Original Article

Tumor location impact in stage II and III colon cancer: epidemiological and outcome evaluation

Nesrine Mejri, Manel Dridi, Houda El Benna, Soumaya Labidi, Nouha Daoud, Hamouda Boussen

Medical Oncology Department, Abderrahmen Mami Hospital, Ariana, Tunisia

Contributions: (I) Conception and design: N Mejri, M Dridi; (II) Administrative support: H Boussen; (III) Provision of study materials or patients: N Mejri, H El Benna, S Labidi; (IV) Collection and assembly of data: N Mejri, M Dridi, H Boussen; (V) Data analysis and interpretation: N Daoud; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Nesrine Mejri. Medical Oncology Department, Abderrahmen Mami Hospital, Ariana, Tunisia. Email: nesrinemejriturki@yahoo.fr.

Background: We aimed to describe clinico-pathological characteristics and differences between right-sided (RCC) and left-sided colon cancer (LCC) in Tunisian population. We also analyzed outcome to determine whether location is of prognostic significance.

Methods: Clinico-pathological characteristics and Kaplan Meier survival were compared between two groups of LCC [150] and RCC [53] patients with stage II and III adenocarcinoma treated with curative intent between 2003–2014.

Results: RCC patients were significantly more likely to be female, (56.6% *vs.* 39.3%, P=0.029) and to have undifferentiated tumor (87.1% *vs.* 8.4%, P=0.014), then LCC. After a median follow up of 49 months, 5-year overall survival (OS) was significantly worse in RCC *vs.* LCC [42% *vs.* 78%; hazard ratio (HR) =2.07; 95% CI: 1.05–4.09; P=0.03], no difference in relapse free survival (RFS) was observed. Median time to relapse was significantly shorter in RCC (15 months) *vs.* LCC (24 months), P=0.005. Tumor location significantly impacted survival in stage III, 5-year OS was 45% in RCC, and 63% in LCC, (HR =2.28; 95% CI: 1.01–5.24; P=0.04), there was no impact of tumor location in stage II, (HR =1.94; 95% CI: 0.54–6.93; P=0.29).

Conclusions: Prognostic impact of tumor location should be considered as a stratification factor in the future clinical trials.

Keywords: Colon cancer (CC); anatomic side; survival; early stage; adjuvant therapy

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Introduction

Colon cancer (CC) is a public health problem worldwide and in Tunisia. The incidence is estimated to be 1.2 million per year, and more than 600,000 deaths every year (1). In the recent years, with knowledge advancement in genetic and molecular mechanism of carcinogenesis, CC is no longer considered as a unique disease. Distinguishing CC based on anatomical location was first described by Bufill *et al.* in 1990 (2). Subsequent publications pointed out several differences between right-sided (RCC) and left-sided CC (LCC) regarding epidemiology, pathogenesis, embryologic, genetic-epigenetic alterations, molecular pathways and outcome (2-4). Roughly, it is suggested that anatomical site could have, in the future, an impact in the management of CC. However, data regarding prognosis remain controversial and a great debate is open whether tumor location itself plays a prognostic role. A poorer survival of RCC was reported by most studies (5,6). These observations are more evident in advanced stage with differences in response to targeted therapies (7,8). In a large population based study of 57,847 patients from the surveillance, epidemiology and end results (SEER) database, disease specific survival was significantly worse in RCC patients *vs.* LCC patients, with a hazard ration of 0.77 (0.72±0.81) in stage IV (4). However, in early stage data are less defined

and prognostic role is still under investigation. Patterns of such anatomical distribution in various population would help a better understanding of this issue. We aimed in our current study to describe clinico-pathological characteristics and differences between RCC and LCC in Tunisian population. We also analyzed outcome to determine whether location is of prognostic significance.

