Articles

Clinical and pathological comparison of proximal and distal colorectal adenocarcinoma

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ABSTRACT

AIM: Colorectal cancer is a major cause of morbidity and mortality worldwide. Recent studies suggest that proximal and distal colorectal cancers may represent different forms of the disease. The purpose of this study was to evaluate demographic, clinical and pathologic characteristics of colorectal cancer regarding the distribution within the colon and rectum.

METHODS: One hundred fifty-five consecutive patients with primary colorectal carcinoma were analyzed. Proximal (up to the splenic flexure) and distal (splenic flexure to the rectum) colorectal cancers were compared regarding age, gender, stage, differentiation, mucinous content and the presence of distant metastases and peritoneal carcinosis.

RESULTS: No significant difference in age and gender was observed between proximal and distal tumors. Proximal tumors were not significantly more advanced at the time of diagnosis compared to distal tumors according to tumor size, Dukes and Astler-Coller classification. However, proximal tumors had significantly higher frequency of pT4 stage, liver metastases, peritoneal carcinosis and poor differentiation. Mucinous carcinomas were found more often in the proximal colon, but not significantly.

CONCLUSION: These results support the hypothesis that proximal and distal colorectal cancers may have different biological behavior. Further large studies should be performed to evaluate the clinical significance of differences found in this study, and possible impact on screening, diagnosis, therapy and survival.

KEY WORDS: colorectal neoplasms; surgery; human

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INTRODUCTION

The incidence of colorectal cancer has greatly increased in the past five decades (1, 2). Today, cancer of the colon and rectum represents a major cause of morbidity and mortality worldwide, with over 300000 new cases and about 200000-300000 deaths per year in Europe and the United States (3, 4).

Recently published epidemiological studies suggest that the distribution of cancer within the colon and rectum may have undergone a distal to proximal shift during last decades (5, 6). This redistribution of colorectal cancer has been attributed to different demographic, geographic, environmental and genetic factors as well as screening and diagnostic interventions (7).

Epidemiological studies of colorectal cancer revealed differences regarding anatomical distribution within the colorectum, suggesting that site-specific colorectal cancers may represent different forms of the disease (7, 8).

This hypothesis was further supported by studies that linked the site-specific characteristics of colorectal cancer to hormonal (9, 10) and genetic factors, microsatellite instability (11) and the expression and prognostic value of p53 protein (12, 13), which was found to be a significant prognostic indicator in colorectal cancer (14). These molecular characteristics were found to differ between proximal (up to the splenic flexure) and distal colorectal cancers (13). Although the incidence of proximal colon cancer is known to increase with age, it's prognosis remains unclear (15).

The purpose of this study was to evaluate demographic, clinical and pathologic characteristics of colorectal cancer regarding anatomical site distribution, which may have important implications regarding screening, diagnosis, treatment and follow-up.

PATIENTS AND METHODS

One hundred and fifty-five consecutive patients with primary colorectal carcinoma treated during 1998 at the Surgical Clinic were analyzed. Those with proven diagnosis of familial adenomatous polyposis (FAP) as well as patients with recurrent carcinomas were not included.

Age and gender were obtained from admission records. Localization of the tumor and the presence of liver metastases or peritoneal carcinosis were determined by colonoscopy and preoperative CT scan or ultrasound, but also from the operating surgeon report and release records. Tumors arising in the cecum, ascending colon, hepatic flexure and transverse colon were considered right-sided (proximal) tumors. Those arising at the splenic flexure, descending and sigmoid colon, rectosigmoid junction or rectum were considered left-sided (distal) tumors. Tumors were classified according to Dukes, Astler-Coller and pTNM classifications. Total number of harvested lymph nodes and the number of positive nodes were obtained from pathologists' reports. According to mucin content, tumors were classified as non-mucinous (less than 50% mucinous component) and mucinous carcinomas (those with 50% or more mucinous component).

Mann-Whitney U-test was used to compare variables between groups. Differences in percentages were analyzed using Chi-square test. Values of $p < 0.05$ were considered statistically significant.

