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Original article

Comparative Analysis of Clinicopathological Profiles and Survival Outcomes of Early-Onset Versus Late-Onset Colorectal Cancer Patients

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Abdsalam Rabie[1]*, Mamduh Gaber[2], Monsef Algouti[1], Fatma Belgasem[1], Abdusalam Sohoub[1], Makbola Algazeri[1], Mussa Alragig[1], Ibtisam Mlouda[1], Mohamed Elfagieh[1], Eramah Ermiah[2,3]

[1] Department of Surgery, National Cancer Institute, Misurata, Libya
[2] Department of Medical Oncology, National Cancer Institute, Misurata, Libya
[3] Medical Research Unit, National Cancer Institute, Misurata, Libya and Faculty of Medicine, Alzawia University, Alzawia, Libya.
***Correspondence**: elrabei22@yahoo.com

Abstract

Aims*. To study the clinicopathological characteristics and survival of patients with early onset colorectal carcinoma (CRC) (i.e., patients with age of < 50 years at time of diagnosis) versus late onset CRC (i.e., patients with age of ≥ 50 years at time of diagnosis) patients.* ***Methods****. A total of 182 patients with early-onset CRC and 284 patients with late-onset CRC diagnosed during 2008–2017 were included. The demographic and clinicopathological characteristics of patients with early-onset CRC were compared with those of patients with late-onset CRC. Kaplan-Meier survival analysis and Cox regression analysis was performed to determine the patient's prognosis.* ***Results****. The early onset and late onset CRC groups represented of 39.1% and 60.9%, respectively. The late onset group were diagnosed with a higher proportion of positive Rh antigen, comorbidities and obesity (61.4%, 70.6 % and 71.2% respectively). The early onset group was diagnosed with a higher proportion of signet ring cell carcinoma (61.9%, P = 0.018) and distant metastasis (62.0%, p > 0.0001). Moreover, low expression of CEA (CEA < 5ng/ml) was more common in late onset group than early onset (73.1% vs. 26.9%; p < 0.0001). Rectal bleeding and the rectum tumor site were more common among the early onset patients (63.5 % and 60.2 respectively). However, there was no significant difference between the two groups regarding gender distribution, address, family history and histological grade. During a median of 46 months of follow-up, 44.0% of patients had died from CRC. Shorter survival rates were observed in the early onset group CRC (p < 0.0001). The late onset CRC were associated with a low recurrence rate (p < 0.0001). Based on the multivariate analysis, clinical stage and age at diagnosis are independent risk factors for both overall survival and disease-free survival.* ***Conclusion****. The clinical stage and age at diagnosis are an independent prognostic factor for patient's outcome. The early onset group of CRC patients is more advanced at the time of diagnosis, and they should be evaluated promptly and carefully.*

Keywords: *Locally Advanced Rectal Cancer, Colorectal Cancer, Libya, Preoperative and Postoperative Chemoradiation, Patient's Outcomes.*

Introduction

According to the latest global statistics colorectal cancer (CRC) ranks the second cause of death among cancer types (9.4% of cancer deaths in 2020), and the third cancer in regard to the incidence (10% of new cases in 2020 [1]. Recent studies showed an increasing incidence of CRC in younger patient when compared to older patients [2,3].

Patients with early and old-onset CRC differ in demographic, molecular and clinical characteristics [4-6]. Numerous studies show that the young onset has a bad prognosis but other

studies on the other hand do not [7-12]. The possibility of lymph-node involvement and advanced staging of the tumour in young patients (younger than 40 years old) was more than the old ones [9]. In a large study with 369,796 patients (and a cut-off age of 50-year-old), observed that younger patients had bad prognosis with more signet ring cell and potential metastases than older patients [10].

Contrast in the survival rate an additional different conclusion from other studies; as an Iranian study showed lower survival rate in the younger patients (younger than 40 years old), where another study shows no difference in survival rate with patients younger than 50 years old, though the younger patients had a better presentation (with less adenocarcinomas) and some better post-operative scenarios [11,12].