Methods

We retrospectively analyzed a cohort of 203 patients, with histologically confirmed, stage II and III CC with complete work-up and treated with curative intent during the period 2003–2014.The TNM staging system of the American Joint Committee on Cancer (AJCC/UICC 7th edition) was used for staging. Only adenocarcinoma and CC cases were included. We considered two groups: RCC and LCC. The right counterpart or RCC was defined as the colon sections going from the appendix-cecum, ascending colon, hepatic flexure and transverse colon to the left angle before the limit of the splenic flexure. LCC was defined as the sections going from the splenic flexure, descending colon, the sigmoid until the recto-sigmoid junction. If tumors were cited in both left-sided and right-sided locations or the origin could not be ascribed to either side, the patient was excluded from the present analysis. Clinico-pathological data including: age at diagnosis, gender, medical history, tumor location, histological type, grade/stage of tumor, chemotherapy history were collected from patients records and were compared between RCC and LCC. We analyzed outcome parameters were studied: overall survival (OS), relapse free survival (RFS) for both groups. We also reported annual hazard of relapse (AHR) for RCC *vs.* LCC during the first 4 years of follow up.

Statistical analysis

Statistical analysis was performed using the statistical package for the social sciences (SPSS) 16.0. Comparison of variables was performed using Pearson's chi-square test, Fisher's exact test. OS was defined as the time from first therapeutic action to death from any cause or loss to follow up or latest news. RFS was defined as the time from first therapeutic action to first recurrence confirmed by radiological of histological feature or death. Survival analyses were done through a Cox proportional hazard function for both univariate and multivariate analyses, and Kaplan-Meier (log-rank test) curves were plotted. Significance for all statistics were recorded if $P<0.05$. Annual relapse rate was defined as the fraction of followed patients who had recurring disease in a 1-year period restricted to follow-up contribution of each specified time interval.

Looking to the retrospective character of this study, no written informed consent was necessary from patients. Local ethical committee approved the study protocol, which was in accordance with the principles of the Helsinki Declaration.

Results

Overall population

We collected a cohort of 203 patients. Mean age was 58 years ranging from 27 to 85 and sex-ratio was 1.2 with 114 (56.2%) of the patients were male. Family history of colorectal cancer was observed in 32 (15.8%) of patients. Almost all patients (95.6%, 194) had body CT scan for work-up. Surgery was performed for surgical emergency in 15.8% (32 cases: 30 for bowel obstruction and 2 for peritonitis) during which 29 had upfront surgical resection of the tumor. All patients had anatomical tumor resections adapted to tumor location, except for 11 patients who had total colectomy. Pathology showed poorly differentiated tumors in 13 (6.4%), moderately differentiated tumors in 24 (11.8%), and well differentiated tumors in 101 (49.8%), differentiation being not defined in 65 (32%) cases. TNM staging showed: pT2 in 5 (2.5%) of cases, pT3 in 108 (53.2%), pT4 in 44. 3% (90 cases). Nodal involvement/stage III disease was observed in 56.7% (115 patients), among them pT4 stage represented 46.1% (53 patients) and pN2 39.1% (45/115). In stage II patients, pT4 was seen in 42.1% (37/88 patients). Vascular emboli were seen in 24.6% (50 patients) and peri neural invasion in 37 (18.2%). Mean tumor size was 7.6 cm. Adjuvant chemotherapy was indicated in 178 (87.7%) of the patients; 119 (66.9%) received Folfox regimen and 59 (33.1%) received 5-FU based regimen, almost all patients finished 6 cycles of adjuvant therapy (98.8%). Relapse rate was 32.5% (66 cases). Median follow up was 49 months. We observed 150 (73.9%) patients with LCC and 53 (26.1%) patients with RCC. Characteristics of the two groups are described in *Table 1*. We did not observe a statistically significant difference in terms of age, tumor stage and therapy between both groups. RCC patients were significantly more likely to be female then LCC patients (56.6% *vs.* 39.3%, P=0.029). RCC tumors were also significantly more likely to be

