Role of Metastatic Colon Cancer Topography in Pathological and Molecular Variability: A Retrospective Study

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Abstract

Background: Colon cancer represents a major health concern worldwide and ranks as the second most common cause of cancer death. Nowadays, oncologists have strong evidence that colon cancer sidedness has a crucial effect on epidemiological, clinical, pathological, and molecular features of the patients, their response to treatment, and their survival outcomes. Based on these data, our study was conducted to evaluate the effect of primary tumor location in patients with metastatic colon cancer.

Patients and methods: This study is a prospective cohort study conducted among 140 patients with a proven diagnosis of metastatic colon cancer adenocarcinoma (70 with right-sided colon cancer and 70 with left-sided colon cancer) who received treatment at South Egypt Cancer Institute to compare between both groups as regards epidemiological, clinical, pathological, and molecular characteristics, response to first- and second-line treatment, and survival outcomes. Statistical analysis was done using SPSS program version 20. Difference was considered statistically significant at P-value < 0.05. Survival curves were conducted by using the Kaplan-Meier methods and were compared with the log-rank test.

Results: Metastatic Right-sided colon cancer (RCC) occurred at older age and affected more females versus metastatic left-sided colon cancer (LCC). Metastatic RCC was more commonly presented with anemia in contrast to metastatic LCC which was more frequently presented with lower gastrointestinal bleeding or change in bowel habits. More cases of mucinous differentiation and poor or undifferentiated morphology were observed among metastatic RCC patients who also had a more predilection for peritoneal metastases versus hepatic metastases which were more commonly detected among metastatic LCC patients. Wild type (non-mutated KRAS form) of colon cancer was more prevalent among metastatic LCC. Metastatic RCC patients showed a better overall response rate to first-line treatment with chemotherapy plus panitumumab. No significant differences in survival outcomes were found between metastatic RCC and LCC even in patients treated with chemotherapy plus panitumumab.
Conclusion: Metastatic RCC and LCC have significant differences including epidemiology, histo-pathology, clinical presentation and behavior, molecular phenotyping, and response to treatment.

Keywords: Colon cancer, Sidedness, Topography, Right, Left.

Introduction:

Colon cancer is a major health concern worldwide, representing the third most common cancer, the second most common cause of cancer-related mortality and the most common gastrointestinal cancer [1]. Worldwide, about 1.9 million new cases of colorectal cancer occurred in 2018 (10.2% of all cancers). Geographically, the incidence varies with the highest estimated rates in Australia/New Zealand (per 100,000 population, 41.7 in men and 32.1 in women), and the lowest in South-Central Asia (per 100,000 population, 4.5 in men and 3.8 in women). Colon cancer is responsible for about 694,000 deaths annually, representing 8.5% of overall cancer mortality [2]. The mean age at diagnosis is 66 years [3].

Colon cancer accounts for 6,5% of cancers in Egypt without age predilection representing more than one third of its cases in the young population which can't be attributed to heredity factors or to bilharzial infestation [4].

Over the last few years, considerable clinical research has been done to evaluate the differences between right-sided (RCC) and left-sided (LCC) colon cancers concerning the clinico-pathological features and clinical outcomes. Recently, there is a global trend towards considering RCC and LCC as two separate disease entities [5].

Embryologically, cancers arising up to the proximal two thirds of the transverse colon are RCC while LCC includes cancers arising from the distal third of the transverse colon down to the rectum. This cut-point is attributed to the origin of the proximal colon from the midgut which is perfused primarily by branches of the superior mesenteric artery versus the origin of the left

colon from the hindgut which receives blood mainly via the inferior mesenteric artery [6].

With reference to clinico-pathological data and survival outcomes, significant differences have been observed between RCC and LCC; patients with RCC are more likely to be women, older age, presented with subtle symptoms such as anemia and weight loss, have mucinous, undifferentiated, or signet-ring cell histology, associated with a more advanced stage, have the propensity to metastasize to the peritoneum, and have a poorer survival outcomes compared with those with LCC [7]

