The Effect of Primary Tumor Site on Survival in Metastatic Colorectal Cancer Patients and their Relation to KRAS and Biological Therapy

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Abstract:

Background: Depending on whether the primary tumor site is in the right or left colon, previous investigations have indicated differences in biology and prognosis for colorectal cancer. Further divisions into right, left and rectum or even exact primary site have also been analyzed. Possible differences in response to biological agents have also been reported based on primary tumor site.

Methods: We performed a retrospective analysis on 165 metastatic colorectal cancer (mCRC) patients treated in clinical oncology department, Assiut university hospital, Egypt from January 2015 to December 2019. Patients were divided according to their primary site into: right sided colon cancer, left sided colon cancer and rectal cancer. In this study the effect of primary site on survival and their relation to KRAS status and biological therapy were evaluated.

Results: 165 patients were analyzed, mean age was 42 years. Progression free survival (PFS) and overall survival (OS) of right sided tumors were less than survival in left sided tumors and rectum with significant P value for PFS 0.001 and OS 0.01. As for patients who received biological therapy, right sided tumors were associated with decreased OS compared with left sided and rectal tumors with significant P-value; for Panitumumab (P value < 0.001), Cetuximab (P value 0.002), Bevacizumab with wild KRAS (P value 0.3) which was not significant and Bevacizumab with mutant KRAS (P value < 0.001). In right sided wild KRAS tumors, patients who received anti epidermal growth factor receptor (EGFR) therapy had worse OS than vascular endothelial growth factor (VEGF) monoclonal antibody, with OS of anti EGFR was 23 months for panitumumab and 21 months for cetuximab whereas in VEGF monoclonal antibody (Bevacizumab), OS was 30 months. In left sided and rectal wild KRAS tumors, patients who received anti EGFR therapy had better OS than VEGF monoclonal antibody, with OS for left sided and rectal cancer who received panitumumab was 43 and 42 months respectively and for cetuximab 46 and 43 months respectively, whereas for Bevacizumab OS was 35 and 36 months respectively.

Conclusion: Patients with right sided mCRC have worse survival than those with left sided and rectal tumors. In patients with wild type KRAS tumors treatment with anti EGFR therapy showed better survival than bevacizumab in patients with left sided and rectal tumors and was associated with worse survival among those with right sided tumors.

Keywords: Metastatic colorectal cancer, Primary site, Survival, KRAS, Biological therapy

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Introduction:

The molecular diversity of colorectal cancers (CRCs) includes carcinogenic pathways that are partially linked to embryologic origin. The left colon, which is defined anatomically as the distal one-third of the transverse colon through the rectum, comes from the hindgut, whereas the right colon is anatomically described as the cecum through the proximal two-thirds of the transverse colon develops embryonically from the

midgut. There is growing evidence that the genomic patterns of right- and left-sided CRCs differ due to genetic and epigenetic alterations. Right-sided tumors have been found to have a higher incidence of mucinous histologic characteristics, increased microsatellite instability, and greater frequency of KRAS mutations, on the other hand left-sided CRCs have higher expression of c-myc, RAS, and vascular endothelial growth factor (VEGF); amplification of epidermal growth factor receptor (EGFR) and ERBB2 (formerly HER2); and more TP53 gene mutations.[1]

Spread of cancer cells and tumor sidedness weather right or left are both essential factors to establish a proper treatment plan for metastatic colorectal cancer (mCRC) patients. As for tumor sidedness, the efficacy and response of treatment differ from right-sided to left-sided CRC [2, 3]. Previous studies assessed the influence of primary tumor site on survival for mCRC patients. Evidence suggests a prognostic role of primary tumor site among mCRC patients [4,5,6].

Biological therapies (BTs) that target VEGF as bevacizumab and EGFR for example cetuximab have been extensively added to systemic chemotherapy (SC) for the treatment of mCRC patients [7,8].

Previous studies came to conclusion that primary tumor sidedness is related to response to biological therapies among mCRC patients. Right-sided primary tumor site is associated with decreased survival despite the biologic therapy type. Additionally, patients with wild-type RAS right-sided primary tumor site receiving bevacizumab had increase survival compared to cetuximab. On the other hand, patients with left-sided primary tumor location had better survival when treated with cetuximab [7,8].

