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Original Article

Comparison of 627 patients with right- and left-sided colon cancer in China: Differences in clinicopathology, recurrence, and survival

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Abstract

Objective: Recent studies have reported increased mortality for right-sided colon cancers; however, the results are conflicting for different stage tumors. We examined the differences in clinicopathology between right- and left-sided colon cancers and the relationships between colon cancer location (right- and left-side) and 5-year disease-free survival (DFS) and overall survival (OS).

Methods: We identified patients from 2005 to 2008 with stage II/III colon cancer who underwent surgery for curative intent. We explored the impact of the tumor location on the postoperative DFS and OS using univariate and multivariate analyses.

Results: Of 627 patients, 50.6% (317/627) had right-sided colon cancer. These patients were more likely to have weight loss, second primary tumor, elevated preoperative carbohydrate antigen 19-9 (CA19-9), increased incidence of non-adenocarcinoma, more poorly differentiated tumors, vascular invasion, defective mismatch repair, and a lighter smoking history ($P < 0.05$). Right-sided colon cancer had a higher recurrence incidence compared with left-sided cancer (30.6% *vs.* 23.2%, $P = 0.037$), particularly with multiple metastatic sites in the first recurrence (17.5% *vs.* 5.6%, $P = 0.020$). Kaplan−Meier survival curves demonstrated a significant difference in the 5-year DFS rate between right- and left-sided cancers across all stages (68.1% *vs.* 75.2%, $P = 0.043$). However, there was no significant difference in the 5-year OS rate between the two groups (73.8% *vs.* 79.0%, $P = 0.103$). Subgroup analysis demonstrated that patients with left-sided colon cancer had a significantly better 5-year DFS and OS rates compared with those with right-sided disease at stage III (64.3% *vs.* 46.8%, $P = 0.002$; 69.5% *vs.* 53.5%, $P = 0.006$, respectively); there were no significant differences in the 5-year DFS and OS rates at stage II (85.2% *vs.* 85.9%, $P = 0.819$; 89.8% *vs.* 88.5%, $P = 0.803$, respectively). Adjusted Cox regression analysis showed no significant differences in the 5-year OS and DFS rates for stage II [hazard ratio (*HR*) = 1.203, 95% confidence interval (*CI*): 0.605−2.391, $P = 0.598$; *HR* = 0.980, 95%

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CI: 0.542–1.774, $P = 0.948$, respectively] or all stages combined (*HR* = 0.867, 95% *CI*: 0.613–1.227, $P = 0.421$; *HR* = 0.832, 95% *CI*: 0.606–1.142, $P = 0.255$, respectively). However, stage III left-sided cancer had higher 5-year OS and DFS rates (*HR* = 0.626, 95% *CI*: 0.414–0.948, $P = 0.027$; *HR* = 0.630, 95% *CI*: 0.428–0.926, $P = 0.019$, respectively).

Conclusion: We found that right- and left-sided colon cancers had significantly different clinicopathological characteristics. Right-sided colon cancer had a higher incidence of recurrence than left-sided disease. Patients with stage III right-sided colon cancer had a worse prognosis compared with those with stage III left-sided colon cancer.

Keywords: Colon cancer; Location; Recurrence; Survival

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in men and the second in women, with an estimated 1.4 million cases and 693,900 deaths occurring in 2012 worldwide.[1] In China, the incidence of CRC is increasing rapidly and it is now ranked fifth in terms of morbidity and mortality among all malignancies.[2] Studies have shown that right-sided colon cancers are becoming more prevalent, with a decline in the incidence of left-sided colon cancers.[3,4] It has been suggested that there may be two distinct categories of cancer: right- and left-sided colon cancers that arise proximally and distally to the splenic flexure, respectively.[5] Subsequently, several studies have proposed explanations for this difference including genetic, environmental, and embryological factors.[5–7] The primary tumor location has prognostic importance that is related to targeted therapy response in patients with metastatic CRC.[8,9] In 13 first-line randomized controlled trials and one prospective pharmacogenetic study, right-sided colon cancer is associated with a significantly worse prognosis compared to left-sided colon cancer [hazard ratio (*HR*) for overall survival (OS) = 1.56, 95% confidence interval (*CI*): 1.43–1.70, $P < 0.001$)].[8] A meta-analysis of FIRE-3/AIO KRK0306, CALGB/SWOG 80405, and PEAK studies indicated that patients with *RAS* wild-type left-sided colon cancer had a significantly greater survival benefit from the addition of anti-epidermal growth factor receptor (EGFR) treatment compared with anti-vascular endothelial growth factor (VEGF) treatment to standard chemotherapy (*HR* = 0.71, 95% *CI*: 0.58–0.85, $P = 0.0003$).[8]

