Original Article

JHSMR Journal of Health Science and Medical Research

Does the Sidedness of Colon Cancer Affect Long-Term Oncological Outcomes?

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Received 6 August 2024 ● Revised 21 October 2024 ● Accepted 21 November 2024 ● Published online 23 April 2025

Abstract:

Objective: Tumor location, or sidedness, affects the prognosis of colon cancer. While recent studies generally suggest better prognoses for left-sided colon cancer, some report conflicting results. This study examined the association between colon cancer sidedness and oncologic outcomes at Khon Kaen University Hospital.

Material and Methods: Patients with non-metastatic adenocarcinoma of the colon (stage I-III) who received curative treatment at Khon Kaen University Hospital from January 2012 to December 2015 were included. Survival analyses according to primary tumor location (right-sided vs. left-sided) were conducted using the Kaplan-Meier method. Cox proportional hazards regression was used to calculate the adjusted hazard ratios for 5-year overall survival (OS) and 5-year disease-free survival.

Results: Among the 212 patients, 126 had left-sided colon cancer, and 86 had right-sided colon cancer. Those with left-sided colon cancer had better OS in the univariate analysis (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.34-0.96, p-value=0.037), but this was not significant in the multivariate analysis (HR 0.63, 95% CI 0.36-1.09, p-value=0.11). No relationship was found between cancer-sidedness and disease-free survival (Log-rank p-value=0.83). Other factors, including gender, lymph node status, tumor staging, and grading, were non-significant, except for T4 tumor status, which significantly affected OS (HR 3.71, 95% CI 1.91-7.12, p-value<0.001) and disease-free survival (HR 4.42, 95% CI 2.26-8.65, p-value<0.001).

Conclusion: The sidedness of colon cancer did not significantly affect OS and disease-free survival. However, left-sided colon cancer tended to have a better prognosis. T4 tumor status significantly affected oncologic outcomes.

Keywords: colon cancer, left-sided, oncological outcomes, right-sided, sidedness

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J Health Sci Med Res
doi: 10.31584/jhsmr.20251191
www.jhsmr.org

Introduction

Based on the SEER database, adenocarcinoma of the colon and rectum, referred to as colorectal cancer (CRC), is the third most common cancer globally[1,2]. CRC accounts for 10.3% of new cancer cases in Thailand[3] and has a global incidence rate of 19.7 per 100,000 for both genders combined (23.6 per 100,000 for males and 16.3 per 100,000 for females)[4]. In 2018, The National Cancer Institute of Thailand reported a national incidence rate of 16.2 per 100,000 men and 11.2 per 100,000 women[5].

The colon and rectum are different in terms of their embryological origins, anatomical characteristics, treatment modalities, and routes of lymphatic and hematogenous spread. Consequently, the colon and rectum exhibit different clinical features and prognostic outcomes[6]. The 5-year survival rates for colon cancer are as follows: stage I is 92%, stage IIA is 87%, stage IIB is 65%, stage IIIA is 90%, stage IIIB is 72%, stage IIIC is 53%, and stage IV is 12%. In comparison, the survival rates for rectal cancer are slightly poorer: stage I is 88%, stage IIA is 81%, stage IIB is 50%, stage IIIA is 83%, stage IIIB is 72%, stage IIIC is 58%, and stage IV is 13%[4].

Risk factors related to the prognosis of adenocarcinoma of the colon are generally divided into modifiable and non-modifiable factors. Race and ethnicity, gender, age, hereditary mutations, and previous radiation are non-modifiable risk factors, while modifiable risk factors include physical inactivity, smoking, alcohol consumption, diet, and obesity[4].

Recent studies have indicated that the sidedness of colon cancer—left versus right—may significantly influence overall survival (OS). Some studies report a better long-term outcome for right-sided colon cancer (RCC)[7], while others indicate a better prognosis for left-sided colon cancer (LCC)[8-10], or no significant difference between the two[11,12].

The objective of this study was to explore the relationship between colon cancer sidedness and OS among patients at Khon Kaen University Hospital, the largest hospital in northeastern Thailand. We believe that our results provide valuable insights into the prognosis of colon cancer in the Thai population.