The degree to which these differences in treatment outcomes affect survival in mCRC patients within the Egyptian population remains unclear. Most previous studies evaluating the mCRC tumor side were post hoc analyses of randomized clinical trials [8], studies using data from surveillance, epidemiology, and end results (SEER), or Western populations [1]. Yet, the pharmacodynamics of different populations may vary depending on the ethnic variety in pharmacological reactions in the realm of anticancer drugs. [8]. This variety may lead to variations in a drug's recommended safe and effective treatment dose or the avoidance of unsuccessful treatment in various populations. [9,10].

Depending on the evidence that there may be differences in outcome based on primary tumor site, we carried out a study using the records of upper Egyptian mCRC patients to determine if there were differences in survival based on right or left primary tumor site. We also analyzed the individuals with rectal primary and left colon CRC individually to rule out a substantial behavioral difference between the two types of CRC.

Patients and Methods:

Patient and tumor characteristics

This retrospective study analyzed the data of 165 metastatic colorectal cancer patients at the department of clinical oncology, Assiut university hospital, Egypt who presented from January 2015 to December 2019. Patients who had metastatic colorectal cancer were included in this study either synchronously or metachronously. The primary tumor site was divided into right sided mCRC which included (the cecum, appendix, ascending colon, hepatic flexure of the colon and transverse colon), left sided mCRC which included (the splenic flexure, descending colon and sigmoid) and rectum.

Information of patients was obtained covering age, sex, tumor pathology, tumor grade, presenting site, metastatic site, time of metastasis (synchronous or metachronous), KRAS status, surgery, chemotherapy, and target therapy. Patients who were included in this study had the following criteria: age >18 years, pathology proven colon or rectal cancer, adenocarcinoma, stage IV CRC, period of follow up >/= 6 months otherwise patients were excluded from this study.

The ethical committee in our faculty authorized the study protocol and methods, and each participant gave written informed permission.

Follow up

Follow up was through reviewing the patients records at our department and contacting the patients via telephone. Survival was obtained at the last date of contact or March 2022 (last follow up). Progression free survival (PFS) was defined as from the time of diagnosis to time of progression, and overall survival (OS) was defined as from the time of diagnosis to the last follows up or time of mortality.

Statistical analysis

The statistical package for the social sciences (IBM-SPSS) version 26.0 program was used to analyze the data. Qualitative data was expressed as a frequency and percent. All numerical variables were tested before evaluation to determine the normality of data by Shapiro–Wilk test, mean ± SD or median and range were used to express data according to their distribution.

Progression free survival and overall survival were tested by Kaplan-Meier method using Log rank test and Kaplan-Meier curves were done.

Univariate cox regression analysis was performed to association between KRAS, presentation site and overall survival of patients with colorectal cancer.

The level of significance was considered at P value < 0.05.

Results:

A total of 165 patients with mCRC, 66 men and 99 women, mean age was 42 years from 19 to 86 years and diagnosed from January 2015 to December 2019, who were classified as having right sided mCRC, left sided mCRC or rectal cancer and who underwent treatment with systemic chemotherapy alone or systemic chemotherapy and biological therapy were included in this study.

As for demographic data of patients; mean age was 42 years with age ranged from 19 to 86 years, 102 (61%) of patients were < 55 years of age, 66 patients (40%) were males and 99 patients (60%) were females, 123 patients (74%) had classical adenocarcinoma and 111 patients (67%) were Grade 2 as shown in Table (1)

Table (1): Demographic data of metastatic colorectal cancer patients

Variables	N=165	%
Age (years)		
▪ <50	102	61.9
▪ 50-69	57	34.5
▪ ≥70	6	3.6
Mean ± SD **(range)**	42.69±14.36 (19-86)	
Gender		
▪ Male	66	40.0
▪ Female	99	60.0
Pathology		
▪ Classical adenocarcinoma	123	74.5
▪ Mucinous adenocarcinoma	30	18.2
▪ Signet ring adenocarcinoma	12	7.3
Grade		
▪ Grade 1	18	10.9
▪ Grade 2	111	67.3
▪ Grade 3	36	21.8