However, there has been conflicting information regarding the relationship between cancer location and prognosis in patients with stage I–III disease.[10–17] Some studies indicated that right-sided colon cancer has been associated with worse survival than left-sided colon cancer.[10,12] A meta-analysis of 66 studies ($n = 1{,}437{,}846$ patients) with a median follow-up of 65 months revealed that left-sided primary tumor location was associated with a significantly reduced risk of death (*HR* = 0.82, 95% *CI*: 0.79–0.84, $P < 0.001$) independent of the stage.[16] Weiss et al[13] reported no overall difference in 5-year mortality between right- and left-sided colon cancers but found that within stage II disease right-sided cancers had lower mortality while within stage III right-sided cancers had higher mortality. However, Moritani et al[14] found that patients with stage I right-sided colon cancer had a significantly higher 5-year disease-free survival (DFS) rate than did those with left-sided disease; however, there was no significant difference at stages II and III. A population-based analysis of stage I–III colon cancer provided evidence that in stages I and II, the prognosis of right-sided cancer was better for OS (*HR* = 0.89; 95% *CI*: 0.84–0.94 and *HR* = 0.85, 95% *CI*: 0.81–0.89), and a similar prognosis was also observed for stage III (*HR* = 0.99; 95% *CI*: 0.95–1.03).[17]

Therefore, it is unclear whether the primary tumor location is related to DFS and OS among Chinese patients with stage II/III colon cancer. We used a single institutional Chinese database without racial diversity to examine the relationship between tumor site (right-*vs.* left-side) and 5-year mortality. Specifically, we sought to determine if this relationship is consistent across tumor stages.

Methods

Study population

All patients in this study underwent curative resection for colon cancer between January 2005 and December 2008 at the Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China. Histopathological staging was confirmed postoperatively by a consulting pathologist according to American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system. To be eligible for the study, patients had

to be at least 18 years of age, with TNM stage II or III colon cancer, and adequate organ function. The tumor location from the cecum to the sigmoid colon was classified by the seventh edition TNM criteria. The cecum and the ascending and transverse colon were defined as the right-sided colon, whereas the descending and sigmoid colon were defined as the left-sided colon. We excluded patients receiving preoperative chemo- or radiotherapy that can affect the postoperative survival. Patients older than 85 years and those with multiple synchronous large bowel carcinomas or familial adenomatous polyposis were also excluded.

The study protocol was approved by the Medical Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China. The study was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983.

Adjuvant chemotherapy and follow-up

The adjuvant treatment regimens contained oxaliplatin/fluorouracil (FU)/leucovorin (LV) (FOLFOX4), modified FOLFOX6 (mFOLFOX6), and 5-FU/LV. Each cycle of FOLFOX4 consisted of oxaliplatin (85 mg/m^2) on day 1 and LV (200 mg/m^2) and a bolus of 5-FU (400 mg/m^2), followed by a 22-h infusion of 5-FU (600 mg/m^2) on days 1 and 2. This cycle was then repeated every 2 weeks.[18] The formulation of mFOLFOX6 included some modifications to the dosage of LV and the infusion of 5-FU. The 5-FU/LV combination consisted of LV (400 mg/m^2) on day 1 and a bolus of 5-FU (400 mg/m^2) on day 1, followed by a 46-h infusion of 5-FU (2400 mg/m^2). This cycle was repeated every 2 weeks.[19] According to the de Gramont regimen, patients received treatment with a rapid intravenous (i.v.) infusion of LV 200 mg/m^2 and a bolus of 5-FU (400 mg/m^2), followed by a 22-h infusion of 5-FU (600 mg/m^2) on days 1 and 2 which was repeated every 2 weeks.[18] The planned treatment duration according to our standard institutional protocol was 12 cycles.