In the era of precision medicine, eminent data assume that right- and left-sided colon cancers differ in their molecular phenotype. Three molecular carcinogenesis pathways have been identified: (1) chromosomal instability (CIN), (2) microsatellite instability (MSI), and (3) CpG island methylator phenotype (CIMP) or epigenetic instability pathways. The CIN pathway is characterized by chromosomal alterations both in structure and in number together with genetic mutations of proto-oncogenes and tumor suppressor genes. The MSI pathway encompasses changes in the number of nucleotide repeats placed in the exons with subsequent frame-shift mutations in tumor suppressor genes or tumor-related genes. The epigenetic instability (or CIMP) pathway is featured by hypermethylation of many promoter CpG island loci with resulting inactivation of tumor suppressor genes or tumor-related genes [8]. Colon cancers on the left side usually follow the CIN molecular pathway and are characterized by molecular instability [9]. Accordingly, anti-epidermal growth factor receptor (anti-EGFR) therapy with cetuximab or panitumumab is associated with improved survival in cases with KRAS wild type but this is not true for cases on the right side, this data was confirmed by international randomized controlled trials [3]. On the other hand, right-sided colon cancers usually follow the MSI pathway {deficient mismatch repair/microsatellite instability-high (dMMR/MSI-high)} or the CIMP pathway [10]. Consequently, right-sided colon cancers appear to have a better response to immunotherapies with immune checkpoint inhibitors [11].

Patients and Methods:

Our study is a retrospective cohort study conducted at South Egypt Cancer Institute (SECI) aiming at evaluation of the effect of metastatic colon cancer sidedness on clinico-pathological data, molecular features, treatment outcomes, and prognoses among patients with confirmed diagnosis of stage IV colon cancer adenocarcinoma through both imaging and histo-pathological examination who had received treatment at SECI during the period from 1/2010 to 12/2018.

A randomized sample size of 280 cases of metastatic colon cancer patients (140 with metastatic RCC and 140 with metastatic LCC with a ratio of 1:1) was selected from our SECI's tumor registry during the period from 1/2010 to 12/2018.

The diagnostic H&E samples were retrieved from the pathology archive for re-examination. Pathological diagnosis was verified by experienced onco-pathologist with the detection of histological subtype, grade and stage.

Inclusion criteria:

Metastatic adenocarcinoma of the colon in patients aged 18 years or older starting from 2010 to 2018.

Exclusion criteria:

a) Patients aged less than 18 years of age at diagnosis.

b) Patients with transverse colon or rectal cancer.

c) Patients with synchronous left and right-sided colon cancers or with coexisting malignancy elsewhere.

d) Patients who continued treatment out of SECI.

e) Patients with stage 0 – III colon cancer

f) Patients with previous history of colon cancer or any other malignancies

g) Patients with histo-pathological diagnosis other than adenocarcinoma.

Statistical analysis was performed by version 20 of SPSS program. Analysis of categorical variables was done by Fisher exact test and analysis of continuous variables was done by student's t-test. The frequencies of the two arms were compared by Chi-square test. Kaplan-Meier methods were used to perform the survival curves and log-rank test was used for the comparison. The statistical tests applied were two-sided, and a p-value of 0.05 or less was considered statistically significant.

The study was approved by the Medical Ethics Committee of SECI.

Results:

1. Epidemiological, clinico-pathological and molecular characteristics of the patients [table (1)]

Patients with metastatic RCC were significantly older than those with metastatic LCC at time of diagnosis with a mean age of 60.48 ± 11.26 years for RCC versus 56.25 ± 12.37 years for LCC (P-value = 0.002). Females were more prone to metastatic RCC than metastatic LCC (P-value = 0.032). As regards presenting symptoms, more cases of metastatic RCC presented with anemia (P-value = < 0.001) while more cases of metastatic LCC presented with gastrointestinal bleeding (P-value = < 0.001) and change in bowel habits (P-value = < 0.001). Concerning histo-pathological examination and differentiation, metastatic RCC was more commonly associated with mucinous adenocarcinoma (P-value = 0.001) and with poorly or un-differentiated morphology (P-value = 0.002) versus metastatic LCC. Mentioning sites of metastases, RCC had a more predilection for peritoneal metastases (P-value = 0.019), whereas LCC was more commonly associated with hepatic metastases (P-value = < 0.001). Conversely, there were no statistically significant differences between both groups in terms of metastases to lung, lymph nodes, or bone. Coming to KRAS status, non-mutated form (wild-type) was more significantly found among patients with metastatic LCC (P-value = 0.010).

Table 1. Epidemiological, clinico-pathological and molecular characteristics of the study group

