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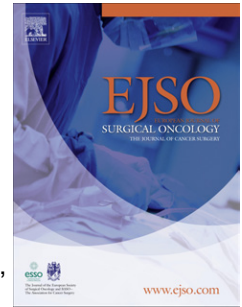
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Colon carcinoma – classification into right and left sided cancer or according to colonic subsite? – Analysis of 29 568 patients

Running head: Colon cancer – a heterogeneous tumor entity?

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Abstract

Background: It is common to distinguish between right and left colon cancer (RCC and LCC). But, little is known about the influence of its exact location on the tumor stage and characteristics when considering the colonic subsite within the right or left colon.

Methods: During a five-year period, 29 568 consecutive patients were evaluated by data from the German multi-centered observational study "Colon/Rectal Carcinoma". Patients were split into 7 groups, each group representing a colonic subsite. They were compared regarding demographic factors, tumor stage, metastatic spread and histopathological characteristics.

Results: Analysis of tumor differentiation and histological subtype revealed a linear correlation to the ileocecal valve, supporting the right and left side classification model. However, cancers arising from the RCC's cecum (52.3%) and LCC's splenic flexure (51.0%) showed the highest proportion of UICC stage III/IV tumors and lymphatic invasion, whereas the RCC's ascending colon (46.5%) and LCC's descending (44.7%) showed the lowest, which supports a more complex classification system, breaking down the right and left sides into colonic subsites.

Conclusions: Age, tumor grade and histological subtype support the right and left side classification model. However, gender, UICC stage, metastatic spread, T and N status, and lymphatic invasion correlated with a specific colonic subsite, irrespective of the side. The classification of RCC or LCC provides a general understanding of the tumor, but identification of the colonic subsite provides additional prognostic information. This study shows that the standard right and left side classification model may be insufficient.

Key words: colon carcinoma, classification, colonic subsite, heterogeneous tumor, prognosis

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Introduction

In the last two decades, a growing amount of studies reported clinical and pathological differences between right-sided colon carcinomas (RCC: cecum, ascending colon, hepatic flexure and transverse colon) and left-sided colon carcinomas (LCC: splenic flexure, descending and sigmoid colon). Epidemiological studies have demonstrated an gender and age relationship with a higher incidence of RCC in women and elderly people [1,2]. There are also differences in histopathological appearance [3-6], and in the molecular biological pattern [7,8]. Therefore, it has been suggested to consider colo-rectal cancer as three distinct tumor entities: RCC, LCC and rectal cancer [9].

Despite data being available on a large number of colon cancer patients, little is known about the impact of the colonic tumor subsite on histopathological characteristics and tumor classification of colon cancer (CC).

In a recently published study by our group [6], significant differences between RCC and LCC were confirmed and this supports the traditional classification system. However, the results opened up further questions. The data showed that there was a definable difference between left and right side colon cancers, but it became clear that further investigation was needed to determine the potential reasons for the heterogeneity within each group. Therefore, the aim of this study was to further evaluate CC from defined colonic subsites: cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon and sigmoid colon, to ascertain if and to what extent a distinct pattern of tumor growth and histopathological features these subsites show, and if there is a correlation between tumor characteristics and distance from the ileocecal valve.

Patients and Methods

Within the German multi-center observational study “Colon/Rectal Carcinoma (Primary Tumor)”, data for 31 261 patients with CC was acquired prospectively within a five-year period.

A standardized questionnaire was completed at the hospital where the patient was treated, to record information about the patient, tumor, operation, final pathology, and perioperative course. The study was conducted according to the Declaration of Helsinki for Biomedical Research. Participation was voluntary, evaluation was based on anonymous data, and the study involved observation only – i.e., it had no influence upon the choice or course of therapy. For these reasons, an Ethics Committee vote was not necessary. All 31 261 patients gave their written consent to data collection and anonymous evaluation.

Inclusion criteria were as follows:

- All patients with invasive carcinomas of the colon recruited between January 1, 2000 to December 31, 2004
- Patients with surgical tumor-resection to ensure final pathology.

Exclusion criteria were as follows:

- Local procedures (wedge resection, endoscopic polypectomy)
- Palliative procedure (i.e. bypass)
- Carcinoma of the appendix and rectum
- Synchronous CC

After considering the above criteria, the patient pool consisted of 29 568 patients.

