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Epidemiology of Colorectal Cancer, Incidence, Survival, and Risk Factors: Cairo University Center of Oncology and Nuclear Medicine Experience

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ABSTRACT

Background: Colorectal cancers are amongst the most common cancers to occur. They are 3rd most prevalent and mortality causing cancers. Colorectal cancers incidence has been rising in developing countries.

Objective: This study aimed to analyze deeply survival rates in correlation with different epidemiological and pathological factors as well as investigation of patterns of disease failure and relapse.

Subjects and Methods: This was a retrospective study of 141 patients of all stages of colorectal cancers being treated at Cairo University Cancer Center (NEMROCK), through the period from 2014 to 2020. Data were followed up until June 2021. Assessments were made according to individual clinicopathological, and clinico-epidemiological specific correlations.

Results: Histopathological evaluation revealed that T3 disease was commonest presenting pathology in 40, while nodal stage N1 was commonest in 17%. The most common disease stage at diagnosis was stage 3 in 43% of patients, while 17% were metastatic at time of diagnosis. Initial pathological staging was the most significant factor to affect DFS with patients from stage 1 had significant longer disease free survival (DFS) 45 months VS stage 2 26 months Vs 3 months for stage 4 p value 0.009. Overall survival was also significantly correlated with pathological stage with difference in median OS 60 months VS 10 months between stage 1 and stage 4, respectively p value 0.002 HR 3.3.

Conclusion: Pathological staging was the most significant factor affecting survival, while patients with locally advanced rectal cancers were potentially curable and had extended survival rates after receiving full multimodality treatments.

Keywords: Cancer rectum, Clinicopathological, Clinicoepidemiological, Neoadjuvant ccrth, Total neoadjuvant treatment, Lower anterior resection, Disease free survival, Overall survival.

INTRODUCTION

CRC is the fourth most common diagnosed cancer and third most common cause of death [(1)]. Although Egypt does not have high rates of incidence like in developed world [(2)], there are increasing trends of developing CRC at younger age in Egypt and other parts of the world, partly due to westernized lifestyle [(3)]. It is still constitute an important cause of mortality especially rectal cancers being mostly advanced at presentation [(4)]. CRC caused nearly 881,000 deaths in 2018, where cancer of the colon being the fifth most deadly cancer accounting for 5.8% of all cancer deaths, and cancer rectum being tenth with 3.2% of all cancer deaths [(5)].

CRC affect various races and ethnicities at different age groups differently. The proportion of CRC amongst patients younger than 50 years old is almost double for blacks (16%) than for whites (9%), and Hispanics (6%)[(6)]. CRC ranked seventh after lung, breast, prostate, liver, and bladder in Egypt with approximately 5,000 patients in 2015 with almost 3.24% of all cancer cases. It has average incidence ASR of 6/100,000 in males, and 4.9/100,000 in females[(2)].

Three risk's levels are identified for colorectal cancer according to personal or familial history: Individuals with middle risk: men and women aged 50 and more. More than 90%of colorectal cancer cases are diagnosed after this age [(7)].

The median age diagnosis for colon cancer, 69 in men and 73 in women, is older than that of rectal cancer, which is 63 in men and 65 in women [(8)]. Individuals with high risk: 1. First-degree relatives of patients with common colorectal cancer or with a large adenoma (>1 cm) have an increased risk of colorectal cancer when occurred before 60 years, or two first-degree relatives of patients with common colorectal cancer or with a large adenoma (>1 cm) have an increased risk of colorectal cancer irrespective of age. 2. History of colorectal cancer or large adenoma. 3. Personal history of chronic gastrointestinal inflammatory bowel disease (ulcerative colitis and Crohn's disease). Individuals with very high risk: familial adenomatosis polyposis and hereditary nonpolyposis colorectal cancer (Lynch syndrome).

Environmental risk factors include excessive alcohol intake, smoking, and excess body weight. A sedentary behavior has been also associated with an increased risk of colorectal cancer [(9,10)]. Other modifiable risk factors that have been convincingly associated with higher colorectal cancer risk are the consumption of red and processed meat [(11)].

PATIENTS AND METHODS

This is a retrospective cohort study of all colorectal cancer patients treated at Cairo University Center of Oncology and Nuclear Medicine. They presented with stages 1-4 who received their multimodality treatment starting from January 2014 and kept under thorough follow up until June 2021.

A Total of 340 records were registered of which total of 141 patients were studied according to eligibility criteria. This retrospective analysis was

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designed to assess various clinicoepidemiological and clinicopathological criteria of cancer patients treated at our center and assessing the treatment outcome of a multimodality treatments offered.

The primary end point included:

- Disease free survival (DFS), which is defined as the time starting from successfully finishing the treatment as disease free until recurrence or relapse occurs.