Table 1 Comparison of clinic-pathological characteristics between LCC and RCC

Variable	LCC [150] N (%)	RCC [53] N (%)	P
Median age	58	63.5	0.114
Age in years			0.2
≥60 years	84 (56.4)	25 (46.2)	
<60 years	66 (43.6)	28 (53.8)	
Gender			0.029
Female	59 (39.3)	30 (56.6)	
Male	91 (60.7)	23 (43.4)	
Differentiation	107	31	0.014
Well	74 (69.2)	4 (12.9)	
Moderate	24 (22.4)	0 (0)	
Poor	9 (8.4)	27 (87.1)	
Mean tumor size (cm)	7.3	8.5	0.529
pT2	5 (3.3)	0 (0)	0.52
pT3	78 (52.7)	29 (54.7)	
pT4	67 (45.0)	24 (45.3)	
pN0	63 (42.0)	25 (47.2)	0.74
pN1	52 (34.7)	18 (34.0)	
pN2	35 (23.3)	10 (18.9)	
Received pN <12	68 (45.3)	18 (34.0)	0.1
AJCC/UICC stage			0.51
Stage II	63 (42.0)	25 (47.2)	
pT3	38 (60.3)	13 (52.0)	
pT4	25 (39.7)	12 (48.0)	
Stage III	87 (58.0)	28 (52.8)	
pT3	41 (47.1)	16 (57.1)	
pT4	46 (52.9)	12 (42.9)	
Therapy			0.77
Surgery alone	17 (11.3)	8 (15.1)	
Surgery + Folfox	89 (59.3)	30 (56.6)	
Surgery + 5FU	44 (29.4)	15 (28.3)	

LCC, left-sided colon cancer; RCC, right-sided colon cancer; AJCC, American Joint Committee on Cancer; UICC, union internationale contre le cancer, 5FU, 5 fluorouracile.

undifferentiated then LCC (87.1% *vs.* 8.4%, P=0.014).

At the last time to follow up, 85.3% of LCC patients were still alive and 73.6% RCC were still alive. Five-year OS was significantly worse in RCC *vs.* LCC (65% *vs.* 82%, hazard ratio (HR) =2.07; 95% CI: 1.05–4.09; P=0.03) (*Figure 1*). There was no difference in relapse free survival between the groups (HR =1.15; 95% CI: 0.66–2.19; P=0.6) (*Figure 2*). Median time to relapse was significantly shorter in RCC (15 months) *vs.* LCC (24 months), P=0.005. Recurrence rate was 32% in both groups, P=0.9. In subgroup analysis,

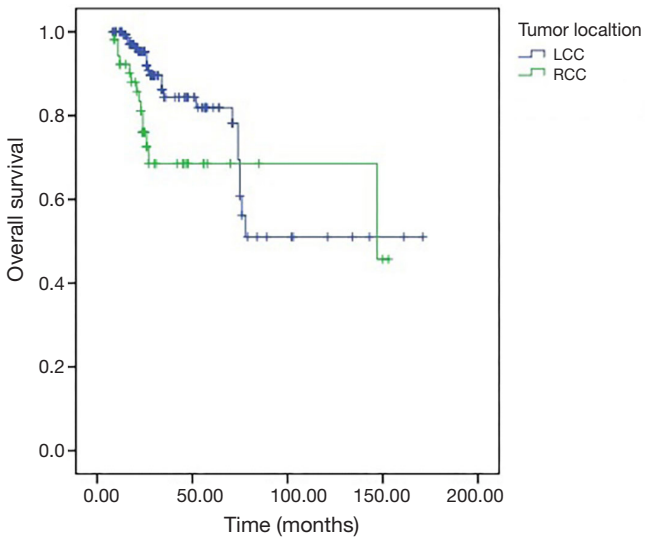

Figure 1 Overall survival difference between LCC and RCC colon cancer. LCC, left-sided colon cancer; RCC, right-sided colon cancer.