They were distributed into seven groups according to the colonic tumor site:

1. cecum; 2. ascending colon; 3. hepatic flexure; 4. transverse colon; 5. splenic flexure; 6. descending colon; 7. sigmoid colon.

If a tumor was located on the border between two colonic subsites, it was considered a tumor of the segment wherever the majority of the tumor was found. The following parameters were analyzed for all patients: age, gender, final tumor stage (TNM and UICC classification), presence and type of synchronous distant metastases, histological subtype, and tumor grade.

Statistics

All data was entered into an MS ACCESS database and were processed by using the statistical package SPSS (version 16.0; SPSS Ltd., Chicago, IL, USA). Frequency testing for categorical variables was conducted by standard methods, and continuous variables were compared by analysis of variance (ANOVA) with subsequent multiple comparison according to Tukey. Differences found in the two-dimensional cross-comparison were tested statistically by Pearson's χ^2 test. Test for linear-by-linear association chi-square, was preferred in order to test the significance of the linear relationship between ordinal variables. Differences between the groups were to be regarded as significant if $p < 0.05$ was found in a two-sided test.

Results

Between January 1, 2000 and December 31, 2004, all consecutive patients operated on CC were considered for this study. Overall, 29 568 patients fulfilled the inclusion criteria and were analyzed. With respect to colonic subsite, sigmoid colon cancer was found to have the most frequent tumors.

Demographics

The male:female ratio for the 29 568 patients was 1:1 and women were more frequently diagnosed with tumors of the cecum, ascending and transverse colon.

Furthermore, analysis of age revealed a linear correlation between patient age and proximity to the ileocecal valve ($p < 0.001$) (Table 1).

UICC stage

Of the 29 568 patients included for analysis, 28 797 patients had complete data regarding UICC stage. The UICC stage was significantly different between RCC and LCC [6], but also between the colonic subsites (Table 1). Of the 28 797, 51.9% of the patients ($n=14\ 958$) had CC with UICC stages I or II. The highest rate of these prognostically favorable stages was found for carcinomas of the descending colon (55.3%) and ascending colon (53.6%), whereas the lowest rate was found for the splenic flexure and cecum (49.0% and 47.7%, respectively). Furthermore, 29.5% of the patients had tumors in UICC stage III, with the highest incidence for cecal carcinoma (32.4%), and the lowest incidence for cancer of the sigmoid colon (28.0%). Presence of synchronous distant metastases was found in 18.6% (UICC stage IV). Cecal tumors were associated with the highest rate of advanced carcinomas with metastatic spread (19.9%), which supports the right and left side classification model, however the lowest proportion of metastatic disease was demonstrated in carcinomas of the descending and ascending colon, 15.4% and 16.4%, respectively (Table 1).

To further analyze the metastatic spread with regard to colonic subsite of the tumor, the records for UICC IV were statistically investigated. There was a difference regarding pattern of metastatic spread between the colonic subsites, irrespective of the side. Synchronous hepatic metastases were less frequently diagnosed in ascending and descending colon carcinoma. Metastatic spread to the lungs was

most seen in CC of the cecum and sigmoid colon. Again, cecal tumors had the highest incidence of peritoneal carcinomatosis (Table 2).

Analysis of T status

In total, 28 925 patients had complete data for this analysis. Our previous research showed that the T status of tumors in the right colon was significantly different from the left. [6] In this analysis, we show how the T status differs between the colonic subsites. Less advanced local tumor growth (pT1 or pT2 stage) was diagnosed in 22.9% of all patients (Table 3) with the lowest proportion of carcinomas of both flexures and the highest rate for sigmoid tumors. 77.1% of the patients had locally advanced tumors (pT3/4 stage) at the time of surgery with T4 carcinomas most frequently being found in the cecum (23.7%). In contrast, patients with cancers in the sigmoid (15.0%), descending (12.5%), but also in the right colon's ascending segment (14.5%) had the lowest proportion of T4 tumors.

Analysis of N status

Overall, 29 088 patients had complete information about lymph node involvement. In 12 838 patients (44.1%), final pathology revealed lymph node positive disease (pN1 or pN2) with the highest proportion being found for the cecum (49.3%) and splenic flexure (47.0%) ($p < 0.01$). In contrast, carcinomas of the ascending, sigmoid and descending colon had the lowest rate of lymphatic spread (43.5, 42.7 and 40.6%, respectively). Previous analysis had already revealed significant differences between carcinoma arising from right and left side of the colon ($p < 0.001$) [6], Table 3 shows that there are also significant differences for N status within the group of right- and left-sided cancer, respectively ($p < 0.001$; $p = 0.001$).

