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Clinicoepidemiological Study and Survival Analysis of Right versus Left Sided Colon Cancer Patients

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ABSTRACT

Background: Recently, there is a great attention, about the clinicopathological differences between right and left colon cancer, and how much these differences will affect the outcomes of colon cancer patients. Many epidemiological studies have demonstrated, that tumor at the right and left colon, respectively, occur with different incidence in diverse region of the world. Differences in clinical presentation, patient's demographics, and tumor biology between right- and left- sided colon cancers have long been reported in the literatures.

Methods: The current study was conducted in Clinical Oncology and Nuclear medicine department, Ain Shams University Hospitals, during the period from January 2011 to December 2015, data on all patients histologically confirmed with colon cancer, were evaluated right-and left-sided cancers were compared with regard to epidemiological, clinical and pathological parameters as well as survival data.

Results: The study showed that, there was 129 patients, 70(54.2%) patients had left-sided colon cancers and 59(45.7%) patients had right-sided colon cancers, most of the cases were aged above 50 years 61.2%. Histopathological type was mainly adenocarcinoma 72.09%, moderately differentiated 79.8%, the mucinous carcinoma was more in right sided colon 56.25%. Comparison of progression free survival in stage IV, showed higher progression rate (58.3%) in right sided patients, than left sided patients (41.6%), this difference was not statistically significant. We also found that patients with right-sided colon cancer had a statistically significantly worse overall survival (OS) P value=0.019, than patients with left-sided colon cancer. We demonstrated that the differences in OS were significant only in patients with stage IV colon cancer.

Conclusion: In conclusion, our results support evidence that there are differences in the biology and outcomes for right- and left-sided colon cancers. Significantly better survival is seen for metastatic colon cancer with a left-sided, and this was confirmed by multivariate analysis. This might have been due to several environmental and lifestyle factors, which contributed to this anatomical shift. The differences in genetic and molecular pathologic profiles in each side of the colon were observed. Stratification based on the primary site should be considered in the future for trials assessing survival for colon cancer.

Keywords: Right colon cancer; Left colon cancer; Differences; Outcome.

INTRODUCTION

Colorectal cancer (CRC) is the third most common tumor in men and the second in women, accounting for 10% of all tumor types worldwide, CRC is the fourth most common cancer-related cause of death in the world**.** In Egypt (CRC) is approximately the 8th most common cancer, and according to the estimated results of national population based registry program the estimated number for colon and rectal cancer cases in 2015 is 3.055 and 922 respectively **[(1,2)]**.

The left and right colon have different embryologic origins, the left colon being from the foregut and the right from the midgut, and different blood supplies, Therefore, left- and right-sided colon cancers are distinct genetic entities . Background differences exist between the proximal and distal colon in terms of developmental origin, exposure to patterning genes, environmental mutagens, and gut flora, little is known on how these differences may affect mechanisms of tumorigenesis side specific therapy response or prognosis**[(3,4)]**.

The data show that patients whose primary tumors originate on the left side of the colon (the descending colon, sigmoid colon, and rectum) survive significantly longer than those whose tumors originate on the right side (the cecum and ascending colon), Even in KRAS-Mutated Tumors, Left-Sided Tumors Are Associated With Improved Survival **.** Several recent studies have reported that the location of CRCs is associated with response to anti- epidermal growth factor receptor (EGFR) antibody. All these studies found that left-sided CRCs are associated with more favorable responses and prognosis than are right-sided. However, the mechanism(s) for this phenomenon has not been identified **[(5,6)]**.

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Venook et al. recently investigated the potential effect of primary tumor location on the clinical efficacy of patients treated on CALGB/SWOG 80405, they determined that 68% of the primary tumors came from the left side of the colon or rectum and 27% of the tumors came from the right side. There was an improvement in overall survival (OS) for patients with left-sided tumors compared with right-sided tumors (33.3 vs. 19.4 months, respectively), which was highly significant ($p < .0001$). For patients treated with bevacizumab, the improvement in OS was maintained in patients with left-sided tumors compared with right-sided tumors, albeit still higher for left-sided primary tumors (31.4 vs. 24.2 months, respectively)[7].

PATIENTS AND METHODS

The current study was conducted in Clinical Oncology and Nuclear medicine department, Ain Shams University Hospitals during the period from January 2011 to December 2015.

Study Design

This was a retrospective clinicoepidemological study. During a 5 year period data on all patients histologically confirmed with colon cancer, were evaluated, right-and left-sided cancers were compared with regard to epidemiological, clinical and pathological parameters as well as survival data.

Patients

The patients were divided according to the anatomical site into:

1- Right colon cancer include: (Cecum, hepatic flexure and transverse colon).

2- Left colon cancer include: (Splenic flexure, descending and sigmoid colon).

Inclusion Criteria

- Aged ≥18 years
- Patients with histological confirmed colon cancers
- All patients recruited between January 1/ 2011 and December 31/ 2015.

Exclusion Criteria

- Carcinoma of the rectum and appendix.
- Synchronous colon cancer.
- Familial adenomatous polyposis colon cancer.
- Age less than 18 years old.

Data collection

We expend nearly one month in data collection in June 2016, a retrospective chart review of 129 patients' medical records was used to collect patient characteristics, including demographic and clinicopathological data, including anatomical site, age, sex, performance status (ECOG), body mass index, comorbidities (diabetes mellitus, hypertension, ischemic heart disease, hepatitis C & B virus), tumor characteristics, presenting symptoms, site and number of metastasis, tumor markers CEA and CA19-9, response to the chemotherapy, toxicity, and survival rates.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

Statistical Methods

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Probability (P-value)
  - P-value <0.05 was considered significant.
  - P-value <0.001 was considered as highly significant.
  - P-value >0.05 was considered not significant.
- Survival (Overall/ Progress free) was tested using Kaplan Meier test.
- Comparing survival among stages of cancer colon was tested using Log rank test.
- Suitable figure for data presentation was used (survival chart) to illustrate over-all survival and event free survival.

