Fall of another myth for colon cancer: Duration of symptoms does not differ between right- or left-sided colon cancers

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ABSTRACT

Background/Aims: Patients with colorectal cancer continue to present with relatively advanced tumors that are associated with poor oncological outcomes. The aim of the present study was to assess the association between localization, symptom duration, and tumor stage.

Materials and Methods: A prospective, multicenter cohort study was conducted on patients newly diagnosed with a histologically proven colorectal adenocarcinoma. Standardized questionnaire-interviews were performed. Data were collected on principal presenting symptoms, duration of symptoms (time to first presentation to a doctor and time to diagnosis) and treatment, diagnostic procedures, tumor site, and stage of the tumor (tumor, node, and metastasis (TNM)).

Results: A total of 1795 patients with colorectal cancer were interviewed (mean age: 60.76±13.50 years, male patients: 1057, patients aged >50 years: 1444, colon/rectal cancer: 899/850, right side/left side: 383/1250, stage 0-1-2/stage 3-4: 746/923). No statistically significant correlations were found between duration of symptoms and either tumor site or stage. Principal presenting symptoms were significantly associated with left colon cancer. Patients who had "anemia," "change in bowel habits," "anal pruritus or discharge," "weight loss," and "tumor in right colon" had a significantly longer symptom time.

Conclusion: Symptom duration is not associated with localization, nor is the tumor stage. Diagnosis of colorectal cancer at an earlier stage may be best achieved by screening of the population.

Keywords: Colorectal cancer, symptom duration, localization

INTRODUCTION

Colorectal carcinoma is the second most common cause of cancer death in Europe and the United States (1,2). Prognosis is poorer in patients with advanced disease, so early detection is important (3). Even though it has been shown that screening for colorectal cancer is both effective and cost-effective, it is a pity that routine screening is not used, and the majority of patients (85%) are still diagnosed after the onset of symptoms (1).

Although it is assumed that a long duration of symptoms might be associated with advanced disease and poor prognosis, many studies have reported that there is no relationship between outcomes and shorter duration of

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symptoms for colorectal carcinomas (4-6). On the other hand, it has been suggested that patients with delayed diagnosis of colorectal cancer might have better outcomes (7). Additionally, Ramos et al. (8,9) showed that delayed diagnosis is not associated with advanced tumor stage or poorer survival.

To assume that patients with left-sided colon cancer would have a shorter duration of symptoms due to the narrower lumen of the left colon that would cause obstruction and bleeding is not irrational. This assumption results in an expectation that patients with right-sided colon cancer might present with a more advanced disease once symptoms appear. However, there are no studies in the English literature that examine this theoretical proposition. The main purpose of the present study was to test whether patients with left-sided colorectal tumors present with a shorter duration of symptoms at an earlier disease stage, whereas patients with right-sided tumors present with a longer duration of symptoms and at a later disease stage. Although there have been many studies investigating the prognosis for colorectal cancer and duration of symptoms or diagnosis, there has been a paucity of data for the relationship of the localization of the tumor and the duration of symptoms of patients with colorectal cancer.

The aim of the present study was to identify the relationship between symptom duration and localization of colon cancer and to determine whether localization and stage of the disease are associated with symptom duration.

MATERIALS AND METHODS

This was a prospective, multicenter study. Data for the present study were collected from a prospective cohort of newly diagnosed, consecutive colorectal carcinoma cases in 15 universities and teaching hospitals between January 2012 and September 2013. Data of consecutive patients with colorectal cancer from January 1, 2012 were included within each center. A total of 1795 patients who were admitted to the hospital for the treatment of confirmed colorectal carcinoma were included in the study. The study was approved by the local ethics committee (October 25, 2010/17-376). A standard questionnaire that queried symptoms and symptom duration was given to all the patients. Questionnaires were filled out by surgical residents at hospital admission prior to surgery by personal interview. Informed consent was obtained from all patients.

Demographic (age and gender) and socio-economic (education, monthly income, and marital status) data, colorectal cancer family history, accompanying inflammatory bowel disease, family history of cancer (ovarian, endometrial, or breast), symptoms, symptom time (time from the onset of symptoms to the admission to a physician), diagnosis time (time from admission to a physician to the establishment of colorectal carcinoma diagnosis), diagnostic tools, treatment methods, tumor localization, and tumor, node, and metastasis (TNM) stage were recorded.