Due to the large variations in the studies of CRC age groups in cut-off for age categories and also different contrasting results. Thus, we conducted the present study to identify the differences, complication and associated problems of each age group in a Libyan cohort with CRC for better understanding. A better understanding of such information will lead our institution (NCI) to take more evidence based clinical decisions, and more science justified policies in the future.

Methods

Study population

A total of 466 patients with CRC (aged 22-90 years, the mean age was 53.26 years) diagnosed and treated from January 2008 to December 2017 at the National Cancer Institute, Misurata, Libya, were studied respectively. The patients were divided into two groups, a younger group (i.e., 182 patients with age of < 50 years at time of diagnosis) and an older group (i.e., 284 patients with age of ≥ 50 years at time of diagnosis).

The data on age, gender. address, occupation, blood group, body mass index, past medical history, family history, clinical presentations, tumour location, lymph node status, histological grade, clinical stage, pre-treatment carcinoembryonic antigen (CEA), type of treatment and follow-up data were recorded for all patients. These data were collected from the patients' records.

Tumour staging of CRC was evaluated according to the American Joint Committee on Cancer (AJCC), TNM classification [13]. A CEA level equal or higher than 5 ng/ml was considered abnormal [6].

Pan-colonoscopy and radiological staging by Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) was performed in all patients to assess tumour extension. The extent of the tumour (local or distant) at the time of diagnosis was confirmed by imaging [CT, MRI, or Positron Emission Tomography (PET)].

Primary tumours located at the cecum, ascending colon, and transverse colon were considered as right colon cancer (RCC), whereas primary tumours located at the splenic flexure, descending colon, and sigmoid colon were considered as left colon cancer (LCC). Primary tumour considered as rectal cancer if it was located within 12 cm from anal verge [14].

Treatment and follow-up.

Radical surgery was done in 329 patients (70.6%), palliative surgery was done in 80 patients, and no surgical intervention for 57 patients who had metastasis at the time of diagnosis. Colonoscopy and/or sigmoidoscopy with biopsy were performed in these patients for histopathological diagnosis.

Following to our institution local guidelines, adjuvant combined chemotherapy based on FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and/or XELOX (oxaliplatin and capecitabine) was given to 318 patients and 113 patients received palliative chemotherapy with FOLFIRI (folinic acid, fluorouracil, and irinotecan) and/or capecitabine. In addition, 35 patients did not receive chemotherapy who had early stage and/or were not eligible for chemotherapy. Neoadjuvant concurrent chemoradiotherapy was given to rectal cancer patients (n=88).

Follow-up of patients was carried out every 3 months for 2 years, 6 months for 5 years, and thereafter every 1 year. Disease recurrence (local or distant metastases) was confirmed by colonoscopy and imaging (CT, MRI, or PET) performed when clinical symptoms suggestive presence of disease recurrence. Patients' outcomes were considered as follows: overall survival (OS), duration between the date of pathological diagnosis to the date of death and/or to date of the end follow up period; disease-free survival (DFS), duration between the date of pathological diagnosis to the date of diagnosis of recurrence (local and/or distant metastases) or death [15].

Patients were followed up until death or to the end of the observation period (until December 2021). The median follow-up duration was 46 months (range, 4-116 months). At the end of follow up period, 205 patients (44.0%) had died of CRC.

Statistical analysis

Data of all categorical variables are summarized using frequencies and percentages. Frequency tables were analysed using the Chi-square test, with likelihood ratio (LR) to assess the significance of the correlation between the categorical variables. Survival analysis (overall survival and disease-free survival) was calculated using Kaplan- Meier curves method. Survival rates were compared by the log-rank test. A multivariate analysis was performed using the Cox model. When a P-value was less than 0.05, the difference was considered significant. SPSS 26.0 statistical software was used for data analysis.

Ethical approval

The cohort study was done under research ethics approval by ethical committee at the National Cancer Institute, Misurata. Written informed consent was obtained from all patients for surgical treatment, pathologic examinations and investigations performed according to the institutional guidelines of the National Cancer Institute, Misurata, Libya.

Results

Patient sociodemographic, genetic, clinicopathological and biological variables.