RESULTS

A total of 129 colon cancer patients including 80 (62.01%) females and 49 (37.9%) males were enrolled in this retrospective cohort study. The characteristics of the patients enrolled in this study are present in table1**.** The majority of cancers were detected in the left side 70(54.2%) versus 59(45.7%). Most of patients was aged above than or equal 50 years 61.2%. Comorbidity mainly not detected in 62.7% of patients. In this study histopathological type was mainly adenocarcinoma 72.09%, and moderately differentiated 79.8%. Regarding lymphovascular and perineural invasion were mainly unknown, and only present in 9.3% in right side and 3.8% in left side.

Table (1): Clinical characteristics of patients with colon cancer

Variables	Subgroups	N (%)
Location	Right colon	59 (45.7)
	Left colon	70 (54.2)
Gender	Male	49 (37.9)
	female	80 (62)
Age (years)	<50	50 (38.8)
	≥50	79 (61.2)
Comorbidity	Absent	81 (62.7)
	present	48 (37.2)
Pathological type	Adenocarcinoma	93 (72.09)
	Mucinous	32 (24.8)
	Signet ring	4 (3.1)
Tumor grade (differentiation)	Poor	11 (8.5)
	Moderate	103 (79.8)
	Well	10 (7.75)
	unassesable	5 (3.8)
Pathological tumor stage	I&II	41 (31.7)
	III	51 (39.5)
	IV	37 (28.6)
Perineural invasion	Absent	95 (73.6)
	Present	5 (3.8)
	unknown	29 (22.4)
Lymphovascular invasion	Absent	79 (61)
	Present	12 (9.3)
	unknown	38 (29.4)

In table 2 the clinicopathological features of the study population according to location status are presented. We did not observe any significant difference between the right- and the left-sided colon cancers with respect to gender, but most of females patients was distributed in left side colon 58.8%.

The mean age of the patients was 51.73 years for right side colon cancer patients and 51.61 years for the left side colon cancer patients. We did not observe any significant difference between the right- and the left-sided cancers with respect to age group. Most of the cases were aged above 50 years 79(61.2%) and only 50(38.8%) cases were aged under 50 years. Histologically, the majority of all colon cancer were adenocarcinoma 55(59.1%) within left side versus 38(40.8%) within right side.

Mucinous adenocarcinoma was more in the right side 18(56.25%) versus 14 (43.7%) but not statistically significant. We observed most of lymphovascular invasion was in the right side 66.6% but not significant. Comorbidity were more common in patients with right colon cancer 52%versus 47% in left side colon but not statistically significant.

Comparison of metastasis according to the anatomical site there was no statistical significant.

Table (2): Clinicopathological features of the study population according to location status

Variables	Total N	Right N (%)	Left, N (%)	Chi-square	P value
Mean age (years)		51.73± 13.268	51.61± 13.587	0.048	0.962
Gender				1.708	0.191
Female	80	33 (41.3)	47 (58.8)		
male	49	26(53.5)	23 (46.9)		
Pathological type				3.612	0.162
Adenocarcinoma	93	38 (40.8)	55 (59.1)		
Mucinous	32	18 (56.2)	14 (43.7)		
Signet ring	4	3 (75)	1 (25)		
Differentiation				0.039	0.84
Well	10	6 (60)	4 (40)		
Moderately	103	44 (42.7)	59 (57.3)		
poorly	11	6 (54.5)	5 (45.5)		
TNM staging				0.135	0.935
I&II	41	19 (46.3)	22 (53.6)		
III	51	24 (47)	27 (52.9)		
IV	37	16 (43)	21 (56.7)		
Lymphovascular invasion				1.85	0.173
Present	12				
Absent	79	8 (66.6)	4(33.3)		
unknown	38	36 (45.5)	43(54.4)		
Perineural invasion				0.104	1.0
Present	5				
Absent	95	2 (40)	3 (60)		
unknown	29	45 (47.3)	50 (52.6)		
Comorbidity				1.24	0.265
Present	48	25 (52)	23 (47.9)		
absent	81	34 (42)	47 (58)		
Age of diagnosis				0.002	0.962
<50	50	23 (46)	27 (54)		
≥50	79	36 (45.5)	43 (54.4)		
Metastasis				0.083	0.774
No	63	28 (44.4)	35 (55.5)		
yes	66	31 (44.9)	35 (53.0)		

Serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9). Comparison at presentation between right and left colon cancer according to the stage presented in table 3, we observed difference in stage III, there was an increase in the mean of both tumor markers in the right sided versus left sided colon cancer (Right mean CEA= 69.97, CA19-9=1844.99, versus left mean CEA =11.86, CA19-9=31.99) these differences did not reach statistical significant.

Table (3): Comparison of serum CEA and CA19-9 according to the location status divided by stages

Variables	Right	Left	T test	P value
Stage I&II				
Mean CEA	8.99±18.638	12.15±24.747	-0.428	0.674
Mean CA19-9	46.89±111.14	12.25±14.319	1.27	0.212
Stage III				
Mean CEA	96.97±302.947	11.86±29.747	0.975	0.335
MeanCA19-9	1844.99±7985.99	31.99±79.648	1.092	0.282
Stage IV				
Mean CEA	90.02±279.938	279.39±628.735	-1.11	0.277
MeanCA19-9	512.50±1173.170	478.80±1705.202	0.063	0.949

Abdominal pain was observed as the most common presenting symptoms followed by bleeding per rectum and intestinal obstruction, the latest one was more prominent in the left side (61.5%). See table 4.

Table (4): Comparison of main presenting symptoms according to location status

Symptoms	Total N	Right N (%)	Left N (%)	Chi-square	P value
Bleeding per rectum	34	16(47.05)	18(52.9)	2.222	0.744
Abdominal pain	48	23(47.9)	25(52.0)		
Intestinal obstruction	26	10(38.4)	16(61.5)		
Weight loss	1	0	1		
Change bowel habit	12	7(58.3)	5(41.6)		

In this study comparison of relapse rate in stage I,II &III after adjuvant chemotherapy presented in table 5 & 6, we found in stage I & II more relapse in left side (62%), while relapse rate in stage III was more in the right side, both was not statistically significant.