Data was expressed as frequency and % or median and range

As for clinical data of patients; regarding presentation site, 37 patients (22.4%) were right colon, 44 patients (26.7%) were left colon and 84 patients (50.9%) were rectal cancer, as for metastatic site 39 patients (23.6%) had liver Metastasis, 15 patients (9.1%) had lung metastasis, 15 patients (9.1%) had Peritoneal metastasis, 30 patients (18.2%) had lymph node metastasis, 33 patients (20%) had multiple metastasis and 33 patients (20%) had others. As for time of metastasis 96 patients (58.2%) were synchronous metastasis and 69 patients (41.8%) were metachronous. As for surgery 123 patients (74.5%) underwent radical surgery, 18 patients (10.9%) underwent palliative surgery, 12 (7.3%) patients underwent biopsy and 12 patients (7.3%) had no surgery, as shown in Table (2)

Distribution of KRAS type among patients, were shown in Table (3), most patients were KRAS wild type 127 patients (77%), 26 patients (15.8%) were mutant type and 12 patients (7.3%) were unknown.

Lines of treatment among our patients were shown in Table (4), 101 patients (61.2%) received target therapy and FOLFOX and 31 patients (18.9%) received target therapy and FOLFIRI. As for chemotherapy alone 21 patients (12.7%) received oxaliplatine based chemotherapy, 10 patients (6.1%) received irinotecan-based chemotherapy and 2 patients (1.1%) received capecitabine alone.

Table (2): Clinical data of metastatic colorectal cancer patients

Variables	N=165	%
Presentation site		
▪ RT colon	37	22.4
▪ LT colon	44	26.7
▪ Rectum	84	50.9
Metastatic site		
▪ Liver	39	23.6
▪ Lung	15	9.1
▪ Peritoneal	15	9.1
▪ LN	30	18.2
▪ Multiple	33	20.0
▪ Others	33	20.0
Time of Metastasis		
▪ Synchronous	96	58.2
▪ Metachronous	69	41.8
Surgery		
▪ Radical	123	74.5
▪ Palliative	18	10.9
▪ Biopsy	12	7.3
▪ No	12	7.3

Data was expressed as frequency and %

Table (3): Distribution of KRAS among patients with colorectal cancer

KRAS type	N=165	%
▪ Unknown	12	7.3
▪ Wild	127	77.0
▪ Mutant	26	15.8

Data was expressed as frequency and % or median and range

Table (4): Lines of treatment among patients with metastatic colorectal cancer

Variables	N=165	%
Target + Chemotherapy		
▪ Target+FOLFOX	101	61.2
▪ Target+ FOLFIRI	31	18.9
Chemotherapy		
▪ FOLFOXor XELOX	21	12.7
▪ FOLFIRI or XELIRI	10	6.1
▪ Xeloda	2	1.1

As for biological therapy that patients received, 84 patients (50.9%) received anti EGFR; 54 received panitumumab (32.7%) and 30 received cetuximab (18.2%), regarding VEGF monoclonal antibody; 48 patients (29.1%) received bevacizumab and 33 patients (20%) did not receive target therapy as shown in Table (5).

As regard progression free survival, PFS in right sided mCRC was 8 months, in left sided mCRC was 10 months and in rectal cancer was 9 months with significant p value 0.001. As regard overall survival, OS in right sided mCRC was 23 months, in left sided mCRC was 41 months and in rectal cancer was 35 months with significant p value 0.01 as shown in Table (6).

Regarding association between primary tumor site, KRAS type and overall survival in mCRC patients; OS in right sided mCRC was 31 months in wild type KRAS and 11 months in mutant type KRAS, OS in left sided mCRC was 36 months for wild type KRAS and 27 months in mutant type KRAS and OS in rectal cancer was 41 months in wild type KRAS and 20 months for mutant KRAS as shown in Table (7).

Regarding Overall survival by tumor location and biological therapy, OS of the right mCRC who received panitumumab was 23 months compared with 43 months in left mCRC and 42 months in rectal cancer with significant p value < 0.001. OS of the right mCRC who received cetuximab was 21 months compared with 46 months in left mCRC and 43 months in rectal cancer with significant p value 0.002. OS of right mCRC who received bevacizumab regardless of KRAS type was 26 months, in left mCRC was 34 months and in rectal cancer was 32 months but the p value wasn't significant 0.197. OS of right mCRC wild KRAS type who received bevacizumab was 30 months compared with 35 months for left sided mCRC and 36 months for rectal cancer but the p value was not significant. OS of right sided mutant KRAS type who received bevacizumab was 7 months compared with 27 months for left sided tumors and 20 months for rectal tumors with significant p value < 0.001 as shown in Table (8).