The Secondary end point included:

- Overall survival OS, which is defined as total time counted from start of diagnosis till death or lost follow-up.

Ethical Approval: Ethical Approval was cleared by Ethical Committee of Department of Clinical Oncology, Kasr El Ainy University Hospital, Cairo University, Cairo, Egypt.

RESULTS

A total of 141 patients were included in our final analysis, patients had a mean age 47.3 ± 13.8 years old. Females predominate males in our study as females were 63.1% versus 36.9% were males. Most of the included patients had ECOG performance status I (48.2%), while PS 0 were 33.3% and PS II 14.2%. Fifty patients (35.5%) had predisposing factors for cancer colon as low fiber diet, chronic constipation, and sedentary lifestyle. Only twenty patients (14.2%) had a positive family history. Sixty-eight patients (48.2%) presented with bleeding per rectum, while thirty-five patients (24.8%) presented with constipation either chronic or absolute constipation (Table 1 and Figure 1).

Clinical assessment of the included patients showed that seventy patients (50.4%) presented with T3 disease, while 22% were T2, 12.85% were T4 and 12% were not assessed before the time of surgery. Thirty-five patients (24.8%) had N1 disease, 24.1% were N2 disease, 10.6% were N3, 10.6% were node negative and 27% of the included patients was not assessed for nodal involvement prior surgery. Radical surgery was conducted in 63.8% of the included patients, while 9.9% had a palliative surgical management. The data revealed different pathological subtypes of biopsies, where majority of tissue specimens were of the classical adenocarcinoma subtype 68.9%. The second most common was mucinous adenocarcinoma 23% while signet ring cell type constituted 4.4% and GIST occurred in 4 patients 3%. Only one patient had rectal melanoma 0.7%. Histopathological evaluation of the collected specimens showed that T3 was the commonest T stage affecting 40.4%, followed by T2 in 12.1% and T4 in 2.8%. Nodal involvement was positive in 29.8% of cases, as N1 was observed in 17.7%, followed by N2 in 10.6% and N3 in 1.4%. Histological grade was II in 69.5% of the specimens and III in 14.9% and grade I in 2.1% of cases. Pathological staging showed that stage 3 was the most common diagnosed stage (43.3%), followed by stage 2 (23.3%), then stage 4 (17.5%) and finally stage 1 in 10% of the included patients. Both radical abdomino-perineal resection and sphincter sparing surgery (lower anterior resection), examples are segmentectomy and doughnut operation. Only 12 patients had palliative colostomies equal in frequencies 27.7% and 28.4%. Other types of radical surgeries constituted 7.8%. Among the included patients 56/141 (39.7%) had a disease recurrence, with median DFS 12 months (IQR 2-33 months). Forty-one of our patients lost follow-up due to different causes; of the rest hundred and one patients, forty-two patients died during follow up with median OS 26 months (IQR 14-47 months) as shown in Table (2).

Disease free survival

Pathological T stage didn't impact DFS with log rank test= 4.4 and p value 0.48, nodal status was significantly correlated to DFS as node negative patients demonstrated the longer DFS period (24 months versus 5 months in N2 disease) log rank test 11.1 and p value 0.049. Histological grade, positive margins, positive CRM, LVI, ECE and PNI was not significantly associated with shorter DFS with p value >0.05. Patients with M0 disease showed longer median DFS 14 months versus 1 month in M1 patients. Mean survival was 38.8 months for M0 patients versus 17 months for M1 patients, which was statistically significant wit p value 0.02. Pathological staging was significantly associated with DFS as patients with stage 1 has significantly longer DFS 45 months, versus 26.5 months in stage 2, 2 months in stage 3 and 3 months in stage 4 disease with p value 0.009 (Tables 3 & 4 and Figures 2 & 3).

Overall survivals

Overall survival was significantly correlated with nodal status, patients with node negative disease had longer overall survival with HR 1.12 and p value 0.004. Patients with metastatic disease had the worst OS with p value 0.0001 and HR 3.17. Pathological staging was significantly correlated to overall survival as stage 1 had median overall survival 60 months versus 10 months for stage 4 with p value 0.002 and HR 3.3. Patients' performance status was statistically significant with OS, with median overall survival for PS 0,1,2,3 was 47, 62, 21, and 13 months respectively with p value <0.001. Overall survival (OS) was significantly correlated with receiving neoadjuvant treatment p value <0.001. Patients receiving neoadjuvant treatment (CCRTH & TNT) had longer median overall survival 62 months vs median OS for upfront surgery 17 months (Table 5 and Figures 4, 5 & 6).