Hematochezia, anemia, change in bowel habits (diarrhea, constipation, and altered stool formation), abdominal pain, anal pruritus and discharge, perianal pain, weight loss, and fatigue were recorded as related symptoms for colorectal carcinoma. In addition, whether diagnosis was made based on a screening modality was recorded.

Time from the onset of symptoms to the admission to a physician (symptom time) and time from admission to a physician to the establishment of colorectal carcinoma diagnosis (diagnosis time) were categorized as 1 month, 1-3 months, 3-6 months, and >6 months. Symptom time was also evaluated as being "early admission (in 1 month)" or "late admission (over 1 month)" for the determination of risk factors.

Tumor localization was documented as cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, or rectum. Carcinomas localized within the colon segments proximal to the splenic flexure were classified as right-sided carcinomas, whereas carcinomas localized within colon segments distal to this point were classified as left-sided carcinomas. In addition, tumors localized within 15 cm from the anal verge were classified as rectal cancer, and all the other proximally localized cancers were classified as colon cancer. Disease stage was recorded as 0, 1, 2, 3, or 4 according to the TNM classification, and patients were classified into two groups as early (0, 1, and 2) or advanced (3 and 4) stage disease according to the TNM stages.

Statistical analysis

Statistical analysis was performed by SPSS (released 2011, IBM SPSS Statistics for Windows, version 20.0.; IBM Corp., Armonk, NY, USA) statistical analysis software. Mean±standard deviation (SD) or median (minimum-maximum) for metric variables and frequency (%) for categorical variables were used as descriptive statistics. Chi-square test was used to compare two independent groups for categorical variables, and Student's t-test or Mann-Whitney U test was used for metric variables.

Pearson correlation coefficient (r) was used to assess the degree of association between two variables. Multivariable logistic regression analysis was used to define the risk factors of outcome variables (being in the early disease stage and early admission). Prior to multivariable logistic regression analysis, the association of each independent variable with the outcome variables, a univariate estimate was performed by means of the logistic regression analysis. The crude and adjusted odds ratio (OR) values and their 95% confidence interval (CI) were given. A p value <0.05 was considered as statistically significant.

The sample size required for the study was calculated based on the primary dependent variable of early admission with the binary independent variable of tumor localization. R^2 was assumed as 0.50 when the tumor localization was regressed on other independent variables, and OR was chosen as 1.5 (under the assumption that the probability of early admission is 0.6 for the right colon and 0.5 for the left colon) (10).

RESULTS

The mean (±SD) age of the patients was 60.76±13.50 years. The characteristics of all patients are summarized in Table 1. Most of the patients were male, comprising 59% of the patients. All consecutive patients within each center completed the questionnaire, but some did not answer all the questions.

Family history of colorectal cancer was present in 16.2% of the patients. Among these patients, 41.2% had a family history of endometrial carcinoma, 33.3% of breast carcinoma, 9.8% of ovarian carcinoma, and 11.8% of inflammatory bowel disease. In addition, 3.9% of the patients had both endometrial and ovarian carcinoma family histories.

The most common symptom was hematochezia (709 times). Change in bowel habits (624 times), abdominal pain (602 times), fatigue (229 times), weight loss (189 times), anemia (138 times), perianal pain (116 times), and anal pruritus or discharge (68 times) were other colorectal cancer-related symptoms. (Numbers in parentheses represent how many times the related symptom was defined by the patients). Colorectal cancer screening was conducted on 38 patients. The distribution of symptom time and definitive diagnosis time by stage is shown in Figures 1 and 2. There was no statistically significant difference between the groups according to the educational status for symptom and definitive diagnosis times (p=0.818 and p=0.271, respectively).

Table 1. Patient characteristics.

Characteristic variable	Frequency	%
Age ≥50 (years)	1444	80.44
Male	1057	59.0
Literacy	1560	88.1
Income ≤1000 TLΨ/month	866	48.7
Diagnosis		
Colon carcinoma	899	50.3
Rectal carcinoma	850	47.6
Both	37	2.1
Localization (original)		
Rectum	846	49.7
Sigmoid colon	328	19.3
Ascending colon	118	6.9
Cecum	105	6.2
Descending colon	76	4.5
Transverse colon	71	4.2
Hepatic flexure	46	2.7
Splenic flexure	43	2.5
Multiple	70	4.1
Localization (right/left colon)*		
Right colon	383	23.5
Left colon	1250	76.5
Stage (TNMθ)		
0	25	1.5
1	265	15.9
2	456	27.3
3	658	39.4
4	265	15.9

*Cases with multiple localizations were discarded in grouping the right and left colon.
ΨTurkish liras.
θTumor, node, and metastasis.

