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Epidemiological and Clinicopathological Data on Metastatic Colorectal Cancer at South Egypt Cancer Institute (SECI)

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ABSTRACT

Background: Globally, colorectal cancer (CRC) is a serious health issue. It is the second most common cause of cancer-related deaths and the third most common kind of cancer. Some individuals improved despite the use of several therapy methods, which prompted the search for novel approaches.

Objects: The present study aimed to analyze epidemiological and clinicopathological data of metastatic CRC patients presented at The Medical Oncology Department, SECI.

Methods: This study included 60 patients with mCRC which were either synchronous or metachronous cases, who met the following criteria: age > 18 years and treatment with first-line oxaliplatin-based chemotherapy followed by second-line irinotecan-based therapy.

Result: In this study, 51.7% of the patients were males and 48.3% were females. Regarding tumor location, 26% had rectal cancer, while the remainder had colonic cancer. Metachronous metastases were more common, observed in 56.7% of cases, and 58.3% of patients had ≤ 2 metastatic sites. Extra-abdominal metastases were more frequent in rectal cancer than in colonic cancer. More than half of the patients had high-risk pathological features. A significant association was observed between tumor deposits and nodal involvement, univariate analysis for overall survival (OS), synchronous metastasis, more than two metastatic sites, positive LVI and right-sided disease were significantly associated with increased risk of death. The median OS was 19.2 months, whereas the median progression-free survival (PFS) was 7.3 months.

Conclusion: Metastatic CRC (mCRC) mostly presents with poor-risk clinicopathological features. Extra-abdominal metastasis is more frequent in the rectal site.

Keywords: Metastasis, Clinicopathological, CRC.

INTRODUCTION

CRC is the second most common cause of cancer-related mortality globally and the third most common cause in the USA [(1)].

In Egypt, colorectal carcinoma ranks 7th and constitutes 3.9% of all cancer diagnoses [(2)]. Surgery in the face of unresectable illness can be beneficial not just for palliation but also for enhancing survival [(3)]. Multimodal treatment for metastatic CRC is now considered the standard of care. Perioperative treatment has been linked to better survival after excision of metastatic areas or the main tumor [(4)].

Colon cancer patients had an overall 5-year relative survival rate of about 63%. If cancer is detected at a localized stage, the survival rate is 91%. When colon cancer metastasizes, the 5-year relative survival rate falls to 13%. Survival rates might vary between colon cancer and rectal cancer. Furthermore, by 2030, the incidence rate of CRC is projected to rise by over 2.2 million cases, leading to more than 1.1 million fatalities [(5)].

Pathologists must accurately assess pathologic staging, analyze surgical margins, look for prognostic factors not included in the staging, such as lympho-vascular and perineural invasion, evaluate the therapeutic effect in patients who received neo-adjuvant therapy, and evaluate molecular tests in addition to providing accurate histopathologic diagnosis [(6)].

PATIENTS AND METHODS

This prospective cohort study was conducted at the Medical Oncology Department of SECI, Assiut University Hospital, and included cases diagnosed with metastasis from June 2022 to December 2024. Data were analyzed according to patients' clinical data, pathological data of available mCRC blocks, response to treatment and survival.

This study included 60 patients with mCRC which were either synchronous or metachronous cases, who met the following criteria: age > 18 years, and treatment with first-line oxaliplatin-based chemotherapy followed by second-line irinotecan-based therapy.

Inclusion criteria: Age ≥ 18 years old, patients with metastatic CRC either synchronous or metachronous cases, CRC patients of both genders were to be included, patients received 1st line with an oxaliplatin based regimen and 2nd line irinotecan-based regimen, adequate CBC and liver and renal function.

Exclusion criteria: Double malignancy occurred concurrently, pregnant and lactating patients, patient < 18 years and serious uncontrolled concomitant disease.

Ethical approval: The South Egypt Cancer Institute and Assiut University Ethics Committee both authorized this study. After receiving all of the information, all participants signed their

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permissions. The Helsinki Declaration was followed throughout the course of the study.