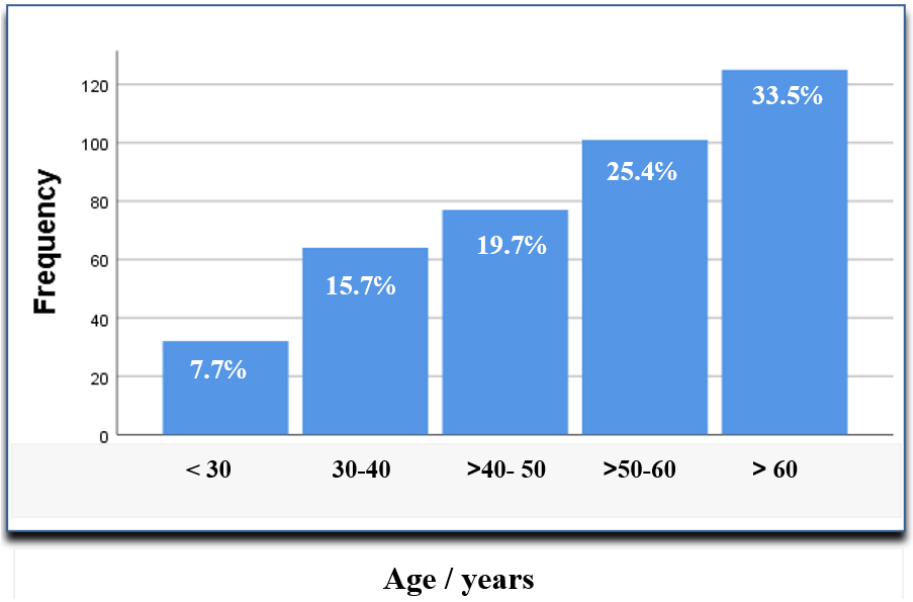
The sociodemographic, genetic, clinicopathological and biological variables of patients according to the age categories (< 50 vs. ≥ 50 years) are represented in Table I and II.

Table I. Comparative analysis of sociodemographic and genetic variables in young (<50 year) and old (≥50 year) CRC patients.

Variables		**No of patients**	**Age group (%)**		**P-value**
			< 50 years	≥ 50 years	
Gender	Male	234	37.2	62.8	0.230
	Female	232	40.9	59.1	
Address	Urban	378	38.6	61.4	0.390
	Rural	88	40.9	59.1	
Body mass index	Underweight	25	44.0	56.0	**0.046**
	Normal	238	39.1	60.9	
	Overweight	130	43.8	56.2	
	Obese	73	28.8	71.2	
ABO blood group	A	205	39.5	60.5	0.141
	B	56	51.8	48.2	
	AB	14	42.9	57.1	
	O	191	34.6	65.4	
Rh antigen	Rh +	386	38.1	61.9	0.347
	Rh -	80	43.8	65.2	
Co-morbidity	Yes	112	29.5	70.6	**0.016**
	No	354	42.1	57.9	
Family history	Positive	15	40.0	60.0	0.569
	Negative	451	39.0	61.0	

The mean age of patients at diagnosis was 53.26 years (range: 22-90 years). Of total, 182 (39.1%) patients were <50 years (the youngers group) and the remaining 284 (60.9%) were ≥ 50 years (the older group) Figure 1.

Figure 1. Age distribution at diagnosis of 366 patients with colorectal cancer in Libya (2008-2017).



Both groups did not differ significantly with respect to gender distribution (p = 0.230), address (p =0.390) and family history (p = 0.569). A higher percentage of older patients reported positivity of Rh antigen in comparison to the other group, but was not statistically significant (61.4% vs. 38.6%; p = 0.096). While, comorbidities and obesity are more prevalent among the older patients (70.6 % and 71.2% respectively) with statistically significant (p= 0.046).

Regarding the clinicopathological and biological variables between two groups. Rectal bleeding was the most prevalent symptom among the younger patients (63.5 % of patients). While, 75% of the older group were presented with bowl habit changes (p= 0.025).

The rectum was the frequent location in CRC, with more frequent among young group than among older ones (60.2 % vs. 39.8%, P > 0.05). While, left colon cancer was more common among older patients in comparison to the younger ones, but was not statistically significant (66.7% vs. 33.3%, p = 0.095).