Analysis of tumor grade

In total, 28 737 patient records had information about tumor differentiation. More than three-fourths (77.3%) of CC were well (G1) or moderately (G2) differentiated. Tumor differentiation showed a linear correlation in relation to the distance from the ileocecal valve, which reached statistical significance ($p < 0.001$). The closer the CC was located to the ileocecal valve, the higher the incidence of G3 / G4 cancers (Figure 1).

Analysis of histological subtype

The vast majority of CC were adenocarcinomas. Mucinous carcinomas accounted for less than 10% of all CC. Diagnosis of other subtypes (signet-ring cell carcinoma $n=128$ [0.4%], squamous cell carcinoma $n=22$ [0.1%], adenosquamous carcinoma $n=15$ [0.1%], small cell carcinoma $n=16$ [0.1%], undifferentiated carcinoma $n=103$ [0.4%]) were rare events. As demonstrated for tumor differentiation, the same significant linear correlation was found for histological subtype: with increasing distance from the ileocecal valve, a higher proportion of non-mucinous adenocarcinoma was present. In contrast, mucinous carcinomas showed that the closer the tumor was to the ileocecal valve, the higher the incidence, with cecal carcinomas having more than double the rate compared to the sigmoid colon ($p < 0.001$) (Figure 2).

Lymphatic invasion

Information about lymphatic invasion was available for 68.0% ($n=20\ 115$) of all patients. Lymphatic invasion was detected in 40.2% of all tumors and varied significantly within the group of right- and left-sided carcinoma, respectively ($p=0.013$; $p=0.01$). There was no linear correlation as demonstrated for tumor grade and histological subtype. However, again CC of the cecum and splenic flexure had the

highest proportion of carcinoma with angiolymphatic invasion and tumors of descending colon had the lowest.

Venous invasion

In 37.3%, no information about venous invasion was recorded (n = 11 038). Venous invasion was diagnosed in 16.1% (n=2 977). Although there was a nearly equal distribution, cecal tumors still had the highest rate of venous invasion. However, there was no statistically significant difference, neither between all colonic subsites nor for the right- and left-sided carcinoma, separately ($p=0.066$; $p =0.06$).

Discussion

Over 18 years ago, Bufill proposed for the first time that CC found in the distal and proximal locations of the colon may arise from different biological pathways [7]. Since then, many studies have reported epidemiological, clinical and molecular biological differences between RCC and LCC [1-6]. According to all these differences, it was suggested to consider cancers of the right and left colon as distinct tumor entities which could have an impact on future therapy trials aiming to further optimize CC treatment. However, there is still little information about the influence of the different colonic subsites on these parameters, especially on tumor characteristics. Therefore, the main goal of the present study was to bring more light into this interesting issue.

Age and gender distribution revealed that proximal CC is more common among women and elderly people. There was a linear relationship between age and location of tumor: a younger age was more common the more distal the tumor was found. This supports the right and left side classification model. However, when analyzing the gender distribution, it became apparent that there was a pattern with colonic subsites, irrespective of the side.

Analysis of tumor differentiation and histological subtype revealed a linear correlation in relation to the distance from the ileocecal valve. The more proximal the CC was located, the higher the incidence of G3 / G4 cancers and of mucinous carcinomas. These results are consistent with the findings of other studies [3-6] and also support the right and left side classification model.

However, we found a marked variance regarding distribution of UICC stages among the colonic subsites. The highest rate of less-advanced CC was found for tumors of the ascending and descending colon, whereas the highest proportion of advanced cancer was demonstrated for carcinoma arising from the cecum and splenic flexure. These results were confirmed when the tumor extent and lymph node involvement were investigated separately. Thus, T4 tumors were most frequently found in the cecum and splenic flexure. The lowest rate was found for CC of the ascending, descending and sigmoid colon and hepatic flexure. Likewise, lymph node positive disease was most frequently associated with CC of the cecum and splenic flexure, and least likely in tumors of the descending colon. Analysis of lymphatic invasion confirmed the previous findings with the highest incidence for cancers of the cecum and splenic flexure. In addition, cecal tumors showed the highest rate of venous invasion. A separate analysis of right- and left sided carcinoma, respectively, revealed that there are significant differences within each group regarding UICC-, T- and nodal status, and lymphatic invasion which indicates that left-sided colonic tumors can not be considered as a homogenous group. This is also the case for the right-sided colonic tumors.

