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Right and Left Colon Cancer: Clinico-Pathological Features and Treatment Results (South Egypt Cancer Institute Experience)

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Abstract

Background: Colon cancer (CC) ranks as the third most common cancer worldwide and is considered the second leading cause of cancer death. Recently, many international studies have made the observation that right and left colon cancer have many significant differences regarding clinico-pathological characteristics and primary tumor location has a crucial impact on treatment outcomes and overall survival. Our study was conducted to verify the presence of significant differences between right and left colon cancer. **Patients and Methods:** This study is a retrospective cohort study which aimed at comparing right and left colon cancer as regards clinico-pathological data and treatment results among patients with colon cancer receiving treatment at South Egypt Cancer Institute (SECI) during the period from 1/2008 to 12/2018. A sample size of 160 cases of colon cancer patients (80 diagnosed as right colon cancer and 80 diagnosed as left colon cancer) was randomly selected from our South Egypt Cancer Institute (SECI)'s tumor registry. Statistical analysis was done using SPSS program version 20. Difference was considered statistically significant at P-value < 0.05. Survival curves were conducted using the Kaplan-Meier methods and were compared with the log-rank test. **Results:** Right colon cancer occurred at an older age and was more commonly presented with abdominal pain while left colon cancer was more commonly presented with bleeding manifestations. More cases of the right side underwent curative surgeries whereas more palliative surgeries were performed to left-sided cases. Left sided cases were associated with a more advanced stage at diagnosis while right-sided cases were associated with a better response to first-line chemotherapy. More cases of the left side died due to metastatic disease. On the other hand, our findings demonstrated no differences between both sides regarding gender predilection, risk factors, sites of metastases, number of metastatic organs, histo-pathological examina-

tion and grading, response to second- or third-line chemotherapy, chemotherapy toxicity (hematological or non-hematological), overall survival, progression-free survival, or disease-free survival. **Conclusion:** Primary tumor location of colon cancer has a significant effect on clinico-pathological characteristics and treatment outcomes.

Keywords

Colon Cancer, Right, Left, Tumor Location

1. Introduction

Colon cancer (CC) ranks as the third most common cancer worldwide and is considered the second leading cause of cancer death. In 2018, the cumulative risk of colon cancer was 1.51% among men and 1.12% among women for the population age of 0 - 74 years [1]. The mean age at diagnosis is 66 years [2].

In Egypt, colon cancer is responsible for 6.5% of all cancers and has no age predilection with more than one third of cases affecting young population which can neither be explained on a hereditary basis nor can it be attributed to bilharziasis [3].

Embryologically, right-sided colon cancer (RCC) originates from the midgut, which includes the caecum, ascending colon, and the proximal two-thirds of the transverse colon while left-sided colon cancer (LCC) originates from the hindgut, which includes the distal third of the transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum [4].

Most cases of colon cancer are attributed to aging and lifestyle factors such as smoking, obesity, lack of physical activity, and dietary factors as increased consumption of red meat, processed meat, and alcohol, with only few cases (less than 5%) due to underlying genetic diseases the most common of which are familial adenomatous polyposis and hereditary non-polyposis colon cancer. Another risk factor is inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis [5].

The manifestations of colon cancer are dependent on the site of the tumor in the bowel, and whether metastasis has occurred or not. The classic manifestations include: weight loss, constipation, vomiting, bleeding per rectum, decrease in stool caliber (thickness), and loss of appetite in a person above 50 years old. Around 50% of individuals with colon cancer are asymptomatic [6].

Diagnosis of colon cancer is usually made by obtaining a biopsy through sigmoidoscopy or colonoscopy which is followed by metastatic workup by imaging. Screening is recommended starting from the age of 50 to 75 and is effective for decreasing mortality rate from colon cancer. Aspirin and other non-steroidal anti-inflammatory drugs can decrease the risk; however, their general use is not recommended for this purpose due to their side effects [7].