Table (5): Comparison of relapse rate in stage I&II according to location status after adjuvant chemotherapy

Disease relapse	Total N	Right N (%)	Left N (%)	Chi-square	P value
Relapsed				0.090	0.76
Yes	8	3(37.5)	5(62.5)		
No	33	16(48.5)	17 (51.5)		

Table (6): Comparison of relapse rate in stage III according to location status after adjuvant chemotherapy

Disease relapse	Total N	Right N (%)	Left N (%)	Chi-square	P value
Relapsed				0.05	0.82
Yes	15	9(60)	6 (40)		
No	36	15(41.6)	21(58.33)		

Comparison of response rate in stage IV after 1st line chemotherapy showed no difference between right and left colon cancer. See table (7).

Table (7): Comparison of response rate in stage IV according to location status after 1st line chemotherapy

Disease response	Total N	Right N (%)	Left N (%)	Chi-square	P value
Complete response	5	3(60)	2 (40)	0.765	0.956
Partial response	5	2(40)	3 (60)		
Stationary disease	9	4 (44.4)	5(55.5)		
Progressive disease	12	5 (41.6)	7(58.3)		

Comparison of response rates after 2nd line chemotherapy, showed worse response in right side colon cancer patients, not statistically significant (table 8).

Table (8): Comparison of response rate in stage IV according to location status after 2nd line chemotherapy

Disease response	Total N	Right N (%)	Left N(%)	Chi-square	P value
Complete Response	3	0 (0)	3 (100)	3.02	0.269
Partial response	2	0 (0)	2 (100)		
Stationary Disease	6	1 (16.6)	5 (83.3)		
Progressive disease	9	5 (55.5)	4 (44.4)		

Comparison of response rate in all stages according to location status after finishing all treatment
Comparison of response rate after finishing all treatment lines, we found worse response in the right sided colon than left sided colon as showed in figure (1).

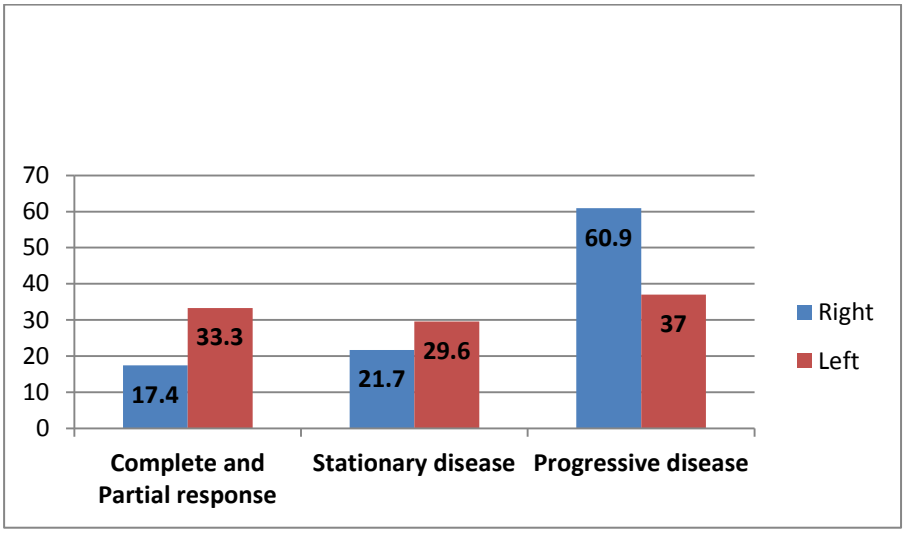

Figure (1): Overall response differences for all patients.

The most common hematological toxicity was neutropenia 81.5% and the most common non hematological toxicity was diarrhea followed by peripheral neuropathy. There is no significant difference between right and left colon, see table (9).

Table (9): Comparison of toxicity grade 2-3 after chemotherapy according to tumor location.

Toxicity	Total N	Right N (%)	Left N (%)	Chi-square	P value
Hematological				0.024	0.877
Yes	27	11(40.7)	16(59.2)		
No	73	31(42.5)	42(57.5)		
Non hematological				0.458	0.498
Yes	35	14 (40)	21 (60)		
No	55	26 (47.2)	29 (52.7)		

Survival analysis by tumor location and stage
Disease and progression free survival

In this study, comparison of disease free survival in stage I&II, we found in the right side only 3(15.8%) patients progressed from 19 patients, and in the left side only 4(18%) patients progressed from 22 patients. Hence there was no significant difference in disease free survival according to tumor location, See table (10) and figure (2).

Table (10): Comparison of disease free survival in stage I &II according to tumor location

Anatomical site	Total N	N of Events	Censored	
			N	Percent
Right	19	3	16	84.2%
Left	22	4	18	81.8%
Overall	41	7	34	82.9%
Overall Comparisons				
Log Rank (Mantel-Cox)	**Chi-Square**		**df**	**Sig.**
	0.040		1	0.842

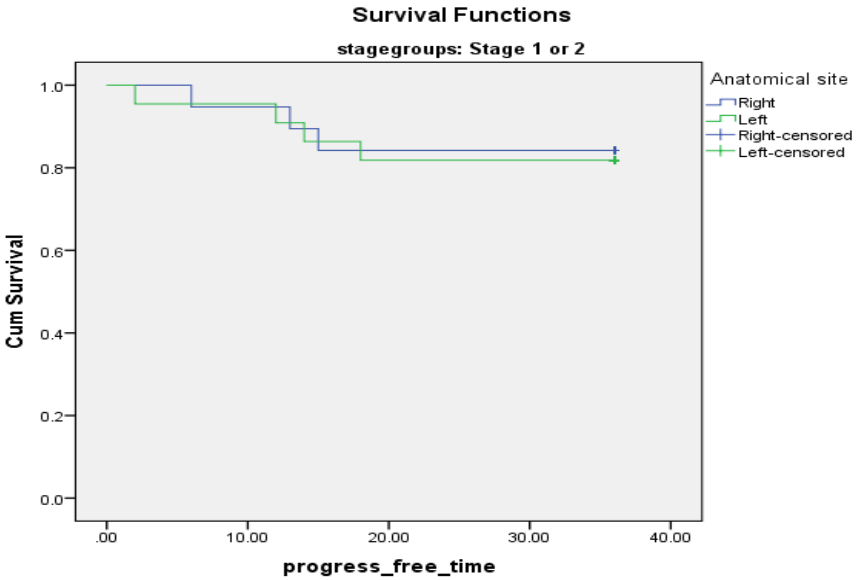

Figure (2): Kaplan-Meier curves of five-year disease-free survival rate of patients with right and left-sided colon cancer stage I & II. There was no significant difference between right- and left-sided disease.