Material and Methods

Patients

This study received approval from the Institutional Ethics Committee of the Faculty of Medicine at Khon Kaen University (No. HE631553), which granted a waiver for informed consent. A prospectively collected database of patients with colon cancer receiving elective curative treatment from January 2012 to December 2015 was reviewed. As the surgeons at our hospital were not familiar with laparoscopic surgery during the study period, all procedures were conducted using an open approach. Patients with rectal cancer and synchronous cancer on both sides of the colon were excluded. Patients under 18 years of age who might have hereditary colon cancer were also excluded as our institute does not routinely test tumor biology in all patients. Although stage IV cancer, particularly with liver and lung metastases, can be treated surgically with curative intent, the variation in treatment strategies for such patients may affect the outcomes of the study. Furthermore, due to limitations within the healthcare system in Thailand, not all patients are able to access the recommended chemotherapy regimens outlined in the guidelines. Therefore, we decided to exclude stage IV patients in order to eliminate this potential confounding factor. Additionally, patients whose data and treatment information were not available in the medical records were excluded.

Data collection, definition of sidedness and primary outcomes

Patient demographic data included age, gender, underlying disease, cancer staging, and pathological details such as lymphovascular status and perineural invasion. The location of colon cancer in the cecum, ascending colon, hepatic flexure, and transverse colon are defined as right-sided colon cancer, whereas cancer in the sigmoid colon, descending colon, and splenic flexure of the colon are referred to as left-sided colon cancer. All surgeries were performed by board-certified general surgeons or colorectal surgeons. Postoperative adjuvant treatment, if required, was administered according to national comprehensive cancer network guidelines. Patients were routinely followed up based on standard guidelines, which included clinical examinations, imaging, and surveillance colonoscopy to monitor for metastasis or disease recurrence.

For the primary outcome, this study aimed to investigate OS and disease-free survival between RCC and LCC. Patients were defined as disease-free if there was no recurrence, metastasis, or death during the follow-up period. Secondary outcomes included other factors that could potentially affect survival.

Statistical analysis

Stata version 15 (StataCorp, College Station, TX, USA) was used to conduct the statistical analysis. Continuous data are presented as mean±standard deviation, whereas categorical data are described as numbers (percentages). The t-test or Mann-Whitney U test was used for comparisons between continuous data, while the chi-square test or Fisher's exact test was used for comparisons between categorical data. Survival probabilities were calculated using the Kaplan-Meier method, and the log-rank test was employed to compare survival curves. The univariate relationship between each variable and primary outcome was analyzed using logistic regression. Factors feasibly related to the outcome in the univariate analysis (p-value<0.2) were also added to the multivariate logistic regression model. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). Statistical significance was defined as a p-value less than 0.05.

Results

Study population and patient characteristics

During the study period, 212 patients met the inclusion criteria. Of these, 126 had left-sided colon cancer, and 86 had right-sided colon cancer. Patient demographic data, including age, gender, American Society of Anesthesiologists (ASA) classification, pathological staging, number of lymph nodes harvested, and chemotherapy regimen, are summarized in Table 1, categorized by the sidedness of colon cancer. There were no statistically significant differences in the demographic characteristics between the LCC and RCC groups. The median follow-up time after surgery was 52.5 months (interquartile range: 22-79.25).

OS

The 12, 24, 36, 48, and 60-month OS rates were 95.7%, 89.4%, 84.8%, 79.2%, and 76.5%, respectively (Figure 1A). The 5-year OS rate in the RCC group was 70.11%, while the OS rate in the LCC group was 80.83%. Unadjusted survival analysis showed higher OS in the LCC group compared to the RCC group (Figure 1B, Log-rank p-value=0.034). The univariate hazard ratio for the LCC group compared to the RCC group was 0.57 (95% CI, 0.34-0.96, p-value=0.037).