Variable	Site of tumor				P-value
	Right colon (n=140)		Left colon (n=140)		
	N	%	N	%	
Age (years), Mean ± SD	60.48 ± 11.26		56.25 ±12.37		0.002*
Gender					
- Male	80	57.14	90	64.29	0.032*
- Female	60	42.86	50	35.71	
Presenting symptoms					
- Anemia	70	50.00	28	20.00	<0.001*
- Lower gastrointestinal bleeding	28	20.00	78	55.71	<0.001*
- Change in bowel habits	38	27.14	60	42.86	<0.001*
- Abdominal pain	40	28.57	44	31.43	0.361
- Symptoms of metastases	74	51.39	86	61.43	0.343
Histo-pathology					
- Mucinous	18	12.86	8	5.71	0.001*
- Non-mucinous	122	87.14	132	94.29	
Differentiation					
- Well- or moderately-differentiated	18	12.86	8	5.71	0.002*
- Poorly- or un-differentiated	122	87.14	132	94.29	
Sites of metastases					
- Liver	64	45.71	84	60.00	<0.001*
- Lung	6	4.29	16	11.43	0.072
- Peritoneum	62	44.29	28	20.00	0.019*
- Lymph nodes	24	17.14	20	14.29	0.771
- Bone	14	10.00	8	5.71	0.385
KRAS status					
- Not done	90	64.29	66	47.14	
- Wild type (non-mutated)	26	18.57	54	38.57	0.010*
- Mutated	24	17.14	20	14.29	

SD: standard deviation, **KRAS:** Kirsten rat sarcoma viral oncogene homolog

2. Response to chemotherapy and targeted therapy [table (2)]

No statistically significant differences were noted between metastatic RCC and LCC in response to their first- (P-value = 0.837) and second-line (P-value = 0.085) treatment with chemotherapy only. On the other hand, adding panitumumab (anti-EGFR therapy) to chemotherapy in patients with proved KRAS wild-type metastatic colon cancer was accompanied by a significantly better response to first-line treatment in metastatic LCC group versus metastatic RCC group (P-value = 0.005) which was not the case with second-line treatment with chemotherapy plus panitumumab (P-value = 0.349).

3. The correlation between tumor sidedness and the survival

For patients receiving chemotherapy alone, no statistically significant differences were observed between metastatic RCC and LCC concerning progression free survival (PFS) {median = 18 months vs. 11 months, P-value = 0.907, (figure 1)}, nor overall survival (OS) {median = 42 months vs. 29 months, P-value = 0.624, (figure 2)}. Similarly, no significant survival benefit was noted among patients receiving chemotherapy plus panitumumab in terms of PFS {median = 21 months vs. 11 months, P-value = 0.237, (figure 3)}, and OS {median = 41 months vs. 21 months, P-value = 0.07, (figure 4)}.

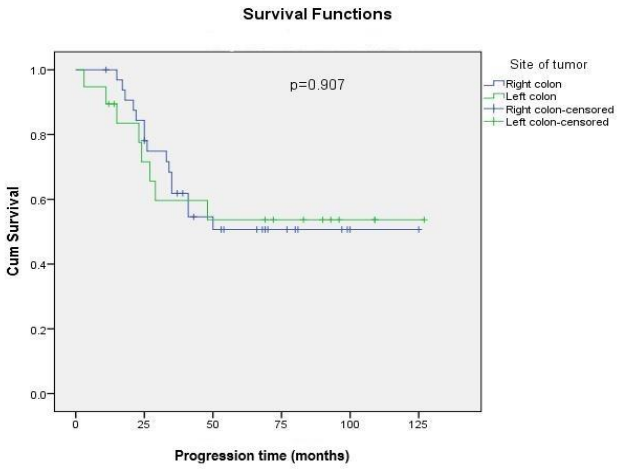

Figure 1. PFS curve of patients receiving chemotherapy alone according to primary tumor side

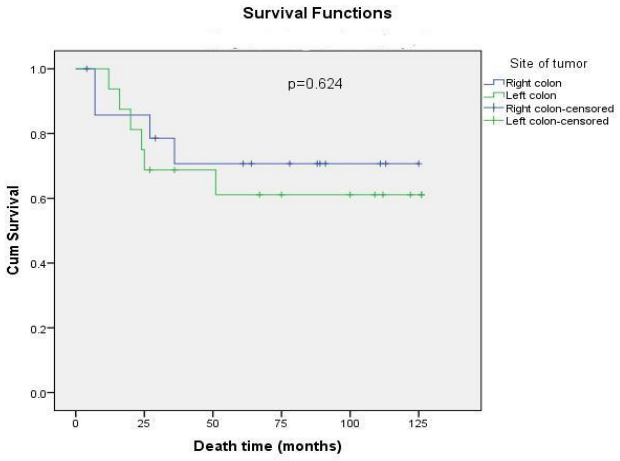

Figure 2. OS curve of patients receiving chemotherapy alone according to primary tumor side