Treatment for colon cancer may include some combination of surgery, chemotherapy and targeted therapy. Localized cancers within the wall of the colon are curable with surgery, while the treatment goals in metastatic cancers are cure (if possible in very selected cases), prolongation of life, palliation of symptoms, improvement of quality of life, and delaying disease progression and tumor shrinkage [8]. The worldwide five-year survival rate is about 65%. The likelihood of survival depends on tumor stage, the possibility of surgical removal and the patient's overall health [9].

Differences in the clinical features, chromosomal and molecular characteristics between the right-sided and the left-sided colon have been reported. Over the past few years, the distinction between right- and left-sided colon cancers has been brought into focus due to having different outcomes, prognosis, and clinical responses to chemotherapy [4].

Concerning molecular profile, all recent scientific international data suggest that right and left-sided colon cancer have different molecular phenotyping. Left-sided colon cancers are frequently chromosomal instable tumors following the CIN molecular pathway which is commonly characterized by mutations of Kirsten ras homolog (KRAS) oncogene, resulting in constitutively active RAS protein, which in turn activates the downstream pathways leading to cell proliferation and survival [10]. Anti-epidermal growth factor receptor (anti-EGFR) therapies as cetuximab and panitumumab improved overall survival in patients with left-sided KRAS wild type colon cancer but not in right-sided colon cancer based on many international randomized controlled trials [2]. On the other hand, right-sided colon cancers are predominantly characterized by microsatellite instability {deficient mismatch repair/microsatellite instability-high (dMMR/MSI-high)} which is caused by defects in the DNA mismatch repair system [11]. Consequently, right-sided colon cancers appear to benefit more from immunotherapies such as immune checkpoint inhibitors [12].

2. Patients and Methods

This study is a retrospective cohort study which aimed at comparing right and left colon cancer as regards clinico-pathological data and treatment results among patients with colon cancer receiving treatment at South Egypt Cancer Institute (SECI) during the period from 1/2008 to 12/2018.

The sample was calculated by using G power version 3.1. Based on a study done by (Miao-Zhen Qiu *et al.*, 2018) which showed that there was a difference in the mean values of the age at the time of diagnosis between the 2 groups (right and left sided colon cancer) to be (0.399), and the mean values were 69.49 ± 13.27 and 64.15 ± 13.48, minimum sample size needed is 158 patients to show the same effect of this study with a power of 80% of the test and two-sided significance of 0.05 with a ratio of 1:1 (79 patients per group) [13].

After reviewing patients' files, a sample size of 160 cases of colon cancer patients (80 diagnosed as right colon cancer and 80 diagnosed as left colon cancer)

was randomly selected from our South Egypt Cancer Institute (SECI)'s tumor registry during the period from 1/2008 to 12/2018.

Verification of pathological diagnosis, histological subtype, grade, and stage was performed after the retrieval of H&E slides concerning the diagnostic and the post-operative specimens from the pathology archive to be re-examined by experienced pathologist.

The inclusion criteria included those patients diagnosed with stage I to IV colon cancer at 18 years of age and above between 2008 and 2018.

The exclusion criteria included all of the following:

1) Age younger than 18 years old at time of diagnosis.

2) Transverse colon cancer or rectal cancer.

3) Synchronous left and right-sided colon cancer.

4) Patients continued the care out of SECI.

5) Patients without exactly primary location of colon cancer registered in the clinical file.

6) Stage 0 or *in situ* tumor.

7) Previous history of colon cancer.

8) Coexisting malignancy or history of malignancies other than colon cancer.

The study was conducted according to Ethical Committee rules at South Egypt Cancer Institute.

3. Statistical Analysis

Statistical analysis was done using SPSS program version 20. Categorical variables were analyzed using the Fisher exact test, and continuous variables were analyzed using the student's t-test. Chi-square test was used to compare frequencies between the two arms. Survival curves were conducted using the Kaplan-Meier methods and were compared with the log-rank test. All applied statistical tests were two-sided, and a p-value less than 0.05 was considered statistically significant.