In addition to the sidedness of colon cancer, we aimed to identify other factors potentially affecting OS, including gender, staging, and tumor grading. From the initial analyses, none of these factors showed a significant impact on OS. Therefore, focusing on staging, we decided to

analyze T4 tumor status (compared to T1-3) and lymph node status as separate factors. In this analysis, all factors except gender showed the potential to affect OS in the univariate analysis (p-value<0.2). However, in the multivariate analysis, only T4 tumor status significantly influenced OS (HR 3.71, 95% CI 1.91–7.12, p-value<0.001) (Table 2).

Disease free survival

The overall disease-free survival rates were 88.1%, 81.6%, 77%, 71.7%, and 69.5% at 12, 24, 36, 48, and 60 months, respectively (Figure 2A). The 5-year disease-free survival rates in the RCC and LCC groups were 69.1% and 70.4%, correspondingly. Unlike OS, there were no statistically significant differences in disease-free survival based on sidedness (Figure 2B, Log-rank p-value=0.83). The univariate hazard ratio comparing the LCC and RCC groups also showed no significant relationship (HR 0.95, 95% CI 0.56-1.58, p-value=0.83).

We also aimed to identify other factors that might affect disease-free survival by analyzing the same factors as in the OS analysis. Factors significantly associated with disease-free survival in the univariate analysis were lymph node status and T4 tumor status. However, only T4 tumor status significantly impacted disease-free survival in the multivariate analysis (HR 4.42, 95% CI 2.26–8.65, p-value<0.001) (Table 3).

Table 1 Patient demographic data according to the sidedness of colon cancer

Demographic characteristic	LCC (n=126)	RCC(n=86)	p-value
Age (years)	59.619±11.13	59.616±12.09	0.99
Male sex	72 (57)	48 (55.8)	0.84
ASA classification			0.58
ASA 1	85 (67.5)	61 (70.9)	
ASA 2	41 (32.5)	25 (29.1)	
Pathological staging			0.28
stage I	23 (18.3)	12 (14.0)	
stage II	56 (44.4)	34 (39.5)	
stage III	47 (37.3)	40 (46.5)	
T staging			0.24
T1	4 (3.2)	3 (3.5)	
T2	26 (20.6)	11 (12.8)	
T3	87 (69.1)	60 (69.8)	
T4	9 (7.1)	12 (13.9)	
N staging			0.083
N0	81 (64.3)	46 (53.5)	
N1	28 (22.2)	31 (36.0)	
N2	17 (13.5)	9 (10.5%)	
Number of lymph nodes harvested	14.82±7.87	17.88±9.04	0.17
Chemotherapy regimen			0.28
No chemotherapy	32 (25.4)	24 (27.9)	
FOLFOX	58 (46)	43 (50)	
5-FU/LV	18 (14.3)	12 (13.9)	
UFUR	6 (4.8)	3 (3.5)	
Xeloda	5 (3.9)	1 (1.2)	
XELOX	7 (5.6)	3 (3.5)	

Values are presented as mean±standard deviation or number (%)

LCC=left-sided colon cancer, RCC=right-sided colon cancer, ASA=American society of anesthesiologists, UFUR=Tegafur+Uracil, FOLFOX =Fluorouracil+Leucovorin+Oxaliplatin,XELOX=Capecitabine+Oxaliplatin