Table (1): Demographics data

		Count	Column N %
Age (mean ± SD)		47.3	13.8
Gender	Male	52	36.9%
	Female	89	63.1%
PS	0	47	33.3%
	I	68	48.2%
	II	20	14.2%
	III	6	4.3%
Predisposing factors	No	91	64.5%
	Yes	50	35.5%
Family history	Negative	121	85.8%
	Positive	20	14.2%
Presenting symptoms	Bleeding	68	48.2%
	Constipation	35	24.8%
	Intestinal obstruction	4	2.8%
	None	9	6.4%
	Occult blood	2	1.4%
	Pain	23	16.3%

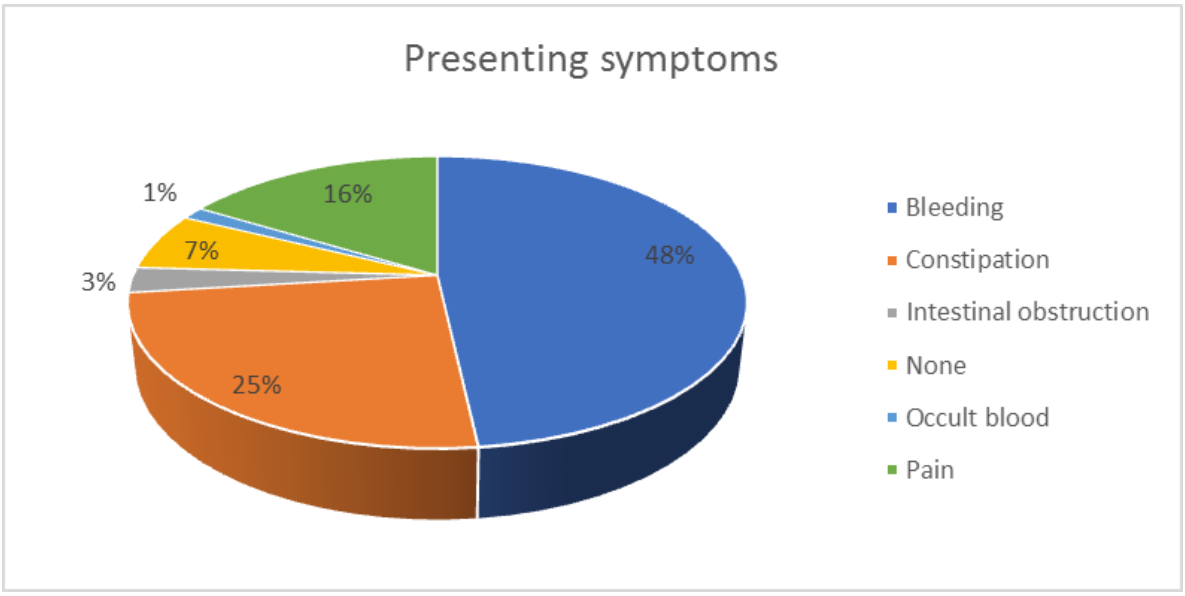

Figure (1): Pie chart showing the percenatge of presenting symptoms

Table (2): Clinicopathological data

		Count	Column N %
Clinical T stage	Unknown	4	2.8%
	T2	31	22.0%
	T3	71	50.4%
	T4	18	12.8%
	Tx	17	12.0%
Clinical N stage	Unknown	4	2.8%
	N0	15	10.6%
	N1	35	24.8%
	N2	34	24.1%
	N3	15	10.6%
	Nx	38	27.0%
M stage	Unknown	4	2.8%
	M1	25	17.7%
	Mx	112	79.4%
Neo-adjuvant CCRTH	Upfront surgery	49	34.8%
	CCRTX	5	3.5%
	Induction chemotherapy	36	25.5%
	Induction chemo plus CCRTX	51	36.2%
Response to neo-adjuvant TTT	Unknown	54	38.3%
	CR	8	5.7%
	Progressive	19	13.5%
	Regressive	39	27.7%
	Stationary	21	14.9%
Type of surgery	None	37	26.2%
	Palliative	14	9.9%
	Radical	90	63.8%
Pathological T stage	Unknown	21	14.9%
	T0	1	0.7%
	T2	17	12.1%
	T3	57	40.4%
	T4	4	2.8%
	Tx	41	29.1%
Pathological N stage	Unknown	23	16.3%
	N0	42	29.8%
	N1	25	17.7%
	N2	15	10.6%
	N3	2	1.4%
	Nx	34	24.1%
Grade	1	3	2.1%
	2	98	69.5%
	3	21	14.9%
	Unknown	19	13.5%
Margin	Negative	137	97.2%
	Positive	4	2.8%
CRM	Negative	122	86.5%
	Positive	19	13.5%
LVSI	Negative	129	91.5%
	Positive	12	8.5%
ECE	Negative	137	97.2%
	Positive	4	2.8%
PNI	Negative	138	97.9%
	Positive	3	2.1%
Pathological staging	Unknown	7	5.8%
	Stage 1	12	10.0%
	Stage 2	28	23.3%
	Stage 3	52	43.3%
	Stage 4	21	17.5%
Adjuvant TTT	CCRTH	19	13.5%
	Chemo	73	51.8%
	None	48	34.7%

