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ORIGINAL ARTICLE

Differences in colorectal cancer patterns between right and left sided colorectal cancer lesions

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Summary

Purpose: *Colorectal carcinomas that arise proximal (right) or distal (left) to the splenic flexure exhibit different clinical and biological characteristics. Although various hypotheses have been proposed to explain these differences, their origin remains unclear. In this study we investigated the clinicopathologic differences between left and right colon tumors and comment on the possible explanatory theories behind them.*

Methods: *This study included a total of 388 retrospectively collected cases of colorectal cancer, surgically treated from 1999 to 2004. Differences of patients' demographic data and tumor micro- and macroscopic characteristics between left and right-sided tumors were investigated and analysed.*

Results: *Patients with right-sided colon cancer were significantly older (mean age 70 vs. 68 years; $p < 0.05$) and had more lymph nodes examined than patients with left colon tumors (mean number of nodes 18.9 vs. 12.6; $p < 0.05$). There was a lower proportion of T1 stage right-sided tumors (3.1 vs. 5%) and a higher proportion of stage T2-4 (96.9 vs. 95%) compared with left-sided tumors ($p < 0.001$ for x^2 test of all T stages). Furthermore, right-sided tumors had a higher mean width and depth (4.3 vs. 3.8 cm and 1.8 vs. 1.6 cm, respectively; $p < 0.05$). Finally, there was a higher percentage of poorly differentiated right colon tumors (41.4 vs. 17.5%; $p < 0.001$).*

Conclusion: *Right-sided colon tumors affect older patients and are diagnosed at more advanced disease stages. The underlying mechanisms that provoke these differences remain unclear. Further studies are needed in order to better understand the true nature of these differences and their possible clinical implications.*

Key words: cancer, left colon, right colon, tumor grade, tumor stage

Introduction

Colorectal cancer is the most common malignancy of the gastrointestinal tract and the second leading cause of cancer-related deaths in western societies [1,2]. The concept of two distinct categories of colon cancer was first introduced several years ago [3,4]. The tumor is divided according to its location (proximal or distal to the splenic flexure). This distinction is supported by embryologic, epidemiologic, molecular and physiologic data. The portion of the colon located proximal to the splenic flexure derives from the midgut and is perfused by the superior mesenteric artery [5]. Furthermore, the concentration of various hydrolytic and reductive bacterial enzymes appears to differ within the different portions of the large bowel [6]. These differences in normal, left and right colon, tissue could predispose to different patterns of carcinogenesis. In favor of the latter notion, published data support the uneven distribution of distinct mutational pathways between the two portions of the colon [7,8]. Several researchers have published various reports on the differences between proximal and distal colon tumors [5-8]. Nonetheless, to date, the similarities and dissimilarities between right and left colon cancer remain unclear. In order to further elucidate this issue we conducted a research on the differences between left and right-sided tumors in terms of patient and tumor characteristics.

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Methods

This study was performed at the first Department of Propaedeutic Surgery, Hippocrateion hospital, Athens Medical School. The study protocol was approved by the hospital Research Ethics Committee.

A total of 388 retrospectively collected cases of colorectal cancer surgically treated from 1999 to 2004 were included in this analysis. Histologically diagnosed nonepithelial malignancies, as well as tumors *in situ* were excluded from the analysis. Furthermore, patients with synchronous second cancers who had to undergo total colectomy were also excluded. Right-sided tumors were defined those situated in the cecum, ascending and transverse colon, while left-sided tumors included the descending colon, sigmoid and rectum.

Data were collected from the patients' medical records including the pathological evaluation and the operational data sheet. Our analysis involved a number of factors such as patients' age, gender and number of lymph nodes examined, as well as TNM disease stage, grade of differentiation, length, width, depth and the presence of necrosis, inflammation and ulceration. In order to further elucidate the relationship between age and tumor location, we divided patients into 3 age groups (≤ 60, 61-74, and ≥ 75 years old).

Statistical considerations

A standard statistical software package SPSS (SPSS Inc, Chicago IL) was used for statistical analysis. Descriptive statistics were calculated for all variables. Chi-square test was used to compare categorical variables. Means were compared with the Kruskal-Wallis and the Mann-Whitney U tests. P- values less than 0.05 were considered statistically significant.