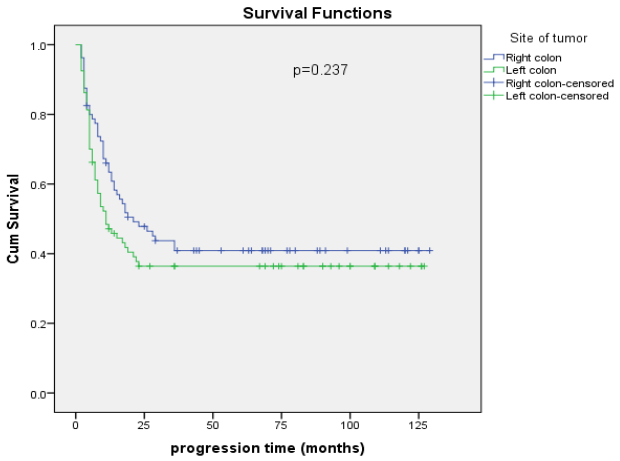

Figure 3. PFS curve of patients receiving chemotherapy plus panitumumab according to primary tumor side

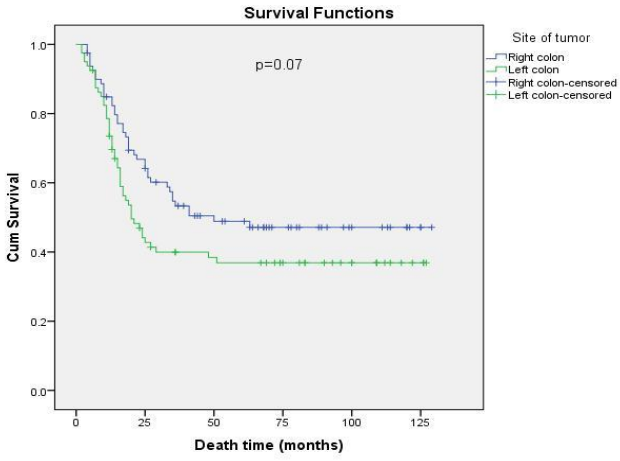

Figure 4. OS curve of patients receiving chemotherapy plus panitumumab according to primary tumor side

Table 2. Response to chemotherapy and targeted therapy

Variable	Site of tumor				P-value
	Right colon (n=140)		Left colon (n=140)		
	N	%	N	%	
Response to first-line treatment in patients receiving chemotherapy only [n=114 (right colon), n=86 (left colon)]					0.837
- CR	2	1.75	2	1.43	
- PR	30	26.30	26	30.27	
- ORR	32	28.05	28	31.70	
- SD	48	42.80	40	56.90	
- PD	34	29.15	18	21.40	
Response to second-line treatment in patients receiving chemotherapy only [n=80 (right colon), n=72 (left colon)].					0.085
- CR	0	0.00	2	2.80	
- PR	6	7.10	14	20.70	
- ORR	6	7.10	16	23.50	
- SD	46	57.20	36	50.00	
- PD	28	35.70	20	26.50	
Response to first-line treatment in patients receiving chemotherapy + panitumumab [(n=26 (right colon), n=54 (left colon)].					0.005
- CR	0	0.00	2	3.70	
- PR	6	23.00	22	40.70	
- ORR	6	23.00	24	44.40	
- SD	12	46.20	24	44.40	
- PD	8	30.80	6	11.20	
Response to second-line treatment in patients receiving chemotherapy + panitumumab [(n=16 (right colon), n=36 (left colon)]					0.349
- CR	0	0.00	0	0.00	
- PR	4	25.00	14	38.90	
- ORR	4	25.00	14	38.90	
- SD	8	50.00	12	33.30	
- PD	4	25.00	10	27.80	

CR: complete response, **PR:** partial response, **ORR:** overall response rate, **SD:** stationary disease, **PD:** Progressive disease.

Discussion:

Globally, many studies have evaluated the effect of colon cancer sidedness on the demographic, clinical, pathological, and molecular data of patients, their response to treatment, and the implication of this on survival outcomes. Our study investigated the presence of significant differences based on primary tumor location among our metastatic colon cancer patients at SECI. We demonstrated that the mean age incidence of metastatic RCC was significantly older than metastatic LCC which was consistent with the results of almost all

studies worldwide such as the study by Yoshiro Itatani et al. [12]. This can be explained by the more obvious symptoms associated with LCC such as lower gastrointestinal bleeding leading to earlier seeking for medical advice when compared to RCC which was commonly presented with subtle symptoms such as anemia [13].

Referring to gender differences, we found that females were more commonly affected by metastatic RCC compared to metastatic LCC which was in concordance with the findings by Ru-Nie Gao and colleagues [14] and may be due to genetic and epigenetic factors or dietary habits [15] but this did not match with the results of the study by R Kandula and colleagues which did not find significant differences in gender predilection [16].