Adenocarcinma was the commonest histological type in CRC and reported in 62.7% of patients ≥ 50 years. Compared with the older group, significantly more patients in the younger group had signet ring cell carcinoma (61.9% vs. 38.1%, P = 0.018).

The percentages of patients with negative lymph nodes, T1 stage, clinical stage I, distance metastasis, and CEA < 5ng/ml were 26.9%, 22.2%, 17.4%, 62.0% and 29.0%, respectively, in the younger group, and 73.1%, 77.8%, 82.6%, 38.0% and 71.0%, respectively, in the older group, with a highly significant differences between the two groups (p <0.0001, <0.0001, <0.0001, <0.0001 and <0.0001, respectively) Table 2.

In this study, there was no significant difference between the two groups in the tumour differentiation (P = 0.552).

Table 2. Comparative analysis of clinicopathological and biological variables in young (<50 year) and old (≥50 year) CRC patients.

Variables		No of patients	Age group (%)		P-value
			<50 years	≥ 50 years	
Presentation at diagnosis	Intestinal obstruction	194	42.3	57.7	0.025
	Rectal bleeding	159	63.5	36.5	
	Bowel habits change	52	25.0	75.0	

	Abdominal pain	29	44.8	55.2	
	Anaemia	20	35.0	65.0	
	Other presentations	12	75.0	25.0	
Site of tumour	Right colon	115	46.1	53.9	0.095
	Left colon	165	33.3	66.7	
	Rectum	186	60.2	39.8	
Histological types	Adenocarcinoma	410	37.3	62.7	**0.018**
	Mucinous carcinoma	35	45.7	54.3	
	Signet ring carcinoma	21	61.9	38.1	
Histological grade	Grade I	60	35.0	65.0	0.552
	Grade II	282	38.3	61.7	
	Grade III	124	42.7	57.3	
Lymph node status	Positive	223	35.4	64.6	**<0.0001**
	Negative	145	26.9	73.1	
	Nx	98	65.3	34.7	
T	T1	9	22.2	77.8	**<0.0001**
	T2	31	32.3	67.7	
	T3	285	31.3	68.2	
	T4	75	37.3	62.7	
	Tx	93	64.5	35.5	
N	N0	143	25.9	74.1	**<0.0001**
	N1	110	31.8	68.2	
	N2	118	39.8	60.2	
	Nx	95	66.3	33.7	
Clinical stage	Stage I	23	17.4	82.6	**<0.0001**
	Stage II	118	26.3	73.7	
	Stage III	188	33.0	67.0	
	Stage IV	137	62.0	38.0	
M	M0	329	29.5	70.5	**<0.0001**
	M1	137	62.0	38.0	
*CEA level (u/ml)	< 5	162	29.0	71.0	**<0.0001**
	≥ 5	237	47.7	52.3	
	Unknown	67	32.8	67.2	

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen

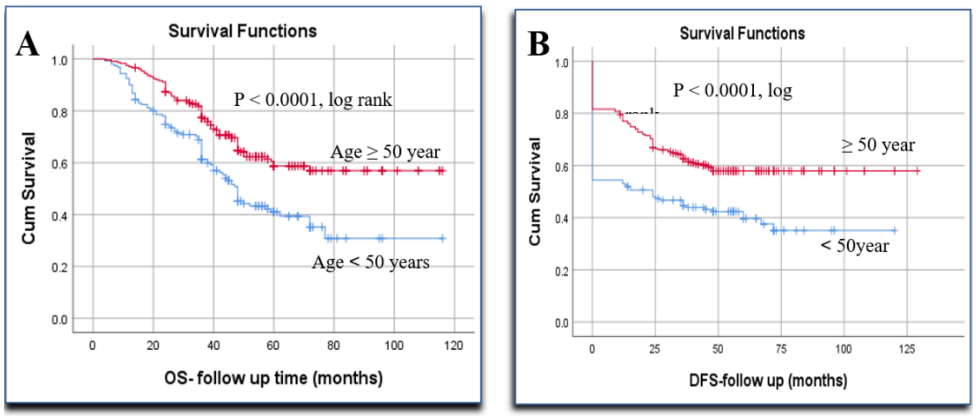
Patients' outcome

Univariate analysis showed that there was a significant difference in overall survival and disease-free survival between the two groups Table 3 and Figure 2. The survival rate was 44.00 % in the younger group and 63.70% in the older group ($p < 0.0001$). Kaplan-Meier survival curves showed that shorter survival was observed in the younger group patients ($p < 0.0001$). On the other hand, old patients were associated with a low recurrence rate and therefore had longer disease-free survival ($p < 0.0001$).