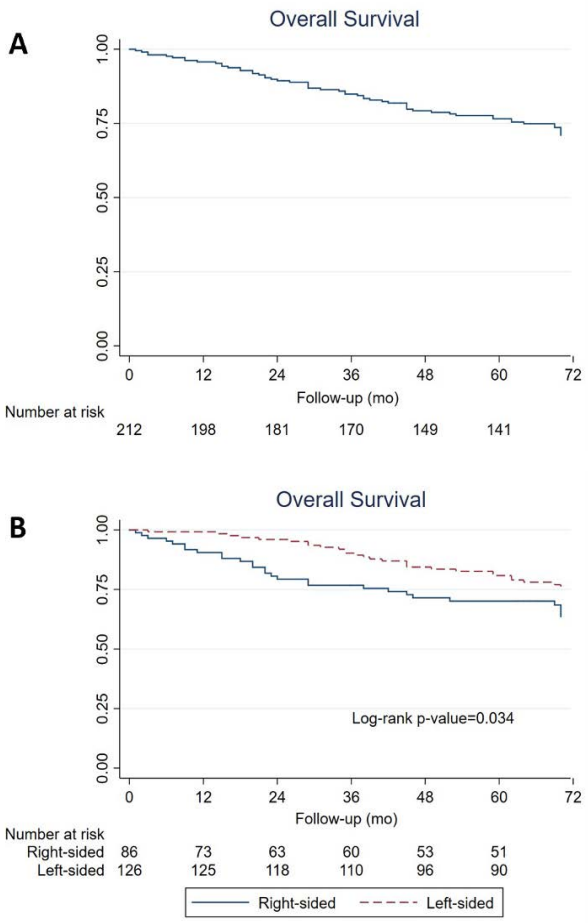

Figure 1 Kaplan-Meier survival function for overall survival (A) and by colon cancer sidedness (B)

Table 2 Factors influencing overall survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sidedness				
Right-sided	Reference	Reference		
Left-sided	0.57 (0.34-0.96)	0.037	0.63 (0.36-1.09)	0.11
Gender				
Male	Reference			
Female	1.25 (0.74-2.11)	0.41		

Table 2 (continued)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Node				
N0	Reference	Reference		
N1	1.92(1.05-3.48)	0.03	1.71(0.15-25.4)	0.27
N2	3.25(1.63-6.49)	0.001	3.51(0.91-7.2)	0.08
T stage				
T1-3	Reference	Reference		
T4	3.91(2.09-7.30)	<0.001	3.71(1.91-7.12)	<0.001
Tumor grading				
Well differentiated	Reference	Reference		
Moderately differentiated	1.56(0.89-2.73)	0.12	1.21(0.71-2.51)	0.52
Poorly differentiated	3.12(1.29-7.54)	0.01	1.46(0.56-3.79)	0.44

HR=hazard ratio, CI=confidence interval

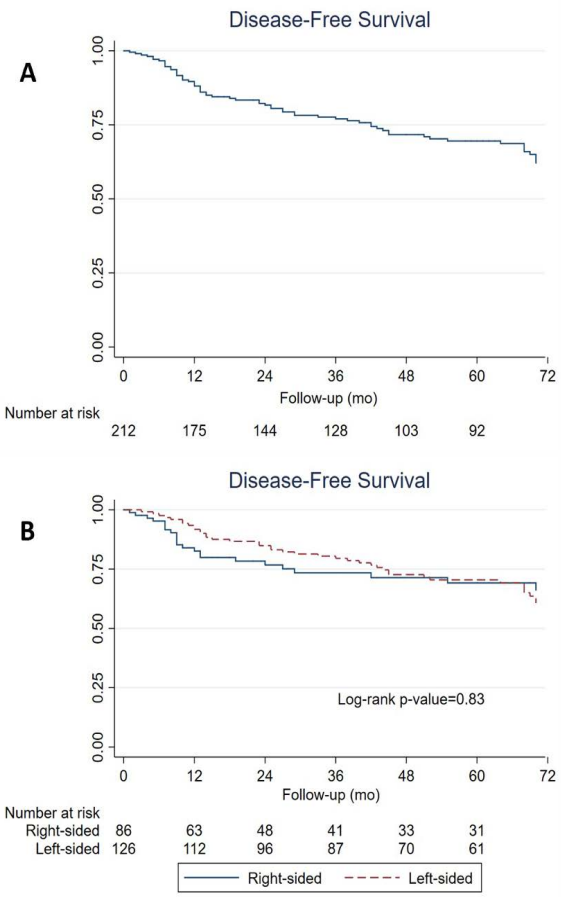

Figure 2 Kaplan-Meier survival function for overall disease-free survival (A) and by colon cancer sidedness (B)