Regarding symptoms at presentation, anemia was considerably more common among patients with RCC due slow loss of occult blood in stool over a long period of time versus LCC which was more significantly presented with lower gastrointestinal bleeding or changes in bowel habits which was based on the anatomical fact that left colon is much narrower than right colon and thus more likely to cause partial or complete bowel obstruction [17]. These findings were in agreement with the study by Cienfuegos Javier-A. et al. which reported similar results [18], whereas these were contrary to the study by Suzanne Dixon et al which stated that RCC was more commonly presented with bleeding manifestations and LCC was more frequently presented with abdominal pain or cramps [19].

Concerning predilection for certain sites of metastases, RCC was more frequently associated with peritoneal metastases and this may be attributed to the higher rate of peritoneal metastases in mucinous adenocarcinoma and the higher prevalence of mucinous adenocarcinoma in RCC [20]. In addition, hepatic metastases were more significantly frequent in LCC which may be explained by the seed-and-soil hypothesis, which states that tumor metastases have a preference for specific organs (e.g., the liver), based on interactions between tumor cells and their microenvironment [21].

However, no significant differences were noted between both groups in terms of pulmonary, lymph nodes, and osseous metastases and this was in agreement with the study by Nelleke PM Brouwer and colleagues [22] and in contrast to the study by Yu-Lun Hsu and colleagues that did not demonstrate significant differences in predilection for certain metastatic sites [23].

With reference to histo-pathological examination and differentiation, our study showed that RCC was more significantly associated with mucinous adenocarcinoma and poorly- or un-differentiated morphology when compared to LCC. These results were in agreement with the study by Yuji Maeda et al [24]. The explanation of these results may be due to the poorly-differentiated tumors being commonly associated with MSI tumors which in turn are almost always associated with RCC [25]. On the other hand, our results did not agree with the results of the study by R Kandula and colleagues which did not demonstrate any significant association between histo-pathological examination or differentiation and the primary tumor location [16].

Coming to KRAS status, KRAS mutation was more significantly prevalent among patients with metastatic RCC versus metastatic LCC which was consistent with the study by Ming-zhi Xie and colleagues [26].

With regard to treatment response, no statistically significant differences were noted between metastatic RCC and LCC in terms of response to first- and second-line treatment among patients receiving chemotherapy alone which was compatible with the study by Feng Wang et al. [27]. On the contrary, addition of panitumumab to traditional chemotherapy in metastatic colon cancer of non mutated KRAS type was associated with better ORR in LCC versus RCC when given as first-line treatment, but not when given as second-line treatment and this was also in concordance with the data from Feng Wang et al. which conducted similar results [27]. This can be attributed to the more prevalence of non-mutated KRAS (wild-type) colon cancer among patients of LCC group as stated above [26]. Our findings were against the results of the study by Jianhong Peng and colleagues which concluded that RCC was associated with better ORR versus LCC [28].

Regarding survival outcomes, no statistically significant differences in PFS or OS were observed between metastatic RCC and LCC patients who received either chemotherapy alone or chemotherapy plus panitumumab as a first-line or second-line therapy. These results were in agreement with the study by Feng WANG et al [27] but did not agree with the study by Christdoulidis G et al. which stated that metastatic LCC was associated with better survival outcomes when compared with metastatic RCC [29].

The potential limitations of our work include its retrospective nature and that it was carried in a single institute experience. The sample size was relatively small for such retrospective studies. In addition, our study lacks assessment of molecular markers other than KRAS such as MSI and BRAF which have proved to play a crucial prognostic role in colon cancer and its treatment decisions.

Conclusion:

Our study concluded that statistically significant differences exist between metastatic RCC and LCC in terms of age at diagnosis, gender predilection, presenting symptoms, histo-pathology and differentiation, sites of metastases, KRAS status, and response to first-line treatment with chemotherapy plus anti-EGFR therapy. Our study is compatible with the results of most of the recent international studies and now there is a global trend for considering RCC and LCC as a two separate diseases. Further research should be done worldwide for more evaluation of the differences between RCC and LCC especially as regards molecular phenotyping and the response to targeted therapy and immunotherapy.

List of abbreviations

BRAF = v-raf murine sarcoma viral oncogene homolog B1
CIMP = CpG island methylator phenotype
CIN = chromosomal instability
CR = complete remission
dMMR = deficient mismatch repair
EGFR = epidermal growth factor receptor
KRAS = Kristen rat sarcoma
LCC = left colon cancer
MSI = microsomal instability
ORR = overall response rate
OS = overall survival
PD = progressive disease
PFS = progression-free survival
PR = partial response
RCC = right colon cancer
SD = stationary disease
SECI = South Egypt Cancer Institute
SPSS = statistical product and service solutions

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