RESULTS

There were 60 female and 95 male patients. No difference in age was observed between female and male patients (median 66.2 [range 34.5-93.7] years vs. median 66.9 [range 36.9-95.8] years, p=0.749). The distribution of tumor within the colon and rectum is presented in Table 1. Twenty-nine patients had tumors of the proximal (right) colon, and 124 had tumors of the distal (left colon). In two patients the exact location could not have been determined because of overlapping or multiple sites, and these two patients were excluded from further analysis. Patients with tumors of the proximal colon had median of 70.4 (36.9-95.8) years, and those with tumors of the distal colon and rectum had median age of 66.7 (34.5-93.7) years. This difference in age was not statistically significant (p=0.132). The distribution of patients with proximal and distal colorectal cancers according to age groups is presented in Table 2.

There was no statistically significant difference in the largest tumor diameter between proximal and distal tumors. Proximal tumors had a median of 5 (2.5-8) cm as compared to distal colorectal tumors, with median of 4 (1-15) cm (p=0.074).

Median number of harvested lymph nodes was greater for proximal tumors (median 12 nodes, range 5-30) than for distal tumors (median 10 nodes, range 0-29). This difference was statistically significant (p=0.035). However, the percentage of positive lymph nodes for Dukes C tumors did not differ significantly (p=0.932).

Distribution of proximal and distal tumors according to Dukes, Astler-Coller and pT classification are presented in Table 3. There were no significant differences between the two groups according to neither classification, except for significantly greater percent of pT4 tumors in the proximal colon.

Mucinous carcinomas were more often found in the proximal colon (17%) than in the distal colon and rectum (9%), but this difference was not statistically significant (p=0.208).

Seven (24%) patients with tumors of the proximal colon had liver metastases at the time of surgery, compared to 13 (10%) patients with tumors of the distal colon and rectum (p=0.043).

Peritoneal carcinosis was found in 7 (24%) patients with proximal tumors and in only one (0.8%) patient with distal colorectal tumor (p<0.001).

Differentiation of proximal and distal colorectal cancers is presented in Table 4. Proximal tumors had significantly greater percentage of poorly differentiated forms.

Table 1. Distribution of colorectal cancer according to site

Location	Frequency	%
Cecum	11	7.1
Ascending colon	8	5.2
Hepatic flexure	4	2.6
Transverse colon	6	3.9
Total proximal tumors	29	18.7
Splenic flexure	2	1.3
Descending colon	6	3.9
Sigmoid colon	38	24.5
Rectosigmoid junction	17	11.0
Rectum	61	39.4
Total distal tumors	124	80.0
Overlapping/multiple sites	2	1.3
Total	155	

Table 2. Distribution of age according to the location of tumor in the colon and rectum

	Right	%	Left	%	p
< 40	2	6.90	3	2.42	0.221
40 < x <= 50	1	3.45	8	6.45	0.537
50 < x <= 60	3	10.34	26	20.97	0.191
60 < x <= 70	7	24.14	41	33.06	0.353
70 < x <= 80	12	41.38	38	30.65	0.269
80 < x <= 90	3	10.34	7	5.65	0.359
90 < x <= 100	1	3.45	1	0.81	0.262
Total	29	100.00	124	100.00	

Right = tumors up to the splenic flexure
Left = tumors from the splenic flexure to the rectum

Table 3. Comparison of proximal and distal colorectal cancer according to Dukes, Astler-Coller and pT classifications

	Right	%	Left	%	p
Dukes A	6	20.69	35	28.23	0.411
Dukes B	7	24.14	27	21.77	0.783
Dukes C	13	44.83	49	39.52	0.601
Missing	3	10.34	13	10.48	0.982
Total	29	100.00	124	100.00	
AC A	0	0.00	5	4.03	0.273
AC B1	6	20.69	30	24.19	0.690
AC B2	6	20.69	27	21.77	0.899
AC C1	1	3.45	6	4.84	0.748
AC C2	13	44.83	42	33.87	0.270
Missing	3	10.34	14	11.29	0.884
Total	29	100.00	124	100.00	
PTis	1	3.45	5	4.03	0.885
pT1	0	0.00	2	1.61	0.493
pT2	7	24.14	34	27.42	0.720
pT3	13	44.83	66	53.23	0.416
pT4	8	27.59	7	5.65	0.001
Missing	0	0.00	10	8.06	0.116
Total	29	100.00	124	100.00	

