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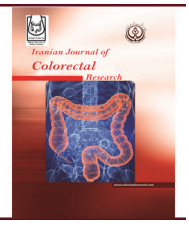

Prognostic Significance of Tumor Location in Oncologic Outcome of Colon Cancer

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Abstract

Background: A growing amount of data has indicated the possibility that tumor location may play a prognostic role in colon cancer. We set out to investigate the relationship between the location of colon cancer (right-sided vs. left-sided) and the patient's oncologic outcome.
Methods: This retrospective cohort study included 654 colon cancer patients treated and followed up at Namazi and Faghihi hospitals in Shiraz and Imam Reza Hospital in Mashhad, Iran, between 2005 and 2014. The Cox regression multivariate analysis model was used to determine the most important independent predictors of oncologic outcomes. We analyzed the prognostic impact of the primary tumor location and other clinical, pathological, and treatment-related factors.
Results: In the univariate analysis, the prognostic factors for disease-free survival (DFS) were the primary tumor stage (P<0.001), node stage (P<0.001), tumor grade (P=0.013), surgical margin status (P=0.001), lymphovascular invasion (LVI) (P<0.001), and perineural invasion (PNI) (P<0.001). Additionally, the prognostic factors for overall survival (OS) were the primary tumor stage (P<0.001), node stage (P<0.001), tumor grade (P=0.036), LVI (<0.001), PNI (P<0.001), and the mucinous type (P=0.042). In the multivariate analysis, LVI, T3-4 lesions, tumor grade II-III, and an advanced disease stage remained independent prognostic factors for DFS and OS. However, the colon cancer location was not a prognostic factor regarding DFS or OS.
Conclusion: Our study indicates that the tumor location is not a significant prognostic factor for DFS and OS in colon cancer patients.

Keywords: Colon cancer, Prognosis, Disease-free survival

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Introduction

Colorectal cancer is the third most common cancer worldwide and the fourth most prevalent in Iran (1). Right-sided colon cancer (RCC) constitutes tumors of the cecum, the ascending colon, hepatic flexure, and the proximal transverse colon. Left-sided colon cancers (LCC) originate from the distal transverse colon, splenic flexure, and the descending and sigmoid colon down to the promontorium (2). Colon cancer laterality, right versus left, is emerging as an essential determinant of tumor behavior. Recent data have reported the prognostic significance of the anatomical location of colon adenocarcinomas (2, 3). Moreover, patients with RCC vs. LCC exhibit different epidemiologic, clinical, pathological, and even molecular characteristics (4-7). Although these apparent distinctions are yet to be thoroughly investigated, they may be related to the different embryogenic origins and blood supplies of the colon's two parts (2).

Distinct biological features characterize the colon's right and left sides. The mismatch repair gene (MMR), KRAS (Kirsten rat sarcoma virus) gene, BRAF (V-Raf Murine Sarcoma Viral Oncogene Homolog B) gene, and microRNA-31 mutations are prominent on the right, while the NRAS gene (Neuroblastoma RAS) and P53 mutations are prominent on the left. These pose important treatment implications as they suggest different disease responses to adjuvant chemotherapy as well as targeted treatments (8). The results of the N0147 trial show better survival rates from an adjuvant FOLFOX regimen among LCC patients than among RCC patients (9). Clinical data suggest that cetuximab offers more benefits for metastatic LCC, even in the KRAS wild-type population. Furthermore, advanced LCC is reportedly more sensitive to anti-angiogenic therapy with bevacizumab than advanced RCC (10). Although some studies on the prognostic value of tumor location have reported a worse oncologic outcome in RCC vs. LCC, controversy still surrounds this subject (11-13). Hence, we set out to investigate the relationship between the location of colon cancer (right-sided vs. left-sided) and the patient's oncologic outcome.

Patients and Methods

This retrospective cohort study included 654 colon cancer patients treated and followed up at three tertiary hospitals (Namazi and Faghihi hospitals in Shiraz and Imam Reza hospital in Mashhad, Iran) between 2005 and 2014 Patient's charts were reviewed. Biopsies were obtained via colonoscopy, pathologically confirming the adenocarcinoma diagnosis in all patients. The colonoscopy findings, computed tomography (CT) scan images, and the operating surgeon's notes identified the primary tumor location. Primary tumors in the cecum, ascending colon, hepatic flexure, and proximal transverse colon were defined as RCC, while those in the distal transverse colon, splenic flexure, descending colon, and sigmoid colon were defined as LCC. The current research was performed according to the ethical standards of the World Medical Association Declaration of Helsinki.

