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Original Article

Epidemiological evaluation focusing on prognostic impact of young age in Egyptian patients with colorectal Cancer, NEMROCK experience

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Background: Colorectal cancer (CRC) is usually a disease of older patients. Despite this fact, we noticed a higher percentage of patients presented at younger age group (between 20 – 40 years). So we planned this study to document the real incidence of age and other epidemiological features of CRC patients, with focus on the prognosis of young age on disease outcome.
Patients and Methods: Between 2005 and 2011, 288 cases with CRC were recruited from Kasr–Al Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK), Faculty of medicine, Cairo University. Epidemiological features were analyzed for all patients and impact of younger age on prognosis was analyzed.
Results: Patient age ranged between (16-80 years) with a median age of (48.0 year). Forty years or younger patients (≤40 years) represented 100/288 patients (34.7%). Male prevalence was higher 164/288 (56.9%). In earlier stages (stage I-III), patients (≤40 years) presented more often with stage III (47.5%) than stage I-II while in patients (> 40 years) usually present with stage I-II (40.8%) not reaching statistical significance (*P*= 0.3). In stage I-III patients, 5-years disease free survival were 47% for patients (≤40 years) versus 60% for older patients (*P*= 0.069). 5-years overall survival for patients (≤40 years) were 50.87% versus 64% for older patients (*P*= 0.037). In stage IV disease, median progression free survival for patients (≤40 years) was 3.5 months (95% 2.276 to 4.724) versus 5 months (95% 2.276 to 4.724) for older patients (*P*= 0.03). Median overall survival for patients (≤40 years) was 8 months (95% 4.736 to 11.264) versus 12 months (95% 10.74 to 13.253) for older patients (*P*= 0.02).
Conclusion: In Egyptian patients with colorectal cancer, a significant higher percentage of patients present with younger age than forty years. In early stage disease (stage I-III), patients ≤40 years carried a worse overall survival, probably due to higher percentage of stage III disease; while in stage IV, younger patients carried a worse prognosis.

Key words: Colorectal cancer, Epidemiology, Young patients, Egypt
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INTRODUCTION

Worldwide, Colorectal cancer (CRC) is the most common malignant tumor of the gastrointestinal tract. It is the third most common cancer after lung and breast cancers and the second most common cause of death in both genders[1,2]. CRC is a disease affecting mainly older persons, more than 90% of patients being diagnosed after the age of 55 years[3]. However, epidemiologic features of CRC vary widely in different parts of the world[4].

Epidemiological studies of CRC in Egypt showed that patients younger than 40 years represented a significant percentage and constituted 30% to 40% of all cases, which is the highest incidence documented in this age group for colorectal cancer patients worldwide[5-7]. In young patients, colorectal cancer tends to present more commonly with stage III or IV disease. Conflicting results about prognosis of younger patients are published, some studies proved bad prognosis and some reported to be the same like older patients[7-9].

Since data regarding prognosis of young patients with CRC in Egypt is limited, we decided to describe the epidemiological characteristics of colorectal cancer patients in Egypt and to focus on the prognosis of young patients. Data was taken from Kasr Al Ainy Center of Clinical Oncology and Radiation Therapy (NEMROCK) at Cairo University.

PATIENTS AND METHODS

From January 2005 to December 2011, 288 cases with CRC were recruited from Kasr–Al Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK),

Faculty of medicine, Cairo University.

Inclusion criteria were adult patients with colorectal cancers and histology of adenocarcinoma. Patient's records were reviewed for age, gender, site of tumor, grade, histological subtype, staging according to TNM staging system[10], date of recurrence or progression of the disease and date of death or last follow-up.

Chemotherapy received:

According to disease stage and performance status of the patients, variable types of chemotherapy regimen were taken.

5-flourouracil and leucovorin:

- Leucovorin 200 mg/m^2 IV over 2 hours on days 1&2.
- Fluorouracil 400 mg/m^2 IV push on days 1&2.
- Fluorouracil 600 mg/m^2/day IV continuous infusion over 22 hours on days 1&2.

Capcitabine:

Capecitabine 1000 mg/m^2 oral twice daily on days 1 to 14 of a 3-week cycle.

FOLFOX:

- Oxaliplatin 85 mg/m^2 IV over 2 hours on Day 1.
- Leucovorin 200 mg/m^2 IV over 2 hours on days 1&2.
- Fluorouracil 400 mg/m^2 IV push on days 1&2.
- Fluorouracil 600 mg/m^2/day IV continuous infusion over 22 hours on days 1&2.

FOLFIRI:

- Irinotecan 180 mg/m^2 over 90 minutes on day 1.
- Leucovorin 200 mg/m^2 IV over 2 hours on days 1&2.
- Fluorouracil 400 mg/m^2 IV push on days 1&2.
- Fluorouracil 600 mg/m^2/day IV continuous infusion over 22 hours on days 1&2.