4. Results

4.1. Clinico-Pathological Features of the Patients [Table 1]

There was significant difference in age incidence with right colon cancer occurring at older age than left colon cancer (p-value = 0.037). On the other hand, there was no statistically significant difference in gender predilection between right and left colon cancer (p-value = 0.343). As regards risk factors, there were no statistically significant differences in presence of definite risk factors between right and left colon cancer (p-value = 0.568). More cases of right colon cancer presented with abdominal pain while more cases of left colon cancer presented with bleeding manifestations which was statistically significant (P-value = 0.0001). No statistically significant difference was noted between right and left colon cancer regarding sites of metastases (p-value = 0.320). There was no significant difference between metastatic right and left colon cancer as regards

Table 1. Clinico-pathological features of the study group.

Variable		Site of tumor				P-value
		Right colon (n = 80)		Left colon (n = 80)		
		N	%	N	%	
Age (years), Mean ± SD		49.06 ± 14.38		44.74 ± 14.83		0.037
	<45 years	27	33.75	40	50.00	
	≥45 years	53	66.25	40	50.00	
Gender	Male	43	53.75	37	46.25	0.343
	Female	37	46.25	43	53.75	
Risk factors	None	41	51.25	35	43.75	0.568
	Family history	14	17.50	20	25.00	
	Smoking	10	12.50	7	8.75	
	Obesity	7	8.75	6	7.50	
	Pre-cancerous lesions	8	10.00	12	15.00	
Presenting symptoms	Abdominal pain	41	51.25	21	26.25	0.001
	Bleeding manifestations	7	8.75	23	28.75	
	Altered bowel habits	16	20.00	15	18.75	
	Intestinal obstruction	16	20.00	18	22.50	
	Intestinal perforation	0	0.00	1	1.25	
	Symptoms of metastases	0	0.00	2	2.50	
Sites of metastases	None	31	38.75	25	31.25	0.320
	Liver	22	27.50	30	37.50	0.177
	Lung	3	3.75	9	11.25	0.072
	Bone	8	10.00	5	6.25	0.385
	Brain	3	3.75	1	1.25	0.620
	Ascites	12	15.00	11	13.75	0.822
	Abdominal LNs	10	12.50	13	16.25	0.499
	Peritoneal deposits	29	36.25	31	38.75	0.744
Number of metastatic sites	0	31	38.75	25	31.25	0.556
	1	20	25.00	21	26.25	
	2	22	27.50	22	27.50	
	3	6	7.50	11	13.75	
	4	0	0.00	1	1.25	
	5	1	1.25	0	0.00	
Pathology	Adenocarcinoma	52	65.00	61	76.25	0.135
	Mucoid adenocarcinoma	23	28.75	14	17.50	
	Signet ring carcinoma	3	3.75	5	6.25	
	Neuroendocrine carcinoma	2	2.50	0	0.00	

Continued

Grade	I	9	11.25	12	15.00	0.781
	II	47	58.75	45	56.25	
	III	24	30.00	23	28.75	
Stage at diagnosis	I	6	7.50	4	5.00	0.041
	II	15	18.75	16	20.00	
	III	33	41.25	19	23.75	
	IV	26	32.50	41	51.25	
Surgery	No surgery	10	12.50	20	25.00	0.006
	Curative surgery	66	82.50	48	60.00	
	Palliative surgery	4	5.00	12	15.00	
Causes of death	No (still alive)	40	50.00	32	40.00	< 0.001
	Local causes related to tumor	8	10.00	6	7.50	
	Causes related to metastatic disease	12	15.00	19	23.75	
	General causes	20	25.00	21	26.25	
	Chemotherapy toxicity	0	0.00	2	2.50	

SD: standard deviation.

number of metastatic organs (p-value = 0.556). More cases of right colon cancer underwent curative surgery, whereas more cases of left colon cancer underwent palliative resection and this was statistically significant (p-value = 0.006). No statistically significant differences were noted between right and left colon cancer as regards histo-pathological examination (p-value = 0.135) nor histological grade (p-value = 0.781). More cases of right colon cancer were stage III at diagnosis while more cases of left colon cancer were stage IV at diagnosis which was statistically significant (p-value = 0.041). More cases of left colon cancer versus right colon cancer died due to causes related to metastatic disease which was statistically significant (p-value ≤ 0.001).