Taking all of these findings together, cancers of the cecum and splenic flexure display less favorable tumor features. In contrast, carcinomas of the ascending, descending and sigmoid colon appear to have much better tumor characteristics.

This calls into question of whether the standard classification of CC into right and left-sided lesions is still sufficient. The results here show that the colonic subsite should be taken into consideration when CC is classified. The results of the present study are at least in part supported by findings of other studies. For example, Nakagoe et al. analyzed carcinomas of the splenic flexure and found a higher risk of obstruction, a greater number of advanced stages, and a lower cure rate, compared to other LCC [10]. In a review of 519 patients with cecal carcinoma, Armstrong et al. described that many tumors were advanced and only 5 % had early tumor stages [11].

There are potential explanations for our findings, including molecular biological differences, colonic transit time, fecal exposure time, colonoscopy limitations (e.g. around the flexures) and lymphatic connections (splenic flexure). However, the impact of these factors requires further investigation and should be the focus of further research.

One possible explanation of the results of the present study is endoscopic accessibility of several parts of the colon. Particularly, early lesions located at the proximal side of folds and the inner aspect of flexures where the instrument can slip during withdrawal is missed during colonoscopy [12]. Furthermore, there is an unknown rate of incomplete colonoscopy, where parts of the right colon, particularly the cecum are not fully visualized and bowel preparation is worse in the right colon. Furthermore, right-sided colonic adenomas are less often pedunculated and are occasionally flat, which makes them harder to identify and remove. However, this explains, in part, the higher incidence of more advanced tumors of the cecum and splenic flexure. But, at least a comparable proportion of less favorable tumor stages of hepatic flexure cancer were expected, which was not confirmed by this study.

Proportion of T4 tumors of hepatic flexure was comparable to those demonstrated for sigmoid CC.

Another potential explanation is the well-described differences in transit time of intraluminal contents in the entire intestine, particularly in the colon, and subsequently distinct exposure of colonic segment to feces and fecal carcinogens. Although it has been reported that colon carcinogenesis can occur in the complete absence of fecal contact, there is also some evidence that fecal cocarcinogens directly enhance the risk of CC, and provide factors favorable for growth and maintenance of the established colon [13]. Several clinical observations have indicated that proximal diversion of the fecal stream (e.g., colostomy) leads to regression or resolution of established distal colonic tumors, both benign and malignant. In a study with a chemically-induced rat colon cancer model by Lewin et al., transection of the proximal colon with reanastomosis to the rectum resulted in significantly fewer carcinomas and fewer tumors > 1cm diameter in the non-functioning compared to the functioning segment, confirming a causative role of feces and intestinal contents, respectively [14]. It is well known that in the cecum, colonic transit time is slowest and absorption higher compared to other parts of the colon. Thus, stool remains longer and subsequently results in a more pronounced contact with fecal carcinogens. Hence, a more intense mucosal damage and thus, a higher susceptibility for carcinogens with a higher rate of tumor promotion was suggested. But how would that explain the comparable incidence of advanced CC of the splenic flexure? One potential causative factor is the anatomical shape of this colonic part, being sometimes acute-angled which explains a reduced transit time and thus a prolonged exposure to fecal carcinogens. There is an interesting study conducted by Hiroz and co-workers which explores this theory in detail [15]. They investigated colonic movements by a magnet tracking system and reported slowest net forward

progress in the cecum-ascending colon. Interestingly, the descending colon segment showed highest frequency of propulsive periods and highest net forward progress. Likewise, the percentage of time that the magnetic pill spent in each colonic segment was highest for the cecum-ascending colon (42%), followed by the second part of transverse colon and splenic flexure (23%), and was lowest for the descending colon (7%). Assuming that prolonged fecal exposure increases cancer risk, the findings of their investigation explain the different tumor growth pattern for CC of the cecum, splenic flexure and descending colon as described in our study.

There is a considerable amount of molecularbiological studies regarding differences of right- and left-sided CC. However, to our knowlegde there are no studies focussing on differences with respect to anatomical subsite. These studies are urgently needed, as they have the potential to further explain the differences described in this study.

