

Variations in Demography and Prognosis by Colon Cancer Location

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Abstract. *Aim: Tumours of the right and left colon are suggested to be different entities with different prognosis. The aim was to explore differences related to the location of a colonic tumour. Patients and Methods: A single-centre retrospective analysis of all patients treated for colon cancer during 1999-2008 (n=1558) was carried out. Assessed data included demography, pathology and survival by cancer location, with left colon also sub-divided into left and sigmoid colon. Results: Right colon carcinoma was associated with female gender, higher age and poor grade of differentiation; left colon carcinoma had characteristics of worse stages and requiring emergency surgery. Sigmoid tumours were of better grade and stage. Survival was related the staging, which varied with location. Right colon carcinoma conferred a worse overall survival (OS) ($p < 0.037$) but not cancer-specific survival (CSS) or disease-free survival compared to the entire left colon, whilst sigmoid tumours conferred a better OS and CSS ($p < 0.001$) when the left colon was sub-divided. Conclusion: There are differences in demography and pathology related to the location of colon cancer. Sigmoid location carries the best prognosis.*

The proximal definition of the colon is the transition from the small bowel at the ileocecal valve and distally continuing to the rectum. The rectum is, in Sweden, defined as the distal 15 cm measured from the anal verge (1). The embryologic origin is from both midgut and hindgut where the latter develops into the rectum and part of the left colon. The colon is a common site for the development of malignancies, the incidence of which are slowly increasing (2, 3). Colorectal cancer has been suggested to be a multi-pathway disease based on different biomolecular properties (4, 5). Some of these characteristics are more frequent in certain locations, such as high microsatellite instability (MSI) in tumours of the right colon.

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Thus, there could also be differences in carcinogenesis and pathology between different parts of the bowel.

Tumours of the right and left colon have been suggested to be different entities with different prognoses (6). Large studies have shown survival differences between patients with disease in the left and right colon (7). The colon has then mostly been analysed as two distinct parts. However, there could be differences within the left colon and thus between the sigmoidal part and the left transverse and descending colon. This could concur with the surgical management, where the three main procedures for colon cancer are right/left colectomy and sigmoidal resection. The hypothesis is that colon cancer is in fact at least three entities, right, left and sigmoidal, when defined by location. Thus, the aim of this study was to further explore differences in demography and prognosis related to the location of colon cancer.

Patients and Methods

The study was a retrospective analysis of all patients treated at a single unit university hospital for colon cancer during 1999-2008 (n=1558). A total of 60 patients were excluded due to having multiple carcinomas. The study was conducted with ethical guidelines and approval. The fifth edition of the TNM classification was used for tumour staging purposes. Patient data including demography, pathology and follow-up were retrieved. Assessment was by cancer location, where the left colon also was sub-divided into left and sigmoidal colon, for demography, pathology and survival. Survival was assessed by location and also stage-specifically as overall survival (OS), cancer-specific survival (CSS) and, for stage III, also disease-free survival (DFS).

Statistical analysis. Statistical analyses were performed using JMP 8.0 software (SAS, Cary, NC, USA). Statistical analyses performed included chi-square, independent-samples *t*-test or ANOVA. Survival was assessed by KaplanMeier method and comparisons between groups by log-rank test. Findings with two-sided *p*-values < 0.05 were considered statistically significant.

Results

Patient characteristics. A summary of the patient characteristics is shown in Table I. Right-sided tumours were more common than left-sided ones (53.0% vs. 47.0%). The

Table I. Patients characteristics by tumour location in colon cancer.

Characteristic	Right colon (n=825)	Left colon (n=289)	Sigmoidal colon (n=444)	p-Value
Age in years (mean±sd)	70.9±0.4	67.3±0.8	68.4±0.6	<0.001
Gender (M/F %)	39.6/60.4	50.5/49.5	54.2/45.8	<0.001
Emergency surgery (no/yes %)	81.8/18.2	62.6/36.4	86.0/14.0	<0.001
Chemotherapy in stage III (yes/no %)	64.0/36.0	73.7/26.3	72.6/27.4	<0.074

Table II. Tumour pathology by tumour location in colon cancer.

Characteristic	Right colon	Left colon	Sigmoidal colon	p-Value
Stage I/II/III/IV (%)	6.1/39.5/37.8/16.6	7.0/29.7/39.3/24.0	11.4/38.5/35.8/14.3	<0.001
Grade: high/medium/low/undiff (%)	5.5/57.2/29.5/7.8	3.1/67.6/19.1/10.2	4.6/82.3/10.4/2.7	<0.001
Assessed nodes (mean±sd)	17.2±0.4	16.8±0.7	15.1±0.5	<0.002
Positive nodes in stage III (mean±sd)	3.9±0.2	3.1±0.35	3.4±0.3	<0.10

patients with right-sided tumours were significantly older than the other patients, less likely to be eligible for chemotherapy in stage III, and were also more likely to be female. There was no gender difference in left colon disease, whilst tumour in the sigmoidal colon was associated with more males. Emergency surgery was foremost associated with disease of the left colon. There was a higher count of assessed nodes for patients with right colon disease but there was no difference by location in meeting the UICC standard of 12 assessed nodes. Neither was there a significant difference in the number of positive lymph nodes found.

