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Right Sided Colon Cancer as a Distinct Histopathological Subtype with Reduced Prognosis

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Key Words
Colon cancer · Location · Left · Right · Prognosis

Abstract
Background/Aims: Recent data suggest that tumors of the right and left colon should be distinguished as they differ in clinical and molecular characteristics. ***Methods:*** A total of 1,319 patients who underwent surgical resection for colon cancer (CC) were investigated. Tumors between the ileocecal valve and the hepatic flexure were classified as right CC (RCC), tumors between the splenic flexure and the rectum as left CC (LCC). ***Results:*** RCC revealed a higher cause-specific mortality risk (hazard ratio 1.36, 95% CI 1.10–1.68, p = 0.005) and lower 5-year cause-specific (RCC 64.9%, 95% CI 60.4–69.4, LCC 70.7%, 95% CI 67.2–74.2, p = 0.032) and disease-free (RCC 56.0%, 95% CI 51.5–60.5, LCC 59.9%, 95% CI 56.2–63.6, p = 0.025) survival rates. RCCs were more often microsatellite instable (RCC 37.2%, LCC 13.0%, p < 0.001) and more often showed *KRAS* (RCC 42.5%, LCC 18.9%, p = 0.001) and *BRAF* mutations (RCC 26.6%, LCC 3.2%, p < 0.001). ***Conclusion:*** RCC and LCC differ significantly regarding clinical, histopathological and molecular genetic features and can be considered as distinct entities. The reduced prognosis of RCC may be caused by higher rates of microsatellite instability, *KRAS* and *BRAF* mutations.

Introduction

Colorectal cancer is the second most common malignant disease in women and the third most common malignant disease in men worldwide [1]. Clinicians distinguish between right colon cancer (RCC) and left colon cancer (LCC). This subdivision is based on a concept that was first published by Bufill [2]. The border between both sides lies near the splenic flexure, thus classifying cecum, ascending colon, hepatic flexure and transverse colon as right colon and descending colon and sigmoid colon as left colon [3]. Many studies have applied this classification system and have reported distinct clinical and histopathological characteristics for both subsections [4, 5].

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RCC is often reported to be more common in women and older patients and is associated with anemia and weight loss [6, 7]. Furthermore, it has been shown that the percentage of mucinous adenocarcinomas and microsatellite instable (MSI) tumors are higher for RCC [3, 8]. Mutations in the proto-oncogene *BRAF* are found in approximately 10% of all colorectal cancer patients [9]. *BRAF* mutations along with microsatellite instability and CpG island methylator phenotype are associated with the 'serrated pathway' leading to flat adenomas [10, 11], which are considered as the precursor lesions of RCC [6, 10].

By contrast, the pathogenesis of LCC is based on the theory of 'adenoma carcinoma sequence' [12]. Here, genetic alterations lead to the activation of oncogenes (*KRAS*) and the inactivation of tumor suppressor genes (*APC*, *p53*) [6]. LCC is associated with rectal bleeding and a change in bowel habits, probably leading to lower tumor stages at the time of diagnosis [3, 6].

Some studies indicate that the incidence of RCC has increased for the last decades [3, 13]. However, Rabeneck et al. [14] hypothesize that there is no actual increase in the incidence of RCC, but rather a decrease in the incidence of LCC. The aging of the population with an associated lower amount of LCC seems to be the reason for this effect [8].

Taking survival analysis into account, authors report contradictory outcomes for RCC and LCC. Meguid et al. [15] showed an inferior overall survival for RCC in a study on about 78,000 patients analyzing the Surveillance, Epidemiology, and End Results Program (SEER) database between 1988 and 2003. It is supposed that the higher rate of locally advanced tumors and the poorer differentiation contribute to the reduced prognosis of RCC [8]. However, in another more recent study on SEER database (cases between 1992 and 2005), no difference in overall survival between both sides was revealed [7].

Thus, besides a plethora of described differences between RCC and LCC, the exact reason for the distinct characteristics still remains unclear. Therefore, it was the aim of this study to identify potential clinical, histopathological and prognostic discrepancies between RCC and LCC in a large and thoroughly characterized retrospective patient collective.