AC = Astler-Coller classification
Right = tumors up to the splenic flexure
Left = tumors from the splenic flexure to the rectum

Table 4. Differentiation of proximal and distal colorectal cancers

	Proximal	%	Distal	%	p
Well differentiated	20	68.97	78	62.90	0.541
Moderately differentiated	5	17.24	16	12.90	0.542
Poorly differentiated	1	3.45	0	0.00	0.040
Missing	3	10.34	30	24.19	0.105
Total	29	100.00	124	100.00	

DISCUSSION

Colorectal cancer represents one of major health problems, causing significant morbidity and mortality in the countries of the western world (1-4). Although colorectal cancer is more common in the distal part of the colon and in the rectum, a redistribution of the site of origin was observed in some studies in the past decades (5, 6, 16). This redistribution related to age, with more cases of right-sided tumors in people over 50 years of age (17). Differences among ethnic groups were also noted (17).

Some researchers believe that these changes in incidence rates according to the site in the colorectum are the result of different development of the colorectal cancer arising at different locations (18).

Classical adenoma-carcinoma sequence of the colorectal carcinoma development may not apply for proximal colorectal cancer, as found by Ikeda et al. (18). In their research, the incidence of adenomatous polyps in patients over 65 years of age was greater in the distal colon, but the incidence of cancer was higher in the proximal colon (18). Analyses of p53 gene mutations revealed that distal colorectal tumors were associated with greater proportion of mutations in the conserved regions of p53 gene. This was linked to poorer differentiation and more aggressive biological behavior of distal colorectal cancers (19).

In this study, the median age of patients with proximal tumors was greater than the age of patient with distal colorectal tumors, but not significantly. It is generally believed that proximal tumors are diagnosed later in their development, due to fewer symptoms compared to left-sided cancers, and that they are more advanced at the time of surgery (15). However, in our research, tumor size determined by measuring the largest diameter did not differ significantly between proximal and distal tumors, although proximal tumors tended to be larger.

If proximal tumors were discovered later in their development, it would be reasonable to expect the greater proportion of locally advanced tumors as compared to early tumors. The results of this study do not support this hypothesis. No significant differences in the frequency of early stages were observed when proximal and distal cancers were compared according to Dukes, Astler-Coller and pT classifications, used routinely for staging colorectal cancer and determining subsequent adjuvant therapies. Also, the percentage of positive lymph nodes did not differ significantly.

Patients with proximal tumors presented more frequently with liver metastases and peritoneal carcinosis. Also, there was significantly greater percentage of poorly differentiated tumors in the group of proximal colorectal cancers. Furthermore, mucinous carcinoma was more often found in proximal colon, but not significantly. Since there are more than one criterion for determining mucinous colorectal cancer (20), different criteria from the one that was used could yield different results. Regardless, mucinous tumors were found in 17% of proximal colon cancers and in only 9% of distal colorectal tumors. Mucinous colorectal cancer was found to be more aggressive, with higher incidence of local invasion and lymph node metastases, higher recurrence rates and poorer survival (20).

The results of this study demonstrated that proximal colon cancer may indeed represent a distinct form of colorectal neoplasm, with different biological behavior. This is opposite to the results of other authors who found distal colorectal tumors to be more aggressive and associated with poorer survival (13, 19).

Results presented in this study should be interpreted in the light of relatively high rate of non-resectable tumors, comprising approximately 10% of cases, mostly due to peritoneal carcinosis or diffuse, inoperable liver metastases. However, the resectability rate was almost identical in proximal and distal tumors ($p>0.1$).

Further research with large studies should be performed to evaluate the clinical significance of differences found in this study, and possible impact on screening, diagnosis, therapy and survival.

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