Table (3): Survival data

		`1	Column N %
Relapse	Yes	56	39.7%
	No	85	60.3%
DFS (months) (mean ± SD)		19.9 (21.8)	12 (2-33)
Status	Dead	42	46.2%
	Alive	49	53.8%
OS (months) (mean ± SD)		32 (22.4)	26 (14-47)

Table (4): Disease free survival

		DFS (months)					Log rank test	P value
		Mean	SD	Median	25th	75th		
pT	T0	4.0	.	4.0	4.0	4.0	4.4	0.48
	T2	24.8	25.2	20.0	2.0	46.0		
	T3	22.2	22.8	14.0	4.0	33.0		
	T4	8.0	9.2	6.0	.0	18.0		
	Tx	17.3	19.9	9.0	.0	34.0		
pN	N0	26.9	21.3	24.0	7.0	36.0	11.1	0.02
	N1	10.4	17.4	2.0	.0	15.0		
	N2	20.7	27.1	5.0	.0	48.0		
	N3	15.0	21.2	15.0	.0	30.0		
	Nx	17.1	21.8	7.0	.0	45.0		
Metastatic at time of diagnosis	No	21	21	14	2	34	3.3	0.069
	Yes	11	25	1	0	8		
Grade	I	52.0	.	52.0	52.0	52.0	3.9	0.14
	II	21.3	22.0	14.0	4.0	33.0		
	III	11.1	16.7	1.0	.0	30.0		
Margin	Negative	20.6	22.1	12.5	2.0	33.5	0.1	0.75
	Positive	7.0	7.7	5.0	2.0	12.0		
CRM	No	21.3	21.5	14.5	2.0	34.5	3.5	0.06
	Yes	12.1	22.9	3.0	.0	11.0		
LVSI	No	19.5	20.7	12.5	2.0	33.0	0.05	0.81
	Yes	24.5	32.2	9.0	.0	50.0		
ECE	No	19.3	21.1	12.0	2.0	33.0	0.23	0.63
	Yes	36.0	39.3	30.0	.0	78.0		
PNI	No	20.0	22.1	12.0	2.0	33.0	0.23	0.63
	Yes	19.3	16.8	28.0	.0	30.0		
Pathological staging	Stage 1	37.6	24.6	45.0	18.0	50.0	13.5	0.009
	Stage 2	28.6	20.3	26.5	12.5	36.0		
	Stage 3	12.0	17.8	2.0	.0	22.0		
	Stage 4	12.8	26.7	3.0	.0	9.0		