Statistical analysis:
The data were analyzed using the SPSS version 26.0 software. Frequencies and percentages were used to convey qualitative data. The Shapiro-Wilk test was performed to assess the normality of all numerical variables prior to examination. Data were expressed according to their distribution using mean ± SD or median and range. The X^2-test was used to compare categorical variables and Fisher's exact test was used when anticipated cell counts were less than five. The Kaplan-Meier technique was used to evaluate PFS and OS with a log-rank test, and Kaplan-Meier curves were generated. Univariate Cox regression analysis was used to determine the relationship between various factors and overall or PFS in CRC patients. P-values ≤ 0.05 were deemed significant.

RESULTS

1- **Demographic data of studied cases:** The mean age of the studied patients was 48 years, with approximately 66.6% aged ≤ 49 years, while the remaining patients were above 49 years. Most cases were males in 51.7% of cases, and 48.3% of patients were females. Most of the patients had an ECOG performance status (PS) of 0 to 1, and only ten patients had a PS of 2. 40% of cases had a family history of CRC. The mean body mass index (BMI) was 30, approximately 45% were non-obese, while 55% were obese, as shown in table (1).

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Table (1): Distribution of the studied cases according to demographic data (n = 60)

	N (60)	%
Sex		
Male	31	51.7
Female	29	48.3
Age (years)		
Min. – Max.	34.0 – 67.0	
Mean ± SD.	48.0 ± 9.09	
Median (IQR)	49.0 (40.50 – 55.0)	
≤49	40	66.66
>49	20	33.3
BMI (kg/m2)		
≤30	27	45.0
>30	33	55.0
Family history of CRC		
No	36	60.0
Yes	24	40.0
Performance status		
0-1	50	83
2	10	17

2- Distribution of the studied cases according to clinical data: About 26% of the patients had rectal tumors, while the others had colonic tumors. Regarding the pattern of metastatic cases, synchronous metastases were found in 43.3% and the remaining 56.7% had metachronous metastases. Most patients had ≤ two metastatic sites in 58.3% of cases, while 41.7% had more than two. The most frequent site of metastases was the liver, observed in 58.3% of cases. According to the serum level of carcinoembryonic antigen (CEA), 60% of patients had elevated levels. Perforation occurred in 25% of cases, and 30% developed obstruction, as shown in table (2).

Table (2): Distribution of the studied cases according to clinical data (n = 60)

	No.	%
Status of Metastasis		
Metachronous	34	56.7
Synchronous	26	43.3
Number of sites of metastasis		
Low (≤2)	35	58.3
High (>2)	25	41.7
Sidedness		
Right	25	41.7
Left	19	31.7
Rectum	16	26.7
Metastatic site		
Distant LN	15	25.0
Peritoneal deposit	25	41.7
Ascites	16	26.7
Lung	12	20.0
Bone	15	25.0
Liver	35	58.3
complications related to 1ry site (CRC)		
Obstruction	18	30
Perforation	15	25
Bleeding	10	16.7
Abdominal pain	9	15
Constipation	11	18.3
CEA pre-treatment		
Normal	24	40.0
High	36	60.0

3- Distribution of the studied cases according to pathological data: Adenocarcinoma was the most frequent histological type, occurring in 76.7% of cases, followed by mucinous or signet ring variants in 23.3%. More than half of the patients had high-risk pathological features, including T3 and T4 in 70% of patients, nodal positivity in 65%, tumor deposits in 51%, lympho-vascular invasion (LVI) and perineural invasion (PNI) in 53.4% of cases. Wild-type K-RAS status was found in 56.7% of patients, but 43.3 % of cases had a mutated pattern, with no correlation detected between the K-RAS pattern and the sidedness. Moderate or high tumor

grade was found in 68.3% of patients. Half of the patients had a brisk immune response, while the other half had a non-brisk immune response as shown in table (3).