Table 3. Univariate survival analysis (overall survival) of young and old CRC patients (n=399).

Variables	Age group	No of patients	Survival analysis Overall survival (OS)			P-value
			Median OS (months)	Mean OS (months)	Survival rate (percent)	
All patients		466	46.00	47.40	56.00	**<0.0001**
Age at diagnosis / years	< 50	182	38.17	41.10	44.00	
	≥ 50	284	47.79	49.05	63.70	

Figure 2. (A and B). A: OS according to analysis of age at diagnosis (young vs old) in CRC patients (Kaplan-Meier curves). B: DFS according to analysis of age at diagnosis (young vs old) in CRC patients



However, Cox regression analysis revealed clinical stage (p <0.0001) and age at diagnosis (p = 0.017) are an independent of overall survival as assessed in a multivariate survival (Cox) analysis containing gender, tumour site, histology type and histological grade variables. For DFS, the same model was used to assess the role of these variables (age at diagnosis, gender, tumour site, histology type, histological grade and clinical stage) as an independent predictor of DFS. The clinical stage also proved to be an independent predictor (p <0.0001), again with age (p = 0.019) table 4.

Table 4. Multivariate analysis (Cox proportional hazard model) of prognostic factors for 466 patients with colorectal cancer.

Variables	Overall survival model			Disease free survival model		
	Hazard Ratio (95% CI)	SE	P value	Hazard Ratio (95% CI)	SE	P value
Age (<50 years / ≥50 years)	1.407 (1.063-1.861)	0.143	**0.017**	1.378 (1.055-1.799)	0.136	**0.019**
Gender (male / female)	0.938 (0.708-1.241)	0.148	0.653	0.980 (0.752-1.277)	0.135	0.882
Clinical Stage (I + II / III + IV)	20.532 (9.547-44.155)	0.391	< **0.0001**	11.637 (6.293-21.650)	0.315	**<0.0001**
Tumour site (Colon / rectum)	1.207(0.906-1.608)	0.141	0.199	1.110 (0.847-1.455)	0.138	0.449

Histology type (adenocarcinoma /others)	0.807 (0.527-1.236)	0.217	0.324	0.926 (0.619-1.385)	0.205	0.707

Discussion

A plethora of studies over the last ten years have highlighted the epidemiologic phenomenon of early-onset CRC [4-6]. Nevertheless, this is the first age-stratified analysis in Libya to assess and compare the demographic features, clinicopathological profile, and survival outcomes in CRC patients.

For a long time, CRC was considered the disease of the elderly. Albeit the incidence of early-onset CRC has appallingly increased in several countries over the past decade, mainly in European and western countries [16, 17]. In the absence of a standard definition of "young patients", it is difficult to compare among different reports. Several studies have used a cut-off age of 40 [9]. whereas some have used an age of 50 years [10]. In this study, we defined an age of 50 based on the recommended age for initiating CRC screening in the general population according to several guidelines [18].

Among a total of 466 patients with CRC diagnosed and treated at our institution from 2008 to 2017, 182 (39.1%) were young patients; this incidence is in line with a recent study in Iran [11], and higher than previous data in other African countries, which reported a lower proportion of that age group [19]. The mean age of patients at diagnosis was 53.26 years, which conforms with the previous study conducted in Libya [20] and others in Egypt [21]. Comorbidities and obesity are more prevalent among the older patients compared with the younger patients, whereas there is no significant difference concerning gender distribution, family history, and positivity of the Rh-antigen among both groups.

Early-onset CRC presents with rectal bleeding, abdominal pain, changes in bowel habits, unintended weight loss, and iron-deficiency anaemia. Our data revealed that among the younger patients, rectal bleeding was the most prevalent symptom (63.5% of patients), whereas 75% of the older patients presented with bowel habit changes.