Table 3 Factors influencing disease-free survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sidedness				
Right-sided	Reference			
Left-sided	0.95 (0.56-1.58)	0.83		
Gender				
Male	Reference			
Female	1.12 (0.68-1.85)	0.65		
Node				
N0	Reference		Reference	
N1	1.79 (1.02-3.15)	0.04	1.90 (0.52-3.35)	0.25
N2	3.23 (1.67-6.26)	0.001	3.56 (0.89-6.94)	0.09
T stage				
T1-3	Reference		Reference	
T4	3.81 (1.97-7.37)	<0.001	4.42 (2.26-8.65)	<0.001
Tumor grading				
Well differentiated	Reference			
Moderately differentiated	1.36 (0.81-2.29)	0.25		
Poorly differentiated	1.20 (0.37-3.90)	0.76		

HR=hazard ratio, CI=confidence interval

Discussion

In our study, colon cancer sidedness, lymph node status, T4 tumor status, and tumor grading significantly affected OS in univariate analysis. In multivariate analysis, only T4 tumor status remained significant. Although not statistically significant, patients with left-sided colon cancer tended to have a better prognosis compared to those with right-sided colon cancer (HR 0.63, 95% CI 0.36-1.09, p-value=0.11). Consistent with a study by Karim et al.[13], our results show no relationship between sidedness and recurrence/disease-free survival. The only factor found to significantly affect disease-free survival was T4 status. Hence, similar to a study by Min Sung et al.[14], we found that T4 tumor status was a strong prognostic factor influencing both OS and disease-free survival.

Many recent large studies agree that LCC has a better prognosis compared to RCC[8-10]. However, some studies report controversial results, with some indicating that RCC has better oncological outcomes. Tamas et al.[15] and Wang et al.[16] demonstrated that right-sided tumors had a better OS rate than left-sided tumors, but these studies focused on only stage II colon cancer. Hutchins et al.[17] suggested that RCC patients have a better prognosis and better benefit from chemotherapy compared to LCC patients. Additionally, many patients in the right-sided group had microsatellite instability-high (MSI-H) tumors, a factor for better prognosis. In contrast, a recent study by Karim et al.[13] reported that LCC and RCC showed no statistically significant difference in terms of survival. They concluded that the sidedness of colon cancer is not related to long-term OS or cancer-specific survival. However, the RCC group in their study was more frequently staged as T4 and exhibited poorly differentiated histologic features. Nevertheless, one of the largest studies on this topic, a

systematic review and meta-analysis encompassing more than 1.4 million patients from 66 different studies by Petrelli et al.[18], concluded that having primary cancer on the left side of the colon is significantly correlated with a 19% lower absolute risk of death. Additionally, their study demonstrated that tumor-sidedness has prognostic value regardless of race, stage, and adjuvant chemotherapy.

Several theories attempt to explain why RCC demonstrates a worse prognosis compared to LCC. Beyond anatomical differences due to embryonic origin, RCC and LCC also exhibit marked differences in molecular profiles[19]. Many recent studies state that RCC has a high incidence of MSI-H[20,21], which is considered a favorable prognostic factor[22]. However, MSI alone cannot explain the differences in prognosis, as RCC also has higher rates of BRAF mutations[23] and high CpG island methylator phenotype mutations[23,24], which are both associated with poorer prognostic outcomes[23].

Several limitations must be mentioned regarding this study. First, the sample size was relatively small. Some factors that significantly affected survival in the univariate analysis, including sidedness, might also have shown significance in the multivariate analysis with a larger sample size. Second, we did not routinely test the molecular profile of every patient, as this test is not covered by the standard hospital course. Several molecular profiles are associated with oncologic outcomes, and having this information might have affected our results. Lastly, due to the lack of biological profiles, we excluded patients under 18 years of age in order to avoid including hereditary colon cancer cases. This approach may have inadvertently excluded sporadic colon cancer patients under 18, which could have potentially affected the overall results of this study.

Conclusion

Although not statistically significant, patients with left-sided colon cancer tended to have better OS compared to those with right-sided colon cancer. However, our study shows no association between the sidedness of colon cancer and disease-free survival. T4 tumor status was the only significant factor impacting both OS and disease-free survival. These results may be useful in comparing clinical outcomes to those in other regions of the world.

Acknowledgement

The authors would like to thank Dr. Dylan Southard from Khon Kaen University International College for editing the English language in this paper.

Conflict of interest

There are no potential conflicts of interest to declare.

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