Comparison of disease free survival in stage III, we found in the right side only 8(33.3%) patients progressed from 24 patients, and in the left side only 7(26%) patients progressed from 27 patients. Hence there was no significant difference in disease free survival according to tumor location, See table (11) and figure (3).

Table (11): Comparison of Disease free survival in stage III according to tumor location

Anatomical site	**Total N**	**N of Events**	**Censored**	
			N	**Percent**
Right	24	8	16	66.7%
Left	27	7	20	74.1%
Overall	51	15	36	70.6%
Overall Comparisons				
Log Rank (Mantel-Cox)	**Chi-Square**		**df**	**Sig.**
	0.300		1	0.584

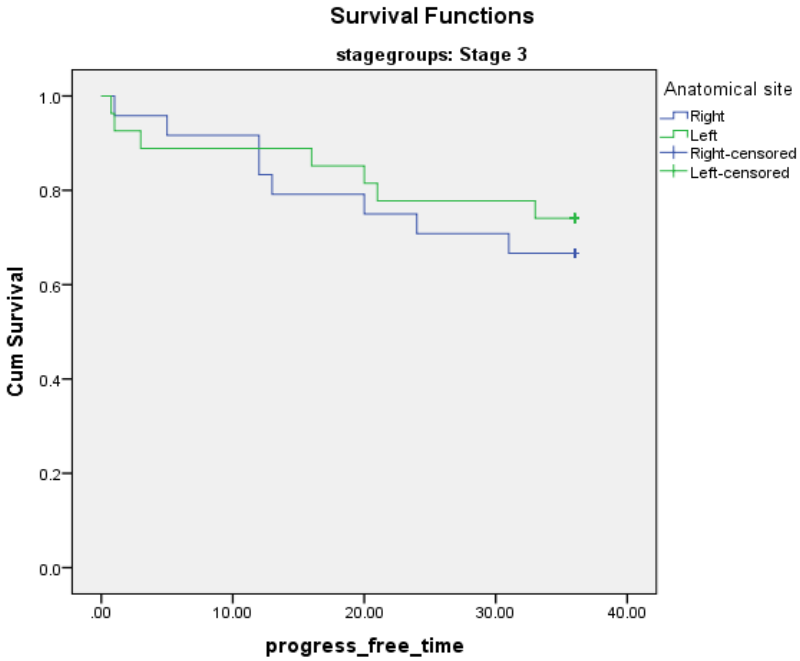

Figure (3): Kaplan-Meier curves of five-year disease-free survival rate of patients with right and left-sided colon cancer stage III. There was no significant difference between right- and left-sided disease.

Comparison of progression free survival in stage IV, we found in the right side only 7(43.7%) patients progressed from 16 patients, and in the left side only 5(23.8%) patients progressed from 21 patients. There was no statistical significant difference in progression free survival according to tumor location, See table (12) and figure (4).

Table (12): Comparison of progression free survival in stage IV according to tumor location

Anatomical site	Total N	N of Events	Censored	
			N	Percent
Right	16	7	9	56.3%
Left	21	5	16	76.2%
Overall	37	12	25	67.6%
Overall Comparisons				
Log Rank (Mantel-Cox)	**Chi-Square**		**df**	**Sig.**
	0.488		1	0.222

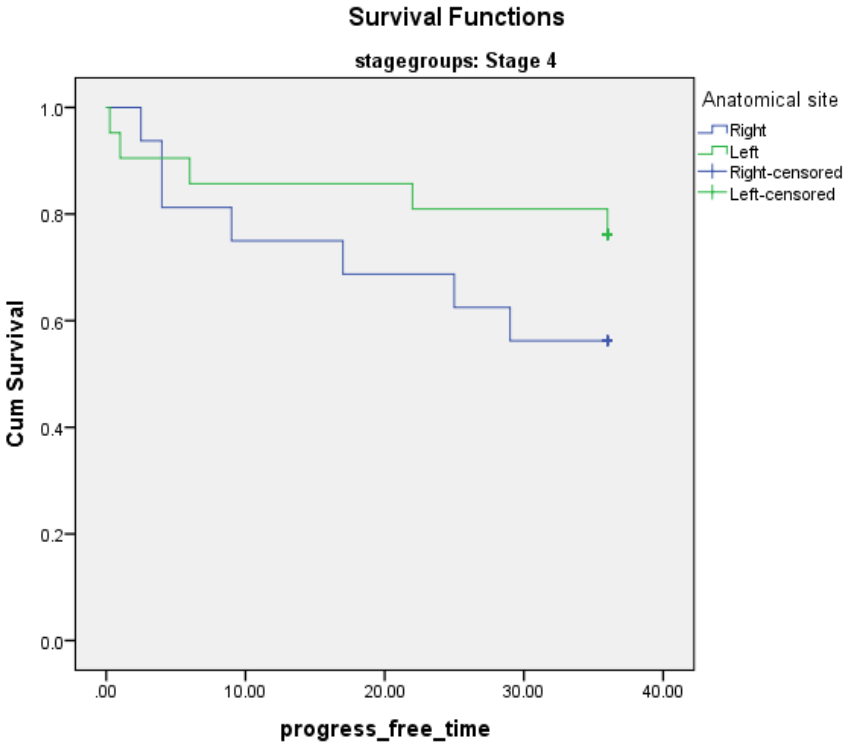

Figure (4): Kaplan-Meier curves of five-year progression free survival rate of patients with right and left-sided colon cancer stage IV. There was no significant difference between right- and left-sided disease.