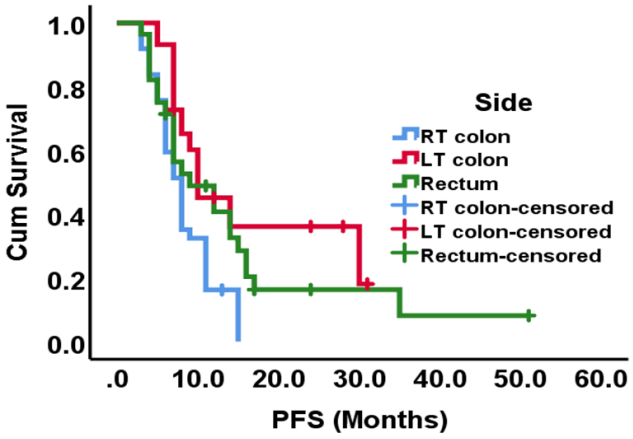

Figure (1): Kaplan Meir curve for PFS according to presentation site of tumor among patients with metastatic colorectal cancer

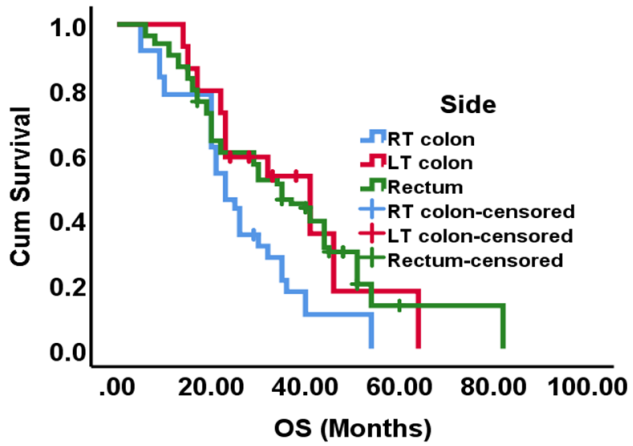

Figure (2): Kaplan Meir curve for OS according to presentation site of tumor among patients with metastatic colorectal cancer

Table (5): Types of biological therapy received among patients with m CRC

Target therapy	N=165	%
▪ **Anti EGFR**	**84**	**50.9**
- **Panitumab**	**54**	**32.7**
- **Cetuximab**	**30**	**18.2**
▪ **VEGF monoclonal antibody** - **Bevacizumab**	**48**	**29.1**
▪ **No**	**33**	**20.0**

Table (6): Progression free survival (PFS)and overall survival (OS) according to presentation site in metastatic colorectal cancer patients

Variable	PFS Median (months), (95% CI)	P-Value* Log rank test	OS Median (months), (95% CI	P-Value* Log rank test
Presentation site				
▪RT colon	8.00 (6.73-9.26)		23.00 (18.75-27.24)	
▪LT colon	10.00 (6.83-13.16)	**0.001**	41.00 (26.33-55.67)	**0.010**
▪Rectum	9.00 (5.53-12.46)		35.00 (27.95-42.03)	

CI (confidence interval), *log rank test
Median survival time

Table (7): Association between KRAS, presentation site, and overall survival of patients with colorectal cancer

Variables	KRAS Wild	Mutant	Unknown
RT colon			
▪Median OS (months)	31.0 (27.21-36.47)	11.0 (6.93-15.72)	10.0 (7.0-12.0)
P-Value		**<0.001**	
▪HR (95%CI)	**Ref**	19.22 (5.11-72.43)	22.87 (3.32-78.21)
P-Value		**<0.001**	0.001
LT colon			
▪Median OS (months)	36.0 (29.71-43.05)	27.0 (21.45-32.54)	41.0 (41.0-41.0)
P-Value		0.915	
▪HR (95%CI)	**Ref**	1.1 (0.23-2.69)	1.2 (0.24-4.69)
P-Value		0.699	0.940
Rectum			
▪Median OS (months)	41.0 (35.70-46.08)	20.0 (15.56-21.44)	16.0 (7.68-24.31)
P-Value		**<0.001**	
▪HR (95%CI)	**Ref**	4.17 (1.79-9.73)	5.12 (2.24-11.71)
P-Value		**0.001**	**<0.001**