Progression free survival (PFS) was calculated from the date of starting chemotherapy to date of the confirmation of disease progression or death or last follow-up. Disease free survival (DFS) was calculated from the date of surgery to the date of disease recurrence or death or last follow-up. Overall survival (OS) is defined as the time from date of surgery or pathological diagnosis until the date of death (from any cause) or the date of last follow-up.

Statistical analysis:

Data was analyzed using SPSSwin statistical package version 17 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. A P-value ≤ 0.05 was considered statistically significant. Progression and survival times were estimated using the Kaplan-Meier method.

RESULTS

This study includes 288 patients. Their age ranged between (16-80 years) with a median age of 48.0 years. In (fig.1) the age distribution is demonstrated. Patients forty years or younger represent 34.7%, and those older than forty years represent 64.3%. Out of the 288 patients, 164 patients were male (56.9%) and 124 patients were female (43.1%).

Younger patients (≤40 years) had statistical significant correlation with tumor grade III (35%) versus (7.97%) for older patients (P= 0.05). The relationship between age groups and tumor stages was statistically significant as analysis for non- metastatic patients revealed that (≤40 years) had higher incidence of stage III (59%) than in the older age group which had higher incidence of Stage II (61%) (P= 0.04) as seen in Table (1).

Regarding the histo-pathological examination, all specimens were invasive adeno-carcinoma. From all specimens 28.8% were mucinous type. Statistically analyzing data for colon and rectal cases versus various clinic-epidemiological aspects like age groups, gender, histopathology, grade, and stage of disease did not show any statistical significance of any over the other as seen in Table (2).

Patients with stage I disease (9 patients) received no treatment, just follow-up. For stage II disease (75 patients) fourteen patients were on follow-up, thirty two patients received 5-flourouracil and leucovorin regimen, five patients received capcitabine tablets and twenty four received FOLFOX regimen. For stage III disease (82 patients) seventy one patients received FOLFOX regimen and seven patients received 5-flourouracil and leucovorin regimen and four patients were on follow-up only. For stage IV disease (76 patients) forty three patients received FOLFOX regimen as a first-line treatment, twenty eight patients received FOLFIRI regimen and five patients received 5-flourouracil and leucovorin regimen.

For the purpose of prognosis of younger patients on different stage of CRC, patients were divided into two groups first one include early stage cases (stage I-III) and second group include metastatic cases (stage IV).

In the first group (stage I-III), we found 166 patients, 57 of them were 40 years or younger. 5-years DFS for (≤40 years) were 47% versus 60% for above 40 years patients (*P*= 0.069). 5-years OS for (≤40 years) were 50.87% versus 64% for older patients (*P*= 0.037). Figure (2) and (3) represent Kaplan-Meier curves of DFS and OS respectively of the first group. Second group include 76 cases with 25 cases of them where 40 years or younger. Median PFS for (≤40 years) was 3.5 months (95% 2.276 to 4.724) versus 5 months (95% 2.276 to 4.724) for older patients (*P*= 0.03). Median OS for (≤40 years) was 8 months (95% 4.736 to 11.264) versus 12 months (95% 10.74 to 13.253) for older patients (*P*= 0.02). Figure (4) and (5) represent Kaplan-Meier curves of PFS and OS, respectively of the second group.

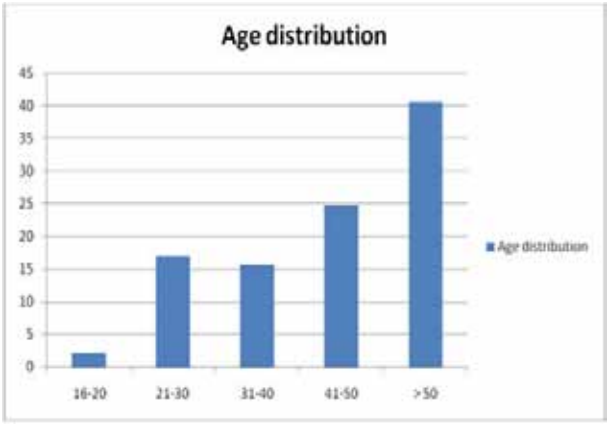

Figure 1: Age distribution in CRC patients (numbers in years).