There was no statistically significant difference with respect to stage, early or advanced disease stage, symptom time, definitive diagnosis time according to the patient age (older or younger than 50 years), gender, or tumor lo-

Table 2. The cross tabulation of different tumor localization groups by symptom time.*

	Symptom time				
	<1 month	1-3 months	3-6 months	>6 months	p
Right colon (n=376)	208 (55.3)	85 (22.6)	29 (7.7)	54 (14.4)	0.169
Left colon (n=1231)	622 (50.5)	277 (22.5)	138 (11.2)	194 (15.8)	
Colon carcinoma (n=881)	480 (54.5)	188 (21.3)	88 (10.0)	125 (14.2)	0.156
Rectal carcinoma (n=837)	410 (49.0)	198 (23.7)	95 (11.4)	134 (16.0)	
Cecum (n=103)	59 (57.3)	25 (24.3)	6 (5.8)	13 (12.6)	0.231
Ascending colon (n=116)	60 (51.7)	32 (27.6)	7 (6.0)	17 (14.7)	
Hepatic flexure (n=46)	25 (54.3)	8 (17.4)	5 (10.9)	8 (17.4)	
Transverse colon (n=69)	33 (47.8)	18 (26.1)	8 (11.6)	10 (14.5)	
Splenic flexure (n=42)	31 (73.8)	2 (4.8)	3 (7.1)	6 (14.3)	
Descending colon (n=76)	46 (60.5)	11 (14.5)	9 (11.8)	10 (13.2)	
Sigmoid colon (n=322)	169 (52.5)	69 (21.4)	34 (10.6)	50 (15.5)	
Rectum (n=833)	407 (48.9)	197 (23.6)	95 (11.4)	134 (16.1)	

*As the symptom times of some patients were unknown, the total number of patients for each localization group is different from those given in Table 1. Cells represent frequency (%) values.

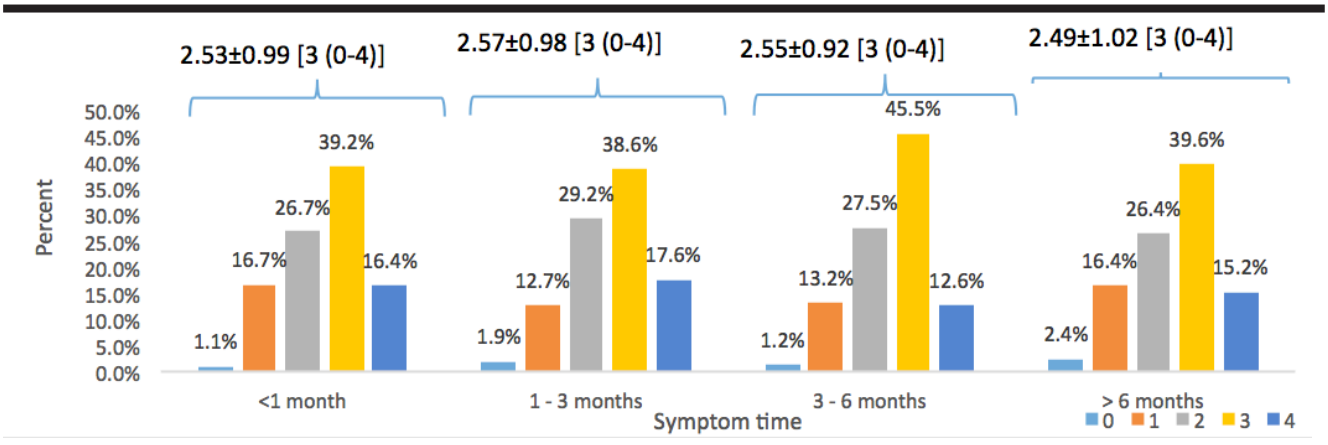

Figure 1. The distribution of symptom time and stage. Descriptive statistics for stage by symptom time.* Cells under the descriptive statistics column represent mean (±SD) (median (min-max)); all other cells represent frequency (%) values.
*As the symptom times of some patients were unknown, the total number of patients for each stage is different from those given in Table 1.

calization (right-sided or left-sided carcinomas). Although the mean stages were 2.57±0.94 for the colon carcinoma group and 2.48±1.04 for the rectal carcinoma group, this difference was not statistically significant (p=0.222). In addition, early or advanced disease stage, symptom time, and definitive diagnosis time did not differ between the colon and rectal carcinoma groups (Table 2, 3).