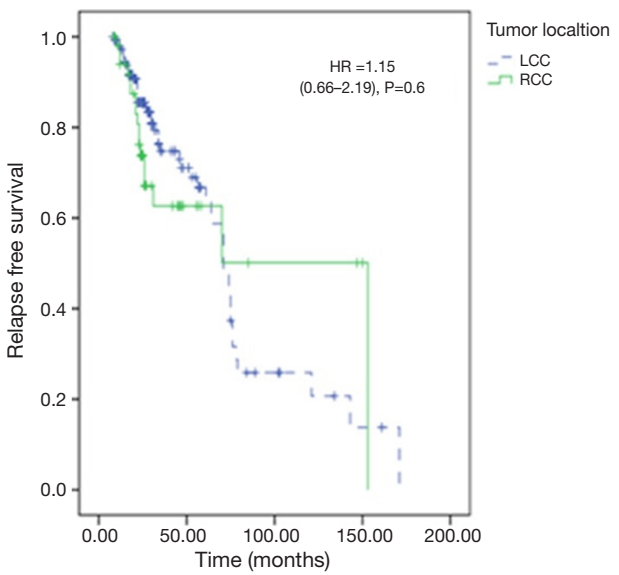

Figure 2 Relapse free survival difference between LCC and RCC colon cancer. LCC, left-sided colon cancer; RCC, right-sided colon cancer.

there was no impact of tumor location on survival for stage II disease, 5-year OS was 78% in RCC *vs.* 82% in LCC (HR =1.94; 95% CI: 0.54–6.93; P=0.29). However, tumor location significantly impacted survival in stage III disease, 5-year OS was 45% in RCC, and 63% in LCC (HR =2.28; 95% CI :1.01–5.24; P=0.04). During the interval first-second year to follow up, we observed an annual relapse rate peak of 15.6% in RCC group *vs.* 3.2% in LCC with a significant P value, P=0.026. We did not observe a significant difference in annual relapse rate between the groups in the other year-intervals of follow up.

Discussion

Our study showed differences in clinic-pathological and outcome characteristics between RCC and LCC locations. Patients with RCC were more likely to be female, with poorly differentiated tumors and worse survival, especially in stage III. RCC patients tended to relapse earlier with a peak in the first-second year to follow-up. Our results go along with results of previous studies. Differences between both anatomic sides of the colon can be due to numerous reasons: different embryological origin, different microbiota, different genetic pathways…These differences translate into the clinical presentation; the incidence of RCC is associated with a number of risk factors, female gender, old age, previous cancer history, and insulin resistance, while LCC is related to individuals with a low fiber diet, heavy smokers, and alcohol consumers (9). In comparison with LCC, RCC has a prevalence toward being poorly-differentiated, commonly mucinous histology type, a more advanced disease and often involving satellite the lymph nodes or peritoneal region rather than the liver or lung, which are the most common sites of metastasis from left CC (7).

Exact anatomical definition of RCC and LCC is still unclear, for now the consensus is to consider the splenic flexure as the cut-off limit. In Meguid *et al.* study; analysis of anatomic stratification showed that mortality risk was 8.0% greater in case of location between hepatic flexure and splenic flexure compared with those having a tumor located between the descending colon and sigmoid colon (HR 1.08; 95% CI: 1.05–1.11; P<0.001). Subjects with cancer between the cecum and ascending colon had a 3.7% greater mortality risk compared with those with cancer between the descending colon and sigmoid colon (HR 1.037; 95% CI: 1.01–1.06; P=0.007) (10). Prognostic significance was reported by several studies; however, the implication on our current practice is still unclear. Should we change our decisions in regard to indication of adjuvant therapy or of particular regimens based on tumor location? This is a question without a clear answer. The predictive value on survival in metastatic setting was confirmed in many clinical trials (11-13). It seems that left-sided primary tumor site is a useful predictor of improved cetuximab efficacy in

Table 2 Survival difference between RCC and LCC in stage I–III CC from SEER data base studies

Author, year	Year at diagnosis	Number of patients	Difference in survival between RCC *vs.* LCC		
			Stage I	Stage II	Stage III
Warschkow *et al*., 2016 (15)	2004–2012	91,416	Yes favoring LCC	Yes favoring LCC	No
Yang *et al*., 2016 (4)	2000–2012	57,847	Yes favoring LCC	Yes favoring RCC	Yes favoring LCC
Weiss *et al*., 2011 (5)	1992–2003	53,801	No	Yes favoring RCC	Yes favoring LCC
Meguid *et al*., 2008 (10)	1988–2003	77,978	No	Yes favoring LCC	Yes favoring LCC
Our study	2003–2014	203	–	No	Yes favoring LCC

LCC, left-sided colon cancer; RCC, right-sided colon cancer; CC, colon cancer; SEER, surveillance, epidemiology and end results.