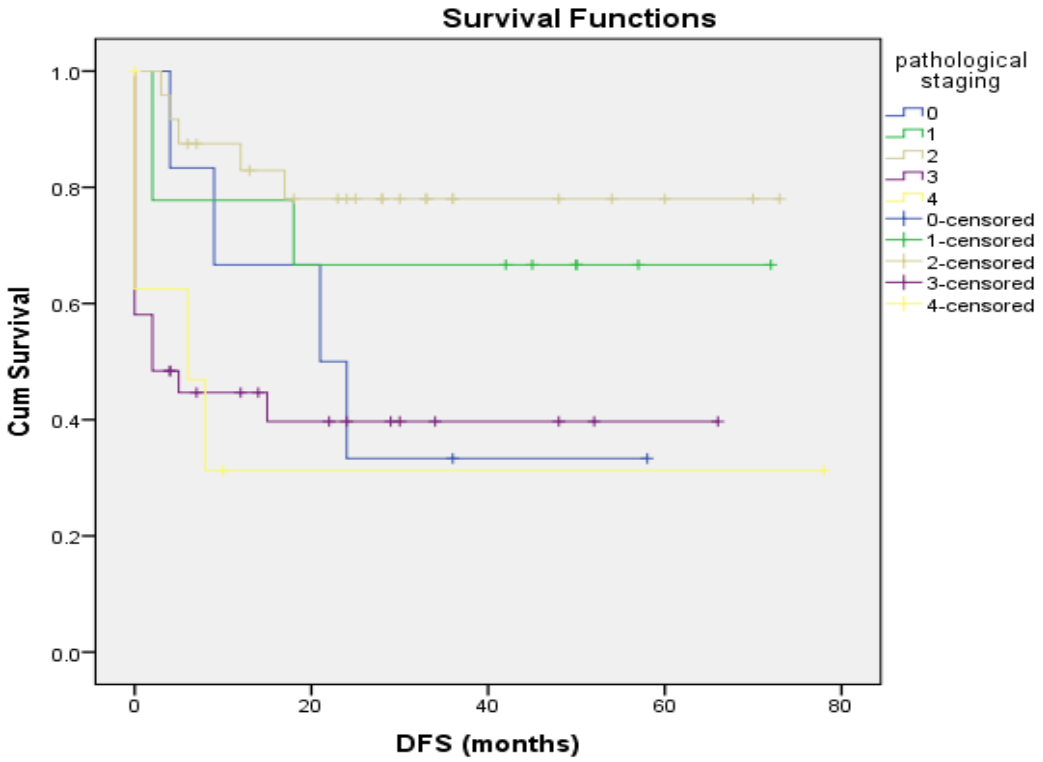

Figure (2): Kaplan Meier curve showing DFS based on pathological staging.

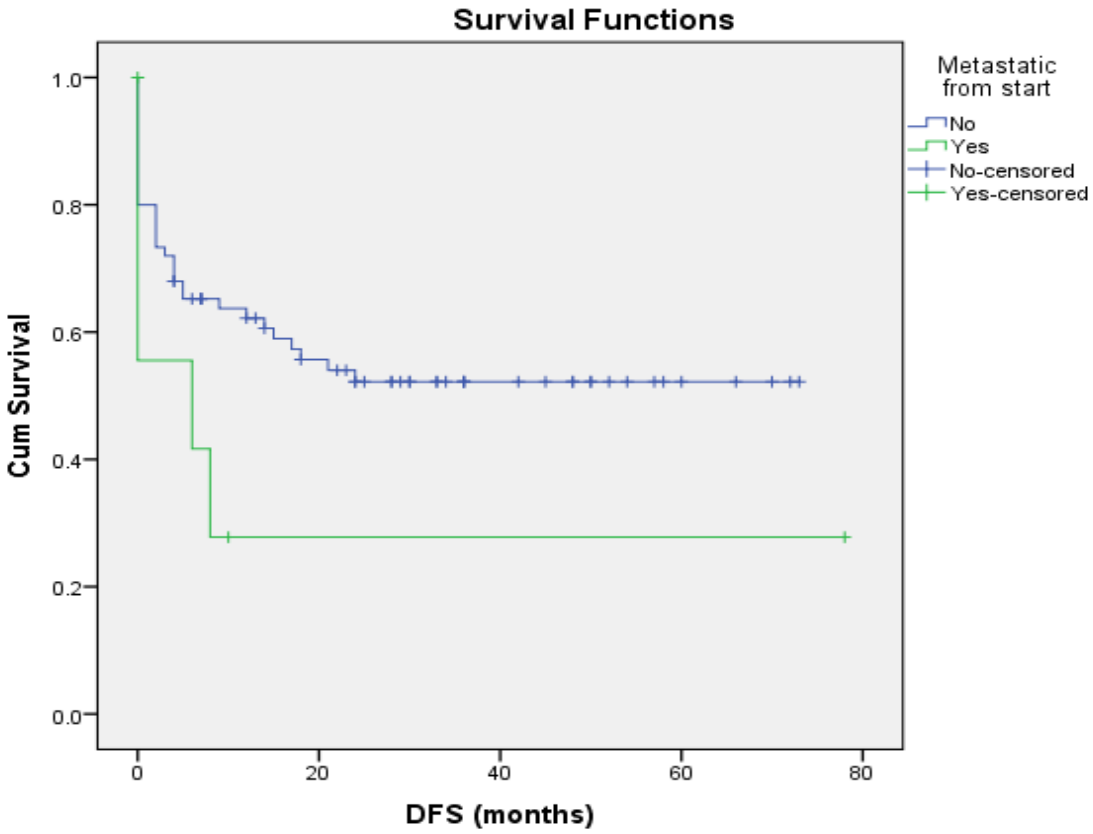

Figure (3): Kaplan Meier curve showing DFS based on M stage.