Patients with advanced disease stage were admitted to more number of doctors than patients with earlier disease stage (r=0.05; p=0.037). Nevertheless, a statistically significant difference was not detected between the early and advanced disease stage groups according to educational status, monthly income, symptom time, and definitive diagnosis time.

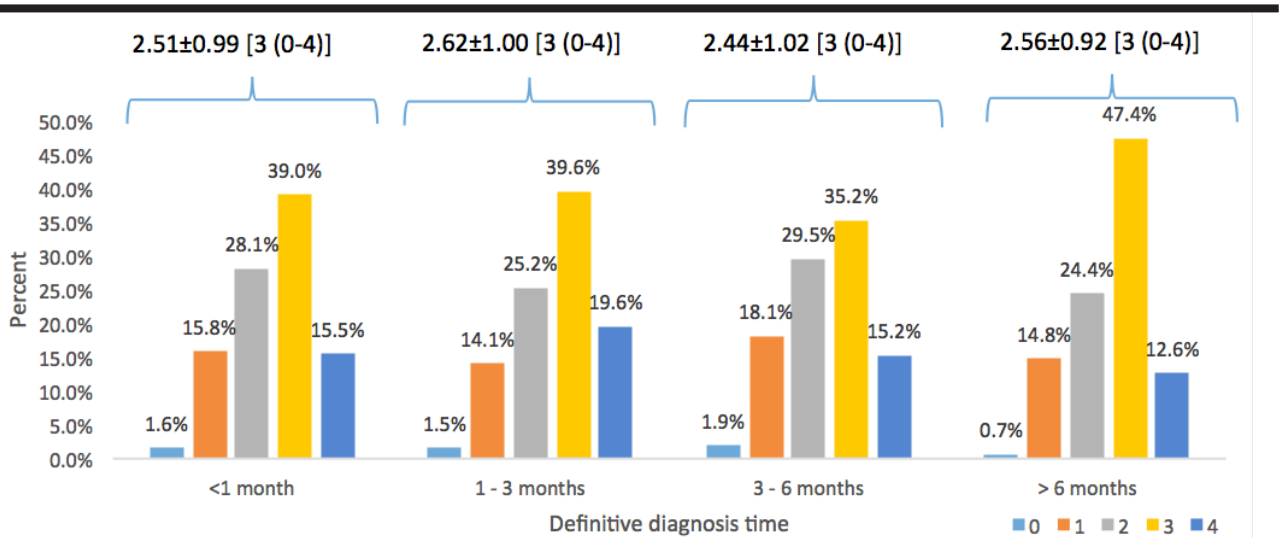

Figure 2. The distribution of definitive diagnosis time and stage. Descriptive statistics for stage by definitive diagnosis time.* Cells under the descriptive statistics column represent mean (±SD) (median (min-max)); all other cells represent frequency (%) values.
*As the definitive diagnosis times of some patients were unknown, the total number of patients for each stage is different from those given in Table 1.

Table 3. The cross tabulation of different tumor localization groups by definitive diagnosis time.*

	Definitive diagnosis time				
	<1 month	1-3 months	3-6 months	>6 months	p
Right colon (n=381)	263 (69.0)	64 (16.8)	21 (5.5)	33 (8.7)	0.889
Left colon (n=1244)	861 (69.2)	199 (16.0)	81 (6.5)	103 (8.3)	
Colon carcinoma (n=896)	601 (67.1)	156 (17.4)	63 (7.0)	76 (8.5)	0.727
Rectal carcinoma (n=845)	583 (69.0)	133 (15.7)	54 (6.4)	75 (8.9)	
Cecum (n=105)	68 (64.8)	15 (14.3)	7 (6.7)	15 (14.3)	0.336
Ascending colon (n=117)	80 (68.4)	28 (23.9)	5 (4.3)	4 (3.4)	
Hepatic flexure (n=46)	34 (73.9)	4 (8.7)	3 (6.5)	5 (10.9)	
Transverse colon (n=70)	52 (74.3)	12 (17.1)	3 (4.3)	3 (4.3)	
Splenic flexure (n=43)	29 (67.4)	5 (11.6)	3 (7.0)	6 (14.0)	
Descending colon (n=76)	52 (68.4)	11 (14.5)	5 (6.6)	8 (10.5)	
Sigmoid colon (n=327)	231 (70.6)	55 (16.8)	21 (6.4)	20 (6.1)	
Rectum (n=841)	578 (68.7)	133 (15.8)	55 (6.5)	75 (8.9)	

*As the definitive diagnosis times of some patients are unknown, the total number of patients for each localization group is different from those given in Table 1. Cells represent frequency (%) values.