Comparison of disease free survival in all patients according to tumor location

Comparison of disease free survival in all patients, we found that the right side only 11(25.5%) patients relapsed from 43 patients, and in the left side only 11(22.4%) patients relapsed from 49 patients. Although the relapse rate was higher in the right sided colon but there was no statistical significant difference (table 13 and figure 5).

Table (13): Comparison of disease free survival in all patients according to tumor location

Anatomical site	Total N	N of Events	Censored	
			N	Percent
Right	43	11	32	74.4%
Left	49	11	38	77.6%
Overall	92	22	70	76.1%
Overall Comparisons				
Log Rank (Mantel-Cox)	**Chi-Square**		**df**	**P value**
	0.111		1	0.739

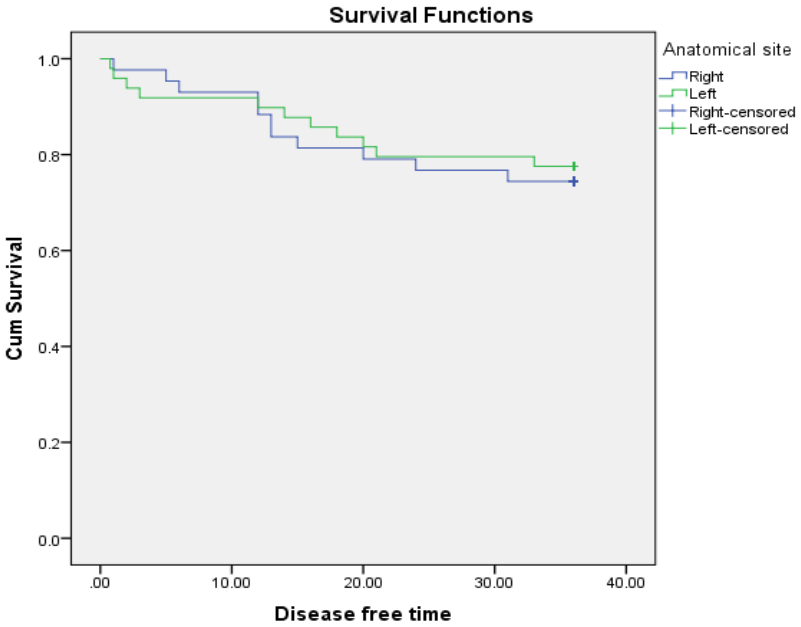

Figure (5): Kaplan-Meier curves of five-year disease-free survival rate of patients with right and left-sided colon cancer in all patients. There was no significant difference between right- and left-sided disease.

Comparison of progression free survival rates in all stages according to the tumor location

Comparison of progression free survival rates in all colon cancer stages, we found in the right side 16(27.1%) patients progressed from 59 patients, and in the left side 15(21.4%) patients progressed from 70 patients. As we show the progression rate was higher in the right sided colon but there was no statistical significant difference(table 14 and figure 6).

Table (14): Comparison of progression free survival in all stages according to tumor location

Anatomical site	Total N	N of Events	Censored	
			N	Percent
Right	59	16	43	72.9%
Left	70	15	55	78.6%
Overall	129	31	98	76.0%
Overall Comparisons				
Log Rank (Mantel-Cox)	**Chi-Square**		**df**	**P value**
	0.488		1	0.485

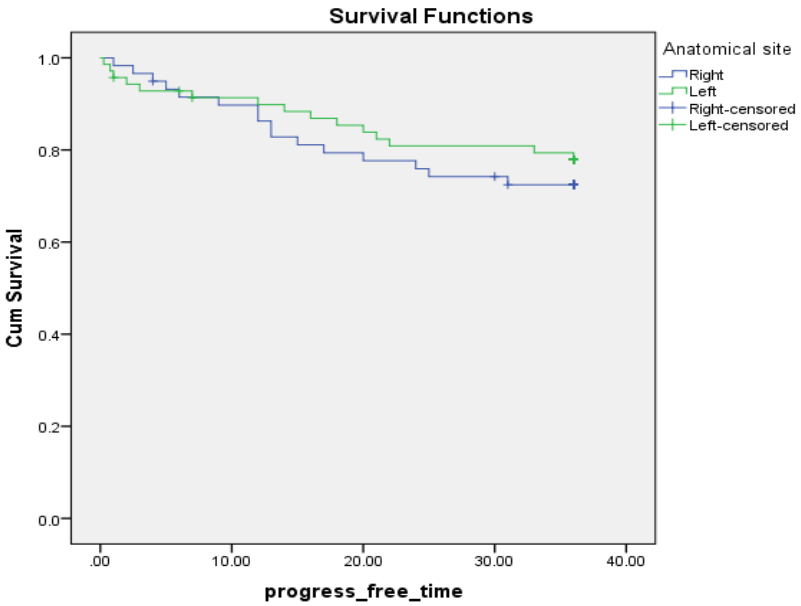

Figure (6): Kaplan-Meier curves of five-year progression free survival rate of patients with right and left-sided colon cancer all stages. There was no significant difference between right- and left-sided disease.

Overall survival analysis

In the study comparison of overall survival, in stage I&II according to tumor location , in the right side there was 1(5.5%) patient recorded died in hospital from 18 patients, and in the left side there was 2(10.5%) recorded died in hospital from 19 patients. There was some patients lost follow up, so were not included in our statistical results. There was no significant difference in overall survival according to tumor location. See table (15) and figure (7).