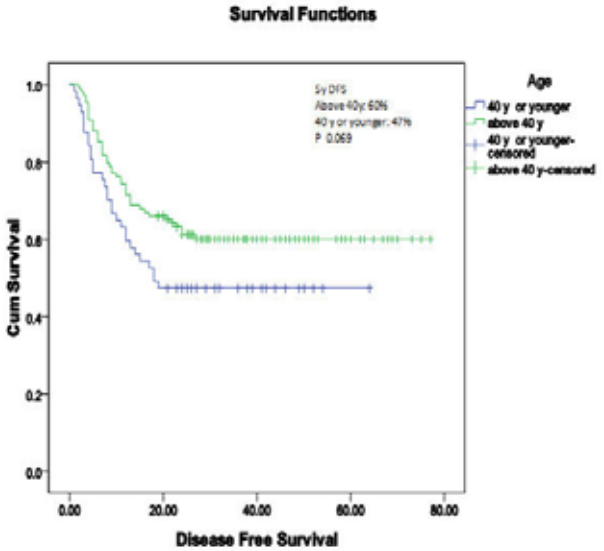

Figure 2: Kaplan-Meier curves of Disease Free Survival for stage (I-III) patients.

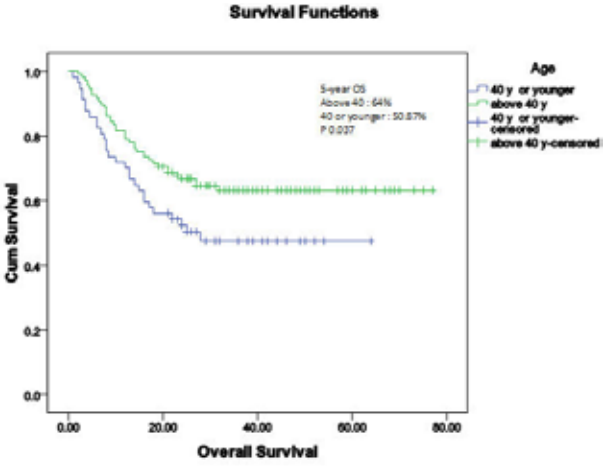

Figure 3: Kaplan-Meier curves of Overall Survival for stage (I-III) patients.

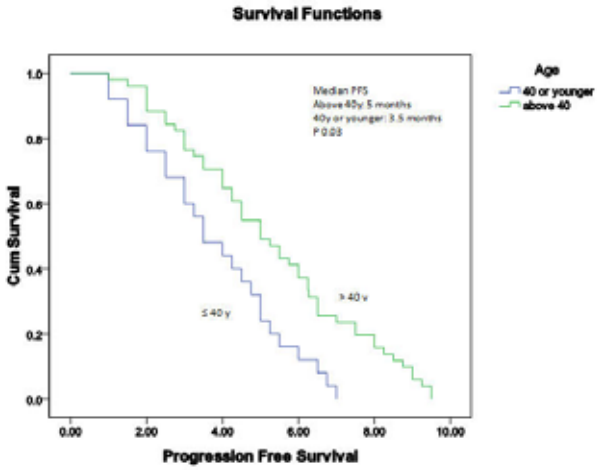

Figure 4: Kaplan-Meier curves of Progression Free Survival for stage IV patients.

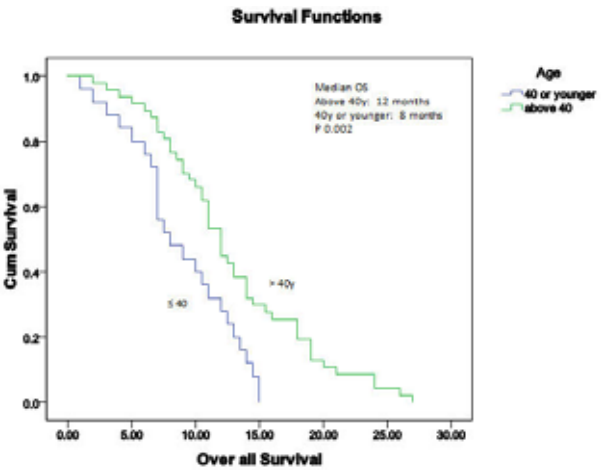

Figure 5: Kaplan-Meier curves of Overall Survival for stage IV patients.

Table 1: Patients characteristics and Pathological data of all patients (N= 288).

Variable	All patients 288 patients Number (%)	≤ 40years 100 patients Number (%)	> 40 years 188 patients Number (%)	*P* value
Sex				
Male	164 (56.9)	51 (51)	113 (60.1)	0.2
Female	124 (43.05)	49 (49)	75 (39.89)	
Tumor site				
Right colon	99 (34.37)	39 (39)	60 (31.91)	
Left colon	90 (31.25)	28 (28)	62 (32.97)	0.17
Transverse colon	9 (3.12)	4 (4)	5 (2.65)	
Rectum	90 (31.25)	30 (30)	60 (31.91)	
Mucinous subtype				
Yes	83 (28.81)	45 (45)	38(20.21)	
No	205 (71.18)	55 (55)	150(79.78)	0.2
Grade				
I	8 (2.78)	4 (4)	4(2.12)	
II	229 (79.79)	61 (61)	168(89.36)	
III	50 (17.42)	35 (35)	15(7.97)	0.05
Unknown	1	0	1	
TNM Staging				
Stage I	9 (3.7)	3 (3.65)	6 (3.75)	
Stage II	75 (31)	14 (17.07)	61 (38.12)	
Stage III	82 (33)	40 (48.7)	42 (26.25)	0.07
Stage IV	76 (31.4)	25 (30.48)	51 (31.87)	
Unknown	46	18	28	