R*AS* wild-type metastatic colorectal cancer, but patients with right-sided *RAS* and *BRAF* wild-type metastatic colorectal cancer seemed to derive no benefit from single-agent anti-EGFRs. Upfront comparison between cetuximab and bevacizumab in the FIRE3 study reported similar observations (8,14). It is although important to highlight that all reported studies are retrospective and post hoc unplanned analyses with unbalanced groups and heterogenous definition of tumor side. There is an urgent need to perform clinical trials with pre stratified subgroups to change our clinical practice guidelines. Data in early stage CC are very conflicting. Four published large population cohorts from the SEER data based including patients treated in different periods of time (*Table 2*) showed different results. First, in the study of Meguid *et al.* differences in survival between right- and left-sided CC with stage I were observed (HR =1.003; P=0.93) and stage II right-sided colon cancers had lower HR than those with left-sided colon cancers (HR =0.91; P<0.001) (10). In 2008, Weiss *et al.* reported, in a mortality analysis of 53,801 patients with stage I–III CC, no significant difference in mortality between right and left-sided cancers for all stages combined (HR =1.01; 95% CI: 0.98–1.04; P=0.598) and not for stage I cancers (HR =0.95; 95% CI: 0.88–1.03; P=0.211). However, stage II right-sided cancers had lower mortality than left-sided cancers (HR =0.92; 95% CI: 0.87–0.97; P=0.001), and stage III right-sided cancers had higher mortality (HR = 1.12; 95% CI: 1.06–1.18; P=0.001) (5). Recently Yang *et al.* demonstrated that among stages I and II disease, RCC patients had better disease specific survival than those with LCC. However, among stages III, outcome was worse (4). And finally, Warschkow *et al.* reported that in stage I and II, the prognosis of right-sided cancer was better for overall (HR = 0.89, 95% CI: 0.84–0.94 and HR =0.85, 95% CI: 0.81–0.89) and cancer-specific survival (HR =0.71, 95% CI: 0.64–0.79 and HR =0.75, 95% CI: 0.70–0.80). Right- and left-sided CC had a similar prognosis for stage III (overall: HR =0.99, 95% CI: 0.95–1.03 and cancer-specific: HR =1.04, 95% CI: 0.99–1.09) (15).

In our study, tumor location had impact only in stage III CC. This heterogeneity in reported survival results is due to tumor heterogeneity. In fact, tumor cells with specific genotype in a single tumor, may present variations in response to environment and treatments phenotypes and may change with process of tumor infiltration and metastasis (16,17).

Therapeutic implications in early stage CC of tumor location are now described in several series. Benefit from adjuvant chemotherapy in stage III CC, could be deeper in RCC (HR =0.37; P<0.0001) as reported by Elsaleh *et al.* (18). However in the N0147 trial, survival benefit from adjuvant Folfox in stage III was greater in LCC, this benefit was different between RCC and LCC when mismatch repair status was considered (19). Folfiri which is not a standard of care in the adjuvant setting, was reported to be more effective in stage II RCC then in LCC, in a retrospective analysis of the PETACC3 adjuvant trial (20).

In conclusion, considering tumor location is an important factor for future studies about early and advanced CC. It represents a future possible field into deeper personalized medicine in colorectal cancer (CRC) management.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The protocol was approved by the review board of Abderrahmen Mami Hospital, which is affiliated to Faculty of Medicine Tunis (FMT) (décret n° 94-1939 du 19 septembre 1994).

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