Results

Patient and tumor characteristics are presented in Table 1. Of the 388 patients 129 (33.3%) had tumors located in the right side, while 259 (66.6%) had left-sided tumors. Patients with right-sided colon cancer were significantly older (mean age of 70 vs. 68 years; $p < 0.05$), nevertheless no differences could be detected between different age groups. There was a lower proportion of T1 stage right-sided tumors (3.1 vs. 5%) and a higher proportion of stage T2-4 right-sided tumors (96.9 vs. 95%) compared with left-sided tumors ($p < 0.001$ for x^2 test of all T stages). In agreement with this finding, analysis of the tumor gross characteristics revealed that right-sided tumors had a higher mean width and depth than left-sided tumors (4.3 vs. 3.8 cm and 1.8 vs. 1.6 cm, respectively; $p < 0.05$). Although the presence of lymph node involvement was not significantly associated with tumor location, right-sided tumors had more nodes examined (mean number of nodes 18.9 vs. 12.6; $p < 0.05$). Furthermore, right-sided tumors had a higher degree of adequate lymph node evaluation (≥ 12 nodes) than left-sided ones (71.7 vs. 50.6%; $p < 0.05$). Finally, there was a significantly higher percentage of poorly differentiated right-sided tumors compared with left-sided cancers (41.4 vs. 17.5%; $p < 0.001$).

Statistical analysis showed that gender, TNM stage and the presence of ulceration, inflammation or necrosis were not significantly associated with tumor location.

Discussion

During the last years several researchers, intrigued by the theory regarding the existence of two distinct clinicopathological entities in colon cancer, have provided various data in favor of this concept. Furthermore, several population-based studies have revealed a trend towards an increasing incidence of right-sided tumors [9-11]. According to current literature, compared to left-sided, right-sided tumors affect older and female patients and they are usually diagnosed at more advanced stages [12,13].

This study focused on the clinicopathologic differences between left and right-sided colon cancers. In concordance with previous studies, the present study showed that right-sided tumors affected older patients and were associated with a higher degree of adequate lymph node evaluation, while tumor mass penetrated deeper into the colonic wall and showed poorer differentiation than left-sided tumors.

These results could be attributed to differences at the time of diagnosis. In a study performed by Nawa et al. right-sided tumors were more frequently associated with severe symptoms such as obstructive symptoms or abdominal mass, while bleeding was more difficult to be detected compared to left-sided lesions [14]. These results imply that right-sided tumors tend to remain clinically silent and become apparent at more advanced stages with more severe symptoms. In addition, according to current guidelines, sigmoidoscopy, one of the preferred screening methods for average-risk patients, which although convenient, lacks the ability to detect tumors proximal to the splenic flexure [1].

According to the aforementioned observations, right-sided tumors, either due to lack of symptoms and/or inadequacy of current screening methods, are diagnosed late in the course of the disease and at the time of surgery

Table 1. Patient and tumor characteristics

Characteristics	*Patients n=388*	*Right-sided (n=129)*	*Left-sided (n=259)*	*p-value*
Age, years (mean±SD)	69±12	70±11	68±12	<0.05
Age (years), n (%)				NS
≤60	76 (20.4)	22 (18)	54 (21.6)	
61-74	170 (45.7)	52 (42.6)	118 (47.2)	
≥75	126 (33.9)	48 (39.3)	78 (31.2)	
Gender, n (%)				NS
Male	232 (59.8)	83 (64.3)	149 (57.5)	
Female	156 (40.2)	46 (35.7)	110 (42.5)	
Astler-Coller stage, n (%)				NS
A	16 (4.1)	4 (3.1)	12 (4.6)	
B1	54 (13.9)	10 (7.8)	44 (17)	
B2	121 (31.2)	50 (38.8)	71 (27.4)	
B3	2 (0.5)	1 (0.8)	1 (0.4)	
C1	8 (2.1)	2 (1.6)	6 (2.3)	
C2	157 (40.5)	55 (42.6)	102 (39.4)	
C3	4 (1.0)	2 (1.6)	2 (0.8)	
D	26 (6.7)	5 (3.9)	21 (8.1)	
TNM stage, n (%)				
T				<0.05
T1	17 (4.4)	4 (3.1)	13 (5)	
T2	62 (16)	13 (10.1)	49 (18.9)	
T3	293 (75.5)	109 (84.5)	184 (71)	
T4	16 (4.1)	3 (2.3)	13 (5)	
N				NS
N0	201 (51.9)	65 (50.4)	136 (52.7)	
N1	103 (26.6)	33 (25.6)	70 (27.1)	
N2	83 (21.4)	31 (24)	52 (20.2)	
M				NS
M0	362 (93.3)	124 (96.1)	238 (91.9)	
M1	26 (6.7)	5 (3.9)	21 (8.1)	
Lymph nodes (mean±SD)	14.7±10	18.9±12.2	12.6±7.8	<0.05
≤12, n (%)	163 (42.4)	36 (28.3)	127 (49.4)	<0.05
>12, n (%)	221 (57.6)	91 (71.7)	130 (50.6)	<0.05
Histology, n (%)				NS
Ulceration	232 (60.1)	78 (60.9)	154 (59.7)	
Inflammation	119 (30.8)	38 (29.5)	81 (31.5)	
Necrosis	70 (18.2)	24 (18.9)	46 (17.8)	
Grade of differentiation				
Well	30 (8)	10 (8.1)	20 (7.9)	<0.05
Moderate	250 (66.7)	62 (50.5)	188 (74.6)	
Poor	95 (25.3)	51 (41.4)	44 (17.5)	
Tumor size (cm, mean±SD)				
Length	4.6±1.7	4.9±1.9	4.5±1.6	NS
Width	4.0±1.7	4.3±1.8	3.8±1.6	<0.05
Depth	1.7±1.2	1.8±1.1	1.6±1.2	<0.05