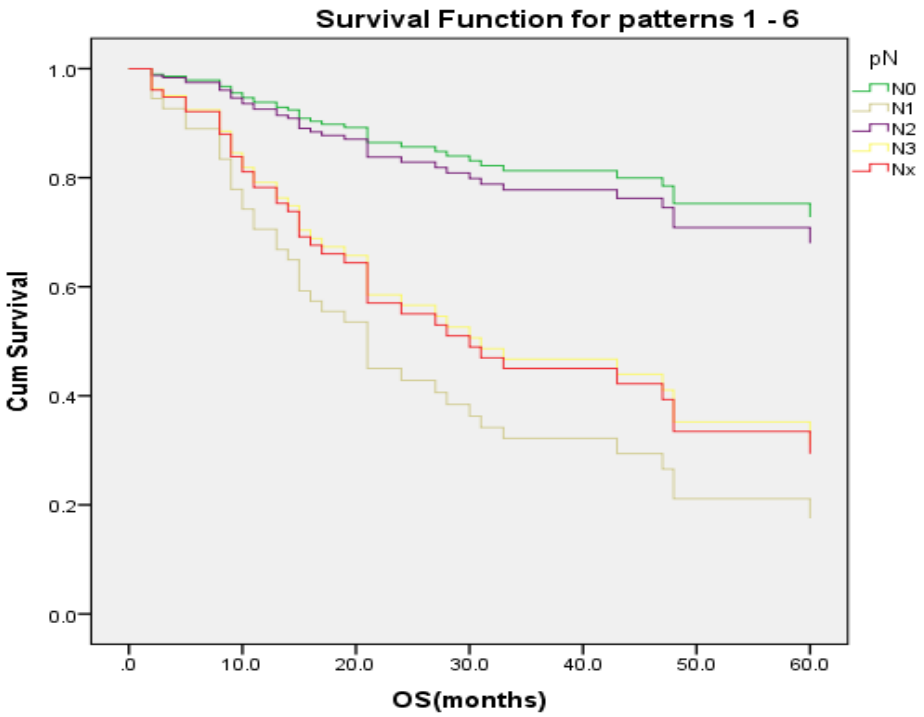

Figure (4): Kaplan Meier curve showing OS based on N stage.

Table (5): Overall survival

		OS (months)					Hazard ratio	P value
		Mean	Standard Deviation	Median	25th	75th		
pT	T0	26.0	0	26.0	26.0	26.0	1.02	0.01
	T2	37.0	26.4	28.0	15.0	63.0		
	T3	40.1	22.5	39.5	19.0	52.0		
	T4	25.5	4.9	25.5	22.0	29.0		
	Tx	25.7	20.6	19.0	9.5	38.5		
pN	N0	44.3	20.3	45.0	29.0	56.0	1.12	0.004
	N1	23.3	19.2	18.5	13.5	27.0		
	N2	35.5	25.2	22.5	18.0	57.0		
	N3	26.0	18.4	26.0	13.0	39.0		
	Nx	25.7	22.2	17.0	9.0	43.0		
Metastatic from start	No	36.6	21.6	33.5	19.0	52.0	3.17	0.0001
	Yes	16.0	17.5	11.0	9.0	15.0		
Grade	1	43.0	31.1	43.0	21.0	65.0	0.56	0.58
	2	35.2	22.4	31.0	17.0	48.0		
	3	22.0	17.1	15.0	11.0	39.0		
Margin	Negative	32.3	22.7	26.0	13.5	47.5	1.2	0.84
	Positive	23.3	5.1	22.0	19.0	29.0		
CRM	No	32.7	22.2	26.0	15.0	48.0	0.68	0.42
	Yes	27.6	24.0	22.0	9.5	39.5		
LVSI	No	31.6	21.4	25.5	14.5	46.5	0.94	0.92
	Yes	37.7	33.8	30.0	10.0	84.0		
ECE	No	31.4	21.9	25.0	14.0	46.0	21.3	0.43
	Yes	61.5	31.8	61.5	39.0	84.0		
PNI	No	32.1	22.6	25.5	14.0	47.5	1.2	0.85
	Yes	29.7	18.8	39.0	8.0	42.0		
Pathological staging	Stage 1	53.9	20.7	61.0	41.0	64.0	3.3	0.002
	Stage 2	46.5	18.7	45.0	35.0	52.0		
	Stage 3	26.7	19.6	21.0	12.0	39.0		
	Stage 4	15.3	18.3	10.0	9.0	15.0		