4.2. Chemotherapy Response and Toxicity [Table 2]

Right colon cancer was associated with a more favorable response to first-line chemotherapy versus left colon cancer and this was statistically significant (p-value ≤0.001). No statistically significant differences were noted between right and left colon cancer as regards response to second-line or third-line chemotherapy (p-value = 0.159) (p-value = 0.548) respectively. As regards toxicity of chemotherapy, no statistically significant differences were observed between right and left colon cancer patients as regards hematological (p-value = 0.254) or non-hematological (p-value = 0.105) toxicity of chemotherapy.

4.3. The Correlation between the Site of the Tumor and the Survival

No statistically significant difference was observed between right and left colon

Table 2. Chemotherapy regimens (response and toxicity).

Variable		Site of tumor				P-value
		Right colon		Left colon		
		N	%	N	%	
First-line chemotherapy regimens (n = 77 (right colon), n = 78 (left colon))	FOLFOX	54	70.10	47	60.30	
	CapeOX	12	15.60	10	12.80	
	FOLFIRI	4	5.20	18	23.10	
	Capecitabine	5	6.50	2	2.60	
	XELIRI	0	0.00	1	1.30	
	Etoposide/Cisplatin	2	2.60	0	0.00	
Response to first-line chemotherapy (n = 77 (right colon), n = 78 (left colon))	Complete response	44	57.10	30	38.50	
	Partial response	1	1.30	2	2.60	
	Stable disease	8	10.40	13	16.70	<0.001
	Progression	24	31.20	33	42.30	
Second-line chemotherapy regimens (n = 41 (right colon), n = 42 (left colon))	FOLFOX	2	4.90	10	23.80	
	CapeOX	0	0.00	1	2.40	
	FOLFIRI	31	75.60	24	57.10	
	FOLFOXIRI	1	2.40	0	0.00	
	Capecitabine	3	7.30	3	7.10	
	Irinotecan	2	4.90	1	2.40	
	XELIRI	1	2.40	1	2.40	
	IROX	1	2.40	2	4.80	
Response to second-line chemotherapy (n = 41 (right colon), n = 42 (left colon))	Complete response	2	4.90	1	2.40	
	Stable disease	4	9.80	4	9.50	0.159
	Progression	35	85.40	37	88.10	
Third-line chemotherapy regimens (n = 14 (right colon), n = 17 (left colon))	Capecitabine	0	0.00	2	11.80	
	FOLFIRI	1	7.10	2	11.80	
	FOLFOXIRI	1	7.10	1	5.90	
	Irinotecan	12	85.70	10	58.80	
	IROX	0	0.00	2	11.80	
Response to third-line chemotherapy (n = 14 (right colon), n = 17 (left colon))	Progression	14	100.00	17	100.00	0.548
Chemotherapy-induced hematological toxicity (grade ≥ 3)	Anemia	13	16.90	17	21.80	
	Neutropenia	10	13.00	9	11.50	0.254
	None or toxicity grade < 3	54	70.10	52	66.70	
Chemotherapy-induced non-hematological toxicity (grade ≥ 3)	Oral mucositis	12	15.60	12	15.40	
	Diarrhea	9	11.70	6	7.70	
	Vomiting	13	16.90	6	7.70	0.105
	Peripheral neuropathy	8	10.40	7	9.00	
	None or toxicity grade < 3	35	45.50	47	60.30	

FOLFOX: 5-fluorouracil + leucovorin + oxaliplatn, **CapeOX:** capecitabine + oxaliplatin, **FOLFIRI:** 5-fluorouracil + leucovorin + irinotecan, **XELIRI:** capecitabine + irinotecan, **FOLFOXIRI:** 5-fluorouracil + leucovorin + oxaliplatin + irinotecan, **IROX:** irinotecan + oxaliplatin.

cancer in overall survival (P-value = 0.07) [Figure 1], progression-free survival (P-value = 0.237) [Figure 2], nor disease-free survival (P-value = 0.346) [Figure 3].