There was no significant difference between the mean disease stages of patients with a family history of colorectal cancer (2.46±1.05) compared with patients with no family history of colorectal cancer (2.54±0.98) (p=0.319).

The mean (±SD) age of the patients was 61.90±13.79 years for patients with right-sided carcinoma, whereas it was 60.39±13.23 years for patients with left-sided carcinoma (p=0.035). There were statistically signifi-

Table 4. Association between symptoms and tumor localization.*

Symptom	Left colon (n=1245)	Right colon (n=381)	p
Hematochezia			
Yes	604 (92.4)	50 (7.6)	<0.001
No	641 (65.9)	331 (34.1)	
Anemia			
Yes	69 (55.2)	56 (44.8)	<0.001
No	1176 (78.3)	325 (21.7)	
Change in bowel habit			
Yes	459 (82.1)	100 (17.9)	<0.001
No	786 (73.7)	281 (26.3)	
Abdominal pain			
Yes	341 (63.3)	198 (36.7)	<0.001
No	904 (83.2)	183 (16.8)	
Anal pruritus or discharge			
Yes	52 (86.7)	8 (13.3)	0.060
No	1193 (76.2)	373 (23.8)	
Perianal pain			
Yes	101 (91.8)	9 (8.2)	<0.001
No	1144 (75.5)	372 (24.5)	
Colorectal cancer screening			
Yes	23 (62.2)	14 (37.8)	0.036
No	1222 (76.9)	367 (23.1)	
Weight loss			
Yes	108 (67.1)	53 (32.9)	0.003
No	1137 (77.6)	328 (22.4)	
Fatigue			
Yes	121 (62.1)	74 (37.9)	<0.001
No	1124 (78.5)	307 (21.5)	

*As the symptoms of some patients were unknown, the total number of patients for each tumor localization is different from those given in Table 1. Cells represent frequency (%) values.

cant age differences according to tumor localization (p=0.002). The mean age of patients with cecum-localized carcinoma (64.34 years) was significantly higher than those with carcinoma in the ascending colon (61.58 years), transverse colon (59.74 years), or rectum (59.60 years).

The differences between right- and left-sided carcinomas according to the colorectal cancer-related symptoms are described in Table 4. For all symptoms, the proportion of patients displaying the symptom differed significantly between the groups.

When the univariate logistic regression analysis was performed, symptoms of anemia, change in bowel habits, anal pruritus or discharge, and weight loss were found to be statistically significant risk factors for early admission (Table 5). However, in light of multivariable logistic regression, it could be concluded that patients who had "anemia," "change in bowel habits," "anal pruritus or discharge," "weight loss," and "tumor in right colon" were admitted to the hospital for a longer time (Table 6). In addition, the odds of being in the early disease stage were higher in patients who suffered hematochezia (OR 1.296, 95% CI 1.063-1.583, p=0.011) and who had colorectal cancer screening (OR 2.756, 95% CI 1.323-5.742, p=0.007).

DISCUSSION

The anatomical variation between the right and left sides of the colon might cause an expectation that left-sided tumors would present with a shorter duration of symptoms. This expectation rises on two basic rationales; patients with rectal cancer experience rectal bleeding or discharge or tenesmus when tumors are small in size. Patients with descending or sigmoid colon also experience symptoms, such as obstruction or bleeding due to the narrowing of the lumen. However, the right colon has a wider lumen, and obscure bleeding is usually the only sign that brings the patient to the colorectal surgeons. Therefore, patients with right-sided carcinomas are expected to present with a shorter duration of symptoms, whereas patients with left-sided tumors present with a longer duration of symptoms. However, our study refuted this proposition; localization of the colon carcinoma does not affect symptom time or diagnosis time.