The initial investigations included a comprehensive history and physical examination, colonoscopy, chest, abdominal, and pelvis CT scans, and laboratory tests for the carcinoembryonic antigen (CEA), complete blood count, and renal and liver function. Except for 34 (5%) subjects, all patients underwent standard curative surgery. The majority of the patients (73%) received adjuvant chemotherapy. The patients' cancers were reclassified according to the American Joint Committee on Cancer (AJCC) (14).

All statistical analyses were conducted using IBM SPSS statistics software, version 22.0. We analyzed all potentially important clinical (age, sex, tumor location) and pathological variables (tumor stage, node stage, tumor grade, lymphovascular invasion, perineural invasion, tumor size, surgical margin status, and median number of evaluated lymph nodes). The chi-squared or Fisher's exact test assessed the correlation between the primary tumor location and other categorized clinical and pathologic variables. The Kaplan–Meier method was used for the univariate analysis of disease-free survival (DFS) and overall survival (OS) rates, while the log-rank test compared the prognostic factors. To determine the most important independent factors for oncologic outcomes, the Cox regression multivariate analysis model was used. We analyzed the prognostic impact of the primary tumor location and other clinical, pathological, and treatment-related factors. Two-sided P-values less than 0.05 were considered significant.

Results

This study included 357 men and 297 women with a median age of 55 (range 17–90) years. Surviving patients' median follow-up time was 46 (range 27–122) months. There was 234 patients with RCC and 420 patients with LCC.

Table 1 summarizes the association of the clinical and pathological characteristics with the tumor location. Accordingly, there was a significant difference between RCC and LCC in terms of patient gender (P=0.012), primary tumor size (P<0.001), histologic type (P=0.003), primary tumor stage (P=0.022), tumor grade (P=0.012), and the median number of evaluated lymph nodes (P=0.008). In the univariate analysis for disease-free survival (DFS), the prognostic factors were the primary tumor stage (P<0.001), node stage (P<0.001), tumor grade (P=0.013), surgical margin status (P=0.001), lymphovascular invasion (LVI) (P<0.001), and perineural invasion (PNI) (P<0.001). However, in the stratified log-rank test, no significant differences

Table 1: Association of the clinical and pathological characteristics with tumor location in 654 patients with colon cancer

Variable	Right-sided colon cancer	Left-sided colon cancer	P value
Total	234	420	
Sex			0.012
Male	143	214	
Female	91	206	
Age (mean±SD)	54.2±13.9	55.6±13.3	0.190
Tumor size (mean±SD)	5.8±2.6	4.8±2.0	<0.001
Preoperative CEA level (median)	4.3	4.8	0.919
Histologic type			0.003
Mucinous	42	41	
Non mucinous	192	379	
Tumor stage			0.022
T1	0	9	
T2	31	77	
T3	158	255	
T4	20	23	
Tx	25	56	
Node stage			0.444
N0	124	223	
N1	57	84	
N2	22	52	
Nx	31	61	
Disease stage			0.198
Stage I	25	70	
Stage II	104	172	
Stage III	76	127	
Stage IV	16	24	
Tumor grade			0.012
Grade I	118	239	
Grade II	74	125	
Grade III	29	25	
Surgical margin status			0.438
Free	230	408	
Involved	4	12	
Lymphovascular invasion			0.061
Positive	69	96	
Negative	165	324	
Perineural invasion			0.409
Positive	45	70	
Negative	189	350	
Number of evaluated LNs (median)	7	5	0.008
Number of involved LNs (median)	0.0	0.0	0.717