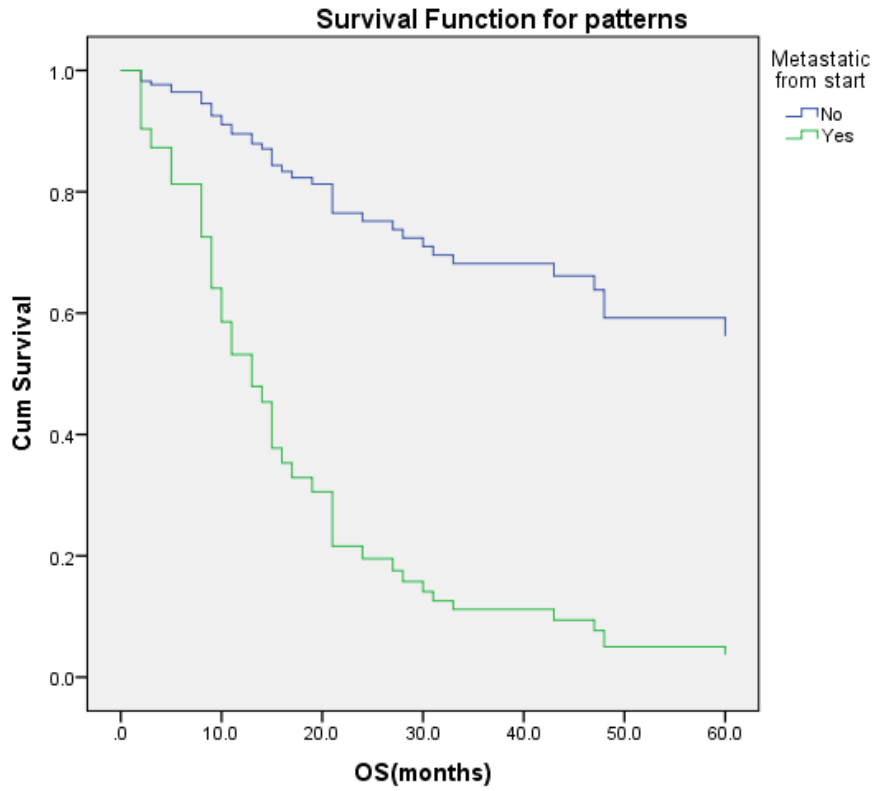

Figure (5): Kaplan Meier curve showing OS based on M stage.

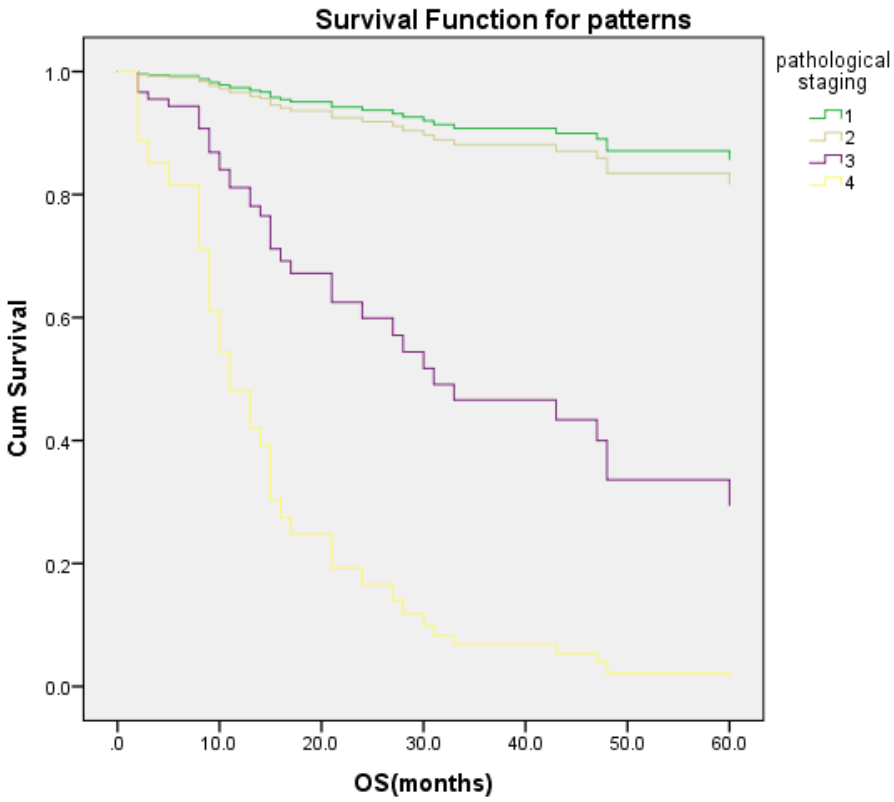

Figure (6): Kaplan Meier curve showing OS based on pathological staging.

DISCUSSION

In our retrospective study, which included patients with colorectal cancer presented at our department during the period from 2013 to 2020, the age ranged from 22 years to 72 years old with mean age of 47.3. According to the American cancer society, the mean age of incidence of rectal cancer in the United States was 63 both in males and females. Fifty-eight patients were younger than the age of 40, around 41% and 63 patients (44.6%) were younger than the age of 50. This is in alignment with the world trend of increasing incidence among young ages, as the median age of incidence has dropped from 72 years to 63 years old, indicating more adoption of sedentary westernized lifestyles among patients [(12)]. Surprisingly in our sample females 89 outnumbered males 52 (63% vs 37%, respectively), which is opposite to the international male domination over females of incidence (62% vs 38%) [(12)] raising further social study questions of acquiring more sedentary lifestyles amongst females e.g., obesity, immobility or improper diet.