Table (15): Comparison of overall survival in stage I &II according to tumor location

Anatomical site	Total N	N of Events	Censored	
			N	Percent
Right	18	1	17	94.4%
Left	19	2	17	89.5%
Overall	37	3	34	91.9%
Overall Comparisons				
Log Rank (Mantel-Cox)	**Chi-Square**		**df**	**Sig.**
	0.298		1	0.585

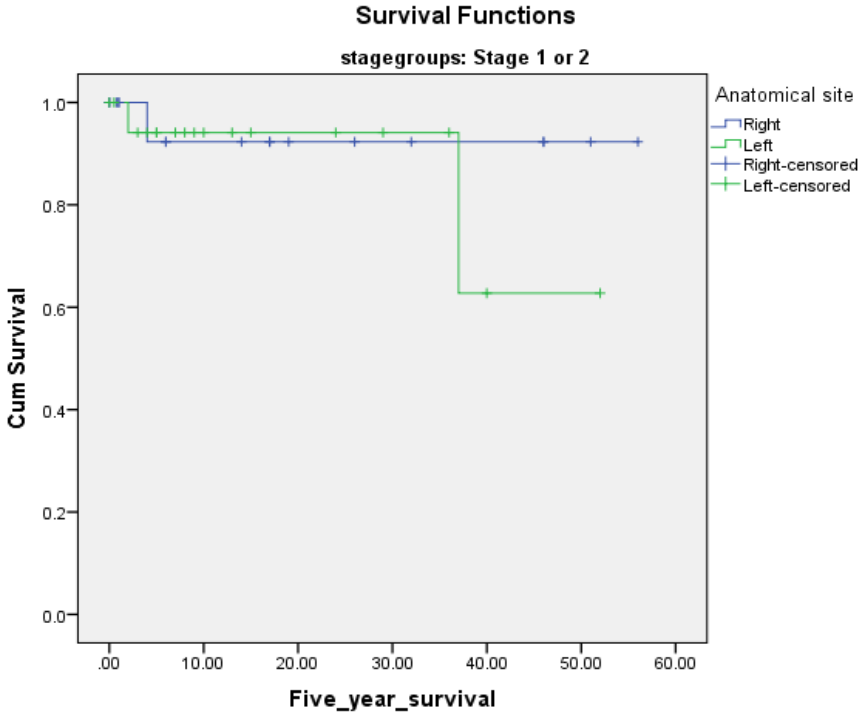

Figure (7): Kaplan-Meier curves of five-year overall survival rate of patients with right and left-sided colon cancer stage I&II. There was no significant difference between right- and left-sided disease.

Comparison of overall survival, in stage III according to tumor location, in the right side there was 2(8.33%) patient recorded died in hospital from 24 patients, and in the left side there was 3(11.1%) recorded died in hospital from 27 patients. There was some patients lost follow up, so were not included in our statistical results. There was no significant difference in overall survival according to tumor location. See table (16) and figure (8).

Table (16): Comparison of overall survival in stage III according to tumor location

Anatomical site	Total N	N of Events	Censored	
			N	Percent
Right	24	2	22	91.7%
Left	27	3	24	88.9%
Overall	51	5	46	90.2%
Overall Comparisons				
Log Rank (Mantel-Cox)	**Chi-Square**		**df**	**Sig.**
	0.000		1	0.994

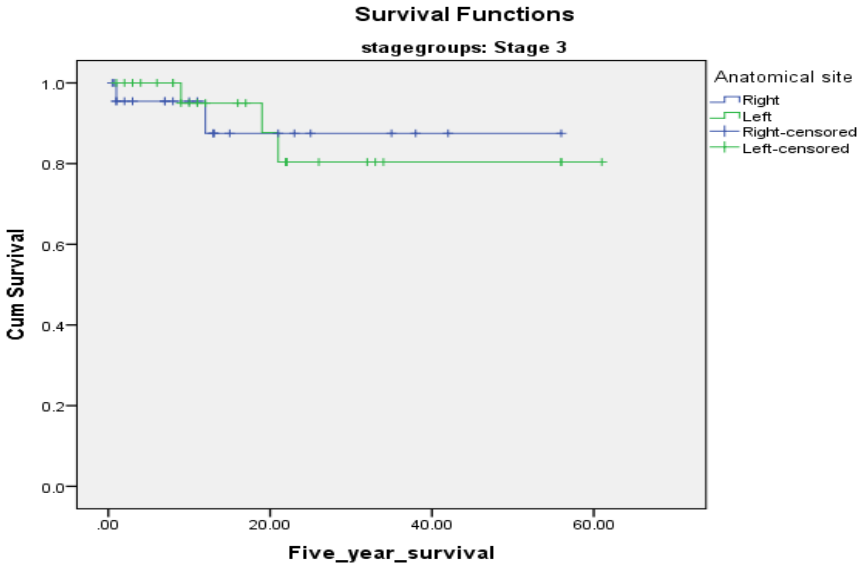

Figure (8): Kaplan-Meier curves of five-year overall survival rate of patients with right and left-sided colon cancer stage III. There was no significant difference between right- and left-sided disease.

Comparison of overall survival, in stage IV according to tumor location, in the right side there was 6(37.5%) patient recorded died in hospital from 16 patients, and in the left side there was 2(9.5%) recorded died in hospital from 21 patients. There was some patients lost follow up, so were not included in our statistical results. There was significant difference in overall survival according to tumor location in stage IV, P value=0.019, as we notice that right side colon cancer patients had worse overall survival than the left side colon cancer patients. See table (17) and figure (9).

Table (17): Comparison of overall survival in stage IV according to tumor location

Anatomical site	**Total N**	**N of Events**	**Censored**	
			N	**Percent**
Right	16	6	10	62.5%
Left	21	2	19	90.5%
Overall	37	8	29	78.4%
Overall Comparisons				
Log Rank (Mantel-Cox)	**Chi-Square**		**df**	**Sig.**
	5.478		1	0.019