Table 2: Difference between colon and rectal cancer among different factors:

Variable		Colon	Rectum	*P* value
		Valid %		
Age groups	≤40 years	67	72.2	0.37
	>40 years	33	27.8	
Gender	Male	73.4	26.6	0.50
	Female	70.1	29.9	
Stage	I & II	37.2	35.2	0.70
	III	31.1	37	
	IV	31.7	27.8	
Grade	I	1	3.7	0.18
	II	79.9	82.2	
	III	19.1	13.6	
Mucinous adenocarcinoma	Yes	31.8	23.2	0.15
	No	68.2	76.8	

DISCUSSION

A major concern needing to be addressed in CRC is the correlation of age with prognosis, especially that world wide data regarding this point is conflicting[7-9]. ** Egyptian CRC patients carries unique genetic features that differ from European and American races[11,12]. Accordingly, this study was planned to evaluate the real incidence of younger patients and its impact with different epidemiological features on the prognosis in different stages of CRC.

Considering age distribution, 34.7 % of our patients were 40 years old or younger which coincides with the previous Egyptian studies, in which the incidence of CRC in patients 40 years old or younger ranged from 30% to 40%5-7 In contrast to western countries where the risk of CRC begins to increase after the age of 40 years and rises sharply at ages 50 to 55 years; the risk doubles with each succeeding decade, and continues to rise exponentially, 90% of these cancers occur in people older than 50 years of age & the incidence of colorectal cancer peaks at about age 65 years.3 Similarly in the United Kingdom, only 2 to 3 per cent of colon cancer occurs in patients younger than the age of 40 years[13], the high prevalence of the Egyptian CRC in the young could not be explained by Lynch or other hereditary syndromes[12,14,15], but could be explained by exposure to oncogenic agents at younger age, an explanation which needs more evaluation via environmental and genetic testing.

On the other hand, we noticed that younger patients have more advanced stages and poorer grades than older patients at presentation. This is similar to data of the study conducted by Minardi *et al*; where more aggressive tumor behavior and worse overall survival rate have been noted in patient with colon cancer, whose disease was diagnosed before the age of 40 years[16] other explanation for advanced stage at presentation could be that young patients with colorectal cancer may be diagnosed late due to low suspicion of malignancy in these patients.

Regarding gender, we found insignificant male predominance. Slightly more than half the cases were males (56.9%), giving a male: female ratio of 1.3:1 which is nearly similar to the results of previous Egyptian studies[5-7]. In our study, 28.8% of patients had mucinous adenocarcinoma, which were nearly similar to that reported by the study conducted by Soliman *et al.* study, where 30.6% of patients had mucin-producing tumors[5].

In this study, we found that epidemiological features of patients with rectal carcinoma were similar to colonic carcinoma with regard to age, sex, histological types and TNM stages. This is similar to previous Egyptian studies with the exception of El-Bolkainy *et al.* data from the National Cancer Institute, Cairo University; where it was found that rectal carcinoma patients were younger than those with colonic carcinoma[17].

Regarding the prognosis of younger patients in CRC, we reported a non-significant worse DFS and significant worse OS for stage I-III patients, in addition to significant worse PFS and OS for stage IV patients. This means that younger patients carry a bad prognosis relative to older patients. These results could be similar to the results of a large pooled Analysis over 6,284 patients from nine phase III trials of advanced colorectal Cancer. With only 188 of these patients (3% of total patients) were younger than 40 years old, and they found that younger patients had worse PFS but not OS[9].

This difference between our data and world wide data can be explained mainly by different genetic features for Egyptian patients. Delayed presentation and also it can be due to less available effective treatment available than European or American hospitals. For stage I-III patients we reported non-significant worse DFS (P= 0.069) and significant worse OS (P= 0.037). It is worth mentioning that incidence of stage III in regard to stage I-II was significantly higher in younger patients than older ones, a finding that might explain the worse survival for younger patients in early disease.

CONCLUSION

In Egyptian CRC patients, higher percentage of younger patients was noticed. In stage I-III disease, patients ≤40 years carried a worse OS due to higher percentage of stage III disease; while in stage IV, patients ≤40 years carried a worse PFS and OS. Large national study to focus on different oncogenic agents that promote for higher incidence of CRC in younger patients will be satisfactory in the near future.

Disclosure

The authors report no conflicts of interest in this work.

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