Table (3): Distribution of the studied cases according to pathological data (n = 60)

	No.	%
T (depth)		
T1	4	6.7
T2	14	23.3
T3	21	35
T4	21	35
Lymph node		
N(negative)	21	35
N (positive)	39	65
LVI		
No	28	46.6
Yes	32	53.4
Tumor deposit		
No	29	48.3
Yes	31	51.7
Immune response		
Not brisk	30	50
Brisk	30	50
Type of tumor		
Adenocarcinoma	46	76.7
Other (mucinous, signet ring)	14	23.3
Grade		
Grade 1	19	31.7
Grade2	15	25.0
Grade3	26	43.3
PNI		
No	28	46.6
Yes	32	53.4
KRAS		
Mutated	26	43.3
Wild	34	56.7

A significant correlation between tumor deposits and nodal involvement was detected, with a p-value of 0.018, as shown in table (4).

Table (4): Relation between TR deposit and nodal involvement (n = 60)

	Nodal involvement				P-value
	-ve (n = 21)		+ve (n = 39)		
	No.	%	No.	%	
TR deposit					
Yes	6	1%	25	41.7	.018
No	15	25%	14	23.3	

3- **Metastatic pattern of colon versus rectal cancer:** Extra-abdominal metastases were more frequently observed in rectal cancer, with bone metastases being significantly higher (p = 0.015). In contrast, nodal metastases were more common in colon cancer (p = 0.049), as shown in table (5) and figure (1).

Table (5): Comparison between colon and rectum according to site of metastasis

	Sidedness				P
	Colon (n = 44)		Rectum (n = 16)		
	No.	%	No.	%	
Metastatic site					
LN	14	31.8	1	6.3	0.049*
Peritoneal deposit	19	43.2	6	37.5	0.693
Ascites	13	29.5	3	18.8	0.520
Lung	6	13.6	6	37.5	0.066
Bone	7	15.9	8	50.0	0.015*
Liver	26	59.1	9	56.3	0.844

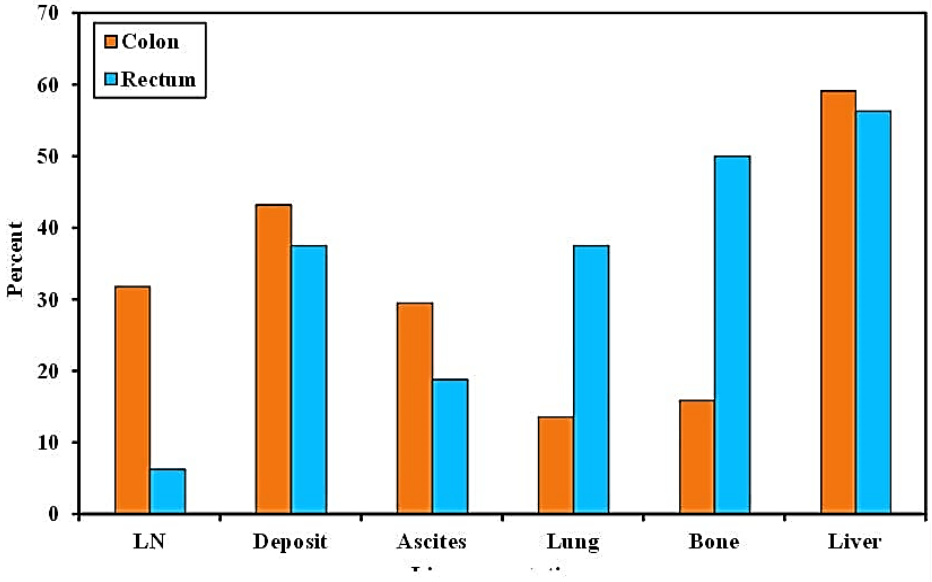

Figure (1): Comparison between colon and rectum according to site of metastasis.

4- **Survival data (OS, PFS):** The median OS was 19.2 months. Twenty-nine patients were alive, and thirty-one had died by the end of the study, as shown in figure (2). The median PFS was 7.3 months, as shown in figure (3).