Pathology and survival. A summary of the pathology data is shown in Table II. Stage I disease was most common with sigmoidal location and stage IV with the left colon. There was no major difference in the proportions of patients of stage III disease. The right colon was associated with a higher proportion of poorly differentiated tumours, whilst the left colon with more undifferentiated tumours. The median follow-up was 74 months. Disease of the right colon conferred a worse OS ($p<0.037$) but not CSS than that of the entire left colon. Analyzed by stage, there were no survival differences for stages I, II and IV related to location. The difference in stage III was seen for OS and CSS but not DFS. When the left colon was sub-divided, there was no difference between right and left colon whilst sigmoidal tumours had a better OS and CSS, both overall and in stage III disease (Figure 1, $p<0.001$).

Discussion

The division of the colon into three different units for the study was derived out of surgical practice. The three most common procedures for colonic cancer are left and right

colectomies and sigmoidal resection, which is often performed as a high anterior resection (1). Shorter and segmental resections are at times performed for various reasons, such as palliative surgery, or due to high patient comorbidity. Other conditions, such as multiple synchronous tumours, can require extended resections. Thus, the treatment and the surgical practice can support such a division into three entities rather than just that of a left and right spectrum. The results in this study do hint at differences between the left and the sigmoidal colon. A sigmoidal location was associated with male gender and better differentiation grades, which is in line with findings reported by Wray *et al.* (8). The differentiation grade itself is associated with other factors of the TNM system, including the risk of having node metastasis, which can affect staging and prognosis (9). There was also less emergency surgery than with location in the left colon itself. This may be related overall to emergency colorectal surgery with a high frequency of sigmoidal location but then mainly due to benign causes such as diverticulitis (10).

There are several differences in demography and pathology related to the location of the colonic tumour, such as age and gender distribution. There are also differences in survival. A right-sided location was the most frequent in this study, which concurs with other findings (11). A location in the right colon has been described in several large studies to carry a significantly worse prognosis (7, 12). This does partly concur with the results in this study but then only for OS. The lack of difference in CSS is interesting and there are probably several reasons for it. One is associated with the age of patients related to the location of tumour. A higher age often means a higher risk of death due to causes other than cancer, which will then translate into a difference

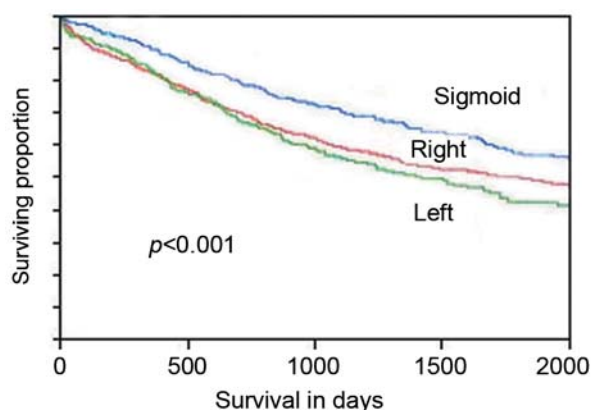


Figure 1. Overall survival by tumour location in colon cancer.

between the two outcome parameters of OS and CSS (13, 14). Higher age is also associated with lower rates of inclusion in adjuvant chemotherapy programs for stage III disease. The sigmoidal tumours did confer the best overall survival prognosis (Figure 1). This is plausibly related to and concurs with the findings of better overall stages and better differentiation grades associated with the sigmoidal location. The lack of survival difference in stage I and II also indicate that the overall survival findings are related to pathology and staging rather other entities. In contrast, the left colon had a tendency to confer worse prognosis, possibly related to being a common location of obstruction and thus emergency surgery and high frequencies of metastatic disease as described by Nakagoe *et al.* and therefore more advanced stages of disease (15). The joint left colon disease data, with best and worst data, could then add up to better prognosis than that for the more frequent right-sided tumours, which could form a plausible explanation for the overall findings.

Biomolecular differences within the colon have been described, where MSI frequency is one example (16). This has also, at least in part, lead to the development of theories of colon cancer a heterogenic disease evolving along several pathways and with differing properties. There could be some implications from these findings. One aspect is for conducting and evaluating translational research. The possibility that some markers could be expressed differently in various parts of the bowel is interesting and may warrant further studies (17). A difference due to location could then be at risk of being misinterpreted as a difference due to tumour pathology. Another aspect is the evaluation of treatment including studies on new chemotherapies. The findings of Bleeker *et al.* of higher frequency of mutations in *KRAS* in tumours of the right colon could serve as an example (18). This would then concern both the outcome parameter and also the number of patients with each specific

tumour location in each treatment arm. The latter could include both differences in pathology and possible differences in risk of chemotherapy related toxicity due to different location-associated tissue properties (19).

This study was retrospective and the number of patients is low in comparison to some of the referenced publications. However, the data is from a single centre where all the patients have been assessed and treated along the same principles. The surveillance and follow-up was carried out and recorded by the same staff. The population served by the hospital is also geographically defined, which facilitates the follow-up. We did, in many instances, have information on the cause of death and whether it was cancer-related or not, which provides the chance of using cancer-related survival as an outcome parameter. In cases of doubt, the individual case was recorded as being cancer-related for registration purposes. The pathology assessments were of good standard in meeting the UICC requirements and thus reducing the risk of stage migration phenomena, which also can add strength to the results (9). The findings support the hypothesis that the colon should be regarded as comprising at least three parts, where sigmoidal tumours have better pathology factors and thus survival prognosis. The findings could also challenge the hypothesis of right-sided tumours conferring a worse survival prognosis.

Conclusion

There are differences in demography and pathology related to the location of a colon tumour. Disease of the sigmoidal colon had a better cancer-specific survival prognosis, whilst there was no difference between left- and right-sided locations.

Conflict of Interest

There was no conflict of interest for the authors.

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