Most patients were followed according to our standard institutional protocol, which consisted mainly of physical examination, measurement of the serum tumor markers [carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9)], computed tomography, and colonoscopy. For the remaining patients, information regarding clinical outcome and survival was obtained by direct telephone interviews with the patients or their relatives. Tumor recurrence was detected by physical examination, serum CEA assay, and chest, abdominal, and pelvic imaging every 3−6 months for 3 years, and then every 6 months for the following 2 years. After this, patients had annual follow-up examinations. A decision to perform pathological confirmation was made by the treating oncologist. The duration of follow-up was defined as the time between surgery and disease recurrence, or death, or when a patient was "lost to hospital contact" (scheduled follow-up or telephone contact). The cutoff date for our analysis was July 1, 2013.

Statistical evaluations

Demographic and clinicopathological features of the study population were stratified according to primary colon tumor location. Categorical variables were expressed as count and percentage, and the differences were tested using Chi-square test or Fisher's exact test when appropriate. DFS was calculated from the date of colon cancer resection to the date of proven recurrence or death. For patients lost to follow-up, data were censored on the date when the patient was last seen alive without recurrence. OS was calculated from the date of colon cancer resection until the date of death from any cause or of latest follow-up. Five-year DFS and OS were estimated using the Kaplan−Meier method. The effect difference between factors was determined by Log-rank test. Tumor location (right-sided vs. left-sided) was assessed as a prognostic factor for OS and DFS in Cox regression analysis with and without risk-adjustment for age, gender, weight loss, smoking, CEA, CA19-9, tumor grade and adjuvant chemotherapy. The reported P-values were two-sided and P-values <0.05 were considered statistically significant. All data were analyzed using SPSS statistical software Version 17.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

A total of 627 patients with stage II or III colon cancer were initially enrolled in the study. The mean follow-up time was 67.9 months (median: 66.0 months; range: 40−102 months). Right-sided colon cancer was present in 50.6% (317/627) of the included patients. The clinical and pathologic characteristics of the right- and left-sided colon cancer patients are summarized in Table 1. Patients with right-sided cancer were significantly more likely to experience weight loss (32.2% *vs.* 20.6%, $P = 0.001$), had higher possibility of second primary tumor (8.2% *vs.* 3.9%, $P = 0.023$), elevated preoperative CA19-9 (24.1% *vs.* 11.9%, $P < 0.001$), more poorly differentiated tumors (24.0% *vs.* 13.5%, $P = 0.001$), and a higher likelihood of non-adenocarcinoma (10.4% *vs.* 5.5%, $P = 0.023$),

Table 1
Clinicopathological characteristics of right- and left-sided colon cancer.

Characteristics	All, *n*	Right-sided cancer, *n* (%)	Left-sided cancer, *n* (%)	*P*
Age				0.326
≤60	368	180 (56.8)	188 (60.6)	
>60	259	137 (43.2)	122 (39.4)	
Gender				0.242
Male	384	187 (59.0)	197 (63.5)	
Female	243	130 (41.0)	113 (36.5)	
Smoking				0.030
Heavy smoking	41	14 (4.4)	27 (8.7)	
No smoking or little	586	303 (95.6)	283 (91.3)	
Weight loss				0.001
No	461	215 (67.8)	246 (79.4)	
Yes	166	102 (32.2)	64 (20.6)	
Second primary tumor				0.023
Yes	38	26 (8.2)	12 (3.9)	
No	589	291 (91.8)	298 (96.1)	
CEA[a]				0.121
<5 ng/ml	353	169 (56.3)	184 (62.6)	
≥5 ng/ml	241	131 (43.7)	110 (37.4)	
CA19-9[a]				<0.001
<37 U/L	485	227 (75.9)	258 (88.1)	
≥37 U/L	107	72 (24.1)	35 (11.9)	
Tumor grade				0.001
Well and moderately	509	241 (76.0)	268 (86.5)	
Poorly	118	76 (24.0)	42 (13.5)	
Histology				0.023
Adenocarcinoma	577	284 (89.6)	293 (94.5)	
Non-adenocarcinoma	50	33 (10.4)	17 (5.5)	
Vascular invasion				0.048
Yes	43	28 (8.8)	15 (4.8)	
No	584	289 (91.2)	295 (95.2)	
T stage				0.034
T1−T3	231	104 (32.8)	127 (41.0)	
T4	396	213 (67.2)	183 (59.0)	
MMR status[a]				<0.001
dMMR	90	62 (27.7)	28 (13.0)	
pMMR	350	162 (72.3)	188 (87.0)	
Tumor stage				0.192
Stage II	332	176 (55.5)	156 (50.3)	
Stage III	295	141 (44.5)	154 (49.7)	

CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; MMR: mismatch repair; dMMR: defective mismatch repair; pMMR: proficient mismatch repair.
[a] Some patients did not examine CEA, CA19-9 and MMR status.

vascular invasion (8.8% *vs.* 4.8%, $P = 0.048$), and defective mismatch repair (dMMR) (27.7% *vs.* 13.0%, $P < 0.001$) compared with those with left-sided cancer. A higher percentage of patients with left-sided cancers had a history of heavy smoking (8.7% *vs.* 4.4%, $P = 0.030$) compared with right-sided cancer patients. The percentages of non-recurrent patients in dMMR and proficient MMR (pMMR) stage II patients were 85.5% (53/62) and 81.5% (132/162) respectively, showing no significant difference ($P = 0.480$). The percentages of non-recurrent patients in dMMR and pMMR stage III patients were 67.9% (19/28) and 54.8% (103/188) respectively, exhibiting no significant difference ($P = 0.193$).

Adjuvant chemotherapy

Among the 627 patients, 475 patients received adjuvant chemotherapy. In right-sided colon cancers, 46 patients received adjuvant chemotherapy of 5-FU/LV and 193 patients received adjuvant chemotherapy of FOLFOX. In left-sided colon cancers, 41 patients received 5-FU/LV treatment and 195 patients FOLFOX treatment. There was no significant difference in adjuvant chemotherapy regimens between right- and left-sided colon cancers. The median number of cycles of chemotherapy received was eight in both groups; 19.2% (46/239) patients with right-sided colon cancers and 22.0% (52/236) patients with left-sided colon cancers received the planned 12 cycles ($P = 0.364$). Adjuvant chemotherapy is listed in Table 2.

Survival analysis by tumor location and stage

The Kaplan−Meier survival curves demonstrated a significant difference in the 5-year DFS rates between right- and left-sided cancers for all stages (68.1% *vs.* 75.2%, $P = 0.043$). However, there was no significant difference in the 5-year OS rates between the two groups (73.8 *vs.* 79.0%, $P = 0.103$) (Fig. 1). The subgroup analysis demonstrated that patients with left-sided colon cancer had a significantly improved 5-year DFS and OS rates than did those with right-sided within stage III disease (64.3% *vs.* 46.8%, $P = 0.002$; 69.5% *vs.* 53.5%, $P = 0.006$, respectively). However, there were no significant differences in the 5-year DFS and OS rates between right- and left-sided colon cancers within stage II disease (85.2% *vs.* 85.9%, $P = 0.819$; 89.8% *vs.* 88.5%, $P = 0.803$, respectively)

Table 2
Adjuvant chemotherapy of right- and left-sided colon cancer, *n* (%).

Items	Right-sided cancer ($n = 317$)	Left-sided cancer ($n = 310$)	*P*
Treatment model			0.850
Surgery alone	78 (24.6)	74 (23.9)	
5-Fu treatment	46 (14.5)	41 (13.2)	
5-Fu + L-OHP	193 (60.9)	195 (62.9)	
Cycles of chemotherapy			0.469
1−6	44 (18.4)	34 (14.4)	
7−10	125 (52.3)	126 (53.4)	
11−12	70 (29.3)	76 (32.2)	

5-Fu: 5-fluorouracil; L-OHP: oxaliplatin.