The results of this study have shown that three factors; age, tumor grade and histological subtype have a linear correlation with the distance from the ileocecal valve, and this supports the standard right and left side classification.

However, tumors of the cecum and splenic flexure display a more aggressive tumor growth pattern, whereas descending and ascending colon cancer are most frequently associated with less advanced tumor stages. Further analysis of tumor, lymphatic and metastatic factors did not correlate with the distance from the ileocecal valve (and hence with right and left-side classification), instead they correlated with one of the seven colonic subsites, irrespective of the side. Right- and left-sided colonic carcinoma are heterogeneous groups of tumor and the colonic subsite can be used in the classification. The reasons for this are not fully understood. Nonetheless, the results of this study show that the standard classification of right and left-sided colon

cancer can be improved upon by noting the colonic subsite, which also carries significant prognostic information.

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Conflict of interest statement:

The authors declare no conflicts of interest.

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Table 1 Distribution of gender, age and UICC stage according to colonic subsite

Tumor-bearing site	Male /female ratio	Mean Age years±SD ¹ <i>p</i> <0.001 ^a	UICC stage groups (%)			
			UICC I	UICC II	UICC III	UICC IV
Cecum	0.68	71.6±10.8	16.5	31.2	32.4	19.9
Ascending colon	0.82	71.4±10.8	16.5	37.1	30.1	16.4
Hepatic flexure	1.1	70.7±10.7	14.5	37.7	29.7	18.2
Transverse colon	0.87	70.2±11.3	15.1	36.3	29.0	19.6
<i>p</i> <0.001 ^b						
Splenic flexure	1.2	69.5±10.8	12.5	36.5	31.4	19.6
Descending colon	1.1	68.5±11.2	17.4	37.9	29.3	15.4
Sigmoid colon	1.2	68.3±10.5	23.1	29.8	28.0	19.2
<i>All locations</i>	<i>1.0</i>	<i>69.7±10.9</i>	<i>18.8</i>	<i>33.1</i>	<i>29.5</i>	<i>18.6</i>

¹SD Standard deviation*p*<0.001^b^a significant linear correlation for the age: lower age with increasing distance from the ileocecal valve^b significant differences within the group of right- and left-sided carcinoma, respectively

Table 2 Distribution of metastatic site in relation to colonic segments

Tumor-bearing site	Distant metastases (total) n (%) <i>p</i> <0.001 ^a	Hepatic metastases n (%) <i>p</i> <0.001 ^a	Pulmonary metastases n (%) <i>p</i> <0.001 ^a	Peritoneal carcinomatosis n (%) <i>p</i> <0.001 ^a
Cecum	910 (19.9)	631 (13.8)	102 (2.2)	292 (6.4)
Ascending colon	807 (16.4)	639 (12.9)	68 (1.4)	159 (3.2)
Hepatic flexure	364 (18.2)	282 (14.1)	32 (1.6)	82 (4.1)
Transverse colon	435 (19.6)	311 (14.0)	32 (1.4)	124 (5.5)
<i>p</i> <0.001 ^b				
Splenic flexure	268 (19.9)	212 (15.7)	30 (2.2)	51 (3.8)
Descending colon	276 (15.4)	229 (12.8)	30 (1.7)	50 (2.8)
Sigmoid colon	2 286 (19.2)	1 901 (15.9)	287 (2.4)	396 (3.3)
<i>p</i> <0.001 ^b				
<i>All locations</i>	<i>5 346 (18.6)</i>	<i>4 217 (14.6)</i>	<i>581 (2.0)</i>	<i>1 154 (4.0)</i>

^a indicating significant differences between all colonic subsites

^b indicating significant differences within the group of right- and left-sided carcinoma, respectively