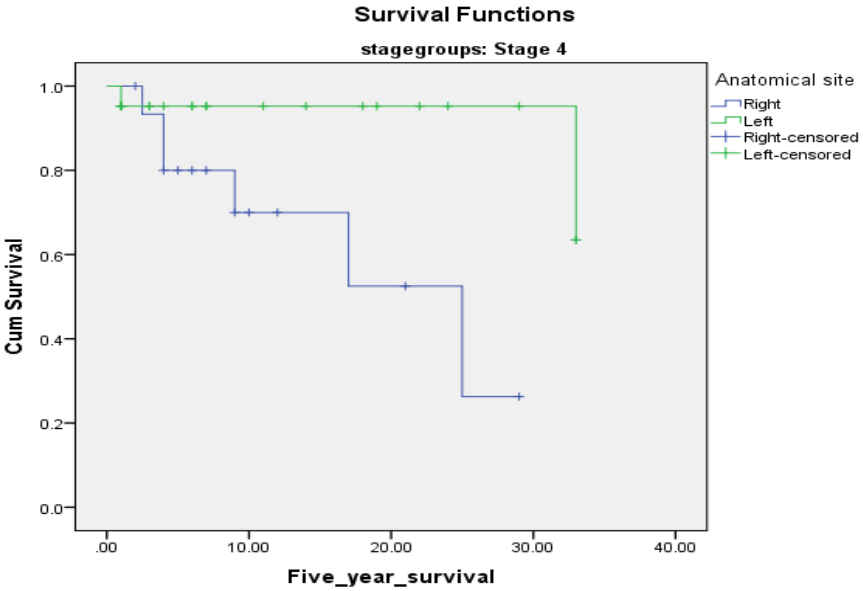

Figure (9): Kaplan-Meier curves of five-year overall survival rate of patients with right and left-sided colon cancer stage IV. There was significant difference between right- and left-sided disease *P* = 0.019.

Comparison of Overall Survival for all stages according to the tumor location:
Comparison of overall survival, in all stages according to the tumor location, in the right side there was 9(15.3%) patient recorded died in hospital from 59 patients, and in the left side there was 7(10.0%) recorded died in hospital from 70 patients. There was some patients lost follow up, so were not included in our statistical results. As we notice death rate was higher in the right sided colon cancer patients, but there was no statistical significant difference(table 18 and figure 10).

Table (18): Comparison of overall survival in all stages according to tumor location

Anatomical site	Total N	N of Events	Censored	
			N	Percent
Right	59	9	50	84.7%
Left	70	7	63	90.0%
Overall	129	16	113	87.6%
Overall Comparisons				
g Rank	**Chi-Square**		**df**	**Sig.**
antel-Cox)	0.002		1	0.968

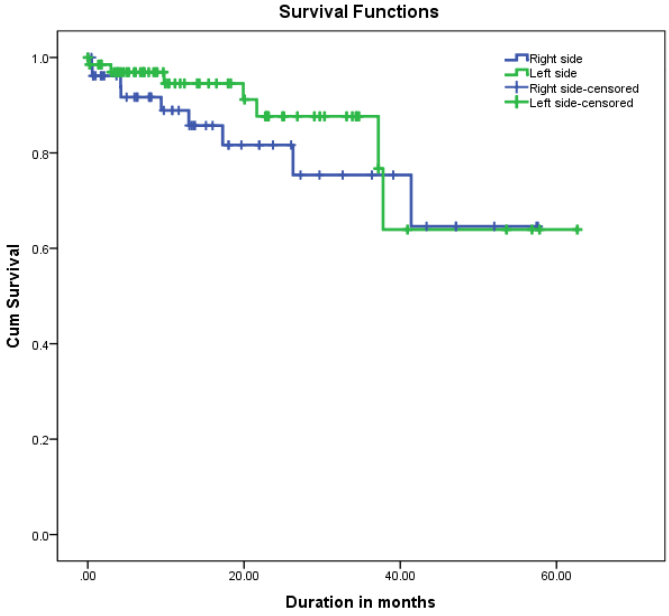

Figure (10): Kaplan-Meier curves of five-year overall survival rates of patients with right and left-sided colon cancer all stages. There was no significant difference between right- and left-sided diseases.

DISCUSSION

In recent years, there is a great attention, about the clinicopathological differences between right and left colon cancer, and how much these differences will affect the outcomes of colon cancer patients.

Many epidemiological studies have demonstrated, that tumor at the right and left colon, respectively, occur with different incidence in diverse region of the world. Differences in clinical presentation, patient's demographics, and tumor biology between right- and left- sided colon cancers have long been reported in the literatures.

The large intestine can be differentiated to proximal and distal part in relation to the splenic flexure because the two parts have two different embryologic origins, with differing physiological and biological characteristics [(8)].

Differences in gene expression between normal mucosa as well as between adenocarcinomas of the caecum and sigmoid or rectosigmoid exist and should be taken into account when examining new targeted therapeutic regimens [(9)].

In the present study, there was 129 patients, 70(54.2%) patients had left-sided colon cancers and 59(45.7%) patients had right-sided colon cancers. Most of the patients were female patients 80(62%), there was no significant predilection to the right side colon in female patients. In the present study, most of the cases were aged above 50 years 79(61.2%). There was no statistical

significant differences, between right versus left-sided colon cancer patients according to age group distribution.

Also in this study, the histopathological type was mainly adenocarcinoma 72.09% followed by mucinous carcinoma 24.8%. There was right side predilection for mucinous carcinoma 56.25%, but not statistically significant. Regarding differentiation, most of the cases was moderately differentiated 103 (79.8%), without significant difference according to tumor location.

In contrast, a study was conducted by ***Hansen & Jess*** [10], revealed that, right-sided colon cancers mostly occur at an older age and in the female gender, present with advanced stages, and have increased tumor sizes with poorly differentiated features, poorer prognosis, and a larger amount of positive lymph nodes.

On the other hand, a study done by ***Sava et al.*** [11], compared cancer localizations with reference to age, they found young patients tended to have right-sided colon tumors, but those in patients >40 years of age were frequently localized at the left colon and rectum.

As a retrospectively study done by ***Ishihara et al.*** [12], on Stage IV colon cancer treated from January 1997 to December 2007 (n = 2208) revealed that, right-sided colon cancer was associated with older age, female sex, larger tumor size, poorly differentiated adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma.

In this study, we also found increase in the means of both serum CEA&CA19.9 at presentation in stage III right sided colon cancer versus left sided colon cancer (Right mean: CEA= 69.97, CA19.9=1844.99, while left mean: CEA =11.86, CA19.9=31.99) these results was not statistically significant.

Similar trend was observed by ***Huang et al.*** [13], who revealed a higher postoperative serum CEA levels in patients with right-sided colon cancers than in those with left-sided colon cancers.