Methods

Patient Recruitment

The initial data set contained 2,305 patients who underwent surgical resection for CC at the Department of Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, from January 1990 to May 2013. Records included information about age, sex, date of surgery, tumor location and the effect on other organs. Routine follow-up examination was arranged by our department according to the recommendations of the German Cancer Society [16]. Follow-up data included information about vital status, local or distant recurrences and, where applicable, the cause of death (tumor-dependent or tumor-independent). Patients were periodically interviewed by phone about whether they had undergone follow-up care at another institution, and the corresponding results were requested. The latest date of follow-up examinations was May 31, 2013. Data were only collected if patients agreed to participate in this study, and written informed consent was signed. This study was approved by the Institutional Review Board (#1926/07).

A total of 294 cases were excluded because of palliative surgery or unknown tumor stage. Further 317 patients were excluded as they already had another tumor before or simultaneously had a second tumor in a different organ. Finally, 375 cases were excluded because the cancer was located in the vermiform appendix or in the intermediate area (right colic flexure, transverse colon or left colic flexure).

Tumors of the vermiform appendix were not considered because the primary malignant lesions of the vermiform appendix are neuroendocrine tumors [17]. The transverse colon partly derives from the embryonic midgut (proximal two-thirds) and partly from the embryonic hindgut (distal third) [15]. As a consequence, tumors of the distal third of the transverse colon are macroscopically considered as RCC although they are genetically related to the left colon. Consequently, the transverse colon and the right and left colic flexure were excluded in order to receive unbiased results as those anatomic sections could not unambiguously be assigned to the right or the left colon.

Thus, finally 1,319 patients with histopathologically confirmed primary single colon carcinomas were included in this study and employed for further characterization.

Tumors were considered as RCC if they were located in the cecum or in the ascending colon and as LCC if they were located in the descending colon or in the sigmoid colon.

Pathological Examination

After surgical resection, formalin-fixed specimens were stained with hematoxylin and eosin and routinely microscopically examined by 2 pathologists. In order to demonstrate mucin, samples were processed following a Periodic Acid Schiff staining protocol. Thus, information about local tissue invasion, lymph node affection, distant metastases, residual tumor, grading, histological tumor entity and resection margins was obtained. The pathological classification was conducted according to the World Health Organization and the International Union against Cancer (7th edition) [18, 19].

Molecular Genetic Analysis

For a subset of patients, snap frozen tissue was available for molecular testing regarding microsatellite instability and *KRAS* and *BRAF* mutational status. Genomic DNA of tumor and corresponding normal colon mucosa were extracted and analyzed for microsatellite instability using the Qiagen® Type-it Microsatellite PCR Kit (Qiagen GmbH, Hilden, Germany), as described before [20]. Following procedures for routine diagnostics, results of PCR analysis were interpreted by an experienced pathologist and were classified into microsatellite stability, low grade microsatellite instability and high grade microsatellite instability. As no low grade

MSI tumors were detected, examinations were restricted to microsatellite stable (MSS) and high grade MSI tumors. The mutational status of the genes *KRAS* and *BRAF* was assessed by high-resolution melting analysis of genomic DNA on a LightCycler® 480 II platform (Roche, Mannheim; SYBR Green I/HRM Dye Protocol), as previously described [20].

Statistical Analysis

Nominal-scaled and ordinal-scaled variables were compared using Pearson's chi-square test. Normally and non-normally distributed continuous data were analyzed by the Mann–Whitney U test and corresponding values for median and interquartile range (IQR) are reported. Cause-specific and disease-free survival analysis was carried out using the Kaplan–Meier method with comparison of subgroups by the log-rank test. Cox proportional hazard regression analysis was used to assess the influence of various variables on cause-specific survival. Hazard ratios (HRs) and 95% CIs are reported.

All the conducted tests were two-sided, and p values <0.05 were considered to be statistically significant.

Statistical analysis was performed using the IBM SPSS Statistics 21.0 (International Business Machines Corporation, Endicott, N.Y., USA) and was supervised by a statistician.

Results

Patient Characteristics and Clinical Parameters

A total of 59.2% of the tumors were located in the left colon and 40.8% in the right colon. Most neoplasms occurred in the sigmoid colon (51.7%), 22.4% were localized in the ascending colon, 18.4% in the cecum and 7.5% in the descending colon, respectively.