Cox regression analysis
HR: hazard ratio
95% CI: 95% confidence interval
Median survival time

Table (8): Overall survival by tumor location and biological therapy

Treatment line	Median OS (months), 95% CI			P value
	RT colon	LT colon	Rectum	
PANTIMUMAB	23.0 (21.30-24.69)	43.3 (30.79-55.70)	42.0 (37.34-46.7)	**<0.001**
CETUXIMAB	21.0(17.68-30.9)	46.0 (28.68-42.51)	43.0 (23.82-55.2)	0.002
BEVACIZUMAB	26.0 (18.2-34.65)	34.0 (27.52-39.57)	32.0 (20.89-43.1)	0.197
▪ Wild KRAS	30.0 (25.33-35.84)	35.0 (29.12-40.88)	36.0 (22.14-49.85)	0.363
▪ Mutant KRAS	7.0 (5.24-8.75)	27.00 (21.45-32.54)	20.0 (20.00-20.00)	**<0.001**

CI (confidence interval), *log rank test

Discussion:

Our study showed that right sided tumors had worse survival compared with left sided and rectal tumors regardless of KRAS type or biological therapy received.

Patients with a right-sided primary tumors have more unfavorable prognostic factors and certainly have worse outcomes compared with those with left-sided primary tumors. Multivariate analysis adjusting for known prognostic factors supports side of primary as an independent prognostic factor in mCRC, with left-sided colonic (including rectum) primary cancers having better survival than right-sided primary. [11]

In our study we also evaluated the relation between tumor site, response to biological therapy and survival. In a study by Aljehani et al they assessed the relationship between tumor site, response to treatment with bevacizumab or cetuximab and survival among patients with mCRC. Their results showed that primary tumor site may be related to response to biological therapy (BT) and survival outcome in mCRC. Patients with right-sided mCRC, irrespective of the type of BT received, showed higher mortality compared with patients with left-sided mCRC, emphasizing the relation between primary tumor site and outcomes in mCRC.[1] Also a retrospective study by Ramadan et al showed a decrease in mortality for left sided mCRC treated with BT compared with right-sided mCRC.[12]

This data was similar to our results where left sided and rectal tumors had superior outcome compared to right sided tumors irrespective of the BT received.

Also Aljehani et al reported that, in patients treated with SC and bevacizumab, primary tumor location was significantly related to survival, with right-sided mCRC related to worse overall survival than left-sided mCRC. Other studies have demonstrated similar survival differences with bevacizumab therapy in right- and left-sided mCRC. Aljehani et al also observed the relation between the primary tumor site and response to treatment with cetuximab. Patients with right-sided tumors who received cetuximab had significantly poor survival, compared with those receiving bevacizumab. On the other hand, patients with left-sided tumors had better survival. Patients receiving cetuximab showed better survival compared with bevacizumab in patients with wild-type KRAS left-sided tumors.[1] These results were similar to our results where in right sided tumors bevacizumab showed superior outcome compared to cetuximab and in left sided and rectal tumors bevacizumab showed inferior outcome compared to cetuximab.

Our results are similar to the findings demonstrated in a retrospective study of the CALGB/SWOG 80405 trial. In this study by Venook et al they evaluated the relationship between primary tumor site and survival outcomes in patients with wild-type RAS tumors who received systemic chemotherapy and bevacizumab or systemic chemotherapy and cetuximab in mCRC. The study showed that cetuximab had better overall survival compared with bevacizumab treatment for left-sided mCRC (39.3 vs 32.6 months) and survival for both biological therapy groups with right-sided m CRC was (13.6 vs 29.2 months). Similar retrospective analyses of other randomized clinical trials by various authors have consistently shown that right side mCRC is associated with poor response to anti-EGFR therapy despite wild-type RAS status. Based on the data from various studies, the NCCN (National comprehensive cancer network) has recently revised its recommendations for the use of anti-EGFR therapy for first-line treatment in mCRC. Anti EGFR treatment is now recommended only for wild-type RAS and left-sided mCRC. [13] Our results showed worse overall survival for anti EGFR in right sided tumors compared with bevacizumab and better survival of anti EGFR than bevacizumab in left sided tumors.