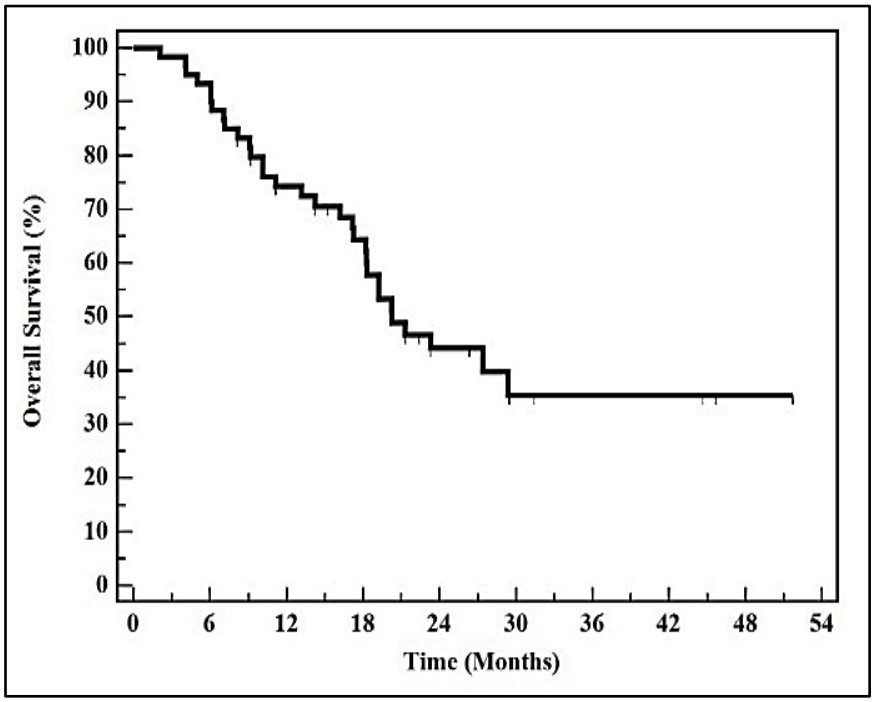

Figure (2): Kaplan-Meier survival curve for OS.

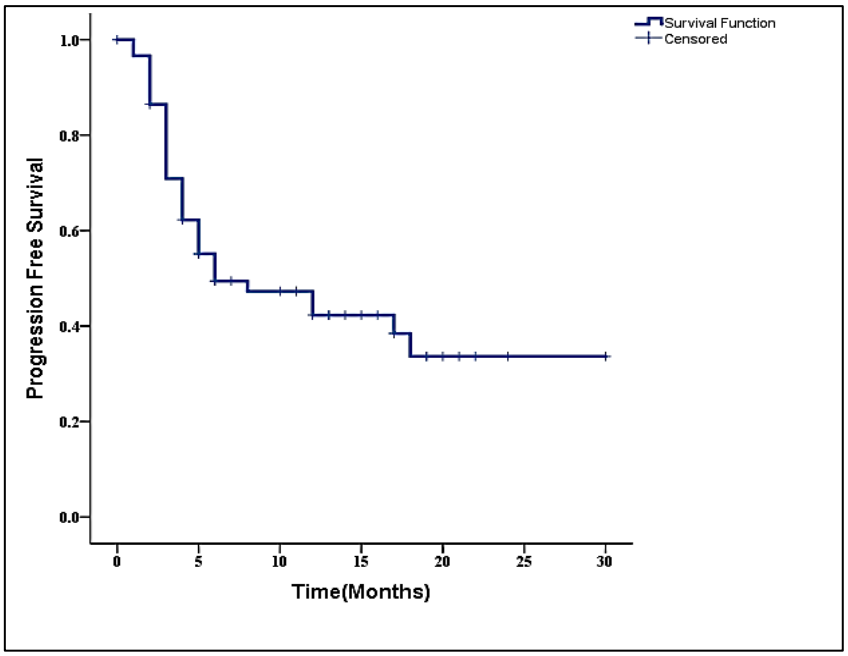

Figure (3): Kaplan-Meier survival curve for PFS.