The ratio of RCC was significantly higher in women (RCC 47.8%, LCC 40.6%, p = 0.010) and patients with RCC were significantly older (RCC median 68.0 years, IQR 17.0 years, LCC 64.0 years, IQR 15.0 years, p < 0.001). RCC featured larger diameters compared to LCC (p < 0.001; table 1).

Histopathological Characteristics

RCC showed a higher amount of mucinous adenocarcinomas (RCC 15.4%, LCC 5.5%, p < 0.001), but lower amount of classical tubulovillous adenocarcinomas (RCC 80.3%, LCC 93.2%, p < 0.001) and were more often poorly differentiated (G3/G4 RCC 46.4%, LCC 31.3%, p < 0.001).

There was no statistical difference detected between RCC and LCC regarding the depth of tumor infiltration (p = 0.087), nodal status (p = 0.093), distant metastases (p = 0.949) and residual tumor (p = 0.576; table 1). The localization of distant metastases (p = 0.299) and cancer recurrences (p = 0.149) were also similar in both groups. RCCs were significantly more rarely stage 1 tumors (RCC

Table 1. Clinical and histopathological characteristics of RCC compared to LCC

	n	RCC		LCC		p value
		n	%	n	%	
Sex	1,319	538	100	781	100	0.010
Male		281	52.2	464	59.4	
Female		257	47.8	317	40.6	
Age at surgery						<0.001
RCC		Median 68.0 years, IQR 17.0 years				
LCC		Median 64.0 years, IQR 15.0 years				
Tumor size						<0.001
RCC		Median 5.0 cm, IQR 3.0 cm				
LCC		Median 4.0 cm, IQR 3.0 cm				
Histological type	1,319	538	100	781	100	<0.001
Classical adenocarcinoma		432	80.3	728	93.2	
Mucinous adenocarcinoma		83	15.4	43	5.5	
Others		23	4.3	10	1.3	
Tumor grade	1,313	537	100	776	100	<0.001
G1/G2		288	53.6	533	68.7	
G3/G4		249	46.4	243	31.3	
Missing	6					
Depth of tumor infiltration	1,305	536	100	769	100	0.087
T1		39	7.3	85	11.1	
T2		75	14.0	119	15.5	
T3		308	57.5	405	52.7	
T4		114	21.3	160	20.8	
Missing	14					
Nodal status	1,310	534	100	776	100	0.093
N0		277	51.9	439	56.6	
N+		257	48.1	337	43.4	
Missing	9					
Distant metastases	1319	538	100	781	100	0.949
M0		410	76.2	594	76.1	
M1		128	23.8	187	23.9	
Distant metastases	1,319	538	100	781	100	0.299
Liver		93	17.3	139	17.8	
Lung		18	3.3	14	1.8	
Others		16	3.0	19	2.4	
Multiple		411	76.4	609	78.0	
Residual tumor	1,204	534	100	670	100	0.576
R0		439	82.2	559	83.4	
R1/R2		95	17.8	111	16.6	
Missing	115					
UICC tumor stage	1,319	538	100	781	100	0.049
1		89	16.5	176	22.5	
2		173	32.2	225	28.8	
3		148	27.5	193	24.7	
4		128	23.8	187	23.9	

Table 2. Characteristics of molecular parameters

	RCC		LCC		p value
	n	%	n	%	
Mismatch repair (n = 202)	94	100	108	100	<0.001
MSS	59	62.8	94	87.0	
MSI	35	37.2	14	13.0	
KRAS (n = 175)	80	100	95	100	0.001
Wild type	46	57.5	77	81.1	
Mutation	34	42.5	18	18.9	
BRAF (n = 172)	79	100	93	100	<0.001
Wild type	58	73.4	90	96.8	
Mutation	21	26.6	3	3.2	