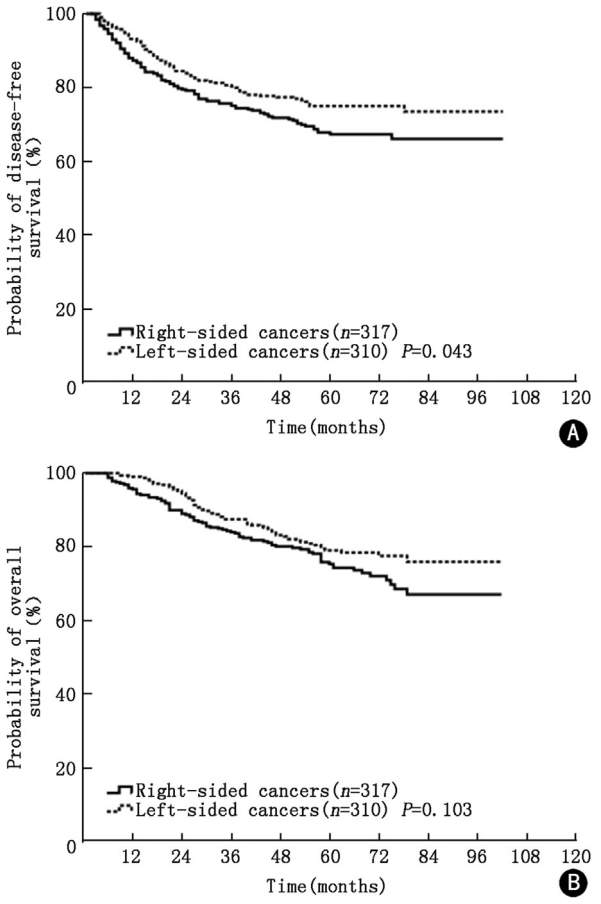

Fig. 1. Kaplan–Meier survival estimates for patients with right- and left-sided colon cancer. (A) Disease-free survival; (B) overall survival.

(Fig. 2). Unadjusted OS and DFS models with tumor location as the explanatory variable showed no significant difference in OS rates between right- and left-sided cancers for all stages combined (*HR* = 0.765, 95% *CI*: 0.553–1.058, *P* = 0.105) or in OS and DFS rates for stage II (*HR* = 1.086, 95% *CI*: 0.565–2.089, *P* = 0.804; *HR* = 0.936, 95% *CI*: 0.530–1.651, *P* = 0.819, respectively), but significant differences in DFS for all stages combined (*HR* = 0.738, 95% *CI*: 0.548–0.992, *P* = 0.044). For stage III cancers, patients with left-sided tumors had a decreased risk of mortality (*HR* = 0.594, 95% *CI*: 0.408–0.865, *P* = 0.007; *HR* = 0.586, 95% *CI*: 0.414–0.830, *P* = 0.003, respectively). After adjustment, there were still no significant differences in the 5-year OS and DFS rates between left- and right-sided cancers for all stages combined (*HR* = 0.867, 95% *CI*: 0.613–1.227, *P* = 0.421; *HR* = 0.832, 95% *CI*: 0.606–1.142, *P* = 0.255, respectively) or stage II (*HR* = 1.203, 95% *CI*: 0.605–2.391, *P* = 0.598; *HR* = 0.980, 95% *CI*: 0.542–1.774, *P* = 0.948, respectively). Stage III left-sided cancers had improved OS and DFS rates compared with right-sided cancers (*HR* = 0.626, 95% *CI*: 0.414–0.948, *P* = 0.027; *HR* = 0.630, 95% *CI*: 0.428–0.926, *P* = 0.019, respectively) (Table 3).

Details of recurrence and treatment after recurrence

Postoperative recurrence occurred in 169 patients, 97 of whom had right-sided colon cancer. The details of the recurrent sites by each tumor location are shown in Table 4. Right-sided colon cancer had an increased incidence of recurrence compared with left-sided cancer (30.6% *vs.* 23.2%, *P* = 0.037). There were no significant differences in single organ recurrence between tumor locations [73.2% (71/97) *vs.* 81.9% (59/72), *P* = 0.182]. However, right-side colon cancers had a higher percentage of multiple metastatic sites in the first recurrence (17.5% *vs.* 5.6%, *P* = 0.020). The treatment after recurrence was not significantly different between right- and left-sided colon cancers and included salvage surgery in 28 patients [15.5% (15/97) *vs.* 18.1% (13/72), *P* = 0.654] and systemic chemotherapy in 141 patients [84.5% (82/97) *vs.* 81.9% (59/72), *P* = 0.654].