6- COX regression analysis of parameters affecting OS and PFS: COX regression for OS showed that synchronous metastasis increased the risk of death by 2.49-fold compared to metachronous metastasis (HR 2.49; 95% CI (1.214–5.121); p = 0.013). A greater number of metastatic sites (>2) increased the risk of death by 2.27-fold (HR 2.27; 95% CI (1.106–4.683); p = 0.026). The presence of LVI doubled the risk of death compared to its absence (p = 0.03). Right-sided tumors were associated with worse survival (p = 0.038). A brisk immune response was associated with 73% reduction in the risk of death. No statistically significant correlation was found with other parameters. According to COX regression for PFS, synchronous metastasis increased the risk of progression by 2.4 times (HR 2.400; CI (1.202–4.791); p < 0.01). A high number of metastatic sites (>2) increased the risk of progression by 2.991-fold (HR 2.991; CI (1.740–4.151); p = 0.021). No other statistically significant factors were detected, as shown in table (6).

Table (6): Cox regression for parameters affecting OS and PFS

	Overall survival (OS)		Progression-free survival (PFS)	
	P-value	HR (LL – UL 95% C.I)	P	HR (LL – UL 95% C.I)
KRAS				
Mutated	0.396	1.409 (0.638 – 3.110)	906.	1.049 (0.476 – 2.312)
Wild		1.000		1
Status of metastases				
Metachronous		1.000		1
Synchronous	0.01*	2.49 (1.214-5.121)	02*.	2.1 (1.202 – 4.791)
Number of metastases				
Low (≤2)		1.000		1
High (>2)	0.026*	2.276 (1.106-4.683)	021*.	2.991 (1.740 – 4.151)
Sidedness				
Left/ Rectum		1		1
Right	0.038*	1.54 (1.248 – 2.962)	299.	1.518 (0.691 – 3.335)
LVI				
Yes	0.03*	2.27(1.106-3.683)	314.	1.815 (0.568 – 2.795)
No		1.000		1
Immune response				
Non brisky		1.000		1
Brisky	0.020*	0.275 (0.093 – 0.816)	654.	0.545 (0.039 – 3.699)
Sex				
Male		1.00		1
Female	0.8	1.789 (1.706 – 3.970)	540.	0.771 (0.336 – 1.769)
Age				
<\= 49		0.762 (0.389 – 1.493)	2640	0.545 (0.039 – 3.699)
>49	0.428	1.00		1

7- Distribution of the studied cases according to response to treatment: The overall response rate (CR + PR + SD) to first-line oxaliplatin-based chemotherapy was 58.4%, which exceeded that observed with second-line irinotecan-based chemotherapy (43.5%). Targeted therapy was added when indicated, with an ORR was 25% in 35% of cases who received targeted TTT, as shown in table (7).

Table (7): Distribution of the studied cases according to response to treatment

	Response to oxaliplatin (1st L) (n = 60)		**Response to irinotecan (2nd L)** (n = 30)		**Response to the target (n = 21)**	
	No.	%	No.	%	No.	%
CR	1	1.7	0	0.0	1	4.8
PR	16	26.7	6	20.2	7	33.3
SD	18	30.0	7	23.3	7	33.3
PD	25	41.6	17	56.6	6	28.6

DISCUSSION

Despite increasing survival rates, mCRC remains a lethal disease with a 5-years survival rate of approximately 14% [7]. In our study, the mean age of patients was 48 years. The decreasing age of incidence of CRC has been observed in many recent studies, both internationally and within Egypt, such as **Siegel *et al.*** [8] and **Rashad *et al.*** [9] respectively. This pattern of younger age at incidence may be attributed to unhealthy dietary habits, environmental factors, and hereditary/genetic predisposition.

In our study, 40% of cases had a family history of CRC, which is similar to **Butterworth *et al.*** [10] who concluded that family history is common in CRC cases. But, **Murff *et al.*** [11] showed that most CRC cases had no family history, with only <10% of cases having a positive history.

In terms of gender distribution, the incidence in males was higher than in females, which is consistent with the study by **Alan *et al.*** [12] who reported a higher incidence in males. However, the study by **Ibrahim *et al.*** [13] showed nearly equal gender distribution.

Adenocarcinoma was the most frequent histopathological variant in our study (76.7%), which aligns with **Fleming *et al.*** [14], who reported that the majority of samples were adenocarcinoma (83.4%), followed by mucinous adenocarcinoma and signet-ring carcinoma.

