	1.28 (1.06,1.54)	0.009
Undifferentiated	1.26 (0.85,1.86)	0.246	1.11 (0.75,1.64)	0.604
Stage (AJCC 6th edition)				
IIA	Reference		Reference	
IIB	2.79 (2.52,3.09)	<0.001	2.54 (2.29,2.82)	<0.001
CEA				
Positive	Reference		Reference	
Negative	0.56 (0.50,0.62)	<0.001	0.45 (0.40,0.50)	<0.001
Borderline	0.77 (0.43,1.36)	0.366	0.43 (0.24,0.75)	0.003
Unknown	0.75 (0.68,0.83)	<0.001	0.64 (0.58,0.71)	<0.001
Primary site				
Left	Reference		Reference	
Right	0.82 (0.76,0.89)	<0.001	0.79 (0.72,0.86)	<0.001

AJCC: American Joint Committee on Cancer; CEA: carcinoembryonic antigen; HR: hazard ratio; CI: confidence interval.

DISCUSSION

Our study demonstrated the impact of tumor location on survival outcomes in patients with stage II colon cancer enrolled in the SEER database from 2004 to 2009. The results revealed that stage IIRCC had a significantly better overall survival and cancer-specific survival than stage II LCC after controlling for clinicopathological features using propensity score matching analysis.

We focused on stage II colon cancer because the impact of tumor location on survival outcomes is controversial. To achieve valid results, we applied strict inclusion and exclusion criteria. A recent study (7) included all patients in the SEER Medicare database from 1992 to 2005. The age of the patients included was 66 years and older at the time of diagnosis, whereas our study included patients who were 18 years and older. Although the results were similar, our study applies to a broader age group.

Table 4. Characteristics of patients after propensity score matching.

Characteristics	Right-sided cancer (3,719; n, %)	Left-sided cancer (3,719; n, %)	p
Sex			0.816
Male	1,778 (47.8)	1,768 (47.5)	
Female	1,941 (52.2)	1,951 (52.5)	
Age (years)			0.493
<65	764 (20.5)	788 (21.2)	
≥65	2,955 (79.5)	2931 (78.8)	
Race			0.114
White	3,059 (82.3)	3,122 (83.9)	
Black	390 (10.5)	365 (9.8)	
Other	270(7.3)	232(6.2)	
Tumor grade			0.860
Well differentiated	234 (6.3)	217 (5.8)	
Moderately differentiated	3,064 (82.4)	3,075 (82.7)	
Poorly- differentiated	406 (10.9)	413 (11.1)	
Undifferentiated	15 (0.4)	14 (0.4)	
Stage (AJCC 6th edition)			0.430
IIA	3,411 (91.7)	3,392 (91.2)	
IIB	308(8.3)	327 (8.8)	
CEA			0.748
Positive	381(10.2)	394 (10.6)	
Negative	1,632 (43.9)	1,643 (44.2)	
Borderline	15 (0.4)	20 (0.5)	
Unknown	1,691 (45.5)	1,662 (44.7)	

AJCC: American Joint Committee on Cancer; CEA: carcinoembryonic antigen; HR: hazard ratio; CI: confidence interval.

Although we used the SEER database and their assigned stage II colon cancer, we excluded patients with less than 12 lymph nodes detected. This exclusion could have 2 effects. First, fewer lymph nodes detected could lead to omission of positive lymph nodes and incorrect staging. A consensus recommendation has stated that at least 12 nodes must be sampled to adequately stage a patient (17). Second, patients with stage II colon cancer with fewer than 12 lymph nodes examined could benefit from adjuvant chemotherapy (18). We also excluded patients who received adjuvant chemotherapy according to the SEER database, which only listed chemotherapy as either "yes" or "no/unknown"; details about the chemotherapy regimens could not be obtained. Moreover, only a small subset benefit from chemotherapy, whereas other patients experience harm, poorer quality of life, and no net benefit (19).

In our study, RCC was associated with an increased risk of overall mortality in unadjusted and risk-adjusted Cox proportional hazard regression analyses but this result was not maintained in the propensity score matching analysis. The prognosis of colon cancer is influenced by many clinicopathological features, such as patients' age, race, and tumor stage and differentiation (20-23). Some studies have found that preoperative CEA level is an independent prognostic factor in potentially curative colon cancer, particularly in those classified as having stage II disease (24). In our study, RCC was associated with a higher propensity of women, older patients, and poorly differentiated or undifferentiated grading. The heterogeneity of these factors between the groups may confound the results.

In other research, RCC has more frequently had high microsatellite instability (MSI) and had deleterious mutations of BRAF. LCC has had more chromosome instability and p53 gene mutation (25). Moreover, MSI and BRAF mutation gradually decreased from the ascending colon to the rectum (26). A greater number of stage II colon cancers were MSI-high compared with stage III, and MSI-high was considered as an independent favorable prognostic factor of survival in patients with colon cancer (27, 28). BRAF gene mutation was an adverse prognostic factor in patients with colon cancer; the adverse effect often occurred in microsatellite stable and MSI-low colon cancers, and the effect was less in tumors with high MSI (29, 30). Chromosome instability and p53 mutation are the factors responsible for poor survival in patients with colon cancer, and p53 mutation type is more common in stage II LCC than in RCC (31). All these factors might be responsible for better survival of patients with stage II RCC than with LCC.

Our study was population based and had adequate sample size; thus, we had enough power to detect the significant differences in overall survival and cancer-specific survival in patients with stage II colon cancer. Propensity score matching was used to balance the known baseline confounders for drawing reliable results. However, our study also had its limitations. First, it was a retrospective study and had the unavoidable bias of this design. We included patients from 2004 to 2009.Medical and surgical

developments over the past period may affect survival. Second, although adjusted for many confounders, data on other factors that may have been important, such as lymph vascular and perineural invasion, were unavailable from the SEER database (32). Thus, our results could be subject to confounding. Finally, the level of MSI, mutations of BRAF and p53 and chromosome instability were unknown. These deficiencies contributed to our inability to directly identify the factor(s) that might be responsible for better survival in stage II RCC than in LCC.

In conclusion, patients with stage II RCC had a better prognosis than did patients with stage II LCC after adjusting for multiple clinic pathological features. Studies should be undertaken to identify the genetic or molecular mechanisms responsible for these differences.

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Informed Consent: N/A.

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