Discussion

Our study demonstrates that left-sided colon cancer had a higher 5-year DFS rate than right-sided colon cancers. Importantly, this relationship is not consistent across tumor stages. Stage II right-sided cancers showed no difference in the 5-year DFS and OS rates compared with left-sided cancers, whereas stage III right-sided cancers had lower DFS and OS rates than left-sided cancers.

Our study contained stage II and III colon cancers, which differed substantially from those in four recent studies by Benedix et al,[12] Weiss et al,[13] Moritani et al,[14] and Holch et al.[8] The study by Benedix et al[12] included stage I–IV colon cancer and showed a higher risk of mortality for right-sided cancers (*HR* = 1.12; *P* = 0.02) than left-sided cancers. However, the results were conflicting when stratified by stage. Similar to the results of the current study, their unadjusted analysis indicated significantly lower 5-year survival rates for right-sided cancer for stage I (78% *vs.* 84%; *P* = 0.01) and stage III (55% *vs.* 60%; *P* < 0.01) but not stage II (74% *vs.* 72%). The study contained approximately 17,000 German patients with colon cancer and analysis was controlled for multiple disease- and patients-related variables, including comorbidity. Weiss et al,[13] whose study included stage I–III colon

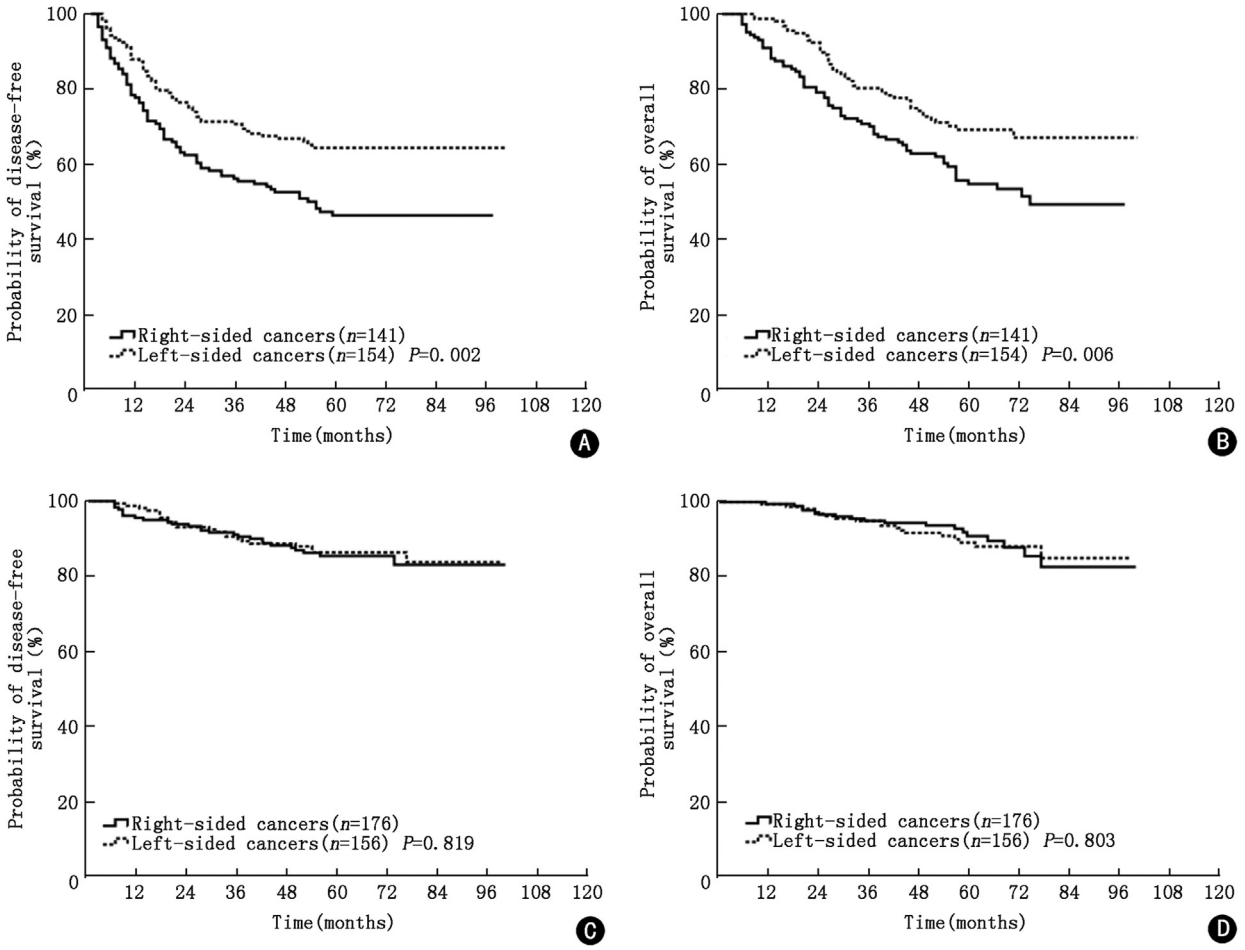

Fig. 2. Kaplan–Meier survival estimates for patients with right- and left-sided colon cancer. (A) Disease-free survival for stage III; (B) overall survival for stage III; (C) disease-free survival for stage II; (D) overall survival for stage II.

Table 3
Adjusted *HR*s and 95% *CI*s for 5-year OS and DFS by stage.

Analysis types	All stages combined (n = 627)			Stage II (n = 332)			Stage III (n = 295)		
	HR	95% *CI*	*P*	*HR*	95% *CI*	*P*	*HR*	95% *CI*	*P*
Unadjusted (OS)									
Right-sided	1.000			1.000			1.000		
Left-sided	0.765	0.553–1.058	0.105	1.086	0.565–2.089	0.804	0.594	0.408–0.865	0.007
Adjusted for all covariates[a] (OS)									
Right-sided	1.000			1.000			1.000		
Left-sided	0.867	0.613–1.227	0.421	1.203	0.605–2.391	0.598	0.626	0.414–0.948	0.027
Unadjusted (DFS)									
Right-sided	1.000			1.000			1.000		
Left-sided	0.738	0.548–0.992	0.044	0.936	0.530–1.651	0.819	0.586	0.414–0.830	0.003