CEA: Carcinoembryonic antigen; SD: Standard deviation; LN: Lymph node

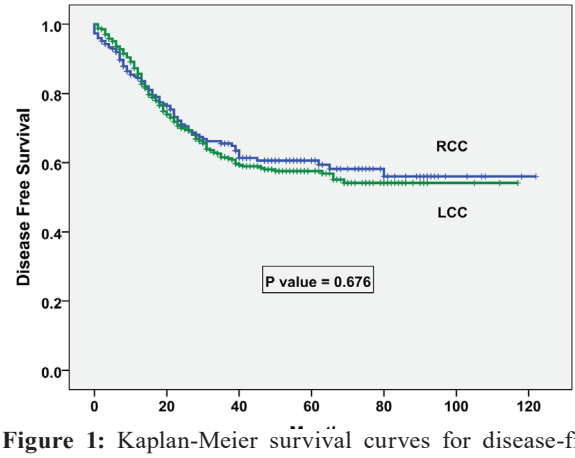

Figure 1: Kaplan-Meier survival curves for disease-free survival, categorized according to the colon cancer location. RCC: right-sided colon cancer; LCC:left-sided colon cancer

in terms of DFS were detected between RCC and LCC (P=0.676) (Figure 1) . Table 2 summarizes the differences in DFS between right-sided and left-sided colon cancers.

Regarding overall survival (OS), the prognostic factors were the primary tumor stage (P<0.001), node stage (P<0.001), tumor grade (P=0.036), LVI (P<0.001), PNI (P<0.001), and the mucinous type (P=0.042) (Table 3). However, regarding OS, we found no significant differences between the cancers of the right and left colon (P=0.743) (Figure 2) .

In the Cox regression multivariate analysis model, the following independent prognostic factors for DFS were identified: LVI [HR=1.74; 95% CI=1.27–2.37; P<0.001], T3-4 lesions [HR=1.70; 95% CI=1.04–2.77; P=0.032], tumor grade II-III [HR=1.53; 95% CI=1.14–2.06;

Table 2: Differences in disease-free survival (DFS) between right-sided and left-sided colon cancers

Variable	5-year DFS (%)		P value	HR	95% CI
	RCC (N=234)	LCC (N=420)			
Sex			0.594	0.92	0.706-1.221
Male	60.9	53.9			
Female	60.4	61.3			
Age (years)			0.676	0.94	0.719-1.239
Age≤55	59.1	58.8			
Age>55	62.9	56.2			
Tumor size			0.766	0.95	0.718-1.276
≤5 cm	54.7	56.0			
>5cm	65.2	62.7			
Tumor stage			0.285	0.85	0644-1.140
T1-2	75.6	81.9			
T3-4	57.0	48.7			
Node stage			0.847	0.97	0.728-1.297
N0	68.0	84.6			
N1-2	45.5	31.6			
Disease stage			0.529	0.91	0.696-1.205
Stage I-II	69.9	66.4			
Stage III-IV	42.2	38.2			
Tumor grade			0.427	0.89	0.676-1.181
Grade I	64.4	61.2			
Grade II-III	54.7	49.2			
Surgical margin status			0.804	0.96	0.735-1.270
Free	61.2	58.4			
Involved	25.0	25.5			
Lymphovascular invasion			0.416	0.89	0.680-1.173
Negative	70.1	65.1			
Positive	37.9	34.6			
Perineural invasion			0.415	0.89	0.679-1.173
Negative	67.6	64.7			
Positive	38.0	27.0			
Number of evaluated LNs			0.632	0.93	0.693-1.249
<12	58.3	57.4			
≥12	61.3	52.1			
Mucinous subtype			0.527	0.91	0.692-1.206
Yes	59.8	38.1			
No	60.7	59.5			
Total	60.6	57.6	0.686	0.94	0.720-1.242

RCC: Right-sided colon cancer; LCC: Left-sided colon cancer; DFS: Disease-free survival; HR: Hazard ratio; CI: Confidence interval; SD: Standard deviation; LN: Lymph node

P=0.004], and an advanced disease stage [HR=1.82; 95% CI=1.33–2.48; P<0.001]. Likewise, the following factors exerted a negative influence on OS: LVI [HR=1.90; 95% CI=1.37–2.64; P=0.001], T3-4 lesions [HR=1.95; 95% CI=1.11–3.43; P=0.020], tumor grade II-III [HR=1.49; 95% CI=1.07–2.07; P=0.016], and an advanced disease stage [HR=1.64; 95% CI=1.16–2.33; P=0.005. However, the colon cancer location (right or left) was not a prognostic factor regarding DFS or OS (Table 4).