SD: standard deviation, NS: nonsignificant

are found more advanced than left-sided cancers. Nonetheless, in this study, although we were able to show a significant association of tumor location with T stage, depth and width, no similar results were found with nodal status, presence of metastasis and TNM stage. These findings could imply that right-sided tumors show a tendency towards specific histopathologic features-and thus question the aforementioned theory about differences at the time of diagnosis; nevertheless, the low statistical power of this study precludes us from making such a suggestion.

While delayed diagnosis of right colon tumors could serve as a possible explanation for our findings, it is not the only one. Several authors have published various studies commenting on the embryologic, physiologic and biochemical differences between normal right and left colon [5,8]. Moreover, a recent study performed by Meguid et al. showed that right-sided tumors had a worse prognosis even after adjusting for patient and tumor characteristics [15]. This observation denotes the probable role of genetic and environmental factors in the detection of different characteristics between the two sides. In favor of this theory some studies have shown that two different genetic mechanisms, microsatellite instability (MSI) and chromosomal instability (CIN), contribute to carcinogenesis in the proximal and distal segments of the large bowel, respectively [16,17]. MSI is characterized by the mutation of short repetitive DNA sequences known as microsatellites, while CIN represents large-scale chromosomal instability, which mostly involves the mutation of genes such as *K-ras* and *p53*. MSI tumors appear in a higher percentage in the proximal colon and they are associated with a better prognosis [18]. Besides the presence of different mutational pathways several researchers have commented on the effect of various environmental factors on the development of right and left-sided colon cancer [19-21]. In a case-control study by West et al. high dietary fat intake was linked to an increased risk of proximal cancers, while high protein intake was associated with an increased incidence of distal cancers [19]. Moreover, a meta-analysis by Giovannucci et al. showed that cholecystectomy was associated with increased risk of proximal but not distal colon cancer [21].

Another noteworthy finding of this study was that tumor location affected the number of the resected lymph nodes. In agreement with our observation, a recent study on the impact of tumor location on nodal evaluation showed that patients with right-sided colon cancers had more nodes examined than patients with left-sided colon cancers [22]. The reason for this remains unclear; nevertheless, the practice of different surgical techniques could serve as a possible explanation.

This study has some limitations. During analysis, rectal carcinomas were included in the category of left-sided tumors. Review of the current literature on the existence of two sides of colon cancer does not reveal a uniform approach towards the inclusion of rectal tumors. Several researchers have excluded them due to their differences in morphology and pathogenesis from the rest of colon tumors [15,23]. Furthermore, this study was conducted in one center and included a relative small number of patients; however, our observations are in agreement with those of larger series.

In conclusion, we found that right colon tumors are diagnosed at more advanced stage and in older patients. The reason for this remains unclear. The existence of two distinct molecular pathways or simply, difference at the time of diagnosis (frequent delay of diagnosis in right-sided tumors) could serve as possible explanation. Further studies are needed in order to better understand the reasons for the observed differences and their possible clinical implications.

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