Table 3. Univariate Cox regression analysis

	HR	95% CI		p value
Side				
LCC	1			
RCC	1.19	0.97	1.46	0.095
Age	1.00	0.99	1.01	0.773
Sex				
Male	1			
Female	1.18	0.97	1.45	0.101
UICC tumor stage				
1	1			
2	2.23	1.10	4.53	0.026
3	10.42	5.45	19.91	<0.001
4	55.82	29.51	105.58	<0.001
Cancer recurrence				
No	1			
Yes	224.59	92.82	543.40	<0.001
Histological type				
Classical adenocarcinoma	1			
Mucinous adenocarcinoma	1.04	0.74	1.47	0.804
Tumor grade				
G1/G2	1			
G3/G4	2.47	2.02	3.02	<0.001

16.5%, LCC 22.5%, p = 0.049). For tumor stage 2 (RCC 32.2%, LCC 28.8%, p = 0.049) and stage 3 (RCC 27.5%, LCC 24.7%, p = 0.049), RCC was prevailing.

The incidence rates of RCC and LCC did not change over the observed time period (1990–2013, p = 0.233).

Molecular Characteristics

For a subset of patients, data on molecular characteristics were available for mismatch repair status (202 patients), *KRAS* mutations (175 patients) and *BRAF* status (172 patients).

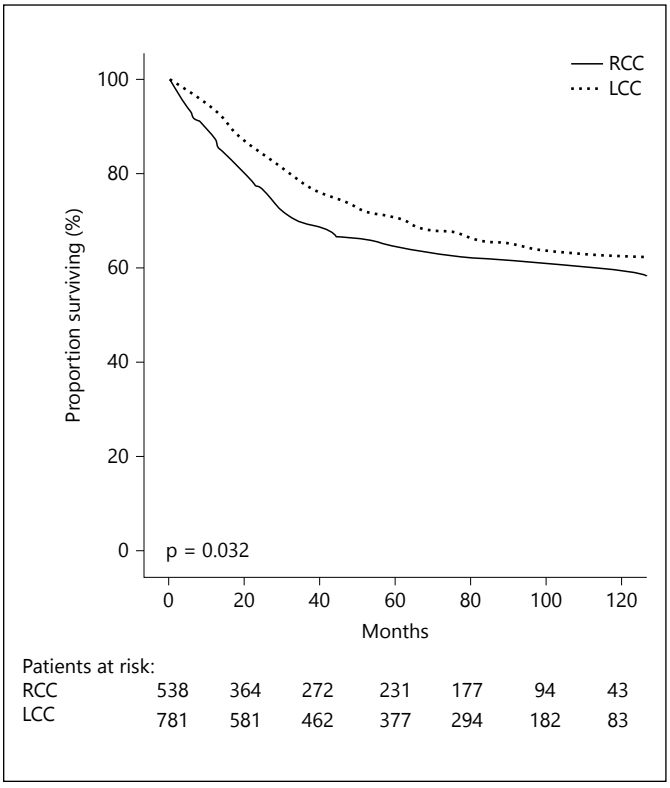

Fig. 1. Cause-specific survival of RCC compared to LCC.

RCCs were significantly more often MSI (RCC 37.2%, LCC 13.0%, p < 0.001) and showed higher rates of *KRAS* mutations (RCC 42.5%, LCC 18.9%, p = 0.001). Furthermore, RCCs were associated with mutations of the *BRAF* gene (RCC 26.6%, LCC 3.2%, p < 0.001; table 2).

Survival Analysis

RCC was associated with a significantly worse prognosis (table 3; fig. 1) showing a 5-year cause-specific survival rate of 64.9% (95% CI 60.4–69.4) compared to 70.7% (95% CI 67.2–74.2) for LCC (p = 0.032). Five-year disease-free survival was reduced for RCC (RCC 56.0%, 95% CI 51.5–60.5, LCC 59.9%, 95% CI 56.2–63.6, p = 0.025) as well.

There was no difference observed in cause-specific survival between both sides for stage 1 (p = 0.966) and stage 2 (p = 0.702) tumors, but RCC was associated with a reduced prognosis in stage 3 (RCC 59.0%, 95% CI 50.2–67.8, LCC 74.5%, 95% CI 67.6–81.4, p = 0.018) and stage 4 (RCC 7.6%, 95% CI 1.9–13.3, LCC 16.9%, 95% CI 10.8–23.0, p < 0.001) disease.