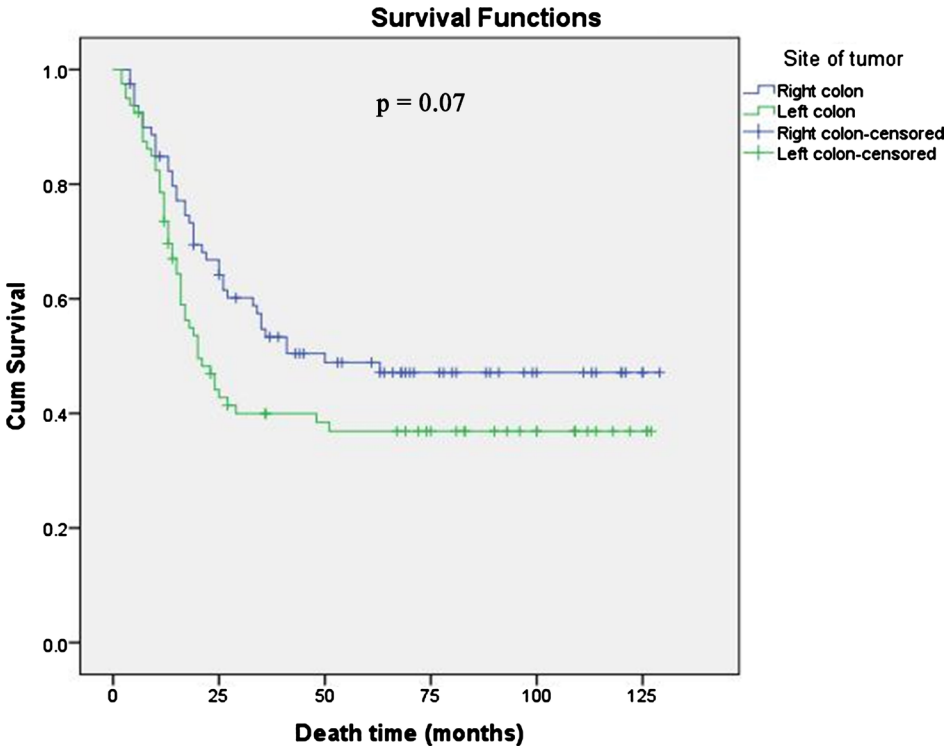

Figure 1. Overall survival curve of study group according to the site of tumor.