Positive family history was present in 20 patients (14%) which was comparatively acceptable percentage worldwide. In some other countries like in the united states screening efforts and early detection in positive family has achieved fruitful lowered incidence rates amongst diagnosed patients than most internationally cited 10%[(13)]. Most of our patients presented with performance status of 1 (48%), which is logical to be linked to the fact that majority of tumors are locally advanced T3 upon presentation, causing local symptoms earlier as the rectum being anatomically distal. The CAIRO study revealed more favorable median OS of 20 months with good performance status vs 10 months with patients with PS2 [(14)].

The most common presenting symptoms were bleeding per rectum 48% followed by change in bowl habits 26% then pain 15%. These are similar to study performed in Boston USA [(15)]. More than 90% of the patients presented with adenocarcinoma with the mucinous subtype comprising 23%, this was in accordance with the international rate of adenocarcinoma prevalence except that mucinous adenocarcinoma globally occurs at a rate of no more than 5-15 % [(16)]. Signet ring cell carcinoma represented 4.5% of all cases where globally it does not occur in more than 1% of the cases, together mucinous and signet ring behave more aggressively than conventional adenocarcinoma and carry worse prognosis [(17)]. Other subtypes encountered were GIST, neuroendocrine, and rectal melanomas, no medullary subtypes were encountered. In conventional adenocarcinoma, moderately differentiated type comprised 70% of the cases while poorly differentiated represented around 15%, which is same to the incidental percentage globally [(17)].

Viewing importance of tumor markers in screening and early diagnosis of colorectal cancers, carcinoembryonic antigen (CEA) is a simple and cheap test for a glycoprotein that is secreted from the epithelial cells of the colorectum, and in elevated levels in CRC. Normal cut off upper level 5 ng/dl. Out of 62 available pretreatment CEA levels in our study, elevated CEA were detected in 31 patients with 50% sensitivity. In a study of 450 Chinese colorectal cancer elevated CEA were found in 39-41% of population between stages 2-3 while sensitivity for elevated CEA in rectal cancer was 35% with p value 0.223, which concludes that pretreatment CEA levels where not sensitive in detecting CRC in early stages, rendering reliance alone on serum tumor markers in diagnosis of CRC, of no greater value rather than assessment and follow up of the tumor burden [(18)].

In our survival analysis the pT stage was not found to significantly impact DFS (p value 0.48) with median DFS for pT2 cases was 20 months vs 6 months for T4 and 9 months for Tx. However in a single institutional retrospective study revealed statistically significant effect of T stage on DFS (p value 0.003 & HR 0.165) [(19)].

The most important factor impacting DFS was the overall pathological staging, having median DFS of 45 months for stage 1, 26.5 months for stage 2 and 3 months for stage 3 (p value 0.009) this is compared with another single institutional retrospective cohort that revealed p value less than 0.0001. However, median follow up survival periods were significantly better than in our study median DFS for stage 1 was 110 months vs 25 months in stage 4 which necessitates the need for further investigation in standards of care differences for significantly shortened survival rates for our study population [(20)].

Regarding overall survival, there was a significant correlation on basis on T stage unlike DFS with p value 0.01; mean OS for T2 is 37 vs unassessed Tx was 25.7. Nodal status was also significant with (p value 0.004) with longer OS for node negative than positive patients (HR 1.12). This is when compared to a meta-analysis of 5 randomized rectal trials in north America that revealed also statistically significant ($p< 0.001$) impact of pT stage on OS with difference in 5 year OS between T2 and T4 75% and 47% respectively, and p value < 0.001 for N stage with 5 year OS 74% for N0 vs 43% in N2 [(21)]. Again the overall stage had the strongest significance on OS p value 0.002 HR 3.3, according to **Jarrar *et al***. [(20)].

The OS survival was found to be significantly correlated with PS (p value < 0.001), longest OS was for patients with PS 0 and 1 (47 and 62 months, respectively). Compared to less favorable OS for patients with PS 2 and 3 (21 and 13 months, respectively). The OS survival rates were actually longer when compared to a survival analysis done to

patients of the CAIRO study, which was also significant based on PS (p value <0.001) with median OS for patients PS 0,1,2 were 18.9, 14.7, and 12.9 months, respectively [17].

CONCLUSION

Pathological staging was the most significant factor affecting survival, while patients with locally advanced rectal cancers were potentially curable and had extended survival rates after receiving full multimodality treatments.

Fund: None
Conflict of Interest: None.

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