A reduced 5-year cause-specific survival rate of RCC was shown for classical tubulovillous adenocarcinomas

(RCC 65.7%, 95% CI 60.8–70.6, LCC 71.8%, 95% CI 68.3–75.3%, p = 0.028), whereas a better prognosis of RCC was found for mucinous adenocarcinomas (RCC 76.2%, 95% CI 65.8–86.6, LCC 55.4%, 95% CI 38.3–72.5, p = 0.009; fig. 2). However, this result should be interpreted with caution, as only 126 patients had mucinous adenocarcinomas.

Upon multivariable survival analysis, tumor location (RCC HR 1.36, 95% CI 1.10–1.68, p = 0.005) was detected as independent prognostic factor (table 4).

Discussion

Here, we confirm the side of CC (right vs. left) as a distinct parameter that is related to specific histological, molecular and clinical features. RCC is an independent predictor of poor prognosis. Strength of this study is the large, thoroughly documented patient collective, which is characterized by its high amount of registered variables including histopathological and molecular data.

Due to its retrospective design, this study is limited in its validity compared to randomized controlled trials and the single-center approach restricting the number of cases. Furthermore, molecular data were not available for the whole patient collective.

This study differs from other publications in the definition of RCC and LCC [4, 15, 21]. Without clear evidence, many authors refer to the anatomic structure of the splenic flexure in order to distinguish between right colon and left colon. However, considering the embryonic origin of the colon shows a potential flaw in this classification system. Roughly, the proximal two thirds of the transverse colon are derived from the midgut, whereas the distal third is derived from the hindgut [15]. Thus, tumors of the distal third of the transverse colon would be classified as RCC, though being genetically related to LCC. In this study, we aimed to put emphasis on histopathological and molecular parameters and, therefore, restricted the analyses to tumors which could unambiguously be classified as RCC and LCC. Of note, the significantly reduced prognosis for RCC remained upon analysis of all locations, including the transverse colon and the flexures (p = 0.043, data not shown).

Tumor Distribution within the Colon

Similar results for the tumor distribution within the colon have already been depicted by other authors [4].

Patients with RCC were significantly older. These results are consistent with previous studies [4, 22]. The cur-

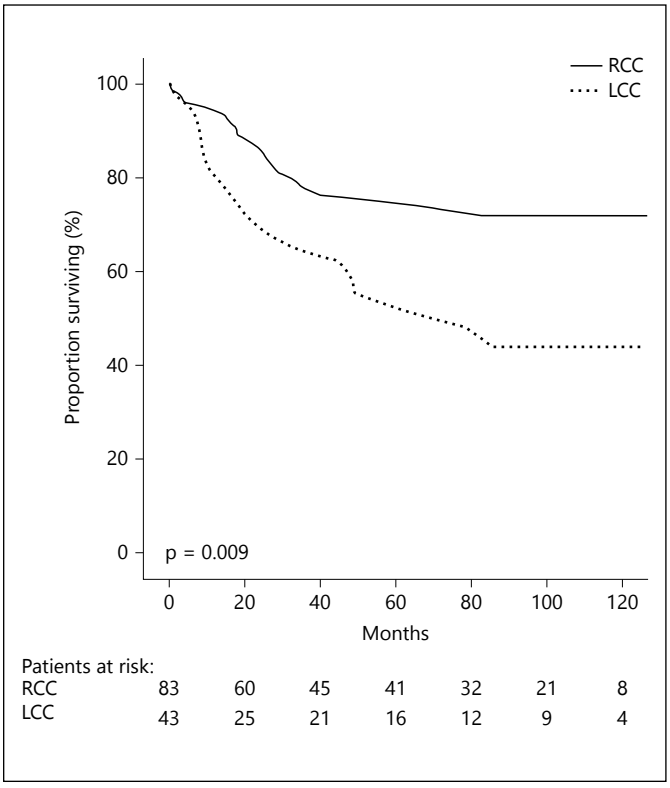

Fig. 2. Cause-specific survival of mucinous adenocarcinomas.