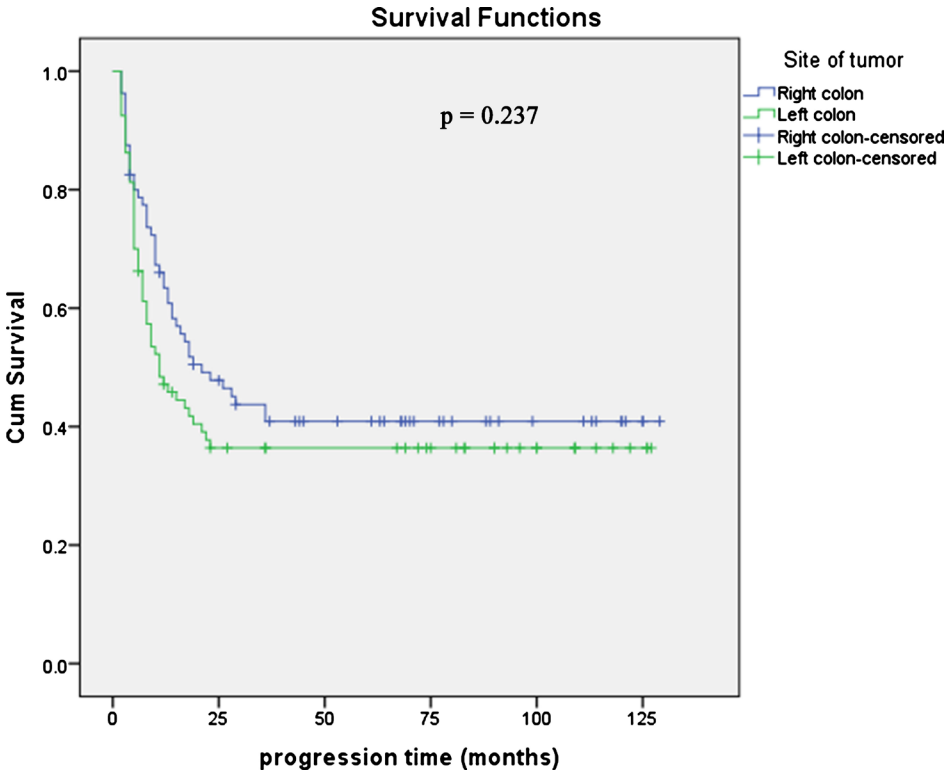

Figure 2. Progression-free survival curve of study group according to the site of the tumor.

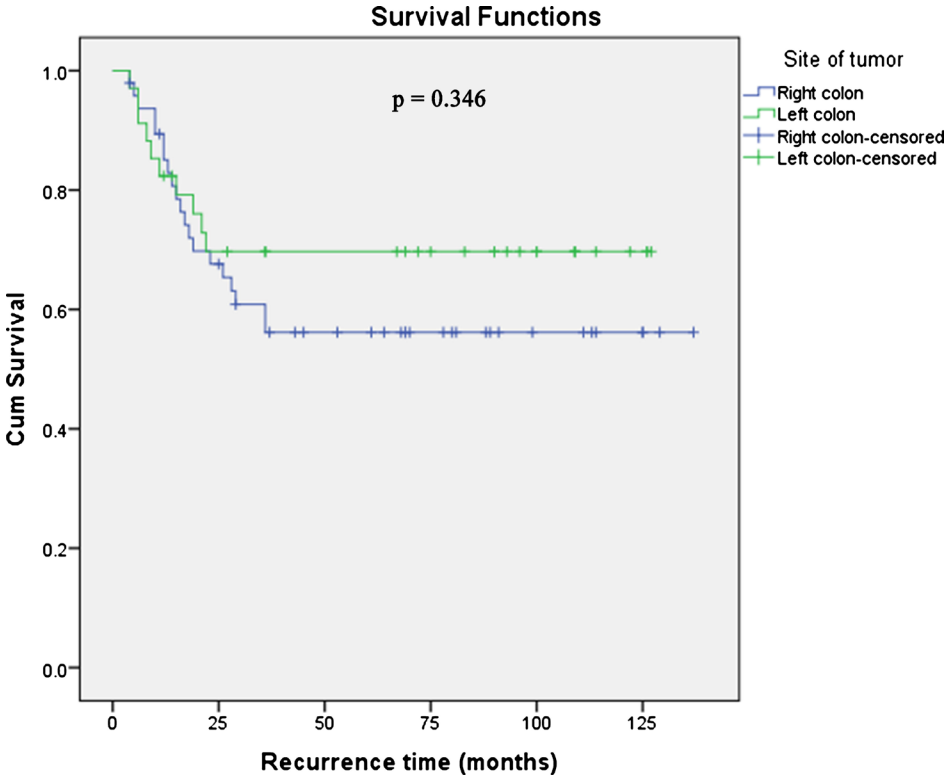

Figure 3. Disease-free survival curve of study group according to the site of tumor.

5. Discussion

Colon cancer (CC) is the third most frequent cancer worldwide and ranks as the second leading cause of death from cancer. Several studies were done worldwide in an attempt to demonstrate the differences in clinico-pathological characteristics and oncological outcomes between right and left-sided colon cancer.