Adjusted for all covariates[a] (DFS)									
Right-sided	1.000			1.000			1.000		
Left-sided	0.832	0.606–1.142	0.255	0.980	0.542–1.774	0.948	0.630	0.428–0.926	0.019

HR: hazard radio; *CI*: confidence interval; OS: overall survival; DFS: disease-free survival.

[a] Cox regression model controlling for age, gender, smoking, weight loss, adjuvant chemotherapy, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and tumor grade.

Table 4
The site of recurrence of right- and left-sided colon cancer.

Variables	Total, *n*	Right, *n* (%)	Left, *n* (%)	*P*
Number of patients with recurrence	169	97 (30.6)	72 (23.2)	0.037
Site of single organ recurrence				
Liver	46	24 (24.7)	22 (30.6)	0.401
Lung	22	12 (12.4)	10 (13.9)	0.772
Colon	53	29 (29.9)	24 (33.3)	0.634
Peritoneum	9	6 (6.2)	3 (4.2)	0.563
Multiple metastatic sites	21	17 (17.5)	4 (5.6)	0.020
Unknown site	18	9 (9.3)	9 (12.5)	0.502

cancers, reported no difference in the 5-year OS rate between right- and left-sided colon cancers when analysis was adjusted for multiple patient, disease, comorbidity, and treatment variables. However, right-sided cancers had lower mortality (*HR* = 0.92, 95% *CI*: 0.87–0.97, *P* = 0.001) within stage II disease but a higher mortality within stage III disease (*HR* = 1.12, 95% *CI*: 1.06–1.18, *P* < 0.001), which is consistent with our findings for stage III patients. Moritani et al[14] reported that the 5-year DFS rates were not significantly different between right- and left-sided colon cancers within stage II/III, which is inconsistent with our results. The main reasons for this may be the difference in cohorts, which included stages I–III, and that Moritani et al[14] did not further analyze stages II and III. Holch et al[8] suggested that after propensity score matching, the prognosis of right-sided carcinomas was better regarding OS (*HR* = 0.92, 95% *CI*: 0.89–0.94, *P* < 0.001) and cancer-specific survival (*HR* = 0.90, 95% *CI*: 0.87–0.93, *P* < 0.001). In the population-based analysis, the cohort was partitioned into subgroups containing one or more patients with right-sided colon cancer who were matched to one or more patients with left-sided colon cancer with similar values in the observed covariates in the risk set. We did not include propensity score adjusted analysis.