Wild-type KRAS (56.7%) was more common in our study than the mutated pattern, which is consistent with **Oukkal *et al.*** [15] who reported that wild-type KRAS is predominant in the Middle East and North Africa compared to Western countries. The cause may be attributed to genetic and environmental factors.

Right-sided colorectal cancer was the most dominant location in our study (56.3%) compared to rectosigmoid tumors. This agrees with **Griffith *et al.*** [16]. However, this contrasts with **Lee *et al.*** [17] who concluded that right-sided CRC was the least common.

In COX regression analysis, right-sided tumors had worse survival, which is consistent with **Price *et al.*** [18] likely due to a later stage at diagnosis and more aggressive tumor biology.

Most of the patients in our study had high-risk pathological features. A larger proportion had moderate to high-grade tumors, which aligns with **Wang *et al.*** [19]**.** T3/T4 stage and nodal involvement were most common, which is in agreement with **Iliklerden *et al.*** [20]**.**

Approximately 53.4% of studied patients had lympho-vascular invasion (LVI) and perineural invasion (PNI)—both were considered adverse prognostic factors. This is in agreement with **Al-Sukhni *et al.*** [21] who reported similar findings. However, this differs from a large U.S.-based study by **Gabriel *et al.*** [22]**,** which found that only 22.2% of cases had LVI and 11.5% had perineural invasion (PNI).

A positive correlation between LVI and the presence of tumor deposits (TDs) was demonstrated in our findings (p = 0.0157), which is consistent with **Heng *et al.*** [23] who also reported a statistically significant association between TDs and lymph node metastasis (p = 0.000). In Cox regression analysis, the presence of LVI was associated with worse survival (**p = 0.03**), which is consistent with **Wang *et al.*** [24].

In our study, half of the cases had a brisk immune response, while the other half had a non-brisk immune response. COX regression analysis showed that brisk immune response was associated with improved survival (**p = 0.02**), which is in line with **Deschoolmeester *et al.*** [25] who emphasized the role of regulatory T cells in attacking cancer cells.

The liver was the most common site of metastasis in our study. This could be explained by the liver's anatomical location and dual blood supply, which is consistent with **Chen *et al.*** [26]**.** The occurrence of hepatic metastases in left-sided CRC may be explained by the "seed-and-soil" hypothesis, which suggests that tumor cells have organ preferences based on microenvironment compatibility as discussed by **Ribatti *et al.*** [27]**.** Extra-abdominal metastasis was more common in rectal cancer than in colon cancer, likely due to the absence of peritoneal covering over the rectum, which facilitates this spread as reported by **Qiu *et al.*** [28]**.**

In our study, more than half of the cases had metachronous metastases (56.7%) with ≤ 2 metastatic sites (58.3%). This disagrees with **Meyer *et al.*** [29] who reported that only 14% developed metachronous metastases—a difference possibly due to variability in patient characteristics.

In COX regression, synchronous metastasis and having > 2 metastatic sites were both associated with worse survival (p = .013 and .026, respectively). This is in agreement with **Reboux *et al.*** [30] because of more aggressive biological behavior.

Most cases (60%) had elevated CEA levels, which is in line with **Sefrioui *et al.*** [31] who supported its role in predicting tumor progression.

Irinotecan and oxaliplatin are standard first-line therapeutic agents in mCRC, with similar efficacy but different toxicity profiles [32]. All patients in our study received oxaliplatin-based therapy as first-line, and thirty patients received irinotecan as 2nd line, with targeted therapy added when indicated. First-line therapies generally offer a better chance of achieving a response, which aligns with **Adlar *et al.*** [33]**.** These can be explained by the fact that delaying effective first-line treatment allows tumor resistance to develop, reducing the effectiveness of subsequent therapies [34].

CONCLUSION

Metastatic CRC mostly presents with poor-risk clinicopathological features. Extra-abdominal metastasis is more frequent in the rectal site. Right-sided tumors, the presence of LVI, synchronous metastasis, a high number of metastatic sites and a non-brisk immune response were associated with worse survival.

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