Our study demonstrated that right colon cancer tends to occur at a significantly older age than left colon cancer. This result was in concordance with the study by Saltzstein and colleagues [14]. The explanation of this relationship between age and tumor location may be that left colon cancer more commonly presents with obvious symptoms such as bleeding per-rectum.

As regards gender, our study demonstrated no significant differences in gender predilection between right and left colon cancer. These results were in accordance with the results by R Kandula and colleagues [15]. However, the results were against the study by Javier-A Cienfuegos and colleagues which reported the more frequent incidence of right-sided colon cancer in females [16].

Concerning presenting symptoms, our study demonstrated significant association between presenting symptoms and the side of colon cancer as right colon cancer more was significantly presented with abdominal pain and left colon cancer more significantly presented with bleeding manifestations. Similarly, our results were consistent with the study by Young-Zu Kim and colleagues which reported the same results [17]. On the other hand, Our results were against the results published by Suzanne Dixon *et al.* which found that bleeding was the

main presenting symptom in right-sided colon cancer while left colon cancer more frequently presented with abdominal pain or cramps [18] and also against the results of the study by Javier-A. Cienfuegos and colleagues concluded that right-sided colon cancer presented mainly with anemia in contrast with left-sided colon cancer which mainly presented with changes in bowel habits [16]. The higher bleeding tendency of left colon cancer can be attributed to the fact that left colon is much narrower than right colon producing symptoms more quickly with fresh bleeding per-rectum, whereas right colon is more capacious allowing the mass to grow and expand to a large size producing mainly abdominal pain while blood often dries before leaving colon, so blood in stool is often undetectable in right colon cancer.

Referring to sites and number of metastases, our study did not demonstrate any significant association between side of colon cancer and the sites or number of metastases which was in agreement with the study by Yu-Lun Hsu *et al.* which did not demonstrate statistically significant differences in incidence and number of metastatic sites between the right-sided colon cancer and left-sided colon cancer groups [19]. This is in contrast with the results of the study by S. Y. Brule *et al.* which concluded that left-sided colon cancer was more frequently associated with hepatic and pulmonary metastases than right-sided colon cancer [20].

Concerning surgery and its aim, our study demonstrated significant association between aim of surgery and side of colon cancer with more cases of right colon cancer underwent curative resection while more cases of left colon cancer underwent palliative or emergent resection which were the same as the results reported in the study by Kumar S and colleagues [21]. These results were in contrast with the results of the study by Iben Onsberg Hansen *et al.* which stated that there was not statistically significant difference in aim of surgery between both arms [22]. Our results may be explained by the more advanced stage of left colon cancer versus right colon cancer in our study group and the smaller diameter of left colon compared to right colon.

Regarding histo-pathological examination, our study reported no significant association between the histo-pathological type and the side of colon cancer which was in accordance with the study by R Kandula and colleagues which reported the same results [15]. However, this did not agree with the results of the study by Leonardo Alfonso Bustamante-Lopez *et al.* which reported that mucinous histological type was more frequent in right-sided colon cancer [23].

Our study did not demonstrate any significant association between tumor grade and the side of colon cancer which was in agreement with the study by Leonardo Alfonso Bustamante-Lopez *et al.* [23]. On the other hand, this was in contrast with the study by Javier-A Cienfuegos and colleagues which reported that right-sided tumors were more significantly undifferentiated than left-sided tumors [16].

As for stage at diagnosis, our study demonstrated that most right-sided cases were stage III while left-sided cases were stage IV and these results were in

agreement with the results of the study by Paul J Ross *et al.* [24]. Conversely, these results did not agree with the study by Mark B. Ulanja *et al.* which reported that right-sided colon cancer was more significantly associated with a more advanced stage when compared to left-sided colon cancer [25]. This can be due to the more advanced tumor (T) and lymph node (N) stages in right colon cancer versus the more potential for metastases (M stage) in left colon cancer in our study group.