Our study found that, abdominal pain was the most presenting symptoms, followed by bleeding per rectum and intestinal obstruction, intestinal obstruction was more in the left sided colon cancer 61.5%.

A study done by ***Yamauch et al.*** [14], found that, right-sided colon cancers tend to be bulky and causing anemia. While, left-sided colon cancers tend to be, constricting lesions and causing obstruction.

Another prospective German study (n=17641), carried out by ***Benedix et al.*** [15], found that the right sided colon cancer patients typically present clinically at more advanced stage with symptoms of abdominal pain, weight loss and anemia, while left colon cancer patients came with rectal bleeding and change in bowel habits.

The chemotherapeutic regimen which were used are (FOLFOX, FOLFIRI, XELOX, XELIRI and monotherapy based on capecitabine), no target therapy were used, because it was not available. The most common hematological toxicity was neutropenia 81.5%, and the most common non hematological toxicity was diarrhea followed by peripheral neuropathy. There was no significant difference between right and left colon cancer.

A randomized study done by ***Tournigand et al.*** [16], who found two sequential regimens incorporating oxaliplatin and irinotecan in the treatment of advanced colorectal cancer, showed that Gastrointestinal toxicities, were more frequent with FOLFIRI while hematologic and neurotoxicity was more frequent with FOLFOX.

A recent retrospective survey of 158 consecutive metastatic colon cancer patients, done by ***Chen et al.*** [17], demonstrated that, the patients who experienced a higher grade of neutropenia with FOLFOX chemotherapy have longer survival time than patients who have lower grade of neutropenia or absent.

Our results also found that relapse rate after adjuvant chemotherapy in stage I&II was more in the left sided colon cancer (62%), while relapse rate in stage III was more in the right sided colon cancer 60%. Both differences were not statistically significant.

A similar results in a retrospective study done by ***Moritani et al.*** [18], enrolled 820 patients with stage I/II/III colon cancer. Concluded that right-sided colon cancer at stage I has a significantly better prognosis. While right-sided colon cancer at stage II&III carried a significant risk factor for recurrence.

We found, that response rate in stage IV colon cancer patients after 2nd line chemotherapy, revealed worse response in right sided colon cancer, but did not reached statistical significant. Also when we compare the response rates for all stages, after finishing all treatments lines, we found a worse response in right sided colon patients.

On the other hand, a study done by ***Wang et al.*** [19], reported that, there was no difference between right and left sided mCRC in response rate after chemotherapy alone, while the combination of cetuximab with chemotherapy had a tendency to improve the response rate in

the left sided colon cancer patients compared with right sided colon cancer patients.

In this study, there was no significant difference in disease free survival in stage I,II&III, according to the tumor location. While comparing progression free survival between right and left sided colon cancer in stage IV, we found higher progression rate (58.3%) in right sided patients, than left sided patients (41.6%). This difference was not statistically significant.

A (SEER) database (2004–2012), in stage I, II&III colon cancer provided by ***Warschkow et al.*** [(20)], showed evidence that the prognosis of patients with right-sided colon cancer is better compared to left-sided colon cancer mostly due to a better survival in stage I and stage II patients.

In this study when we compare disease free and progression free survival rates in all stages according to the tumor location, we found a higher relapse rate in the right sided colon (25.6%) versus (22.4%) in the left sided colon, we also found a higher progression rate in the right sided colon (27.1%) versus (21.4%) in the left sided colon, all was not statistically significant.

Also, a Taiwanese study, done by ***Huang et al.*** [(13)], evaluated the clinicopathologic features and outcomes of Taiwanese patients with right-sided versus left-sided colon cancer according to various cancer stages demonstrated poorer OS and cancer-specific survival (CSS) in patients with right-sided versus those with the left-sided colon cancers, but significant differences were noted only in stage III patients.

In this study we found that patients with right-sided colon cancer had a statistically significantly worse overall survival (OS) **P value=0.019**, than patients with left-sided colon cancer. We demonstrated that the differences in OS were significant only in patients with **stage IV** colon cancer.

In this study, when we compare the overall survival rate for all patients stages, we found worse right sided overall survival rate (84.7%) than the left sided (90.0%), but the results did not reach the significant.

A recent trial (PROVETTA; NCT01363739) done by ***Loupakis et al.*** [(21)], enrolled 455 mCRC patients ,evaluated the association between tumor location and survival parameters in patients with previously untreated mCRC receiving first-line chemotherapy ± bevacizumab, found association of right-sided cancers with chemoresistance, but the response rates and PFS were statistically significantly higher in patients with left-sided tumors, data suggested only patients with left-side colon or rectal cancer could get survival benefit from the addition of bevacizumab to first-line chemotherapy**.**

A recent data presented in ***ASCO*** [(22)], revealed that KRAS wild type mCRC patients with primary tumor in left-sided colon have better clinical outcome when treated with anti-EGFR-based therapy. In metastatic disease, primary right-sided KRAS wild type carcinoma is associated with short PFS and OS across all anti-EGFR-based treatment lines.

Limitation of the study

There are several limitations to the present study. First, the present study was a retrospective study of patients at only a single-institution. Second, for a retrospective study, the sample size was relatively small due to incomplete files, patients lost follow up and files lose. Third, we did not examine the RAS, BRAF, and MSI statuses of the colon cancer patients; hence, any relevant information regarding the correlation between molecular biological status and the prognoses of patients with colon cancer is lacking. No target therapy was given for stage IV patients, only chemotherapy, hence any comparison with western studies which mainly demonstrated its' differences due to target therapy, will not be fair.

CONCLUSION

In conclusion, our results support evidence that there are differences in the biology and outcomes for right- and left-sided colon cancers. Significantly better survival is seen for metastatic colon cancer with a left-sided, and this was confirmed by multivariate analysis. This might have been due to several environmental and lifestyle factors, which contributed to this anatomical shift. The differences in genetic and molecular pathologic profiles in each side of the colon, stratification based on site of primary should be considered in the future for trials assessing survival for colon cancer.

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