In contrast to our findings, which reveal that there was no significant difference between the two groups in tumor differentiation, various studies have reported that CRC in young patients is more likely to have poor differentiation [22].

Previous studies have established that CRCs in young patients are located predominantly in distal locations, a cohort study reported that 39.3% of CRCs in young patients are located in the rectum. Whereas in patients over the age of 50, this percentage drops to 26.7% [23]. In this study, 63.5% of CRCs in young patients occurred in the rectum, which was in agreement with other studies [16 and 23].

Whereas among older patients, the left colon was the most frequent site, however, these findings were not statistically significant. Our data showed that significantly more patients in the younger group had signet ring cell carcinoma, and this has been demonstrated in several previous studies [10 and 24]. Whereas adenocarcinoma was the most prevalent histological type in CRC and was reported in 62.7% of older patients. In the present study, more young patients had advanced-stage cancers at stage III or IV compared with older patients. A systematic review has found an average of 66% of young patients presented with later stages at the time of diagnosis [25].

It is worth noting that negative lymph nodes, T1 stage, clinical stage I, and CEA < 5ng/ml are observed more in the older patients' group. In addition, distant metastasis was more common among younger patients, which were 62 %, as compared to 32 % in the older age group. The presence of a higher proportion of advanced cancers can be ascribed to the absence of population-based screening and well-time access to healthcare [26]. Furthermore, the possibility of delayed diagnosis resulting from low suspicion of malignancy in this age group is another contributing factor [27].

In addition to demographic and pathological characteristics, our analysis addressed survival outcomes. During a median of 46 months of follow-up, 205 patients (44.0%) had died from CRC. In terms of overall survival and disease-free survival, there was a significant difference between the two groups. Shorter survival rates were observed in the younger patients compared to older patients, the survival rates in the younger group and the older group were 44.00 % and 63.70% respectively. furthermore, old patients were associated with a low recurrence rate, consequently, they had longer disease-free survival, these findings were in agreement with several previous reports [6-8]. Moreover, Shuyuan et al accomplished a large multi-institutional database analysis and reported that young patients presented with

more advanced disease and were more likely to have a recurrence, however, overall and stage-specific survival in young patients were better than in older patients [28].
According to multivariate analysis, clinical stage and age at diagnosis are independent risk factors for both overall survival and disease-free survival. There is a perception that CRC in young patients has a worse prognosis than in older patients, nevertheless, this remains controversial [9-12]. This perceived worse prognosis is thought to be attributed to the aggressive histopathological features of CRC tumors. Other contributing factors include delay in diagnosis and the absence of a proper screening thought to be of significance [26 and 27].
This analysis has some limitations. Given that this was a single- institution retrospective analysis, only a single source of previously documented data was available for assessment. In addition, genetic testing was not conducted in these patients, and the frequency of hereditary non-polyposis colorectal cancer was not collected in the current database and could not be analyzed. Notwithstanding, the study population was relatively large, and the median duration of follow-up was 47 months. Moreover, owing to the relevant data regarding the clinicopathological profile and survival outcomes, this study provides another piece of knowledge to both regional and world databases, supporting further valid conclusions.
In summary, the current study revealed that patients with early-onset CRC have more signet ring-cell carcinoma, a later stage, and more distant metastasis compared with late-onset CRC patients. Furthermore, they have worse survival outcomes. Despite these specific clinicopathological characteristics, the delayed diagnosis could be one of the contributing factors to the overall survival outcome. Hence, along with the proper screening, clinicians should set a low threshold for suspicion in young patients presenting with symptoms similar to those of CRC to overcome a delayed or missed diagnosis in young patients. Further prospective studies are required to emphasize these analysis findings, alongside the constant collection of clinical data, for more comprehensive and precise results in the future

Authors' contributions

AR performed designed the present study, drafted manuscript and the writing. MG, MA, FB, AS, MA, MR and IM analyzed data, review the manuscript, performed data interpretation and analysis. ME drafting and proof reading and discussions. EE conducts the statistical analysis and prepares the figures and Tables and reviewed the study, interpreted data and aided in drafting and proof reading of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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