Table 3 Analysis of T and N status according to colonic subsite

T status n (%)					
Tumor-bearing site	pT1	pT2	pT3	pT4	p
Cecum	257 (5.6)	682 (14.9)	2 546 (55.7)	1 082 (23.7)	< 0.001
Ascending colon	287 (5.6)	699 (14.2)	3 234 (65.5)	715 (14.5)	
Hepatic flexure	96 (4.8)	244 (12.1)	1 346 (67.0)	323 (16.1)	
Transverse colon	134 (6.0)	271 (12.1)	1 403 (62.7)	430 (19.2)	
Splenic flexure	52 (3.8)	157 (11.5)	890 (65.0)	271 (19.8)	< 0.001
Descending colon	139 (7.7)	244 (13.5)	1 193 (66.2)	225 (12.5)	
Sigmoid colon	1 472 (12.3)	1 896 (15.8)	6 835 (56.9)	1 802 (15.0)	
<i>All locations</i>	<i>2 437 (8.4)</i>	<i>4 193 (14.5)</i>	<i>17 447 (60.3)</i>	<i>4 848 (16.8)</i>	
N status n (%)	pN0	pN1	pN2		
Cecum	2 343 (50.7)	1 015 (22.0)	1 261 (27.3)		< 0.001
Ascending colon	2 817 (56.5)	1 069 (21.4)	1 100 (22.1)		
Hepatic flexure	1 125 (55.9)	482 (23.9)	407 (20.2)		
Transverse colon	1 246 (55.8)	534 (23.9)	451 (20.2)		
Splenic flexure	728 (53.0)	338 (24.6)	308 (22.4)		= 0.001
Descending colon	1 061 (59.4)	425 (23.8)	299 (16.8)		
Sigmoid colon	6 930 (57.3)	2 906 (24.1)	2 243 (18.6)		
<i>All locations</i>	<i>16 250 (55.8)</i>	<i>6 769 (23.3)</i>	<i>6 069 (20.9)</i>		

p value refers to differences within the group of right- and left-sided carcinoma, respectively

Figure 1 Distribution of tumor grade (differentiation) in relation to anatomical subsite ($p < 0.001$)

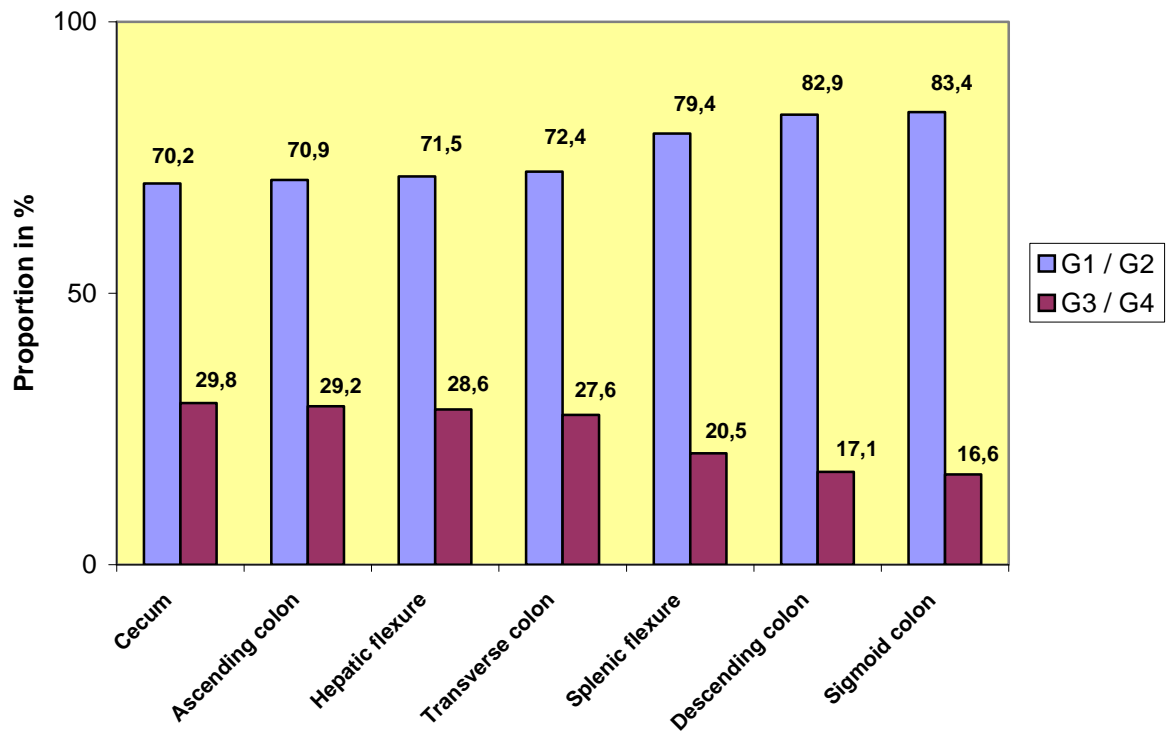


Figure 2 Distribution of histological subtype according to anatomical subsite ($p < 0.001$)