Survival differences between right and left primary tumor location may result from genetic factors. A study by Missiaglia et al showed that right-sided primary tumors are characterized by more heterogeneous phenotypes, including poor sensitivity to EGFR inhibitors, on the other hand there is higher prevalence of an EGFR inhibitor-sensitive phenotype in left-sided metastatic colon tumors. Right-sided tumors have also been shown to have more microsatellite instability and BRAF mutations previously associated with increased mortality.[6]

The limitations to our study were the retrospective nature of the study included a limited number of patients from a single cohort. So, the need for a larger prospective study is essential. Also, the small sample size may have led to the misinterpretation of the prognostic effect of tumor location on treatment. Also, KRAS and BRAF mutation status were not available for all patients in the patients' records for the period of our study. Those data would have allowed additional evaluation of the predictive role of primary tumor site in specific subgroups.

Conclusion:

Our study showed that right sided tumors had worse survival compared with left sided and rectal tumors regardless of KRAS type or biological therapy received. As for kRAS wild type tumors, in right sided tumors bevacizumab showed superior outcome compared to anti EGFR therapy and in left sided and rectal tumors bevacizumab showed inferior outcome compared to anti EGFR therapy. So selecting the proper biological therapy according to primary tumor site and response to treatment will help to exclude ineffective and expensive treatment in mCRC patients.

List of abbreviations

mCRC	Metastatic colorectal cancer
PFS	Progression free survival
OS	Overall survival
EGFR	Epidermal growth factor receptor
VEGF	Vascular endothelial growth factor
CRC	Colorectal cancer
SEER	Surveillance, epidemiology, and end results
SC	Systemic chemotherapy
BT	Biological therapy
FOLFOX	Folinic acid, 5FU and Oxaliplatin
FOLFIRI	Folinic acid, 5FU and Irinotecan
XELOX	Xeloda and Oxaliplatin
XELIRI	Xeloda and Irinotecan
NCCN	National comprehensive cancer network
SPSS	Statistical package for the social science
Xeloda	capecitabine

References:

1- Aljehani MA, Morgan JW, Guthrie LA, et al. Association of primary tumor site with mortality in patients receiving bevacizumab and cetuximab for metastatic colorectal cancer. JAMA Surg. 2018 Jan 1;153(1):60-67.
2- Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. J Surg Oncol. 2004 Dec 15;88(4):261-6.
3- Salvatore L, Aprile G, Arnoldi E, et al. Management of metastatic colorectal cancer patients: guidelines of the Italian Medical Oncology Association (AIOM). ESMO Open. 2017 Apr 12;2(1):e000147.
4- Loupakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst. 2015 Feb 24;107(3):dju427.
5- Amri R, Bordeianou LG, Sylla P, et al. Variations in metastasis site by primary location in colon cancer. J Gastrointest Surg. 2015 Aug;19(8):1522-7.
6- Missiaglia E, Jacobs B, D'Ario G, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol. 2014 Oct;25(10):1995-2001.
7- Yasuda SU, Zhang L, Huang SM. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. Clin Pharmacol Ther. 2008 Sep;84(3):417-23.
8- O'Donnell PH, Dolan ME. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. Clin Cancer Res. 2009 Aug 1;15(15):4806-14.
9- Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer: Retrospective Analyses of the CRYSTAL and FIRE3 Trials. JAMA Oncol. 2017 Feb 1;3(2):194-201.
10- Lee YC, Lee YL, Chuang JP, et al. Differences in survival between colon and rectal cancer from SEER data. PLoS One. 2013 Nov 12;8(11):e78709.
11- Price TJ, Beeke C, Ullah S, et al. Does the primary site of colorectal cancer impact outcomes for patients with metastatic disease? Cancer. 2015 Mar 15;121(6):830-5.
12- Ramadan M, Alfayea T, Alsofyani A, et al. Primary tumor location and survival among metastatic colorectal cancer patients treated with systemic chemotherapy and biologic therapies: Retrospective analysis. Cancer Treat Res Commun. 2022;33:100632..
13- Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1{o}) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol. 2016;34(15)(suppl):3504.