Moreover, the tumor stage does not affect symptom time or diagnosis time, either. Since carcinogenesis is a multiyear process, colorectal carcinomas may take up to 10-15 years to develop after the detection of adenomas (11,12). Many years might pass before patients become symptomatic, and this might delay the diagnosis. The time between the onset of symptoms and the diagnosis is usually between 3 and 6 months (1,13-15). Therefore,

Table 5. The results of univariate logistic regression.

	Early admission, n (%)	Late admission, n (%)	p	Crude OR (95% CI)
Presence of hematochezia	358 (39.3)	344 (40.7)	0.534	0.941 (0.777-1.139)
Presence of anemia	60 (6.6)	77 (9.1)	0.048	0.702 (0.494-0.998)
Change in bowel habit	291 (31.9)	330 (39.1)	0.002	0.731 (0.601-0.890)
Presence of abdominal pain	316 (34.6)	282 (33.4)	0.573	1.059 (0.869-1.290)
Presence of anal pruritus or discharge	25 (2.7)	42 (5.0)	0.015	0.539 (0.325-0.892)
Presence of perianal pain	52 (5.7)	64 (7.6)	0.114	0.738 (0.505-1.077)
Having colorectal cancer screening	16 (1.8)	12 (1.4)	0.576	1.240 (0.583-2.636)
Presence of weight loss	80 (8.8)	108 (12.8)	0.007	0.656 (0.483-0.891)
Presence of fatigue	105 (11.5)	120 (14.2)	0.092	0.786 (0.594-1.041)
Tumor being in the left colon	622 (74.9)	609 (78.4)	0.104	0.825 (0.654-1.040)

OR, odds ratio; CI, confidence interval.

Table 6. The results of multivariable logistic regression analysis for early admission.

Independent variables	Adjusted OR (95% CI)	p
Presence of anemia	0.668 (0.457-0.975)	0.036
Change in bowel habits	0.750 (0.609-0.924)	0.007
Presence of anal pruritus or discharge	0.546 (0.316-0.945)	0.030
Presence of weight loss	0.694 (0.496-0.970)	0.033
Tumor being in the left colon	0.813 (0.640-1.032)	0.090

OR, odds ratio; CI, confidence interval

whether the symptomatic period is a few months shorter or longer may not be affected from tumor stage. This may explain why the present study failed to show an association between disease stage and symptom duration. Many other studies also report no association between delay in the diagnosis of colorectal carcinoma and disease stage (1,6,8,9,12,16,17). Additionally, subgroup analyses showed no significant difference with respect to stage, early or advanced disease stage, symptom time, definitive diagnosis time, or tumor localization according to patient age (older or younger than 50 years), gender, or tumor localization (right or left colon).

In the present study, hematochezia, change in bowel habits, and abdominal pain were the most common symptoms of colorectal carcinoma, consistent with previous studies (18-20). Hematochezia, change in bowel habits, and perianal pain were mostly related to left-sided localized tumors, whereas abdominal pain, fatigue, and weight loss were related to right-sided tumors. Patients with left-sided tumors had a significantly longer symptom time. In addition, the probability of being in the early disease stage was higher in patients who suffered hematochezia (OR 1.296, 95% CI 1.063-1.582, p=0.011) or who had colorectal cancer screening (OR 2.756, 95% CI 1.323-5.742, p=0.007).

Patients with rectal or left-sided carcinoma were younger than patients whose tumors were localized in the cecum, and patients with colon carcinoma had a more advanced disease stage on average than patients with rectal carcinoma (p=0.002). These findings are also similar to previous studies in the literature; patients with right-sided tumors are older and have worse outcomes than those with left-sided tumors (21-23). The cause behind this is unclear. Prolonged fecal exposure, presentation with

non-specific symptoms, late presentation of disease due to the large anatomic space, and decreased success rate for colonoscopic detection of lesions in right-sided tumors may explain this finding. However, our results revealed no statistically significant difference for symptom duration according to tumor localization.

The main strength of the present study is the large prospective cohort. Referral bias is the main limitation. Since the present study was performed in tertiary medical institutions, patients with non-specific symptoms or with advanced disease might be referred more frequently from peripheral hospitals. Another issue is that patients might have under- or over-reported their symptoms.

In conclusion, no association was detected between tumor stage or localization and symptom time. The symptomatic period of colorectal carcinoma is a very short part of a long process. Our data highlight the importance of screening; screening asymptomatic patients for earlier detection of tumors is more crucial than rapid diagnosis.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of Ankara University School of Medicine (Decision Date/Number: October 25, 2010/17-376).

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