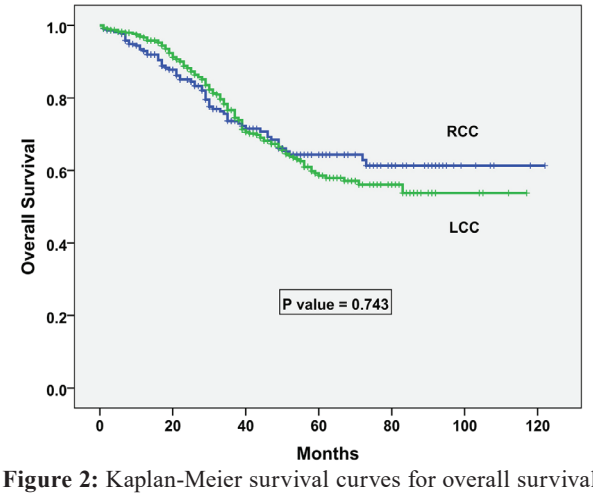

Figure 2: Kaplan-Meier survival curves for overall survival, categorized according to the colon cancer location. RCC: right-sided colon cancer; LCC:left-sided colon cancer

Discussion

In the literature, data regarding patient demographics and the tumor characteristics of cancers in the right and left colon are inconsistent. The present study evaluated the possible clinical, pathological, and

Table 3: Differences in overall survival (OS) between right-sided and left-sided colon cancers

Variable	5-year OS (%)		P value	HR	95% CI
	RCC (N=234)	LCC (N=420)			
Sex			0.630	0.92	0.682-1.260
Male	64.7	53.5			
Female	64.2	63.6			
Age (years)			0.766	0.95	0.703-1.296
Age≤55	64.1	62.2			
Age>55	64.7	55.0			
Tumor size			0.831	0.96	0.699-1.333
≤5 cm	58.4	58.3			
>5cm	68.7	56.0			
Tumor stage			0.384	0.86	0.631-1.194
T1-2	73.5	85.1			
T3-4	61.5	48.8			
Node stage			0.856	0.97	0.705-1.337
N0	69.9	67.2			
N1-2	63.8	40.9			
Disease stage			0.734	0.94	0.699-1.287
Stage I-II	71.6	67.9			
Stage III-IV	47.8	38.7			
Tumor grade			0.567	0.91	0.669-1.247
Grade I	67.3	62.4			
Grade II-III	58.9	49.2			
Surgical margin status			0.794	0.96	0.707-1.303
Free	64.7	59.1			
Involved	50.0	39.8			
Lymphovascular invasion			0.551	0.91	0.671-1.238
Negative	71.0	67.5			
Positive	48.2	34.4			
Perineural invasion			0.457	0.89	0.655-1.211
Negative	69.0	67.0			
Positive	49.5	28.5			
Number of evaluated LNs			0.535	0.90	0.649-1.253
<12	62.8	58.8			
≥12	66.2	50.1			
Mucinous subtype			0.548	0.91	0.669-1.239
Yes	65.4	61.4			
No	59.7	34.0			
Total	64.3	68.6	0.743	0.95	0.700-1.290

RCC: Right colon cancer; LCC: Left colon cancer; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; SD: Standard deviation; LN: lymph node

prognostic differences of 654 patients with colon adenocarcinoma in the right versus left colon. We encountered LCC more frequently than RCC (64% vs. 36%). This finding concurs with several previous studies (15, 16). According to most studies, Asian ethnicity is associated with a greater likelihood of developing distal colon cancer (17, 18). This may be attributed to a specific lifestyle that has exposed patients to carcinogens that more strongly affect the left colon.

Although there are reports of a higher proportion of female patients with RCC, the male-to-female ratio in the present study was 1:5 for the right side. Patients with RCC were more likely to be diagnosed with a larger-sized, advanced T stage and poorly differentiated tumors. This is consistent with the results of several studies (including a systematic review by Petrelli et al.) that reported more advanced stages and higher tumor grades in RCC upon diagnosis (19-22). Multivariate survival analysis has indicated that a higher T stage, advanced disease stage, higher tumor grade, and lymphovascular invasion negatively impact disease-free and overall survival.