Table 4. Multivariate Cox regression analysis

	HR	95% CI		p value
Side				
LCC	1			
RCC	1.36	1.10	1.68	0.005
Age	1.02	1.01	1.03	<0.001
Sex				
Male	1			
Female	1.27	1.03	1.56	0.023
UICC tumor stage				
1	1			
2	1.56	0.74	3.25	0.251
3	3.21	1.61	6.42	0.001
4	8.81	4.43	17.51	<0.001
Cancer recurrence				
No	1			
Yes	113.56	46.32	278.40	<0.001
Histological type				
Classical adenocarcinoma	1			
Mucinous adenocarcinoma	0.80	0.57	1.14	0.222
Tumor grade				
G1/G2	1			
G3/G4	1.19	0.97	1.47	0.099

rently assumed underlying mechanisms are the prolonged transportation of feces in the right colon in older patients resulting in a longer exposition of possible carcinogens to the colon mucosa as well as modified lifestyle among the elderly [8, 21].

An increase of RCC was detected with rising age in women ($p = 0.001$, data not shown). Discrepancies in hormonal status could cause the age-dependent increase of RCC between younger and older women [23]. Adherence to full colonoscopies upon screening, instead of sigmoidoscopies only, especially in women and elderly patients, may thus help to identify RCC in earlier tumor stages and improve the prognosis of these patients.

Survival

RCC showed a significantly reduced prognosis compared to LCC. These findings are consistent with results of other groups [4, 15]. However, there are publications which obtained contradictory outcomes [7, 24] or showed no difference in prognosis between both sides [25]. A meta-analysis on colorectal cancer including 44 studies and over 220,000 patients revealed a higher relative risk for proximal cancers (i.e., proximal to the splenic flexure, RR 1.55, 95% CI 1.53–1.58) [26], but the underlying mechanisms for this distinctive behavior still remain unclear. Thus, current treatment recommendations are limited to secondary preventive strategies like intensified adjuvant treatment regimens and shorter follow-up periods for patients with RCC [6]. Some studies indicate that the lower mortality risk of LCC is associated with an earlier diagnosis applying endoscopy [6]. Even though we could find larger diameters for RCC, there was no difference detected between RCC and LCC regarding the TNM system.

Gao et al. [27] detected tumor location as an independent prognostic factor in mucinous adenocarcinomas, leading to a better outcome for right-sided mucinous adenocarcinomas compared to rectal mucinous adenocarcinomas. Of note, in our study, significantly more mucinous adenocarcinomas were found on the right side and this histological entity was accompanied with a better survival of RCC, too. This effect could be explained by the high amount of MSI RCCs as microsatellite instability is associated with mucinous adenocarcinomas [16] and MSI tumors demonstrate a better prognosis compared to MSS tumors [6].

However, considering the whole patient collective, RCC revealed a reduced prognosis despite the higher amount of mucinous adenocarcinomas and MSI tumors. The worse prognosis of RCC compared to LCC is thought to be associated with the underlying molecular pathway of cancer development, which, at least in part, may be embryologic determined [6]. Tumors arising from the so-called serrated pathway [6, 20] are characterized by an initial *BRAF* mutation, subsequently followed by the CpG island methylator phenotype, with either MSS or MSI status, and a reduced prognosis [6, 11]. A significant correlation between *BRAF* mutations and MSI was revealed ($p < 0.001$, data not shown), and both characteristics were more often found for RCC. These alterations (i.e., *BRAF* mutations, MSI) suggest tumor origination from the serrated pathway and therefore could explain the reduced prognosis of RCC [6, 11].

Current treatment recommendations can help to improve the prognosis of CC on a personalized and molecular genetic basis. For example, routine molecular genetic testing for CC, especially if RCC, advises against 5-FU based chemotherapeutic regimens if microsatellite instability is present due to a lack of benefit in this subset of patients [28]. In fact, this study did not reveal a significant difference in cause-specific survival between RCC and LCC for MSS/MSI, *KRAS* and *BRAF* status in general or in subgroup analyses. However, due to the relative low number of cases, these results should be interpreted with caution.

Conclusions

RCC and LCC show significant differences regarding patient characteristics and long-term outcomes. The reduced prognosis of RCC is assumed to be caused by clinical factors (delayed diagnosis, advanced patient age with prolonged transportation times of feces and carcinogens), histopathological factors (poor differentiation, histological tumor subtype) and molecular genetic factors (serrated pathway, MSI, *KRAS* and *BRAF* mutations).

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