With regard to response to first-line chemotherapy regimens, our study reported that right colon cancer was more significantly associated with complete response to first-line chemotherapy while left colon cancer was more significantly associated with stable disease or progression to first-line chemotherapy which was in accordance with the study by Jianhong Peng and colleagues which reported similar results [26]. These results were against those published by Xia-Hong You *et al.* which did not find statistically significant differences in response to first-line chemotherapy between both arms [27]. This can be explained by our finding that left-sided colon cancer was associated with a more advanced stage than right-sided colon cancer; however, this was not associated with statistically significant differences in survival outcomes between two arms as stated below.

Coming to response to second-line chemotherapy regimens, our study did not demonstrate any statistically significant differences between right and left-sided colon cancer which was in agreement with the results of the study by Feng Wang *et al.* which reported similar results [28]. On the other hand, this did not agree with the results of the study by Paul J Ross *et al.* which reported that left-sided colon cancer was associated with a better response to second-line chemotherapy [24].

And finally the response to third-line chemotherapy regimens, our study did not demonstrate any statistical differences between right and left-sided colon cancer which was consistent with the results of the study by S. Y. Brule *et al* which demonstrated similar results [20]. These results were against the study by Nele Boeckx *et al.* which concluded the better response of left-sided versus right-sided colon cancer to third-line chemotherapy regimens [29].

Coming to chemotherapy toxicity (whether haematological or non-haematological toxicity), our study did not demonstrate any statistically significant differences between right and left-sided colon cancer which was in agreement with the study by Jianhong Peng *et al.* which reported similar results [26].

Mentioning causes of death, our study demonstrated that left colon cancer was more significantly associated with death cases owing to metastatic disease when compared to right colon cancer and this was consistent with the results of the study by Miaozhen Qiu *et al.* which demonstrated the same results [30]. This was also consistent with what we stated above about the more tendency of left colon cancer to metastasize (stage IV).

Regarding survival analysis, we did not demonstrate any statistically signifi-

cant differences in disease-free survival (DFS), progression-free survival (PFS), or overall survival (OS) between right and left sided colon cancer neither generally in all stages of disease nor in comparison of stage by stage and this was in accordance with the results of the study by Leonardo Alfonso Bustamante-Lopez *et al.* which reported that colon cancer sidedness did not have a significant influence on survival [23]. Conversely, our results did not agree with results of the study by Christodoulidis G *et al.* which concluded that left-sided colon cancer was significantly associated with better survival outcomes versus right-sided colon cancer [31].

Our study has some limitations. To begin with, it was a retrospective analysis of patients carried out at only a single-institution and, therefore, the conclusions may be more limited than those from controlled randomized clinical trials or studies based on extensive databases. The sample size of our study was relatively small for a retrospective study. Also, lack of data with regard to the molecular phenotype of the tumor (such as KRAS, microsatellite instability (MSI), or BRAF) was a significant limitation of our study which precluded further analysis of relationship between tumor location and molecular phenotyping. Another limitation was lack of assessment of effect of tumor location on response to targeted therapy as anti-VEGF (Vascular Endothelial Growth Factor) and anti-EGFR (Epidermal Growth Factor Receptor) agents in stage IV colon cancer patients as our institute provides treatment for uninsured population of Egyptians for free and these agents are very expensive and were not funded by the government during the period our patients received their treatment (1/2008 - 12/2018) as we are in a developing country.

6. Conclusion

We found that right and left-sided colon cancers are different from each other in terms of age at diagnosis, presenting symptoms, aim of surgery, stage at diagnosis, response to first-line chemotherapy, and causes of death. Several recent international studies support the findings of our work and nowadays there is a global trend towards considering right and left-sided colon cancer as two distinct disease entities. Further research and multi-institutional studies should be done worldwide for providing more evidence of the impact of colon cancer sidedness with special emphasis on molecular phenotype and effect of targeted therapy and immunotherapy on survival outcomes.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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