The reason for the observed difference in prognosis for patients with right- and left-sided colon cancer is not clear. Right- and left-sided colon cancers have different clinicopathological characters, including the level of preoperative CA19-9, tumor grade, second primary tumor, tumor histology, vascular invasion, and MMR status. These factors might be associated with the prognosis of colon cancer. Nozoe et al[20] reported that an increase in both CEA and CA19-9 can be useful as an independent prognostic indicator for patients with colorectal carcinoma. The VACCR study showed that signet ring cell carcinoma of the colon had poor survival rates compared with other histological subtypes.[21] Campos et al[22] reported that vascular invasion was also associated with a lower 5-year survival rate. In our study, patients with right-sided colon cancer had a higher level of preoperative CA19-9, more non-adenocarcinoma, and vascular invasion; therefore, they may have a lower 5-year DFS rate than those with left-sided colon cancer. At the same time, right-sided colon cancer had a higher possibility of other malignancies (8.2% *vs.* 3.9%, *P* = 0.023), which added non-colon related death especially in stage III. More importantly, we found that patients with right-sided colon cancer had significantly increased multiple metastases compared to those with left-sided colon cancer, which meant that more patients were ineligible to undergo salvage surgery. This is consistent with results of a retrospective study that suggested patients with right-sided primary tumors were more likely to have advanced disease recurrence (≥four recurrences) (*P* < 0.01), with worse survival after recurrence (*P* = 0.01).[23]

Studies have also suggested that the disease biology is different between right- and left-sided colon cancers.[24–27] Microsatellite instability is more common in right-sided cancers, whereas chromosomal instability is more characteristic of left-sided cancers.[28] Many studies have found that patients with microsatellite instability tumors have a better prognosis and that DNA MMR status is an independent favorable predictor of survival.[29–31] MMR status is predominantly seen in right-sided colon cancers,[24] and less than 5% of left-sided cancers show dMMR.[27] dMMR tumors also have a more favorable stage profile.[32] Additional evidence showed that the prognostic impact of MMR depended on tumor site in stage III colon cancer and favorable DFS was observed for dMMR versus pMMR in right-sided tumor (*HR* = 0.71, 95% *CI*: 0.53–0.94, *P* = 0.018) but not dMMR in left-sided tumors (*HR* = 1.71, 95% *CI*: 0.99–2.95, *P* = 0.056).[33] In our study, MMR status was not found to be an independent prognostic factor for stage II and stage III colon cancer, which may be associated with a relatively small number of patients with dMMR.

Prior studies have demonstrated significant gene expression differences between right and left colon cancers.[25,26,34,35] Glebov et al[25] found that more than 1000 genes were expressed differentially in adult ascending versus descending colon, with 165 genes showing >2-fold and 49 genes showing >3-fold difference in expression levels. Papagiorgis et al[26] reported that the pattern of EGFR expression varies with disease progression and aggressiveness in CRC depends on tumor location. *BRAF* mutations are observed more frequently in right-sided colon cancer[35] and the *BRAF* V600E mutation is an independent unfavorable

prognostic factor for survival in stage II−III colon cancer patients.[36]

This study has several limitations. First, as a retrospective study from a single institution the statistical power is limited. Second, the regimens of adjuvant chemotherapy and the cycles of postoperative chemotherapy were different, although there was no significant difference between patients with right- and those with left-sided colon cancer. Third, we did not explore *KRAS* and *BRAF* status that might affect the prognosis of colon cancer.[37,38]

In conclusion, we found that right- and left-sided colon cancers were significantly different in clinicopathological characteristics, and that right-sided colon cancer had higher recurrence than left-sided colon cancer. We also found that the prognostic value of tumor location was stage dependent; stage II right-sided cancers showed no survival difference compared with left-sided cancers; and stage III right-sided cancers showed increased mortality. The reason for this phenomenon remains unclear but may be due to clinicopathological and genetic factors. Additional research needs to be done to more clearly define these factors. Moreover, understanding differences in tumor biology may ultimately affect the treatment modalities, specifically chemotherapy and targeted therapy regimens.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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