In patients with colorectal cancer, there has been increasing evidence of the prognostic and predictive role of the tumor site. However, the current study found no relation between tumor location and survival. According to the literature, patients with RCC may have inferior survival rates than those with LCC (11-13, 23). It must be noted that several contradictory reports indicate equal survival rates in RCC vs. LCC and even better oncologic outcomes in LCC (22, 24, 25). Consistent with the results of the present research, Karim et al.'s retrospective cohort study (26), as well as the work by Powell and Weiss

Table 4: Multivariate analysis of prognostic factors for disease-free survival and overall survival rates in 654 patients with colon cancer

Variables	Disease-free survival (DFS)		Overall survival (OS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex	1.05 (0.790-1.416)	0.705	1.10 (0.799-1.523)	0.551
Male				
Female				
Age (years)	1.09 (0.815-1.460)	0.558	0.97 (0.701-1.350)	0.870
Age≤55				
Age>55				
Tumor size ≤5 cm >5cm	1.25 (0.935-1.695)	0.130	1.21 (0.873-1.679)	0.252
Tumor location	0.87 (0.650-1.189)	0.402	0.90 (0.641-1.266)	0.547
Right colon				
Left colon				
Tumor stage	1.70 (1.048-2.779)	0.032	1.95 (1.113-3.432)	0.020
T1-2				
T3-4				
Node stage	1.30 (0.600-2.841)	0.502	1.25 (0.571-2.768)	0.570
N0				
N1-2				
Disease stage	1.82 (1.330-2.489)	0.001	1.64 (1.165-2.334)	0.005
Stage I-II				
Stage III-IV				
Tumor grade	1.53 (1.144-2.060)	0.004	1.49 (1.078–2.07)	0.016
Grade I				
Grade II-III				
Surgical margin status	0.98 (0.440-2.206)	0.970	1.36 (0.535-3.459)	0.518
Free				
Involved				
Lymphovascular invasion	1.74 (1.275-2.374)	<0.001	1.76 (1.247-2.448)	0.001
Positive				
Negative				
Perineural invasion	0.76 (0.529-1.100)	0.147	0.74 (0.496-1.106)	0.142
Positive				
Negative				
Mucinous subtype	0.86 (0.575-1.285)	0.451	0.763 (0.502-1.159)	0.205
Yes				
No				

HR: Hazard ratio; CI: Confidence interval; SD: Standard deviation

et al., found no significant difference in survival rates related to disease laterality (27). This was observed despite the more aggressive features and advanced T stages of the RCC cases in these studies.

The present paper showed a significantly higher mean number of evaluated lymph nodes in the right-sided tumors than in the left-sided ones. As a surrogate for extensive surgical resection, extensive lymph node dissection in such patients may play a role in the non-significant survival difference. Although a higher prevalence of microsatellite instability (MSI) in right-sided colon adenocarcinoma has resulted in a greater response to fluorouracil-based adjuvant chemotherapy (27, 28), there are several other hypothetical explanations for increased mortality and aggressive behavior in RCC. To explain the worse clinical outcome for RCC vs. LCC, the following factors may be taken into account: the BRAF and KRAS mutation status related to a lower response to anti-EGFR agents including cetuximab (29-31), the more frequent mucinous histology (26, 32, 33), and the inability of extensive surgery (34-36).

The limitations of the present study are important to note. Two intrinsic weaknesses that should be addressed are the study's retrospective nature and the dataset's lack of information on the MSI and RAS status. Well-designed prospective trials are needed to assess if treatment should be tailored according to the tumor location in colorectal cancer patients.

Conclusion

According to the results of the current paper, although right-sided colon cancers may present more aggressive clinical features, tumor laterality is not a prognostic factor for survival in colon cancer patients.

Compliance with Ethical Standards

This present study was approved by the University Research Ethics Committee, and all procedures were performed per the National Research Committee's ethical standards and the Helsinki Declaration.

Authors' Contribution

SH, MM, MB, SKM: substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; FB, MRS, MT, and RS: data interpretation and drafting the article and revising it critically for important intellectual content. All authors have reviewed and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest: None declared.

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